

Coronavirus Pandemic

Severe acute respiratory syndrome coronavirus-2 antibody response after Moderna vaccine booster on healthcare providers

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Abstract

Introduction: As an endeavor to control SARS-CoV-2 infection, the Moderna vaccine booster was given to healthcare workers to prevent reinfection and reduce the risk of complications from COVID-19. A heterologous booster vaccine is also thought to provide better protection against the current SARS-CoV-2 variants of concern. However, research that evaluates the effectiveness of the Moderna vaccine booster and the resulting SARS-CoV-2 antibody concentration is needed.

Objective: To evaluate the concentration of SARS-CoV-2 antibodies after the Moderna vaccine booster and the severity of SARS-CoV-2 infection before and after the Moderna vaccine booster.

Results: A total of 93 healthcare providers who received Moderna vaccine booster were included in the study. Examination of antibody concentration 3 months after the booster showed an average concentration of 10081.65 U/mL. There was an increase in antibody concentration before the booster and 3 months after, from a median of 1.7 U/mL to 9540 U/mL. Every subject showed a statistically significant increment of antibody concentration 3 months after the booster ($p < 0.01$). Thirty-seven (39.8%) subjects received two doses of the Sinovac vaccine and were confirmed to have COVID-19 with the Delta variant. After the booster, 26 (28%) subjects were infected with the Omicron Variant. Among the subjects who received two doses of the Sinovac vaccine and were confirmed with COVID-19, 36 (30.1%) had mild symptoms, and 1 (1.1%) was asymptomatic.

Conclusions: Heterologous Moderna vaccine booster effectively increases antibody response against SARS-CoV-2 variants and shows mild symptoms of COVID-19 infection.

Key words: COVID-19; vaccination; booster; Moderna; healthcare providers.

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Introduction

At the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, as the cause of coronavirus disease 2019 (COVID-19). The virus spread to other cities and then to other countries. World Health Organization (WHO) declared a global pandemic in March 2020. COVID-19 significantly increases the morbidity and mortality of those inflicted [1,2].

Research has shown that the adaptive and innate immune systems have viral clearance functions [3]. Infections and vaccination could evoke immune responses to SARS-CoV-2, protecting from reinfection and reducing complications [4]. Four studies in the United States, United Kingdom, and Denmark estimated 80-90% protection against reinfection after SARS-CoV-2 infection. However, the formed

immunity declines over time; neutralizing antibodies only last 8 months after infection [4,5].

Vaccine-induced immune response creates antibodies against viral spike protein. Anti-spike (Anti-S) antibody serves as an indicator for protection against viruses. From this indicator, it was elucidated that the variety of SARS-CoV-2 vaccines had different efficacy ranging from 50% to 95% [5]. However, the emergence of SARS-CoV-2 variants of concern (VOC) demonstrated a significant impact on the pandemic trend. The five most noticeable VOCs include Alpha (B.1.1.7, United Kingdom), Beta (B.1.351, South Africa), Gamma (P1, Japan/Brazil), Delta (B.1.617.2, India), and Epsilon (B.1.427/B.1.429, United States). Due to extensive mutations on the spike protein and receptor-binding protein (RBD), not only VOCs have higher transmissibility and higher virulence but are shown to be more resistant to neutralization, thus

posing a threat to the efficacy of current vaccine-induced protection and therapeutics [6-9]. Current circulating VOC, the Omicron variant (B.1.1.529, multiple countries), has evoked global concern due to its strong immune evasion after vaccination and natural infection [9].

The Moderna vaccine booster is a heterologous booster that can effectively increase the neutralizing antibody titer against wild-type and delta variants to as much as 3-4 times the original amount. Thus, giving heterologous boosters is a viable strategy for immunological protection against SARS-CoV-2. This study aimed to evaluate SARS-CoV-2 antibody concentration in healthcare providers, consisting of pulmonology specialists and pulmonology residents in Persahabatan National Respiratory Referral Hospital Jakarta, and to determine the duration of this protection and whether a booster with a differing vaccine will elicit a better response [10].

