

Risk of carditis after three doses of vaccination with mRNA (BNT162b2) or inactivated (CoronaVac) covid-19 vaccination: a self-controlled cases series and a case-control study



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Summary

Background Large-scale comparative research exploring the risk after the third dose and after inactivated covid-19 vaccination is limited. This study aimed to assess the risk of carditis following three doses of BNT162b2 or CoronaVac.

Methods We conducted a self-controlled case series (SCCS) and a case-control study using electronic health and vaccination records in Hong Kong. Carditis incidents within 28 days of covid-19 vaccination were included as cases. In the case-control study, up to 10 hospitalized controls were selected with stratified probability sampling by age, sex, and hospital admission (± 1 day). The incidence rate ratios (IRRs) were reported from conditional Poisson regressions for SCCS, and adjusted odds ratios (ORs) were reported from multivariable logistic regressions.

Findings A total of 8,924,614 doses of BNT162b2 and 6,129,852 doses of CoronaVac were administered from February 2021 to March 2022. The SCCS detected increased carditis risks after BNT162b2: 4.48 (95%confidence interval [CI]:2.99–6.70) in 1–14 days and 2.50 (95%CI:1.43–4.38) in 15–28 days after first dose; 10.81 (95%CI:7.63–15.32) in 1–14 days and 2.95 (95%CI:1.82–4.78) in 15–28 days after second dose; 4.72 (95%CI:1.40–15.97) in 1–14 days after third dose. Consistent results were observed from the case-control study. Risks were specifically found in people aged below 30 years and males. No significant risk increase was observed after CoronaVac in all primary analyses.

Interpretations We detected increased carditis risks within 28 days after all three doses of BNT162b2 but the risk after the third doses were not higher than that of the second dose when compared with baseline period. Continuous monitoring of carditis after both mRNA and inactivated covid-19 vaccines is needed.

Funding : This study was funded by Hong Kong Health Bureau (COVID19F01).

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The Lancet Regional Health - Western Pacific
2023;35: 100745

Published Online 25 March 2023

<https://doi.org/10.1016/j.lanwpc.2023.100745>

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Keywords: Adverse events of special interest; Myocarditis; Pericarditis; Covid-19 vaccines; Vaccine safety

Research in context

Evidence before this study

On 1st November, 2022, we searched PubMed with the search term " (Carditis OR Myocarditis OR Pericarditis) AND (BNT162 OR CoronaVac) AND (Third or Booster)". No additional restrictions were set. This search yielded 26 studies, leaving 25 after removing replicates: 1 published not in English; 9 case reports or case series; 5 reviews or letters, 5 descriptive studies, 2 with population-level incidence comparison, and 1 focusing on heterologous vaccine types. Only two articles examined the risk of carditis following the third dose of mRNA covid-19 vaccines. A phase-3 randomized placebo-controlled trial conducted in the United States detected zero myocarditis or pericarditis cases following the BNT162b2 third dose. However, the trials inherent have strong exclusion criteria. Another UK study reported a modest increase in carditis risk after a third dose of BNT162b2 from a self-control case series study among participants ages 13 years or older. However, this study was published with a short follow-up time after the recommendation of third dose vaccination. In addition, there are no large-scale comparative studies published about carditis risk after any kind of inactivated covid-19 vaccine.

Added value of this study

To our knowledge, this is among the first analytic studies to examine the risk of carditis after third dose of mRNA and inactivated Covid-19 vaccines: BNT162b2 and CoronaVac. We found increased carditis risks after all three doses of BNT162b2, the risk of third dose was not higher than that of the second dose. A significantly increased risk was observed among males and those aged below 30 years for BNT162b2. No significant risk increase was observed after CoronaVac in all analyses except for the female subgroup analysis in the case-control design.

Implications of all the available evidence

Our findings highlighted that there is increased risk following the BNT162b2 vaccination, especially in the male and the younger. However, the risk after third dose was not higher than that of the second dose. This evidence suggests the importance of continuous monitoring of the high-risk population after mRNA Covid-19 vaccination. Further safety monitoring for inactivated Covid-19 vaccines is warranted.

Introduction

Numerous case reports and case series have reported on the occurrence of carditis, including both myocarditis and pericarditis, particularly after mRNA covid-19 vaccines.¹ An increasing number of analytic studies suggested this association. The risk was estimated to be higher among males, adolescents, and young adults.^{1–6} However, there are inconsistent findings globally. Studies in Hong Kong and Israel estimated an approximately threefold increased risk of myocarditis after Pfizer-BioNtech BNT162b2.^{7,8} A Danish cohort study did not find an overall increased risk after BNT162b2, except an approximately threefold increased risk in women.⁹ Another cohort study conducted using administrative claims data from the United States concluded that the risk of myocarditis and pericarditis after the mRNA vaccine (mRNA-1273 or BNT162b2) was highest among men aged between 18 and 25 years; however, the incidence was low.¹⁰ All these studies supported the risk of carditis after the first and second doses of BNT162b2. Several possible underlying mechanisms were proposed: it could be the cross-reaction between a myocardial α -myosin heavy chain and antibodies directed to the spike protein of SARS-CoV-2 from the mRNA vaccines, or pre-existing immune pathway in certain individuals with predisposition; immune response to mRNA which

