Original Article
Acta Medica Academica 2022;51(2):69-78
DOI: 10.5644/ama2006-124.374

Evaluation of SARS-CoV-2 Antibody Response Post Third Dose COVID-19 mRNA Vaccination at Universitas Indonesia Hospital

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Received: 12 August 2022; **Accepted:** 29 August 2022

Abstract

Objective. The longevity of vaccine effectiveness and antibody titer after the Moderna mRNA COVID-19 vaccination booster in healthcare workers in Indonesia is not known. **Materials and Methods.** We performed a prospective observational study of healthcare workers at the Universitas Indonesia Hospital after Moderna mRNA COVID-19 booster vaccination. An Immunology Analyzer with Chemiluminescence Immunoassay (CLIA) test was used to examine Anti SARS-CoV-2 S-RBD levels. Antibody levels were classified into two systems (3 categories, and 2 categories). **Results.** There were 31 male subjects (75.6%), 33 subjects (80.5%) aged 25-39 years, 17 subjects (41.5%) with overweight BMI, 35 subjects (85.4%) without comorbidities, and 29 subjects without previous history of COVID-19 infection (70.7%) who had antibody titer >1000 AU/ml. There were 27 subjects (65.9%) who had a booster shot ≥6 months after the second vaccination with antibody titer >1000 AU/ml. In this study, there was no significant correlation between antibody titer with factors such as gender, age, BMI, comorbidities, history of COVID-19 infection and time between the 2nd vaccination and booster vaccination. **Conclusion.** There is no significant correlation between antibody titer with factors such as gender, age, BMI, comorbidities, history of COVID-19 infection and time between the 2nd vaccination and booster vaccination

Key Words: COVID-19 ▪ SARS-CoV-2 ▪ Vaccine.

Introduction

On March 11, 2020, WHO declared COVID-19 infection a pandemic. COVID-19 is caused by SARS-CoV-2 and does not yet have a primary therapy that can directly kill the virus, making vaccine the main hope for stopping this pandemic (1). The SARS-CoV-2 vaccination has proven effective in inducing an immune response and progressively open the way to overcome the COVID-19 pandemic (2). The goal of SARS-CoV-2 vaccines is to produce anti-spike neutralizing antibodies (nAbs) that recognize the viral S protein. Theseanti-spike nAbs can prevent virus–human cell interaction and aid in the elimination of infection in its early stages (3). A previous study showed there are several factors that influence antibody levels, including age, infection history, and virus mutation (3). The effectiveness of vaccines in reducing the spread of COVID-19 has been proven. In Indonesia, along with the increase in the vaccination rate, the number of hospitalizations, deaths due to COVID-19 and confirmed positive cases decreased compared to 2020 when vaccination was not used in general (4).

Studies have already demonstrated that the third dose increases immunogenicity against SARS-CoV-2, reflected in a rapid and broad immune response to the third mRNA vaccine BNT162b2 dose (5). In July 2021, the third dose of vaccination was intended for all health workers. The third

dose or booster vaccination for health workers in Indonesia uses two types of vaccine, which are the CoronaVac vaccine and mRNA-1273 vaccine (Moderna vaccine). The first and second dose for health workers used the CoronaVac vaccine (4). Compared to the homologous boosting type, the heterologous boosting type of vaccine administration was expected to widen cellular and humoral immunogenicity against COVID-19 infection (6, 7). The heterologous boosting between Coronavac and mRNA vaccine gives better antibody response than other vaccine booster options, and also shows great protection against the delta and omicron variants (8-10). The Moderna vaccine is an mRNA-based vaccine that has several advantages, one of which is the fast and specific formation of immunogens. The Moderna vaccine showed efficacy of 94 after two doses in a phase 3 trial (11). Various side effects of mRNA vaccines can occur locally or systemically (3). Antibodies formed after the administration of the vaccine serve as biomarkers of immunity, so that the detection of specific antibodies can provide information about adaptive immunity against SARS-CoV-2. Quantitative assays for detecting anti-SARS-CoV-2 antibodies can help determine vaccine-specific antibody responses, individual antibody titer, and longitudinal monitoring of antibody responses. The test can also assess whether a person's antibody levels are the result of an adaptive immune response induced by infection, or a vaccine-induced response (12). A study by Ibarguengoitia et al. shows that the median antibody titer ranged from 379-2960 AU/ml in the group with negative COVID-19 history, and 590-3090 AU/ml in the group with positive COVID-19 history (13). The purpose of this study was to determine the SARS-CoV-2 antibodies response after the third dose of mRNA-based vaccination in health workers at Universitas Indonesia Hospital