Methodology

This prospective cohort study involved 107 subjects consisting of pulmonology specialists and pulmonology residents in Persahabatan National Respiratory Referral Hospital Jakarta. The study received ethical approval from the Institutional Review Board (IRB) of the

Faculty of Medicine, Universitas Indonesia (Number KET-442/UN2.F1/ETIK/PPM.00.02/2021) and informed consent from each participant. All subjects were vaccinated with Sinovac® inactivated virus vaccine from January to February 2021 with or without prior SARS CoV-2 infection and then vaccinated with Moderna heterologous vaccine booster from July-August 2021. Sampling was done one month after the second vaccine, three months after the second vaccine, and three months after the booster. The study also observed confirmed SARS CoV-2 infected cases after the Moderna vaccine booster, which were proven clinically and via reverse-transcriptase polymerase chain reaction (RT-PCR).

Subjects underwent antibody concentration examination independently at Prodia® laboratory using Cobas e601 tool and Elecsys Electrochemiluminescence immunoassay analyzer (ECLIA) examination method from Roche Diagnostics. The anti-SARS-CoV-2 quantitative examination aimed to measure IgG antibody titer against the S1 subunit of the SARS-CoV-2 protein spike receptor-binding domain (RBD) on blood samples. The laboratory cut-off value for the titer was 0.8 U/mL. The antibody concentration ranges from 0.4 U/mL to > 250 U/mL; a result above 250 U/mL will require a tenfold dilution. Afterward, if the result was still above 250 U/mL, dilution was done 100 times.

Data analyses were done with SPSS software version 25. Descriptive data of every categoric variable were stated by total (n) and percentage (%). Bivariate analyses were done to compare first-month antibody concentration with third-month antibody concentration and to compare antibody concentration before and 3 months after the booster. Paired T-test would be used if the data were normally distributed, and the Wilcoxon test would be used if the data were not normally distributed. A comparative test between antibody concentration and COVID-19 cases after the Moderna booster would be done with an unpaired T-test if the data were not normally distributed, and a Mann-Whitney test would be used if the data were not normally distributed.

Results

Subject Characteristic

The total of subjects recruited for the study was 107, 14 subjects were excluded for not participating in sampling at the specified time, and 3 subjects among them showed antibody concentration > 25 after 100 times dilution. Subjects' ages ranged from 26 to 79 years old, with an average age of 36.86. There were 88

Table 1. Subject Characteristic.

Characteristic	n (%)
Age (years), median (min-max)	34 (26-79)
Sex, n (%)	
Female	57 (61.3)
Male	36 (38.7)
BMI (kg/m²), median (min-max)	24.74 (19.48-51.94)
Comorbidity n (%)	
Asthma	13 (14)
History of Pulmonary Tuberculosis	3 (3.2)
Diabetes Mellitus	4 (4.3)
Dyslipidemia	4 (4.3)
Hypertension	7 (7.5)
Chronic Heart Disease	1 (1.1)
Antibody Concentration After Sinovac Vaccination (U/mL), median (min-max)	
1 month	2.5 (0.08-1794.00)
3 months	1.7 (0.13-1099.00)
Antibody concentration After Booster (U/ml), mean ± SD	
3 months	10081.65 ± 5248.126
Vitamin D concentration (U/ml), median (min-max)	0.84 (0.21-26.00)
History of COVID-19 before booster, n (%)	
Yes	37 (39.8)
No	56 (60.2)
History of COVID-19 after the booster, n (%)	
Yes	26 (28)
No	67 (72)

BMI: body mass index; COVID-19: coronavirus infection disease 2019; SD: standard deviation.

(94.6%) subjects who were aged < 60 years old and 5 (5.4%) who were aged > 60 years old. Sex-wise, the subjects consisted of 57 (61.3%) female and 36 (38.7%) male (Table 1).

There were 20 (21.5%) subjects with a history of COVID-19 before the booster and 26 (28%) subjects with COVID-19 after the booster, regardless of COVID-19 history. All subjects infected between June and July 2021 were infected by the Delta variant, while infections after the booster, which occurred between January and March 2022, were that of the Omicron variant. All COVID-19 cases were confirmed with rt-PCR.

