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Medical Immunology (Russia)

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Our decision is to: accept submission

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Areg Totolian
totolian@spbraaci.ru

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phey liana <pheyliana@fk.unsri.ac.id>   Sen, 22 Agu 2022, 09.27
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Editor/Author Correspondence

Author
2022-
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05:13
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Subject: Anti-SARS-Cov-2 Spike Receptor Binding Domain (S-RBD) IgG Antibodies Delete
Following CoronaVac Administration: A Longitudinal Study

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Editor in Chief

Medical Immunology (Russia)

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ANTI-SARS-COV-2 SPIKE RECEPTOR BINDING DOMAIN (S-RBD) IgG ANTIBODIES FOLLOWING CORONAVAC ADMINISTRATION: A LONGITUDINAL STUDY

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АНТИТЕЛА IGG ANTI-SARS-COV-2 SPIKE RECEPTOR BINDING DOMAIN (S-RBD) ПОСЛЕ ВВЕДЕНИЯ КОРОНАВАКА: ДЛИННОЕ ИССЛЕДОВАНИЕ

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Abstract.

The SARS-Cov-2 infection has emerged as an issue globally with its serious pathogenicity and contagious potential. Vaccination is one of the most important measure to overcome the burden of SARS-CoV-2 infection. The main strategy employed in various COVID-19 vaccine candidates is to create vaccines capable of inducing antibodies against the receptor-binding domain (RBD). Some vaccines have been developed rapidly, with varying mechanisms of action. One method for determining the immune response to vaccines is to evaluate the level of antibodies formed after vaccination. Reports on antibody titers following CoronaVac administration are still scarce, particularly when it comes to the post-vaccination effectiveness of CoronaVac in the Indonesian population. The purpose of this study is to determine the efficacy of COVID-19 vaccination by comparing the IgG levels against the s1 subunit of SARS-CoV-2 RBD after the first and second vaccinations. The data collection was done in two instances: questionnaires and blood testing. The questionnaire includes sociodemographic information and history of confirmed COVID-19 cases (for exclusion of participants who have been contracted with COVID-19). The researchers collected venous blood samples from participants after they received the CoronaVac 600 SU/0.5 mL vaccine at two different intervals (13-14 days after the first dose of vaccination and 30±2 days after the second dose of vaccination). Blood was drawn twice (after the first and second vaccinations) and tested for antibodies (positive antibody detection value of 50 AU/mL). Paired data were analyzed by using either the Wilcoxon test (numerical data) due to abnormal data distribution or the McNemar test (categorical data). The median IgG1 levels in the 14-day interval between vaccine doses were 64.40 AU/mL and IgG2 levels were 886.10 AU/mL. Meanwhile, the median IgG 1 level was 146.10, and IgG 2 level was 688.00.AU/mL in the group with a 28-day interval between vaccine doses. After the first vaccination, 60.00 % of study subjects had positive IgG levels, which increased to 98.57% after the second vaccination. Following the full-dose vaccination, all participants had higher antibody levels, which is considered

significant (p<0.05). The effect was stronger in the group that received the vaccine at 14-day intervals. CoronaVac has also been shown to increase the prevalence of detectable antibody positivity in study participants.

Keywords: Antibody, arbitrary unit (AU), CoronaVac, longitudinal study, receptor binding domain, SARS-CoV-2

Резюме.

Инфекция SARS-Cov-2 стала глобальной проблемой из-за ее серьезной патогенности и заразного потенциала. Вакцинация является одной из наиболее важных мер по преодолению бремени инфекции SARS-CoV-2. Основная стратегия, используемая в различных вакцинах-кандидатах против COVID-19, заключается в создании вакцин, способных индуцировать антитела против рецептор-связывающего домена (RBD). Некоторые вакцины были разработаны быстро, с различными механизмами действия. Одним из методов определения иммунного ответа на вакцины является оценка уровня антител, образующихся после вакцинации. Сообщений о титрах антител после введения CoronaVac по-прежнему мало, особенно когда речь идет об эффективности CoronaVac после вакцинации среди населения Индонезии. Целью данного исследования является определение эффективности вакцинации против COVID-19 путем сравнения уровней IgG против субъединицы s1 RBD SARS-CoV-2 после первой и второй вакцинации. Сбор данных проводился в двух случаях: анкетирование и анализ крови. Анкета включает социально-демографическую информацию и историю подтвержденных случаев COVID-19 (за исключением участников, которые были заражены COVID-19). Исследователи собрали образцы венозной крови у участников после того, как они получили вакцину CoronaVac 600 SU/0,5 мл с двумя разными интервалами (13–14 дней после первой дозы вакцины и 30 ± 2 дня после второй дозы вакцины). Кровь брали дважды (после первой и

