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Comparative effectiveness and safety of BNT162b2 and CoronaVac in Hong Kong: A target trial emulation

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ABSTRACT

Objectives: To evaluate the difference between BNT162b2 and CoronaVac in vaccine effectiveness and safety.

Methods: This target trial emulation study included individuals aged ≥12 during 2022. Propensity score matching was applied to ensure group balance. The Cox proportional hazard model was used to compare the effectiveness outcomes including COVID-19 infection, severity, 28-day hospitalization, and 28-day mortality after infection. Poisson regression was used for safety outcomes including 32 adverse events of special interests between groups.

Results: A total of 639,818 and 1804,388 individuals were identified for the 2-dose and 3-dose comparison, respectively. In 2-dose and 3-dose comparison, the hazard ratios (95% confidence intervals [CI]) were 0.844 [0.833-0.856] and 0.749 [0.743-0.755] for COVID-19 infection, 0.692 [0.656-0.731] and 0.582 [0.559-0.605] for hospitalization, 0.566 [0.417-0.769] and 0.590 [0.458-0.76] for severe COVID-19, and 0.563 [0.456-0.697] and 0.457 [0.372-0.561] for mortality for BNT162b2 recipients versus CoronaVac recipients, respectively. Regarding safety, 2-dose BNT162b2 recipients had a significantly higher incidence of myocarditis (incidence rate ratio [IRR] [95% CI]: 8.999 [1.14-71.017]) versus CoronaVac recipients, but the difference was insignificant in 3-dose comparison (IRR [95% CI]: 2.000 [0.500-7.996]).

Conclusion: BNT162b2 has higher effectiveness among individuals aged ≥12 against COVID-19-related outcomes for SARS-CoV-2 omicron compared to CoronaVac, with almost 50% lower mortality risk.

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Introduction

During the COVID-19 pandemic, several vaccines have been developed and demonstrated effective against SARS-CoV-2 infection, COVID-19 severity, and related mortality. Among the various vaccines available to date, modified-nucleotide messenger ribonucleic acid (mRNA) and inactivated whole virus vaccines account for at least 90.3% of the global market [1]. Both types of vaccines have shown promise as prevention options in several studies [2-8]. However, direct evidence comparing their effectiveness and safety was limited. Understanding their relative effectiveness and safety profiles is important for guiding clinical practice, consolidating public health policy, and informing future vaccine development.

In Hong Kong, a mRNA vaccine of BNT162b2 by Fosun Pharma/BioNTech and an inactivated vaccine of CoronaVac by Sinovac Biotech (HK) Limited have been available for free mass COVID-19 vaccination program since 2021. Both vaccines have performed well in their respective randomized controlled trials. Multinational randomized controlled trials on BNT162b2 showed an 86-91.7% efficacy in two doses of vaccine for protection against infection and severe disease caused by the original strain of SARS-CoV-2 within a 6-month timeframe in 2020 [2,3]. Multiple phases 2 and 3 clinical trials on the efficacy of CoronaVac have been conducted in Brazil, Chile, Turkey, and Indonesia, suggesting efficacy of 50.7-83.5% for two doses of vaccines [4-7]. Despite the extensive research conducted on the effectiveness of various COVID-19 vaccines, limited studies evaluated the direct comparison of the effectiveness. Furthermore, the findings from these studies have been inconsistent. A cohort study conducted in Singapore showed that individuals who received the BNT162b2 vaccine had a lower risk of COVID-19 infection and complications compared to those who received the CoronaVac vaccine [8]. On the other hand, a cohort study conducted in Hong Kong demonstrated no significant difference between the BNT162b2 and CoronaVac vaccines in terms of protection against COVID-19 infection [9]. Direct comparison of the effectiveness of vaccines in preventing SARS-CoV-2 Omicron infection and severe complications during Omicron wave and comparison among people of different ages, sex, and health conditions is unavailable. Apart from limited and various findings in effectiveness, evidence related to the direct comparison in the safety profile between BNT162b2 and CoronaVac vaccine, specifically, remains lacking in scope.

Given that inadequate evidence on the relative effectiveness and safety between BNT162b2 and CoronaVac, this study aims to provide a head-to-head comparison of the real-world effectiveness and safety of BNT162b2 and CoronaVac during the omicron wave of COVID-19, based on population-based electronic health records.

Methods

Data sources

This target trial emulation study was conducted based on clinical information using routine electronic health records of the Hospital Authority (HA), records of vaccinations, and confirmed COVID-19 cases from the Department of Health (DH) of the Government of the Hong Kong Special Administrative Region (HKSAR). As the official organization responsible for managing all public inpatient and most outpatient services in Hong Kong, the HA maintains the electronic healthcare record system that collects comprehensive real-world information, including patients' demographics, physiological measurements, diagnoses, prescriptions, and inpatient admissions in routine practices across all public clinics and hospitals. The database maintained by the DH consists of all COVID-19 vaccination records as well as all confirmed COVID-19 cases based on positive polymerase chain reaction or rapid antigen test results in Hong Kong. Death records were obtained from the Hong Kong Deaths Registry, a government agency responsible for maintaining records of all registered deaths for all Hong Kong residents. All databases are interconnected by a deidentified unique identifier and have been used in many previous high-quality studies concerning the effectiveness of COVID-19 vaccination and the risk of adverse effects [10-12].

Study design and eligibility criteria

To compare the vaccination effectiveness and potential risks associated with 2 or 3 doses of BNT162b2 and CoronaVac vaccinations, an emulation of randomized controlled trial was conducted. This approach has been shown to be effective in reducing immortal time and selection biases caused by common flaws in traditional observational studies' design and analyses [13-15]. Supplementary Table 1 contains the specifications and emulation details for the target trial. The inclusion period was from January 1, 2022, to December 31, 2022, during which Hong Kong experienced its most severe wave of COVID-19, primarily driven by the Omicron variant [16]. Individuals aged $\geq$12, who received 2-dose or 3-dose vaccine with the same brand during the inclusion period were eligible for this study. The index date was defined as the date of receiving the second/third vaccination.

