









## ORIGINAL RESEARCH

# BNT162b2 or CoronaVac Vaccinations Are Associated With a Lower Risk of Myocardial Infarction and Stroke After SARS-CoV-2 Infection Among Patients With Cardiovascular Disease

Xuxiao Ye , MSc\*; Vincent K. C. Yan , BPharm\*; Hei Hang Edmund Yiu , PhD; Jessica J. P. Shami, PhD; Wei Kang , MSc; Tiantian Ma, PhD; Xiwen Qin, PhD; Celine S. L. Chui, PhD; Francisco T. T. Lai, PhD; Xue Li , PhD; Eric Y. F. Wan , PhD; Carlos K. H. Wong , PhD; Ian C. K. Wong , PhD; Esther W. Chan , PhD

**BACKGROUND:** COVID-19 vaccines have demonstrated effectiveness against SARS-CoV-2 infection, hospitalization, and mortality. The association between vaccination and risk of cardiovascular complications shortly after SARS-CoV-2 infection among patients with cardiovascular disease remains unknown.

**METHODS AND RESULTS:** A case-control study was conducted with cases defined as patients who had myocardial infarction or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022. Controls were defined as all other patients who attended any health services and were not cases. Individuals without history of cardiovascular disease were excluded. Each case was randomly matched with 10 controls according to sex, age, Charlson comorbidity index, and date of hospital admission. Adjusted odds ratio with 95% CI was estimated using conditional logistic regression. We identified 808 cases matched with 7771 controls among all patients with cardiovascular disease. Results showed that vaccination with BNT162b2 or CoronaVac was associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection with a dose-response relationship. For BNT162b2, risk decreased from 0.49 (95% CI, 0.29–0.84) to 0.30 (95% CI, 0.20–0.44) and 0.17 (95% CI, 0.08–0.34) from 1 to 3 doses, respectively. Similar trends were observed for CoronaVac, with risk decreased from 0.69 (95% CI, 0.57–0.85) to 0.42 (95% CI, 0.34–0.52) and 0.32 (95% CI, 0.21–0.49) from 1 to 3 doses, respectively.

**CONCLUSIONS:** Vaccination with BNT162b2 or CoronaVac is associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection among patients with cardiovascular disease.

**Key Words:** BNT162b2 ■ CoronaVac ■ COVID-19 vaccines ■ myocardial infarction ■ stroke

Since the outbreak of COVID-19, SARS-CoV-2 was reported to influence both the respiratory system and several other organs, including the cardiovascular system.<sup>1</sup> Although the initial main concern focused

on the risk of pneumonia progressing to acute respiratory distress syndrome,<sup>2</sup> there are increasing reports of cardiovascular manifestations following COVID-19 with high risk of morbidity and mortality. Studies showed that

Correspondence to: Esther W. Chan, PhD, and Ian C. K. Wong, PhD, Centre for Safe Medication Practice and Research Department of Pharmacology and Pharmacy General Office, L02-56 2/F, Laboratory Block LKS Faculty of Medicine, The University of Hong Kong 21 Sassoon Rd, Pokfulam, Hong Kong SAR, China. Email: ewchan@hku.hk, wongick@hku.hk

\*X. Ye and V. K. C. Yan are co-first authors.

This manuscript was sent to Mahasin S. Mujahid, PhD, MS, FAHA, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.029291>

For Sources of Funding and Disclosures, see page 9.

© 2023 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- Vaccination with BNT162b2 or CoronaVac was associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection among patients with cardiovascular disease.
- A dose–response relationship between the number of doses received and the reduced risk was observed.

### What Are the Clinical Implications?

- Vaccination with BNT162b2 or CoronaVac can not only prevent SARS-CoV-2 infection, hospitalization, and mortality but also prevents the severe cardiovascular complications after infection.
- It is important for patients with cardiovascular disease to receive vaccination to prevent the potential severe cardiovascular complications if infected.

## Nonstandard Abbreviations and Acronyms

<b>BNF</b>	British National Formulary
<b>HA</b>	Hospital Authority

COVID-19 is a risk factor for acute myocardial infarction (MI) and stroke and can also lead to postacute COVID-19 sequelae of the cardiovascular system including cerebrovascular disorders, dysrhythmias, ischemic and nonischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease.<sup>3,4</sup> The acute and postacute cardiovascular complications represent a part of the clinical picture of COVID-19, and highlight the need for vaccination among patients with cardiovascular disease (CVD).

COVID-19 vaccines are shown to prevent severe outcomes after SARS-CoV-2 infection and the American College of Cardiology demonstrated the importance of vaccination, especially for patients with a high cardiovascular risk.<sup>5</sup> Both BNT162b2 (Comirnaty, BioNTech/Pfizer/Fosun) and CoronaVac (Sinovac Life Sciences) COVID-19 vaccines have demonstrated efficacy against SARS-CoV-2 infection with good safety and tolerability profiles in clinical trials and observational studies.<sup>6–9</sup> The 2 vaccines were reported to have no association with major adverse cardiovascular events in patients with CVD,<sup>10</sup> and a Korean study showed that vaccination can protect against MI and stroke that occurred 31 to 120 days after COVID-19 diagnosis.<sup>11</sup> However, previous studies also showed a high risk of MI and stroke during the first 2 to 4 weeks after SARS-CoV-2 infection,<sup>3,12</sup> and it remains unknown whether

the 2 vaccines can prevent MI and stroke during that interval. Also, patients with CVD might be more concerned about the association between COVID-19 vaccination and MI and stroke after SARS-CoV-2 infection. Therefore, the aim of this study is to investigate the association between COVID-19 vaccinations and the risk of MI and stroke shortly after SARS-CoV-2 infection among patients with CVD.

## METHODS

The data will not be made publicly available to other researchers for the purpose of reproducing the results or replicating the simulation as the data custodians have not given permission. The analysis codes support the findings are available from the corresponding author upon reasonable requests.

### Study Design and Data Sources

We conducted a population-based case–control study to investigate the association between BNT162b2 or CoronaVac vaccinations and the risks of MI and stroke after SARS-CoV-2 infection in patients with CVD.

This study was conducted using electronic health records in the clinical management system from the Hong Kong Hospital Authority (HA) linked with vaccination records provided by the Department of Health, the government of Hong Kong Special Administrative Region. The HA is a statutory administrative organization in Hong Kong that manages all publicly funded acute health care facilities including 43 public hospitals, 49 specialist outpatient clinics, and 73 primary care clinics.<sup>13</sup> Individual patient-specific data include demographic characteristics, diagnoses, medication dispensing records, outpatient and primary care clinics, emergency department attendances, laboratory tests, and hospitalization details, all comprehensively recorded for research and auditing purposes. The Department of Health provided COVID-19 vaccination records of BNT162b2 and CoronaVac vaccines from February 23, 2021, when the mass COVID-19 vaccination program in Hong Kong was launched, until August 15, 2022. The 2 databases are linked according to a unique identifier derived from the Hong Kong Identity Card. A previous study showed high coding accuracy for cardiovascular diagnosis in HA's electronic health records, with positive predictive values estimated to be ≈85% to 91%<sup>14</sup> and have been used for pharmacovigilance of cardiovascular medications,<sup>15,16</sup> and prior COVID-19 vaccine safety studies.<sup>17–20</sup>