were treated as antigens; and dysregulated cytokine expression.^{4,11,12}

In December 2021, the WHO recommended administration of the third dose of covid-19 vaccine to restore vaccine effectiveness.¹³ From early 2022, an increasing number of case reports and case series of carditis after the third dose were published.^{1,14,15} A UK study investigating myocarditis incidence after each of the three doses of ChAdOx1, BNT162b2, and mRNA-1273 suggested risk elevation following all three doses of BNT162b2.¹⁶ However, the new study did not examine the incidence of pericarditis, and we have a longer follow-up period after the third dose. No published literature reports any risk of carditis after inactivated covid-19 vaccines.

In Hong Kong, both the BNT162b2 mRNA vaccine (Comirnaty, distributed by BioNTech/Fosun Pharma, equivalent to the Pfizer-BioNTech vaccine outside China) and the inactivated vero cell vaccine (CoronaVac, distributed by Sinovac) were available as part of the mass vaccination program. Using a territory-wide clinical database, we assessed the risk of carditis-related admission after each dose of covid-19 vaccines in Hong Kong with a modified self-controlled case series (SCCS) study, a within-individual comparison design; and a case-control study, a between-individual design.

Methods

This study aimed to estimate the risk of carditis after all three doses of BNT162b2 and CoronaVac covid-19 vaccination among people in Hong Kong by using SCCS and case-control study design. This study obtained ethical approval from the Institutional Review Board of the University of HK/HA HK West Cluster (UW20-556, UW21-149 and UW21-138); and the DH Ethics Committee (LM21/2021).

Data source

We obtained data on the diagnosis, prescription, and laboratory results from the Hospital Authority (HA), a statutory body funding healthcare and acute care provider in Hong Kong. All Hong Kong residents across all socioeconomic classes are eligible to have publicly subsidized healthcare services provided by HA, which captured over 70% of all hospitalization in Hong Kong.¹⁷ The Clinical Data retrieved from HA has previously been used to evaluate many diseases or medications.^{18–20} The current database includes all clinical information up to 31st March, 2022.

We obtained the covid-19 vaccination records from the Department of Health (DH). In Hong Kong, the covid-19 vaccination program was launched on 23rd February, 2021 for CoronaVac and 6th March, 2021 for BNT162b2. Since November 2021, the third dose of both vaccines has been available to eligible Hong Kong citizens.²¹ A detailed dosing schedule of the mass vaccination program in Hong Kong is presented in [Appendix a](#).²²

A de-identified unique pseudo ID was used to match the vaccination records with the medical records. This dataset has been used to evaluate safety of covid-19 vaccines, including carditis,^{8,23} multimorbidity,²⁴ Bell's palsy,²⁵ rheumatoid arthritis,²⁶ liver injury,²⁷ thromboembolism and haemorrhagic stroke.²⁸

Study design

We used both SCCS and case-control study design. SCCS design uses individuals as their controls, eliminating time-invariant confounders and away from selection bias.²⁹ This study design was specifically developed for transient exposure and events, like vaccine safety studies.^{30,31} The method has been used in many contemporary covid-19 vaccine safety studies.^{6,32–34} There were three major assumptions detailed in [Appendix b](#) to ensure the appropriate application of SCCS.^{29,35} One of the main assumptions is to ensure that the occurrence of carditis would not lead to the cancellation of a subsequent dose of covid-19 vaccination, i.e. not an event-dependent exposure. A recent study by Ghebremichael-Weldeslassie et al. suggested using the modified SCCS method, which was designed for event-dependent exposure and is considered most appropriate for covid-19 vaccine safety studies.³⁵ The modified SCCS requires to include people without exposure but having

the outcomes, which is different from standard SCCS. The included people without exposure may indicate the cancellation of exposure due to the events. The modified SCCS model considers this group of people using the estimating equations derived under a counterfactual in which no exposure can occur after an event. Many contemporary studies have also adapted the modified SCCS method in covid-19 vaccine safety studies; therefore, we adopted the same method in this study.^{36–38} In addition, a case-control study within hospitalized patients was conducted to serve as an internal validation. We chose a case-control study over a cohort study because SCCS is designed based on a cohort study.

