Jurnal Kedokteran dan Kesehatan: Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya
Volume 10, No 2. 2023/DOI: 10.32539/JKK.V10I2.20872
p-ISSN 2406-7431; e-ISSN 2614-0411

ANTIBODY IgG LEVELS AND ADVERSE EVENTS FOLLOWING IMMUNIZATION AFTER THIRD DOSE OF MODERNA VACCINE IN HEALTHWORKERS AFTER TWO DOSES OF SINOVAC VACCINE

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Received 23 Maret 2023; accepted 17 Mei 2023; published 23 Mei 2023

Abstract

Health Care Workers (HCWs) are a top priority to receive the vaccination for Coronavirus Disease 2019 (Covid-19). After two doses of the Sinovac vaccine as the primary vaccine, protection against Covid-19 weakens over time, so a booster vaccination is considered to produce more antibodies. In addition, each vaccine is inseparable from Adverse Event Following Immunization (AEFI). This study compares antibody levels and AEFIs between two doses of the Sinovac vaccine with the Moderna booster. This research is an observational analytic study with a cross-sectional study design and the sampling method is random sampling with a total of 74 HCWs using a consecutive sampling method. Samples that had received two doses of the Sinovac vaccine or booster doses of the Moderna vaccine after two doses of the Sinovac vaccine were included. Samples that had been infected with Covid-19 before vaccination were excluded. IgG antibody levels were measured using Chemiluminescent Microparticle Immunoassay (CMIA), while vaccine type and AEFI were gathered via questionnaire. The severity of AEFIs is based on WHO classification. The data analysis used the Mann-Whitney and Chi-Square tests with a 95% Confidence Interval (CI) to determine the relationship between variables. Twenty-nine subjects received two doses of the Sinovac primary vaccine (38.2%), and forty-five received the Moderna booster vaccine (59.2%). In booster doses of the Moderna vaccine recipients, antibodies tended to be higher, and the most common AEFIs were systemic. There was a significant difference in IgG antibody levels between recipients of two doses of the Sinovac vaccine (median=2888.8 AU/mL) and booster Moderna vaccine recipients (median=18081.04 AU/mL) ($p=0.000$, $p<0.05$). There were significant differences in AEFI in the groups receiving two doses of the Sinovac vaccine and those receiving the booster vaccine ($p=0.000$, $p<0.05$). This study concludes that there is a significant correlation between administering the Covid-19 vaccine and post-vaccination IgG antibody levels and AEFI.

Keywords: Covid-19, vaccines, antibodies, AEFI

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus that causes Coronavirus Disease 2019 (Covid-19). This virus first appeared in Wuhan in December 2019, resulting in an outbreak that spread rapidly globally. This condition led to the World Health Organization (WHO) declaring Covid -19 as a pandemic on March 11, 2020.[1] In this situation, where there are no definitive treatment options to overcome SARS-CoV-2 infection, vaccines are one of the interventions in the pandemic in the hope of achieving "herd immunity".[2]

Quantitative tests to detect anti-SARS-CoV-2 antibodies can help determine specific antibody responses to vaccines, individual antibody levels, and longitudinal monitoring of antibody responses.[3] Research conducted by Braun *et al* (2022), found that immunoglobulin G (IgG) antibody levels can be a reference in predicting the protection an individual has against SARS-CoV-2 infection. Until thelevel of antibodies after vaccination can be an illustration to determine how much protection a person gets after vaccination.[3,4]

The vaccination program in Indonesia uses the Sinovac vaccine for primary vaccination, given in two doses with an interval of about 14-28 days.[5] The duration of immunity induced by the primary vaccine is unknown, giving rise to concerns that the immunity provided by the primary vaccine has decreased, so further consideration is given to giving a booster dose. In several previous studies, it was known that there was a gradual decrease in antibodies over time when using two doses of inactivated vaccines. In the vaccination program in Indonesia, Health Care Workers (HCWs) also have the priority to get a booster vaccine, namely the Moderna vaccine.[6–8]