Sequential trial emulation

Under the same study design, two trials were emulated separately for the 2-dose and 3-dose comparison. The treatment effect was estimated by comparing the effect of receiving the corresponding dose of BNT162b2 vaccine on the risk of COVID-19-related events and adverse events with that of receiving the same dose of CoronaVac vaccine using the sequential trial approach [13,15], which mimics a sequence of "trials" on each day from January 1, 2022, to December 31, 2022. Taking the comparison of 3 doses as an example, the "Jan 1 2022" trial included subjects aged $\geq$12, who received 3-dose of BNT162b2 and 3-dose of CoronaVac on January 1, 2022 with the index date defined as the date of vaccination. The included subjects were assigned to the BNT162b2 and CoronaVac group accordingly based on their vaccination records. The randomization of the trial was emulated by applying 1 to 1 propensity score matching with narrow calliper of 0.01. The baseline covariates used for matching and the estimated coefficients were demonstrated in Supplementary Table 2. To increase the number of subjects for each group of comparison, the inclusion and matching procedure was applied on each day between January 1, 2022, and December 31, 2022. Thus, a total of 365 trials were emulated, which the enrollment period for each trial was 1 day. Subjects were followed up from the index date until the outcome occurrence, death, 180 days after the index date (for vaccination effectiveness outcomes), 21 days after the index date (for adverse event of special interests [AESI] outcomes), or the administrative end of follow-up (January 31, 2023), whichever occurs earlier.

Outcome measurement

The present study focuses on several key outcomes concerning vaccination effectiveness as well as vaccination safety. The primary outcome was vaccination effectiveness including (1) COVID-19 infection, determined by a positive PCR or RAT result; (2) 28-day hospitalization after COVID-19 infection, determined by admission to a hospital within 28 days after COVID-19 infection; (3) severe COVID-19, which was defined as an ICU admission or use of ventilatory support within 7 days after COVID-19 infection; and (4) 28-day mortality after COVID-19 infection, which was defined as death within 28 days after COVID-19 infection. Ventilatory support use

was identified by referring to ICD-9 procedure codes (39.65, 89.18, 93.90, 93.95, 93.96, 96.7, 96.04). Secondary outcome was vaccination safety using a predetermined list of AESIs suggested by the World Health Organization and the European Medicines Agency for COVID-19 vaccine safety surveillance. The list of AESI outcomes is shown in Supplementary Table 3.

Baseline covariates

Baseline covariates were measured at the index date for each subject, including age, sex, Charlson comorbidity index (CCI), history of COVID-19 infection, cancer, chronic kidney disease, respiratory disease, diabetes, myocardial infarction, cerebrovascular disease, dementia, hypertension, and medication use within 90 days on or before the index date (renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, antiplatelets, immunosuppressants, oral anticoagulants).

Statistical analysis

The difference of baseline covariates after matching was evaluated by calculating the standardized mean difference (SMD) between BNT162b2 and CoronaVac in 2-dose and 3-dose comparison. Kaplan–Meier estimator was used to present the cumulative incidence curves and age-specific cumulative incidence curves with reported p-values of log-rank test. Regarding vaccination effectiveness, Cox proportional hazard model was used to estimate the risk of COVID-19 infection, severity, 28-day hospitalization, and 28-day mortality after COVID-19 infection between BNT162b2 and CoronaVac. Meanwhile, due to rare number of AESI events, Poisson regression adjusted with all baseline covariates was conducted to evaluate the risk of AESI between BNT162b2 and CoronaVac. For the analysis of each AESI outcome, subjects with a history of corresponding AESI outcome at the index date were excluded.

To identify potential heterogeneity regarding the difference of vaccine effectiveness in subgroups, subgroup-specific hazard ratios (HRs) were estimated by age (12-17, 18-64, or ≥65), gender (male or female), and CCI (0-4 or ≥5). For each subgroup, a model with an interaction term between the vaccination treatment and subgroup was fitted to estimate the subgroup-specific HRs for each comparison. Six sensitivity analyses were conducted for vaccine effectiveness outcomes to evaluate the robustness of our main results, which comprised: (1) excluding subjects with outcomes within the first 14 days of follow-up before matching; (2) reducing the maximum follow-up period to 90 days; (3) increasing the maximum follow-up period to 270 days; (4) reducing the 28 days to 21 days for the outcome of hospitalization and mortality after COVID-19 infection; (5) using PCR positive test only for identification of COVID-19 infection cases; (6) using cancer within 180 days of follow-up as a negative control outcome to detect potential unmeasured or unmeasurable sources of bias. Regarding vaccination safety, one sensitivity analysis by increasing the length of follow-up period from 21 to 28 days was further done to ensure robustness.

All statistical tests were performed as two-sided tests, and *P*-values less than .05 were considered to be statistically significant. The statistical analysis was conducted using R version 4.0.3 (www.R-project.org). Two investigators (BW, JZ) independently conducted the statistical analyses to ensure quality assurance.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The corresponding authors had complete access to all the data in the study and took full responsibility for the decision to submit the study for publication.

