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Vaccine effectiveness of BNT162b2 and CoronaVac against SARS-CoV-2 omicron infection and related hospital admission among people with substance use disorder in Hong Kong: a matched case-control study

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Summary

Background People with substance use disorder have a high risk of SARS-CoV-2 infection and subsequent poor outcomes. Few studies have evaluated COVID-19 vaccine effectiveness among people with substance use disorder. We aimed to estimate the vaccine effectiveness of BNT162b2 (Fosun-BioNTech) and CoronaVac (Sinovac) against SARS-CoV-2 omicron (B.1.1.529) infection and related hospital admission in this population.

Methods We did a matched case-control study using electronic health databases in Hong Kong. Individuals diagnosed with substance use disorder between Jan 1, 2016, and Jan 1, 2022, were identified. People aged 18 years and older with SARS-CoV-2 infection from Jan 1 to May 31, 2022, and people with COVID-19-related hospital admission from Feb 16 to May 31, 2022, were included as cases and were matched by age, sex, and previous clinical history with controls from all individuals diagnosed with substance use disorder who attended the Hospital Authority health services: up to three controls for SARS-CoV-2 infection and up to ten controls for hospital admission. Conditional logistical regression was used to evaluate the association between vaccination status (ie, one, two, or three doses of BNT162b2 or CoronaVac) and the risk of SARS-CoV-2 infection and COVID-19-related hospital admission, adjusted for baseline comorbidities and medication use.

Findings Among 57 674 individuals with substance use disorder, 9523 people with SARS-CoV-2 infections (mean age 61·00 years, SD 14·90; 8075 [84·8%] males and 1448 [15·2%] females) were identified and matched to 28 217 controls (mean age 60·99 years, 14·67; 24 006 [85·1%] males and 4211 [14·9%] females), and 843 people with COVID-19-related hospital admissions (mean age 70·48 years, SD 14·68; 754 [89·4%] males and 89 [10·6%] females) were identified and matched to 7459 controls (mean age 70·24 years, 13·87; 6837 [91·7%] males and 622 [8·3%] females). Data on ethnicity were not available. We observed significant vaccine effectiveness against SARS-CoV-2 infection for two-dose BNT162b2 vaccination (20·7%, 95% CI 14·0–27·0, p<0·0001) and three-dose vaccination (all BNT162b2 41·5%, 34·4–47·8, p<0·0001; all CoronaVac 13·6%, 5·4–21·0, p=0·0015; BNT162b2 booster after two-dose CoronaVac 31·3%, 19·8–41·1, p<0·0001), but not for one dose of either vaccine or two doses of CoronaVac. Significant vaccine effectiveness against COVID-19-related hospital admission was detected after one dose of BNT162b2 vaccination (35·7%, 3·8–57·1, p=0·032), two-dose vaccination (both BNT162b2 73·3%, 64·3 to 80·0, p<0·0001; both CoronaVac 59·9%, 50·2–67·7, p<0·0001), and three-dose vaccination (all BNT162b2 86·3%, 75·6–92·3, p<0·0001; all CoronaVac 73·5% 61·0–81·9, p<0·0001; BNT162b2 booster after two-dose CoronaVac 83·7%, 64·6–92·5, p<0·0001), but not after one dose of CoronaVac.

Interpretation For both BNT162b2 and CoronaVac, two-dose or three-dose vaccination was protective against COVID-19-related hospital admission and the booster dose provided protection against SARS-CoV-2 infection among people with substance use disorder. Our findings confirm the importance of booster doses in this population during the period dominated by the omicron variant.

Funding Health Bureau, the Government of the Hong Kong Special Administrative Region.

Introduction

Individuals with substance use disorder, including the misuse of tobacco, alcohol, and drugs, carry a higher risk of SARS-CoV-2 infection and related severe outcomes compared with those without.[1–3] This vulnerable population is also at an increased risk of developing medical comorbidities and tends to have compromised immune systems, which could increase the risk of COVID-19 complications and severe outcomes if infection occurs.[4,5]

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See Online for appendix

Research in context

Evidence before this study

To review the literature on the effectiveness of COVID-19 vaccines in people diagnosed with substance use disorder, we searched PubMed on Feb 8, 2023, for all studies reported since database inception in English, with the terms "COVID-19 vaccine", "substance use disorder", and "substance abuse". We found only two papers, which discussed the association between substance use disorder and SARS-CoV-2 breakthrough infection rates. These two studies were done in the USA and both suggested that substance use disorder diagnoses were associated with an increased incidence of SARS-CoV-2 breakthrough infection. No studies to our knowledge have directly estimated the effectiveness of any COVID-19 vaccine among people with substance use disorder. Whether COVID-19 vaccination protects against SARS-CoV-2 infection and severe COVID-19 outcomes in this at-risk population remains unknown.

Added value of this study

To our knowledge, this is the first population-based study to evaluate the effectiveness of BNT162b2 and CoronaVac COVID-19 vaccines in people with substance use disorder during the omicron variant outbreak. Our results show that both vaccines provided protective effects against SARS-CoV-2 infection after two or more doses of BNT162b2, three doses of CoronaVac, and the combined use of two doses of CoronaVac plus a booster dose of BNT162b2 among people diagnosed with substance use disorder. We also observed protective effects against COVID-19-related hospital admission among people with substance use disorder after they received the first two doses, with increased effectiveness if they received a booster dose as well.

Implications of all the available evidence

These findings highlight the importance of booster-dose vaccination to reduce potential severe COVID-19-related outcomes in people diagnosed with substance use disorders. Our research supports policy changes to enhance access to booster vaccination in this vulnerable population.

In Hong Kong, the COVID-19 mass vaccination programme began on Feb 23, 2021, offering vaccination free of charge with either BNT162b2 (Fosun–BioNTech, mRNA vaccine) or CoronaVac (Sinovac Biotech, inactivated vaccine; appendix pp 8–9). Although clinical trials and observational studies have shown that BNT162b2 and CoronaVac vaccines are highly effective against COVID-19-related outcomes,[6] people with substance use disorder were not specifically included and investigated, and little real-world evidence of vaccine effectiveness among this population is available. In addition, substance use disorder could impair immune function by the immunosuppression of macrophages, T cells, and B cells,[5] and previous studies found lower antibody response to some commonly used vaccines (such as hepatitis vaccines) among this population compared with the general population.[7,8] Previous studies found that substance use disorders (including tobacco use disorder and alcohol use disorder) were associated with an increased risk of SARS-CoV-2 breakthrough infection.[9,10] Therefore, there are concerns that the effectiveness of COVID-19 vaccination among individuals with substance use disorder might be lower than in those who do not have substance use disorder. Wang and colleagues[9] and Nishimi and colleagues[10] have assessed the relative risk of SARS-CoV-2 breakthrough infection among fully vaccinated individuals in the USA, and Wang and colleagues also compared the overall risks of hospital admission and mortality between breakthrough and non-breakthrough cohorts separately in fully vaccinated populations with and without substance use disorder. However, to our knowledge, no studies have investigated vaccine effectiveness by measuring how COVID-19 vaccines affect the risk of infection among people with substance use disorder. Instead of looking at breakthrough infection with outcomes of all-cause hospital admissions and mortality, we designed a study to assess vaccine effectiveness against SARS-CoV-2 infection and related hospital admission.

