Effect of Vaccination Status on SARS-CoV-2 Antibody Levels in Gowa Regency Community, Indonesia

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Abstract: *Background*: COVID-19 is a disease caused by infection with SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*). One of the body's immune responses to infection is to produce antibodies. Acute SARS-CoV-2 infection initiates cellular and humoral immune responses. The humoral immune response specifically generates antibodies against virus-specific antigens. Several factors influence the immune response, one of which is vaccination status. Therefore, this study aimed to determine and analyze the effect of vaccination status on SARS-CoV-2 antibody levels.

Methods: An analytical observational study with a cross-sectional design involving 815 samples was conducted. The proportional random sampling technique was employed based on data obtained from the Seroepidemiology Survey. Data analysis was conducted using the STATA version 14.0 program with the Independent T-Test, Mann Whitney test, Kruskal Wallis test, and Multiple logistic regression.

Results: The results showed that there was a significant relationship between the determinant variables of SARS-CoV-2 antibody levels based on gender (p=0.012), vaccination status (p=0.000), and COVID-19 infection history (p=0.000). Furthermore, the multivariate analysis indicated that vaccination status was the variable most associated with SARS-CoV-2 antibody levels ($p = 0.010$). The OR value = 0.16 < 1 and 95%CI (0.04-0.65) which did not contain a value of 1 suggested vaccination status to be a significant protective factor associated with SARS-CoV-2 antibody levels, with a probability value of 94.1%.

Conclusion: The most influential variable on SARS-CoV-2 antibody levels in the Gowa Regency was vaccination status. Moreover, none of the variables measured were identified as confounding factors or showed interaction effects.

Keywords: SARS-CoV-2 antibody, COVID-19, vaccination status, COVID-19 infection history.

INTRODUCTION

COVID-19 is a disease caused by infection with SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*). It is a novel virus and previously unknown before the outbreak in Wuhan, China, in December 2019. The COVID-19 pandemic is a global health crisis of unprecedented magnitude, affecting numerous countries worldwide. The SARS-CoV-2 virus can lead to lower respiratory tract infection and then progress to severe acute respiratory syndrome, multiple organ failure, and even death [1]. COVID-19 is included in the traveling-disease category, meaning that the tie virus can move everywhere and tends to stagnate. It is only moving and moving following the movement of the population. Not here if the intensity of transmission is in line with the high mobility of the population [2].

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As of January 19, 2023, Indonesia has reported a total of 6,727,007 confirmed cases of COVID-19 with 160,756 deaths, according to the World Health Organization (WHO). The number of vaccine dose administered as of January 16, 2023, stand at 444,303,130. Among the provinces, DKI Jakarta has recorded the highest number of cases at 1,141,024 (22.2%) with 12,497 deaths and 1,121,197 recoveries, while South Sulawesi Province ranked 11th reporting 115,909 (2.3%) cases with 1,978 deaths and 113,736 recoveries [3]. Based on data from Gowa Regency Health Office, Gowa Regency ranked 2nd after Makassar City in early January 2023 with a total of 11,427 cases, 11,289 confirmed recoveries, and 136 deaths [4].

One of the body's immune responses triggered by infection is the production of antibodies. Acute SARS-CoV-2 infection initiates both cellular and humoral immune responses. The humoral immune response triggers the production of antibodies against virus-specific antigens. SARS-CoV-2 antibodies are found mainly in IgM, IgG, and IgA isotypes. These antibodies play a role in recognizing and fighting against the virus. Apart from being produced by the body, antibodies can also be obtained from antibody-based interventions such as convalescent plasma therapy and vaccine administration. These interventions are continuously being developed and currently employed worldwide in the management and control of COVID-19. SARS-CoV-2 antibody testing or serology aims to detect antibodies produced by the human body in response to natural infection and vaccination [5].

Acquired immunity is developed at the individual level, either through natural infection with the pathogen or immunization with a vaccine. Meanwhile, herd immunity comes from the effect of individual immunity being scaled up to the population level. It refers to the indirect protection from infection provided to susceptible individuals when a large proportion of the population becomes immune. This population-level effect is often considered in vaccination programs, which aim to build herd immunity to safeguard those who cannot be vaccinated, including young children and people with weakened immune systems, from contracting the disease [6].

