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Letter to the Editor

Vaccine effectiveness of BNT162b2 and CoronaVac against SARS-CoV-2 Omicron BA.2 infection, hospitalisation, severe complications, cardiovascular disease and mortality in patients with diabetes mellitus: A case control study

Dear Editor,

In this journal, Yin and Li et al. (2022) examined the antibody efficacy of CoronaVac (an inactivated vaccine) and suggested that two doses of CoronaVac were insufficient in eliciting adequate antibody response against SARS-CoV-2 Omicron variant[1]. We in turn investigated the real-world effectiveness of the two vaccines that were employed in Hong Kong, namely CoronaVac and BNT162b2, in a group of patients with diabetes mellitus (DM), given their heightened susceptibility to COVID-19 infection and complications; yet limited literature is available for this specific population.

This case-control study extracted data using the population-level electronic health databases from the Hong Kong Hospital Authority (HA) and the Department of Health (DH) of the Government of the Hong Kong Special Administrative Region, China, and enrolled DM patients aged ≥12 years, who had received zero to three doses of BNT162b2 or CoronaVac, during January to March 2022. This period was principally driven by the Omicron BA.2 variant[2], and these databases have previously been applied in several COVID-19 pharmacovigilance studies[3-6]. 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. Each Polymerase Chain Reaction (PCR)-confirmed COVID-19 case was matched with up to 10 controls based on age, gender, and index date for each outcome independently. This study evaluated the vaccine effectiveness (VE) of each dose of BNT162b2 and CoronaVac against any COVID-19 infection, COVID-19-related hospital admission, ICU admission, incident cardiovascular disease (CVD), and all-cause mortality within 28 days after COVID-19 infection during the local outbreak dominated by Omicron BA.2 sublineage. VE was calculated using (1 - adjusted odds ratio (OR)) x 100%, where the adjusted OR was estimated using conditional logistic regression, adjusted for chronic comorbidities including hypertension, cancer, chronic kidney disease, respiratory disease, coronary heart disease, stroke, heart failure, and dementia, along with the use of chronic medications.

A total of 82,587 cases of COVID-19 infection, 10,241 cases of COVID-19 related hospital admission, 539 cases of ICU admission, 135 cases of post-infection incident CVD, and 2898 cases of all-cause mortality were identified. A positive dose-response relationship, between the number of BNT162b2 or CoronaVac doses received and VE, was demonstrated. The characteristics of cases and controls are summarized in Table 1. Table 2 shows the VE for each outcome. A positive dose-response relationship between the number of BNT162b2 or CoronaVac doses received and VE was demonstrated found. VE amongst DM patients against COVID-19 infection after the first dose of BNT162b2 and CoronaVac were 28.4% (95% CI: 24.8 - 31.7) and −6.1% (95% CI: −9.0 - −3.2), respectively. Highest VE against COVID-19 infection was observed in people who received three doses of BNT162b2 [54.8% (95% CI: 53.1 - 56.5) and three doses of CoronaVac [21.2% (95% CI: 18.6 - 23.6)] when compared to those who received fewer doses. VE was higher in terms of other outcomes, reaching 91.7% (95% CI: 89.9 - 93.2) and 86.1% (95% CI: 84.0 - 87.9) against COVID-19 related hospital admission; 87.1% (95% CI: 73.1 - 93.8) and 94.9% (95% CI:86.1 - 98.1) against ICU admission; 91.1% (95% CI: 61.2 - 98.0) and 46.3% (95% CI: −15.8 - 75.1) against incident CVD; and 98.4% (95% CI: 96.1 - 99.3) and 96.1% (95% CI: 93.6 - 97.6) against all-cause mortality in three-dose BNT162b2 recipients and three-dose CoronaVac recipients respectively, in comparison with unvaccinated DM patients. Patients who received two doses of CoronaVac with BNT162b2 as a booster had higher VE against COVID-19 infection [40.8% (95% CI: 37.7 - 43.8)] but had similar VE against hospitalisation, CVD and mortality compared to those who received three doses of CoronaVac. Due to a small number of people who received CoronaVac after two doses of BNT162b2 (n = 313), the VE against different outcomes between heterologous and homologous boosters in people receiving BNT162b2 could not be compared as the primary series.