In early January, 2022, there was a rapid outbreak of the SARS-CoV-2 omicron (B.1.1.529) variant in Hong Kong.[11] Concerns were raised about viral fitness and waning immune responses against SARS-CoV-2 omicron variants,[12] making it important to understand whether COVID-19 vaccines are effective in protecting people with substance use disorder against SARS-CoV-2 during the wave dominated by the omicron variant.

To address these knowledge gaps, we did a case-control study to evaluate the association between BNT162b2 and CoronaVac vaccination and the risk of SARS-CoV-2 infection and COVID-19-related hospital admission among people with substance use disorder during the period dominated by omicron in Hong Kong.

Methods

Study design and population

In this matched case-control study, we used electronic medical records from the Hong Kong Hospital Authority, vaccination records from the Hong Kong Department of Health, and COVID-19-confirmed case records from the Hong Kong Centre of Health Protection. These three databases were linked using unique anonymous pseudoidentifiers. The Hospital Authority is a statutory administrative organisation that manages all public inpatient services and most public outpatient services. The Department of Health manages and retains the

database for all vaccination records. The Centre of Health Protection maintains a database of confirmed COVID-19 cases, including both mandatory and voluntary reporting of positive PCR and rapid antigen test results. Before and during the study, the Hong Kong Government implemented extensive PCR testing for SARS-CoV-2 in public hospitals and clinics for those who had close contact with people who had confirmed COVID-19 and for those who presented with COVID-like symptoms. Territory-wide community testing centres were also set up to screen asymptomatic individuals and provide regular testing to various categories of the workforce with a high risk of exposure, such as those working in nursing homes. Moreover, free rapid antigen test kits were routinely distributed to individuals at high risk and target groups and residents, with mandatory reporting of positive results to the Centre of Health Protection (appendix p 10). The linked records have been previously used to evaluate the safety and effectiveness of COVID-19 vaccines.[13–16]

We identified all individuals who had a diagnosis of substance use disorder between Jan 1, 2016, and Jan 1, 2022, in the Hospital Authority electronic medical records, through the use of the International Classification of Diseases-9, Clinical Modification (ICD-9-CM) codes of 303.x, 304.x, and 305.x (for tobacco use disorder, alcohol use disorder, and drug use disorder). For SARS-CoV-2 infection, cases were defined as individuals among those with substance use disorder who had a first positive COVID-19 test between Jan 1, 2022, and May 31, 2022. All other individuals from those identified with substance use disorder who attended any Hospital Authority health service without confirmed positive SARS-CoV-2 infection results (ie, hospital admissions and outpatient clinics) during this period were selected as controls. The index date was defined as the date of the first positive test result for those in the infection case group. For those in the infection control group, the index date was defined as the date of attendance at any Hospital Authority service; if an individual had multiple attendances at Hospital Authority services during the study period, one of the attendances was randomly selected to define the index date.

For COVID-19-related hospital admission, cases were defined as individuals with substance use disorder who were admitted to hospital within 28 days of SARS-CoV-2 infection between Feb 16, 2022, and May 31, 2022. All other individuals with substance use disorder who attended any Hospital Authority health services during this period were selected as controls. Index date was defined as the first attendance date of COVID-19-related hospital admission for the admission case group. For the admission control group, index date was defined as the date of attendance at any Hospital Authority service; if an individual had multiple attendances at Hospital Authority services during the study period, one of the attendances was randomly selected to define the index date.

Only individuals aged 18 years or older were included and individuals with a history of SARS-CoV-2 infection before the index date were excluded, as were those with incomplete or invalid vaccination records.

To balance the baseline characteristics between the two groups in each test, we matched cases and controls by sex, age (5-year band), index date (within 3 calendar days), and Charlson Comorbidity Index (0, 1–2, 3–4, and ≥5). Sex data were included in the electronic medical records. Matching between cases and controls was done independently for each outcome. For SARS-CoV-2 infection matching, up to three controls were randomly matched with one case. The same matching steps were used for estimating the risk of COVID-19-related hospital admission, with up to ten controls for each case.

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).

Exposures

We included one-dose, two-dose, and three-dose vaccinations as exposures of interest. In Hong Kong, citizens must receive the same vaccine for their second dose as they received for their first dose, and they can choose either vaccine for their third dose. Therefore, COVID-19 vaccination status was classified into eight mutually exclusive groups based on the number of vaccine doses and vaccine type administered: (1) one dose of only BNT162b2; (2) one dose of only CoronaVac; (3) two doses of only BNT162b2; (4) two doses of only CoronaVac; (5) three doses of only BNT162b2; (6) three doses of only CoronaVac; (7) two doses of CoronaVac with a BNT162b2 booster (referred to as C-C-B); and (8) two doses of BNT162b2 with a CoronaVac booster (referred to as B-B-C). Individuals were considered vaccinated 14 days after a vaccine dose to account for the time needed to acquire immunity after receipt of COVID-19 vaccination. A 2022 systematic review and meta-analysis[17] reported that the effectiveness or efficacy of vaccines against infection and symptomatic disease decreased significantly after 180 days following COVID-19 vaccination. Therefore, vaccine recipients were defined as individuals who received the latest dose of vaccination within 180 days before the index date for the infection analysis.

Measures

The outcomes were the risk of SARS-CoV-2 infection and COVID-19-related hospital admission, both measured via the COVID-19 confirmed case records and electronic medical records. SARS-CoV-2 infection was defined based on a positive PCR test using a throat swab, nasopharyngeal aspirate, deep throat sputum specimens, or a positive rapid antigen test, confirmed by the Centre of Health Protection. COVID-19-related hospital admission was defined as hospital admission within

28 days of SARS-CoV-2 infection. In Hong Kong, patients with COVID-19 could be admitted to a hospital regardless of symptom severity before Feb 15, 2022, and people with mild cases were advised to stay at home or attend designated clinics after Feb 15, 2022. Therefore, only those with COVID-19 identified after Feb 15, 2022, were included in the analysis for COVID-19-related hospital admission.

