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Heterologous prime-boost with the mRNA-1273 vaccine among CoronaVac-vaccinated healthcare workers in Indonesia

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Purpose: This study was performed to investigate humoral immune response and adverse events upon the heterologous prime-boost with a single dose of the mRNA-1273 vaccine among fully CoronaVac-vaccinated, infection-naïve healthcare workers in Indonesia.

Materials and Methods: One hundred twenty-five eligible healthcare workers were recruited from one hospital for this prospective cohort study. Blood collection was conducted twice, i.e., on 7 days before and 28 days after the booster vaccination. The titer of anti-SARS-CoV-2 receptor-binding domain (RBD) antibodies was quantified accordingly. The post-vaccination adverse event was recorded for both CoronaVac and mRNA-1273 vaccinations. Any breakthrough infection was monitored during the follow-up period. Wilcoxon matched-pairs signed rank test was used to test differences between groups.

Results: A significant increase was observed in the titer of anti-SARS-CoV-2 RBD antibodies upon receiving the mRNA-1273 booster (geometric mean titers of 65.57 and 47,445 U/mL in pre- and post-booster, respectively), supporting the argument to use heterologous prime-boost vaccination to improve the protection against COVID-19 in a high-risk population. The mRNA-1273 vaccine, however, caused a higher frequency of adverse events than the CoronaVac vaccine. Nonetheless, the adverse events were considered minor medical events and temporary as all subjects were not hospitalized and fully recovered. Of note, no breakthrough infection was observed during the follow-up to 12 weeks post-booster.

Conclusion: The heterologous prime-boost vaccination of healthcare workers with a single dose of the mRNA-1273 vaccine generated a significant elevation in humoral immune response towards RBD of SARS-CoV-2 and was associated with a higher frequency, but minor and transient, adverse events.

Keywords: Coronavirus disease 2019, Heterologous prime-boost, CoronaVac, 2019-nCoV vaccine mRNA-1273, Anti-SARS-CoV-2 RBD

Introduction

The current pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is partially controlled by the availability of COVID-19 vaccines. CoronaVac, an inactivated SARS-CoV-2 and aluminum hydroxide-adjuvanted vaccine (Sinovac Life Sciences, Beijing, China), was the first vaccine used in the COVID-19 emergency vaccination program in Indonesia [1,2]. The first group in Indonesia to be vaccinated was the healthcare workers (HCWs) as they have a higher risk of SARS-CoV-2 infection compared with the general population.

We recently had reported our findings on the magnitude and durability of the humoral immunity upon CoronaVac-vaccination among HCWs at various hospitals in Indonesia [2], demonstrating that two doses of CoronaVac generated seroconversion in most subjects (approximately 99%), based on the detection of anti-SARS-CoV-2 receptor-binding domain (RBD) antibodies. The titer was assessed because as an important subset of SARS-CoV-2-specific neutralizing antibodies, anti-SARS-CoV-2 RBD antibodies inhibit the interaction between the viral RBD and angiotensin-converting enzyme 2 on host cells, thus blocking the viral entry [3]. We also observed that despite the titer of anti-SARS-CoV-2 RBD antibodies having remained detected until day 98 among fully vaccinated HCWs, the titers had shown a declining trend from the second month after the 2nd dose of vaccination [2]. These findings were in line with the preprint data by Sinovac Life Sciences, reporting that the titer of neutralizing antibodies induced by two doses of CoronaVac declined after 6 to 8 months to below the threshold [4]. Taken together, this suggests a need among Indonesian HCWs to receive a booster vaccine to protect them against SARS-CoV-2 [5].

The common practice in booster vaccination is to use the same vaccine prescribed in the earlier priming, known as the homologous prime-boost strategy [6]. However, as it is already known that the current inactivated vaccines for COVID-19 are less immunogenic than the viral-vectored or nucleic acid vaccines, another approach was proposed, i.e., sequential immunization or heterologous prime-boost strategy [7,8]. In this approach, different platforms between primer and booster vaccines were utilized, with the notion that the booster vaccine should be more immunogenic than the primer vaccine. A pre-clinical data had supported this hypothesis, reporting that boosting with either subunit protein, viral-vectored, or mRNA vaccine after two doses of inactivated vaccine increased neutralizing antibody and IFN-γ levels in a murine model [9].