### Patient Identification and Study Outcomes

We identified all patients who had a history of CVD before the outcome event. As only electronic health records on or after January 1, 2018 can be accessed, history of

CVD was defined as patients with a diagnosis of CVD between January 1, 2018 and the day before the outcome event. The definition of CVD included atherosclerotic cardiovascular disease, heart failure, and atrial fibrillation. The outcome investigated was a composite of MI and stroke within 28 days after SARS-CoV-2 infection defined as a documented diagnosis of MI and stroke made by clinicians, which were extracted from the HA's electronic health records using the *International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM)* codes (Table S1). The coding accuracy of the outcomes in the HA's electronic health records had been validated in previous studies with positive predictive values 85% for MI and 91% for stroke.<sup>14,21,22</sup> SARS-CoV-2 infection was defined as a positive polymerase chain reaction (PCR) test using throat swab, nasopharyngeal aspirate, or deep throat sputum specimens. PCR test results are recognized as the criterion standard diagnostic criteria for SARS-CoV-2 infection and are provided by the Public Health Laboratory Services Branch of Department of Health and HA.

### Definition of Vaccine Exposure

The 2 COVID-19 vaccines, BNT162b2 and CoronaVac, have been available to individuals aged 16 years old or above in Hong Kong since February 23, 2021 and were extended to individuals aged 12 years or above since June 2021 for BNT162b2 and November 2021 for CoronaVac. The third doses of BNT162b2 and CoronaVac were made available for priority groups on November 11, 2021 and the scheme was subsequently expanded to the general population from January 1, 2022.<sup>23,24</sup> Details of the priority groups roll-out schedule of the vaccination program in Hong Kong are listed in Table S2. Individuals are not permitted to switch between vaccine types for the first 2 doses but can choose to switch vaccine types for the third dose. Therefore, COVID-19 vaccination status was classified into 8 groups based on the number of doses and vaccine type administered: (1) 1-dose-only BNT162b2, (2) 1-dose-only CoronaVac, (3) 2-doses-only BNT162b2, (4) 2-doses-only CoronaVac, (5) 3-doses (all BNT162b2), (6) 3-doses (all CoronaVac), (7) 3-doses (2-dose BNT162b2 followed by CoronaVac), and (8) 3-doses (2-dose CoronaVac followed by BNT162b2).

### Definition of Cases and Controls

Cases were defined as patients with CVD who had MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022. Controls were defined as all other patients with CVD who attended any HA health services and were not cases. We excluded patients who had a history of COVID-19 before January 1, 2022, who had incomplete vaccination records and those without history of CVD. Up to

10 controls were randomly matched with the cases according to sex, age (5-year band), date of attendance (within 3 calendar days), and Charlson Comorbidity Index (categorized as 0, 1–2, 3–4, and  $\geq 5$ ).

### Statistical Analysis

Conditional logistic regressions were applied to evaluate the association between vaccination status and risk of MI or stroke after COVID-19 diagnosis. Chronic comorbidities including cancer, chronic kidney disease, respiratory disease, diabetes, dementia, and medication use including renin-angiotensin-system agents,  $\beta$ -blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulin, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants were adjusted to balance the baseline characteristics. The *ICD-9-CM* codes used for identification of comorbidities are presented in Table S1. The British National Formulary codes used for medication use are presented in Table S3. We also conducted subgroup analyses investigating MI or stroke after SARS-CoV-2 infection separately and their association with each dose of BNT162b2 or CoronaVac vaccination. Risk of MI or stroke was reported as adjusted odds ratio (OR) with 95% CI.

Four sensitivity analyses were conducted. First, cases were defined as patients who had MI or stroke within 28 days after a positive PCR or rapid antigen test instead of PCR-confirmed cases only since rapid antigen tests can also indicate a positive COVID-19 infection. Second, cases were defined as patients who had MI or stroke within 14 days instead of 28 days after PCR confirmed SARS-CoV-2 infection to test the sensitivity of definition of COVID-19-related MI or stroke. Third, cases were defined as only patients who had MI or stroke as the inpatient primary diagnosis within 28 days after the PCR-confirmed test to test the sensitivity of MI or stroke diagnosis in the inpatient records. Last, instead of including patients with CVD, only patients with atherosclerotic cardiovascular disease such as coronary heart disease, cerebrovascular disease, peripheral vascular disease, and cardiovascular surgery were included as cases and controls. All statistical tests were 2-sided, and  $P$  values  $< 0.05$  were considered statistically significant. Statistical analysis was conducted using R version 4.0.3 ([www.R-project.org](http://www.R-project.org)). At least 2 investigators conducted the statistical analyses independently for quality assurance (X.Y. and V.K.C.Y.). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklists were followed to guide transparent reporting of the case-control study.

### Ethics Approval

This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong

(CIRB-2021-005-4) and the Department of Health Ethics Committee (LM171/2021). Informed written consent has been waived by the ethics committees as this is an observational study using deidentified electronic health records.

## Role of the Funding Source

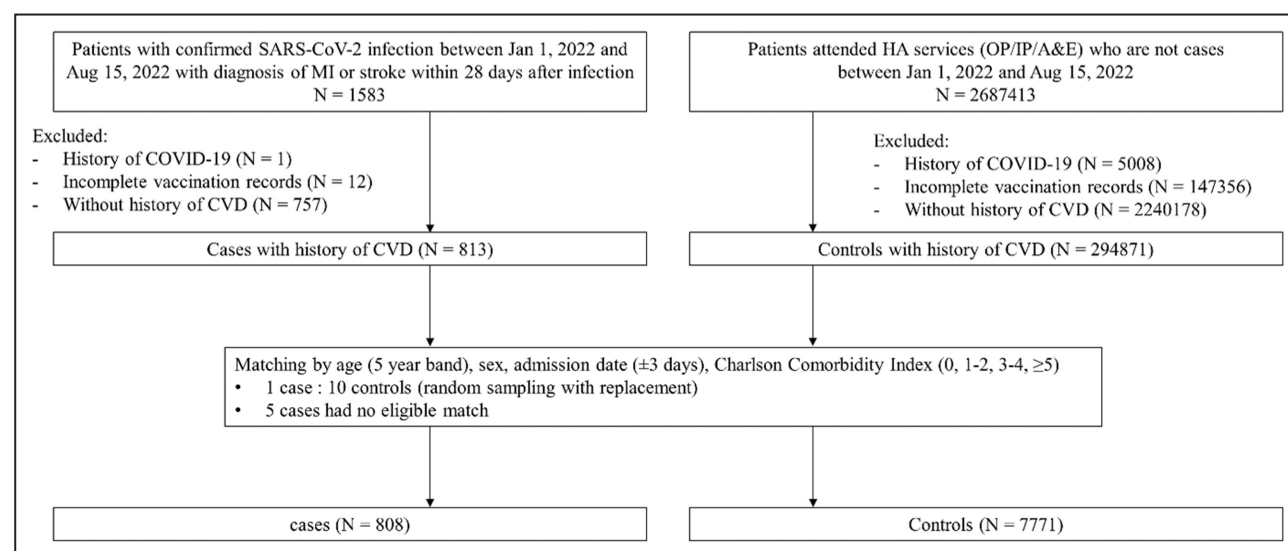
The funder has no role in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding authors had full access to all the data in the study and took final responsibility for the decision to submit for publication.

