Letter to the Editor

Title: 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

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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 attention being drawn to this specific population.

This case-control study extracted data using the population-level electronic health databases from Hong Kong Hospital Authority (HA) and the Department of Health (DH) of the Government of the Hong Kong Special Administrative Region, China in Hong Kong, 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. Through 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, 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 obtained in the conditional logistic regressions.

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 2,898 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. VE among 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 booster in people receiving BNT162b2 as the primary series could not be compared.

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 a prior study 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 similar findings against the Omicron variant from a study in Hong Kong (10). Given that limited people received heterologous boosters in this 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 are also several limitations. Only patients with positive PCR and RAT were required to report to the DH. Hence, the current dataset cannot apply a test negative case control study design. There is a possibility that people with asymptomatic COVID-19 infections could be misclassified as controls, leading to bias in the estimates towards the null. Meanwhile, we defined the need of ventilatory support merely based on the procedure codes recorded in the electronic database, and in such case underdiagnosis might have occurred. Moreover, ICU bed spaces 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 dose should be encouraged to reduce morbidity and mortality after COVID-19 infection in diabetic population.

Declaration of Competing Interest

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Government of the Hong Kong Special Administrative Region, and the Hong Kong Research Grants Council, outside the submitted work. FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, outside the submitted work. CSLC has received grants from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA, and Amgen; and personal fees from PrimeVigilance; outside the submitted work. XL has received research grants from the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region; 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. ICKW receives research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, National Institute for Health Research in England, European Commission, and the National Health and Medical Research Council in Australia; has received speaker fees from Janssen and Medice in the previous 3 years; and is an independent non-executive director of Jacobson Medical in Hong Kong. All other authors declare no competing interests. EWC reports grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region; honorarium from Hospital Authority; outside the submitted work.

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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