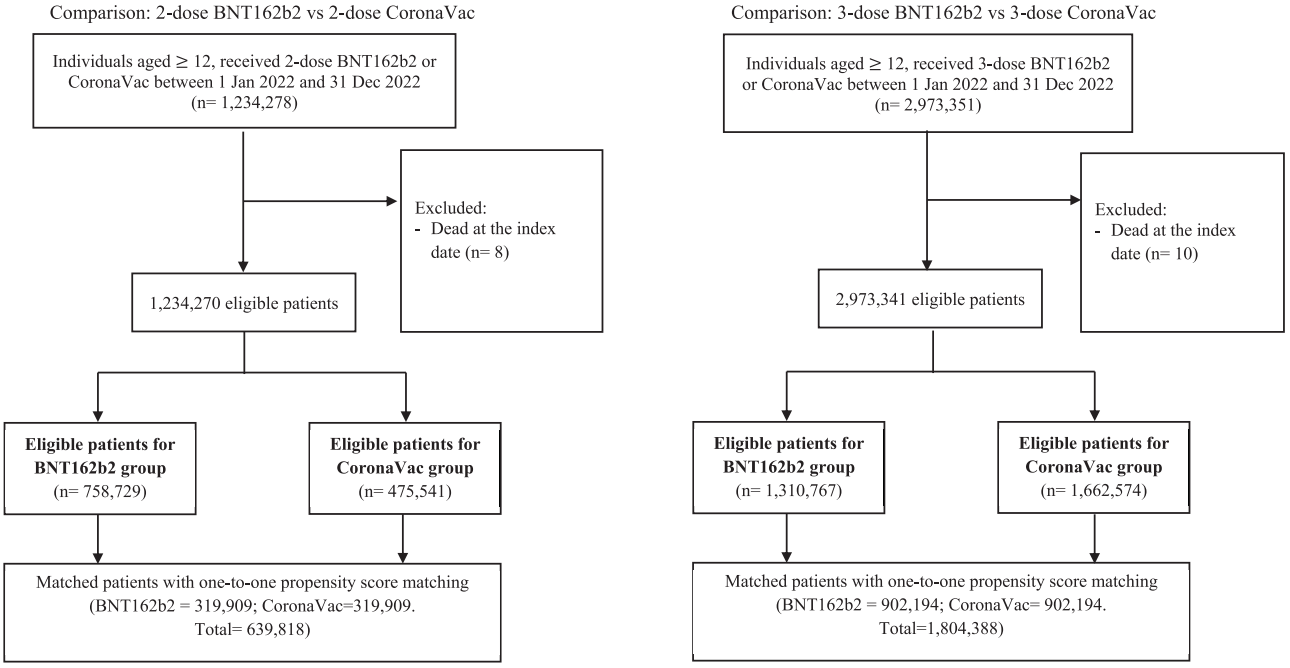
Result

After exclusion and matching, 639,818 (379,909 in each BNT162b2 and CoronaVac group) and 1804,388 (902,194 in each BNT162b2 and CoronaVac group) subjects with 2-dose and 3-dose vaccination, respectively, were included for analysis (Figure 1). In subjects receiving 2-dose vaccination, the mean (SD) age was 53.83 (20.32) for BNT162b2 recipients and 53.85 (20.38) for CoronaVac recipients, with male participants comprising 43.9% and 43.2% of the two groups. In subjects receiving 3-dose vaccination, the mean (SD) age was 55.54 (15.99) and 55.59 (15.99) years, with male participants comprising 45.4% and 43.6% for the two groups. The compared groups were well-balanced regarding baseline characteristics, with a SMD of less than 0.1 (Table 1).

The 180-day cumulative incidence of vaccination effectiveness outcomes by vaccination type in subjects with 2-dose and 3-dose vaccination is presented in Figure 2. During the follow-up period, BNT162b2 recipients had lower incidence rates of all vaccination effectiveness outcomes than CoronaVac recipients (Tables 2 and 3). Consistent results were observed in HRs after the adjustment of baseline characteristics (Tables 2 and 3). The HRs (95% confidence intervals [CIs]) were 0.844 (0.833-0.856) for COVID-19 infection, 0.692 (0.656-0.731) for 28-day hospitalization after COVID-19 infection, 0.566 (0.417-0.769) for severe COVID-19 and 0.563 (0.456-0.697) for 28-day mortality after COVID-19 infection for subjects receiving 2-dose vaccination. For subjects receiving 3-dose vaccination, the HRs (95% CIs) for the aforementioned four outcomes were 0.749 (0.743-0.755), 0.582 (0.559-0.605), 0.590 (0.458-0.76) and 0.457 (0.372-0.561).

With regard to safety outcomes, the incidence of all AESIs was rare (<1 per 10,000 person-days) in both BNT162b2 and CoronaVac recipients (Tables 2 and 3). However, a higher proportion of myocarditis cases in the BNT162b2 group was still observed in both the 2-dose (incidence rate [95% CI]: BNT162b2: 0.013 [0.006-0.025]; CoronaVac: 0.001 [0.000-0.008] per 10,000 person-days; incidence rate ratio [IRR] [95% CI]: 8.999 [1.14-71.017]) and 3-dose (incidence rate [95% CI]: BNT162b2: 0.003 [0.001-0.007]; CoronaVac: 0.002 [0.000-0.005] per 10,000 person-days; IRR [95% CI]: 2.000 [0.500-7.996]) recipients when compared to the CoronaVac group, although the only the IRR for the 2-dose group was statistically significant. IRRs for other AESIs did not show a difference in the risk of outcome between the two vaccines. No evidence of overdispersion or zero inflation in the Poisson model for all AESIs was identified (Supplementary Table 5).

Regarding the results of subgroup-specific HRs, the magnitude of vaccine effectiveness differences between 2 vaccines against severity and 28-day mortality were similar in age, sex, and CCI subgroups (Supplementary Tables 6 and 7). However, the magnitude of vaccine effectiveness differences in preventing COVID-19 infection increased in older age groups and higher CCI subgroups, and the magnitude of vaccine effectiveness differences in preventing hospitalization decreased in higher CCI subgroups. In the 2-dose comparison, the HR (95% CI) of COVID-19 infection decreased from 0.938 (0.891-0.988) in the 12-17 years age group to 0.775 (0.757-0.794) in the ≥65 years age group, and from 0.853 (0.841-0.865) in the CCI of 0-4 subgroup to 0.756 (0.721-0.792) in the ≥5 subgroup. In the 3-dose comparison, the HR (95% CI) of COVID-19 infection decreased from 0.922 (0.883-0.962) in the 12-17 years age group to 0.702 (0.691-0.713) in the ≥65 years age group, and from 0.751 (0.745-0.757) in the CCI of 0-4 subgroup to 0.708 (0.682-0.735) in the ≥5 subgroup. Regarding 28-day hospitalization, the HR (95% CI) increased from 0.619 (0.579-0.663) in the CCI of 0-4 subgroup to 0.767 (0.700-0.842) in the ≥5 subgroup



Notes: The patients were matched by age, gender, Charlson comorbidity index, history of COVID-19, cancer, chronic kidney disease, respiratory disease, diabetes, myocardial infarction, cerebrovascular disease, dementia, hypertension, and medication use within 90 days at the index date.

Figure 1. Flowchart of person trials in the analysis.

Table 1
Baseline characteristics.