Adverse events following immunization (AEFI) are any undesirable medical events that occur after immunization and do not necessarily have a causal relationship with vaccine use. Side effects can include unwanted signs, abnormal laboratory findings, symptoms or disease. Each vaccine product must meet the requirements for safety and effectiveness, however, no vaccine is free of AEFI.[8] Vaccine administration, both primary and booster, will often cause AEFI (Adverse Events Following Immunization). Previous studies found that the most common AEFIs in both the Sinovac and Moderna vaccines were relatively the same but with different percentages.[9,10] On other similar study, it was found that there was a relationship between sex, age, and levels of SARS-CoV-2 IgG antibodies with KIPI. Most AEFIs, especially after the second dose, are significantly associated with higher levels of IgG antibodies and are directly proportional to the increase in side effects.[4]

Research on vaccine administration and its relationship with IgG antibody levels and AEFI still needs to be improved. In Bengkulu, this research is the first study regarding the relationship between vaccine types with IgG levels and AEFI. Therefore, the authors will examine the differences in IgG levels and AEFIs that occurred in recipients of two doses of the Sinovac vaccine and Moderna booster vaccine.

2. Method

This study is an observational analytic study with a cross-sectional study carried out from July 2021 to December 2021 at Harapan dan Doa Hospital (RSHD) Bengkulu City. The population is Health Care Workers (HCWs) who have received the Covid-19 vaccine. The accessible population is the HCws at RSHD Bengkulu City who have received two doses of the Sinovac vaccine or a booster dose of Moderna after two doses of the Sinovac vaccine.

Sampling was done by consecutive sampling technique using the sample calculation formula to test the hypothesis of two proportions (Lemeshow, 1997).

$$n' = \frac{Z_\alpha\sqrt{2P(1-P)} + Z_\beta\sqrt{P_1(1-P_1)+P_2(1-P_{2)}}^2}{(P_1-P_2)^2}$$

Descriptipn:

n : Total samples
Zα : Z value for α or type I error (α=5%, Zα = 1,96)
Zβ : Z value for β or type II errors (β 80%, Zβ = 0,84)
P : (P1 + P2)/2
P1 : Estimated proportion in group 1 (Sinovac) (Obtained from previous studies); P1 = 0,416 (Xia et al., 2020)
P2 : Estimated proportion in group 2 (Sinovac - Modernda) (Obtained from previous studies); P2 = 0,736 (Choi et al., 2021)

$$n' = \frac{\{1.96\sqrt{2(0.576)(0.424)} + 0.84\sqrt{0.416(1-0.416)+0.736(1-0.736)}\}^2}{(0.416 - 0.736)^2}$$

$$n' = 37$$

$$n = 2 \times n' = 74$$

The results of sample calculations were 74 samples with **inclusion criteria**: HCWs at the Bengkulu City Hospital, recipients of two doses of the Sinovac vaccine, recipients of Moderna booster dose in the same hospital after two doses of Sinovac vaccine, recipients of the booster dose, get a booster dose no later than 6 months after receiving the second dose of Sinovac vaccine, taking samples no later than nine months after vaccination, and willing to participate in the study. **The exclusion criteria** were SARS-CoV-2 infection prior to vaccination.

The independent variable in this study was the administration of Covid-19, and the dependent variable was the levels of IgG and AEFI antibodies. Covid-19 and AEFI vaccine data will be collected using a questionnaire. IgG antibody levels are ratio data to be measured using the Chemiluminescent Microparticle Immunoassay (CMIA) method. The SARS-CoV-2 IgG II Quant Assay from Abbott can detect IgG antibodies to the SARS-CoV-2 S protein in the serum or plasma of individuals infected with SARS-CoV-2 using the CMIA method. This test has also detected an immune response to a protein-based S-RBD (Receptor Binding Domain) vaccine with or without prior infection. Abbott's SARS-CoV-2 IgG II Quant Assay measurement interval is 21.0 AU/mL – 40000 AU/mL. Antibody levels above 50 AU/mL in this test are considered positive.[11]

The data obtained in the study will be further processed using software Microsoft Excel 2019 and Statistical Program for Social Science (SPSS) version 26. To find out the relationship between variables, the data analysis used is the Mann-Whitney and Chi-Square test with degrees of 95% CI.

