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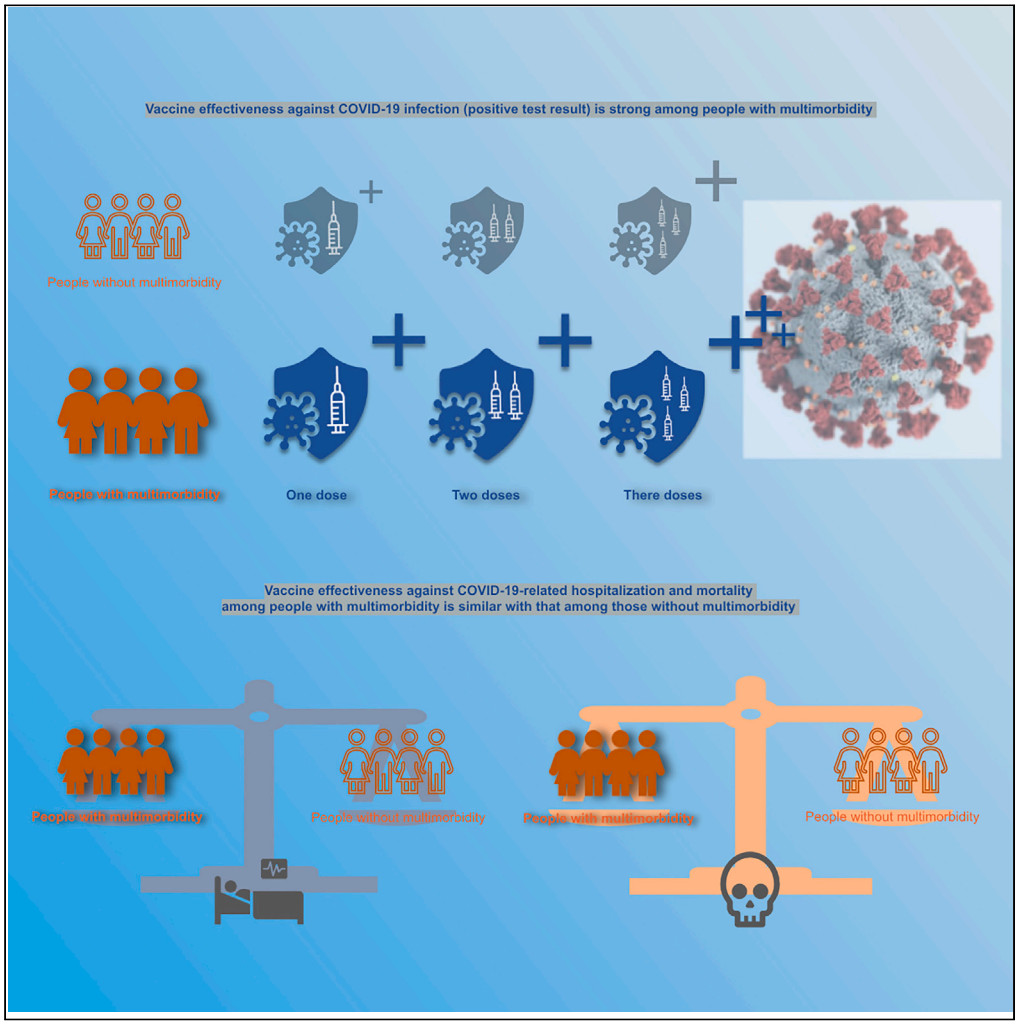

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Highlights

Good vaccine effectiveness (VE) against COVID-19 among people with multimorbidity

Booster doses correlated with better VE

Small VE differences in severe COVID-19 between those with/without multimorbidity

People with multimorbidity should be prioritized for vaccination

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COVID-19 vaccine effectiveness against the Omicron variant of SARS-CoV-2 in multimorbidity: A territory-wide case-control study

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SUMMARY

Multimorbidity entails a higher risk of SARS-CoV-2 infection and COVID-19 complications. We examined vaccine effectiveness (VE) stratified by multimorbidity using a case-control study of territory-wide electronic health records in Hong Kong. Cases of infection (testing positive), hospitalization, and mortality were identified from January to March 2022. Controls were matched by age, sex, outpatient attendance/hospitalization date, and Charlson Comorbidity Index. We demonstrated a consistently good VE among people with increased multimorbidity burden; even more so than among those with minimal such burden. There was also a significantly greater VE after a third dose of BNT162b2 or CoronaVac against infection. The difference in VE between those with multimorbidity and those without was less pronounced for hospitalization, and such difference for COVID-19-related mortality was negligible. In conclusion, VE of both examined vaccines against SARS-CoV-2 infection among people with more complex multimorbidity burden is significant. Further vaccine roll-out should prioritize people with multimorbidity.

INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more chronic conditions in an individual.[1] As world populations age, this health state is increasingly prevalent in both developed and developing societies.[2] Multimorbidity has been shown to be associated with poorer quality of life, higher rates of healthcare utilization, and heightened risk of mortality.[3,4] In addition, people living with multimorbidity are affected by the ongoing COVID-19 pandemic far more than those without it, with a substantially higher risk of developing severe disease once infected.[5]

Our earlier work has demonstrated a good safety profile of COVID-19 vaccines, BNT162b2 (Pfizer-BioNTech) and CoronaVac (Sinovac), in populations with multimorbidity.[6] Nevertheless, recent research has shown that people with chronic conditions or multimorbidity may still be hesitant toward vaccine uptake.[7] In the face of the ever-evolving variants of SARS-CoV-2, it is important to disseminate comprehensible and relatable data on the potential benefits of vaccination specific to those with various clinical characteristics such as multimorbidity. Research evidence of the effectiveness of vaccines in populations with and without multimorbidity is thus much warranted to further inform vaccination uptake and public policies. It is also of great importance to investigate how an increased burden of multimorbidity in an individual, i.e., three, four or even more comorbidities, can potentially affect vaccine effectiveness (VE) in terms of infection, hospitalization, and mortality from COVID-19, especially the currently dominant Omicron variant of SARS-CoV-2.

In this study, we aimed to use a territory-wide case-control study to estimate the effectiveness of each of the three doses of BNT162b2 or CoronaVac, including a heterologous third dose, amid the Omicron epidemic,[8] among people living with multimorbidity and those who do not. Our secondary objective was to examine how stratification of the sample by multimorbidity, i.e., increased number of chronic conditions, affects this effectiveness estimate.

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RESULTS

The selection of cases and controls for the COVID-19 infection and complications analysis is shown in Figure 1. For COVID-19 infection, a total of 101,427 cases and 404,647 matched controls with multimorbidity and 411,485 cases and 822,844 matched controls without multimorbidity were included. There were 16,675 cases of post-infection hospital admission with multimorbidity and 164,290 matched controls, as well as 17,333 cases without multimorbidity and 171,818 matched controls. 5,371 post-infection deaths with multimorbidity were identified and matched with 52,715 controls, while 2,325 mortality cases without multimorbidity were matched with 22,624 controls. The characteristics of cases and controls are summarized in Table 1, which shows an unsurprisingly higher prevalence of chronic conditions and medication use among participants with multimorbidity.