Methods

Examination of IgG S-RBD SARS-CoV-2 Antibodies

The investigation was carried out at the Clinical Pathology Laboratory of Universitas Indonesia Hospital using the Mindray CL-900i Immunology Analyzer manufactured by Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China (14). The sensitivity value of the analyzer was 0.006ng/mL, with a measurement range of 0.006–50 ng/mL. The analyzer was calibrated at the beginning of the study. The quality control (QC) results of the analyzer were within QC limits. If subject's antibody was >1000 AU/ml, it was shown as it is, but if the antibody level was <1000 AU/ml, it showed as the exact number.

Study Design and Population

The research design was a prospective cohort method conducted in August 2021-January 2022 at Universitas Indonesia Hospital, one of the COVID-19 center hospitals in Indonesia. The target population in this study were all health workers at Universitas Indonesia Hospital receiving the third dose of Moderna vaccine, without any limitations in duration between the booster injection and laboratory testing. The research inclusion criteria were Universitas Indonesia Hospital health workers who had received the first and second doses with inactivated whole-virus CoronaVac vaccine, and the third dose with Moderna vaccine, and health workers who were registered as permanent employees and part timers at Universitas Indonesia Hospital. The exclusion criteria were Universitas Indonesia Hospital health workers who had a history of allergies to Moderna vaccine, and Universitas Indonesia Hospital health workers who received some other vaccine than Moderna as

the third dose. This study involved 49 Universitas Indonesia Hospital health workers who were tested for IgG S-RBD SARS-CoV-2 antibodies in their serum and plasma using the CLIA Anti-SARS-CoV-2 principle. A relatively small number of subjects was chosen as this study acts as a preliminary study. Our research divided antibody titer into two systems. In the first we divided antibody titers into categories: <500; 500-1000; >1000 AU/ml based on the tests.

Data Collection and Statistical Analysis

Respondents supplied their data using a form filled in directly by the research subject. The analytical study was conducted on 49 samples (Figure 1). The questionnaire data were entered into a Microsoft Excel sheet. Data were statistically analyzed using Microsoft Excel 2019 and SPSS 24. Nominal categorical data were displayed in percentage graphs, and numerical data presented along with mean data and standard deviations. Analysis of categorical data was carried out using the chi square, or alternatively Fisher's test if they did not meet the chi square rule. Meanwhile, analysis of numerical data was carried out using one way ANOVA or an unpaired T test for comparison with samples of less than two groups. If the data did not meet the normality test, the Kruskal Wallis and Mann Whitney tests were carried out.