The heterologous prime-boost strategy, arguably, becomes crucial due to the emerging variants of SARS-CoV-2, particularly the Delta variant. It was reported that the Delta variant was more infectious than the Alpha variant as it was highly transmissible, it had a higher replication efficiency and it was less sensitive to neutralizing antibodies from recovered individuals [10,11]. The Delta variant indeed had spread rampantly across Indonesia, inflicting a surge of COVID-19 among its CoronaVac-vaccinated HCWs, causing it to become Asia's new pandemic epicenter during July–August 2021 and almost collapsing its public health services [12]. The Indonesian Ministry of Health, therefore, adopted the heterologous prime-boost strategy by providing a dose of the mRNA-1273 SARS-CoV-2 vaccine to approximately 1.5 million HCWs in Indonesia [13].

We, therefore, recruited fully CoronaVac-vaccinated and infection-naïve HCWs in the Siloam Hospitals Lippo Cikarang, Indonesia and measured titers of anti-SARS-CoV-2 RBD antibodies pre- and post-booster vaccination. In addition, reactogenicity within a week upon receiving the mRNA-1273 vaccine was recorded as well. We observed that the heterologous prime-boost strategy with the mRNA-1273 vaccine generated a significant elevation of anti-SARS-CoV-2 RBD antibodies and that the administration of the mRNA-1273 vaccine was associated with a higher frequency of, but temporary, adverse events.

Materials and Methods

Study subjects

A prospective cohort study was performed to assess humoral immune response and adverse effects upon booster with the mRNA-1273 SARS-CoV-2 vaccine among fully CoronaVac-vaccinated, infection-naïve HCWs at the Siloam Hospitals Lippo Cikarang (SHLC) from August to October 2021. This study was approved by the Mochtar Riady Institute for Nanotechnology Ethical Committee (#023/MRIN-EC/ECL/IX/202). During the period pre-CoronaVac vaccination, a routine seroprevalence survey using the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostic, Mannheim, Germany) had been conducted for all HCWs at SHLC. After the CoronaVac vaccination as well as during the follow-up period after the mRNA-1273 booster vaccination, all HCWs went for routine screening of COVID-19 (with rapid antigen screening and the routine reverse-transcriptase quantitative polymerase chain reaction assay) conducted by the hospital surveillance unit. All subjects had received two doses of CoronaVac (14-day interval between doses) in January and February 2021, hence the duration between the second dose of CoronaVac and the mRNA-1273 booster was between 5.5 and 6.5 months. The inclusion criteria were HCWs at the SHLC (1) who had completed two doses of CoronaVac vaccination and received the mRNA-1273 booster vaccine; (2) who were in healthy conditions; and (3) who consented to complete the online questionnaire. The exclusion criteria were HCWs (1) who had a history of confirmed COVID-19 before the mRNA-1273 booster vaccination; (2) who

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had chronic lung disease, cardiac disease, diabetes, liver disease, infection with human immunodeficiency virus, or other acute illness; or (3) who was pregnant. The minimum sample estimation was 32 subjects (calculated by paired sample numeric number, with Zα of 1.96 and Zβ of 0.8, based on the preliminary finding of titer of quantitative antibodies post-CoronaVac vaccination).

Booster vaccination

The booster vaccine was administered through an intramuscular injection in a volume of 0.5 mL containing 100 μg of mRNA-1273. A single dose of 100 μg was chosen due to the uncontrolled spread of the Delta variant in Indonesia from July to August 2021 [12] as well as to the safety profile, the high immunogenicity, and the effectiveness of this dosage against the Delta variant [14-16]. All subjects were continuously monitored by the contact-tracing team at the hospital to determine the occurrence of COVID-19.

Sera collection

Blood samples of each subject were collected twice: 7 days before and 28 days after the mRNA-1273 booster vaccination. The sera samples were subsequently aliquoted into multiple tubes and frozen at -80°C. Each tube was used only once after thawing.

Immunogenicity analysis

The Elecsys Anti-SARS-CoV-2 S assay, an electrochemiluminescence immunoassay, was used to measure the titer of anti-SARS-CoV-2 RBD antibodies. Briefly, this assay was performed according to the manufacturer's instruction by using the Cobas e 411 analyzer (Roche Diagnostic). The absolute titer was determined up to 125,000 U/mL. The cut-off was at 0.8 U/mL, in which a value below 0.8 U/mL was considered non-reactive for anti-SARS-CoV-2 RBD antibodies.

