Short Communication

Assessment of Post-Vaccination Immunologic Responses in Inactivated Virus COVID-19 Respondents

Elisabeth L. S. Setianingrum, Kartini Lidia[1], Kristian Ratu[2], Samson E. Teron[3]

Departments of Clinical Pathology, [1]Pharmacology, [2]Obstetrics and Gynecology, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, Kupang City, East Nusa Tenggara, [3]Indonesian Red Cross Blood Transfusion Unit, East Nusa Tenggara Province, Indonesia

Abstract

Introduction: The Indonesian Government's plan to contain the COVID-19 pandemic, aside from implementing health protocols, also involves vaccinating everyone with the inactivated SARS CoV2 vaccine until herd immunity is reached. The aim of this study was to assess the post-vaccination immune response to inactivated SARS CoV2 vaccine, namely Sinovac/Sinopharm, by measuring the antibodies (IgM and IgG) in subjects after their second dose of vaccination. **Materials and Methods:** The design of the study was a cohort study using simple random sampling with 51 respondents aged 18–56 years who had received two doses of inactivated SARS-CoV-2 vaccine. All respondents were screened for SARS-CoV-2 infection prior to inclusion. Serum IgM and IgG antibodies were detected using a specific and sensitive automated chemiluminescent immunoassay (CLIA). CLIA uses the Cut Off Point (COI) value of >1 AU/ml for IgM and the Reactive Value of >10 AU/ml for IgG. **Results:** This study showed that the IgM levels using a reactive Cut Off Point (COI) >1 were 18% in the first month, 14% in the third month, and 10% in the sixth month. There was a constant decline in the third comparison. Meanwhile, compared to the first month, 59% of respondents had IgG levels with reactive values over 10 AU/ml, which after decreasing by 35% in the third month, the number increased by 47% in the sixth month. **Conclusion:** It has been evident that IgG and IgM antibody response could be induced by inactivated SARS-CoV-2 vaccine which can be influenced by age and detection time after the second dose of vaccination. Boosters, however, must be given after six months of the second dose, since antibody levels were seen to decrease after this period.

Keywords: COVID-19, immunoglobulin, inactivated virus, neutralizing antibody, vaccination

Introduction

In 2019, the Corona Virus Disease 2019 (COVID-19) pandemic originated in Wuhan, China, and has spread worldwide. The symptoms of COVID-19 include fever, dry cough, tiredness, aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell, skin rash, or discolored fingers or toes. An incubation period of five to six days is required for the COVID-19 virus to cause symptoms. The longest incubation period lasted fourteen days.[1]

COVID-19 patients in Indonesia as of March 12, 2021, were 6,412 new cases, bringing the total to 1,410,134 positive cases. The government has made various efforts to contain the spread of COVID-19, including introducing and practicing strict health protocols, including wearing masks, washing hands with soap and running water, avoiding crowds, limiting mobilization, as well as tracing quarantine efforts to the point where vaccination efforts are used to contain the infection as well as help boost the economy.[2-5]

The ability to achieve post-vaccination neutralizing antibodies, which will prevent the SARS CoV2 virus from entering the target host cell, and prevent infection with spike-binding antibodies, is directly proportional to the ability to achieve post-vaccination antibody neutralization and to support and strengthen the immune response.[6-10] It has been reported that the antibody response of post-infection SARS COV2 patients

Address for correspondence: Dr. Elisabeth L. S. Setianingrum, Department of Clinical Pathology, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, Kupang City, East Nusa Tenggara, Indonesia.
E-mail: elisabeth_setianingrum@staf.undana.ac.id

Access this article online

Quick Response Code:

Website: www.ijcm.org.in

DOI: 10.4103/ijcm.ijcm_477_22

How to cite this article: Setianingrum EL, Lidia K, Ratu K, Teron SE. Assessment of post-vaccination immunologic responses in inactivated virus COVID-19 respondents. Indian J Community Med 2023;48:357-60.

Received: 03-06-22, **Accepted:** 01-02-23, **Published:** 07-04-23

was greatest at two weeks to 28 days post-infection and that it declined until 3-4 months post-infection, in addition to the level of IgG antibody titers against spike protein and nucleoprotein, which are correlated with neutralizing antibodies (nAb).[11,12]

The level of neutralizing antibodies (nAbs) formed following vaccination will accelerate the occurrence of herd immunity and reduce symptoms and the spread of COVID-19. This will be evaluated through a study conducted on residents of Kupang city after vaccination. Is there a significant immune response arising from neutralizing antibodies obtained post-vaccination an inactivated vaccine (Sinovac) recipients? This study will evaluate the Sinovac/Sinopharm vaccine after the second dose.