Characteristic	2-dose comparison			3-dose comparison		
	All BNT162b2 (N = 319,909)	All CoronaVac (N = 319,909)	SMD	All BNT162b2 (N = 902,194)	All CoronaVac (N = 902,194)	SMD
Age, y (mean (SD))	53.83 (20.32)	53.85 (20.38)	0.001	55.54 (15.99)	55.59 (15.99)	0.003
Sex, male (%)	140,440 (43.9)	138,177 (43.2)	0.014	409,739 (45.4)	393,003 (43.6)	0.037
Charlson comorbidity index (mean (SD))	1.85 (1.96)	1.80 (1.87)	0.027	1.67 (1.62)	1.65 (1.60)	0.008
Comorbidities—no. (%)						
History of COVID-19	32,013 (10.0)	31,473 (9.8)	0.006	76,843 (8.5)	74,927 (8.3)	0.008
Cancer	14,137 (4.4)	13,117 (4.1)	0.016	27,427 (3.0)	24,807 (2.7)	0.017
Chronic kidney disease	8448 (2.6)	7603 (2.4)	0.017	14,767 (1.6)	13,419 (1.5)	0.012
Respiratory disease	7992 (2.5)	7214 (2.3)	0.016	17,305 (1.9)	14,942 (1.7)	0.020
Diabetes	44,779 (14.0)	41,970 (13.1)	0.026	110,429 (12.2)	105,602 (11.7)	0.016
myocardial infarction	2984 (0.9)	2805 (0.9)	0.006	5221 (0.6)	4849 (0.5)	0.006
Cerebrovascular disease	13,809 (4.3)	13,030 (4.1)	0.012	25,379 (2.8)	24,487 (2.7)	0.006
Dementia	847 (0.3)	845 (0.3)	<0.001	956 (0.1)	986 (0.1)	0.001
Hypertension	85,171 (26.6)	81,687 (25.5)	0.025	225,799 (25.0)	219,771 (24.4)	0.015
Medication use within 90 d—no. (%)						
Renin-angiotensin-system agents	57,547 (18.0)	53,160 (16.6)	0.036	139,518 (15.5)	131,877 (14.6)	0.024
Beta-blockers	38,853 (12.1)	35,903 (11.2)	0.029	84,690 (9.4)	79,739 (8.8)	0.019
Calcium channel blockers	76,574 (23.9)	73,121 (22.9)	0.025	195,660 (21.7)	190,626 (21.1)	0.014
Diuretics	13,448 (4.2)	12,225 (3.8)	0.019	24,309 (2.7)	22,832 (2.5)	0.010
Nitrates	9489 (3.0)	8599 (2.7)	0.017	18,021 (2.0)	17,118 (1.9)	0.007
Lipid-lowering agents	80,493 (25.2)	75,548 (23.6)	0.036	205,945 (22.8)	196,225 (21.7)	0.026
Insulins	8368 (2.6)	7487 (2.3)	0.018	15,312 (1.7)	13,838 (1.5)	0.013
Antidiabetic drugs	44,332 (13.9)	41,341 (12.9)	0.027	107,999 (12.0)	102,912 (11.4)	0.018
Antiplatelets	33,364 (10.4)	30,580 (9.6)	0.029	69,443 (7.7)	65,646 (7.3)	0.016
Immunosupressants	2754 (0.9)	2332 (0.7)	0.015	5020 (0.6)	3920 (0.4)	0.017
Oral anticoagulants	5719 (1.8)	5266 (1.6)	0.011	8864 (1.0)	8311 (0.9)	0.006

SMD, standardized mean difference.

in the 2-dose comparison and increased from 0.541 (0.517-0.567) in the CCI of 0-4 subgroup to 0.662 (0.613-0.714) in the ≥5 subgroup in the 3-dose comparison.

The findings for all sensitivity analyses were similar to the main analysis (Supplementary Tables 8-14). The results using cancer as the negative control outcome were insignificant, suggesting no significant source of bias.

Discussion

Our study findings suggest that the BNT162b2 vaccine, administered in two or three doses, was more effective in preventing COVID-19 infection, hospital admission, severe complications, and mortality compared to the same dosage of CoronaVac. Moreover, the BNT162b2 vaccine is effective in preventing these outcomes