Vaccination is one of the crucial efforts to cope with the COVID-19 pandemic. The Government Regulation was enacted in response to the dynamics of the pandemic to control morbidity and mortality from COVID-19 infection as well as achieve herd immunity [7]. Motivation is a situation in a person's personality that encourages individual desire to carry out certain activities to achieve goals such as vaccination which aims to re-establish SARS-CoV-2 antibodies [8].

Several factors can influence the immune response to vaccination, including internal and external factors. Internal factors include age, gender, genetics, and birth history (gestational age, birth weight, maternal antibodies, and comorbidities). Meanwhile, external factors include behavioral characteristics (smoking, alcohol consumption, sleep, exercise), nutrition (body mass index, micronutrients), environment, as well as vaccine-related factors including vaccine type, product, dose, vaccination schedule, route of administration, and timing of vaccination [9]. Based on questionnaire data variables, respondents' characteristics are gender, age, jobs, SARS-CoV-2 Antibody Level, vaccination status, history of comorbidity, vaccine dose, and independent variables are gender, vaccination status, COVID-19 infection history, smoking history, and 3M behavior with the dependent variable SARS-CoV-2 antibody levels. Based on this previous information, this study aims to determine and analyze the effect of vaccination status on SARS-CoV-2 antibody levels in the Gowa Regency.

METHODS

Type, Design, and Location of Study

This was a quantitative study conducted in Gowa Regency using an analytic observational approach with a *Cross-Sectional* design.

Study Sample

The sample consisted of 815 people who had SARS-CoV-2 serology and questionnaire data. The *proportional random sampling* technique was used by selecting samples in each village in the Gowa Regency based on the inclusion criteria, namely having complete serology and questionnaire data.

Instruments and Procedures

This study used secondary data from the results of the COVID-19 Seroepidemiological Survey conducted in the Gowa Regency in March 2022. Data were in the form of SARS-CoV-2 serology and questionnaire data related to the variables studied.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted by the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Faculty of Public Health, Hasanuddin University with number 3007/UN4.14.1/TP.01.02/2023.

Data Analysis

Data processing and analysis were performed using the STATA version 14.0 program. The bivariate analysis employed the Independent t-test, Mann-Whitney test, and Kruskal Wallis test to determine the relationship between independent variables (gender, vaccination status, COVID-19 infection history, smoking history, and 3M behavior) with the dependent variable (SARS-CoV-2 antibody levels). Meanwhile, the multivariate analysis used multiple logistic regression tests with the Backward method to determine variables with the most significant influence on SARS-CoV-2 antibody levels.

RESULTS

Table **1** presents the distribution of respondents according to their SARS-CoV-2 antibody levels. The

Table 1: Distribution of Respondents Based on Characteristics in Gowa Regency in 2022

Respondents' Characteristics	Total (n=815)	(%)
SARS-CoV-2 Antibody Level (AU/ml)		
<50	9	1,10
50-1000	62	7,61
1001-10000	416	51,04
>10000	328	40,25
Total	**815**	**100,0**
SARS-CoV-2 Antibody Level Category		
Reactive	804	98,65
Non Reactive	11	1,35
Total	**815**	**100,0**
Gender		
Male	396	48,59
Female	419	51,41
Total	**815**	**100,0**
Age (Year)		
1-14	64	7,85
15-29	158	19,39
30-49	386	47,36
≥50	207	25,40
Total	**815**	**100,0**
Jobs		
Low Exposure Risk Occupation	260	31,90
Medium Exposure Risk Occupation	413	50,67
High Exposure Risk Occupations	142	17,42
Total	**815**	**100,0**
History of Comorbidity		
Yes	110	13,50
No	705	86,50
Total	**815**	**100,0**
Vaccination Status		
Yes	764	93,74
No	51	6,26
Total	**815**	**100,0**
Vaccine Dose		
1st Dose	82	10,73
2nd Dose	549	71,86
3rd Dose	133	17,41
Total	**764**	**100,0**

Source: COVID-19 Seroepidemiology Data Kab. Gowa, 2022.

highest percentage of 51.04% was found in the category of 1001-10000 AU/ml range. In terms of reactive SARS-CoV-2 antibody levels, 98.65% of the respondents exhibited reactivity, with a male gender of 48.59% and a female of 51.41%.