Reactogenicity analysis

Data on adverse events post-booster was obtained through an online survey and conducted on the seventh-day post-booster. The subjects were asked to recall and record all physical manifestations within the first seven days after the mRNA-1273 vaccination. The subjects were also asked to recall any past adverse events after the second dose of CoronaVac vaccination. The adverse events comprised local (pain, induration, and erythema at injection's site) and systemic symptoms (headache, arthralgia, myalgia, diarrhea, vomiting, nausea, fatigue, chills, and fever) [17]. For pain-related adverse events, i.e., local pain at injection site, headache, arthralgia, and myalgia, the numeric rating scale (0–10) was used. The results were subsequently classified into four groups: no pain (0), mild pain (1–3), moderate pain (4–6), and severe pain (7–10) [18].

Statistical analyses

Data analyses were performed using the IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented and the difference between the two groups was calculated using the Wilcoxon matched-pairs signed rank test with $p<0.05$. Data visualization was performed using the GraphPad Prism ver. 9.1.2 (GraphPad Software, San Diego, CA, USA).

Results

Demographic profiles

There were 125 fully CoronaVac-vaccinated, infection-naïve HCWs participating in this prospective cohort study, with their demographic profiles shown in Table 1. The median age of all subjects was 32 years old (range, 21 to 60 years old) and the majority were females (n=90, 72%). In addition, the median body mass index of the subjects was 23.44 kg/m^2 (range, 16.56 to 35.30 kg/m^2), indicating a slight overweight among subjects.

Table 1. Demographic profiles of healthcare workers participating in this study

Characteristic	Value
Age (yr)	32 (21–60)
20–29	54 (43.2)
30–39	34 (27.2)
40–49	28 (22.4)
≥50	9 (7.2)
Sex	
Male	35 (28.0)
Female	90 (72.0)
Body mass index (kg/m^2)	23.44 (16.56–35.30)
Underweight (≤18.5)	9 (7.2)
Normoweight (18.51–22.99)	43 (34.4)
Overweight (23–24.99)	26 (20.8)
Obesity I (25–29.99)	36 (28.8)
Obesity II (≥30)	11 (8.8)

Values are presented as median (range) or number (%).

Titer of anti-SARS-CoV-2 RBD antibodies

All participating HCWs underwent two rounds of testing for anti-SARS-CoV-2 RBD antibodies, i.e., on 7 days before and 28 days after receiving a single dose of mRNA-1273 booster vaccination, respectively. As shown in Table 2 and Fig. 1A–C, the geometric mean titer (GMT) of pre-booster antibodies among all subjects was 65.57 U/mL, in the GMT values among male and female subjects were 45.18 and 75.78 U/mL, respectively. The booster vaccination significantly elevated the titer of anti-SARS-CoV-2 RBD antibodies (approximately 700-fold increment) among the subjects, irrespective of the sex. Table 2 and Fig. 1A–C showed that the GMT of post-booster antibodies among all subjects was 47,445 U/mL, in the GMT values among male and female subjects were 39,174 and 51,115 U/mL, respectively. There was no significant difference in the GMT of post-booster antibodies between male and female subjects (p=0.6799) (Fig. 1D). Of note, all HCWs were followed up for 12 weeks post-booster and no breakthrough infection was observed thus far. Taken together, the booster with a single dose of the mRNA-1273 vaccine among CoronaVac-vaccinated HCWs generated a significant increase in anti-SARS-CoV-2 RBD antibodies, which might help to protect this high-risk population against COVID-19.

Local and systemic adverse events after vaccination

Data on any adverse event that occurred after vaccination with the CoronaVac or mRNA-1273 vaccine was obtained from all subjects. As displayed in Fig. 2, while the most common adverse event upon CoronaVac vaccination was local pain at the injection's site (73.6% of all participants), the systemic adverse events were much less reported by the subjects with the highest systemic symptom was myalgia (36.0% of all participants). In contrast, the same participants reported higher percentages of both local and systemic adverse events upon mRNA-1273 vaccination. The most common adverse event upon mRNA-1273 vaccination was local pain at the injection site as well (97.6% of all participants). Next, the intensity of pain-related adverse events, i.e., myalgia, arthralgia, headache, and local pain, were assessed with the numeric rating scale and the results were categorized into no, mild, moderate, or severe pain. Fig. 3 depicted that a majority of CoronaVac-vaccinated HCWs reported no or mild pain. A

Table 2. Geometric mean titer of anti-severe acute respiratory syndrome coronavirus 2 receptor-binding domain antibodies among the subjects

	Geometric mean titer		
	All	Male	Female
Pre-booster: 7 days before (U/mL)	65.57 (54.62–78.70)	45.18 (30.05–67.92)	75.78 (62.35–92.12)
Post-booster: 28 days after (U/mL)	47,445 (42,470–53,041)	39,174 (29,294–52,385)	51,115 (45,945–56,866)

Values are presented as mean (95% confidence interval).