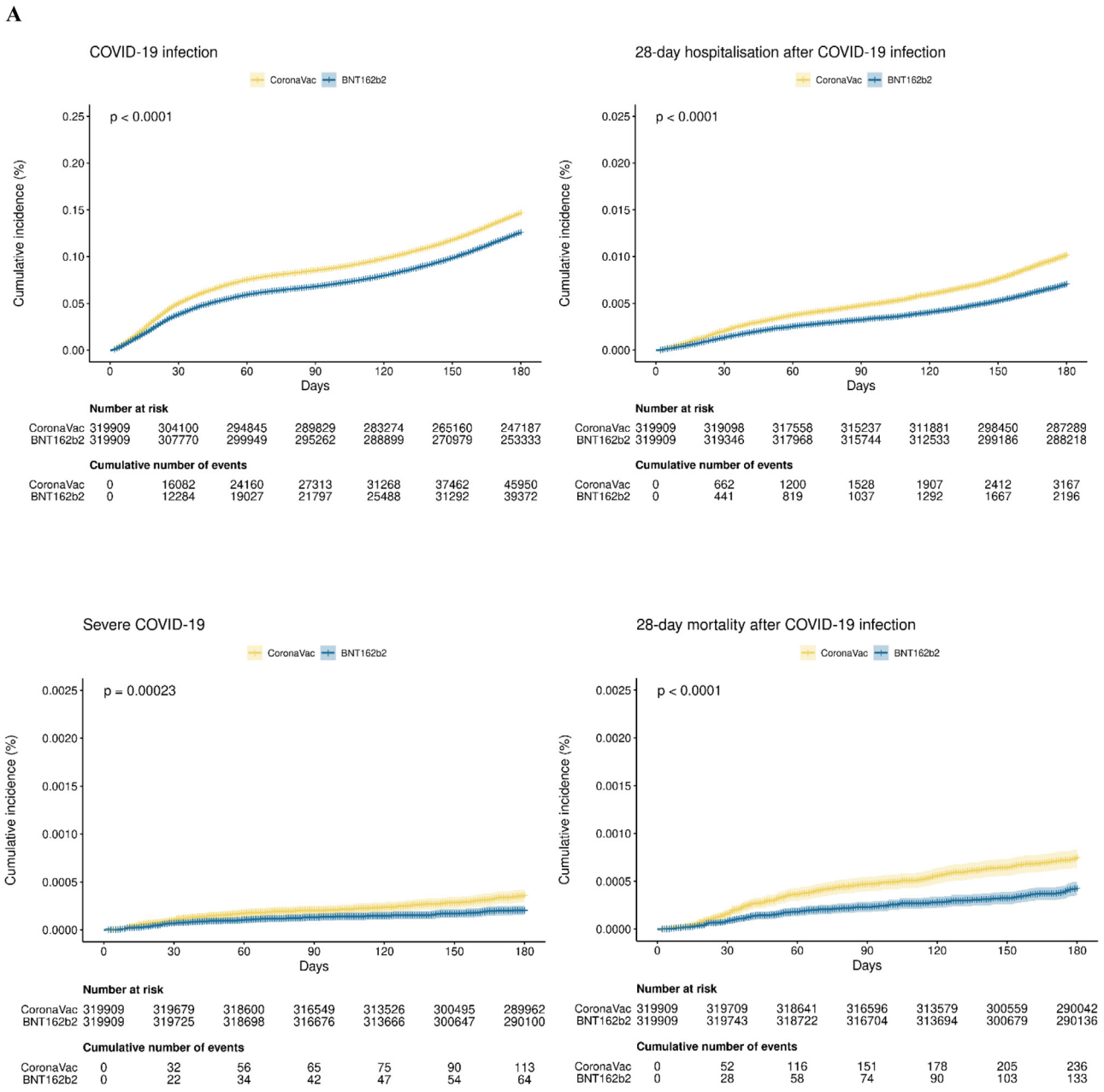


Figure 2. (A) 180-day cumulative incidence of vaccination effectiveness outcomes in 2-dose recipients. (B) 180-day cumulative incidence of vaccination effectiveness outcomes in 3-dose recipients.

across different age, sex, and comorbidity subgroups, with a stronger effect against COVID-19 infection observed in older and higher comorbidity subgroups. Regarding vaccine safety, the incidence of AESI was rare in both groups, with no significant difference in risk between BNT162b2 and CoronaVac. However, it is important to note that our study had limited statistical power to detect significant differences in AESI between the two vaccines, despite a higher proportion of myocarditis cases in the BNT162b2 group.

Contrary to our study, a Hong Kong cohort study including a total of 3228 2-dose and 3482 3-dose BNT162b2 or CoronaVac recipients showed no difference in vaccine effectiveness against asymptomatic and symptomatic infection of SARS-CoV-2 omicron BA.2 between BNT162b2 and CoronaVac. Nonetheless, this study was conducted shortly after introducing a booster dose of the vaccine. Therefore, it was not able to include many people who had taken the booster shot at the time [17]. Our study had a larger sample size and number of events, which provided us with greater statistical power to detect differences. Meanwhile, another Singapore cohort study had the same conclusion our study, that BNT162b2 vaccine recipients had a lower risk of COVID-19 infection and complications compared to CoronaVac vaccine recipients. However, this study was limited by a relatively small proportion of CoronaVac recipients (n = 60,407) compared to BNT162b2 recipients (n = 2001,181), as well as residual confounding from comorbidities. On the other hand, our population-based study included a larger number of CoronaVac recipients and comprehensively adjusted for potential confounding factors, such as comorbidities and drug prescription records. As a result, our study provides more robust and reliable evidence to support the greater clinical benefit of BNT162b2 vaccination.

The difference between the observed effectiveness of BNT162b2 and CoronaVac may be attributed to their different mechanisms of action in vaccination technology. BNT162b2, developed by Pfizer