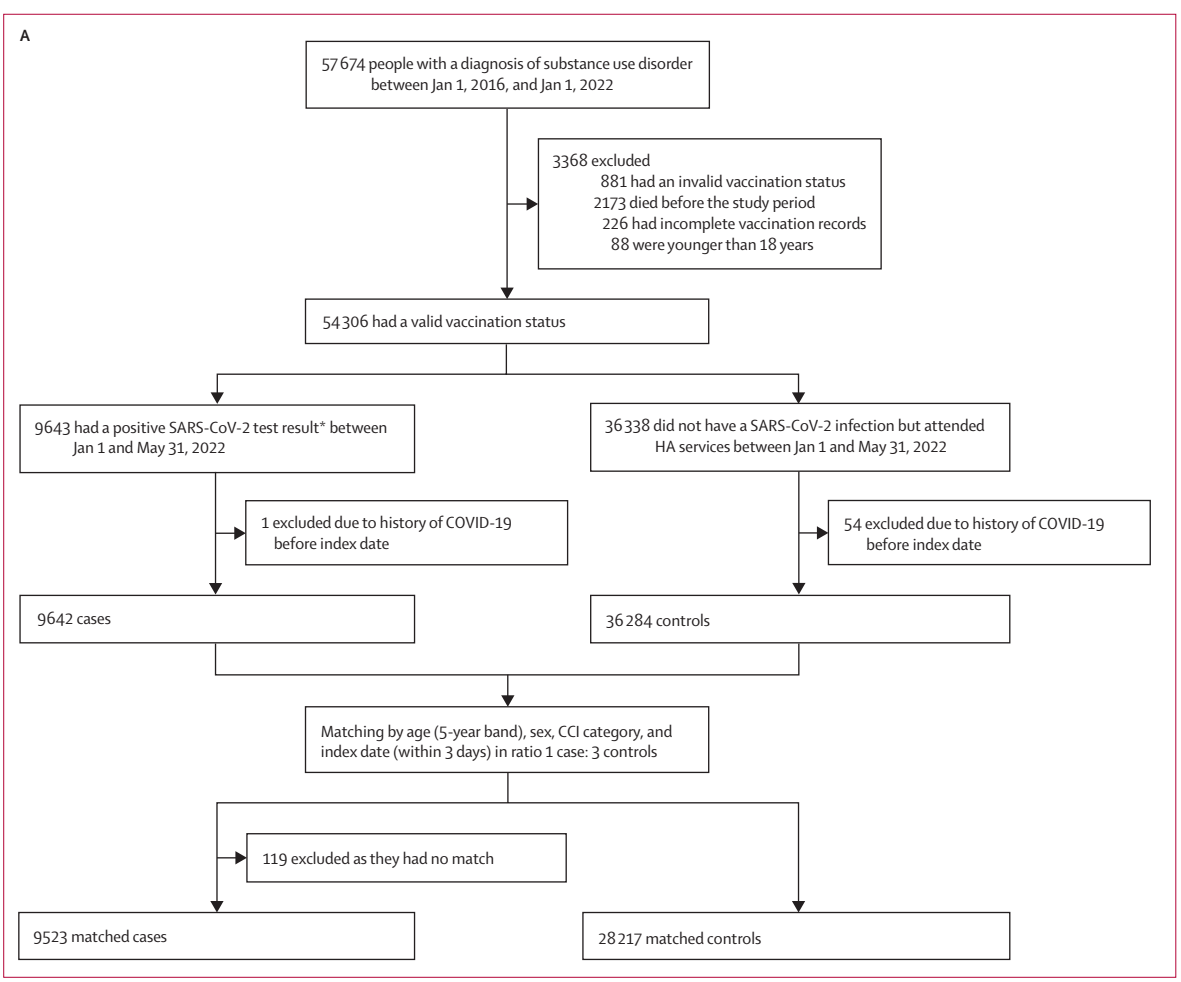
Patient characteristics were described as means (with SDs) for continuous variables and as frequencies for categorical variables. Potential confounders were adjusted for, including baseline comorbidities and medication use.

Statistical analysis

We used conditional logistical regression to evaluate the association between vaccination status and the risk of SARS-CoV-2 infection and COVID-19-related hospital admission, adjusting for confounders. Both crude and adjusted odds ratios (ORs) with a 95% CI were reported. Vaccine effectiveness was estimated by (1−adjusted OR)×100%.

Because substance use disorder type might not be mutually exclusive among people with substance use disorders and could not be a matching variable in primary analysis, we did a secondary analysis adjusting for substance use disorder types. Three substance use disorder types were identified by ICD-9-CM codes (305.1 for tobacco use disorder, 303.x and 305.0 for alcohol use disorder, and 304.x and 305.2–305.9 for drug use disorder). An interaction term between substance use disorder type and vaccination status was added to the conditional logistical regression model to evaluate whether the effect of vaccination varies by substance use disorder type. The variable of substance use disorder type contains seven mutually exclusive groups: (1) tobacco use disorder only; (2) alcohol use disorder only; (3) drug use disorder only; (4) concurrent tobacco use disorder and alcohol use disorder; (5) concurrent tobacco use disorder and drug use disorder; (6) concurrent alcohol use disorder and drug use disorder; and (7) concurrent tobacco use disorder, alcohol use disorder, and drug use disorder.

