A Randomized Clinical Trial Using CoronaVac or BNT162b2 Vaccine as a Third Dose in Adults Vaccinated with Two Doses of CoronaVac

To the Editor:

CoronaVac is one of the World Health Organization–approved inactivated virus vaccines, and over 750 million doses have been administered in more than 40 countries. Phase three randomized clinical trials (RCTs) of CoronaVac showed efficacies against symptomatic illness of 50.65%, 65.30%, and 83.50% in Brazil, Indonesia, and Turkey, respectively (1). Since these efficacy studies assessed outcomes within a few months after vaccination, the impact of antibody waning on virus variants has not been assessed. Breakthrough infections, some leading to severe disease and death, have been reported in CoronaVac vaccinated adults and have raised concern (2). Our recent observational study showed that the immunogenicity of CoronaVac is much lower compared with the BNT162b2 mRNA vaccine, and we estimated that waning immunity would lead to a loss of protection within a few months (3, 4). A third vaccine dose was considered for CoronaVac vaccinated individuals. Here, we report the results of an RCT to compare the immunogenicity of using BNT162b2 and CoronaVac as the third dose for adults with low antibody response to two doses of CoronaVac.

Some of the results of these studies have been previously reported in the form of a preprint (medRxiv; [accessed 2021 Nov 3]; https://doi.org/10.1101/2021.11.02.21265843).

Methods

Of the 360 participants who had received two doses of CoronaVac as part of our previous study (3), 260 showed surrogate neutralization test (sVNT) results below 60% in their plasma specimens that were collected 1 month after the second dose. Eighty participants, aged 34–73 years, were randomly invited from the 260 participants and randomized to receive a third vaccine dose of either BNT162b2 or CoronaVac between August 18, 2021, and October 26, 2021. This clinical trial has been registered at ClinicalTrials.gov with identifier NCT04611243.

The primary outcome was antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) measured by sVNTs, plaque reduction neutralization tests (PRNTs), and N-terminal domain (NTD) ELISA in plasma samples collected 1 month after the third dose of vaccination, which was performed according to our previous study (3). The secondary outcome was the occurrence of adverse reactions within 7 days and 1 month after the third dose of vaccination. The standard deviation of the percentage of inhibition in the sVNT in the postvaccine plasma from our cohort for BNT1626 and CoronaVac was 3.45 and 16.72, respectively (3). Therefore, a sample size of 40 patients in each group was estimated to have over 90% power to detect a difference of 10% in sVNT by using a two-sided, unpaired *t* test.

Results

Additional details of the study design and the demographic information can be found at https://www.mect.cuhk.edu.hk/paper/Supporting-Information.pdf. The age and gender of the participants were not significantly different between the two groups (Table 1). Local and systemic adverse reactions were assessed and compared between the two groups (Table 1). More participants in the BNT162b2 (third dose) group reported pain ($P < 0.001$) and swelling ($P < 0.05$) at the injection site than those receiving CoronaVac as the third dose. Significantly more participants in the BNT162b2 (third dose) group complained of fatigue ($P < 0.01$) and muscle pain ($P < 0.05$) compared with the CoronaVac (third dose) group. However, none of these side effects were considered unacceptable by the participants.

We used sVNT (5), PRNT, and NTD ELISA to quantify levels of SARS-CoV-2–specific antibody from the plasma samples collected before vaccination, at 1 month after the second dose, and before and at 1 month after the third dose of vaccination. Antibody levels from vaccinees in the two groups were negative in sVNT before any vaccination, and the sVNT showed comparable results in the two groups at 1 month after the second dose, as expected. One month after the third dose of vaccination, the mean percentage of inhibition in the sVNT in the plasma for the BNT1626 and CoronaVac groups was 96.83% and 57.75%, respectively ($P < 0.0001$) (Figure 1A). The 90% plaque reduction neutralization ($PRNT_{90}$) geometric mean titers in the BNT162b2 and CoronaVac groups were 207.49 and 16.53, respectively (Figure 1B); and $PRNT_{50}$ geometric mean titers were 303.79 and 56.67,