второй вакцинации) и тестировали на антитела (значение положительного обнаружения антител 50 AU/мл). Парные данные были проанализированы с использованием либо теста Уилкоксона (числовые данные) из-за аномального распределения данных, либо теста Макнемара (категориальные данные). Средние уровни IgG1 в 14-дневном интервале между дозами вакцины составляли 64,40 AU/мл, а уровни IgG2 составляли 886,10 AU/мл. При этом средний уровень IgG 1 составил 146,10, а уровень IgG 2 — 688,00 AU/мл в группе с 28-дневным интервалом между дозами вакцины. После первой вакцинации 60,00 % обследованных имели положительный уровень IgG, который увеличился до 98,57 % после второй вакцинации. После вакцинации полной дозой у всех участников был более высокий уровень антител, что считается значимым ($p < 0,05$). Эффект был сильнее в группе, получавшей вакцину с 14-дневным интервалом. Также было показано, что CoronaVac увеличивает распространенность обнаруживаемых положительных антител у участников исследования.

Ключевые слова: Антитело, условная единица (AU), CoronaVac, продольное исследование, рецептор-связывающий домен, SARS-CoV-2

1 **Introduction**

2 The SARS-Cov-2 infection has emerged as an issue globally with its serious

3 pathogenicity and contagious potential. It is based on the presence of virus

4 transmission from asymptomatic and presymptomatic individuals. Hence, various

5 efforts are made to control and prevent infection, including vaccination. The

6 development of a vaccine is implemented quickly which aims to avoid infection and

7 prevent symptoms of COVID-19, thus reducing harmful consequences [20].

8 The main strategy employed in various COVID-19 vaccine candidates is to create

9 vaccines capable of inducing antibodies against the receptor-binding domain (RBD)

10 [15]. As widely known, SARS Cov 2 has a spike protein (S) on its surface. The viral

11 S protein will attach to its receptor on the host surface of the cell, Angiotensin-

12 Converting Enzyme 2 (ACE-2). This attachment process depends on a domain of

13 the S protein known as the RBD. The main immune pathway for preventing infection

14 is to restrict viral binding to ACE-2 [19].

15 Some vaccines have been developed rapidly, with varying mechanisms of action.

16 These include nucleic acid (RNA and DNA) vaccines, viral vector (replicating or

17 non-replicating) vaccines, inactivated viral vaccines, protein subunit vaccines, virus-

18 like particle vaccines, live attenuated vaccines, lentiviral vector-modified artificial

19 antigen-presenting cells (APCs), and dendritic cell vaccines [5, 10, 18]. The non-

20 replicating viral vector-based (24%) and RNA-based (20%) vaccines are two of the

21 most widely developed vaccine forms [18]. Some vaccines have received emergency

22 use authorization (EUA), an approval that allows them to be used in the general

23 population [9].

24 Since early 2021, governments in several countries, including Indonesia, have

25 launched a COVID-19 vaccination campaign to combat the disease's spread.

26 COVID-19 vaccines of various types, including mRNA and inactivated vaccines,

27 are used. However, reports on post-vaccination antibody levels need to be expanded.

28 This is due to the wide variability of immune responses to SARS-CoV-2 following
29 the vaccination [14].

30   The inactivated vaccine (CoronaVac) manufactured by Sinovac is the most
31 commonly used SARS-CoV-2 vaccine in Indonesia [16]. This vaccine is
32 administered intramuscularly in two doses of 0.5 mL each. The interval between
33 each dose is four weeks [22]. From early November 2021, this vaccine is approved
34 for children aged 6 to 11 years [4].