Four sensitivity analyses were done to test the robustness of our findings against variations in some of



(Figure 1 continues on next page)

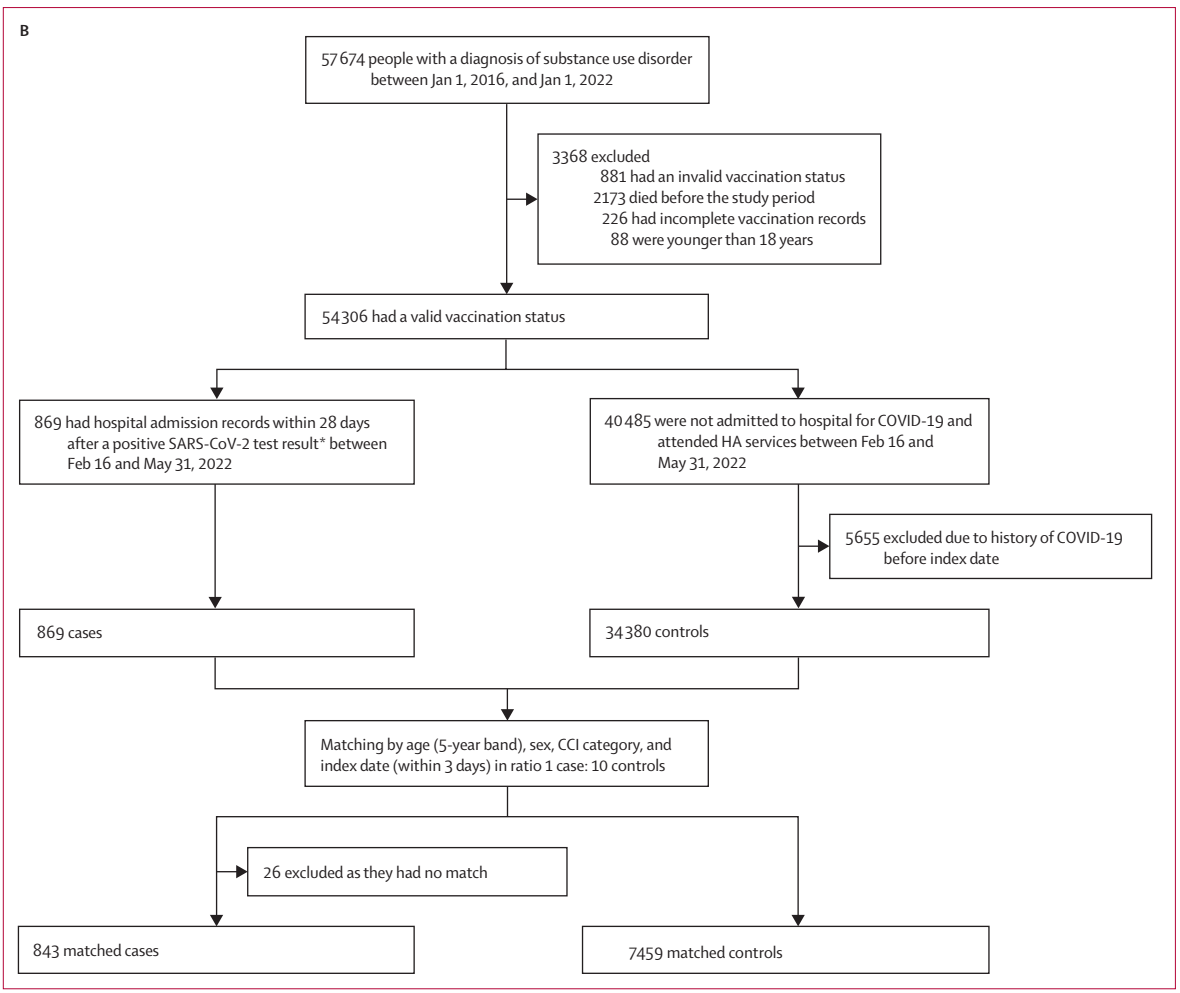


Figure 1: **Study selection**
Study selection for (A) SARS-CoV-2 infection and (B) COVID-19-related hospital admission. HA services included outpatient, inpatient, and accident and emergency. CCI category options were: 0, 1–2, 3–4, or ≥5. HA=Hospital Authority of Hong Kong. CCI=Charlson Comorbidity Index. *Testing was done via PCR or rapid antigen test.

the study definitions. First, to explore whether the potential vaccine-waning effect biased our results, we restricted the limits on vaccine exposure to 90 days for the infection outcome and to 180 days for the hospital admission outcome. Second, doses administered within 14 days before the index date were taken into account when determining the vaccine exposure after the latest dose of vaccination was received, assuming no lag instead of a 14-day lag for immune response to vaccination. Third, analyses were repeated using a one-to-three matching ratio (the same as in the infection analysis) to estimate the risk of COVID-19-related hospital admission. Finally, analyses were repeated including only individuals with COVID-19 that was confirmed at least 28 days before the end of the observation period for COVID-19-related hospital admissions, leaving time to observe occurrence of hospital admission events.

To achieve 80% power with a 0·05 significance level to detect ORs ranging from 0·05 to 0·5 (corresponding to vaccine effectiveness of 50% to 95%), a range of five to 78 matched sets was required when each set had one case and ten controls (ie, for COVID-19-related hospital admission) and a range of six to 94 matched sets was required when each set had one case and three controls (ie, for SARS-CoV-2 infection). Further details on the sample size and power estimation are in the appendix (p 11). All statistical tests were two-sided, and p values less than 0·05 were considered statistically significant. Statistical analyses were done using R (version 4.0.3). Two investigators (CH and YW) did the statistical analyses independently for quality assurance, and statement checklists were followed to guide transparent reporting.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 57 674 individuals with diagnosed substance use disorder, 9642 of whom had a SARS-CoV-2 infection between Jan 1, 2022, and May 31, 2022, and met the inclusion criteria, and 36 284 of whom were classed as controls who attended Hospital Authority services within the analysis period and did not have SARS-CoV-2 infection. After matching, there were 9523 cases (mean age 61·00 years, SD 14·90; 8075 [84·8%] male and 1448 [15·2%] female) and 28 217 controls (mean age 60·99 years, SD 14·67; 24 006 [85·1%] male and 4211 [14·9%] female; figure 1A). From Feb 16, 2022, to May 31, 2022, of the 57 674 people with a substance use disorder diagnosis, 869 individuals who had COVID-19-related hospital admission met the inclusion criteria and 34 830 controls who attended Hospital Authority services within the analysis period were identified. After matching, there were 843 cases (mean age 70·48 years, SD 14·68; 754 [89·4%] male and 89 [10·6%] female) and 7459 controls (mean age 70·24 years, SD 13·87; 6837 [91·7%] male and 622 [8·3%] female; figure 1B). Baseline characteristics of matched cases and controls are shown in table 1. Data on ethnicity were not available.