This study specifically evaluates the real-world effectiveness of an mRNA (BNT162b2) and an inactivated virus (CoronaVac) COVID-19 vaccine against the Omicron BA.2 variant in a DM population. A clear dose-response relationship between the number of vaccine doses received and the magnitude of VE against COVID-19 infection, infection-related complications, and mortality has also been demonstrated. The low VE against COVID-19 infection of two-dose CoronaVac in this study was consistent with the findings from Yin and Li et al. (2022), which revealed a low level of neutralizing antibody against Omicron in healthy volunteers after two doses of CoronaVac[1]. Nonetheless, we noted a relatively high VE against severe COVID-19 disease, all-cause mortality, and incident CVD in booster dose BNT162b2 and CoronaVac recipients, suggesting that adaptive immunity, apart from humoral immunity, might have a more important role in this regard[7].

Another key finding of our study is the effect of vaccination on reducing the risk of developing cardiovascular complications after COVID-19 infection. This reinforced the importance of vaccination in the DM population, and booster shots are necessary to further boost the protection against COVID-19 complications. On the other hand, we observed that a heterologous booster dose of BNT162b2 after two doses of CoronaVac may be more effective than three doses of CoronaVac in our DM population. This is in line with prior studies which revealed a higher rise in antibody concentrations in BNT162b2 booster recipients as opposed to homologous booster recipients after two doses of CoronaVac in Brazil[8,9] and Hong Kong[10]. Given that limited people received heterologous boosters in this

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Table 1
Baseline characteristics of cases and controls. ICU: intensive care unit. All parameters are expressed in either number (percentage) or mean (SD).

Baseline characteristics	Infection		Hospitalisation		ICU admission or ventilatory support		CVD		All-cause mortality	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Number of individuals	82,587	329,560	10,241	100,320	539	5252	135	1335	2898	28,056
Age, years	67.82 (12.51)	67.84 (12.41)	77.69 (12.13)	77.69 (11.79)	76.13 (12.26)	76.30 (11.75)	76.67 (11.74)	76.34 (11.75)	82.86 (9.88)	82.70 (9.55)
Sex, male	44,435 (53.8)	177,349 (53.8)	5679 (55.5)	55,850 (55.7)	314 (58.3)	3052 (58.1)	68 (50.4)	672 (50.3)	1725 (59.5)	16,828 (60.0)
HbA1c,% (mmol/mol)	6.96 (53) (1.19)	6.91 (52) (1.07)	6.94 (52) (1.38)	6.91 (52) (1.12)	7.04 (53) (1.54)	6.92 (52) (1.14)	7.13 (54) (1.25)	6.90 (52) (1.00)	6.92 (52) (1.46)	6.92 (52) (1.17)