Vaccination patterns

As shown in Table 2, among cases of COVID-19 infection with multimorbidity, 2,981 (2.9%), 14,782 (14.6%) and 4,752 (4.7%) received one, two, and three doses of BNT162b2 respectively while 15,628 (15.4%), 27,071 (26.7%), and 8,591 (8.5%) received one, two, and three doses of CoronaVac respectively. Seventy-two (0.0%) received two priming doses of BNT162b2 then a CoronaVac booster dose and 2,161 (2.1%) two priming doses of CoronaVac plus a BNT162b2 booster dose. Among those without multimorbidity, 16,799 (4.1%), 132,097 (32.1%) and 36,094 (8.8%) received one, two, and three doses of BNT162b2 respectively and 26,013 (6.3%), 94,026 (22.9%), and 49,088 (11.9%) received one, two, and three doses of CoronaVac respectively. 559 (0.0%) received two priming doses of BNT162b2 then a CoronaVac booster dose and 13,400 (3.3%) two priming doses of CoronaVac plus a BNT162b2 booster dose. Similar vaccination patterns were observed for COVID-19 related hospitalization and COVID-19-related mortality.

Advanced doses and vaccine effectiveness

Table 2 also shows the VE for each outcome. A positive dose-response relationship, between the number of BNT162b2 or CoronaVac doses received and VE, was demonstrated. VE against COVID-19 infection among participants with multimorbidity after the first dose of BNT162b2 and CoronaVac were 31.5% (95% CI: 28.6 to 34.4) and 1.9% (95% CI: −0.3 to 4.0), respectively while a higher effectiveness was shown in vaccine recipients who received three doses of BNT162b2 [58.8% (95% CI: 57.3 to 60.2)] or CoronaVac [29.4% (95% CI: 27.3 to 31.4)]. A similar dose-response relationship was observed for both participants with and without multimorbidity and for effectiveness against both hospitalization and all-cause mortality after COVID-19 infection. The VE against post-infection hospitalization and all-cause mortality among those with multimorbidity were 90.4% (95% CI: 88.9 to 91.8) and 97.9% (95% CI: 96.0 to 98.9) after three doses of BNT162b2 and were 86.2% (95% CI: 84.5 to 87.7) and 94.9% (95% CI: 92.7–96.4) after three doses of CoronaVac, respectively. The estimates for heterologous booster doses were based on fewer participants and were less precise for a useful interpretation.

Participants with increased multimorbidity burden versus those without

For COVID-19 infection, VE was estimated to be consistently greater among those with multimorbidity than those without. For instance, after the third dose of BNT162b2 or CoronaVac, effectiveness among those without multimorbidity were only 33.4 (95% CI: 32.3 to 34.5) and −37.7 (95% CI: −40.1 to −35.4), compared with 58.8% (95% CI: 57.3 to 60.2) and 29.4% (95% CI: 27.3 to 31.4) among those with multimorbidity. This observation is consistent but much less pronounced for the outcome of COVID-19- related hospitalization. After the third dose of BNT162b2 or CoronaVac, VE against COVID-19-related hospitalization was 90.4 (95% CI: 88.9–91.8) and 86.2 (95% CI: 84.5–87.7) among those with multimorbidity, compared with 83.8 (95% CI: 82.2–85.3) and 75.0 (95% CI: 72.8–77.0) among those without. For COVID-19-related mortality however, such differences were negligible, if any.

Table 3 shows the VE estimates within those living with multimorbidity stratified by number of underlying chronic conditions. It shows consistent findings that VE against infection tends to be greater in those with increased multimorbidity burden. VE against infection was estimated at 72.1 (95% CI: 54.3 to 82.9) and 64.8 (95% CI:45.7 to 77.2) after three doses of BNT162b2 or CoronaVac among those with five or more chronic conditions, compared with 52.2 (95% CI: 50.1 to 54.3) and 17.5 (95% CI: 14.3 to 20.5) among those with only two conditions.

Subgroup and sensitivity analyses

In the subgroup analyses as shown in Table S2, a similar dose-response relationship was seen in different sex and age subgroups. A slightly greater VE against COVID-19 infection was observed in those aged 80 or older. The results of the three sensitivity analyses are summarized in Tables S3–S5 which support the robustness of the findings in the main analysis.

DISCUSSION

In this study, we compared the VE estimate of BNT162b2 and CoronaVac by dose among those living with multimorbidity and those without. We found a greater estimate of effectiveness for both BNT162b2 and CoronaVac against a positive COVID-19 test result in those living with multimorbidity when compared with those without multimorbidity, with non-overlapping confidence intervals. Greater effectiveness against infection was observed among those with a greater multimorbidity burden, i.e., more chronic conditions. For hospitalization and mortality from COVID-19, marked differences have not been observed. Consistent with current knowledge, for both participants with and without multimorbidity, more advanced doses of vaccines are associated with a notably greater effectiveness in all three COVID-19-related outcomes.