Antibody concentration in the first and third month after Sinovac vaccination

Anti-SRS-CoV-2 examination one month after the vaccination showed 0.08 U/mL as the lowest value and > 250 U/mL as the highest. The average concentration one month after vaccination was 81.04 U/mL with a standard deviation of 307.84. Three months after vaccination, the antibody concentration was between

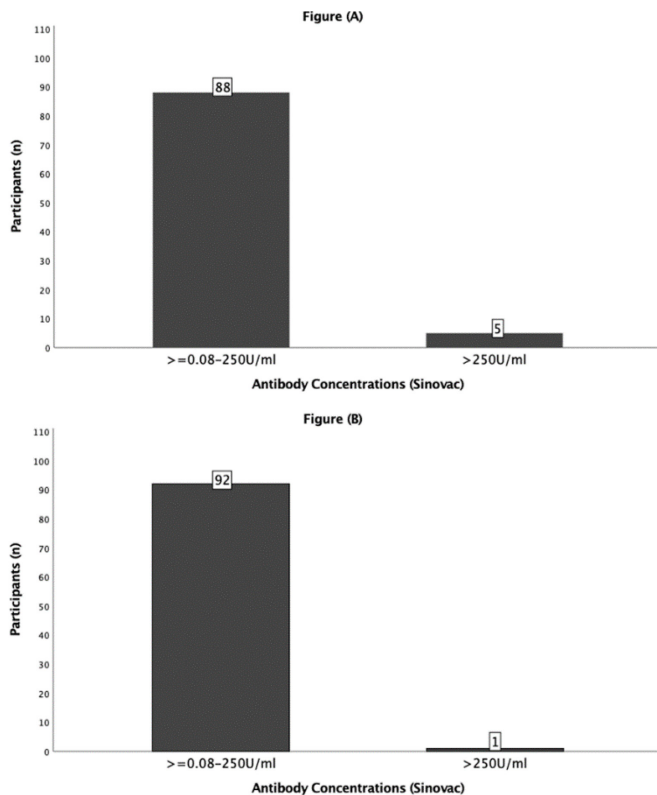
0.13 U/mL and > 250 U/mL, with an average of 24.07 U/mL and a standard deviation of 114.44.

Figure 1 depicts the overall decrease in antibody concentration between one month and three months after vaccination. The difference between the median concentration at one month and three months was statistically significant due to 56 subjects having a marked reduction in antibody concentration ($p = 0.01$).

Antibody Concentration before and three months after the booster

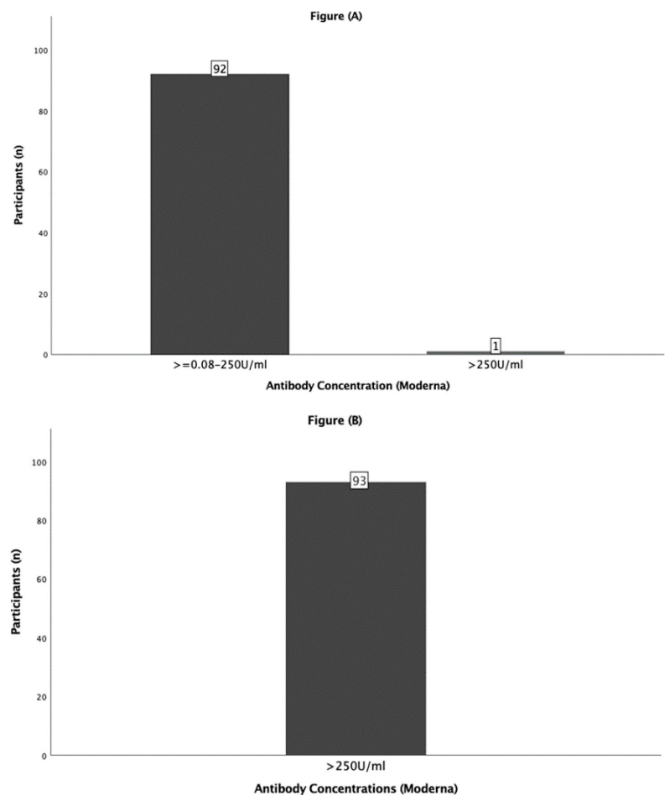
Antibody concentration examination three months after the Moderna vaccine booster showed a mean concentration of 10081.65 U/mL. Antibody concentration before and three months after the booster indicated a marked increment from the median of 1.7 U/mL to 9540 U/mL (Figure 2). All subjects showed a statistically significant increase in antibody concentration three months after the booster ($p < 0.01$). The number of subjects with > 250 U/mL antibody concentration before and three months after the booster was statistically significant (1.1% vs. 100%, $p < 0.0001$).

Figure 1. Antibody concentrations. A) First month after Sinovac vaccination; B) third month after Sinovac vaccination.