Cohort identification, outcome, and exposure definition

In both the modified SCCS and case-control study, all Hong Kong residents aged 12 years or above who had used any HA services between 1st January 2018 and 31st March 2022 were identified. We did not include vaccine recipients under 12 years old because covid-19 vaccines were only licensed for this age group in late January 2022, and relevant data was unavailable at the study time.³⁹ In HA hospitals, an elevated troponin is considered a guide for acute myocarditis. Cardiac magnetic resonance imaging or biopsy will be conducted to confirm the myocarditis diagnosis further. The participants with a diagnosis of acute myocarditis [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-DM): 422.x and 429.0] or acute pericarditis (ICD-9-DM: 420.9 and 423.9) or myopericarditis, defined as the co-existence of the said two diagnoses in the inpatients setting between 23rd February 2021 and 31st March 2022 were included. We excluded 1) patients who had a past history of carditis to ensure they were incident cases; 2) patients with missing date of birth or sex; 3) patients who had a subsequent diagnosis of myocardial infarction (MI) (ICD-9-DM: 410 and 411) in any following hospitalization up to 31st March 2022 to avoid misclassification of carditis as MI; 4) patients who received heterologous covid-19 vaccines to evaluate effects from the same type of vaccines. The crude incidence of carditis cases per 1,000,000 covid-19 vaccine doses administered was then estimated. To avoid misclassifying the effect of covid-19 infection as vaccinated, we excluded patients with a SARS-CoV-2 polymerase chain reaction (PCR) positive test result before (at any point in time in the patient's history) and during the study period in the SCCS study. In the case-control study, cases who were SARS-CoV-2 PCR positive before the diagnosis date were excluded, while those patients with at least one SARS-CoV-2 positive result during their lifetime were excluded from the controls. The exposures were defined as receiving the first, second, and third doses of covid-19 vaccines, either BNT162b2 or CoronaVac.

Modified self-controlled case series study

The observation period was from 23rd February 2021 to 31st March 2022. The day of each covid-19 vaccination was defined as day 0. Risk periods of 0, 1–14 and 15–28 days from the vaccination date of each dose were pre-defined to assess the risk of carditis. The risk at day 0 is excluded to ensure it is neither included in the non-risk nor risk period.³⁵ If the time of vaccination between two doses is less than 28 days, the risk period of the first dose was censored on the second vaccination date. All other non-risk periods within the observation period were considered as baseline periods to ensure no overlap of risk periods. Conditional Poisson regression was used to estimate the incidence rate ratio (IRR) between each risk period and the baseline period, with a 95% confidence interval. Calendar months were included for adjusting the seasonal effect. The data schema illustrating the risk periods is displayed in [Appendix c](#).

The modified SCCS requires the inclusion of unvaccinated cases to provide information for adjustment when people did not receive the vaccines after having the event (i.e. carditis).^{31,35} Such adjustment is done by adjustment of seasonal effects and do not directly contribute to the estimation of the risks. Omission of unvaccinated individuals in a modified SCCS will introduce bias.³⁵ The analysis assessed the risk of carditis for each risk period of each dose, with seasonal effects adjusted by month. A collapsed risk period of 1–28 days was also estimated to compare with the results from the case-control study.

Case-control study

Hospitalization of patients without any carditis diagnosis were identified as controls. Incidence density sampling was applied that up to ten controls were selected by stratified probability sampling and matched with each case according to age, sex, and date of admission (within one calendar day). Cases were allowed to be controls before their incident carditis hospitalization. The index date was defined as the date of hospitalization for controls and the date of carditis-related hospitalization for cases. The cases and controls who took the vaccines within 28 days before the index date was categorized as an exposure, while others were considered as non-exposed. Conditional logistic regression stratified by matched sets, was used to examine the association between vaccines and carditis. In the multivariable regression, a binary cardiovascular medication history within 90 days before admission and clinical history were included as covariates for adjustment. The clinical history includes diabetes, hypertension, coronary heart disease, stroke, heart failure, myositis, encephalitis. The cardiovascular medication includes anticoagulants, antiplatelets, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -adrenoceptor blockers, calcium-channel blockers, digoxin, and statins ([Appendix d](#)). The crude odds ratio (OR) and adjusted OR were reported.

Subgroup and sensitivity analysis

We conducted subgroup analyses by sex and age group (age ≥ 30 and < 30 years). A subgroup analysis by myocarditis and pericarditis was conducted in the case-control study but not in SCCS due to the small sample size. In the case-control study, an additional analysis for separated effects for each dose was analyzed by categorizing exposure into seven groups: first, second, and third doses of BNT162b2 and CoronaVac, and an unvaccinated group. A direct comparison of effects between the second and third doses BNT162b2 was conducted to assess the difference between them. We adopted the criteria of Brighton Collaboration in the sensitivity analysis, including those patients with at least one troponin assay with readings higher than the reference range during the episode in both study designs. Such case definition was also used in previous studies.^{8,9}

The number of samples ranging from 5077 to 116 were required to achieve 80% power to detect the incidence rate ratio from 1.11 to 1.80. A detailed sample size calculation is provided in [Appendix e](#). All statistical tests were two-sided. The analysis was independently conducted by MF and FWTC. All analyses were performed in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), the modified SCCS were conducted using R-package "eventdepenexp".⁴⁰