Based on the results, the age group with the highest percentage was 30-49 years (47.36%), while the age group with the lowest percentage was 1-14 years (7.85%). In terms of occupation, the highest percentage was in the category of work with a moderate exposure risk of 50.67% and the lowest was in the category of work with a high exposure risk of 17.42%. Based on the history of comorbidity the highest percentage was in the category of respondents who did not have a history of comorbidity (86,50%) and

Table 2: Differences in SARS-CoV-2 Antibody Levels Based on Study Variables in Communities in Gowa Regency in 2022

Determinants of SARS-CoV-2 Antibody Levels	SARS-CoV-2 Antibody Level Category				Total	
	Non Reactive		Reactive			
	n=11	%	n=804	%	n=815	%
Gender						
Male	7	1.77	389	98.23	396	100
Female	4	0.95	415	99.05	419	100
History of Comorbidity						
Yes	2	1.82	108	98.18	110	100
No	9	1.28	696	98.72	705	100
Vaccination Status						
Yes	8	1.05	756	98.95	764	100
No	3	5.88	48	94.12	51	100
History of COVID-19 Infection						
Yes	0	0.00	62	100	62	100
No	11	1.46	742	98.54	753	100
Smoking History						
No Smoking	7	1.13	613	98.87	620	100
Light Smokers	2	1.37	144	98.63	146	100
Heavy Smokers	2	4.08	47	95.92	49	100
3M Behavior						
Good	7	1.79	383	98.21	390	100
Less	4	0.94	421	99.06	425	100

Source: COVID-19 Seroepidemiology Data Kab. Gowa, 2022.

based on the data, 21 people had diabetes, 67 with hypertension, and 10 have coronary heart disease. In terms of vaccination status, (93,74%) of respondents who vaccinated with the highest frequency of doses at the 2nd vaccine dose (71,86%).

Table **2** shows that the proportion of respondents who have reactive antibodies is highest in the female gender (99.05%) and in respondents who are vaccinated (98.95%), the proportion of respondents who have the highest reactive antibodies is shown in respondents who have a history of Covid-19 infection (100%) and who did not have history of comorbidity (98.72%), besides that the proportion of respondents who have the highest reactive antibodies in non-smokers (98.87%) and the proportion of respondents who have the highest reactive antibodies in respondents who have less 3M behavior (99.06%).

Table **3** shows that the average SARS-CoV-2 antibody levels in respondents who were female, vaccinated, had a history of COVID-19 infection, did not have a history of smoking, and had good 3M behavior were 12073.296 AU/ml, 11768.533 AU/ml, 15970.76 AU/ml, 11522.42 AU/ml, and 10933.265 AU/ml, respectively.

The results of the analysis of this study also showed that between the history of covid-19 infection and vaccination status with SARS-CoV-2 antibody levels showed that the average SARS-CoV-2 antibody levels of those who had a history of covid-19 infection and had been vaccinated were higher at 16366.07 AU/ml while those who did not have a history of covid-19 infection but vaccinated had an average SARS-CoV-2 antibody level of 11376.7 AU/ml.

Statistical analysis using the Independent t-test, Mann Whitney, and Kruskal Wallis test showed that variables significantly associated with SARS-CoV-2 antibody levels included gender (p = 0.012) vaccination status (p = 0.000) and history of COVID-19 infection (p = 0.000). In contrast, variables that were not associated included smoking history (p=0.614) and 3M behavior ($p=0$.148).

Based on confounding and interaction analysis, the variables of gender, COVID-19 infection history, vaccination status, smoking history, and 3M behavior were not confounding variables. Additionally, no interaction was observed between variables, as indicated by the absence of a change in RR, which was <10% and a p-value> 0.05.