*Wilcoxon test; 56 subjects with reduced antibody concentration, 36 subjects with increased concentration, and 1 subject with steady concentration.

Figure 2. Antibody concentrations. A) Before the booster; B) Three months after the booster



Number of COVID-19 cases Before and after Moderna vaccine booster

Two variants of SARS-CoV-2 were observed in the study. The Delta variant infected 37 (39.8%) subjects after the Sinovac vaccination. After the booster, the Omicron variant infected 26 (28%) subjects between January to April 2022. Some of the subjects had comorbidity; 13 (14%) subjects had asthma, 3 (3.2%) subjects had a history of pulmonary tuberculosis, 4 (4.3%) subjects had diabetes mellitus, 4 (4.3%) subjects had dyslipidemia, 7 (7.5%) subjects had hypertension, and 1 (1.1%) subject had chronic heart disease. Among all subjects who received the Sinovac vaccine and were infected with the Delta variant, 36 (38.7%) subjects had mild symptoms, and 1 (1.1%) were asymptomatic. Subjects with mild symptoms received care while under quarantine, home-based, or in-patient care.

Discussion

This study showed the concentration of SARS-CoV-2 antibody as well as the severity of SARS-CoV-2 infection before and after Moderna vaccine booster in patients who have received 2 doses of Sinovac vaccines 6 months prior. In this study, quantitative anti-SARS-CoV-2 concentration after vaccination showed a significant reduction after three months ($p = 0.01$) and a significant increase after the Moderna vaccine booster ($p < 0.01$). This result is consistent with the findings by Naaber *et al.*, who found a reduction of S-RBD IgG concentration after three months to 5226 AU/mL (3097-6924) and after six months to 1383 AU/mL (893-2463) [14]. Another study found a significant-RBD antibody and ELISA anti-N reduction in the plasma between 1.3 and 6.2 months [15]. Barin *et al.* compared the bond between anti-SARS-CoV-2 spike receptor and the IgG antibody domain response from three kinds of vaccines (Pfizer, AstraZeneca, Sinovac); reduction in antibody was found from the first month to the third month after vaccination with Sinovac observed to have the fastest decline [16].

Many studies have proven that vaccination creates T-cell response memory and strong effector functions to particular viral epitopes. T cell response, memory B cells, and neutralizing antibody secrete effective antibody which enhances immunity. Moderna is a mRNA vaccine that uses genetically modified DNA or RNA as a blueprint (mRNA) to produce protein to elicit an immune response. From the SARS-Cov-2 virus, mRNA sequence responsible to translate and codify virus spike protein is isolated and enveloped in a lipid nanoparticle. The vaccine is administered intramuscularly. Once the vaccine is attached to the

host cells, mRNA is inserted into the cytoplasm, where the mRNA reaches ribosomes and is then used to synthesize viral protein spike production, the process called translation. Protein will reach cell membrane and evolve into MHC-1 complex (in all nucleated cells of the host) and MHC-2 complex (in B-cells, dendritic cells, and macrophages). Through activation by the s protein, MHC-2 attracts and interacts with CD 4 (produced by the Th cells). Interaction between MHC2 and CD4 produces cytokines (IL-2, IL-4, IL5) which induce B cells to produce antibodies against the spike protein, preventing SARS-CoV-2 infection by neutralizing or destroying the virus. Interleukins also induce Th cells to proliferate T memory. Meanwhile, MHC-1 interacts with T-cytotoxic (Tcx) and generates CD8 protein, which enables Tcx cells to produce compounds able to cause cell death once the cell is infected with the virus [11-13].

Sinovac (CoronaVac) uses inactive or weakened whole viruses as antigens to generate an immune response without causing disease. Sinovac was one of the first vaccines introduced globally. Wilder-Smith *et al.* found that 750 doses of the Sinovac vaccine have been administered across more than 40 countries. The effectiveness of a full-dose Sinovac vaccination against a variety of symptomatic manifestations was shown to have peaked in Brazil (50.65%), Indonesia (65.30%), and Turkey (83.50%) within a 2-month observation. On the other hand, the effectiveness of the Sinovac vaccine against hospitalization rate and mortality was 100% but with a wide confidence interval. This rate is not representative of every country; Indonesia still deals with many COVID-19 cases involving healthcare providers, some showing severe manifestations and leading to death even with full-dose vaccination. Another study evaluating the use of the Sinovac vaccine also revealed a reduction in the seropositive population by as much as 17%, which means the overall immunity could decline quickly [17]. These findings are consistent with this study, where 37 (39.8%) subjects were infected with COVID-19 even after a full-dose Sinovac vaccination. Among the infected, 36 (38.7%) had mild symptoms, and 1 (1.1%) was asymptomatic.