Research Methods

The cohort study was observed for the next six months, namely from administering the Sinovac/Sinopharm vaccine and observed in the first, third, and sixth months. The sample was selected by simple random sampling from 64 people who signed the informed consent and met the inclusion and exclusion criteria.

The inclusion criteria were respondents aged 18- and 56 years (adult age) who had received the Sinovac/Sinopharm inactivated virus vaccine. Exclusion criteria were COVID survivors/infected during the study, recipients who did not receive two doses of the vaccine, and those who were sick/suffering from serious diseases and comorbid. There were three drop-outs of respondents due to several reasons, thus, their samples were discarded.

Approximately 3ml of blood was drawn from the Median Cubital Vein/peripheral vein, which was easy to collect and centrifuged at 2500 rpm for 5 minutes to separate the blood cells and serum. In order to check the levels of IgM and IgG, the blood serum was then sent to the Provincial Blood Transfusion Unit of East Nusa Tenggara, Indonesia, which is commonly used to measure antibody levels in convalescent plasma for COVID-19 survivors. CLIA uses the Cut Off Point value of greater than one for IgM and the Reactive Value greater than 10 AU/ml for IgG.

We performed the normality test on the data; an abnormal distribution was found, so we performed a Friedman comparison test and a Wilcoxon *post hoc* test.

Results

Distribution of respondent

Based on Table 1 about the characteristics of the research respondents above, it can be seen that the age distribution is in the age range of 21-30 years old and the least is in the range of 51-60 years old.

At the time of collection, the IgM levels using a reactive Cut Off Point (COI) >1 were 18% in the first month, 14% in the third month, and 10% in the sixth month. There was a constant decline in the third comparison. Meanwhile, compared to the first month, 59% of respondents had IgG levels with reactive values over 10 AU/ml, which after decreasing by 35% in the third month, the number increased by 47% in the sixth month.

Table 1: Characteristics of respondents

Variable	Category	Frequency (N)	Percentage (%)
Age (year)	21-30	19	37.3
	31-40	16	31.4
	41-50	13	25.5
	51-60	3	5.8
Gender	Male	30	58.5
	Female	21	41.2
IgM First Month	< 1 COI	42	82
	>1 COI	9	18
IgM Third Month	< 1 COI	44	86
	>1 COI	7	14
IgM Sixth Month	< 1 COI	46	90
	>1 COI	5	10
IgG First Month	< 10 AU/ml	11	41
	>10-100 AU/ml	24	47
	>100 AU/ml	6	12
IgG Third Month	< 10 AU/ml	33	65
	>10-100 AU/ml	17	33
	>100 AU/ml	1	2
IgG Sixth Month	< 10 AU/ml	27	53
	>10-100 AU/ml	12	23
	>100-1000 AU/ml	8	16
	>1000 AU/ml	4	8

The most age distribution is 42 years old as many as six respondents (11.7%) as shown in Figure 1, and the highest range is at the age of 21-30 years old.

Results of post-vaccination IgM antibody examination in all respondents

Table 2 depicts the distribution of antibody data (IgM and IgG) formed in the respondents as a whole, as well as differences in levels that occur due to differences in the sexes of men and women during the first, third, and sixth months. The results of the examination are stated in the Cut Off Index (COI) for IgM and AU/ml for IgG in the table. Because the data in Table 2 is not normally distributed, it is presented in the median (mean-max). Below are images 2 and 3 box plots comparing the levels of the three examinations in the first [Figure 2], third, and sixth months. In the first month, respondents' IgG levels ranged from 1.53 to 328.77 AU/ml.

The data distribution is not normal, as evidenced by the box plot comparison of IgM antibody levels in the three groups, with the mean IgM Cut Off Point (COI) from the first month decreasing in the third and sixth months (0.65; 0.485; 0.403), and the median (min-max) 0.4 (0.14-3.62) in the first month, 0.24 (0.1-3.49) in the third month, and 0.21 (0.08-2.16) in the sixth month.