## RESULTS

In total, there were 1583 patients diagnosed with MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022 and 2687413 patients who attended HA services and were not cases. After excluding patients with a history of COVID-19, incomplete vaccination records, or without a history of CVD, we identified 813 patients with CVD who had MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022 and 294871 CVD patients without any MI or stroke at the same time as the controls. There were 5 cases that did not match with any control during the matching process and were excluded. The final cohort included 808 cases matched with 7771 controls (Figure 1). Cases and controls had a similar mean age of 81 years with  $\approx 54\%$  male patients in both groups. Cases generally had larger Charlson Comorbidity Index compared with the controls, and a larger proportion of

cases were prescribed with renin-angiotensin system agents,  $\beta$ -blockers, diuretics, nitrates, insulin, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants, but more controls received calcium channel blockers (Table 1).

After adjusting the baseline characteristics in the model, the adjusted ORs for MI or stroke within 28 days after SARS-CoV-2 infection are shown in Table 2. Both BNT162b2 and CoronaVac vaccination were associated with a significantly lower risk of MI or stroke and higher effectiveness was observed with an increasing number of doses (Figure 2). For BNT162b2, risk decreased from 0.49 (95% CI, 0.29–0.84) to 0.30 (95% CI, 0.20–0.44) and 0.17 (95% CI, 0.08–0.34) from 1 to 3 doses, respectively. Similar trends were observed for CoronaVac, with risk decreased from 0.69 (95% CI, 0.57–0.85) to 0.42 (95% CI, 0.34–0.52) and 0.32 (95% CI, 0.21–0.49) from 1 to 3 doses, respectively. Patients with 2 doses of CoronaVac and a third dose of BNT162b2 also had a low risk 0.09 (95% CI, 0.02–0.40) compared with the unvaccinated. The number of patients who received 2 doses of BNT162b2 and a third dose of CoronaVac is too low to calculate the OR. The subgroup analyses identified 745 cases of MI within 28 days after SARS-CoV-2 infection matched with 6952 controls and 594 cases of stroke within 28 days after SARS-CoV-2 infection matched with 5588 controls (Table 3). The results showed that BNT162b2 had a risk of 0.47 (95% CI, 0.28–0.81) of MI within 28 days after SARS-CoV-2 infection with only 1 dose, and the risk decreased to 0.12 (95% CI, 0.06–0.24) with 3 doses. For CoronaVac, the risk of MI within 28 days after SARS-CoV-2 infection was 0.73 (95% CI, 0.58–0.92) with only 1 dose, and decreased



**Figure 1. Inclusion and exclusion criteria of the case-control analysis.**

A&E indicates accident and emergency; CVD, cardiovascular disease; HA, hospital authority; IP, inpatient; MI, myocardial infarction; N, number; and OP, outpatient



**Table 1. Baseline Characteristics of Cases and Controls in the Main Analysis**

Characteristics	Cases	Controls	P value
Number of individuals	808	7771	
Age, y, mean (SD)	81.73 (11.02)	81.68 (10.80)	0.907
Sex, male, no. (%)	439 (54.3)	4230 (54.4)	0.986
Charlson Comorbidity Index, mean (SD)	2.36 (1.78)	2.14 (1.62)	<0.001
Time since most recent dose, mean (SD)	65.21 (65.79)	55.45 (63.28)	0.004
Pre-existing comorbidities, no. (%)			
Cancer	52 (6.4)	605 (7.8)	0.192
Chronic kidney disease	134 (16.6)	998 (12.8)	0.003
Respiratory disease	82 (10.1)	821 (10.6)	0.759
Diabetes	353 (43.7)	3240 (41.7)	0.291
Dementia	54 (6.7)	408 (5.3)	0.102
Medication use within 90 d, no. (%)			
Renin-angiotensin-system agents	460 (56.9)	3884 (50.0)	<0.001
$\beta$ -blockers	394 (48.8)	2822 (36.3)	<0.001
Calcium channel blockers	421 (52.1)	4307 (55.4)	0.077
Diuretics	279 (34.5)	1623 (20.9)	<0.001
Nitrates	244 (30.2)	1318 (17.0)	<0.001
Lipid-lowering agents	594 (73.5)	5742 (73.9)	0.850
Insulin	151 (18.7)	582 (7.5)	<0.001
Antidiabetic drugs	285 (35.3)	2514 (32.4)	0.100
Oral anticoagulants	129 (16.0)	1037 (13.3)	0.044
Antiplatelets	582 (72.0)	4927 (63.4)	<0.001
Immunosuppressants	19 (2.4)	42 (0.5)	<0.001

to 0.19 (95% CI, 0.12–0.30) with 3 doses. For risk of stroke within 28 days after SARS-CoV-2 infection, 1 dose of BNT162b2 or CoronaVac both had no statistically significant association with ORs 0.75 (95% CI, 0.43–1.30) and 1.01 (95% CI, 0.79–1.29). However, the risk decreased to 0.13 (95% CI, 0.07–0.25) and 0.19 (95% CI, 0.13–0.30) after 3 doses of each vaccine, respectively. Two doses of CoronaVac and a third dose of BNT162b2 also had a low risk of MI with OR 0.16

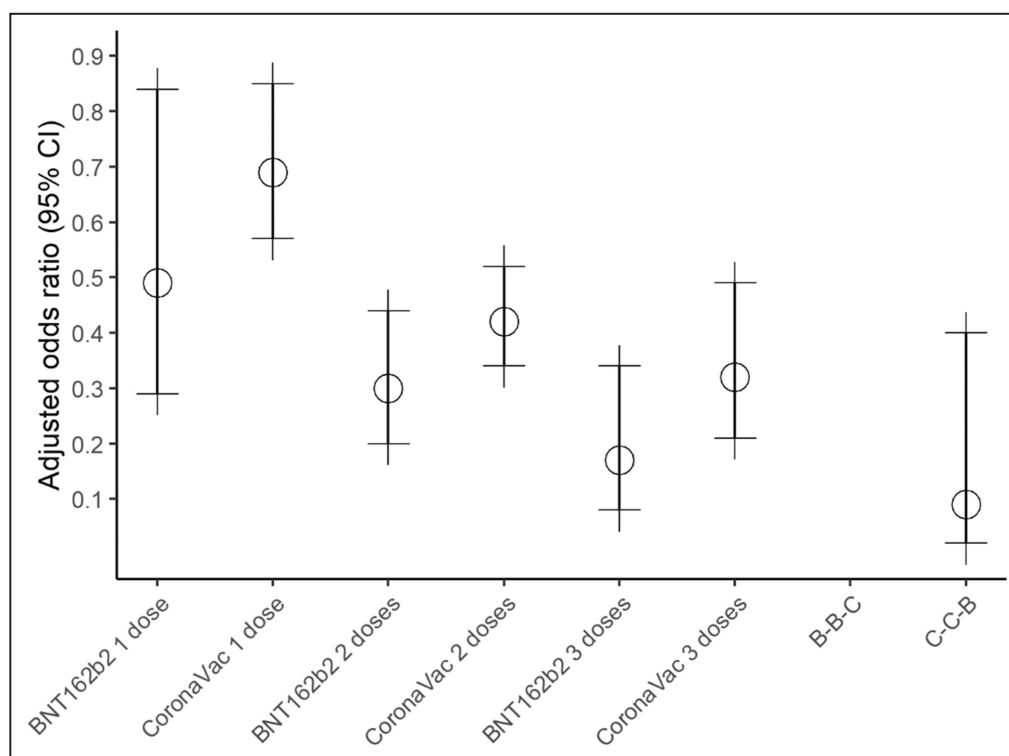
(95% CI, 0.04–0.53) and stroke with OR 0.28 (95% CI, 0.11–0.72) within 28 days after SARS-CoV-2 infection (Table 3).