Table 3: Relationship between Determinants and SARS-CoV-2 Antibody Levels Based on Study Variables in Gowa Regency in 2022

Determinants of SARS-CoV-2 Antibody Levels	SARS-CoV-2 Antibody Level (AU/ml)			
	n (815)	Mean	SD	*p-value*
Gender				
Male	396	10881.969	10731.04	0.012***
Female	419	12073.296	10497.83	
Vaccination Status				
Yes	764	11768.533	10637.3	0.000***
No	51	7388.4608	9579.573	
History of COVID-19 Infection				
Yes	62	15970.76	12377.14	0.000***
No	753	11125.875	10388.16	
Smoking History				
No Smoking	620	11522.42	10717.14	0.614*
Light Smokers	146	11747.762	10437.26	
Heavy Smokers	49	10385.665	10081.27	
3M Behavior				
Good	390	10933.265	10380.76	0.148**
Less	425	12009.406	10825.2	

Source: COVID-19 Seroepidemiology Data Kab. Gowa, 2022.
Description:
*: Kruskal wallis test.
**: Independent t-test.
***: Mann Whitney test.

Table 4: Multivariate Analysis of Determinants of SARS-CoV-2 Antibody Levels in Gowa Regency in 2022

Determinants Variable	Model 1		Model 2	
	p	OR (CI 95%)	*p*	OR (CI 95%)
Gender	0.381	1.74 (0.50-6.07)	0.396	1.71 (0.49-5.98)
Vaccination Status	0.039	0.22 (0.05-0.93)	0.032	0.21 (0.05-0.87)
3M behavior	0.443	1.63 (0.46-5.70)		
Determinants Variable	**Model 3**			
	p	**OR (CI 95%)**	**Coefficient/ Constant**	
Vaccination Status	0.010	0.16 (0.04-0.65)	-1.776/ 4.548	

Source: COVID-19 Seroepidemiology Data Kab. Gowa, 2022.

Table **4** presents the results of three models used in the multivariate analysis. In multivariate analysis, the variables tested in the analysis model are variables that have a *p-value* <0.25 based on the results of the bivariate test. The variables included in the multivariate analysis modeling using multiple logistic regression tests include gender, vaccination status, and 3M behavior. The COVID-19 infection history variable cannot be included in the multivariate analysis model because there are empty cells so it cannot be analyzed.

The most influential variable on SARS-CoV-2 antibody levels was vaccination status (*p* = 0.010), with an OR value of 0.16 and 95%CI (0.04-0.65). This indicated that vaccination status served as a significant protective factor because it did not reach a value of 1. To determine the variable probability value, a logistic regression equation was utilized by determining the coefficient value for each variable and the constant value. The coefficient value was found to be -1.776 and the (-) was found based on the statistic result and the constant value was 4.548.

The logistic regression equation is Y so the equation of logistic regression is Y = 4.548 + (-1.776) = 2.772. A prediction is a value between 0 and 1. 0 indicates an event that is unlikely to occur and 1 indicates the maximum likelihood that the event will occur. Furthermore, the value of Y can be calculated by giving the value of 1, namely Y = 4.548 + (-1.776) *1 = 2.772. After obtaining the Y value, the probability of the subject was calculated with the following formula:

$$P = 1/(1+\exp^{(-y)}) \qquad Y\ value = 2.772$$

By using Stata, the P value can be calculated

$$P = 1/(1+\exp(-2.772)) \\ = 0.94114387$$

Based on this value, the probability of SARS-CoV-2 antibody levels in respondents from the Gowa Regency with a vaccination status was 94.1%.

DISCUSSION

The results of the analysis showed that there was a relationship between gender and SARS-CoV-2 antibody levels with a value of 0.012 or <0.05. Similar results were reported by (Bayram *et al*., 2021) Seropositivity was higher among females (467/552; 84.6%) than males (367/520; 70.6%) (p < 0.001) and was found to be highest in both women and men between the ages of 18–34 (88.9% and 79.5%, respectively) [10]. Another interesting finding is that men tend to have a steeper decline of the antibody titer with increasing age and Other major studies detected a correlation of lower antibody concentrations after vaccination with male sex and older age [11]. Based on research by the University of Ghent (Belgium) focusing on microRNAs, it has been confirmed that the excess X chromosome in women is the reason why they have a stronger immune system. Testosterone is the trigger for a weaker antibody system in men [12].