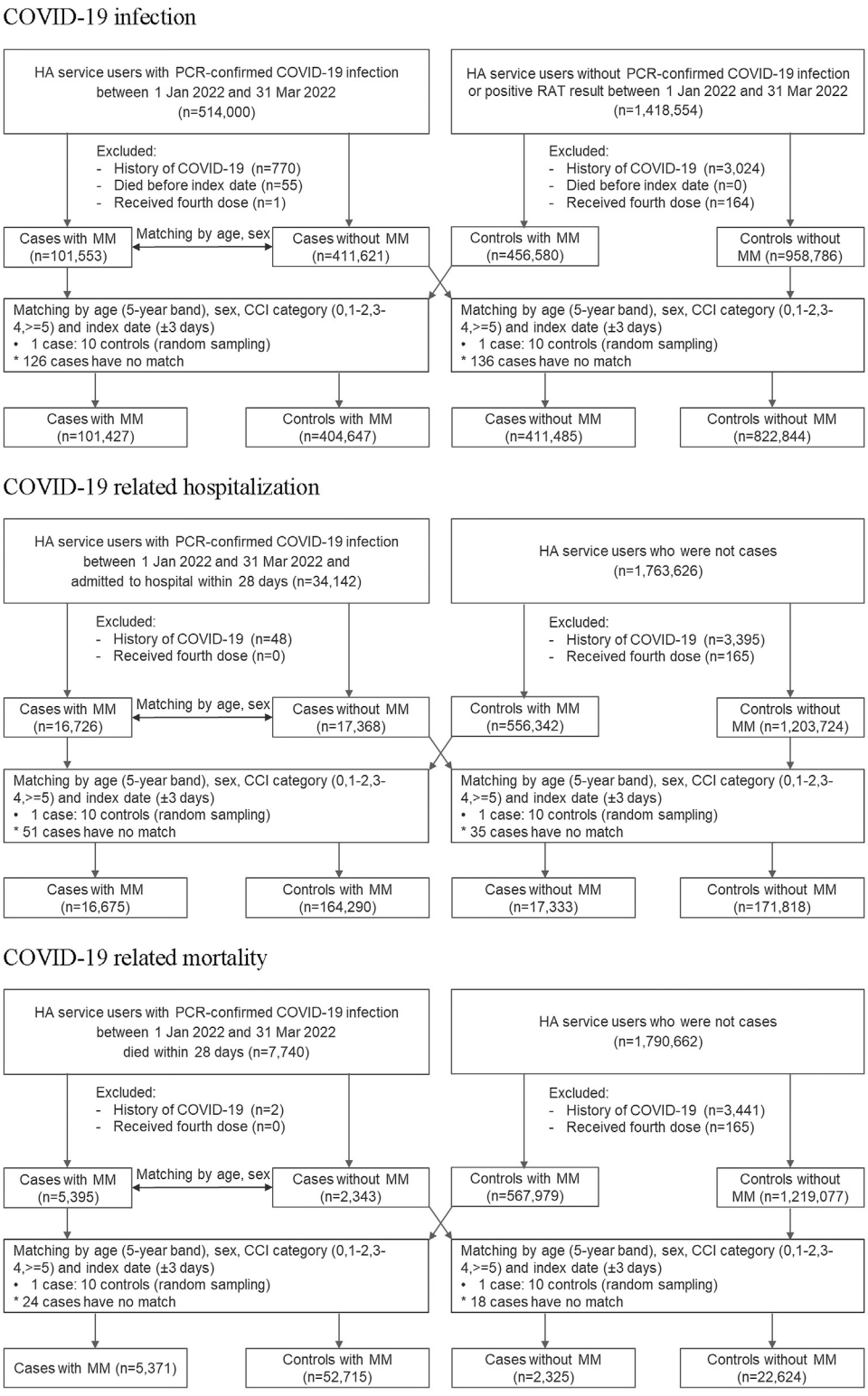

Figure 1. Selection of cases and controls

Table 1. Baseline characteristics

	COVID-19 infection				COVID-19 related hospitalization				COVID-19 related mortality			
	MM		No MM		MM		No MM		MM		No MM	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
N	101427	404647	411485	822844	16675	164290	17333	171818	5371	52715	2325	22624
Age, years	69.73 (13.29)	69.78 (13.15)	49.34 (17.31)	49.38 (17.33)	78.58 (12.98)	78.63 (12.49)	62.37 (22.99)	62.17 (22.87)	83.94 (10.45)	83.70 (10.14)	83.94 (13.06)	83.60 (12.91)
Sex, male	53442 (52.7)	213217 (52.7)	191134 (46.4)	382208 (46.4)	9209 (55.2)	90946 (55.4)	8407 (48.5)	83339 (48.5)	3218 (59.9)	31767 (60.3)	1346 (57.9)	13107 (57.9)
Charlson Comorbidity Index	1.43 (1.56)	1.37 (1.48)	0.09 (0.40)	0.09 (0.38)	2.22 (2.02)	2.03 (1.92)	0.32 (0.81)	0.24 (0.59)	2.55 (2.17)	2.34 (2.05)	0.52 (1.02)	0.42 (0.78)
Alcohol misuse	1358 (1.3)	4880 (1.2)	438 (0.1)	996 (0.1)	200 (1.2)	1547 (0.9)	30 (0.2)	150 (0.1)	61 (1.1)	451 (0.9)	5 (0.2)	9 (0.0)
Asthma	3977 (3.9)	13927 (3.4)	2487 (0.6)	4148 (0.5)	577 (3.5)	5831 (3.5)	92 (0.5)	1483 (0.9)	136 (2.5)	1967 (3.7)	5 (0.2)	172 (0.8)
Cancer, lymphoma	585 (0.6)	1325 (0.3)	327 (0.1)	494 (0.1)	236 (1.4)	941 (0.6)	94 (0.5)	193 (0.1)	66 (1.2)	326 (0.6)	9 (0.4)	31 (0.1)
Cancer, metastatic	2605 (2.6)	9270 (2.3)	350 (0.1)	695 (0.1)	854 (5.1)	8124 (4.9)	85 (0.5)	281 (0.2)	310 (5.8)	3176 (6.0)	22 (0.9)	93 (0.4)
Cancer, non-metastatic	5284 (5.2)	17656 (4.4)	2087 (0.5)	3656 (0.4)	1321 (7.9)	11708 (7.1)	319 (1.8)	1519 (0.9)	359 (6.7)	3860 (7.3)	24 (1.0)	175 (0.8)
Chronic pain	12316 (12.1)	35033 (8.7)	6324 (1.5)	12525 (1.5)	2721 (16.3)	16672 (10.1)	390 (2.3)	2998 (1.7)	866 (16.1)	5996 (11.4)	75 (3.2)	561 (2.5)
Chronic pulmonary disease	5620 (5.5)	16002 (4.0)	1412 (0.3)	1981 (0.2)	1965 (11.8)	11453 (7.0)	300 (1.7)	1974 (1.1)	745 (13.9)	5180 (9.8)	70 (3.0)	637 (2.8)
Chronic viral hepatitis B	4501 (4.4)	17375 (4.3)	2673 (0.6)	4511 (0.5)	248 (1.5)	3949 (2.4)	56 (0.3)	633 (0.4)	38 (0.7)	869 (1.6)	2 (0.1)	21 (0.1)
Cirrhosis	1237 (1.2)	3764 (0.9)	242 (0.1)	531 (0.1)	432 (2.6)	2661 (1.6)	41 (0.2)	287 (0.2)	150 (2.8)	873 (1.7)	11 (0.5)	45 (0.2)
Dementia	3210 (3.2)	6642 (1.6)	544 (0.1)	629 (0.1)	1694 (10.2)	6575 (4.0)	273 (1.6)	1076 (0.6)	783 (14.6)	2960 (5.6)	126 (5.4)	453 (2.0)
Depression	5767 (5.7)	19416 (4.8)	5347 (1.3)	22970 (2.8)	852 (5.1)	4874 (3.0)	162 (0.9)	2936 (1.7)	217 (4.0)	1255 (2.4)	15 (0.6)	92 (0.4)
Diabetes	61123 (60.3)	267453 (66.1)	11482 (2.8)	27563 (3.3)	8277 (49.6)	106341 (64.7)	597 (3.4)	12251 (7.1)	2455 (45.7)	32410 (61.5)	98 (4.2)	1932 (8.5)
Hypertension	83332 (82.2)	348691 (86.2)	47035 (11.4)	166249 (20.2)	12777 (76.6)	141176 (85.9)	2177 (12.6)	41810 (24.3)	3977 (74.0)	45484 (86.3)	359 (15.4)	7392 (32.7)
Hyperthyroidism	4966 (4.9)	21506 (5.3)	3345 (0.8)	16197 (2.0)	663 (4.0)	5933 (3.6)	91 (0.5)	1947 (1.1)	177 (3.3)	1648 (3.1)	7 (0.3)	103 (0.5)
Inflammatory bowel disease	180 (0.2)	642 (0.2)	237 (0.1)	1299 (0.2)	34 (0.2)	109 (0.1)	27 (0.2)	139 (0.1)	6 (0.1)	27 (0.1)	0 (0.0)	4 (0.0)
Irritable bowel syndrome	317 (0.3)	953 (0.2)	306 (0.1)	598 (0.1)	23 (0.1)	225 (0.1)	5 (0.0)	86 (0.1)	5 (0.1)	67 (0.1)	0 (0.0)	2 (0.0)
Parkinson's disease	1163 (1.1)	3155 (0.8)	263 (0.1)	644 (0.1)	489 (2.9)	1803 (1.1)	91 (0.5)	268 (0.2)	257 (4.8)	754 (1.4)	37 (1.6)	63 (0.3)
Peptic ulcer disease	2559 (2.5)	8789 (2.2)	714 (0.2)	1011 (0.1)	593 (3.6)	5577 (3.4)	59 (0.3)	619 (0.4)	193 (3.6)	2125 (4.0)	11 (0.5)	139 (0.6)
Peripheral vascular disease	459 (0.5)	1697 (0.4)	53 (0.0)	151 (0.0)	112 (0.7)	899 (0.5)	7 (0.0)	51 (0.0)	34 (0.6)	332 (0.6)	1 (0.0)	10 (0.0)
Psoriasis	608 (0.6)	1934 (0.5)	337 (0.1)	716 (0.1)	91 (0.5)	610 (0.4)	16 (0.1)	103 (0.1)	23 (0.4)	157 (0.3)	0 (0.0)	6 (0.0)
Rheumatoid arthritis	1229 (1.2)	4004 (1.0)	959 (0.2)	2631 (0.3)	241 (1.4)	1405 (0.9)	66 (0.4)	823 (0.5)	62 (1.2)	406 (0.8)	8 (0.3)	91 (0.4)