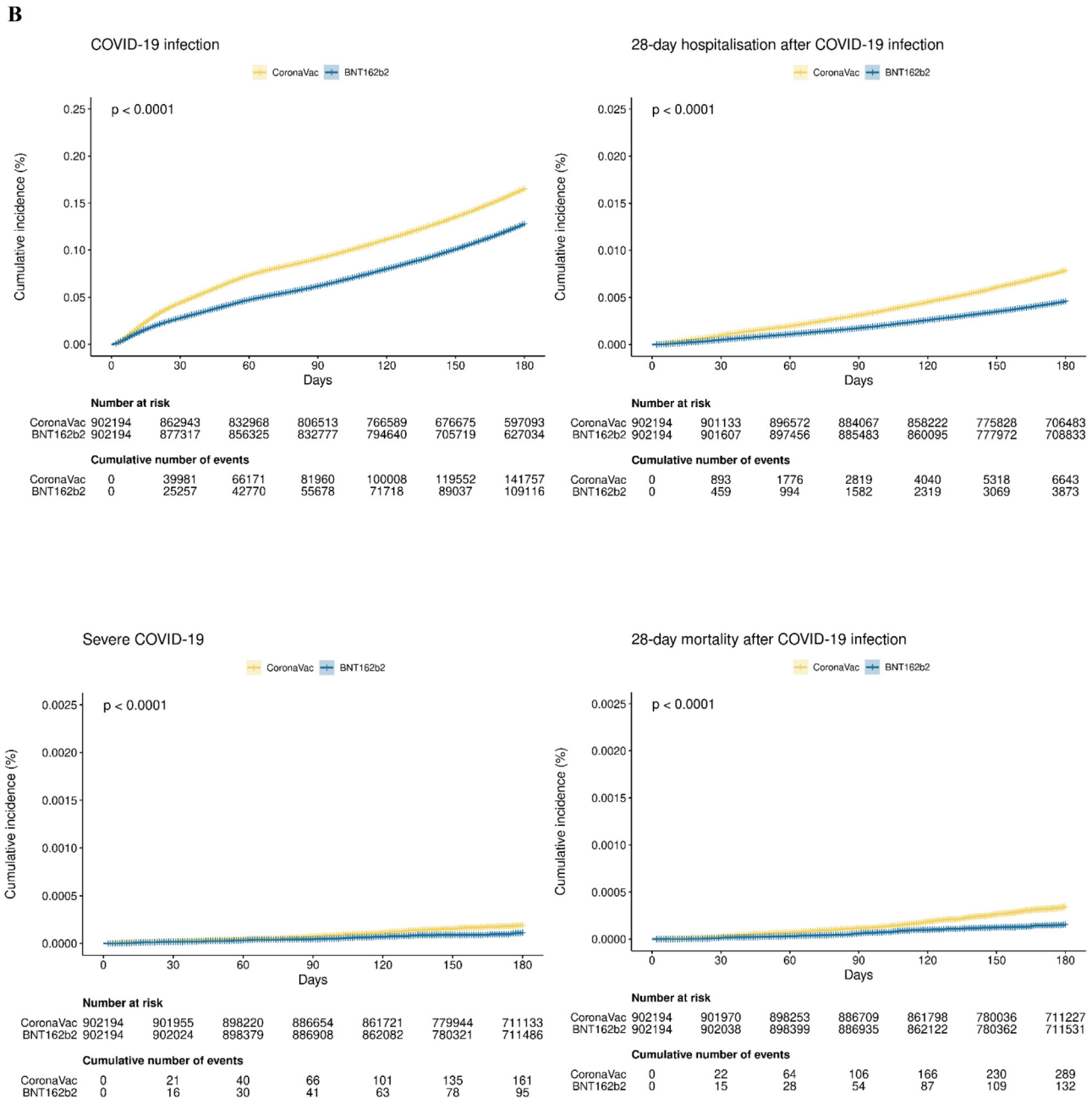


Figure 2. Continued

and BioNTech, utilizes mRNA as its active component to encode the most immunogenic spike protein of SARS-CoV-2, thereby triggering a robust cellular and humoral response against the virus [18]. CoronaVac, on the other hand, is an inactivated whole-virus vaccine developed by Sinovac Biotech, which contains chemically killed whole viruses, mostly stimulating the humoral immune response only [18]. Rigorous serological and immunological studies that investigate the immunogenicity of mRNA and inactivated vaccines have suggested that mRNA vaccines elicit a higher antibody titer and T-cell response against SARS-CoV-2 compared to inactivated vaccines, which may explain the discrepancy between the immunogenicity of BNT162b2 and CoronaVac [19-21]. Studies have shown that the Omicron variant was able to evade neutralizing antibodies elicited by both vaccines, but the vaccines maintained effectiveness through nonneutralizing antibodies. While both vaccines elicited extraneutralizing antibodies that maintained reduced but sufficient antigen-binding ability against the Omicron variant, higher effector action was identified in BNT162b2-induced antibodies [22]. Serologically, BNT162b2 seems to elicit a stronger and more potent humoral response than CoronaVac, which is indirectly reflected in their effectiveness against COVID-19 infection. The potency of vaccination-induced immunity may also explain the more pronounced HR against infection observed in those aged ≥65 years or with Charlson index ≥5. Aging is known to interfere with the strength of immune response stimulated by vaccination [23]. In this case, a more potent mRNA vaccine that induces a higher cellular and humoral response that lasts longer provides more protection against COVID-19 infection, as immunological markers are correlated with protectiveness [24]. Moreover, it has been shown in previous studies that elderly individuals, or those with more comorbidities, tended to reduce social contact to due to the fear of COVID-19 and the possible life-threatening disease triggered by

Table 2
Risk of outcomes in 2-dose BNT162b2 recipients compared to CoronaVac recipients.

Outcome	BNT162b2 recipients			CoronaVac recipients			Relative risk (95% CI)
	Events	Follow-up (person-d)	Incidence rate (per 10,000 person-d)	Events	Follow-up (person-d)	Incidence rate (per 10,000 person-d)	
Effectiveness outcomes							**Hazard ratio**
COVID-19 infection	39,372	5248,7899	7.501 (7.427-7.576)	45,950	51,628,743	8.900 (8.819-8.982)	0.844 (0.833-0.856)
28-d hospitalization after COVID-19 infection	2196	56,079,452	0.392 (0.375-0.408)	3167	55,990,451	0.566 (0.546-0.586)	0.692 (0.656-0.731)
Severe COVID-19	64	56,247,066	0.011 (0.009-0.015)	113	56,229,705	0.020 (0.017-0.024)	0.566 (0.417-0.769)
28-d mortality after COVID-19 infection	133	56,251,557	0.024 (0.020-0.028)	236	56,237,935	0.042 (0.037-0.048)	0.563 (0.456-0.697)
Adverse events of special interest (AESI)							**Incidence rate ratio**
Anaphylaxis and autoimmune disorders							
Anaphylaxis	10	6643,419	0.015 (0.007-0.028)	14	6642,284	0.021 (0.012-0.035)	0.714 (0.317-1.608)
Acute aseptic arthritis	3	6684,099	0.004 (0.001-0.013)	4	6684,600	0.006 (0.002-0.015)	0.75 (0.168-3.351)
Acute disseminated encephalomyelitis	0	6716,453	0.000 (0.000-0.005)	0	6716,449	0.000 (0.000-0.005)	-
Guillain-Barré syndrome	0	6710,804	0.000 (0.000-0.005)	0	6713,026	0.000 (0.000-0.005)	-
Idiopathic thrombocytopenia	1	6698,027	0.001 (0.000-0.008)	2	6697,811	0.003 (0.000-0.011)	0.500 (0.045-5.513)
Narcolepsy	9	6589,837	0.014 (0.006-0.026)	7	6611,604	0.011 (0.004-0.022)	1.29 (0.48-3.463)
Subacute thyroiditis	0	6716,873	0.000 (0.000-0.005)	0	6716,428	0.000 (0.000-0.005)	-
Type 1 diabetes	0	6709,546	0.000 (0.000-0.005)	1	6710,099	0.001 (0.000-0.008)	-
Cardiovascular system							
Major CVD	68	6076,612	0.112 (0.087-0.142)	88	6119,296	0.144 (0.115-0.177)	0.778 (0.567-1.068)
Heart failure	18	6620,168	0.027 (0.016-0.043)	18	6629,774	0.027 (0.016-0.043)	1.001 (0.521-1.924)
Myocardial Infarction	23	6393,099	0.036 (0.023-0.054)	33	6424,346	0.051 (0.035-0.072)	0.7 (0.411-1.193)
Arrhythmia	24	6493,391	0.037 (0.024-0.055)	32	6490,551	0.049 (0.034-0.070)	0.75 (0.442-1.273)
Microangiopathy	0	6716,768	0.000 (0.000-0.005)	0	6716,974	0.000 (0.000-0.005)	-
Myocarditis	9	6716,060	0.013 (0.006-0.025)	1	6715,530	0.001 (0.000-0.008)	8.999 (1.14-71.017)
Pericarditis	1	6711,455	0.001 (0.000-0.008)	3	6710,711	0.004 (0.001-0.013)	0.333 (0.035-3.204)
Circulatory system							
Thromboembolism	55	6342,546	0.087 (0.065-0.113)	68	6364,821	0.107 (0.083-0.135)	0.812 (0.569-1.158)
Ischemic stroke	27	6610,838	0.041 (0.027-0.059)	32	6614,792	0.048 (0.033-0.068)	0.844 (0.506-1.409)
Transient ischemic attack	5	6676,152	0.007 (0.002-0.017)	8	6682,575	0.012 (0.005-0.024)	0.626 (0.205-1.912)
Intracranial hemorrhage	17	6677,273	0.025 (0.015-0.041)	22	6676,415	0.033 (0.021-0.050)	0.773 (0.41-1.455)
Hemorrhagic disease	16	6522,299	0.025 (0.014-0.040)	19	6524,214	0.029 (0.018-0.045)	0.842 (0.433-1.638)
Single organ cutaneous vasculitis	0	6706,436	0.000 (0.000-0.006)	0	6705,901	0.000 (0.000-0.006)	-
Hepato-renal system							
Acute kidney injury	8	6589,369	0.012 (0.005-0.024)	8	6591,620	0.012 (0.005-0.024)	1 (0.375-2.665)
Acute liver injury	4	6597,653	0.006 (0.002-0.016)	0	6598,653	0.000 (0.000-0.006)	-
Acute pancreatitis	4	6702,269	0.006 (0.002-0.015)	5	6702,349	0.007 (0.002-0.017)	0.8 (0.215-2.979)
Nervous system							
Bell's palsy	9	6693,174	0.013 (0.006-0.026)	3	6693,239	0.004 (0.001-0.013)	3.003 (0.812-11.109)
Herpes zoster	2	6610,571	0.003 (0.000-0.011)	3	6626,239	0.005 (0.001-0.013)	0.668 (0.112-3.999)
Meningoencephalitis	0	6709,397	0.000 (0.000-0.005)	0	6710,800	0.000 (0.000-0.005)	-
Seizure	8	6659,672	0.012 (0.005-0.024)	9	6634,493	0.014 (0.006-0.026)	0.886 (0.342-2.295)
Transverse myelitis	0	6716,348	0.000 (0.000-0.005)	0	6716,407	0.000 (0.000-0.005)	-
Skin and musculoskeletal							
Chilblain-like lesions	0	6716,747	0.000 (0.000-0.005)	0	6716,743	0.000 (0.000-0.005)	-
Erythema multiforme	0	6716,327	0.000 (0.000-0.005)	0	6715,938	0.000 (0.000-0.005)	-
Rhabdomyolysis	1	6709,369	0.001 (0.000-0.008)	1	6708,084	0.001 (0.000-0.008)	1 (0.063-15.979)