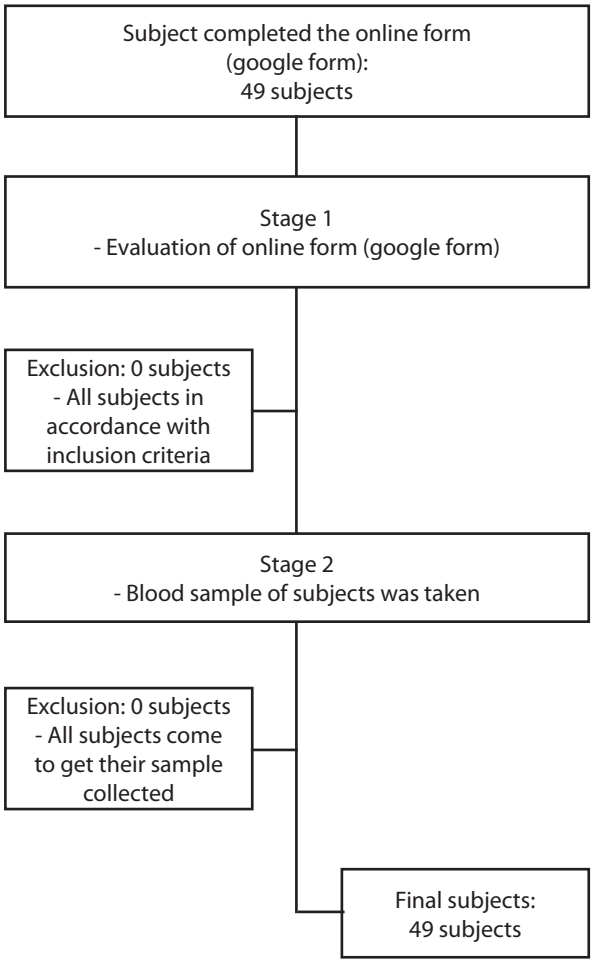

Figure 1. Subject recruitment process.

Ethics Statement

This research was approved by the Ethics Committee of Universitas Indonesia Hospital, approval number S-010/KETLIT/RSUI/II/2022, with protocol number 2021-09-099. This research also followed Declaration of Helsinki guidelines.

Results

In this study, a total of 49 subjects took part (Table 1). The majority of subjects were male, that is 36 subjects (73.5%). There are 40 subjects (81.6%) who were 25-39 years old. We divided their BMI into four groups: underweight, normal weight, overweight, and obese. The subjects were dominantly in the normal weight BMI group, that is 22 of them (44.9%), and 19 subjects (38.8%) were overweight. There are 7 subjects (14.3%) who had comorbidities, which were hypertension (3 subjects, 6.1%), diabetes mellitus (2 subjects, 4.1%), and coronary artery disease (CAD) and asthma with 1 subject each (2%). There are 13 subjects (26.5%) who had a previous history of COVID-19. Thirty-three subjects (67.3%) received the 3rd vaccine within 6 months after the 2nd vaccine.

Table 2 shows the evaluation of antibody titers after administration of the Moderna booster vaccine, using the first category, whereby we divided the antibody titer into three groups. There were 31 subjects (86.1) with antibody titer >1000 AU/

Table 1. Demographic Characteristics

Characteristic	N (%)	Mean (±SD)
Gender		
Female	13 (26.5)	-
Male	36 (73.5)	-
Age group (years old)		30.0 (±6.7)
<25	6 (12.2)	-
25-39	40 (81.6)	-
≥40	3 (6.1)	-
BMI (kg/m^2)		25.4 (±4.6)
Underweight <18.5	2 (4.1)	-
Normal weight 18.5-24.9	22 (44.9)	-
Overweight ≥ 25	19 (38.8)	-
Obese ≥30	6 (12.2)	-
Comorbidity		
Yes	7 (14.3)	-
No	42 (85.7)	-
Comorbidity		
Diabetes mellitus	2 (4.1)	-
Hypertension	3 (6.1)	-
CAD	1 (2)	-
Asthma	1 (2)	-
History of previous COVID-19 infection		
Yes	13 (26.5)	-
No	36 (73.5)	-
2nd to 3rd vaccine duration (months)		5.6 (±1.6)
< 6	16 (32.7)	-
≥6	33 (67.3)	-
Antibody titer (AU/mL)		
<500	4 (8.2)	-
500-1000	4 (8.2)	-
>1000	41 (83.7)	-

ml. Thirty-three subjects (82.5) aged 25-39 years had antibody titer >1000 AU/ml. Seventeen subjects (89.4) in the overweight BMI category had antibody titer >1000 AU/ml. Thirty-five subjects (83.4) with no comorbidities had antibody titer >1000 AU/ml. Twenty-nine subjects (80.6) with no previous history of COVID-19 infection had antibody titer >1000 AU/ml. In this study, 27 subjects (81.8) who had the 3rd booster vaccine ≥6 months from the second vaccine had antibody titer >1000 AU/ml. Four subjects (9.5) had antibody titer <500 AU/ml, while none of them had a comorbid disease. Of these 4 subjects, one had a history of previous COVID-19 infection. In this study, there was no significant correlation between antibody titer and gender, age, BMI, the presence of comorbid diseases, a previous history of infection with COVID-19, or the time between the 2nd and the booster vaccination.