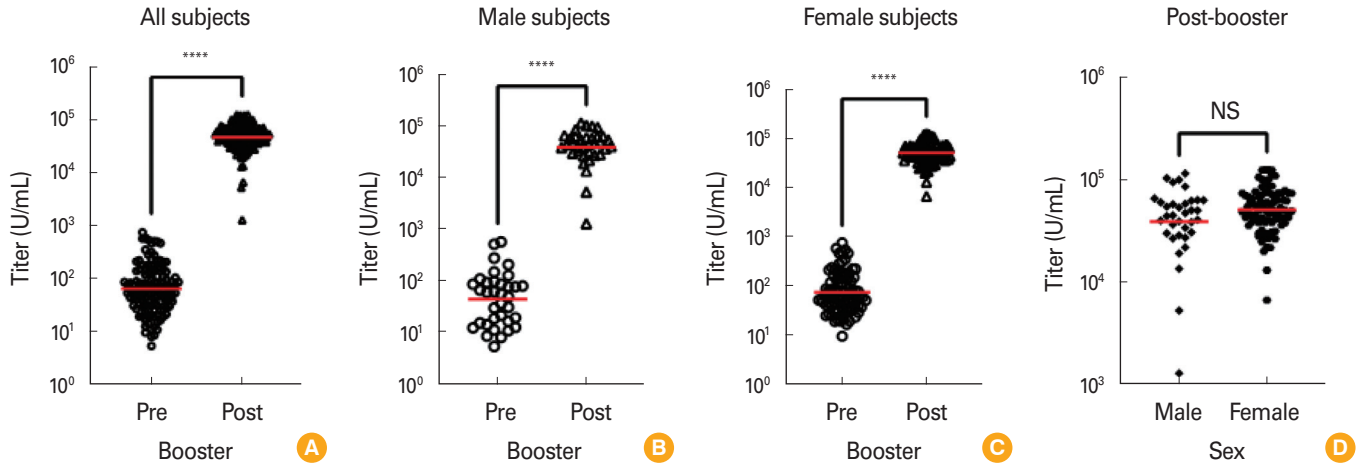

Fig. 1. Titer of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor-binding domain (RBD) antibodies pre- and post-booster with the mRNA-1273 vaccine. The comparison between titers pre- and post-booster are shown for all subjects (A), only male subjects (B), and only female subjects (C). A comparison between both sexes is shown in (D). Titer of anti-SARS-CoV-2 RBD antibodies is shown in the y axis at a base-10 logarithmic scale. Red horizonal lane indicates the geometric mean titer. Wilcoxon matched-pairs signed rank test was used to calculate p-values. A sign of **** indicates p<0.0001 and "not significant (NS)" indicates not significant as p>0.05.

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larger proportion among the mRNA-1273-vaccinated HCWs, contrastingly, reported moderate or severe pain in all related adverse events. In addition, the proportion of HCWs who reported severe pain in those adverse events was more than 30%, in which the highest proportion was found for the local pain (64.8%). Nonetheless, all subjects were not hospitalized