Table 1. Subjects Characteristics

	Total (n = 74)	**Vaccine Doses**	
		Subjects Receiving Two Primary Doses of Sinovac (n = 29)	**Subjects Receiving Moderna Booster Doses (n = 45)**
Age, n(%)			
<50	66 (89,19)	29 (39,19)	37 (50)
≥ 50	8 (10.81)	0 (0)	8 (10.81)
Gender, n (%)			
Woman	55 (74,32)	20 (27,32)	35 (47,30)
Man	19 (25,68)	9 (12,16)	10 (13.51)
BMI (kg/m2), n (%)			
<25	35 (47,30)	16 (21,62)	19 (25,68)
≥25	39 (52,70)	13 (17,57)	26 (35,14)
Chronic Disease, n (%)	11 (14.78)	4 (5,41)	7 (9.46)
Drug Consumption, n (%)	10 (13.51)	4 (5,41)	6(8,11)
History of Infection After Vaccination, n (%)			
Infected	36 (48,65)	24 (32,43)	12 (16,22)
Not Infected	38 (51,38)	5 (6.76)	33 (44,59)

3. Results

Of the 74 subjects, 29 only received two doses of Sinovac (38.2%), 45 received the third dose of Moderna vaccine (59.2%), fifty-five female subjects (74.32%), and 19 male subjects (25.68%). Of all subjects, 66 of them were under 50 years old (89.19%), and eight subjects were over 50 years old (10.81%) (**Error! Reference source not found.**).

Most systemic reactions occurred in the Moderna booster dose group (43.2%). Meanwhile, without AEFI, it most often occurred in subjects who received two doses of

Sinovac (25.7%). Severe AEFI did not occur in either subjects who received the primary dose of the Sinovac vaccine or subjects who received booster doses of the Moderna vaccine in this study (Figure 1).

In this study, subjects who received the booster dose Moderna vaccine had a more extensive range of IgG antibody levels and tended to be higher (median 18081.4 UmL; IQR=6359.85 AU/mL – 31912.15 AU/mL) than those who received only two Sinovac vaccine doses (median=2888.8 AU/mL; IQR = 859.85 AU/mL – 6536.15 AU/mL). (Figure 2).

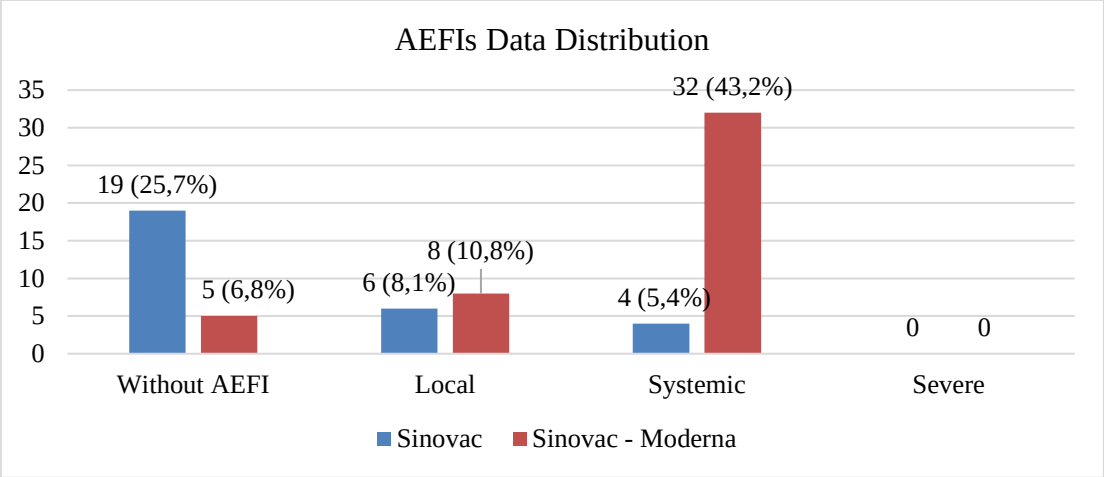

Figure 1. Data Distribution of Adverse Events Following Immunization (AEFI)
Analysis of the relationship between vaccines and the severity of AEFIs was carried out using the Chi-Square Test and the results obtained were p = 0.000

The Mann-Whitney test is used to analyze differences in post-vaccination IgG antibody levels in subjects who received two doses of the Sinovac vaccine and those who received a booster dose of the Moderna vaccine. The results of this analysis obtained p = 0.000 (Supp. Table 5), meaning that statistically, there was a significant difference in IgG antibody levels between the Sinovac vaccine group and the Sinovac – Moderna (booster) vaccine group (p=0.000, p <0.05) (Figure 2). Using the Chi-Square test to analyze the correlation between vaccine administration and AEFIs, the p-value obtained from this analysis is p = 0.000 (Supp. Table 6). The results from this statistical analysis mean that there was a significant AEFI difference between the Sinovac vaccine group and the Sinovac – Moderna (booster) vaccine group (p=0.000, p <0.05) (Figure 1).