Charlson Comorbidity Index	3.61 (1.89)	3.56 (1.81)	5.32 (2.14)	5.10 (2.02)	5.22 (2.16)	5.04 (2.10)	4.30 (1.67)	4.16 (1.48)	6.30 (2.13)	5.98 (1.99)
Pre-existing comorbidities										
Hypertension	55,905 (67.7)	228,158 (69.2)	7359 (71.9)	78,251 (78.0)	384 (71.2)	4021 (76.6)	79 (58.5)	961 (72.0)	2143 (73.9)	23,086 (82.3)
Cancer	3680 (4.5)	12,546 (3.8)	947 (9.2)	9161 (9.1)	39 (7.2)	491 (9.3)	5 (3.7)	50 (3.7)	297 (10.2)	3245 (11.6)
Chronic Kidney Disease	4497 (5.4)	19,617 (6.0)	1729 (16.9)	16,151 (16.1)	114 (21.2)	885 (16.9)	12 (8.9)	78 (5.8)	666 (23.0)	6614 (23.6)
Respiratory disease	3006 (3.6)	9698 (2.9)	826 (8.1)	5736 (5.7)	41 (7.6)	294 (5.6)	2 (1.5)	35 (2.6)	282 (9.7)	2351 (8.4)
Coronary Heart Disease	8235 (10.0)	29,217 (8.9)	1791 (17.5)	12,930 (12.9)	103 (19.1)	722 (13.7)	0 (0.0)	0 (0.0)	721 (24.9)	4530 (16.1)
Stroke	7873 (9.5)	27,910 (8.5)	2203 (21.5)	16,319 (16.3)	111 (20.6)	818 (15.6)	0 (0.0)	0 (0.0)	877 (30.3)	5986 (21.3)
Heart Failure	3373 (4.1)	9111 (2.8)	1349 (13.2)	7153 (7.1)	73 (13.5)	413 (7.9)	0 (0.0)	0 (0.0)	560 (19.3)	3240 (11.5)
Dementia	917 (1.1)	1756 (0.5)	501 (4.9)	1771 (1.8)	27 (5.0)	93 (1.8)	5 (3.7)	5 (0.4)	234 (8.1)	857 (3.1)
Medication use										
Oral anti-diabetic drugs	62,696 (75.9)	254,833 (77.3)	7333 (71.6)	73,019 (72.8)	384 (71.2)	3831 (72.9)	109 (80.7)	996 (74.6)	1921 (66.3)	19,380 (69.1)
Insulin	10,795 (13.1)	31,178 (9.5)	2662 (26.0)	11,649 (11.6)	154 (28.6)	688 (13.1)	25 (18.5)	120 (9.0)	1606 (55.4)	3643 (13.0)
Renin-angiotensin-system agents	44,554 (53.9)	180,751 (54.8)	5630 (55.0)	58,366 (58.2)	306 (56.8)	3032 (57.7)	82 (60.7)	744 (55.7)	1468 (50.7)	16,290 (58.1)
Beta-blockers	23,306 (28.2)	91,318 (27.7)	3788 (37.0)	31,887 (31.8)	218 (40.4)	1744 (33.2)	48 (35.6)	387 (29.0)	1151 (39.7)	9155 (32.6)
Calcium channel blockers	47,403 (57.4)	193,345 (58.7)	6232 (60.9)	65,400 (65.2)	327 (60.7)	3399 (64.7)	77 (57.0)	882 (66.1)	1745 (60.2)	18,574 (66.2)
Diuretics	9895 (12.0)	29,073 (8.8)	2902 (28.3)	14,343 (14.3)	168 (31.2)	814 (15.5)	19 (14.1)	135 (10.1)	1211 (41.8)	5023 (17.9)
Nitrates	6064 (7.3)	16,781 (5.1)	1533 (15.0)	8436 (8.4)	87 (16.1)	426 (8.1)	13 (9.6)	46 (3.4)	544 (18.8)	2928 (10.4)
Lipid-lowering agents	59,383 (71.9)	246,231 (74.7)	7134 (69.7)	75,808 (75.6)	364 (67.5)	3909 (74.4)	89 (65.9)	969 (72.6)	1854 (64.0)	20,822 (74.2)
Oral anticoagulants	2907 (3.5)	8238 (2.5)	887 (8.7)	5166 (5.1)	48 (8.9)	259 (4.9)	7 (5.2)	40 (3.0)	299 (10.3)	1993 (7.1)
Antiplatelets	19,532 (23.7)	70,071 (21.3)	4321 (42.2)	31,051 (31.0)	236 (43.8)	1639 (31.2)	35 (25.9)	211 (15.8)	1511 (52.1)	10,058 (35.8)
Immunosuppressants	646 (0.8)	1811 (0.5)	210 (2.1)	561 (0.6)	13 (2.4)	38 (0.7)	2 (1.5)	4 (0.3)	197 (6.8)	143 (0.5)