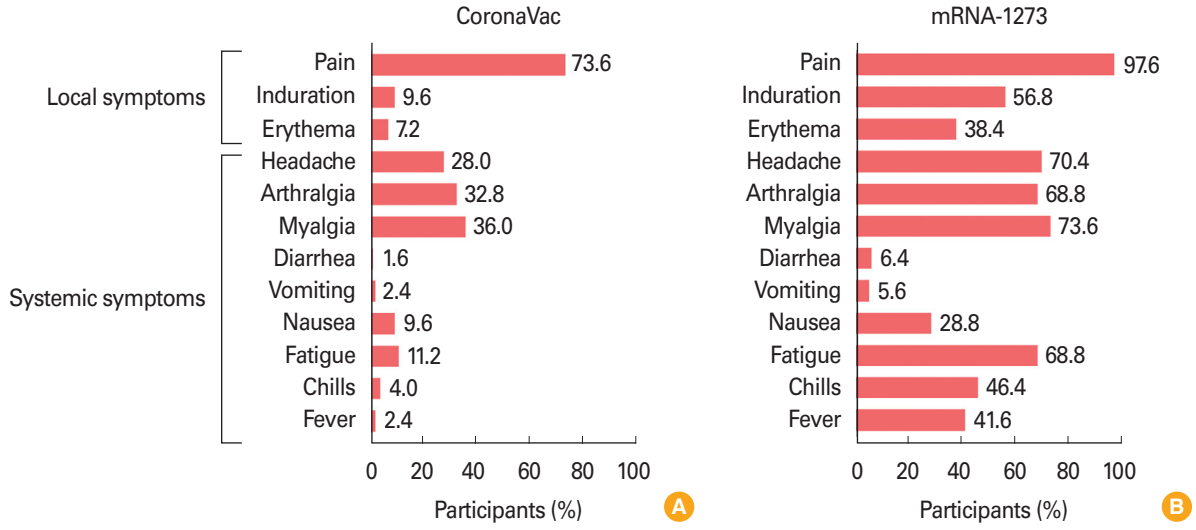

Fig. 2. Compilation of adverse events post-CoronaVac and post-mRNA-1273 vaccination. Various adverse events are shown in the vertical axes following second dose of CoronaVac (A) or mRNA-1273 vaccination (B). Frequency of each adverse event is shown in the horizontal axes in term of percentage of participants. The proportion of participants reporting each adverse event is shown at the end of each bar.