Based on the box plot comparison of IgG antibody [Figure 3] levels in the three groups, it is clear that the data distribution is not normal, with varying levels of IgG in the first month; the mean IgG is 43.66 AU/ml, 19.58 AU/ml (decreased), and 146,70

Table 2: List of IgM and IgG antibody levels in respondents

	Ig First Month Med (min-max)	*P*	Ig Third Month Med (min-max)	*P*	Ig Sixth Month Med (min-max)	*P*
IgM total (COI)	0.4 (0.14-3.62)	0.000	0.24 (0.1-3.49)	0.000	0.21 (0.08-2.16)	0.000
IgG total (AU/ml)	15.11 (1.53 – 328.77)	0.000	6.93 (1.14 – 128.74)	0.000	7.19 (0.92 – 1658.20)	0.000
IgM (COI) Male	0.37 (0.14-3.62)	0.000	0.22 (0.1-3.49)	0.000	0.18 (0.08-2.16)	0.000
IgM (COI) Female	0.45 (0.14-2.05)		0.26 (0.1-2.27)		0.29 (0.09-1.7)	
IgG (AU/ml) Male	11.86 (1.53-249.20)	0.000	4.8 (1.14-128.74)	0.000	4.34 (0.92-402.91)	0.000
IgG (AU/ml) Female	26.3 (4.55-328.77)		9.64 (1.93-98.44)		34.5 (0.94-1658.20)	

P<0.05 data is not normally distributed. Description : COI (Cut Off Point)

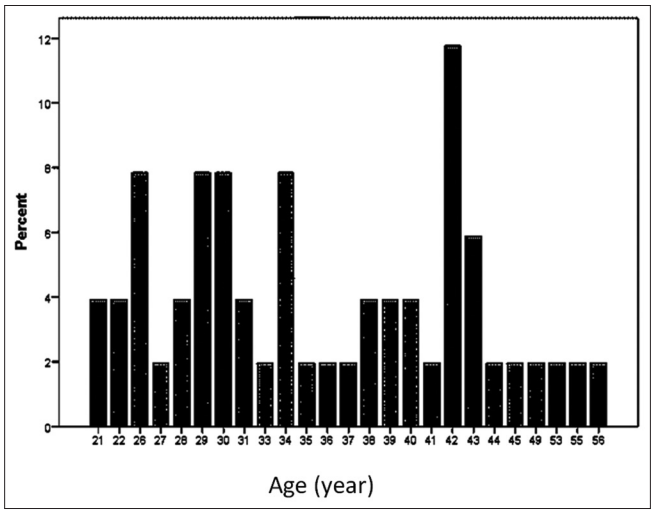

Figure 1: Bar graph of the age distribution of respondents

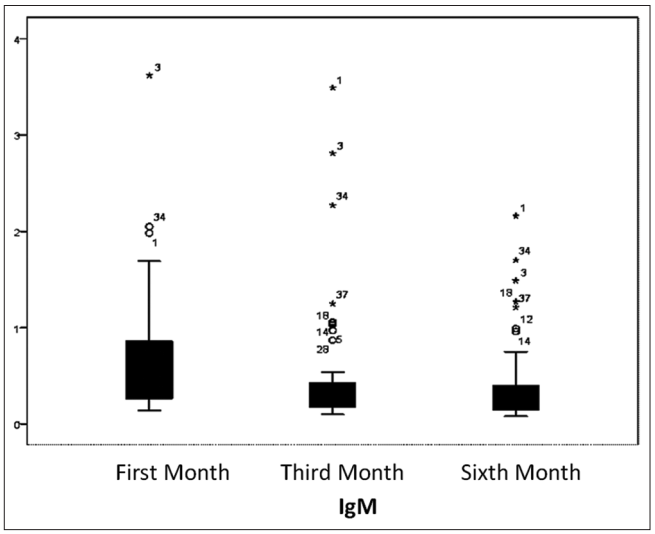

Figure 2: Box Plot of IgM antibody levels at months 1, 3 and 6 in respondents with measured levels in the Cut off Point (COI)

AU/ml (an increase) again in the sixth month. In the first, third, and sixth months, the median (min-max) is 15.11 (1.53-328.77); 6.93 (1.14-128.74); and 7.19 (0.92 – 1658.20). The data for the sixth month is more diverse because respondent 6 has the highest antibody level, followed by respondents 38, 8, 16, and 50.

Furthermore, because the data distribution was not normal, the Friedman Comparative Test was used, and the *P* value = 0.000 was obtained in more than two pairs of groups. Overall antibody levels decreased steadily after the Friedman test was followed by the *Post Hoc* analysis test (Wilcoxon test). The highest level was found in the first month following vaccination, followed by a decrease in the third month and a further decrease in the sixth month. IgM with a reactive COI greater than one and reactive IgG greater than 9 AU/ml. In the sixth month of research data, five respondents (10%) had reactive IgM, and 24 (47%) had reactive IgG. For some respondents, there was a significant increase at the end of the due to several causes; in those who had a number of IgG antibodies greater than 100 AU/ml, there was even the possibility of experiencing COVID-19 infection with mild symptoms.