Role of funding source

This study was funded by a research grant from the Health Bureau, The Government of the Hong Kong Special Administrative Region (reference COVID19F01). 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

A total of 8,924,614 doses of BNT162b2 and 6,129,852 doses of CoronaVac were administered from 23rd February 2021 to 31st March 2022. Among the 6,518,189 Hong Kong residents who were vaccinated, 56.8% ($n = 3,700,823$) and 43.2% ($n = 2,817,366$) received BNT162b2 and CoronaVac as their first dose; 89.2% received second dose ($n = 3,402,482$ for BNT162b2 and $n = 2,408,665$ for CoronaVac), and 41.8% received the third dose ($n = 1,821,309$ for BNT162b2 and $n = 903,821$ for CoronaVac) by the end of the study period, respectively. Within the study period, 1213 patients were hospitalized with a diagnosis of carditis, including 202 myocarditis, 973 pericarditis, and 38 with myopericarditis. After removing patients without demographic information, with past history carditis, with a further diagnosis of MI, and with heterologous vaccines, 1029 patients with incident carditis were identified ([Fig. 1](#)). The crude incidence of per 1,000,000 doses were 18.94 and 5.22 for BNT162b2 and CoronaVac, respectively

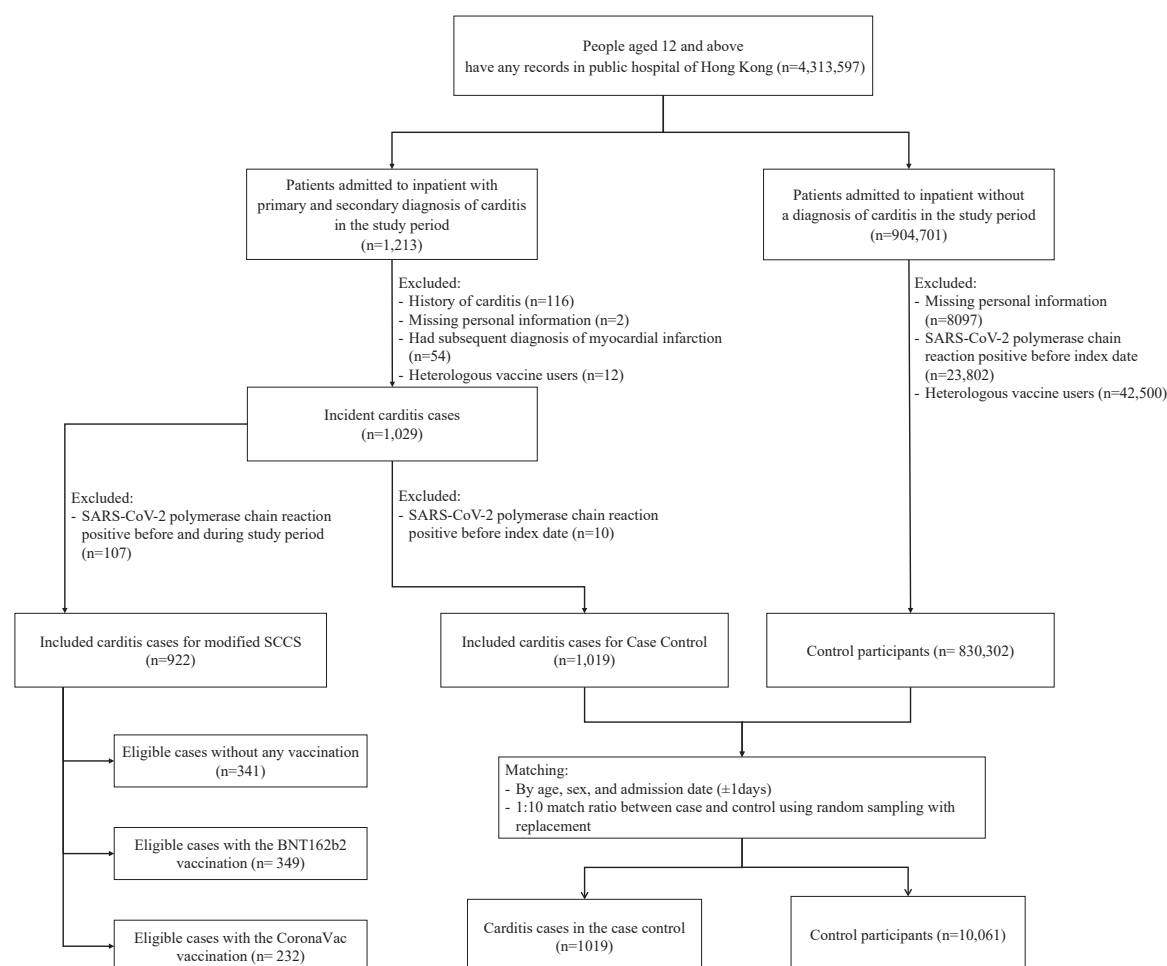


Fig. 1: Flowchart of participant selection for the self-controlled case series and case-control design.

during the study period. The crude incidence of the second dose of BNT162b2 was the highest among the three doses; whilst the incidence rate in all three doses of CoronaVac were similar (Fig. 2).