A significantly decreased risk of SARS-CoV-2 infection was observed among people with substance use disorder following two doses of BNT162b2 vaccine (vaccine effectiveness 20·7%, 95% CI 14·0 to 27·0, p<0·0001), three doses of BNT162b2 (41·5%, 34·4 to 47·8, p<0·0001), three doses of CoronaVac (13·6%, 5·4 to 21·0, p=0·0015), and C-C-B (31·3%, 19·8 to 41·1, p<0·0001; table 2). One-dose vaccination (BNT162b2 7·4%, 95% CI –6·5 to 19·6, p=0·28; CoronaVac –13·5%, –22·9 to –4·8, p=0·0019) and two doses of CoronaVac vaccine (6·1%, –0·5 to 12·3, p=0·07) showed no protection against SARS-CoV-2 infection. People with all other vaccination statuses, including B-B-C and four-dose vaccination, were categorised as other; the small sample size precluded estimation of vaccine effectiveness for these categories.

For COVID-19-related hospital admission, the vaccine effectiveness of one-dose BNT162b2 vaccination was

	SARS-CoV-2 infection			COVID-19-related hospital admission		
	Cases (n=9523)	Controls (n=28 217)	SMD	Cases (n=843)	Controls (n=7459)	SMD
Age, years	61·00 (14·90)	60·99 (14·67)	<0·001	70·48 (14·68)	70·24 (13·87)	0·017
Male	8075 (84·8%)	24 006 (85·1%)	0·008	754 (89·4%)	6837 (91·7%)	0·076
Female	1448 (15·2%)	4211 (14·9%)	0·008	89 (10·6%)	622 (8·3%)	0·076
Charlson Comorbidity Index	0·83 (1·29)	0·79 (1·17)	0·035	1·93 (2·22)	1·52 (1·74)	0·207
Time since most recent vaccine dose, days	68·06 (55·79)	63·99 (54·00)	0·074	81·55 (74·44)	85·76 (72·14)	0·057
Pre-existing comorbidities						
Cancer	406 (4·3%)	1038 (3·7%)	0·030	124 (14·7%)	752 (10·1%)	0·141
Chronic kidney disease	285 (3·0%)	926 (3·3%)	0·017	68 (8·1%)	638 (8·6%)	0·018
Respiratory disease	847 (8·9%)	2051 (7·3%)	0·060	181 (21·5%)	1073 (14·4%)	0·186
Diabetes	3112 (32·7%)	9864 (35·0%)	0·048	308 (36·5%)	3569 (47·9%)	0·231
Cardiovascular disease	5973 (62·7%)	18 804 (66·6%)	0·082	602 (71·4%)	5830 (78·2%)	0·156
Chronic viral hepatitis	182 (1·9%)	353 (1·3%)	0·053	33 (3·9%)	105 (1·4%)	0·156
Dementia	72 (0·8%)	95 (0·3%)	0·057	33 (3·9%)	67 (0·9%)	0·198
Pre-existing substance use disorder type						
Tobacco use disorder	6349 (66·7%)	20 361 (72·2%)	0·119	508 (60·3%)	5910 (79·2%)	0·422
Alcohol use disorder	2094 (22·0%)	4838 (17·2%)	0·122	228 (27·1%)	1232 (16·5%)	0·257
Drug use disorder	1455 (15·3%)	4350 (15·4%)	0·004	151 (17·9%)	608 (8·2%)	0·293
Medication use within 90 days						
Renin-angiotensin-system agents	3349 (35·2%)	10 933 (38·8%)	0·074	328 (38·9%)	3482 (46·7%)	0·158
β blockers	1928 (20·3%)	6022 (21·3%)	0·027	202 (24·0%)	1748 (23·4%)	0·012
Calcium channel blockers	4623 (48·6%)	15 056 (53·4%)	0·096	430 (51·0%)	4535 (60·8%)	0·198
Diuretics	633 (6·7%)	1631 (5·8%)	0·036	142 (16·8%)	686 (9·2%)	0·229
Nitrates	398 (4·2%)	913 (3·2%)	0·050	70 (8·3%)	381 (5·1%)	0·128
Lipid-lowering agents	4554 (47·8%)	15 110 (53·6%)	0·115	422 (50·1%)	4780 (64·1%)	0·286
Insulins	426 (4·5%)	946 (3·4%)	0·058	87 (10·3%)	400 (5·4%)	0·185
Antidiabetic drugs	2759 (29·0%)	8681 (30·8%)	0·039	263 (31·2%)	3027 (40·6%)	0·197
Oral anticoagulants	152 (1·6%)	295 (1·1%)	0·048	43 (5·1%)	166 (2·2%)	0·154
Antiplatelets	1639 (17·2%)	4607 (16·3%)	0·024	250 (29·7%)	1959 (26·3%)	0·076
Immunosuppressants	26 (0·3%)	52 (0·2%)	0·019	6 (0·7%)	30 (0·4%)	0·042

Data are mean (SD) or n (%), unless otherwise stated. SMD=standardised mean difference.