The results of the sensitivity analyses were consistent with the main analysis when we defined cases as patients who had MI or stroke within 28 days after a positive PCR or rapid antigen test instead of PCR-confirmed cases only (Table S4), when we defined cases as patients who had MI or stroke within 14 days

**Table 2. Results of the Main Analysis**

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Unvaccinated	437	2781	(Ref)	(Ref)
1 dose only				
BNT162b2	16	207	0.47 (0.28–0.80)	0.49 (0.29–0.84)
CoronaVac	147	1361	0.68 (0.55–0.83)	0.69 (0.57–0.85)
2 doses only				
All BNT162b2	33	663	0.27 (0.18–0.39)	0.30 (0.20–0.44)
All CoronaVac	134	1889	0.39 (0.31–0.48)	0.42 (0.34–0.52)
3 doses				
All BNT162b2	9	294	0.15 (0.07–0.30)	0.17 (0.08–0.34)
All CoronaVac	30	465	0.28 (0.18–0.43)	0.32 (0.21–0.49)
B-B-C	0	7	...	...
C-C-B	2	104	0.09 (0.02–0.40)	0.09 (0.02–0.40)

B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; C-C-B, 2 doses of CoronaVac followed by BNT162b2; and OR, odds ratio.



**Figure 2. Adjusted odds ratios of risk of myocardial infarction or stroke after BNT162b2 or CoronaVac vaccinations.**

B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; and C-C-B, 2 doses of CoronaVac followed by BNT162b2. The adjusted odds ratio in the B-B-C group cannot be estimated due to limited sample size.

instead of 28 days after PCR-confirmed SARS-CoV-2 infection (Table S5), when we only included cases of the inpatient primary diagnosis (Table S6), and when we included patients with atherosclerotic cardiovascular disease (Table S7).

## DISCUSSION

This study reported a lower risk of MI or stroke after SARS-CoV-2 infection among patients with CVD after receiving BNT162b2 or CoronaVac. The results showed that both BNT162b2 and CoronaVac can significantly reduce the risk of MI or stroke after SARS-CoV-2 infection, and we observed a clear dose-response relationship between the number of doses received and the reduced risk. Results from our subgroup analyses showed that both BNT162b2 and CoronaVac can reduce the risk of MI after SARS-CoV-2 infection and at least 2 doses of either BNT162b2 or CoronaVac can reduce the risk of stroke after SARS-CoV-2 infection.

Patients infected with SARS-CoV-2 were reported to be at a higher risk of death, use of health resources and incident sequelae in the respiratory system, nervous system, neurocognitive disorders, mental health disorders, metabolic disorders, gastrointestinal disorders,

and cardiovascular disorders.<sup>1</sup> Among all the sequelae, the cardiovascular complications can occur in both the acute and postacute phase of SARS-CoV-2 infection from the first 2 to 4 weeks up to 12 months.<sup>3,4,12</sup> The possible mechanism could be lingering damage from direct viral invasion of cardiomyocytes and subsequent cell death, transcriptional alteration in heart tissue, persistent hyperactivated immune response, or integration of the SARS-CoV-2 genome into DNA of infected human cells.<sup>25,26</sup> This was also reported by previous studies where infections with other viruses or bacteria transiently increased the risks of MI and stroke.<sup>27,28</sup> Recent studies reported that the risk following SARS-CoV-2 infection is higher compared with influenza.<sup>29,30</sup> This might be due to direct viral entry through the angiotensin-converting enzyme-2 receptor and damage to the myocardium, systemic inflammation, hypoxia, cytokine storm, interferon-mediated immune response, and plaque destabilization.<sup>31</sup> It was also proposed that SARS-CoV-2 had a direct effect on endothelial cells, and patients with pre-existing endothelial dysfunction and risk factors such as male sex, smoking, hypertension, diabetes, obesity, and established CVD are associated with adverse outcomes from COVID-19.<sup>32</sup> Therefore, patients with CVD should

**Table 3. Results of the Subgroup Analysis**

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Association between vaccination and risk of myocardial infarction within 28 d after SARS-CoV-2 infection				
Unvaccinated	387	2243	(Ref)	(Ref)
1 dose only				
BNT162b2	18	189	0.52 (0.31–0.86)	0.47 (0.28–0.81)
CoronaVac	136	1088	0.72 (0.58–0.89)	0.73 (0.58–0.92)
2 doses only				
All BNT162b2	40	532	0.34 (0.24–0.49)	0.38 (0.26–0.55)
All CoronaVac	124	1891	0.30 (0.24–0.38)	0.33 (0.26–0.42)
3 doses				
All BNT162b2	10	360	0.11 (0.05–0.21)	0.12 (0.06–0.24)
All CoronaVac	27	553	0.17 (0.11–0.26)	0.19 (0.12–0.30)
B-B-C	0	5	...	...
C-C-B	3	91	0.13 (0.04–0.43)	0.16 (0.04–0.53)
Association between vaccination and risk of stroke within 28 d after SARS-CoV-2 infection				
Unvaccinated	219	1384	(Ref)	(Ref)
1 dose only				
BNT162b2	17	140	0.78 (0.46–1.32)	0.75 (0.43–1.30)
CoronaVac	122	768	1.04 (0.82–1.33)	1.01 (0.79–1.29)
2 doses only				
All BNT162b2	42	442	0.50 (0.35–0.72)	0.49 (0.34–0.72)
All CoronaVac	146	1643	0.49 (0.39–0.62)	0.48 (0.38–0.61)
3 doses				
All BNT162b2	11	405	0.13 (0.07–0.25)	0.13 (0.07–0.25)
All CoronaVac	32	697	0.21 (0.14–0.31)	0.19 (0.13–0.30)
B-B-C	0	10	...	...
C-C-B	5	99	0.26 (0.10–0.65)	0.28 (0.11–0.72)

B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; C-C-B, 2 doses of CoronaVac followed by BNT162b2; and OR, odds ratio.

be more concerned about the severe outcomes following SARS-CoV-2 infection, and providing data on the effectiveness of vaccinations in protection against MI or stroke after SARS-CoV-2 infection will be important for this population.