Table 2. Antibody Titer for the First System

Characteristics	<500 AU/ml N (%)	500-1000 AU/ml N (%)	>1000 AU/ml N (%)	P*
Gender				
Female	2 (15.4)	1 (7.7)	10 (76.9)	0.54
Male	2 (5.6)	3 (8.3)	31 (86.1)	
Age (years)				
<25	1 (16.7)	0(0)	5 (83.3)	0.77
25-39	3 (7.5)	4(10)	33 (82.5)	
≥40	0 (0)	0 (0)	3 (7.3)	
BMI (kg/m^2)				
Underweight	0 (0)	0 (0)	2 (100)	0.68
Normal weight	3 (13.6)	3 (13.6)	16 (72.6)	
Overweight	1 (5.3)	1 (5.3)	17 (89.4)	
Obese	0 (0)	0 (0)	6 (100)	
Comorbidity				
Yes	0 (0)	1 (14.3)	6 (85.7)	0.59
No	4 (9.5)	3 (7.1)	35 (83.4)	
History of previous COVID-19 infection				
Yes	1 (7.7)	0 (0)	12 (92.3)	0.44
No	3 (8.3)	4 (11.1)	29 (80.6)	
2nd to 3rd vaccine duration (months)				
<6 months	2 (12.5)	0 (0)	14 (87.5)	0.28
≥6 months	2 (6.1)	4 (12.1)	27 (81.8)	

*Chi-square test.

Discussion

In this study, we found that age was not significantly related to antibody titer. This is in line with research conducted by Richards et al. (15) where there was no significant difference in antibody titer between subjects under 50 years old and those over 50 years old who received either Pfizer or Moderna vaccine. Sinto et al. (16) also found in their study that there was no significant correlation between antibody titer and age (16). A study conducted by Bates et al. (17) also showed no significant age-related trend among participants. Different results were found in the study by Cucunawangsih et al. (18) where age significantly correlated with antibody titer.

The study by Jalkanen et al. showed that after the first BNT162b2 mRNA vaccine dose, anti-S1 IgG antibody levels and neutralization titers were significantly lower in the older age group (55–65 years) compared to the younger age groups (20–34 and 35–44 years). However, after the second mRNA vaccine dose, the neutralization titers were similar in all the age groups (20–34, 35–44, 45–54, and 55–65 years) (19). Our subjects' mean age was 29 years old, younger than the subjects in the studies by Cucunawangsih et al. and Jalkanen et al.

Our study shows that antibody titer was not significantly correlated with gender. This result is also supported by the studies by Richards et al., (15), Sinto et al., (16) and Cucunawangsih et al. (18) who found in their studies that gender did not have a significant relationship with antibody titer. However, another study conducted by Ibarguengoitia et al. (13) showed a difference in terms of patient gender with significant correlations, since females had higher antibody titers. The study by Jalkanen et al. (19) showed that after the

second dose of BNT162b2 mRNA vaccine, female vaccinees had slightly higher neutralization titers than males, although the anti-S1 IgG antibody levels remained the same. Our study differs from the studies by Romero-Ibarguengoitia et al. and Jalkanen et al., because our study was dominated by male subjects and gender did not have any direct pathophysiology in the antibody-forming response (20).