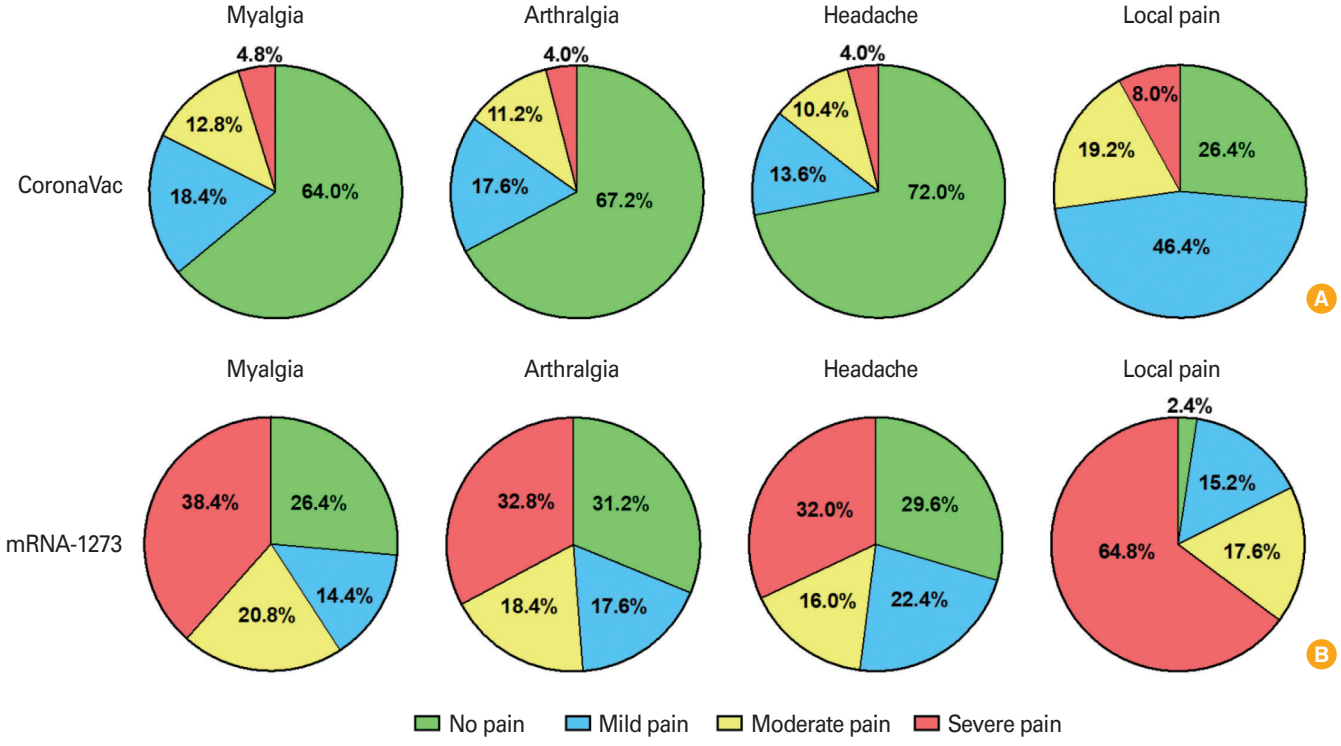

Fig. 3. Severity in four pain-related adverse events post-CoronaVac and post-mRNA-1273 vaccination. In adverse events of myalgia, arthralgia, headache, and local pain at injection's site, the severity of reported pain from all subjects were classified into four grades: no pain represented by green, mild pain represented by blue, moderate pain represented by yellow and severe pain represented by red color. The proportion of each group is depicted inside the pie charts. (A) Severity in pain-related adverse events after second dose of CoronaVac vaccination. (B) Severity in pain-related adverse events after mRNA-1273 vaccination.

and fully recovered after several days, supporting the safety profile of the mRNA-1273 vaccine [19]. Collectively, the mRNA-1273 vaccine, as compared to the CoronaVac vaccine, induced a higher frequency, but minor and transient adverse events.

Discussion

We hereby reported our single-center, prospective cohort study investigating immunogenicity and reactogenicity of heterologous prime-boost with a dose of the mRNA-1273 vaccine among fully CoronaVac-vaccinated, infection-naïve HCWs. Our findings can be summarized into three points. Firstly, the mRNA-1273 booster vaccination generated a significant elevation in the titer of anti-SARS-CoV-2 RBD antibodies among all subjects. An approximately 700-fold increase was observed in the titers measured 28 days post-booster vaccination, from the ones measured a week before booster vaccination. We quantified the titer of anti-SARS-CoV-2 RBD antibodies as these antibodies could block the viral entry into host cells [3] and as several groups, including ours, had reported a highly linear association between the titer of anti-SARS-CoV-2 RBD antibodies and percentage of inhibition in RBD–ACE-2 binding via various neutralization assays [20,21]. The increment in titer of anti-SARS-CoV-2 RBD antibodies post-booster with the mRNA-1273 vaccine was in line with the previous publication, reporting that the mRNA-1273 vaccination generated robust humoral and cellular immune responses toward spike protein of SARS-CoV-2 [14]. In addition, our finding complements a preprint result, showing that a booster with the mRNA-1273 vaccine also enhanced humoral immune responses among Ad26.COV2.S-vaccinated subjects [15], suggesting the mRNA-based vaccine could be used to boost immune responses of subjects receiving various types of COVID-19 vaccine. Taken together, this indicates that a single booster with the mRNA-1273 vaccine could enhance the immune responses toward the spike protein of SARS-CoV-2 among CoronaVac-vaccinated, infection-naïve individuals.

Secondly, the mRNA-1273 vaccination was associated with a higher frequency in reactogenicity, as compared to the CoronaVac vaccination. This finding was further supported by a higher severity of pain-related adverse events upon the mRNA-1273 vaccination. However, a highly reactogenic vaccine does not necessarily equal to an unsafe vaccine. Reactogenicity refers to immediate and expected physical reactions due to inflammatory response to vaccination [22], which in our study was recorded on the seventh-day post-booster vaccination. It is important to note that all subjects were not hospitalized and fully recovered, thus the occurred adverse events were considered minor medical events. This finding was in accordance with the published studies demonstrating that moderate, transient reactogenicity frequently occurred among individuals receiving the mRNA-1273 vaccine [14,19]. As the mRNA-1273 vaccine had demonstrated very high efficacy in preventing COVID-19 illness [19], a high frequency in reactogenicity should not become a deterrent for eligible individuals to be vaccinated with the mRNA-1273 vaccine.