Existing clinical trials and observational studies have thoroughly investigated the effectiveness of BNT162b2 and CoronaVac. The phase 3 clinical trial of BNT162b2 demonstrated 95% effectiveness in preventing SARS-CoV-2 infection with a favorable safety profile before the omicron wave.<sup>6</sup> The effectiveness of a third dose was also proved in a clinical trial and an observational study.<sup>33,34</sup> Although limited protection of BNT162b2 against symptomatic disease caused by the omicron variant was observed,<sup>35</sup> vaccination can still reduce the risk of omicron-associated hospitalization.<sup>36</sup> For CoronaVac, although it demonstrated effectiveness of 65.9% against infection and ~87% against hospitalization or COVID19-related death,<sup>8</sup> the effectiveness dropped to 39.4% against infection and 81.3% against hospitalization or COVID19-related death during the omicron wave.<sup>37</sup> With the decrease in effectiveness of COVID-19 vaccines due to the omicron variant, more

studies are focusing on the effectiveness of the vaccines in lowering mortality and severe complications.<sup>9</sup> One study from Hong Kong reported a dose-response relationship between the doses of BNT162b2 or CoronaVac and mortality and severe complications including admission to the intensive care unit and use of ventilatory support after SARS-CoV-2 infection.<sup>9</sup> Another Korean study reported that 2 doses of mRNA vaccines or viral vector vaccine can significantly protect against secondary complications of COVID-19, including MI and stroke that occurred 31 to 120 days after COVID-19 diagnosis.<sup>11</sup> Although this study showed that vaccination can prevent cardiovascular outcomes of COVID-19 during 31 to 120 days after diagnosis, whether it can prevent acute-phase MI and stroke after SARS-CoV-2 infection is unknown. Previous studies showed a high risk of MI and stroke during the first 2 to 4 weeks after SARS-CoV-2 infection,<sup>3,12</sup> during which whether vaccination can prevent MI and stroke is of great interest, especially for patients with a history of CVD. Our study suggested that BNT162b2 or CoronaVac can also prevent MI or stroke within 4 weeks after SARS-CoV-2 infection and the sensitivity analysis also showed a lower risk of MI or stroke

within 2 weeks after SARS-CoV-2 infection. The results confirmed the importance of patients with CVD receiving COVID-19 vaccination. Our findings also highlight the importance of receiving more than 1 dose to achieve better effectiveness in lowering the risk of MI and stroke.

In clinical practice, uncertainty about the safety of COVID-19 vaccines can lead to vaccine hesitancy, causing low vaccination rates and increasing the risk of infection and severe illness, especially for patients with a disease history.<sup>38</sup> Our data showed that among patients with CVD in Hong Kong by August 15, 2022, 74.9% (321 358/428 808) received at least 1 dose, 70.8% (303 758/428 808) received at least 2 doses, and 47.6% (203 910/428 808) received at least 3 doses of vaccination, compared with 93.9% who received at least 1 dose, 91.6% who received at least 2 doses, and 76.7% who received at least 3 doses of vaccination in the general population. Among patients with CVD who received the vaccination, 69.6% (223 556/321 358) chose CoronaVac, an inactivated vaccine, and 30.4% (97 802/321 358) received BNT162b2 from the mRNA platform. To lower vaccine hesitancy and the risk of complications after SARS-CoV-2 infection in patients with a disease history, not only do we need to provide vaccine safety information on this population, but we also need to provide the vaccine effectiveness data against the complications that certain patient groups are concerned about. To the best of our knowledge, this is the first postmarketing study of the association between BNT162b2 or CoronaVac COVID-19 vaccination and risk of MI or stroke after SARS-CoV-2 infection among patients with CVD. This novel finding contributes to health professionals and the general public's understanding of the vaccines' protection against CVD complications and promotes the importance of vaccination in patients with CVD to prevent potential severe CVD complications if infected.

## Strength and Limitations

The main strength of this study is the focus on patients with CVD who might be more concerned about the potential severe CVD complications after SARS-CoV-2 infection such as MI and stroke. We also included all patients with CVD in Hong Kong and reported the findings on 2 COVID-19 vaccines, including an mRNA vaccine (BNT162b2) and an inactivated virus vaccine (CoronaVac). The dose-specific analysis provides a clear dose-response relationship between the number of doses received and the reduced risk of MI or stroke postinfection. The subgroup and sensitivity analyses also support the robustness of our results. Additionally, the system in Hong Kong was reported to be able to capture >98% of hospital admissions for MI during the COVID-19 pandemic compared with previous years, suggesting the solidity of the database used.<sup>39,40</sup>

Our study has several limitations. First, as our study focused on 2 COVID-19 vaccines, BNT162b2 and CoronaVac, studies of other vaccines are needed. Second, the majority of Hong Kong residents are of Chinese ethnicity and whether our results can be generalized to other countries and ethnicities requires further investigation. Third, the electronic health records from HA include only data from the public hospital sector and information on patients who used private medical services are not captured. However, as the service provided by the public hospitals covers >70% of all hospitalization coverage in Hong Kong, lack of private medical services data is unlikely to change our conclusion.<sup>13</sup> Fourth, as the case-control analysis is an observational study design, the lack of randomization can cause confounding issues and the different health status and socioeconomic conditions might introduce a potential selection bias. Therefore, we not only matched the cases and controls by sex, age, date of attendance, and Charlson Comorbidity Index, but also estimated the OR by adjusting the comorbidities and medication use in the regression model to minimize the confounding effect. Fifth, although we defined the outcome as MI or stroke within 28 days after SARS-CoV-2 infection, we cannot distinguish whether MI or stroke was directly caused by the infection or from other causes. Last, there were a limited number of patients who received a different type of vaccine as their third dose after the first 2 doses and the sample size is too small to show an association between vaccination and MI or stroke after SARS-CoV-2 infection, especially for patients who received 2 doses of BNT162b2 and a third dose of CoronaVac.

## CONCLUSIONS

Vaccination of BNT162b2 or CoronaVac can reduce the risk of MI or stroke after SARS-CoV-2 infection among patients with CVD, and the risk decreased with additional vaccine doses. Therefore, it is important for patients with CVD to receive vaccination to prevent the potential severe CVD complications if infected.

## ARTICLE INFORMATION

Received December 22, 2022; accepted March 24, 2023.

### Affiliations

Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China (X.Y., V.K.Y., H.H.Y., J.J.S., W.K., T.M., X.Q., F.T.L., X.L., E.Y.W., C.K.W., I.C.W., E.W.C.); Laboratory of Data Discovery for Health (D24H), Hong Kong SAR, China (T.M., X.Q., C.S.C., F.T.L., X.L., E.Y.W., C.K.W., I.C.W., E.W.C.); School of Nursing, LKS Faculty of Medicine (C.S.C.) School of Public Health, LKS Faculty of Medicine (C.S.C.) Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine (X.L.) and Department of Family Medicine and Primary Care, School of Clinical Medicine, LKS Faculty of Medicine (E.Y.W., C.K.W.), The University of Hong Kong, Hong Kong SAR, China Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (I.C.W.); Aston



Pharmacy School, Aston University, Birmingham, United Kingdom (I.C.W.); Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China (E.W.C.); and The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China (E.W.C.).

## Acknowledgments

We thank colleagues from the Drug Office of the Department of Health and the Hospital Authority for the generous provision of vaccination and clinical data. We thank Lisa Y. Lam for proofreading the manuscript. X.Y., V.K.C.Y., I.C.K.W., and E.W.C. designed the research; X.Y. and V.K.C.Y. performed the research; X.Y. and V.K.C.Y. analyzed the data; H.H.E.Y., J.J.P.S., W.K., T.M., X.Q., C.S.L.C., F.T.T.L., X.L., E.Y.F.W., and C.K.H.W. provided discussion and revision; I.C.K.W., and E.W.C. provided funding and supervision; X.Y. prepared the manuscript with input from all co-authors.