In this study, we found no significant differences in antibody titers between the under-weight, normal weight, overweight and obese groups. In another study by Pellini et al. (21), it was also found that there was no significant difference in antibody levels after 7 days of giving the Pfizer mRNA vaccine booster in the underweight, normal weight, overweight, and obese groups. In another study by Yamamoto et al. (22), the antibody titer following the Pfizer mRNA vaccine was associated with BMI in the male gender group, where an increase in BMI in men was associated with a lower post-vaccination antibody titer, with P<0.001 for BMI <18.5 kg/m^2 and 27 kg/m^2. In women, an increase in BMI was not associated with post-vaccination antibody titer. Another study of the Pfizer mRNA vaccine by Nam et al. (23) showed that the antibody level was inversely correlated with weight, body mass index, body fat amount, and the body weight to height ratio in the Spearman correlation analysis. In multivariate analysis of categorized variables, a lower serum level of antibodies (<81.5%) was associated with weight ≥55 kg (OR: 9.01; 95 CI 1.44-56.40). The constant state of low-grade inflammation, present in overweight people, can weaken some immune responses, including those launched by T cells, which can directly kill infected cells (24). The increased adipose tissue causes leptin, TNF-α, and IL-6 to be overproduced, while adiponectin is decreased (25). An imbalanced adipocytokine profile can lead to chronic low-grade inflammation, which can induce B-cell immunosenescence, and impair antibody production post-vaccination (26).

In our study, it was found that seven subjects had comorbid diseases. We found no significant correlation between antibody titer and the presence of comorbidities. This is in accordance with a study conducted by Choi et al. (27), where there was no significant difference in antibody titer nAb or S-IgG levels 6 months after of the second dose of SARS-CoV-2 mRNA vaccination in healthy individuals compared to individuals with comorbidities. Another study by Eliakim-Raz et al. (28) showed the same result. Their study reported the evaluation of anti-spike (anti-S) IgG antibody titer after administration of the third dose of mRNA (Pfizer) vaccine in a population over 60 years of age in Israel. They found no significant correlation between comorbidities and post-vaccination antibody titers (28). Pellini et al. (21) in their study found that antibody titer was not significantly correlated with hypertension. Different results were found in the research by Sinto et al. (16), where there was a significant correlation between antibody titer and cardio-vascular disease and diabetes, with p-values of 0.02 and 0.038 respectively. Our study showed there was no correlation between comorbidity and antibody titer. Even though comorbidities are a risk factor for progression of COVID-19 into a severe and critical stage, comorbidities are not significantly correlated to the booster vaccination.

Prior infection may enhance protection from vaccination, raising the question of hybrid immunity. In several studies, the results showed that vaccinations carried out in groups with a history of being infected with COVID-19 had a much higher antibody response than groups that had not been previously infected. Anichini et al. (29) reported that nAb levels following the second dose of vaccine in the group who were not infected with SARS-CoV-2 were lower than following the first dose in the group with a history of COVID-19 infection. Their study also found that there was a significant correlation in IgG levels between the 1-2 month group and the 2-3 month group. The IgG level in the 1-2 month group was higher than the 2-3 month group, while the nAb level in the >3 month group was the highest of all the other groups. This result indicates that the booster response is more effective when the vaccine is given more than 3 months after being infected with

COVID-19 (29). The study by Krammer et al. (30) also demonstrated that a faster immune response was found in the single-dose mRNA group with a history of infection than in the group without a history of infection who had received the full dose. Krammer also reported that SARS-CoV-2 antibodies formed more quickly in the group with a history of infection, where antibody titer had started to form within 0-4 days after vaccination, while in the group without a history of infection the average antibody titer began to form at 9-12 days after vaccination (30). A study conducted by Demonbreun et al. (31) on 33 people who had received a booster mRNA vaccine found that an antibody response formed within 6-10 days after receiving the booster, and the concentration of IgG in the group with a history of infection was higher than in the group without a history of infection.

In our study, we did not find a significant correlation between antibody levels and a history of COVID-19 infection. Although our data did not show any significant difference, from the percentage we can see there was a tendency for subjects with a history of COVID-19 infection to have a higher antibody titer than subjects without a history of COVID-19 , in line with other studies (5, 11). The difference may not be seen as statistically significant due to the small number of samples.