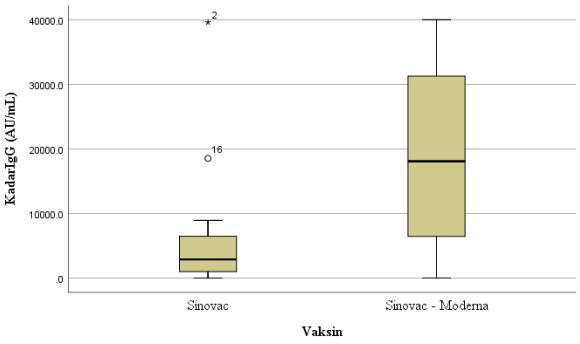

Figure 2. Post-Vaccination IgG Antibody Levels
Data analysis using the Mann-Whitney test, the p-value obtained 0.000 (p = 0.000, p<0.05).

4. Discussion

Of the 74 subjects, all subjects received two doses of Sinovac (38.2%) and 45 of them received a third dose, the Moderna vaccine (59.2%). Female subjects were 55 (74.32%) and male subjects were 19 (25.68%). Of all subjects, 66 were under 50 years old (89.19%) and 8 subjects were over 50 years old (10.81%).

The results showed that systemic reactions were most prevalent in recipients of the Moderna booster dose (43.2%). While in subjects receiving two doses of Sinovac, the group without AEFI was the group that most arose (25.7%). This is directly proportional to the research of Chen et al (2021), in inactivated vaccines, local reactions such as pain, redness, and swelling are only slightly higher or even the same as the control group. While systemic reactions such as fever, headache, and fatigue had no difference with the control group. In mRNA vaccines, systemic and local reactions both had significantly higher values than the control group. This suggests that inactivated vaccines have a lower incidence of AEFI compared to mRNA vaccines. [12]

In this study, it was also found that IgG antibody levels in the infected group (median = 6464.65 AU / mL; IQR=1853.7 AU/mL – 27898.3 AU/mL) had a lower median compared to the median in the uninfected group (median=9640.35 AU/mL; IQR=3119.2 AU/mL – 20932.42 AU/mL), however, the range of antibody levels that appeared was greater in the infected group compared to the uninfected group. The results found that subjects who received a booster dose of Moderna had a greater range of IgG antibody levels and tended to be higher (median 18081.4 UmL; IQR=6359.85 AU/mL – 31912.15 AU/mL) compared to subjects who received only two doses of sinovac vaccine (median=2888.8 AU/mL; IQR = 859.85 AU/mL – 6536.15 AU/mL). This is in line with the results of research by Cucunawangsih et al (2022) which showed that in the administration of the third dose of vaccine using the Moderna vaccine after two doses of the Sinovac vaccine, there was an increase compared to two doses of the Sinovac vaccine (from a median of 41.7 AU/mL to 28394 AU/mL).[13] The same results were also found in the Keskin et al (2022) study, there was a significant increase after receiving the third dose of mRNA vaccine compared to antibody levels after two doses of inactivated vaccine. [14]

The levels of IgG antibodies that appear at each degree of AEFI tend to be different. Antibodies arising in the group without AEFI, tended to be lower than in the other group (median = 5360.75 AU / mL; IQR=1371.175 AU/mL – 6935.4.0 AU/mL). In local AEFI, the variation in antibodies that arise is more than in the group without AEFI, but has a lower median compared to the group without AEFI (median = 3420.0 AU / mL; IQR=1919.9 AU/mL – 13725.1 AU/mL). Meanwhile, in systemic AEFI, the median tends to be higher than other groups (median=18336.8 AU/mL; IQR=6926.4 AU/mL – 35213.6 AU/mL). In this study, it was also found that there were differences in antibody levels arising between local AEFI (median = 3420.0 AU / mL) and systemic AEFI (median = 18336.8 AU / mL), even though both were minor AEFI.