(*Continued on next page*)

Table 1. *Continued*

	COVID-19 infection				COVID-19 related hospitalization				COVID-19 related mortality			
	MM		No MM		MM		No MM		MM		No MM	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Schizophrenia	2032 (2.0)	5097 (1.3)	1583 (0.4)	8053 (1.0)	446 (2.7)	1089 (0.7)	118 (0.7)	804 (0.5)	138 (2.6)	264 (0.5)	23 (1.0)	24 (0.1)
Severe constipation	14888 (14.7)	45992 (11.4)	5971 (1.5)	11249 (1.4)	3130 (18.8)	22483 (13.7)	410 (2.4)	2879 (1.7)	942 (17.5)	7949 (15.1)	67 (2.9)	507 (2.2)
Atrial fibrillation	8143 (8.0)	24553 (6.1)	1101 (0.3)	2659 (0.3)	2679 (16.1)	16279 (9.9)	194 (1.1)	1137 (0.7)	1172 (21.8)	6533 (12.4)	55 (2.4)	285 (1.3)
Congestive heart failure	6759 (6.7)	19013 (4.7)	502 (0.1)	1168 (0.1)	2659 (15.9)	15623 (9.5)	121 (0.7)	907 (0.5)	1162 (21.6)	7021 (13.3)	36 (1.5)	280 (1.2)
Chronic kidney disease	14435 (14.2)	54604 (13.5)	2617 (0.6)	4902 (0.6)	4429 (26.6)	36242 (22.1)	422 (2.4)	1322 (0.8)	1922 (35.8)	14345 (27.2)	139 (6.0)	269 (1.2)
Epilepsy	1339 (1.3)	3121 (0.8)	969 (0.2)	4765 (0.6)	467 (2.8)	1160 (0.7)	162 (0.9)	533 (0.3)	138 (2.6)	469 (0.9)	13 (0.6)	36 (0.2)
Multiple sclerosis	131 (0.1)	424 (0.1)	109 (0.0)	585 (0.1)	26 (0.2)	119 (0.1)	9 (0.1)	82 (0.0)	7 (0.1)	23 (0.0)	1 (0.0)	3 (0.0)
Myocardial infarction	2939 (2.9)	8772 (2.2)	704 (0.2)	1436 (0.2)	978 (5.9)	5814 (3.5)	77 (0.4)	884 (0.5)	650 (12.1)	2491 (4.7)	45 (1.9)	207 (0.9)
Stroke or TIA	9824 (9.7)	36301 (9.0)	1402 (0.3)	2777 (0.3)	2617 (15.7)	21003 (12.8)	221 (1.3)	1887 (1.1)	1044 (19.4)	8081 (15.3)	69 (3.0)	528 (2.3)
Renin-angiotensin-system agents	50068 (49.4)	209628 (51.8)	29684 (7.2)	108748 (13.2)	7649 (45.9)	85531 (52.1)	2489 (14.4)	31356 (18.2)	2248 (41.9)	26687 (50.6)	453 (19.5)	6083 (26.9)
Beta blockers	28791 (28.4)	111484 (27.6)	22072 (5.4)	76160 (9.3)	5563 (33.4)	48040 (29.2)	1977 (11.4)	21875 (12.7)	1893 (35.2)	15269 (29.0)	403 (17.3)	4014 (17.7)
Calcium channel blockers	63269 (62.4)	266317 (65.8)	48488 (11.8)	172135 (20.9)	9662 (57.9)	108146 (65.8)	3881 (22.4)	50086 (29.2)	3062 (57.0)	34428 (65.3)	919 (39.5)	9927 (43.9)
Diuretics	14141 (13.9)	39706 (9.8)	6339 (1.5)	16364 (2.0)	4657 (27.9)	23692 (14.4)	1374 (7.9)	7850 (4.6)	2170 (40.4)	9104 (17.3)	471 (20.3)	1923 (8.5)
Nitrates	7672 (7.6)	20517 (5.1)	5920 (1.4)	14443 (1.8)	2321 (13.9)	13169 (8.0)	765 (4.4)	7000 (4.1)	931 (17.3)	5183 (9.8)	169 (7.3)	1702 (7.5)
Lipid lowering agents	61764 (60.9)	264262 (65.3)	47223 (11.5)	159989 (19.4)	9394 (56.3)	109489 (66.6)	3633 (21.0)	52232 (30.4)	2782 (51.8)	34519 (65.5)	648 (27.9)	10158 (44.9)
Oral anticoagulants	5022 (5.0)	14163 (3.5)	2450 (0.6)	6529 (0.8)	1665 (10.0)	10208 (6.2)	471 (2.7)	3537 (2.1)	635 (11.8)	3993 (7.6)	92 (4.0)	859 (3.8)
Antiplatelets	25832 (25.5)	91146 (22.5)	20304 (4.9)	56932 (6.9)	6684 (40.1)	51199 (31.2)	2936 (16.9)	26754 (15.6)	2606 (48.5)	19220 (36.5)	766 (32.9)	6679 (29.5)
Immunosuppressants	1071 (1.1)	2812 (0.7)	1728 (0.4)	8641 (1.1)	353 (2.1)	973 (0.6)	271 (1.6)	1246 (0.7)	377 (7.0)	226 (0.4)	129 (5.5)	101 (0.4)
Insulin	8035 (7.9)	22114 (5.5)	3570 (0.9)	10883 (1.3)	2416 (14.5)	11523 (7.0)	522 (3.0)	3196 (1.9)	1792 (33.4)	3962 (7.5)	358 (15.4)	566 (2.5)
Anti-diabetic drugs	45165 (44.5)	196390 (48.5)	17558 (4.3)	52285 (6.4)	5846 (35.1)	76208 (46.4)	1494 (8.6)	18794 (10.9)	1644 (30.6)	22125 (42.0)	278 (12.0)	3157 (14.0)

All parameters are expressed in either frequency (percentage) or mean (SD).
MM = multimorbidity.