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Table 1. Adverse Reactions after Receiving the Third Dose of Vaccination

	After Second Dose			After Third Dose		
	C,C,B	C,C,C	*P* Value	C,C,B	C,C,C	*P* Value
n	40	40		40	40	
Age (mean ± SD)				51.20 ± 8.79	51.50 ± 8.83	0.883*
Age (median, IQR)				51.50 (44.25–57)	50.00 (45.25–57)	0.969*
Male (female)				16 (24)	12 (28)	0.482*
Days between first and third dose				126.75	128.75	0.729*
Days between second and third dose				97.95	99.35	0.806*
Local reactions						
Pain	12	13	1.000	34	12	<0.001
Erythema	—	—	N.A.	2	0	0.494
Pruritus	—	—	N.A.	3	1	0.616
Swelling	—	—	N.A.	14	4	0.014
Systemic reactions						
Fever†	2	2	1.000	7	1	0.057
Fatigue	16	14	0.818	24	10	0.003
Diarrhea	2	3	1.000	1	0	1
Muscle pain	8	4	0.348	13	4	0.027
Nausea	—	—	N.A.	2	0	0.494
Headache	5	5	1.000	10	3	0.067
Cough	2	0	0.494	2	2	1
Anorexia	0	1	1.000	4	1	0.359
Hypoesthesia	—	—	N.A.	4	0	0.116
Dizziness	—	—	N.A.	6	2	0.264
Abdominal distention	—	—	N.A.	1	0	1
Peripheral edema	—	—	N.A.	1	0	1
Abdominal pain	—	—	N.A.	1	0	1
Vomiting	0	0	N.A.	0	0	N.A.
Drowsiness	—	—	N.A.	11	8	0.601
Joint pains	—	—	N.A.	6	3	0.482
Rash	—	—	N.A.	2	0	0.494
Palpitation	—	—	N.A.	5	2	0.432
Claimed no adverse effect	15	14	1.000	8	16	0.087

Definition of abbreviations: — = did not include in the questionnaire; B = BNT162b2; C = CoronaVac; C,C,B and C,C,C = vaccines used for the first, second, and third dose of vaccination; IQR = interquartile range; N.A. = not available.
*Analyzed by the Mann-Whitney *U* test. All other comparisons were analyzed by Fisher's exact test.
†Oral temperature above 37.5°C was considered a fever.

respectively. We had previously estimated that 50% of individuals would be protected from infection at a $PRNT_{90}$ titer of ⩾1:8.8 (3). Thus, all BNT162b2 and 35 (87.5%) of 40 CoronaVac-boosted individuals had protective levels of antibody at 1-month after a booster dose of vaccine. The level of NTD IgG antibodies was significantly higher in BNT162b2 recipients (Figure 1C).

We tested the sVNT activity in the plasma samples against different variants of concern. Percent inhibition of sVNT against the β, γ, and δ variants in the BNT162b2 group were 92.29%, 92.51%, and 95.33%, respectively, which are significantly higher than the CoronaVac group (β: 38.79%, $P < 0.0001$; γ: 32.22%, $P < 0.0001$; δ: 48.87%, $P < 0.0001$) (Figure 1D).

Discussion

Reinfection of SARS-CoV-2 in vaccinated individuals is now a public health concern, and breakthrough cases, some severe, are being reported by different countries (2, 6, 7).

Lower immunogenicity of CoronaVac vaccines was previously reported by us and others (3, 8). Two recent studies showed data on using BNT1626 or AZD1222 as the third dose for adults who had received two doses of CoronaVac (9, 10). However, neither study was randomized; they lacked longitudinal data to compare antibody levels before and after receiving the boosting dose, and adverse reactions were not evaluated. This is the first RCT to compare the immunogenicity and adverse effects of using BNT162b2 and CoronaVac as the third dose for vaccination in CoronaVac-immunized individuals, and we showed markedly higher antibody responses in those boosted by the BNT162b2 vaccine.