Modified self-controlled case series study

The flowchart for participants selection is illustrated in Fig. 1. A total of 922 incident carditis cases were included in the SCCS analysis, which the patient characteristics are shown in Appendix f. 341 patients were unvaccinated; 349 patients received BNT162b2; and 232 patients received CoronaVac. Among the carditis cases who received at least one dose of covid-19 vaccine, 79.7% (278/349) and 18.6% (65/349) BNT162b2 recipients had their second and third dose; whilst 66.4% (154/232) and 12.1% (28/232) CoronaVac recipients received the second and third dose.

The modified SCCS model detected an increased risk in all doses of BNT162b2, including the third dose, but not in CoronaVac (Fig. 3). Among patients who received BNT162b2, the seasonality-adjusted IRR of carditis were

4.48 [95% CI 2.99–6.70] in 1–14 days and 2.50 (95% CI: 1.43–4.38) in 15–28 days after first dose; 10.81 (95% CI: 7.63–15.32) in 1–14 days and 2.95 (95% CI: 1.82–4.78) in 15–28 days after second dose; 4.72 (95% CI: 1.40–15.97) in 1–14 days after third dose. After collapsing the risk period into 1–28 days, risks are higher after both first dose (IRR: 3.16, 95% CI: 2.24–4.45) and second dose (IRR: 6.18, 95%CI 4.53–8.43). The subgroup analysis in male and younger age group (age <30) detected a similar elevated risk in BNT162b2 as the primary analysis. When using the second dose as the reference, the IRR for direct comparison with the third dose is 1.77 (95% CI: 0.04–73.15). The numeric results of the IRR in each period from each analysis are shown in Appendix g. The sensitivity analysis of limiting to cases with elevated troponin level showed a similar result (Appendix h).

Case-control study

The selection process for cases and controls is presented in Fig. 1. A total of 1019 cases with incident carditis were matched with 10,061 controls. The characteristics

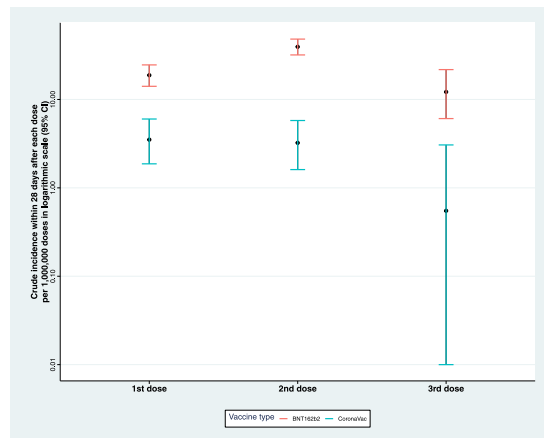


Fig. 2: Crude incidence rate of carditis within 28 days following each vaccine dose per 1,000,000 doses.

of cases and controls were similar, except for the history of heart failure, where cases had a larger proportion than controls (10.0% in cases vs. 5.0% in controls with standardized mean difference: 0.190) ([Appendix i](#)). The patients' characteristics stratified by vaccine type and by carditis type (myocarditis or pericarditis) are reported in [Appendix j](#) and [Appendix k](#).

In multivariable conditional logistic regression ([Fig. 4](#)), the adjusted OR of carditis-related hospitalization for BNT162b2 users was 3.91 (95% CI: 3.16–4.83) compared to controls. In the analysis stratified by

different doses of BNT162b2, the adjusted OR for the first, second, and third doses were 3.00 (95% CI: 2.21–4.09), 4.88 (95% CI: 3.73–6.40) and 3.56 (95% CI: 1.71–7.40), respectively. A positive association was found in all the subgroup analyses for BNT162b2: 4.48 (95% CI: 3.46–5.78) for males, 2.85 (95% CI: 1.92–4.23) for females, 9.82 (95% CI: 6.77–14.24) for people age <30 years, 2.12 (95% CI: 1.56–2.88) for people aged 30 years or above. The numeric results of the adjusted odds ratio for each analysis are shown in [Appendix l](#). In the sensitivity analyses ([Appendix m](#)), the adjusted OR was [6.18 (95% CI: 4.62–8.27)] which limited to cases with elevated troponin levels. The subgroup analyses of both myocarditis and pericarditis reports an increased risk, while the sample size ($n = 32$) for myopericarditis is too small for estimation. The risk of myocarditis (AOR: 17.81, 95% CI: 11.49–27.61) was higher than pericarditis (AOR: 2.07, 95% CI: 1.56–2.74). The AOR of direct comparison between the first and second dose and the third dose is 0.93 (95% CI: 0.14–6.35). No association was found for CoronaVac in primary, subgroup, nor sensitivity analysis, except a higher adjusted OR was detected among females after CoronaVac: 1.96 (95% CI: 1.16–3.32). The sensitivity analysis showed a similar pattern.