Table 2. Vaccine effectiveness against COVID-19-related outcomes and mortality among individuals with different vaccination status

		1 dose only		2 doses only		3 doses			
	Unvaccinated	BNT162b2	CoronaVac	All BNT162b2	All CoronaVac	All BNT162b2	All CoronaVac	B-B-C	C-C-B
COVID-19 infection									
MM									
Case	25390	2981	15628	14781	27071	4752	8591	72	2161
Control	81703	13927	51934	67881	99073	36747	39895	333	13154
VE %	REF	31.5 (28.6–34.4)	−0.1 (−2.4 to 2.2)	29.7 (27.9–31.3)	9.1 (7.2–11.0)	58.8 (57.3–60.2)	29.4 (27.3–31.4)	33.1 (13.5–48.3)	47.3 (44.7–49.9)
No MM									
Case	43409	16799	26013	132097	94026	36094	49088	559	13400
Control	97989	39176	50304	257530	143436	120901	80308	1137	32063
VE %	REF	1.9 (−0.3 to 4.0)	−21.9 (−24.3 to −19.5)	−15.4 (−17.0 to −13.9)	−54.0 (−56.3 to −51.8)	33.4 (32.3–34.5)	−37.7 (−40.1 to −35.4)	−5.9 (−17.5 to 4.6)	6.4 (4.1–8.6)
COVID-19 related hospitalization									
MM									
Case	8859	507	3373	950	2410	181	312	3	80
Control	49000	5177	26807	19587	39029	9258	12042	92	3298
VE %	REF	49.7 (44.5–54.4)	27.4 (24.1–30.5)	74.9 (73.0–76.6)	64.9 (63.1–66.6)	90.4 (88.9–91.8)	86.2 (84.5–87.7)	87.1 (59.1–96.0)	87.9 (84.8–90.4)
No MM									
Case	6249	670	2463	3215	3339	514	713	9	161
Control	35927	7052	16751	41066	35168	15815	15123	170	4746
VE %	REF	49.7 (45.2–53.9)	11.7 (6.9–16.2)	59.0 (56.9–60.9)	46.4 (43.9–48.9)	83.8 (82.2–85.3)	75.0 (72.8–77.0)	75.3 (51.5–87.4)	82.9 (79.9–85.5)
COVID-19 related mortality									
MM									
Case	3688	87	962	103	483	10	34	0	4
Control	17836	1565	9946	4726	12139	2309	3390	18	786
VE %	REF	73.4 (66.6–78.9)	48.9 (44.6–52.9)	89.3 (86.8–91.3)	79.2 (76.9–81.3)	97.9 (96.0–98.9)	94.9 (92.7–96.4)	NA	97.5 (93.2–99.1)
No MM									
Case	1450	41	485	56	270	12	7	0	4
Control	6924	637	3806	2279	5115	1497	1846	23	497
VE %	REF	76.3 (66.4–83.3)	39.1 (31.3–45.9)	91.3 (88.4–93.5)	77.1 (73.5–80.2)	97.5 (95.5–98.6)	98.6 (97.1–99.4)	NA	97.2 (92.3–99.0)

MM, multimorbidity; VE, vaccination effectiveness; CI, confidence interval.

Table 3. Vaccine effectiveness against COVID-19-related outcomes and mortality among individuals with different vaccination status stratified by number of morbidities

	1 dose only		2 doses only		3 doses			
	BNT162b2	CoronaVac	All BNT162b2	All CoronaVac	All BNT162b2	All CoronaVac	B-B-C	C-C-B
COVID-19 infection								
MM = 2	27.4 (23.0–31.5)	−11.1 (−15.0 to −7.3)	18.8 (16.1–21.5)	−8.0 (−11.2 to −4.9)	52.2 (50.1–54.3)	17.5 (14.3–20.5)	22.3 (−4.8 to 42.4)	40.0 (36.2–43.5)
MM = 3	35.6 (27.4–42.9)	5.9 (−0.5 to 11.8)	37.2 (32.4–41.6)	21.0 (16.1–25.6)	63.4 (59.0–67.2)	38.7 (32.8–44.0)	3.2 (−142.8 to 61.4)	51.0 (42.6–58.1)
MM = 4	29.2 (8.6–45.1)	4.1 (−8.9 to 15.6)	52.4 (42.8–60.5)	25.9 (15.8–34.8)	64.7 (51.7–74.2)	42.0 (25.4–54.9)	−90372736.2 (-Inf to 100.0)	61.5 (36.9–76.5)
MM ≥ 5	47.1 (25.5–62.4)	21.3 (7.6–33.0)	42.8 (25.0–56.4)	46.6 (36.3–55.3)	72.1 (54.3–82.9)	64.8 (45.7–77.2)	to NA	66.4 (21.4–85.6)
COVID-19 related hospitalization								
MM = 2	48.5 (39.2–56.5)	21.4 (15.0–27.3)	74.5 (71.5–77.2)	61.6 (58.4–64.6)	90.3 (87.9–92.1)	83.7 (80.8–86.1)	79.6 (13.3–95.2)	87.9 (83.3–91.3)
MM = 3	47.4 (34.7–57.6)	32.8 (25.6–39.3)	75.5 (71.3–79.1)	66.5 (62.6–69.9)	90.6 (87.1–93.1)	88.6 (84.9–91.3)	69.3 (−344.7 to 97.9)	86.4 (77.8–91.7)
MM = 4	41.0 (16.8–58.1)	19.8 (6.7–31.1)	76.3 (68.0–82.4)	64.6 (57.5–70.5)	85.9 (73.7–92.4)	76.3 (62.7–84.9)	NA	87.5 (65.8–95.4)
MM ≥ 5	59.2 (39.1–72.6)	36.6 (24.4–46.8)	70.6 (58.3–79.3)	66.7 (58.4–73.3)	84.7 (65.8–93.1)	83.1 (65.2–91.8)	NA	75.9 (34.1–91.2)
COVID-19 related mortality								
MM = 2	66.8 (48.9–78.5)	46.4 (36.7–54.6)	93.8 (90.3–96.0)	83.5 (79.7–86.7)	98.8 (96.2–99.6)	96.1 (92.9–97.9)	NA	98.8 (91.3–99.8)
MM = 3	80.4 (66.8–88.4)	50.6 (40.5–59.0)	85.4 (78.2–90.2)	75.5 (69.4–80.5)	95.8 (88.4–98.5)	94.3 (88.3–97.2)	NA	NA
MM = 4	80.1 (56.2–91.0)	42.5 (24.4–56.2)	87.1 (74.6–93.4)	75.7 (66.3–82.5)	96.4 (71.9–99.5)	97.2 (86.7–99.4)	NA	99.1 (87.4–99.9)
MM ≥ 5	45.6 (−10.3 to 73.1)	52.2 (37.3–63.6)	83.5 (68.3–91.4)	75.6 (65.5–82.7)	NA	96.4 (73.6–99.5)	NA	92.3 (18.5–99.3)

MM, multimorbidity; VE, vaccination effectiveness; CI, confidence interval.