Discussion

Research by Santi Theresia *et al.*, 2021, older age has weaker antibodies than youngsters, where there is a decrease in cellular and humoral immunity, which will affect the success of vaccination.[13-15] The highest sex distribution in this study was male at 58.5% compared to female at 41.2%. For the sex characteristics of antibodies in this study, it was seen that women had higher levels than men. In this study, there were seven dropout respondents from the initial 64 samples, namely those who were infected with COVID-19 before the sixth month of sampling, all of whom had mild symptoms and were not hospitalized.

IgM (Immunoglobulin M), IgA, and IgG were the first antibodies formed after vaccination. Although IgA was discovered in the mucosa, it was not studied in this study. IgM is the initial antibody response to occur, and it is quickly followed by IgG in a low-to-moderate titer. The IgM response will then drop on the second reinfection or immunological stimulation, whereas the IgG response would rapidly increase. As with IgG, the same is true for the cellular T response. Immunoglobulin M levels are temporary and rapidly decline 14-21 days after exposure, before being replaced by IgG (Immunoglobulin G) for months to years of more stable levels.[16-18]

Women have higher levels of Immunoglobulin IgM and IgG than men, as seen in the sex differences. Adult women have higher levels of Immunoglobulin and B cell responses than men, according to various theories and research. Adult women have higher levels of Immunoglobulin and B cell responses than men, according to various theories and research, and

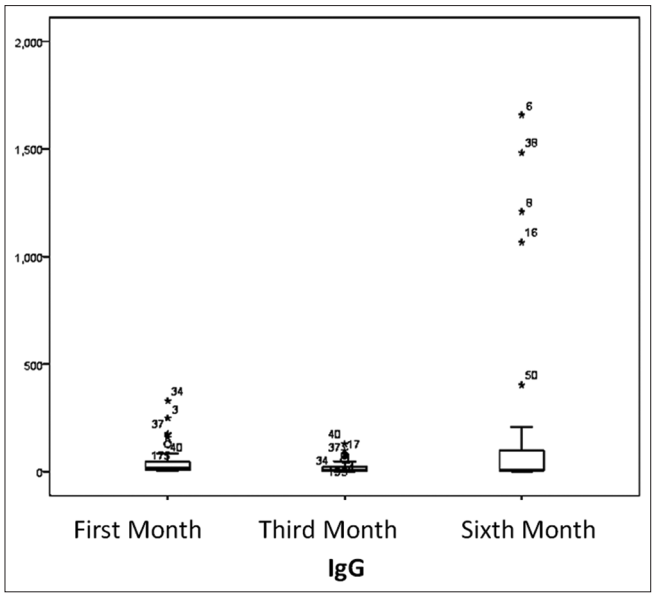

Figure 3: Box plot image of IgG antibody formation in the first, third and sixth months in U/ml

both responses are easily measured. Adult men, on the other hand, had higher T cell proliferation than women, a response that was rarely measured and was not measured in this study. This is consistent with the findings of Heriyanto *et al.*, 2021, who discovered that the female sex influences the formation of neutralizing antibody titers following vaccination.[14,19,20-22]

Conclusion

Between the first and sixth months, there is a decrease in antibody levels, both IgM and IgG. Inactivated virus vaccination has been considered successful in reducing the effects of the pandemic on COVID-19 virus. It is anticipated that the decline in antibody levels will require a repeat booster so that antibody levels will rise again and COVID-19 can be avoided.

Acknowledgments

This research was fully funded and supported by the Universitas Nusa Cendana, Indonesia.