CI, confidence interval.
Major CVD consists of heart failure stroke coronary artery disease.

COVID-19 infection [25,26]. Despite the protective effectiveness of vaccination, individuals with multiple comorbidities remained at high risk for persisting COVID-19 symptoms and hospitalization, which may explain the observed less noticeable HR in preventing hospital admission [27,28].

Our observations showed a lack of evidence of significant differences in the safety profiles in the two vaccines. However, although the study was not sufficiently powered to detect a significant difference statistically, there was a higher incidence of myocarditis in those vaccinated with BNT162b2 compared to CoronaVac-vaccinated individuals. This observation was consistent with previous studies in Hong Kong as well as overseas [29-35]. It has been suggested that the mechanism may be related to the potent immunogenicity of mRNA vaccinations that are not exhibited in other types of vaccines [36]. Nonetheless, the number of events observed remains small in our sample and a rare complication of mRNA vaccination. Further studies on the difference in adverse events of mRNA and inactivated vaccines are needed to better inform differences in safety profiles.

Strengths and limitations

Our study directly compared the vaccine effectiveness of BNT162b2 and CoronaVac in preventing COVID-19 infections, hospital admission, severity, and mortality in a population-based cohort that is highly representative of the real-world setting. Our results agreed with previous findings from clinical trials of individual vaccine and placebo and some other small-scale observational studies of the vaccines of interest and their comparative effectiveness. The use of comprehensive population-wide electronic

Table 3
Risk of outcomes in 3-dose BNT162b2 recipients compared to CoronaVac recipients.