35   The immune response to vaccines is influenced by a variety of factors, including
36 vaccination program quality (type of vaccine, age of recipients, the interval between
37 doses, vaccine potency, formulation and stability, vaccine administration and
38 vaccination schedule), host-related factors (age, gender, genetic factors, smoking,
39 and nutrition), and environmental factors [6]. One method for determining the
40 immune response to vaccines is to evaluate the level of antibodies formed after
41 vaccination. Antibodies produced as a result of vaccination can be IgM at first, then
42 IgG, and finally IgA. IgG is known to have good affinity and neutrality against
43 antigens among these antibody classes, making it reliable for detecting immune
44 response and vaccine effectiveness following COVID-19 vaccination [13].

45   Reports on antibody titers following CoronaVac administration are still scarce,
46 particularly when it comes to the post-vaccination effectiveness of CoronaVac in the
47 Indonesian population [21]. The efficacy of COVID-19 vaccination, particularly the
48 inactivated vaccine type, is still being studied, particularly in terms of a sufficient
49 antibody titer threshold to stimulate a protective effect. The purpose of this study is
50 to determine the efficacy of COVID-19 vaccination by comparing the IgG levels
51 against the s1 subunit of SARS-CoV-2 RBD after the first and second vaccinations.

52

53 **Materials and methods**
54 *Study Overview*

55   We collected data in two instances: through questionnaires and blood testing. The

56   questionnaire includes sociodemographic information and history of confirmed

57   COVID-19 cases (for exclusion of participants who have been contracted with

58   COVID-19). Venous blood samples were obtained to determine post-vaccination

59   immunoglobulin G (IgG) levels after receiving CoronaVac 600 SU/0.5 mL (Sinovac

60   Life Sciences, Beijing, China) with two different dosing interval (14 days and 28

61   days). Sample collection was done between March to June 2021. This study was

62   approved by the Institutional Review Board of Faculty of Medicine, Universitas

63   Sriwijaya (approval number: 062-2021).

64

65   *Blood Collection and Antibody Examination*

66   The blood sampling steps were repeated twice, with 3 cc of blood obtained (from

67   the median cubital vein) for each sample collection (13-14 days after the first dose

68   of vaccination and 30 ± 2 days after the second dose of vaccination). Blood samples

69   were placed in non-anticoagulant tubes to obtain the serum to be examined.

70   IgG concentrations were assessed utilizing Abbott SARS-CoV-2 IgG II Quant

71   assay (from 75 μL of serum sample). The Architect TM i2000 analyzer (Abbott)

72   then analyzed it using the Chemiluminescent Microparticle Immunoassay (CMIA)

73   method. When the antibody titer level reached 50 arbitrary units per milliliter

74   (AU/mL), the result was considered reactive. Meanwhile, a value of <50 AU/mL is

75   defined as non-reactive [2]. Calibration was performed before each test. The IgG

76   evaluation for SARS-CoV-2 RBS subunit s1 was performed in the Clinical

77   Pathology Laboratory of Mohammad Hoesin Hospital.

78

79   *Statistical Analysis*

80   The data was analyzed using the IBM SPSS Statistics for Windows, Version 24.0

81   program (Armonk, NY: IBM Corp.). The characteristics of the research subjects

82   were displayed in the form of a frequency distribution table, including

83   the concentration and dispersion calculations (maximum, minimum, mean, median,

84 and standard deviation values). Differences in first and second IgG levels were

85 analyzed using the paired T-test for data with a normal distribution or the Wilcoxon

86 test for data with an abnormal distribution (numerical variable). Meanwhile, for the

87 categorical variable, McNemar test was conducted. The threshold of significance

88 was set at $p<0.05$.

89

90 **Results**

91   This study included 70 people who had received a complete COVID-19

92 vaccination (2 doses) with the CoronaVac vaccine. Health workers, public-sector

93 employees, and the elderly were among the research participants. **Table 1** displays

94 demographic information about the participants.