In addition, our post-hoc analysis from a population-level perspective comparing the carditis incidence during pre- and post-pandemic period also demonstrated an increasing trend after the introduction of covid-19 vaccine period ([Appendix n](#)).

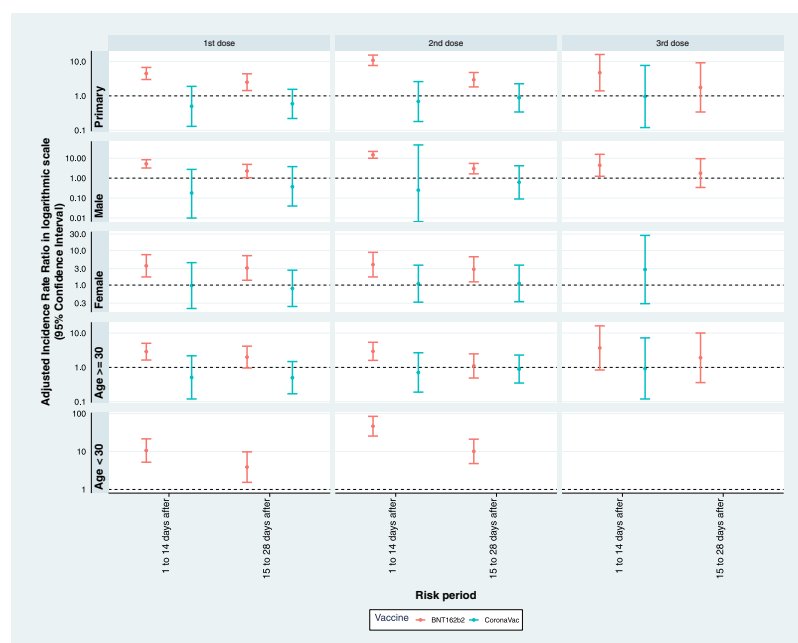


Fig. 3: The incidence rate ratio for carditis risk from self-controlled case series for each vaccine dose in primary and subgroup analyses.

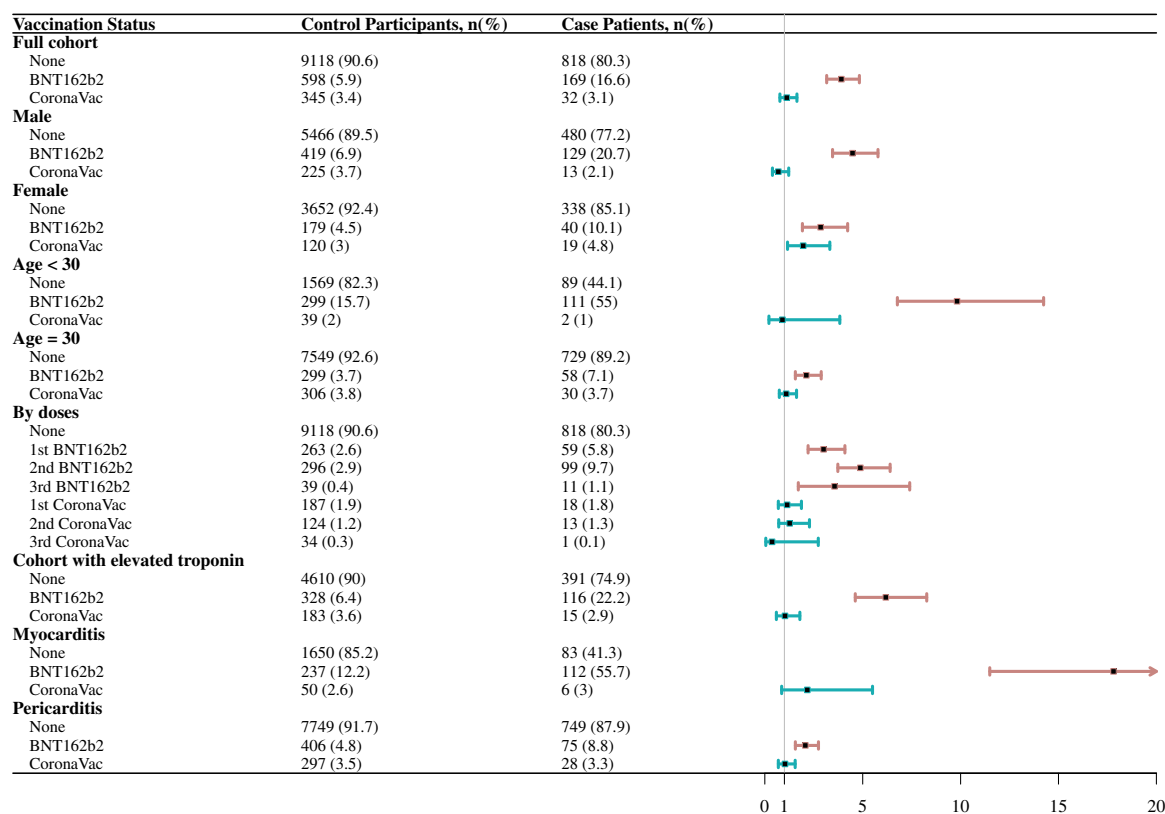


Fig. 4: The adjusted odds ratio for carditis risk from case-control design in primary and subgroup analyses.