## Sources of Funding

This work was funded by a research grant from the Food and Health Bureau; Health and Medical Research Fund Commissioned Research on the Novel Coronavirus Disease, The Government of the Hong Kong Special Administrative Region (Principal Investigator (WP2): E.W.C.; Ref: COVID1903011). The posts of F.T.T.L. (Francisco T.T. Lai) and I.C.K.W. (Ian C.K. Wong) were partly funded by the D24H; hence this work was partly supported by AIR@InnoHK administered by Innovation and Technology Commission. The study's sponsor was involved in the framework of study designs and data collection via the Department of Health. The corresponding author had full access to all data in the study and took final responsibility for the decision to submit for publication.

## Disclosures

C.S.L.C. 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 fees from Primevigilance Ltd.; outside the submitted work. E.Y.F.W. 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. F.T.T.L. has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from Food and Health Bureau of the Government of the Hong Kong SAR, outside the submitted work. X.L. received research grants from Research Fund Secretariat of the Food and Health Bureau (HMRP, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR), Janssen and Pfizer; internal funding from the University of Hong Kong; consultancy fee from Merck Sharp & Dohme, unrelated to this work. C.K.H.W. reports the receipt of General Research Fund, Research Grant Council, Government of Hong Kong SAR; EuroQol Research Foundation; AstraZeneca and Boehringer Ingelheim, all outside the submitted work. I.C.K.W. 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. E.W.C. has received research grants from Research Grants Council (RGC, HKSAR), Research Fund Secretariat of the Food and Health Bureau (HMRP, HKSAR), National Natural Science Fund of China, National Health and Medical Research Council (NHMRC, Australia), Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, Novartis, and Narcotics Division of the Security Bureau of HKSAR; and honorarium from the Hospital Authority, outside the submitted work. The remaining authors have no disclosures to report.

## Supplemental Material

Tables S1–S7  
References<sup>41–48</sup>

## REFERENCES

- Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594:259–264. doi: 10.1038/s41586-021-03553-9
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069. doi: 10.1001/jama.2020.1585
- Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly A-M. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet*. 2021;398:599–607. doi: 10.1016/S0140-6736(21)00896-5
- Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28:583–590. doi: 10.1038/s41591-022-01689-3
- Driggin E, Maddox TM, Ferdinand KC, Kirkpatrick JN, Ky B, Morris AA, Mullen JB, Parikh SA, Philbin DM, Vaduganathan M. ACC health policy statement on cardiovascular disease considerations for COVID-19 vaccine prioritization. *J Am Coll Cardiol*. 2021;77:1938–1948. doi: 10.1016/j.jacc.2021.02.017
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603–2615. doi: 10.1056/NEJMoa2034577
- Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, Al Nusair M, Hassany M, Jawad JS, Abdalla J, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA*. 2021;326:35–45. doi: 10.1001/jama.2021.8565
- Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, Pizarro A, Acevedo J, Leo K, Leon F, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med*. 2021;385:875–884. doi: 10.1056/NEJMoa2107715
- Yan VKC, Wan EYF, Ye X, Mok AHY, Lai FTT, Chui CSL, Li X, Wong CKH, Li PH, Ma T, et al. Effectiveness of BNT162b2 and CoronaVac vaccinations against mortality and severe complications after SARS-CoV-2 omicron BA.2 infection: a case-control study. *Emerg Microbes Infect*. 2022;11:2304–2314. doi: 10.1080/22221751.2022.2114854
- Ye X, Ma T, Blais JE, Yan VKC, Kang W, Chui CSL, Lai FTT, Li X, Wan EYF, Wong CKH, et al. Association between BNT162b2 or CoronaVac COVID-19 vaccines and major adverse cardiovascular events among individuals with cardiovascular disease. *Cardiovasc Res*. 2022;118:2329–2338. doi: 10.1093/cvr/cvac068
- Kim Y-E, Huh K, Park Y-J, Peck KR, Jung J. Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection. *JAMA*. 2022;328:887–889. doi: 10.1001/jama.2022.12992
- Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, Fralick M, Schou M, Lamberts M, Gerds T, et al. Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation*. 2020;142:2080–2082. doi: 10.1161/CIRCULATIONAHA.120.050809
- Leung GM, Wong IO, Chan WS, Choi S, Lo SV. The ecology of health care in Hong Kong. *Soc Sci Med*. 2005;61:577–590. doi: 10.1016/j.socscimed.2004.12.029
- Wong AYS, Root A, Douglas IJ, Chui CSL, Chan EW, Ghebremichael-Weldeselassie Y, Siu C-W, Smeeth L, Wong ICK. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016;352:h6926. doi: 10.1136/bmj.h6926
- Lau WCY, Chan EW, Cheung C-L, Sing CW, Man KKC, Lip GYH, Siu C-W, Lam JKY, Lee ACH, Wong ICK. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. *JAMA*. 2017;317:1151–1158. doi: 10.1001/jama.2017.1363
- Lau WCY, Cheung CL, Man KKC, Chan EW, Sing CW, Lip GYH, Siu CW, Lam JKY, Lee ACH, Wong ICK. Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and risk for osteoporotic fractures among patients with atrial fibrillation: a population-based cohort study. *Ann Intern Med*. 2020;173:1–9. doi: 10.7326/m19-3671
- Li X, Lai FTT, Chua GT, Kwan MYW, Lau YL, Ip P, Wong ICK. Myocarditis following COVID-19 BNT162b2 vaccination among adolescents in Hong Kong. *JAMA Pediatr*. 2022;176:612–614. doi: 10.1001/jamapediatrics.2022.0101
- Lai FTT, Li X, Peng K, Huang L, Ip P, Tong X, Chui CSL, Wan EYF, Wong CKH, Chan EWY, et al. Carditis after COVID-19 vaccination with a messenger RNA vaccine and an inactivated virus vaccine: a case-control study. *Ann Intern Med*. 2022;175:362–370. doi: 10.7326/m21-3700
- Lai FTT, Huang L, Chui CSL, Wan EYF, Li X, Wong CKH, Chan EWW, Ma T, Lum DH, Leung JCN, et al. Multimorbidity and adverse events of