Table 1: **Baseline characteristics of the case and control groups**

	Case group	Control group	Crude OR (95% CI)	Adjusted OR (95% CI)	Vaccine effectiveness, % (95% CI)	p value
SARS-CoV-2 infection						
Unvaccinated	4101/9523 (43·1%)	11 108/28 217 (39·4%)	1 (ref)	1 (ref)	NA	NA
One dose only						
BNT162b2	283/9523 (3·0%)	832/28 217 (3·0%)	0·918 (0·799 to 1·056)	0·926 (0·804 to 1·065)	7·4% (–6·5 to 19·6)	0·28
CoronaVac	1144/9523 (12·0%)	2786/28 217 (9·9%)	1·117 (1·032 to 1·209)	1·135 (1·048 to 1·229)	–13·5% (–22·9 to –4·8)	0·0019
Two doses only						
Both BNT162b2	941/9523 (9·9%)	3255/28 217 (11·5%)	0·779 (0·718 to 0·845)	0·793 (0·730 to 0·860)	20·7% (14·0 to 27·0)	<0·0001
Both CoronaVac	1629/9523 (17·1%)	4873/28 217 (17·3%)	0·906 (0·847 to 0·969)	0·939 (0·877 to 1·005)	6·1% (–0·5 to 12·3)	0·07
Three doses						
All BNT162b2	418/9523 (4·4%)	1955/28 217 (6·9%)	0·572 (0·511 to 0·641)	0·585 (0·522 to 0·656)	41·5% (34·4 to 47·8)	<0·0001
All CoronaVac	779/9523 (8·2%)	2491/28 217 (8·8%)	0·839 (0·768 to 0·918)	0·864 (0·790 to 0·946)	13·6% (5·4 to 21·0)	0·0015
C-C-B	218/9523 (2·3%)	881/28 217 (3·1%)	0·665 (0·570 to 0·775)	0·687 (0·589 to 0·802)	31·3% (19·8 to 41·1)	<0·0001
Other	10/9523 (0·1%)	36/28 217 (0·1%)	..	..	..	..
COVID-19-related hospital admission						
Unvaccinated	378/843 (44·8%)	1779/7459 (23·9%)	1 (ref)	1 (ref)	NA	NA
One dose only						
BNT162b2	32/843 (3·8%)	229/7459 (3·1%)	0·553 (0·372 to 0·821)	0·643 (0·429 to 0·962)	35·7% (3·8 to 57·1)	0·032
CoronaVac	166/843 (19·7%)	1019/7459 (13·7%)	0·751 (0·610 to 0·923)	0·877 (0·708 to 1·087)	12·3% (–8·7 to 29·2)	0·23
Two doses only						
Both BNT162b2	67/843 (8·0%)	1197/7459 (16·1%)	0·223 (0·168 to 0·296)	0·267 (0·200 to 0·357)	73·3% (64·3 to 80·0)	<0·0001
Both CoronaVac	147/843 (17·4%)	1887/7459 (25·3%)	0·330 (0·267 to 0·408)	0·401 (0·323 to 0·498)	59·9% (50·2 to 67·7)	<0·0001
Three doses						
All BNT162b2	13/843 (1·5%)	476/7459 (6·4%)	0·109 (0·061 to 0·192)	0·137 (0·077 to 0·244)	86·3% (75·6 to 92·3)	<0·0001
All CoronaVac	33/843 (3·9%)	643/7459 (8·6%)	0·213 (0·146 to 0·311)	0·265 (0·181 to 0·390)	73·5% (61·0 to 81·9)	<0·0001
C-C-B	7/843 (0·8%)	213/7459 (2·9%)	0·137 (0·064 to 0·296)	0·163 (0·075 to 0·354)	83·7% (64·6 to 92·5)	<0·0001
Other	0/843	16/7459 (0·2%)	..	..	..	..

Data are n (%), unless otherwise stated. The adjusted OR is adjusted for cancer, chronic kidney disease, respiratory disease, diabetes, cardiovascular disease, chronic viral hepatitis, dementia, and medication use in past 90 days (renin-angiotensin-system agents, β blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants). Other includes two doses of BNT162b2 and subsequent CoronaVac booster and four-dose vaccination. NA=not applicable. OR=odds ratio. C-C-B=two doses of CoronaVac and subsequent BNT162b2 booster.

Table 2: **Risk of COVID-19-related outcomes among individuals with different vaccination status**

35·7% (95% CI 3·8 to 57·1, p=0·032). Vaccine effectiveness against COVID-19-related hospital admission was not significant after one-dose CoronaVac vaccination (12·3%, –8·7 to 29·2, p=0·23). Significant reductions were observed among people with substance use disorder following two or more doses of either BNT162b2 or CoronaVac, and the effect size was greater than that for SARS-CoV-2 infection (two-dose BNT162b2 73·3%, 64·3 to 80·0, p<0·0001; two-dose CoronaVac 59·9%, 50·2 to 67·7, p<0·0001; three-dose BNT162b2 86·3%, 75·6 to 92·3, p<0·0001; three-dose CoronaVac 73·5%, 61·0 to 81·9, p<0·0001; and C-C-B 83·7%, 64·6 to 92·5, p<0·0001). For both vaccine types, the vaccine effectiveness for booster dose vaccine recipients was greater than that for two-dose vaccine recipients.

In the secondary analysis adjusting for substance use disorder type and interaction between substance use disorder type and vaccination status, the p values for each interaction term were all non-significant (figure 2, appendix pp 1–4). Among all three groups with only one substance use disorder type, two-dose or three-dose BNT162b2 vaccination was effective against SARS-CoV-2 infection (tobacco use disorder only group: two-dose BNT162b2 16·7%, 95% CI 7·4–25·1, p=0·0007; three-dose BNT162b2 40·2%, 31·2–48·1, p<0·0001; alcohol use disorder only group: two-dose BNT162b2 25·9%, 9·5–39·3, p=0·0033; three-dose BNT162b2 34·1%, 14·8–49·0, p=0·0015; drug use disorder only group: two-dose BNT162b2 22·7%, 6·6–36·1, p=0·0077; three-dose BNT162b2 51·6%, 32·9–65·1, p<0·0001). Among the tobacco use disorder only group, three-dose CoronaVac vaccination was effective against SARS-CoV-2 infection (11·3%, 1·5–20·2, p=0·026) or C-C-B vaccination (31·6%, 17·7–43·2, p<0·0001]). Among the drug use disorder only group, vaccine effectiveness against SARS-CoV-2 infection was observed after two-dose or three-dose CoronaVac vaccination (two-dose 24·3%, 8·5–37·3, p=0·0039; three-dose 48·2%, 27·9–62·8, p<0·0001]) or C-C-B vaccination (60·6%, 27·1–78·7, p=0·0030). Two doses of either vaccine or three doses of