This study reports effectiveness estimates of both examined vaccines against COVID-19 overall regardless of technological platform, which is in line with the existing literature that more advanced doses are associated with better protection in older people.[9–11] Likewise, our results agree with similar studies in the literature examining the immunocompromised populations as well.[12] While multimorbidity is highly prevalent among older people, our novel analysis directly compares individuals with varying multimorbidity burdens. Our work is indeed the first study to demonstrate a higher effectiveness of COVID-19 vaccines against infection among people with a more complex multimorbidity burden compared with those with lesser or minimal such burden within the same population. This greater VE seen in people with greater multimorbidity burden is likely because the baseline unvaccinated risk of infection is intrinsically higher among people with multimorbidity, with a lower proportion of them being able to fend off the virus without the protection conferred by vaccination.[13] Individuals with multimorbidity have a higher baseline risk of COVID-19 infection due to their underlying health conditions. This higher baseline risk makes them more susceptible to the virus and increases their chances of getting infected. Besides, people with multimorbidity may have compromised immune systems, making it more difficult for them to fight off the virus without the protection provided by vaccination. This lower natural immunity also contributes to the higher baseline unvaccinated risk of infection in this population. The higher VE observed in individuals with multimorbidity can be attributed to the combination of their higher unvaccinated baseline risk and the added protection provided by the vaccine. The marginal VE for vaccination roll-outs to these particular people thus tends to be markedly higher. This finding serves as a strong justification for an early focus on those living with multimorbidity.

While there are no marked differences between those living with and without multimorbidity in terms of VE against hospitalization and mortality from COVID-19, it is important to highlight there is increasing evidence on the long-term sequalae of COVID-19, alternatively termed as long COVID syndrome.[14] It has been shown that regardless of disease severity, there is a significant risk of developing long-term

conditions following a SARS-CoV-2 infection.[15] Therefore, a comprehensive evaluation of risks and benefits of vaccines must look beyond acute outcomes and consider the medium-to longer-term.

There are clear strengths to this study. First, the HA EHR covers the whole territory of Hong Kong and ensures a good representativeness of the sample. Second, the Hong Kong Government is solely responsible for the roll-out of COVID-19 vaccines with detailed documentation of each inoculation, and the data linkage between vaccination and EHR is therefore very accurate.

To conclude, we found significant COVID-19 VE against a positive COVID-19 test result among older people with increased multimorbidity burden. This finding supports policies to prioritize people living with multimorbidity in the roll-out of vaccines, such as future booster doses amid emerging epidemics.

Limitations of the study

Several limitations are worthy of mention. First, the list of component diseases of multimorbidity is not exhaustive, although the current list should have covered the most prevalent chronic conditions in the population. Previous research suggests that prevalence estimates tend not to change significantly with lists consisting of 12 or more diseases.[16] Second, a simple count of diseases does not take severity and patterns of disease combinations into consideration. However, cases and controls were matched by Charlson Comorbidity Index, which was calibrated against the risk of subsequent healthcare use based on diseases and their severity. Third, there may be unreported COVID-19 cases among the controls. Fourth, there may be a potential bias arising from the same treatment for symptomatic versus asymptomatic cases.[17–19] Fifth, vaccine uptake is also likely more inseparable with a higher adherence to social distancing and personal hygiene practices particularly among those living with multimorbidity, which might have partially confounded the association. Lastly, the Hong Kong population is predominantly Chinese, and the generalizability of the findings may need to be substantiated by other data sources.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

F.T.T.L., E.Y.F.W., E.W.Y.C., I.C.K.W., and V.K.C.Y. designed and directed this study. E.W.Y.C. and I.C.K.W. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. E.Y.F.W., F.T.T.L., C.I.Y.C., and V.K.C.Y. performed the acquisition and analysis, wrote the algorithm software, and drafted the manuscript. All the authors reviewed, edited, and approved the manuscript.

DECLARATION OF INTERESTS

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REFERENCES

1. Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S., and Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet *380*, 37–43. https://doi.org/10.1016/s0140-6736(12)60240-2.
2. Afshar, S., Roderick, P.J., Kowal, P., Dimitrov, B.D., and Hill, A.G. (2015). Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys. BMC Publ. Health *15*, 776. https://doi.org/10.1186/s12889-015-2008-7.
3. Makovski, T.T., Schmitz, S., Zeegers, M.P., Stranges, S., and van den Akker, M. (2019). Multimorbidity and quality of life: systematic literature review and meta-analysis. Ageing Res. Rev. *53*, 100903.
4. Emerging Risk Factors Collaboration, Di Angelantonio, E., Kaptoge, S., Wormser, D., Willeit, P., Butterworth, A.S., O'Keeffe, L.M., O'Keeffe, L.M., Gao, P., Wood, A.M., et al. (2015). Association of cardiometabolic multimorbidity with mortality. JAMA *314*, 52–60.
5. Norris, T., Razieh, C., Zaccardi, F., Yates, T., Islam, N., Gillies, C.L., Chudasama, Y.V., Rowlands, A.V., Davies, M.J., McCann, G.P., et al. (2022). Impact of cardiometabolic multimorbidity and ethnicity on cardiovascular/renal complications in patients with COVID-19. Heart *108*, 1200–1208. https://doi.org/10.1136/heartjnl-2021-320047.
6. Lai, F.T.T., Huang, L., Chui, C.S.L., Wan, E.Y.F., Li, X., Wong, C.K.H., Chan, E.W.W., Ma, T., Lum, D.H., Leung, J.C.N., et al. (2022). Multimorbidity and adverse events of special interest associated with Covid-19 vaccines in Hong Kong. Nat. Commun. *13*, 411–418.
7. Xiao, J., Cheung, J.K., Wu, P., Ni, M.Y., Cowling, B.J., and Liao, Q. (2022). Temporal changes in factors associated with COVID-19 vaccine hesitancy and uptake among adults in Hong Kong: Serial cross-sectional surveys. Lancet Reg. Health. West. Pac. *23*, 100441. https://doi.org/10.1016/j.lanwpc.2022.100441.
8. Taylor, L. (2022). Covid-19: Hong Kong reports world's highest death rate as zero covid strategy fails. BMJ *376*, o707. https://doi.org/10.1136/bmj.o707.
9. Au, W.Y., and Cheung, P.P.H. (2022). Effectiveness of heterologous and homologous covid-19 vaccine regimens: living systematic review with network meta-analysis. Br. Med. J. *377*, e069989. https://doi.org/10.1136/bmj-2022-069989.
10. Grewal, R., Kitchen, S.A., Nguyen, L., Buchan, S.A., Wilson, S.E., Costa, A.P., and Kwong, J.C. (2022). Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: test negative design study. Br. Med. J. *378*, e071502. https://doi.org/10.1136/bmj-2022-071502.
11. Wright, B.J., Tideman, S., Diaz, G.A., French, T., Parsons, G.T., and Robicsek, A. (2022). Comparative vaccine effectiveness against severe COVID-19 over time in US hospital administrative data: a case-control study. Lancet Respir. Med. *10*, 557–565. https://doi.org/10.1016/s2213-2600(22)00042-x.
12. Di Fusco, M., Lin, J., Vaghela, S., Lingohr-Smith, M., Nguyen, J.L., Scassellati Sforzolini, T., Judy, J., Cane, A., and Moran, M.M. (2022). COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies. Expert Rev. Vaccines *21*, 435–451.
13. Chudasama, Y.V., Gillies, C.L., Appiah, K., Zaccardi, F., Razieh, C., Davies, M.J., Yates, T., and Khunti, K. (2020). Multimorbidity and SARS-CoV-2 infection in UK Biobank. Diabetes Metabol. Syndr. *14*, 775–776. https://doi.org/10.1016/j.dsx.2020.06.003.
14. Ballering, A.V., van Zon, S.K.R., olde Hartman, T.C., and Rosmalen, J.G.M.; Lifelines Corona Research Initiative (2022). Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet *400*, 452–461. https://doi.org/10.1016/S0140-6736(22)01214-4.
15. Blomberg, B., Mohn, K.G.-I., Brokstad, K.A., Zhou, F., Linchausen, D.W., Hansen, B.-A., Lartey, S., Onyango, T.B., Kuwelker, K., Sævik, M., et al. (2021). Long COVID in a prospective cohort of home-isolated patients. Nat. Med. *27*, 1607–1613. https://doi.org/10.1038/s41591-021-01433-3.
16. Fortin, M., Stewart, M., Poitras, M.-E., Almirall, J., and Maddocks, H. (2012). A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. Ann. Fam. Med. *10*, 142–151. https://doi.org/10.1370/afm.1337.
17. Geneletti, S., Richardson, S., and Best, N. (2009). Adjusting for selection bias in retrospective, case–control studies. Biostatistics *10*, 17–31.
18. Ortiz-Brizuela, E., Carabali, M., Jiang, C., Merckx, J., Talbot, D., and Schnitzer, M.E. (2023). Potential Biases in Test-Negative Design Studies of COVID-19 Vaccine Effectiveness Arising from the Inclusion of Asymptomatic Individuals. Preprint at medRxiv. https://doi.org/10.1101/2023.11.16.23298633.
19. Sullivan, S.G., Khvorov, A., Huang, X., Wang, C., Ainslie, K.E.C., Nealon, J., Yang, B., Cowling, B.J., and Tsang, T.K. (2023). The need for a clinical case definition in test-negative design studies estimating vaccine effectiveness. npj Vaccines *8*, 118.
20. Wan, E.Y.F., Chui, C.S.L., Lai, F.T.T., Chan, E.W.Y., Li, X., Yan, V.K.C., Gao, L., Yu, Q., Lam, I.C.H., Chun, R.K.C., et al. (2022). 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. *22*, 64–72. https://doi.org/10.1016/S1473-3099(21)00451-5.