- special interest associated with Covid-19 vaccines in Hong Kong. *Nat Commun*. 2022;13:411. doi: 10.1038/s41467-022-28068-3
20. Wan EYF, Chui CSL, Lai FTT, Chan EWY, Li X, Yan VKC, Gao L, Yu Q, Lam ICH, Chun RKC, 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. *Lancet Infect Dis*. 2022;22:64–72. doi: 10.1016/S1473-3099(21)00451-5
  21. Chan EW, Lau WC, Siu CW, Lip GY, Leung WK, Anand S, Man KK, Wong IC. Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with nonvalvular atrial fibrillation: a population-wide cohort study. *Heart Rhythm*. 2016;13:1581–1588. doi: 10.1016/j.hrthm.2016.03.049
  22. Chan EW, Lau WCY, Leung WK, Mok MTC, He Y, Tong TSM, Wong ICK. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology*. 2015;149:586–595.e583. doi: 10.1053/j.gastro.2015.05.002
  23. Third dose COVID-19 vaccination arrangements for persons under certain groups. The Government of the Hong Kong Special Administrative Region. Accessed November 3, 2021. <https://www.info.gov.hk/gia/general/202111/03/P2021110300536.htm>.
  24. Further expansion of COVID-19 vaccination arrangements from January 1. The Government of the Hong Kong Special Administrative Region. Accessed December 24, 2021. <https://www.info.gov.hk/gia/general/202112/24/P2021122400509.htm>.
  25. Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. *JCI Insight*. 2021;6:6. doi: 10.1172/jci.insight.148980
  26. Zhang L, Richards A, Barrasa MI, Hughes SH, Young RA, Jaenisch R. Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues. *Proc Natl Acad Sci*. 2021;118:e2105968118. doi: 10.1073/pnas.2105968118
  27. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med*. 2019;380:171–176. doi: 10.1056/NEJMra1808137
  28. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J*. 2007;29:96–103. doi: 10.1093/eurheartj/ehm516
  29. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089–1098. doi: 10.1007/s00134-020-06062-x
  30. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, Lantos J, Schenck EJ, Goyal P, Bruce SS, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. 2020;77:1366–1372. doi: 10.1001/jamaneurol.2020.2730
  31. Magadam A, Kishore R. Cardiovascular manifestations of COVID-19 infection. *Cell*. 2020;9:2508. doi: 10.3390/cells9112508
  32. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endothelitis in COVID-19. *Lancet*. 2020;395:1417–1418. doi: 10.1016/S0140-6736(20)30937-5
  33. Moreira ED, Kitchin N, Xu X, Dychter SS, Lockhart S, Gurtman A, Perez JL, Zerbini C, Dever ME, Jennings TW, et al. Safety and efficacy of a third dose of BNT162b2 Covid-19 vaccine. *N Engl J Med*. 2022;386:1910–1921. doi: 10.1056/NEJMoa2200674
  34. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, Reis BY, Balicer RD. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet*. 2021;398:2093–2100. doi: 10.1016/S0140-6736(21)02249-2
  35. Andrews N, Stowe J, Kirsebom F, Toffa S, Rieckard T, Gallagher E, Gower C, Kall M, Groves N, O'Connell A-M, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med*. 2022;386:1532–1546. doi: 10.1056/NEJMoa2119451
  36. Luring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, Ghamande S, Douin DJ, Talbot HK, Casey JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ*. 2022;376:e069761. doi: 10.1136/bmj-2021-069761
  37. Cerqueira-Silva T, Andrews JR, Boaventura VS, Ranzani OT, de Araújo OV, Paixão ES, Júnior JB, Machado TM, Hitchings MDT, Dorion M, et al. Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study. *Lancet Infect Dis*. 2022;22:791–801. doi: 10.1016/S1473-3099(22)00140-2
  38. Rief W. Fear of adverse effects and COVID-19 vaccine hesitancy: recommendations of the treatment expectation expert group. *JAMA Health Forum*. 2021;2:e210804. doi: 10.1001/jamahealthforum.2021.0804
  39. Sofi F, Dinu M, Reboldi G, Stracci F, Pedretti RFE, Valente S, Gensini G, Gibson CM, Ambrosio G. Worldwide differences of hospitalization for ST-segment elevation myocardial infarction during COVID-19: a systematic review and meta-analysis. *Int J Cardiol*. 2022;347:89–96. doi: 10.1016/j.ijcard.2021.10.156
  40. Tam C-CF, Cheung K-S, Lam S, Wong A, Yung A, Sze M, Fang J, Tse H-F, Siu C-W. Impact of coronavirus disease 2019 (COVID-19) outbreak on outcome of myocardial infarction in Hong Kong, China. *Catheter Cardiovasc Interv*. 2021;97:E194–E197. doi: 10.1002/ccd.28943
  41. Government Announces 2019. COVID-19 Vaccination Programme. The Government of the Hong Kong Special Administrative Region. Accessed February 18, 2021. <https://www.info.gov.hk/gia/general/202102/18/P2021021800767.htm?fontSize=1>.
  42. Government expands scope of priority groups and opens more CVCs. The Government of the Hong Kong Special Administrative Region. Accessed March 8, 2021. <https://www.info.gov.hk/gia/general/202103/08/P2021030800738.htm?fontSize=1>.
  43. Vaccination priority groups to be expanded to cover people aged 30 or above. The Government of the Hong Kong Special Administrative Region. Accessed March 15, 2021. <https://www.info.gov.hk/gia/general/202103/15/P2021031500626.htm?fontSize=1>.
  44. COVID-19 Vaccination Programme opens to persons aged 16 or above. The Government of the Hong Kong Special Administrative Region. Accessed April 15, 2021. <https://www.info.gov.hk/gia/general/202104/15/P2021041500565.htm?fontSize=1>.
  45. Secretary for Food and Health approves lowering age limit for receiving Comirnaty vaccine. The Government of the Hong Kong Special Administrative Region. Accessed June 3, 2021. <https://www.info.gov.hk/gia/general/202106/03/P2021060300652.htm?fontSize=1>.
  46. SFH approves lowering age limit for receiving CoronaVac vaccine. The Government of the Hong Kong Special Administrative Region. Accessed November 20, 2021. <https://www.info.gov.hk/gia/general/202111/20/P2021112000292.htm>.
  47. Government extends third dose COVID-19 vaccination arrangements. The Government of the Hong Kong Special Administrative Region. Accessed November 18, 2021. <https://www.info.gov.hk/gia/general/202111/18/P2021111800310.htm>.
  48. Arrangements for children aged 5 to 11 to receive COVID-19 vaccines. The Government of the Hong Kong Special Administrative Region. Accessed January 20, 2022. <https://www.info.gov.hk/gia/general/202201/20/P2022012000714.htm>.

# SUPPLEMENTAL MATERIAL

Table S1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for disease and procedure identification.

	Medical condition	ICD-9-CM Codes
Disease history	Atherosclerotic cardiovascular disease	410-414, 430-438, 440-443, 36
	Heart failure	428
	Atrial fibrillation	427.3
	Cancer	140-209
	Chronic kidney disease	582, 585, 586, 588, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7
	Respiratory diseases	416.8, 416.9, 490-496, 500-505, 506.4, 508.1, 508.8
	Diabetes mellitus	250
	Dementia	290
Outcomes	Myocardial infarction	410
	Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, 436, 437.0, 437.1



Table S2. Details of the priority groups rollout schedule of the vaccination program in Hong Kong.