Using the Mann-Whitney test, we found a statistically significant relationship between IgG antibody levels in subjects who received two doses of the Sinovac vaccine and subjects who received a booster dose of the Moderna vaccine ($p=0.000$, $p<0.05$). In this study, we found that IgG antibody levels tend to be higher in the recipient of a booster dose of Moderna vaccine (median 18081.4 UmL; IQR=6359.85 AU/mL – 31912.15 AU/mL) compared to the recipient of only two doses Sinovac vaccine (median=2888.8 AU/mL; IQR = 859.85 AU/mL – 6536.15 AU/mL). A similar finding was found in a study by Cucunawangsih et al. (2022); after administration of the third dose (booster) of the Moderna vaccine, anti-S antibodies increased significantly from a median of 47.1 U/mL to 28394 U/mL and a $p<0.0001$ value was obtained.[15] Another similar study by Yigit et al. (2022) found a significant

relationship between the booster dose and IgG antibody levels. Two doses of inactivated vaccine.[16] This shows that booster doses of mRNA vaccine can increase IgG antibody levels after two doses of inactivated vaccine. The antibody level after vaccination can predict how much protection a person has against SARS-CoV-2 infection after vaccination.[4] This is in line with the results of other studies, which found that IgG antibody levels were significantly related to the protection rate. Higher antibody levels correlate with a reduced risk of symptomatic infection.[17] The level of Anti-S IgG obtained after vaccination is known to increase protection against infection. After two doses of AstraZeneca, it is estimated that protection against infection will last for 2-3 months with a protection level of at least 67%, 5-8 months after two doses of Pfizer in subjects with no previous infection, and 1-2 years for unvaccinated subjects after natural infection.[18] The same study found that the IgG antibody levels in the Pfizer vaccine were higher compared to AstraZeneca. This shows that the Pfizer vaccine, which produces higher antibodies, provides a better protection compared to AstraZeneca.[18,19]

In this study, to determine the differences in AEFI in subjects who received two doses of the Sinovac vaccine and those who received a booster dose of the Moderna vaccine, an analysis was performed using the Chi-Square test. The analysis showed a statistically significant relationship between these two variables ($p=0.000$, $p<0.05$). The most common AEFI is systemic, arising from the booster doses of Moderna vaccine recipients. While in the two doses of the Sinovac vaccine, the data that appeared the most were without AEFIs. The same results were found in a study by Supangat et al. (2021) in recipients of two doses of the Sinovac vaccine; the data that appears the most is without AEFIs, both at the first dose (62%) and the second dose (65%). In subjects with AEFI, the most common AEFIs are local, 45% in the first dose and 67% in the second dose.[9] In another study by Adjobimey et al. (2022), it was found that the Sinopharm vaccine, which is an inactivated vaccine, causes AEFI with a smaller percentage than the Moderna vaccine.[20]

Differences in these types of vaccines will cause different immune reactions. Differences in immune responses between inactivated and mRNA vaccines mainly lie in the presence or absence of a cellular immune response. In inactivated vaccines, the genetic material has been killed. The vaccine only triggers antibody-mediated immune responses and does not trigger a T-cell response. On the other hand, the mRNA vaccine, significantly Moderna, will trigger cellular immune responses. This cellular immune response can be seen from the increase in T-cells CD4+.[21] mRNA vaccines induce inflammation through several pathways, such as releasing cytokines and chemokines and activating Antigen Presenting Cells (APC), Natural Killer Cells (NKs), Antigen-Specific T Cells, and B Cells. From these several pathways, AEFIs that occur after vaccination are probably caused not only by antibodies but by other inflammatory pathways. Thus, antibody levels are not the only factor that allows AEFIs to occur, and individuals who do not experience AEFIs or only experience local AEFIs still have protection against SARS-CoV-2.[22]

5. Conclusion

Statistically, there is a significant difference between IgG and AEFI antibodies that occurred in recipients of two doses of the Sinovac vaccine and Moderna booster vaccine. IgG antibody levels tend to be higher in Moderna booster vaccine recipients, and systemic AEFIs are more common in Moderna booster vaccine recipients. More research is needed to identify the degree of protection between patients who receive a booster dosage and those who do not, as well as the roles of other inflammatory pathways (e.g T cells) in causing AEFIs.

Acknowledgments

Thanks and appreciation are given to the Faculty of Medicine and Health and the University of Bengkulu who have funded through the 'Antibody Levels against Covid-19 in Health Workers Receiving Covid-19 Vaccination at Harapan dan Doa Hospital Bengkulu City' research program. We would like to thank students and staff of medical education undergraduate program University of Bengkulu and Healthcare Workers of Harapan dan Doa Hospital Bengkulu City.

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