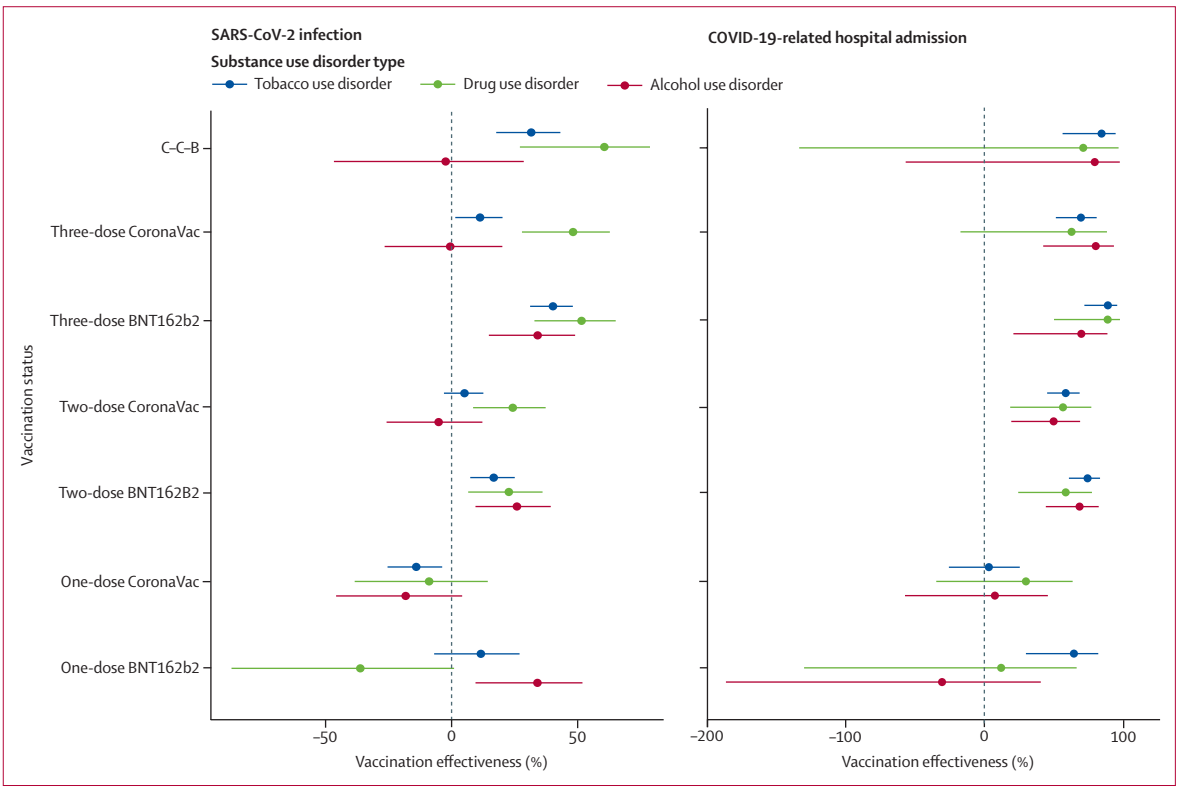


Figure 2: **Secondary analysis by substance use disorder type for the risk of COVID-19 outcomes**
Vaccine effectiveness was adjusted for cancer, chronic kidney disease, respiratory disease, diabetes, cardiovascular disease, chronic viral hepatitis, dementia, and medication use in past 90 days (renin-angiotensin-system agents, β blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants). Error bars show 95% CI. Two doses of BNT162b2 and subsequent CoronaVac booster and four-dose vaccination were not reported as the small sample size precluded estimation of the effect size. C-C-B=two doses of CoronaVac and subsequent BNT162b2 booster.

BNT162b2 vaccine provided protection against COVID-19-related hospital admission among all three single disorder groups (appendix pp 3–4). Three doses of CoronaVac were protective against COVID-19-related hospital admission in people with tobacco use disorder only (69·2%, 51·2–80·6, p<0·0001) or alcohol use disorder only (79·9%, 42·1–93·0, p=0·0029; appendix pp 3–4). Among the tobacco use disorder only group, vaccine effectiveness against COVID-19-related hospital admission was observed after one-dose BNT162b2 (64·2%, 29·7–81·7, p=0·0028) or the C-C-B vaccine combination (84·1%, 56·1–94·2, p=0·0004; appendix pp 3–4). Results for people with at least two substance use disorder types were not reported due to a very small sample size. Results of sensitivity analyses for both SARS-CoV-2 infection and hospital admission events were consistent with the main analysis (appendix pp 5–7).

Discussion

Our study showed that among people with substance use disorder, receipt of three doses of either vaccine, or a booster dose of BNT162b2 after two doses of CoronaVac, was associated with a lower risk of SARS-CoV-2 infection, and receipt of two or three doses of either BNT162b2 or CoronaVac vaccine was associated with a lower risk of COVID-19-related hospital admission. The results show that both vaccines were effective in protecting against COVID-19-related hospital admission during the omicron predominant periods in Hong Kong. There was a clear dose–response relationship between the number of doses received and the magnitude of risk reduction of both SARS-CoV-2 infection and related hospital admission, with both vaccine types. These findings are consistent with previous studies focusing on the omicron variant among the general population in Hong Kong and other regions.[13,18,19] To our knowledge, this is the first study to evaluate the effectiveness of BNT162b2 and CoronaVac vaccines against SARS-CoV-2 infection and related hospital admission among people with substance use disorder during a large omicron wave. This study also provides the first insight, to our knowledge, into the effectiveness of the booster dose among this population.

Vaccine effectiveness against SARS-CoV-2 infection among people with substance use disorder seemed to be lower than that seen in our earlier studies among the general population in Hong Kong,[18] which is probably due to impaired immune systems and rapid waning immunity among this population.[4] Previous studies have reported a poorer response to several commonly used

vaccines—including hepatitis A and B vaccines—in people with substance use disorder compared with the general population.[7,8] In addition, people with substance use disorder are more likely to engage in high-risk behaviours and more likely to have lower adherence to guidelines of infection control measures than the general population, which in turn increases their risk of being exposed to COVID-19.[20] The findings in this study are consistent with such observations.

For two-dose and three-dose vaccination, the vaccine effectiveness of CoronaVac against SARS-CoV-2 infection and related hospital admission seemed to be lower than that of BNT162b2, which could be because the strength of antibody responses to CoronaVac is lower and protection of CoronaVac is more likely to wane over time, especially for infection outcome.[21] Our study also reported that a heterologous BNT162b2 booster dose could be more effective than a homologous CoronaVac booster in our substance use disorder population, which might be attributed to different mechanisms of immune response for different vaccine platforms. Our findings are consistent with previous studies among the general population on the vaccine effectiveness of booster doses.[13,18,22] We did not report the vaccine effectiveness for heterologous CoronaVac boosters as the number of recipients of this vaccine combination was small.

For effectiveness against SARS-CoV-2 infection and related hospital admission, similar dose–response trends to the primary analysis were observed for all three separate substance use disorder types. Further studies are needed to examine this issue, as our sample size was relatively small for these subgroups. Our findings are consistent with previous studies on the change in vaccine protective effectiveness during omicron periods.[23]

Up to May 31, 2022, vaccine coverage of the first booster dose among people with substance use disorder in Hong Kong was 47·9%, which was lower than that among the general population (52·5%). These individuals have higher rates of medical comorbidities, which increases their risk of hospital admission from SARS-CoV-2 infection.[2,3] Our study suggests that the addition of booster vaccines to the two previous doses have much better protective effectiveness against omicron-associated hospital admission than only two doses, which highlights the importance of a booster dose for people with substance use disorder. However, vaccine effectiveness for a booster dose against omicron infection is not considered adequate, and subsequent doses or omicron-specific vaccines could be considered to further reduce the infection risk.[24,25] At the time of this study, there were insufficient numbers of individuals who had received a fourth dose for effectiveness estimation. Health-care providers and policy makers should consider ways to improve booster vaccine uptake among people with substance use disorder, such as co-locating vaccine clinics and substance misuse services, to better protect this vulnerable population and alleviate the increased disease burden.