Finally, no breakthrough infection was observed among all participating HCWs. This was important as it provided evidence of the usefulness of the heterologous prime-boost strategy, particularly with the mRNA-1273 vaccine, to provide adequate protection against COVID-19 [19]. Despite the current presence of the Delta variant of SARS-CoV-2 in Indonesia, no participating HCWs were infected during our follow-up for 12 weeks. This finding, arguably, supports the decision of the Indonesian Ministry of Health to implement the heterologous prime-boost vaccination among HCWs to prevent COVID-19 illness or even to block SARS-CoV-2 transmission. The CoronaVac is the most widely used COVID-19 vaccine as it accounts for almost 2 billion doses delivered globally [5]. Notably, it serves a very important role in supporting less developed nations to fight the pandemic [23]. However, as the generated immune response by the CoronaVac was less potent than the one by mRNA-based vaccine [24] and as the induced neutralizing antibodies by two doses of CoronaVac were no longer sufficient after 6 months [4], several countries had started the booster program. Sinovac Life Sciences indeed recommends the third dose of CoronaVac as the booster for both adults and elderlies 6–8 months after the second dose [4,25]. However, several countries prefer to use different COVID-19 vaccines as the booster for individuals receiving inactivated vaccines. For example, while Thailand chose a combination between one dose of CoronaVac and one of AZD1222, Abu Dhabi in the United Arab Emirates and Chile provided BNT162b2 to boost two doses of either CoronaVac or BBIBP-CorV [5,26,27]. Indonesia, on the other hand, distributed a single dose of mRNA-1273 to boost fully CoronaVac-vaccinated HCWs. Our finding provided reassurance that the heterologous prime-boost with the mRNA-1273 vaccine was safe and highly immunogenic. In addition, the decision to use a 100-μg dose of mRNA-1273 was justifiable as this dose was reported to be highly effective, arguably even

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better than a 30-μg dose of BNT162b2, against any Delta infection as well as Delta-induced morbidity and mortality [16]. There are several limitations in our study. First, our cohort was small as it was a single-center study. Nonetheless, the single-center setting allowed us to carefully screen eligible candidates and to closely monitor all subject for any possible breakthrough infection following the booster vaccination. Second, we only measured titer of anti-SARS-CoV-2 RBD antibodies as a surrogate marker for the vaccine's immunogenicity. The conventional virus neutralization test was indeed the gold standard method in assessing specific neutralizing antibodies. However, its requirement of a biosafety level 3 containment facility as well as its tediousness and time-consuming method hinder the routine application of this test [28]. In addition, T-cell response was not assessed in this study, despite it might play an important role in protection against SARS-CoV-2 [29]. Third, the adverse events were self-reported via an online survey. Although our subjects were HCWs, there might be a bias of over-reporting the adverse events following the mRNA-1273 vaccination because the mRNA-based technology was a novel invention to develop a vaccine, thus many concerns about the vaccine's safety [7,14,19,30]. Fourth, as we recorded both adverse events post-mRNA-1273 and post-CoronaVac vaccination at the same time, the bias for the CoronaVac vaccine-related adverse events was unavoidable. Subjects might report past events in a different manner; hence, it would skew the data and its analysis. Nevertheless, it is a common fact for COVID-19 vaccination that the inactivated vaccines induced fewer adverse events, both frequency and severity, as compared to the mRNA vaccines [7]. Fifth, the reported follow-up period post-booster was short. An extension in following up on those subjects would be important. In addition, although we did not observe any breakthrough infection during the follow-up period, it had been reported that mRNA-1273-vaccinated individuals with breakthrough infections, particularly with Delta variant, tend to be asymptomatic or less severe [31]. Thus, there was a small possibility that infected subjects might go unnoticed during that period.

In conclusion, we observed that the heterologous prime-boost with a single dose of the mRNA-1273 vaccine among fully CoronaVac-vaccinated, infection-naïve HCWs generated a significant elevation in humoral immune response towards RBD of SARS-CoV-2 and that the booster vaccination was associated with a higher frequency, but minor and transient, of adverse events. The profound increase in anti-SARS-CoV-2 RBD antibodies might be important to prevent future infection of SARS-CoV-2.

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References

1. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:181-92.
2. Cucunawangsih C, Wijaya RS, Lugito NP, Suriapranata I. Antibody response to the inactivated SARS-CoV-2 vaccine among healthcare workers, Indonesia. Int J Infect Dis 2021;113:15-7.
3. Barnes CO, Jette CA, Abernathy ME, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature 2020;588:682-7.
4. Pan H, Wu Q, Zeng G, et al. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial. MedRxiv [Preprint] 2021 Jul 23 [Epub]. https://doi.org/10.1101/2021.07.23.21261026.
5. Mallapaty S. China's COVID vaccines have been crucial: now immunity is waning. Nature 2021;598:398-9.
6. Lu S. Heterologous prime-boost vaccination. Curr Opin Immunol 2009;21:346-51.
7. He Q, Mao Q, Zhang J, et al. COVID-19 vaccines: current understanding on immunogenicity, safety, and further considerations. Front Immunol 2021;12:669339.