21. Chua, G.T., Kwan, M.Y.W., Chui, C.S.L., Smith, R.D., Cheung, E.C.-L., Ma, T., Leung, M.T.Y., Tsao, S.S.L., Kan, E., Ng, W.K.C., et al. (2022). Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination. Clin. Infect. Dis. *75*, 673–681. https://doi.org/10.1093/cid/ciab989.
22. Li, X., Tong, X., Yeung, W.W.Y., Kuan, P., Yum, S.H.H., Chui, C.S.L., Lai, F.T.T., Wan, E.Y.F., Wong, C.K.H., Chan, E.W.Y., et al. (2022). Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann. Rheum. Dis. *81*, 564–568. https://doi.org/10.1136/annrheumdis-2021-221571.
23. Li, X., Tong, X., Wong, I.C.K., Peng, K., Chui, C.S.L., Lai, F.T.T., Wan, E.Y.F., Wong, C.K.H., Leung, W.K., and Chan, E.W.Y. (2022). Lack of inflammatory bowel disease flare-up following two-dose BNT162b2 vaccine: a population-based cohort study. Gut *71*, 2608–2611. https://doi.org/10.1136/gutjnl-2021-326860.
24. Wan, E.Y.F., Chui, C.S.L., Wang, Y., Ng, V.W.S., Yan, V.K.C., Lai, F.T.T., Li, X., Wong, C.K.H., Chan, E.W.Y., Wong, C.S.M., et al. (2022). Herpes zoster related hospitalization after inactivated (CoronaVac) and mRNA (BNT162b2) SARS-CoV-2 vaccination: A self-controlled case series and nested case-control study. Lancet Reg. Health. West. Pac. *21*, 100393. https://doi.org/10.1016/j.lanwpc.2022.100393.
25. Xiong, X., Wong, C.K.H., Au, I.C.H., Lai, F.T.T., Li, X., Wan, E.Y.F., Chui, C.S.L., Chan, E.W.Y., Cheng, F.W.T., Lau, K.T.K., et al. (2022). Safety of Inactivated and mRNA COVID-19 Vaccination Among Patients Treated for Hypothyroidism: A Population-Based Cohort Study. Thyroid *32*, 505–514. https://doi.org/10.1089/thy.2021.0684.
26. Tonelli, M., Wiebe, N., Fortin, M., Guthrie, B., Hemmelgarn, B.R., James, M.T., Klarenbach, S.W., Lewanczuk, R., Manns, B.J., Ronksley, P., et al. (2015). Methods for identifying 30 chronic conditions: application to administrative data. BMC Med. Inf. Decis. Making *15*, 31. https://doi.org/10.1186/s12911-015-0155-5.
27. HKSAR Government (2021). Third Dose COVID-19 Vaccination Arrangements for Persons under Certain Groups. https://www.info.gov.hk/gia/general/202111/03/P2021110300536.htm.
28. HKSAR Government (2021). Further Expansion of COVID-19 Vaccination Arrangements from January 1. https://www.info.gov.hk/gia/general/202112/24/P2021122400509.htm.
29. Mesfin, Y., Chen, D., Bond, H., Lam, V., Cheung, J., Wong, J., Ali, S.T., Lau, E., Wu, P., and Leung, G. (2022). Epidemiology of Infections with SARS-CoV-2 Omicron BA. 2 Variant in Hong Kong, January-March 2022. Emerg Infect Dis. *28*, 1856–1858. https://doi.org/10.3201/eid2809.220613.
30. Charlson, M.E., Groll, D., To, T., Bombardier, C., and Wright, J. (2013). Charlson comorbidity index. Nurs. Res. *62*, 2.
31. Thompson, M.G., Burgess, J.L., Naleway, A.L., Tyner, H.L., Yoon, S.K., Meece, J., Olsho, L.E.W., Caban-Martinez, A.J., Fowlkes, A., Lutrick, K., et al. (2021). Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. MMWR Morb. Mortal. Wkly. Rep. *70*, 495–500. https://doi.org/10.15585/mmwr.mm7013e3.
32. Tanriover, M.D., Doğanay, H.L., Akova, M., Güner, H.R., Azap, A., Akhan, S., Köse, Ş., Erdinç, F.Ş., Akalın, E.H., Tabak, Ö.F., et al. (2021). Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet *398*, 213–222. https://doi.org/10.1016/s0140-6736(21)01429-x.
33. Feikin, D.R., Higdon, M.M., Abu-Raddad, L.J., Andrews, N., Araos, R., Goldberg, Y., Groome, M.J., Huppert, A., O'Brien, K.L., and Smith, P.G. (2022). Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet *399*, 924–944.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R version 4.0.3	R Foundation	www.R-project.org
Other		
Ethics Committee approval (Hong Kong)	Hospital Authority Central Institutional Review Board	CIRB-2021-005-4
Ethics Committee approval (Hong Kong)	Department of Health Ethics Committee	LM171/2021

RESOURCE AVAILABILITY

Lead contact

Requests for further information should be directed to and will be fulfilled by the lead contact, Professor Esther Wai Yin Chan (ewchan@hku.hk).