Discussion

To the best of our knowledge, this is among the first analytic studies that examined the risk of carditis after the third dose of BNT162b2 and CoronaVac. Our analysis detected an increased risk of carditis following the third dose, in addition to the first and second doses of BNT162b2, using both SCCS and case-control study designs. Despite having an increased risk after the third dose, the magnitude of such risk was not higher than that of the second dose. No statistically significant risk was detected after the CoronaVac, except for the female subgroup.

Our results from the direct comparison between the third and second doses showed a slightly increased risk with a wide confidence interval, but we lacked sufficient statistical power to draw a meaningful conclusion. A possible explanation for the absence of a dose-response relationship (i.e. increasing immune response with the increasing number of doses) in our study could be the delayed vaccination schedule of the third dose. In Hong Kong, the recommended interval between the second and third dose is six months, which is much longer than 21–28 days for the first and second dose.²³ This delayed gap may reduce the dose-response, thus less occurrence of carditis. However, we did not have an adequate

sample to conduct further analyses on the different durations between the second and third doses. Further studies should be conducted when data is available.

Furthermore, we found that males and individuals <30 years had a more notably increased risk for carditis. Our previous studies also support such findings, Patone et al. and Wang et al. in their first and second dose BNT162b2 studies.^{6,8,10,41} The inflammatory cascade may explain the higher risk observed in males that sex hormones such as testosterone can inhibit anti-inflammatory cells and cause an immune response.^{4,42,43} Further studies are warranted to examine the risk of different vaccination schedules of third doses. However, our case-control study identified an increased risk for females after taking CoronaVac. The sample size was too small to draw any meaningful conclusion from the modified SCCS study. Such risk was also not reported in our previous study of the first and second doses but in a shorter study period.⁸ It is worth noting that the absolute number of patients in the female subgroup analysis was very small (cases: 19; controls: 120). The significant result could be due to the small number of cases. Considering all the current evidence, including the SCCS results and lack of published reports, as well as the small sample size of this subgroup

analysis, we conclude that this signal is not a concern. Nevertheless, we cannot rule out the possibility that some females may be at high risk for myocarditis, especially immune checkpoint inhibitor myocarditis, due to escaped chromosome X-linked inactivation, including genes that regulate the innate and adaptive immune systems that modulate TLR and nuclear factor κ B signaling.⁴³ Further studies on the sex difference risk of carditis after CoronaVac are warranted.

A recent UK study investigating myocarditis incidence after each of the three doses of ChAdOx1, BNT162b2, and mRNA-1273 suggested a consistent, similar risk elevation following all three doses of BNT162b2.¹⁶ Nevertheless, we believe our work remains novel and important because this study did not examine pericarditis, the incidence of which has been demonstrated in our work to be significantly increased. Second, their data only cover 2021, while we included data up to 31st March 2022. Third, we have included CoronaVac, an inactivated vaccine that, to the best of our knowledge, its risk of carditis after the third dose has not been reported in any published literature. CoronaVac is also one of the most commonly used covid-19 vaccines worldwide, especially in developing countries. However, there are very limited studies on CoronaVac whilst other vaccines such as BNT162b2, mRNA-1273 and ChAdOx1 were extensively studied in developed countries. Although this study did not aim to directly compare the risk of carditis after CoronaVac and BNT162b2, our findings did provide a truly global impact on addressing the disparity among evidence of different vaccine platforms. This current study is also novel compared with our previous case-control study⁸ with a study period up to mid-2021 because it had a longer study period of 8 months covering the time when the third dose (November 2021, [Appendix a](#)) is available in Hong Kong, allowing the assessment of risk after the third dose.

In fact, there are inconsistent findings on risks following different doses of BNT162b2 globally. A study in Israel assessed the incidence rate of carditis during different periods.⁴⁴ Compared with the historical incidence, no increased risk was observed after the first dose of BNT162b2 [standardized incidence ratio (SIR): 1.42, 95% CI: 0.92–2.10], but risk increased after the second dose (SIR: 5.34, 95% CI: 4.48–6.40). However, their study adjusted for age and sex only, but not other confounding such as CVD history. Patone et al.⁶ conducted an SCCS in the UK and detected an increased risk of myocarditis in days 1–7 after the second dose of the BNT162b2 vaccine, while no effect was found in their first dose. Although both Patone et al.⁶ and our current study used the SCCS design, they applied a pre-risk period to account for the event-dependent exposure issue, while we applied the modified SCCS design. The difference in study design may contribute to the differences in our findings. In addition, we did not

observe any increased risk shortly before vaccination ([Appendix b](#)), thus, we did not define any pre-risk period in our study.