Outcome	BNT162b2 recipients			CoronaVac recipients			Relative risk (95% CI)
	Events	Follow-up (person-d)	Incidence rate (per 10,000 person-d)	Events	Follow-up (person-d)	Incidence rate (per 10,000 person-d)	
Effectiveness outcomes							**Hazard ratio**
COVID-19 infection	10,9116	144,924,000	7.529 (7.485-7.574)	141,757	140,824,791	10.066 (10.014-10.119)	0.749 (0.743-0.755)
28-d hospitalization after COVID-19 infection	3873	153,875,106	0.252 (0.244-0.260)	6643	153,634,654	0.432 (0.422-0.443)	0.582 (0.559-0.605)
Severe COVID-19	95	154,128,247	0.006 (0.005-0.008)	161	154,086,030	0.010 (0.009-0.012)	0.590 (0.458-0.76)
28-d mortality after COVID-19 infection	132	154,133,163	0.009 (0.007-0.010)	289	154,095,929	0.019 (0.017-0.021)	0.457 (0.372-0.561)
Adverse events of special interest (AESI)							**Incidence rate ratio**
Anaphylaxis and autoimmune disorder							
Anaphylaxis	20	18,780,659	0.011 (0.007-0.016)	21	18,780,605	0.011 (0.007-0.017)	0.952 (0.516-1.757)
Acute aseptic arthritis	8	18,884,354	0.004 (0.002-0.008)	10	18,883,851	0.005 (0.003-0.010)	0.8 (0.316-2.027)
Acute disseminated encephalomyelitis	0	18,944,523	0.000 (0.000-0.002)	0	18,944,127	0.000 (0.000-0.002)	-
Guillain-Barré syndrome	0	18,932,175	0.000 (0.000-0.002)	0	18,935,469	0.000 (0.000-0.002)	-
Idiopathic thrombocytopenia	2	18,911,050	0.001 (0.000-0.004)	2	18,909,490	0.001 (0.000-0.004)	1 (0.141-7.098)
Narcolepsy	49	18,601,021	0.026 (0.019-0.035)	36	18,691,934	0.019 (0.013-0.027)	1.368 (0.89-2.103)
Subacute thyroiditis	0	18,943,998	0.000 (0.000-0.002)	0	18,943,371	0.000 (0.000-0.002)	-
Type 1 diabetes	1	18,930,873	0.001 (0.000-0.003)	1	18,934,256	0.001 (0.000-0.003)	1 (0.063-15.984)
Cardiovascular system							
Major CVD	200	17,659,795	0.113 (0.098-0.130)	188	17,720,914	0.106 (0.091-0.122)	1.068 (0.875-1.303)
Heart failure	27	18,814,284	0.014 (0.009-0.021)	29	18,815,875	0.015 (0.010-0.022)	0.931 (0.551-1.573)
Myocardial infarction	67	18,234,058	0.037 (0.028-0.047)	81	18,292,306	0.044 (0.035-0.055)	0.83 (0.6-1.147)
Arrhythmia	58	18,540,581	0.031 (0.024-0.040)	67	18,525,238	0.036 (0.028-0.046)	0.865 (0.609-1.229)
Microangiopathy	0	18,944,880	0.000 (0.000-0.002)	0	18,944,463	0.000 (0.000-0.002)	-
Myocarditis	6	18,943,478	0.003 (0.001-0.007)	3	18,942,448	0.002 (0.000-0.005)	2.000 (0.500-7.996)
Pericarditis	3	18,935,983	0.002 (0.000-0.005)	2	18,935,081	0.001 (0.000-0.004)	1.5 (0.251-8.977)
Circulatory system							
Thromboembolism	160	18,249,086	0.088 (0.075-0.102)	146	18,269,256	0.080 (0.067-0.094)	1.097 (0.877-1.373)
Ischemic stroke	82	18,761,199	0.044 (0.035-0.054)	71	18,755,807	0.038 (0.030-0.048)	1.155 (0.84-1.586)
Transient ischemic attack	15	18,857,274	0.008 (0.004-0.013)	10	18,874,022	0.005 (0.003-0.010)	1.501 (0.674-3.342)
Intracranial hemorrhage	34	18,879,209	0.018 (0.012-0.025)	26	18,878,933	0.014 (0.009-0.020)	1.308 (0.785-2.179)
Hemorrhagic disease	30	18,581,621	0.016 (0.011-0.023)	18	18,574,847	0.010 (0.006-0.015)	1.666 (0.929-2.988)
Single organ cutaneous vasculitis	0	18,921,129	0.000 (0.000-0.002)	0	18,919,263	0.000 (0.000-0.002)	-
Hepato-renal system							
Acute kidney injury	10	18,709,645	0.005 (0.003-0.010)	8	18,702,424	0.004 (0.002-0.008)	1.25 (0.493-3.166)
Acute liver injury	4	18,567,897	0.002 (0.001-0.006)	5	18,587,146	0.003 (0.001-0.006)	0.801 (0.215-2.982)
Acute pancreatitis	9	18,915,114	0.005 (0.002-0.009)	10	18,913,800	0.005 (0.003-0.010)	0.9 (0.366-2.215)
Nervous system							
Bell's palsy	21	18,891,378	0.011 (0.007-0.017)	20	18,886,565	0.011 (0.006-0.016)	1.029 (0.558-1.899)
Herpes zoster	8	18,634,132	0.004 (0.002-0.008)	9	18,686,742	0.005 (0.002-0.009)	0.891 (0.344-2.31)
Meningoencephalitis	2	18,932,720	0.001 (0.000-0.004)	1	18,933,604	0.001 (0.000-0.003)	2 (0.181-22.052)
Seizure	18	18,856,441	0.010 (0.006-0.015)	25	18,818,468	0.013 (0.009-0.020)	0.719 (0.392-1.317)
Transverse myelitis	0	18,944,376	0.000 (0.000-0.002)	0	18,944,001	0.000 (0.000-0.002)	-
Skin and musculoskeletal							
Chilblain-like lesions	0	18,943,305	0.000 (0.000-0.002)	0	18,943,854	0.000 (0.000-0.002)	-
Erythema multiforme	1	18,943,522	0.001 (0.000-0.003)	0	18,942,741	0.000 (0.000-0.002)	-
Rhabdomyolysis	2	18,931,097	0.001 (0.000-0.004)	5	18,929,293	0.003 (0.001-0.006)	0.4 (0.078-2.062)

CI, confidence interval.
Major CVD consists of heart failure stroke coronary artery disease.

health records and the approach with target trial emulation minimized common biases and challenges faced by classical observational analyses.

The study had several limitations. First, we were not able to separate symptomatic COVID-19 cases from asymptomatic cases, as case definition was determined by positive PCR or RAT results, thus we were not able to capture the full spectrum of COVID-19 severity. Second, in common in other database studies and clinical trials, we were not able to account for lifestyle and behavioral factors such as wearing a face mask and keeping social distance, which may affect the risk and severity of COVID-19 infection. Third, underdiagnosis of outcome events is possible due to diagnostic coding and the voluntary reporting of RAT-positive cases. Finally, the results should be interpreted cautiously as our study is still an observational study. Bias may still be present despite our strict study design and statistical adjustments.

Conclusion

Using a population-based target trial emulation, we observed that BNT162b2 has higher vaccination effectiveness than CoronaVac against reducing infection, hospital admission, severity, and mortality at the same dose, specially almost 50% lower mortality.

Author contributions

Concept and design: EYFW, BW, EWYC, ICKW. Acquisition of data: ICKW. Analysis, or interpretation of data: EYFW, BW, JZ, CSLC, FTTL, XL, CKHW, EWYC, ICKW. Drafting of the manuscript: EYFW, BW, JZ. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: EYFW, BW, JZ. Administrative, technical, or material support: ICKW, EWYC. Supervision: ICKW.

Ethics committee approval

This study was approved by the Central Institutional Review Board of the HA of Hong Kong (CIRB-2021-005-4) and the DH Ethics Committee (LM171/2021).

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Data sharing

Data are not available as the data custodians (the HA and the DH of Hong Kong SAR) have not given permission for sharing due to patient confidentiality and privacy concerns. Local academic institutions, government departments, or nongovernmental organizations may apply for access to data through the HA's data-sharing portal (https://www3.ha.org.hk/data).

Declarations of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107149.

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