Our study has some limitations. First, similar to other retrospective epidemiological studies using electronic medical record data, there might be residual confounding. Second, due to the stigma associated with substance use disorder (especially with drug use disorder), not all individuals with substance use disorder in Hong Kong can be captured in our study. Third, although the number of patients with substance use disorder could have been under-reported during the pandemic years,[26] we identified the study population based on medical records since 2016; therefore, people who were missed were probably new patients with substance use disorder who presented after 2020. The small proportion of missing cases is unlikely to change our study conclusions. Fourth, due to the paucity of variant sequencing information in electronic health records, it was not possible to ascertain the specific variant among the infected cases. However, previous studies[11,12] have shown that the predominant SARS-CoV-2 variant during our study period in Hong Kong was the omicron variant. Fifth, antiviral treatment for COVID-19 was not adjusted in our analysis because it is possible that antiviral drugs for COVID-19 were prescribed in the private health sector, which would not be documented in our dataset from the public sector. Therefore, it is possible that vaccine effectiveness against COVID-19-related hospital admission is underestimated as people with COVID-19-related outcomes are more likely to receive antiviral treatment than those without. The use of anti-COVID-19 drug treatment might dilute the estimation of vaccine effectiveness against the risk of COVID-19-related hospital admission. Furthermore, hospital admission following positive COVID-19 tests does not necessarily indicate that the patient was admitted due to SARS-CoV-2 infection, which could lead to underestimation of vaccine effectiveness against COVID-19-related hospital admission. However, this definition has been widely used in effectiveness studies on COVID-19 vaccine in Hong Kong[15,16,27] and other regions.[28,29] We also excluded individuals infected with COVID-19 before the Hong Kong Government set up special clinics for mild cases to keep all individuals in the case group under the same hospital admission criteria. Last, the small sample size precluded estimations of vaccine effectiveness against COVID-19-related mortality and other severe complications.

Future studies should investigate the effectiveness of a second booster dose of COVID-19 vaccine, or the BioNTech bivalent vaccine, and evaluate the association between vaccination and long-term COVID-19 outcomes, as our study only assessed short-term COVID-19-related outcomes.

In conclusion, the booster dose of either BNT162b2 or CoronaVac was protective against SARS-CoV-2 infection and COVID-19-related hospital admission among people with substance use disorder during the omicron variant outbreak. The risk of COVID-19-related hospital

admission decreased with more doses of the vaccination, especially with the booster dose. Our findings highlight the importance of the booster dose for people with substance use disorder.

Contributors

CH, YW, VKCY, ICKW, and EWC designed the study. CH and YW did the study and analysed the data. VKCY, XY, WK, HHEY, JJPS, BJC, MLT, DJC, CSLC, FTTL, XL, EYFW, CKHW, JFH, WCC, AKKC, and CSL provided discussion and revision. ICKW and EWC secured funding and provided supervision. CH prepared the manuscript with input from all coauthors. CH, YW, ICKW, and EWC had full access to and accessed all underlying data, and all authors had access to the study data and interpreted results. EWC and ICKW verified and take responsibility for the integrity of the underlying data and the accuracy of the data analysis. EWC took final responsibility for the decision to submit for publication. All authors approved the decision to submit for publication.

Declaration of interests

BJC reported receiving consulting fees from AstraZeneca, Fosun Pharma, GlaxoSmithKline, Haleon, Moderna, Pfizer, Roche, and Sanofi Pasteur outside the submitted work. DJC reported receiving personal fees from Seqirus, Lundbeck, and Servier, grants from Boehringer Ingelheim, the National Health and Medical Research Council (Australia), Milken Institute, and Psyche Foundation, is a founder of and holds 50% of the intellectual property for the Optimal Health Program, is part owner (5%) of Clarity Healthcare, and serves as an advisory board chair of an Australian not-for-profit institute specialising in psychedelic medicines research, outside the submitted work. CSLC reported receiving grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region during the conduct of the study; grants from Hong Kong Innovation and Technology Commission, Hong Kong Research Grants Council, Pfizer, Amgen, MSD, and IQVIA; and consultancy fees from Primevigilance outside the submitted work. FTTL reported support from the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region outside the submitted work. XL reported receiving research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region, Research Grants Council Early Career Scheme, Research Grant Council, and Research Impact Fund; research and educational grants from Janssen and Pfizer; internal funding from the University of Hong Kong; and consultancy fees from Merck Sharp & Dohme, unrelated to this work; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer, outside the submitted work. EYFW reported receiving research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region, and the Hong Kong Research Grants Council, and National Natural Science Foundation of China outside the submitted work. CKHW reported receipt of grants from the General Research Fund, Research Grant Council, the Government of Hong Kong, EuroQol Research Foundation, AstraZeneca, and Boehringer Ingelheim, all outside the submitted work. JFH reported receiving grants from UK Research and Innovation, Wellcome Trust, National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and National Institute for Health and Care Research Applied Research Collaboration North Thames during the conduct of the study; personal fees from Wellcome Trust and juli Health; and patent pending for juli Health, outside the submitted work. ICKW reported receiving research funding from Amgen, Bristol Myers Squibb, Pfizer, Janssen, Bayer, GlaxoSmithKline, Novartis, the Hong Kong Research Grants Council, the Hong Kong Health and Medical Research Fund, the Hong Kong Innovation and Technology Commission, the National Institute for Health and Care Research, the European Commission, and the Australian National Health and Medical Research Council; and receiving expert testimony payment consultancy fees from WHO and IQVIA; and is an independent non-executive director of Jacobson Medical in the Hong Kong Court of Final Appeal, outside the submitted work. EWC reported receiving grants from the National Natural Science Foundation of China during the conduct of the study; non-financial support from Wellcome Trust; grants from Research Grants Council, Research Fund Secretariat of the Health Bureau (via the Health and Medical Research Fund), National Health and Medical Research Council (Australia), Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Pfizer, Takeda, Novartis, and RGA Reinsurance Company; and personal fees from Pfizer, AstraZeneca, Novartis, Pfizer, and the Hong Kong Special Administrative Region Hospital Authority outside the submitted work. All other authors declare no competing interests.

Data sharing

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

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