The reduction of antibody quantity showed that as other infection, SARS-CoV-2 vaccine-induced antibodies wane over time. This reduction of efficacy is not only seen in Sinovac, but also other vaccines. A systematic review and meta-regression by Feikin *et al.*, investigating the durability of SARS-CoV-2 vaccine protection, suggested a decrease of vaccine efficacy against infection by 20-30% by 6 months after full vaccination among people of all ages and all vaccine

investigated (Moderna, Pfizer-BioNTech, AstraZeneca, and Janssen). This evidence is limited before Omicron began to emerge [18]. Against VOCs, a study by Peng *et al* suggested that Sinovac vaccine showed significantly lower neutralizing antibody response rates and antibody titers three months after vaccination compared to BNT16b2 (by BionTech SE and Pfizer Inc.), thus facing a higher risk of VOCs breakthrough [9]. Therefore, with the apparent reduction of immunological protection, a third vaccine, booster, is indicated to increase the immune response against SARS-CoV-2 as re-exposure of vaccines induces B cells to proliferate and differentiate into antibody-secreting plasma cells [3].

In individuals with a history of COVID-19 infections, a protective immune response is proven potent. Antibody response is shown to be as high, if not higher, as effective as two vaccine doses in naïve individuals [3]. A study by Callegaro *et al.* [1] demonstrated that after a single mRNA vaccine injection, the median titer for specific antibodies was 30.527 U/mL (interquartile range [IQR]: 19.992-39.288) in individuals with previous COVID-19 infection, which was significantly higher than the median titer naïve individuals after a full dose vaccination (1974.5 U/mL [IQR: 895-3455]). Therefore, a single mRNA vaccine dose is suggested to be sufficient and equivalent to the booster dose in naïve individuals [3].

The administration of the booster vaccine to subjects who had received the Sinovac vaccine becomes a challenging decision due to the reduction of COVID-19 vaccine effectiveness from time to time. However, studies found that boosters provide a jump in antibody concentration which can work against SARS-CoV-2 mutation. Because of this, booster vaccines are given worldwide to control COVID-19 [12,19].

A booster may be administered in two ways: homologous and heterologous. A homologous Sinovac booster is given 8 months after the second dose is proven immunogenic [19]. However, a heterologous booster results in better immunity against current variants of concern [20]. A study in China proved that a heterologous booster of the Sinovac vaccine with type-5 adenovirus recombinant COVID-19 vaccine created a larger concentration of neutralizing antibodies than the homologous booster [21]. Another study supporting heterologous booster was done in Thailand, which compared homologous vaccine with three variations of heterologous booster: AstraZeneca, Pfizer-BioNTech, and Sinopharm. The study used a mice model and showed that 1 of the three heterologous

boosters shows greater efficacy than the homologous booster [22]. Thus, choosing a heterologous booster is a rational decision. In this study, the Moderna vaccine as a booster for the Sinovac vaccine significantly induced antibody response, where the number of subjects with antibody concentration ≥ 0.8 U/mL increased from 66.7% to 100%. COVID-19 cases were also fewer from 37 (39.8%) to 26 (28%). This result is consistent with the study by Cucuwangsih *et al.*, which demonstrated that booster vaccines strongly enhance immunity in healthcare providers, shown by the significant increase of Anti-S antibody to > 210 U/mL in all the study's subjects [23].

Conclusions

A heterologous booster with the Moderna vaccine effectively increases antibody response against SARS-CoV-2 variants and can decrease COVID-19 severity. However, this study has potential limitations. This study did not explain any correlation between the antibody concentration and the COVID-19 cases. The subjects of this study were limited to healthcare professionals, and there was no data on the antibody concentration before the Sinovac vaccination for comparison. Furthermore, there was no vulnerable and control group included in the analysis. The study did not find out for how long the effectiveness of the vaccine was. Thus, further studies are needed specifically to elucidate the issues.

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