8. Chiu NC, Chi H, Tu YK, et al. To mix or not to mix?: a rapid systematic review of heterologous prime-boost covid-19 vaccination. Expert Rev Vaccines 2021;20:1211-20.
9. Zhang J, He Q, An C, et al. Boosting with heterologous vaccines effectively improves protective immune responses of the inactivated SARS-CoV-2 vaccine. Emerg Microbes Infect 2021;10:1598-608.
10. Mlcochova P, Kemp SA, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021;599:114-9.
11. Callaway E. The mutation that helps Delta spread like wildfire. Nature 2021;596:472-3.
12. Dyer O. COVID-19: Indonesia becomes Asia's new pandemic epicentre as Delta variant spreads. BMJ 2021;374:n1815.
13. Saifuddin A, Koesnoe S, Kurniati N, Sirait S, Arisanty R, Yunihastuti E. COVID arm after Moderna booster in healthcare worker: a case report. Acta Med Indones 2021;53:326-30.
14. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2: preliminary report. N Engl J Med 2020;383:1920-31.
15. Atmar RL, Lyke KE, Deming ME, et al. Heterologous SARS-CoV-2 booster vaccinations: preliminary report. medRxiv [Preprint] 2021 Oct 15 [Epub]. https://doi.org/10.1101/2021.10.10.21264827.
16. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med 2021;27:2136-43.
17. Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville (MD): Food and Drug Administration; 2007.
18. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth 2008;101:17-24.
19. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.
20. Jochum S, Kirste I, Hortsch S, et al. Clinical utility of Elecsys anti-SARS-CoV-2 S assay in COVID-19 vaccination: an exploratory analysis of the mRNA-1273 phase 1 trial. Front Immunol 2022;12:798117.
21. Jo J, Sanjaya A, Pinontoan R, Aruan M, Wahyuni RM, Viktaria V. Assessment on anti-SARS-CoV-2 receptor-binding domain antibodies among CoronaVac-vaccinated Indonesian adults. Clin Exp Vaccine Res 2022;11:116-20.
22. Herve C, Laupeze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines 2019;4:39.
23. Jara A, Undurraga EA, Gonzalez C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med 2021;385:875-84.
24. Saure D, O'Ryan M, Torres JP, Zuniga M, Santelices E, Basso LJ. Dynamic IgG seropositivity after rollout of CoronaVac and BNT162b2 COVID-19 vaccines in Chile: a sentinel surveillance study. Lancet Infect Dis 2022;22:56-63.
25. Li M, Yang J, Wang L, et al. A booster dose is immunogenic and will be needed for older adults who have completed two doses vaccination with CoronaVac: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. MedRxiv [Preprint] 2021 Aug 3 [Epub]. https://doi.org/10.1101/2021.08.03.21261544.
26. Wanlapakorn N, Suntronwong N, Phowatthanasathian H, et al. Immunogenicity of heterologous inactivated and adenoviral-vectored COVID-19 vaccine: real-world data. Vaccine 2022 Apr 18 [Epub]. https://doi.org/10.1016/j.vaccine.2022.04.043.
27. Yorsaeng R, Vichaiwattana P, Klinfueng S, et al. Immune response elicited from heterologous SARS-CoV-2 vaccination: Sinovac (CoronaVac) followed by AstraZeneca (Vaxzevria). medRxiv [Preprint] 2021 Sep 1 [Epub]. https://doi.org/10.1101/2021.09.01.21262955.
28. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. Nat Biotechnol 2020;38:1073-8.
29. Swadling L, Diniz MO, Schmidt NM, et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. Nature 2022;601:110-7.
30. Kang YM, Lim J, Choe KW, et al. Reactogenicity after the first and second doses of BNT162b2 mRNA coronavirus disease vaccine: a single-center study. Clin Exp Vaccine Res 2021;10:282-9.
31. Chia PY, Ong SW, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine breakthrough infections: a multicentre cohort study. Clin Microbiol Infect 2022;28:612.