Ethics

This study has received ethical approval from the Health Research Ethics Commission of the Faculty of Medicine, University of Nusa Cendana.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Republic of Indonesia KK. REV-4 COVID Guidelines. Guidelines for the Prevention and Control of Coronavirus Disease (COVID-19). 2020;1 (4th Revision):1-125.
2. Government of Indonesia. Presidential Regulation of the Republic of Indonesia No. 99 of 2020 concerning Vaccine Procurement and Vaccination Implementation in the Context of Combating the Corona Virus Disease 2019 (COVID-19) Pandemic. 2020.
3. Ali H, Alahmad B, Al-Shammari AA, Alterki A, Hammad M, Cherian P, *et al*. Previous COVID-19 infection and antibody levels after vaccination. Front Public Health 2021;9:778243. doi: 10.3389/fpubh. 2021.778243.
4. Ophinni Y, Hasibuan AS, Widhani A, Maria S, Koesnoe S, Yunihastuti E, *et al*. COVID-19 vaccines: Current status and implication for use in Indonesia. Acta Med Indones-Indones J Intern Med 2020;52:388-412.
5. Suwantika AA, Dhamanti I, Suharto Y, Purba FD, Abdulah R. The cost-effectiveness of social distancing measures for mitigating the COVID-19 pandemic in a highly-populated country: A case study in Indonesia. Travel Med Infect Dis 2022;45:102245. doi: 10.1016/j.tmaid. 2021.102245.
6. Cucunawangsih C, Wijaya RS, Lugito NPH, Suriapranata I. Post-vaccination cases of COVID-19 among healthcare workers at Siloam Teaching Hospital, Indonesia. Int J Infect Dis 2021;107:268-70.
7. Jain S, Batra H, Yadav P, Chand S. Covid-19 vaccines currently under preclinical and clinical studies, and associated antiviral immune response. Vaccines 2020;8:1-16.
8. Shrestha Y, Venkataraman R. The prevalence of inverse health consequences of COVID-19 vaccines: A post-vaccination study. Vacunas 2022;23:S67-76.
9. Suah JL, Husin M, Tok PSK, Tng BH, Thevananthan T, Low EV, *et al*. Waning COVID-19 Vaccine Effectiveness for BNT162b2 and CoronaVac in Malaysia: An Observational Study. medRxiv 2022. doi: 10.1101/2022.01.15.22269326.
10. Grigoryan L, Pulendran B. The immunology of SARS-CoV-2 infections and vaccines. Semin Immunol 2020;50:101422. doi: 10.1016/j.smim. 2020.101422.
11. Iyer AS, Immunol S, Iyer AS, Jones FK, Nodoushani A, Kelly M, *et al*. Persistence and decay of human antibody responses to the receptor-binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5:eabe0367. doi: 10.1126/sciimmunol.abe0367.
12. Isho B, Immunol S, Isho B, Abe KT, Zuo M, Jamal AJ, *et al*. Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. Sci Immunol 2020;5:eabe5511. doi: 10.1126/sciimmunol.abe5511.
13. Infantino M, Pieri M, Nuccetelli M, Grossi V, Lari B, Tomassetti F, *et al*. The WHO international standard for COVID-19 serological tests: Towards harmonization of anti-spike assays. Int Immunopharmacol 2021;100108095. doi: 10.1016/j.intimp. 2021.108095.
14. Salmerón Ríos S, Cortés Zamora EB, Avendaño Céspedes A, Romero Rizos L, Sánchez-Jurado PM, Sánchez-Nievas G, *et al*. Immunogenicity after 6 months of BNT162b2 vaccination in frail or disabled nursing home residents: The COVID-A study. J Am Geriatr Soc 2022;70:650-8.
15. Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. Clin Microbiol Rev 2019;32:e00084-18. doi: 10.1128/CMR.00084-18.
16. Röltgen K, Powell AE, Wirz OF, Stevens BA, Hogan CA, Najeeb J, *et al*. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. Sci Immunol 2020;5:eabe0240. doi: 10.1126/sciimmunol.abe0240.
17. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, *et al*. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020;92:1518-24.
18. Alqassieh R, Suleiman A, Abu-Halaweh S, Santarisi A, Shatnawi O, Shdaifat L, *et al*. Pfizer-BioNTech and Sinopharm: A comparative study on post-vaccination antibody titers. Vaccines 2021;9:1223. doi: 10.3390/vaccines9111223.
19. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626-38.
20. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, *et al*. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med 2021;384:2259-61.
21. Santi T, Samakto B, Kamarga L, Hidayat, FK, Hidayat F. Factors Associated with SARS-CoV-2 Antibody Titer After Sinovac Vaccination Among Health Care Workers. Acta Medica Indonesiana, 2021;53:374-84.
22. Heriyanton RS, Kurniawan A, Wijovi F, Halim DA, Jodhinata C, Marcella E, *et al*. The role of COVID-19 survivor status and gender towards neutralizing antibody titers 1, 2, 3 months after Sinovac vaccine administration on clinical-year medical students in Indonesia. International Journal of Infectious Diseases, 2021;113:336-8.