Zhao et al. (32) found in their research that the levels of antibody formation against the omicron variant of COVID-19 were 62, 56, and 100, respectively, for recipients of the inactivated virus booster vaccine, recipients of the protein subunit ZF2001 at a one-month interval, and recipients of the protein subunit ZF2001 at a four-month interval. In addition, antibody levels to the omicron variant compared to the SARS-CoV-2 prototype were 5.1 times lower in the inactivated virus vaccine group, 10.26 times in the ZF2001 protein subunit vaccine group at a one month interval, and 3.1 times in the ZF2001 protein subunit vaccine group at a four month interval. This shows that a longer interval to booster administration is directly proportional to the increase in antibody titer (32). This result is expected because antibody maturation time is better in the group with a longer interval (33).

Our study did not show any significant difference in the antibody titer between intervals less than six months and more than six months. Our study used an interval duration of 6 months because in Indonesia's national program the administration of boosters is at an interval of 8 months after the first dose of vaccination in health workers. However, we compared the percentages that showed that subjects with boosters <6 months were better than subjects with a ≥6 months booster, with an average interval of almost 6 months. This contrasts with Zhao's study and a meta-analysis by Cromer et al. that showed that the administration of a booster at a six-month interval gave a 4.9-fold increase in titer compared to administration at a one-month interval, where it only increased by 1.3-2.1-fold (32, 34). Our study could have shown different results if we had more subjects and checked their antibody titers in the first, third, and sixth months.

There are concerns that the efficacy of the previous two doses vaccines might decrease due to weakening antibody levels and the appearance of new variants of SARS-CoV-2, with amino acid changes in the spike protein and elsewhere in the viral genome (5). A study in UK conducted by Andrews et al. showed evidence of a substantial increase in protection against symptomatic COVID-19 disease after a booster dose of BNT162b2 or mRNA-1273 vaccine during the period when the Delta variant was the dominant strain in that country. Very high levels of protection were seen against hospitalization or death with a BNT162b2 booster (35). According to the Ministry of Health's weekly report on COVID-19 of October 2021, in Indonesia, the Delta Variant sequence still dominated the reported variants. Sequencing results showed the Variant of Concern (VoC) Delta in as many as 98.9 cases (274/277) (36). However, we do not know the COVID-19 variant for sure because we did not perform genome sequencing at the time in the patients infected with COVID-19. We consider that 3 months should pass before giving the booster vaccination if the delta variant is the most common variant in Indonesia.

Limitations of the Study

The main limitation of this study is the relatively small number of subjects and that it is limited to one center. Data about the time duration between booster injection time and the antibody laboratory testing would improve the results of this study.

Conclusion

In this study, it was found that the antibody titer after receiving the Moderna mRNA vaccine booster was sufficient within 3 months after vaccination. There were 41 subjects (83.7) with antibody titer >1000 AU/ml. S-IgG antibody levels were maintained for 3 months after the booster vaccination. In this study, antibody titers did not have a significant correlation with the variables of gender, age, BMI, comorbidities, history of being infected with COVID-19 and time after vaccination. Further studies are required to better understand the factors that can affect antibody titers when using the Moderna vaccine. In addition, a similar study with more subjects and multi-centered research would be beneficial and may provide more significant correlations.

What Is Already Known on This Topic:
Vaccine is beneficial against some diseases. There are some options for COVID-19 vaccine with some differences in efficacy. Study of COVID-19 booster vaccination is limited in Indonesia. Moderna shows relatively low efficacy in comparison with other vaccines in terms of main dose administration (2).

What This Study Adds:
The efficacy of Moderna vaccine as a booster dose is shown. This study can be a guide for booster administration, mainly in Indonesia.

Authors' Contributions: Conception and design: RH, APM, FA, ZD, DDW, RAP, HML, VD, GCF, AW, MHA, Y, SA, MR, NDI and AG; Acquisition, analysis and interpretation of data: RH, APM, FA, ZD, DDW, RAP, HML, VD, GCF, MR, NDI and AG; Drafting the article: RH, APM, FA, ZD, DDW, RAP, HML, VD and GCF; Revising it critically for important intellectual content: RH, AW, MHA and Y; Approved final version of the manuscript: RH, AW, MHA and Y.

Conflict of Interest: The authors declare that they have no conflict of interest.

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