This study is subject to several limitations. In the case-control study, it was also conducted within the hospitalized patients in HA which its generalisability may be limited to hospitalized patients. We also observe a slight difference in baseline characteristics among the vaccinated and non-vaccinated groups. However, the SCCS study relied on within person-comparison and thus inherently accounted for the time-invariant confounders in the analysis. The consistent results with the case-control study also reassured the internal validity of our findings. We therefore believe the confounding stemming from the difference in characteristics is minimal in our study. There may be a misclassification of carditis cases as we did not limit the cases to those with a carditis diagnosis and elevated troponin level. However, our sensitivity analysis limiting to those with elevated troponin levels demonstrated similar results as the primary analysis. It is worth noting that all diagnoses within the HA were made through vigorous clinical workups by hospital physicians. Therefore, we believe such misclassification bias should be minimal. We also cannot rule out the possibility of enhanced surveillance of carditis after mass vaccination compared to other periods before vaccine availability. In addition, our study does not aim to demonstrate a causal relationship between carditis and covid-19 vaccines. The carditis cases that occurred within 28 days after vaccination, although likely to be associated with the vaccine, were not necessarily due to immunogenic effect of the vaccines. Despite detecting a statistically meaningful risk estimate in the primary analysis of SCCS, we could not draw any conclusion in certain subgroup analyses, such as female and younger age groups. Further analyses should be conducted when we accumulated more data of these subgroups. SCCS could not control for time-varying unmeasured confoundings such as a drastic change in co-morbidities and covid-19 infection status. However, we adjusted for seasonality by month in the SCCS study and excluded patients who had a positive SARS-CoV-2 PCR test before and during the study period to minimize misclassifying of the effect attributed to carditis. Our case-control study, which adjusted relevant co-morbidities, showed consistent findings with our SCCS, reassuring that the bias from time-varying confounding was minimal. Last, most of the study population is Chinese, which limited the generalisability of the findings in regions with predominantly non-Chinese ethnic groups. However, the observed elevated carditis risk following mRNA vaccines is consistent with most studies conducted in Western countries. Since the SCCS design relies on the within-individual comparison, the results are not affected by the differences across cohorts who received different vaccine types. Lastly, the carditis risk difference between

vaccine types was not specifically explored. The risk estimates of the two vaccine types should not be simplistically compared as they were based on two samples with different characteristics. Further study with a head-to-head comparison between the two platforms is warranted to explore this difference.

Conclusion

We detected an increased risk of carditis that led to hospitalisation within 28 days following all three doses after BNT162b2, but not CoronaVac when compared with baseline period. The risk estimation after the third doses BNT162b2 is not higher than that of the second dose. Overall, males and those aged less than 30 years are of higher risk of myocarditis. Further studies in other regions and continuous surveillance are needed to assess the benefit and risk of the third dose.

Contributors

MF, FTTL, 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. MF and FWTC undertook the statistical analysis. MF, NT, CSLC and ICKW wrote the first draft of the manuscript. MF, FTTL, FWTC, CSLC extracted data from the source database. CSLC and ICKW are the principal investigator and provided oversight for all aspects of this project. XL, EYFW, CKHW, EWYC, and KHY 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. MF, FTTL, 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.

Data sharing statement

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

Declaration of interests

FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region, outside the submitted work. XL has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region; research and educational grants from Janssen and Pfizer; internal funding from the University of Hong Kong; and consultancy fees from Merck Sharp & Dohme, unrelated to this work. EYFW has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region, and the Hong Kong Research Grants Council, outside the submitted work. CKHW reports receipt of research funding from the EuroQoL Group Research Foundation, the Hong Kong Research Grants Council, and the Hong Kong Health and Medical Research Fund; outside of the submitted work. EWYC reports honorarium from Hospital Authority; and grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, outside the submitted work. CSLC has received grants from the Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA, MSD, and Amgen; and personal fees from PrimeVigilance; outside the submitted work. ICKW reports research funding outside the submitted work from

Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Health Bureau of the Government of the Hong Kong Special Administrative Region, National Institute for Health Research in England, European Commission, and the National Health and Medical Research Council in Australia; has received speaker fees from Janssen and Medice in the previous 3 years; and is an independent non-executive director of Jacobson Medical in Hong Kong. All other authors declare no competing interests.

Acknowledgements

We thank colleagues from the Department of Health and from the Hospital Authority for their provision of data and support. We thank Ms. Iris Lai for technical support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanwpc.2023.100745>.

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