There were some limitations in our study. The sample size in our study was adequate for assessing immunogenicity but too small to fully assess rare adverse effects. Our study cohort only focused on those who had a poor response to the CoronaVac vaccine. Elderly and immunosuppressed patients, who are known to respond poorly to the coronavirus disease (COVID-19) vaccine, need to be investigated in future studies. T-cell responses were not assessed in this study.

In conclusion, our RCT showed that both CoronaVac and BNT162b2 vaccines boosted antibody responses in CoronaVac-immunized individuals, but BNT162B2 was markedly superior in immunogenicity. BNT162b2 not only elicited a higher level of

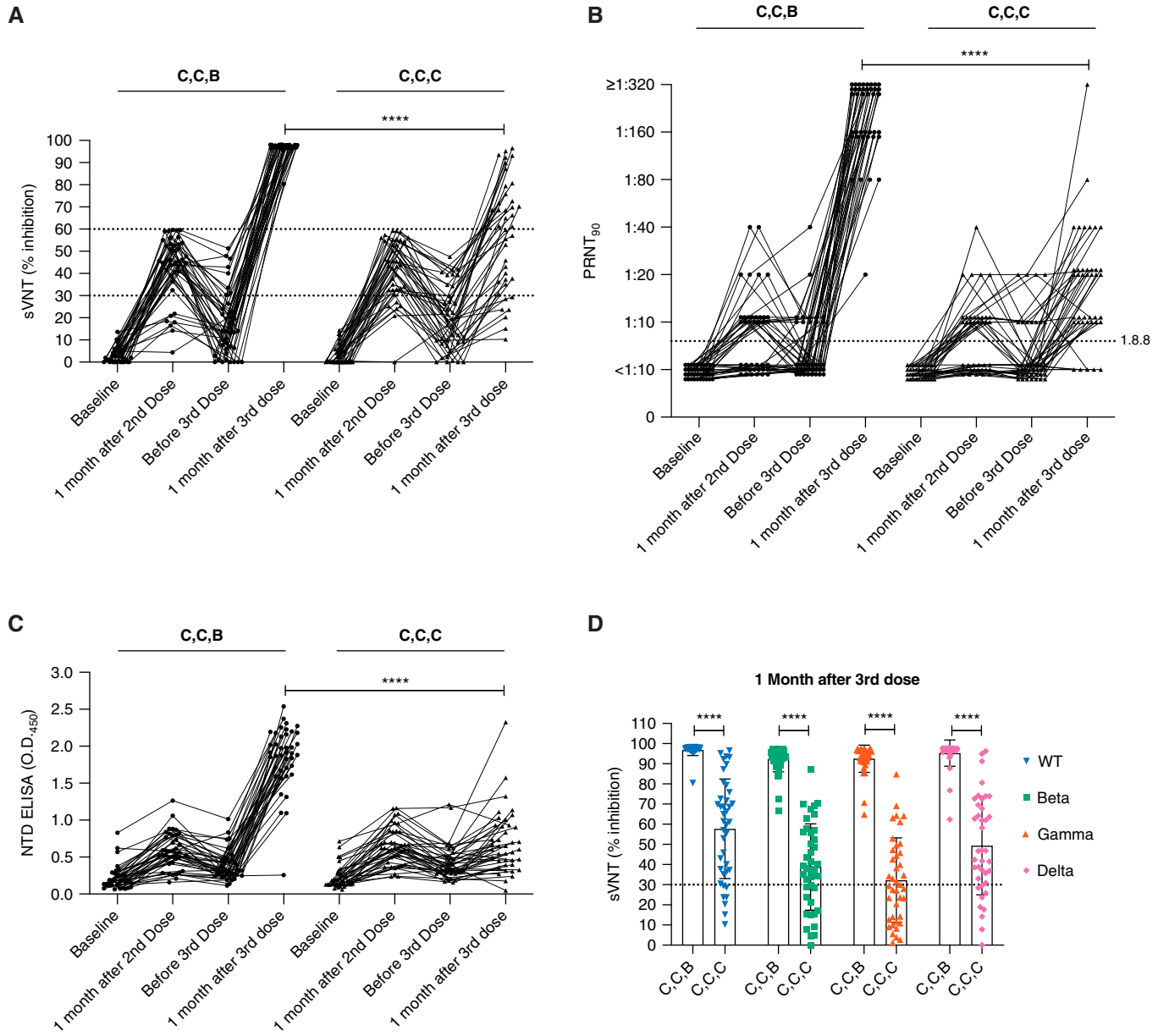

Figure 1. Antibody responses of individuals before and after the third dose of either BNT162b2 or CoronaVac. The levels of antibodies after the third dose of either BNT162b2 ($n = 40$) or CoronaVac ($n = 40$) were detected from the plasma collected from vaccinated adult individuals who had received two doses of CoronaVac. (*A*) Surrogate virus neutralization test (sVNT). (*B*) A 90% plaque reduction neutralization ($PRNT_{90}$). The titers have been jittered to avoid overlap. The dotted line denotes the threshold for protection of 50% of individuals from infection (3). (*C*) N-terminal domain (NTD)-specific immunoglobulin G (IgG) antibodies. (*D*) The percentage of inhibition against the wild-type, β, γ, and δ variants was compared between the two groups at 1 month after the third dose of vaccination. Comparison between groups was analyzed by the nonparametric Mann-Whitney *U* test. ****$P < 0.0001$. B = BNT162b2; C = CoronaVac; C,C,B and C,C,C = vaccines used for the first, second, and third dose of vaccination; WT = wild type.

SARS-CoV-2-specific antibodies but also led to higher levels of cross-neutralizing antibody levels to different variants of concern. The adverse reactions were mild and short lived. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Awake Extracorporeal Membrane Oxygenation for COVID-19–induced Acute Respiratory Distress Syndrome

To the Editor:

The outcome of patients with coronavirus disease (COVID-19) treated in ICUs is unsatisfying (1). Venovenous extracorporeal membrane oxygenation (vvECMO) can serve as a rescue strategy when patients deteriorate during invasive ventilation (2, 3). Using ECMO in awake patients without endotracheal intubation (awake-ECMO) has shown satisfying results in immunocompromised patients or as a bridge-to-transplant strategy (4–6) but bears ECMO-specific risks, such as bleeding and, specifically in awake patients, self-inflicted lung injury (7). Reports on awake-ECMO for COVID-19 are currently limited to case reports (8, 9).

Informed consent for the initiation of ECMO or awake-ECMO as part of intensive care measures for severe COVID-19 was obtained by the patient or legal representative. Patients undergoing ECMO were included in the prospective Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI) COVID ECMO registry, which has been approved by the ethics committee of the University of Würzburg (Ethik-Kommission der Universität Würzburg 131-20), the institutional review board of the board of physicians of the Federal State of Hessen (Ethik-Kommission bei der Landesärztekammer Hessen 2020-2135-AF and 2020-1653-zvBO, for the sites Kassel and Offenbach, respectively), the institutional review board of the board of physicians of the Federal State of Saarland (Ethikkommission der Ärztekammer des Saarlandes 208/20), and the ethical committee of Hannover Medical School (Ethikkommission der Medizinischen Hochschule Hannover 9411_BO_K_2020). Informed consent for the analysis of data was waived by the institutional review board because of the anonymous and retrospective analysis of data.

We report 18 adult patients with real-time RT-PCR–confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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Author Contributions: P.M.L., R.M.M., C.R., and S.M. drafted the study. C.R., H.M., P.M.L., and S.M. oversaw collection, review, and/or analysis of the data. C.R., P.M.L., and S.M. drafted the manuscript. H.M., R.N., C.L., D.G.-S., R.B., G.D., P.M., A.C., C.K., P.M.L., and R.M.M. revised the manuscript for important intellectual content. P.M.L. takes responsibility for the integrity of the work as a whole, from inception to published article. All authors have seen and approved the final version of the manuscript.

Availability of data and materials: Data can be provided on request addressed to the corresponding author. All data-sharing statements are subject to conformity with German data protection legislation and rules (Datenschutzgrundverordnung [DGSVO]).

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