95   Table 1 shows that the majority of the participants were between the ages of 26

96 to 45. The subjects in the study ranged in age from 20 to 68 years old, with an

97 average age of 35.63 years (median: 35 years). The number of male and female

98 participants was almost equitably spread. In terms of vaccine intervals, the majority

99 of study subjects (61.43%) had vaccine intervals of 28 days.

100   We observed the clinical effect of CoronaVac vaccination on participant antibody

101 formation. All participants had elevated antibody counts from the first to the second

102 vaccination, with only one subject (1.43%) having undetectable antibody levels

103 despite being fully vaccinated. Table 2 contains the specifics. **Table 2** contains the

104 specific details.

105   Regarding the clinical implication, we examined the vaccine's efficacy based on

106 dosing intervals (14-days or 28-days). Following the full dose, we discovered that

107 both types of vaccines were able to raise antibody levels, resulting in a positively-

108 detected quantity of antibodies (≥ 50 AU/mL). We also discovered that

109 the elevation of antibody amount between the first and second doses was significant

110 in both dosing, but it appears to be more significant in the group that received the

111 full dose within 14 days of the interval ($p<0.001$ vs. $p=0.036$). The same result was

112   obtained when the analysis was performed without regard for the respective dosing

113   interval group (p<0.001). Table 3 contains more information on these findings.

114

115   **Discussion**

116   COVID-19 vaccination using various vaccine types has been implemented

117   globally to counter the effects of the pandemic. Vaccination is effective in

118   preventing serious disease manifestation, hospitalization, and mortality [1, 7]. Our

119   study included 70 people who had received a full COVID-19 vaccination (2 doses)

120   with the CoronaVac vaccine, with either a 14-day or a 28-day dosing interval.

121   According to the findings of this study, approximately 60% of the participants

122   had positive IgG levels after the first vaccination, whilst almost all of the participants

123   had positive IgG amounts after the second vaccination. These findings are similar to

124   those of Binay et al. who found that 100% of participants had positive IgG levels

125   after receiving two doses of the CoronaVac vaccine [3]. Meanwhile, Bayram et al.

126   found that after CoronaVac vaccination, IgG was found to be positive in 77.8% of

127   participants after the first vaccination and 99.6% of subjects after the second

128   vaccination [2].

129   The IgG assessment after the first and second vaccinations was found to be

130   highly variable in this study, and mainly explained as the effect of heterogenous

131   individual immune response [11]. The median IgG1 (first dose) level was 64.40

132   AU/mL and the IgG2 (second dose) level was 886.10 AU/mL in the 14-day

133   dosing interval. Meanwhile, the median IgG1 level for the group with a 28-day

134   dosing interval was 146.10 AU/mL, and the IgG2 level was 688.00 AU/mL.

135   Conversely, in phase 1/2 trials conducted by Zhang et al. with participants aged 18-

136   59 years, they discovered that subjects who had a 28-day interval between

137   CoronaVac vaccine doses had higher antibody levels than those with a 14-day

138   interval [23]. However, a Turkish study found that vaccine effectiveness (as

139   measured by seroconversion rates) did not differ significantly between vaccine

140   schedules (14-day or 28-day intervals) [20].

141   The differences identified in this research may be explained by the age
142 differences between the study subjects in both interval groups. The 14-day vaccine
143 interval group was significantly younger than the 28-day vaccine interval group
144 (median: 21.00 years vs. 42.00 years). Previous research on the use of the
145 CoronaVac vaccine has described this age-related phenomenon, with older
146 age being associated with lesser immune response, lower maximum antibody levels,
147 and faster antibody decline [17]. Other potential reasons for this finding are related
148 to immunodominance. Immunodominance is an immunological condition in which
149 immune responses are directed against only a subset of the antigenic peptides
150 formed. Previous research has discovered at least six immunodominant epitopes that
151 differ from the previously identified immune response (reflected as specific
152 antibodies production) and can alter vaccination efficacy [12]. However, no specific
153 explanation regarding the influence of age (mean or median value) and vaccination
154 interval which has been described in previous study [23].