Table 2
Vaccine effectiveness against COVID-19-related outcomes and mortality amongst individuals with different vaccination status. VE: vaccine effectiveness; CI: confidence interval; REF: reference level; CVD: cardiovascular disease; B-B-C: two doses of BNT162b2 followed by CoronaVac; C–C-B: two doses of CoronaVac followed by BNT162b2; NA: Not available due to insufficient number; ICU: intensive care unit. Vaccine effectiveness was adjusted by HbA1c, comorbidities (hypertension, cancer, chronic kidney disease, respiratory disease, coronary heart disease, stroke, heart failure, dementia), chronic medication uses in the past 90 days (renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, oral anticoagulants, antiplatelets, immunosuppressants, oral anti-diabetic drugs, and insulin).

Outcome	Unvaccinated	1 dose only		2 doses only		3 doses			
		BNT162b2	CoronaVac	All BNT162b2	All CoronaVac	All BNT162b2	All CoronaVac	B-B-C	C-C-B
Infection									
Case	16,707	2424	12,090	13,336	23,608	4339	7992	67	2024
Control	56,596	11,486	39,653	59,421	83,073	32,659	34,759	246	11,667
VE%	REF	27.8	−7.3	22.1	−0.3	54.2	19.8	12.1	39.9
(95% CI)		(24.2 - 31.2)	(−10.3 - −4.4)	(20.0 - 24.2)	(−2.7 - 2.1)	(52.4 - 55.9)	(17.2 - 22.3)	(−15.8 - 33.3)	(36.6 - 42.9)
Hospitalisation									
Case	5122	310	2151	639	1633	109	229	0	48
Control	27,368	3207	15,891	12,645	24,968	6052	7975	44	2170
VE%	REF	51.0	24.4	74.2	64.2	91.4	85.4	NA	89.5
(95% CI)		(44.5 - 56.8)	(19.9 - 28.7)	(71.7 - 76.4)	(61.8 - 66.4)	(89.5 - 92.9)	(83.2 - 87.3)		(85.9 - 92.2)
ICU admission or ventilatory support									
Case	271	21	120	23	90	8	5	0	1
Control	1421	194	852	695	1266	310	385	2	127
VE%	REF	44.6	16.1	82.3	58.1	86.3	94.8	NA	95.9
(95% CI)		(8.6 - 66.4)	(−7.9 - 34.7)	(72.1 - 88.8)	(45.0 - 68.1)	(71.5 - 93.4)	(85.8 - 98.1)		(70.3 - 99.4)
CVD									
Case	46	2	27	16	30	2	10	0	2
Control	296	43	174	198	357	113	124	0	30
VE%	REF	69.4	−3.1	50.3	48.4	90.9	46.3	NA	52.3
(95% CI)		(−35.8 - 93.1)	(−77.5 - 40.1)	(5.1 - 73.9)	(10.8 - 70.2)	(60.2 - 97.9)	(−16.0 - 75.1)		(−116.6 - 89.5)
All-cause mortality									
Case	1938	50	547	55	284	5	18	0	1
Control	8898	862	5092	2834	6640	1343	1911	18	458
VE%	REF	67.8	44.7	90.3	74.8	98.2	94.9	NA	98.7
(95% CI)		(55.8 - 76.5)	(37.6 - 51.1)	(86.9 - 92.9)	(70.7 - 78.3)	(95.5 - 99.3)	(91.6 - 96.9)		(90.4 - 99.8)

study, further studies are warranted to confirm our findings. By and large, both homologous and heterologous boosters were effective in protecting against severe COVID-19 diseases in the DM population.

There were several limitations in this study. Only patients with positive PCR and RAT results were required to report to the DH. Hence, we could not apply a test-negative case-control study design to the current dataset. There is a possibility that people with asymptomatic COVID-19 infections could be misclassified as controls, leading to bias in the estimates towards null. Meanwhile, we defined the need for ventilatory support merely based on the procedure codes recorded in the electronic database, hence may have been underestimated. ICU admissions may have been limited by bed availability, which were fully occupied during the peak of the outbreak. Lastly, we did not consider the effect of different health-seeking behaviours in T2DM patients on the risk of catching COVID-19 infection.

Overall, booster shots should be encouraged to reduce morbidity and mortality after COVID-19 infection in patients with diabetes.

Ethics approval

This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong (CIRB-2021–005–4) and the Department of Health Ethics Committee (LM171/2021).

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Author contributions

Concept and design: EYFW, AHYM, VKCY, ICKW, EWC

Acquisition, analysis, or interpretation of data: EYFW, AHYM, VKCY, BW, RZ, SNH, FTTL, CSLC, XL, CKHW, KCBT, CSL, ICKW, EWC

Drafting of the manuscript: EYFW, AHYM, VKCY, SNH

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: EYFW, VKCY, BW, RZ

Administrative, technical, or material support: ICKW, EWC

Supervision: ICKW, EWC

Declaration of Competing Interest

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Eric Yuk Fai Wan[1]
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Anna Hoi Ying Mok[1]
Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Vincent Ka Chun Yan[1]
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Boyuan Wang, Ran Zhang, Sabrina Nan Hong
Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Celine Sze Ling Chui
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Xue Li
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Carlos King Ho Wong
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
Department of Family Medicine and Primary Care, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Francisco Tsz Tsun Lai
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China

Kathryn Choon Beng Tan, Chak Sing Lau
Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Ian Chi Kei Wong**
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom
Aston Pharmacy School, Aston University, Birmingham B4 7ET, United Kingdom
Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Esther Wai Yin Chan*
Centre for Safe Medication Practice and research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The

University of Hong Kong, Hong Kong Special Administrative Region, China
Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China
Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

*Corresponding author at: Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, Li Ka Shing Faculty of Medicine, The University of Hong Kong, L02-56 2/F, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.
**Corresponding author at: Department of Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, Li Ka Shing Faculty of Medicine, The University of Hong Kong, L02-57 2/F, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.
E-mail addresses: wongick@hku.hk (I.C.K. Wong), ewchan@hku.hk (E.W.Y. Chan)
[1] Co-first authors with equal contributions.