Materials availability

This study did not create new unique reagents.

Data and code availability

- The data reported in this study was provided by the Hospital Authority of Hong Kong and the Department of Health. and cannot be deposited in a public repository. Data will not be available for others as the data custodians have not given permission.
- This paper does not report the original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This case-control study was stratified by multimorbidity status. The study participants included men and women of all ages among the Hong Kong population, which is predominantly Chinese in ancestry and ethnicity. Those who had a previous COVID-19 infection before the index date or had received the fourth dose of COVID-19 vaccine were excluded from the analysis. Data were extracted from the electronic health database from the Hospital Authority (HA), which records information on patient demographics, diagnosis, prescriptions, and laboratory tests, in addition to real-time data support and monitoring across all clinics and hospitals in the HA for routine clinical management. As a statutory administrative organization in Hong Kong, the HA provides all public inpatient services and most public outpatient services. The COVID-19 infection and vaccination records were obtained from the Department of Health (DH) of the Government of the Hong Kong Special Administrative Region, China, which manages and retains all vaccination records in Hong Kong.

Datasets provided by the DH were linked to the HA database using anonymized unique Hong Kong Identity Card Numbers or other personal identification numbers. These databases use International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) diagnostic codes and International Classification of Primary Care, 2nd Edition (ICPC-2) for diagnosis documentation and have previously been applied in COVID-19 vaccines pharmacovigilance studies.[6,20–25]

METHOD DETAILS

Ethics considerations

As only anonymized secondary data analysis was involved, no informed consent was required. This research is approved by the Hospital Authority Central Institutional Review Board (ref: CIRB-2021-005-4) and the DH Ethics Committee (LM171/2021).

Multimorbidity

Multimorbidity was operationalized as the presence of two or more of a list of 30 chronic conditions as of, or prior to, the index date of the cases and controls.[26] Please see Table S1 for the corresponding ICD-9-CM and ICPC-2 codes for each of the conditions.

Exposure – Vaccination

Two COVID-19 vaccines, BNT162b2 and CoronaVac, have been provided by the Hong Kong government for emergency use in individuals aged 16 years or above since 23 February 2021. Starting from 11 November 2021, booster shots were in use among older people, and this was subsequently extended to the general population on 1 January 2022.[27,28] The public can choose either BNT16b2 or CoronaVac

as their priming first dose, but the priming second dose has to be homologous, i.e., the same vaccine type as first dose. For the booster third dose, either a homologous or heterologous booster was permitted. Therefore, the COVID-19 vaccination status was categorized into nine groups according to the types of vaccine and the number of doses administered as follows: (i) unvaccinated, (ii) one dose of BNT162b2 only, (iii) one dose of CoronaVac only, (iv) two doses of BNT162b2 only, (v) two doses of CoronaVac only, (vi) three doses of BNT162b2, (vii) three doses of CoronaVac, (viii) two doses of BNT162b2 followed by a CoronaVac booster, and (ix) two doses of CoronaVac followed by a BNT162b2 booster.

Outcome – COVID-19 infection and complications

A positive COVID-19 case was defined based on the positive Polymerase Chain Reaction (PCR) test results. Subjects in the control group who only reported positive Rapid Antigen Test (RAT) results in the voluntary reporting platform online but without a valid positive RCR test result were excluded from the analysis. The outcomes of this study include (a) any COVID-19 infection; (b) hospital admission within 28 days of COVID-19 infection; (c) post-infection all-cause mortality, defined as all-cause mortality within 28 days after COVID-19 infection. All cases hospitalized for COVID-19 had been confirmed by a positive COVID-19 PCR test before admission. The information on all-cause mortality was provided by the Hong Kong Deaths Registry, which officially records all registered deaths of Hong Kong residents. The Hong Kong government has implemented extensive PCR testing for SARS-CoV-2 in public hospitals (mandatory) and clinics for close contacts with confirmed cases and those who presented with COVID-like symptoms. The government also set up territory-wide community testing centers to screen asymptomatic individuals and provide regular testing to various groups with a high risk of exposure, such as those working in nursing homes. The current database is therefore likely adequate to capture the vast majority of the covid-19 infection case.

Case and control selection

To assess the effectiveness of BNT162b2 and CoronaVac during the Omicron BA.2 outbreak, the inclusion period of each outcome in this study was from 1 January 2022 to 31 March 2022.[29] Matching procedure was applied for each outcome separately. Taking COVID-19 infection as an example, a case was defined as a patient with COVID-19 infection during the inclusion period. Control participants were selected from patients without COVID-19 infection. The index date was the date of documented infection for the case, and the date of hospitalization or attendance at outpatient clinic for the control. For each case, up to 10 matched controls based on age (5-year band), sex, date of attendance (within three calendar days) and Charlson Comorbidity Index (0,1-2,3-4, $\geq$5)[30] were randomly selected.

QUANTIFICATION AND STATISTICAL ANALYSIS

Stratified by multimorbidity status (yes or no), the association between vaccination and each outcome was evaluated using conditional logistic regressions stratified by matched sets of the same age, sex, index date, and Charlson Comorbidity Index score and adjusted for chronic conditions used to count towards multimorbidity. The use of renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, oral anticoagulants, antiplatelets, immunosuppressants, anti-diabetic drugs and insulin was also adjusted. Vaccine effectiveness was calculated using (1 - adjusted odds ratio (OR)) x 100%, where the adjusted OR was obtained in the conditional logistic regressions.

Among those living with multimorbidity, we further estimated the vaccine effectiveness stratified by number of chronic conditions (2, 3, 4, $\geq$5). Subgroups analyses stratified by sex (male; female) and age (60-79, $\geq$80) were conducted.

There were three sensitivity analyses in this study. First, cases who developed infection less than 14 days after the second dose of vaccine were excluded, as vaccination was considered complete 14 days following vaccination.[31,32] Second, cases who received their last dose of vaccine more than 180 days before the index date were excluded, since waning immunity after vaccination is well-recognized after six months.[33] The third sensitivity analysis adopted the mandatory and voluntary reporting of positive either PCR test or positive RAT result to define cases.

All statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using R version 4.0.3 (www.R-project.org). Two investigators (VKCY, CIYC) conducted the statistical analyses independently for quality assurance. The absence of a diagnosis or medication record was considered the absence of the diseases or non-use of the medication. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists were followed to guide transparent reporting of the case-control study.[20]