Order of expansion	Date of rollout	Vaccination group
First <sup>41</sup>	Feb 26, 2021	<ol style="list-style-type: none"> <li>1) Healthcare workers and staff involved in anti-epidemic work</li> <li>2) Persons aged 60 or above (and a maximum of 2 carers accompanying elderly people aged above 70)</li> <li>3) Residents and staff of residential care homes for the elderly and persons with disabilities</li> <li>4) People providing essential public services</li> <li>5) People providing cross-boundary transportation or working at control points and ports</li> </ol>
Second <sup>42</sup>	Mar 9, 2021	<ol style="list-style-type: none"> <li>1) Staff of food and beverage premises, markets, supermarkets, convenience stores, couriers and takeaway delivery (including takeaway food delivery)</li> <li>2) Staff of local public transport service operators</li> <li>3) Registered construction workers</li> <li>4) Staff of property management</li> <li>5) Teachers and school staff</li> <li>6) Staff of the tourism industry</li> <li>7) Staff of scheduled premises under the Prevention and Control of Disease (Requirements and Directions) (Business and Premises) Regulation</li> </ol>
Third <sup>43</sup>	Mar 16, 2021	<ol style="list-style-type: none"> <li>1) People aged between 30 and 59</li> <li>2) Students studying outside Hong Kong (aged 16 or above)</li> <li>3) Domestic helpers</li> </ol>
Fourth <sup>44</sup>	Apr 23, 2021	<ol style="list-style-type: none"> <li>1) People aged 16 to 29 (<math>\geq 18</math> for person receiving CoronaVac)</li> </ol>
Fifth <sup>45</sup>	Jun 14, 2021	<ol style="list-style-type: none"> <li>2) People aged 12 to 15 for BNT162b2</li> </ol>
Sixth <sup>23</sup>	Nov 11, 2021	<ol style="list-style-type: none"> <li>3) Eligible persons under certain groups can receive a third dose of COVID-19 vaccine free of charge</li> </ol>
Seventh <sup>46</sup>	Nov 23, 2021	<ol style="list-style-type: none"> <li>4) Members of the public who received two doses of the CoronaVac vaccine with the second dose received six months prior, irrespective of whether they belonged to certain groups, can reserve and receive a third dose of a COVID-19 vaccine</li> </ol>
Eighth <sup>47</sup>	Dec 2, 2021	<ol style="list-style-type: none"> <li>5) People aged 12 to 17 for CoronaVac</li> </ol>
Ninth <sup>24</sup>	Jan 1, 2022	<ol style="list-style-type: none"> <li>6) Provision of a third dose vaccination service to all eligible persons who have received two doses of the BNT162b2 vaccine with the second dose received six months prior</li> </ol>
Tenth <sup>48</sup>	Jan 21, 2022	<ol style="list-style-type: none"> <li>7) People aged 5 to 11 for CoronaVac</li> </ol>

Table S3. British National Formulary (BNF) codes for medication history.

Drug	BNF
Renin-angiotensin-system agents	2.5.5
Beta blockers	2.4
Calcium channel blockers	2.6.2
Diuretics	2.2
Nitrates	2.6.1
Lipid lowering agents	2.12
Insulins	6.1.1
Antidiabetic drugs	6.1.2
Oral anticoagulants	2.8.2
Antiplatelets	2.9
Immunosuppressants	8.2

Table S4. Results of sensitivity analysis when cases were defined as patients who had MI or stroke within 28 days after a positive PCR or RAT test instead of PCR-confirmed cases only. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Unvaccinated</b>	443	2813	(Ref)	(Ref)
<b>1 dose only</b>				
<b>BNT162b2</b>	16	195	0.50 (0.30 - 0.85)	0.52 (0.30 - 0.90)
<b>CoronaVac</b>	152	1377	0.70 (0.57 - 0.85)	0.71 (0.58 - 0.87)
<b>2 doses only</b>				
<b>All BNT162b2</b>	33	691	0.25 (0.17 - 0.37)	0.29 (0.20 - 0.42)
<b>All CoronaVac</b>	138	1955	0.38 (0.31 - 0.47)	0.41 (0.33 - 0.51)
<b>3 doses</b>				
<b>All BNT162b2</b>	9	286	0.15 (0.07 - 0.30)	0.17 (0.08 - 0.34)
<b>All CoronaVac</b>	31	481	0.27 (0.18 - 0.41)	0.30 (0.19 - 0.45)
<b>B-B-C</b>	0	9	~	~
<b>C-C-B</b>	2	106	0.09 (0.02 - 0.39)	0.10 (0.02 - 0.41)

Table S5. Results of sensitivity analysis when cases were defined as patients who had MI or stroke within 14 days instead of 28 days after PCR confirmed SARS-CoV-2 infection. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Unvaccinated</b>	372	2419	(Ref)	(Ref)
<b>1 dose only</b>				
<b>BNT162b2</b>	15	192	0.48 (0.28 - 0.82)	0.49 (0.28 - 0.86)
<b>CoronaVac</b>	128	1185	0.69 (0.55 - 0.86)	0.70 (0.56 - 0.88)
<b>2 doses only</b>				
<b>All BNT162b2</b>	28	526	0.29 (0.19 - 0.44)	0.32 (0.21 - 0.48)
<b>All CoronaVac</b>	105	1557	0.37 (0.29 - 0.47)	0.40 (0.31 - 0.51)
<b>3 doses</b>				
<b>All BNT162b2</b>	7	231	0.15 (0.06 - 0.32)	0.16 (0.07 - 0.36)
<b>All CoronaVac</b>	28	370	0.33 (0.21 - 0.51)	0.35 (0.22 - 0.54)
<b>B-B-C</b>	0	5	~	~
<b>C-C-B</b>	2	83	0.12 (0.03 - 0.51)	0.11 (0.02 - 0.49)



Table S6. Results of sensitivity analysis when cases were defined as only patients who had MI or stroke as the inpatient primary diagnosis within 28 days after PCR confirmed SARS-CoV-2 infection. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Unvaccinated</b>	164	1070	(Ref)	(Ref)
<b>1 dose only</b>				
<b>BNT162b2</b>	8	101	0.50 (0.24 - 1.06)	0.54 (0.25 - 1.16)
<b>CoronaVac</b>	56	571	0.65 (0.47 - 0.90)	0.66 (0.47 - 0.92)
<b>2 doses only</b>				
<b>All BNT162b2</b>	17	269	0.38 (0.22 - 0.64)	0.39 (0.22 - 0.67)
<b>All CoronaVac</b>	80	912	0.52 (0.39 - 0.70)	0.56 (0.41 - 0.76)
<b>3 doses</b>				
<b>All BNT162b2</b>	6	157	0.20 (0.09 - 0.48)	0.23 (0.10 - 0.55)
<b>All CoronaVac</b>	18	232	0.41 (0.24 - 0.71)	0.45 (0.25 - 0.79)
<b>B-B-C</b>	0	4	~	~
<b>C-C-B</b>	2	50	0.21 (0.05 - 0.93)	0.17 (0.03 - 0.78)

Table S7. Results of sensitivity analysis when patients with ASCVD were included instead of patients with CVD. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Unvaccinated</b>	369	2221	(Ref)	(Ref)
<b>1 dose only</b>				
<b>BNT162b2</b>	16	177	0.51 (0.30 - 0.86)	0.48 (0.28 - 0.83)
<b>CoronaVac</b>	122	1107	0.64 (0.51 - 0.79)	0.67 (0.53 - 0.84)
<b>2 doses only</b>				
<b>All BNT162b2</b>	26	587	0.22 (0.14 - 0.33)	0.23 (0.15 - 0.36)
<b>All CoronaVac</b>	106	1551	0.34 (0.27 - 0.43)	0.37 (0.29 - 0.47)
<b>3 doses</b>				
<b>All BNT162b2</b>	7	247	0.12 (0.05 - 0.26)	0.14 (0.06 - 0.31)
<b>All CoronaVac</b>	26	436	0.24 (0.16 - 0.38)	0.27 (0.17 - 0.42)
<b>B-B-C</b>	0	6	~	~
<b>C-C-B</b>	0	101	~	~