Based on the results, immune response and SARS-CoV-2 antibody levels can be influenced by several factors that have been studied including gender, vaccination status, a history of COVID-19 infection, smoking history, and 3M behavior. Among the five variables, vaccination status was found to have the most significant impact on SARS-CoV-2 antibody levels. Respondents who were vaccinated had higher average antibody levels of 11768.533 AU/ml compared to those who were not vaccinated

The COVID-19 infection history variable showed a significant relationship with SARS-CoV-2 antibody levels with a value of (*p=0*.000) even though it was not included in the multivariate analysis model. Based on the analysis results, people who have a history of COVID-19 infection had a higher average antibody level of 15970.76 AU/ml, while those without a history of infection had a lower average of 11125.875 AU/ml.

Despite more than 76 million infections worldwide and ongoing transmission, evidence of post-infection immunity emerged, as reported cases of re-infections with SARS-CoV-2 were rare, most occurring after mild or asymptomatic primary infection [13]. This suggests that SARS-CoV-2 infection confers immunity to reinfection in most people. In addition, according to small-scale reports, neutralizing antibodies may protect against infection [14].

Analyses were also conducted to assess the relationship between COVID-19 infection history and vaccination status on SARS-CoV-2 antibody levels. The analysis results showed that the average antibody levels of those who had a history of infection and were vaccinated were higher at 16366.07 AU/ml. Meanwhile, those who did not have a history of infection but were vaccinated had an average of 11376.7 AU/ml.

35.8% of the unvaccinated participants who were infected no longer had detectable antibodies more than one year after infection. Vaccination induces a higher response in previously infected individuals and they have significantly higher antibody levels over time compared to unvaccinated people. It was also shown that infected people can benefit from vaccination given the significant increase in antibody levels after vaccination [15].

This suggested that vaccination helps the body respond to produce more antibodies against the COVID-19 virus [16]. Post-infection immunity can be provided by humoral and cellular immune responses [14]. The immune response varies greatly with different vaccine types and products. For example, live vaccines often induce a high response leading to lifelong protection after a single dose, while inactivated, subunit, or toxoid vaccines usually require multiple doses, including booster doses, to achieve similar protection. Responses to different subunit vaccines may also vary [9]. Measurement of antigen-specific antibody levels is critical in identifying the efficacy of vaccination and determining whether factors, such as age, associated clinical conditions, and gender affect an individual's response [17].

A previous study by (Rotty *et al*., 2022) generally showed an increase in SARS-CoV-2 specific antibody titers (IgG) in vaccinated subjects. There was an increase in antibodies formed at the first examination compared to the second examination, from a median of 418.3 AU/mL to 457.7 AU/ml. This increase was also observed at the third examination, to 457.7 AU/ml, although there was a decrease in the mean from 525.5 AU/ml to 457.7 AU/ml [18].

A study (Jabal *et al*., 2021) involving 51 health workers from the UK showed that previously infected people exhibited higher levels of SARS-CoV-2 anti-S antibody titers than those without previous infection [19]. It was also found that survivors with more severe symptoms showed a stronger antibody response than asymptomatic or mildly symptomatic survivors. Higher titers of IgM, IgG, and IgA levels were detected, and they persisted in the body for a longer duration [20].

After the first vaccine, the antibody positivity rate and total antibody titers were found to be higher in those with COVID-19 than those without, and the differences were statistically significant ($p<0.001$ and $p<0.001$, respectively). These results indicate that people infected with COVID-19 can produce high levels of antibodies even with only one dose of vaccination, allowing for different vaccination schedules [10].

Another study found that antibody levels were significantly higher in fully vaccinated individuals with prior COVID-19 infection (natural immunity) than in those without prior infection (acquired immunity). In addition, individuals without a prior history of infection showed a faster decline in antibodies over time [21]. Similar results were reported by (Vicenti I *et al*., 2021) who observed a rapid linear decline in IgG levels over time among previously uninfected individuals, compared to those who had antibodies produced after infection and vaccination [22].

These findings showed that antibody levels increase after vaccination and a history of COVID-19 infection. However, there is a need for further vaccination to re-establish antibodies.

CONCLUSION

In conclusion, vaccination status was found as the most influential variable on SARS-CoV-2 antibody levels. Therefore, it is recommended that continued vaccination be carried out by the community to re-establish and maintain antibodies against SARS-CoV-2 infection.

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CONFLICT OF INTEREST

We have no competing interests.

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