155   Our study had a higher median SARS-CoV-2 anti-spike IgG2 value
156 (following two CoronaVac 766.15 AU/mL vs. 547.7 AU/mL) than Keskin et al
157 (766.15 AU/mL vs. 547.7 AU/mL). However, no specific dosing intervals were
158 mentioned in the comparison study [8]. Meanwhile, we measured the IgG2 level one
159 month after the second dose of vaccination. Some important factors causing these
160 differences (as observed in several studies) include the length of follow-up
161 and country-level experience with inactivated virus vaccines [22].

162   Our research has several limitations. Mainly, it is related to the small sample
163 size used in this study. Then, due to the government vaccination regulation of
164 CoronaVac, which follows a 4 week (28 day) interval between vaccine doses, no
165 additional participants with a 14-day interval can be included. Our analyses were
166 affected by the absence of more refined covariates such as chronic illness
167 (comorbidities) which could influence vaccine effectiveness.

168

169 **Conclusion**

170   CoronaVac administration at both dosing intervals (14-days and 28-days) is
171 effective in enhancing antibody levels ($p<0.05$). The effect appears to be prominent
172 in the 14-day dosing interval group. Our study also discovered that 60.00% of
173 participants have positive IgG levels ($\geq$50 AU/mL) after the first vaccine dose, and
174 this number rises to 98.57% after the second vaccination. Future studies with larger
175 samples and correlating the results with genetic factors of participants due to
176 interpersonal immune variability can be proposed. Further comparison with similar
177 research, particularly in the Indonesian population, is required for improved overall
178 validity. In addition, due to contradictory results with the established protocols
179 (longer interval gives a better level of detected antibody), it is suggested to assess
180 total antibody and antibody against different inductors (such as protein N) in
181 forthcoming studies.

182

Acknowledgments

TABLES

Table 1. Subject characteristics

Variabel	Median ± IQR	Mean ± SD	n	%
Age (Years)	35.00 ± 23.00	35.63 ± 13.91		
Age (14-days interval)	21.00 ± 1.00	23.07 ± 5.34		
Age (28-days interval)	42.00 ± 21.00	43.51 ± 11.63		
Age Group (Years)				
18 - 25			25	35.71
26 - 45			29	41.43
46 - 65			14	20.00
≥ 65			2	2.86
Gender				
Male	-	-	33	47.14
Female	-	-	37	52.86

Table 1. Subject characteristics

First and Second Vaccination Interval				
14 Days	-	-	2 7	3 8.5 7
28 Days	-	-	4 3	6 1.4 3

Note: IQR = Interquartile range, SD = Standard deviation

Table 2. Antibody response assessment

Variable	After 1st dose	After 2nd dose
Positive (%)	42 (60.00%)	69 (98.57%)
Negative (%)	28 (40.00%)	1 (1.43%)
Elevated antibody (%)	70 (100.00%)	

Table 3. Antibody levels following the vaccination with Coronavac

Variable	After 1st dose	After 2nd dose	P value
Serum Sample			
Antibody (+)			
28 days interval	28 (65.1%)	42 (97.7%)	1.000[a]
14 days interval	14 (51.9%)	27 (100.0%)	
Antibody level			
28 days interval	146.10 ± 845.00 AU/ml	688.00 ± 1157.80 AU/ml	0.036[b]
14 days interval	64.40 ± 759.90 AU/ml	886.100 ± 683.40 AU/ml	<0.001[b]
Total	88.60± 759.90 AU/ml	766.15 ± 968.32 AU/ml	<0.001[b]

Note: Data were presented Median ± Interquartile Range (IQR). Statistical analysis was done using the (a) McNemar and (b) Wilxocon test, p<0.05

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АНТИТЕЛА IGG ANTI-SARS-COV-2 SPIKE RECEPTOR BINDING DOMAIN (S-RBD) ПОСЛЕ ВВЕДЕНИЯ КОРОНАВАКА: ДЛИННОЕ ИССЛЕДОВАНИЕ

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