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Original Article

Post COVID-19 vaccination binding and neutralizing antibody with or without previous infection: An 18-month longitudinal study in Indonesia

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Abstract

Due to the persisting development of SARS-CoV-2 variants, studies on the kinetics, duration, and function of antibodies are essential for vaccine development and long-term immunity prediction. This longitudinal study examined post-vaccination antibody responses in people after receiving CoronaVac or ChAdOx1 vaccines with or without a history of SARS-CoV-2 infection. Conducted in Indonesia between August 2021 and May 2023, this study involved 121 participants divided into two groups based on the received vaccine types and monitored for 18 months post-second dose vaccination by assessing the binding antibody (BAb) level and neutralizing antibody (NAb) inhibition rate at six time points. The study also documented the participants' age, gender, and body mass index (BMI). Before the first dose vaccination, 85 (70.2%) participants were reactive BAb (defined by BAb level ≥50 AU/mL) indicating a history of infection. In the CoronaVac group, only 53.1% were reactive BAb. However, 100% of participants were positive NAb (defined by NAb inhibition rate ≥30%), which indicates a past history of infection with low initial or rapidly decreasing BAb levels. In the ChAdOx1 group, 81.9% of participants were reactive, while only 54.2% were positive NAb, suggesting a recent infection with a high BAb level but a relatively low NAb inhibition rate. During the 18 months post-second dose vaccination, the BAb levels fluctuated. However, 100% of participants were positive NAb. No significant difference in antibody response was documented among participants with or without infection history. Also, no significant impact was presented by the factors of sex, age, and BMI. The findings highlight the crucial of the vaccine in public health and how vaccination strategies could be optimized effectively during and after the post-pandemic.

Keywords: COVID-19, binding antibody, neutralizing antibody, CoronaVac, ChAdOx1

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has reshaped global public health and healthcare systems [1]. The global COVID-19 battle has shown fluctuating trends, with the declines often followed by resurgences [2]. Significant surges in COVID-19 cases were reported in December 2023 [3], May 2024 in Singapore [4], and June 2024 in the United States [5], underlining the ongoing risk of COVID-19 and the need for sustained vigilance and preparedness. Therefore, investigating the immune response to SARS-CoV-2 remains crucial as cases emerge in the post-pandemic era [6,7]. This includes the roles of binding and neutralizing antibodies [8].

Received: June 29, 2024 - Accepted: August 29, 2024 - Published online: August 31, 2024

Binding antibodies (BAbs) are essential to the human immune response, targeting epitopes on the SARS-CoV-2 spike protein to prevent viral entry into host cells. The BABs are crucial for initial viral recognition and containment, facilitating subsequent immune responses [9,10]. Neutralizing antibodies (NAb), a subset of binding antibodies, have potent antiviral activity by directly blocking viral entry or disrupting viral replication in host cells [11,12]. NAbs correlate with decreased disease severity and improved viral clearance in convalescent individuals and vaccine recipients, showing a stronger correlation with protection than BAb [13,14].

Exploring the kinetics, durability, and functional significance of BAbs and NAbs is crucial for advancing vaccine development, evaluating immune responses across populations, and predicting long-term immunity against SARS-CoV-2 [15]. The emergence of new variants of SARS-CoV-2 has highlighted the need to study how mutations affect antibody-mediated immunity and vaccine efficacy [16,17]. Therefore, understanding the interplay and duration of antibodies' protection against COVID-19 remains crucial in the post-pandemic era [18-20].

Indonesia offers a unique opportunity to study adult immune responses amidst high infection rates [21-23]. A study reported that vaccines induced anti-receptor-binding domain (RBD) antibody levels as high as the natural infection with lower neutralization capacity, and it did not boost immunity in pre-infected persons. The report measured antibodies from April to December 2021 in the participants with primary doses of CoronaVac COVID-19 vaccination [24].

This study aimed to investigate more detailed post-vaccination kinetics (BAb level) and functional responses (NAb inhibition rate) by comparing those with and without prior history of SARS-CoV-2 infection during 18 months after the second dose of CoronaVac or ChAdOx1 vaccine, focusing on immunoglobulin G (IgG) BAb levels and NAb inhibition rate to the RBD spike protein of SARS-CoV-2. Additionally, age, gender, and body mass index (BMI) were evaluated to determine their possible effects on antibody response. The findings may provide insights into the development of strategies and policies for managing potential endemicity and future post-pandemic resurgences.

Methods

Study design and setting

A longitudinal cohort study was conducted from August 2021 to May 2023 in collaboration with the Indonesian Ministry of Health (MoH) on its vaccination program [25]. The study involved ChAdOx1 and CoronaVac-vaccinated participants and was conducted in two cities. ChAdOx1 was administered in Bogor, West Java, and CoronaVac was administered in Sleman, Jogjakarta. The number of participants, types of vaccines, and the sites of study in these cities were determined based on the recommendation of the MoH and the local governments [25].

Samples and sampling method

The study was based on the differentiation analysis of the BAb levels and NAb inhibition rates between the CoronaVac- and ChAdOx1-vaccinated participants with and without a history of SARS-CoV-2 infection. The two groups were unpaired. Considering the percentage of error type I at 5% and type II at 10%, and the estimated standard of deviation at 40, the minimal number of samples was 44 in each group [26]. The study implemented the total sampling method for all eligible participants as samples.

Participants and criteria

All participants who met the inclusion criteria (18–59 years old and had no record of previous COVID-19 positive) were considered eligible for the study. The criteria referred to technical guidelines for pre-COVID-19 vaccination recipient screening issued by the Indonesian MoH [27]. The exclusion criteria included those with the therapy of hematological disease, diabetes mellitus to a certain level based on the HbA1c level, heart failure, autoimmune disease, on routine hemodialysis treatment, rheumatoid arthritis or autoimmune rheumatoid, immunocompromise diseases, pregnant or on breast-feeding, asthma, and tuberculosis [27].

Blood sample collection

Blood samples of participants were drawn at six time points (TPs): before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6). On each TP, the resulting serum was aliquoted into three tubes, which were prepared for immediate BAb level measurement, delayed NAb inhibition rate measurement, and backup, respectively. The second and third tubes were kept in cold storage (-80°C) until the time of measurement. No repeated freeze-and-thawing processes were allowed until the measurement was performed.

Study variables

The independent variables were the types of vaccine and any history of SARS-CoV-2 infection, while the dependent variables were BAb levels and NAb inhibition rate. The BAb was categorized as reactive when the level was ≥50 AU/mL [28]. A reactive BAb at TP1 indicated a history of SARS-CoV-2 infection since there was no vaccination before TP1. The higher the BAb level, the higher the level of binding toward SARS-CoV-2 spike RBD.

The NAb inhibition rate represented the serum's capability to inhibit the binding between the angiotensin-converting enzyme 2 (ACE2) receptor and the SARS-CoV-2 spike protein's RBD. An inhibition rate of ≥30% was considered positive NAb, while <30% was considered negative, as previously described [29-31]. The higher the NAb inhibition rate, the higher the capacity of NAb to neutralize the SARS-CoV-2 spike RBD.

In addition, participant's characteristics were documented including sex, age (categorized based on the MoH guideline [32] and BMI. The BMI was calculated based on body weight and body height with categorization as follows: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2).

Binding antibody and neutralizing antibody measurement

The BAb level and NAb inhibition rate were measured at each time point. A chemiluminescence immunoassay (CMIA), SARS-CoV-2 IgG II quantitative assay (Abbott Core of Laboratory System, Illinois, USA), was used to measure BAb levels using ARCHITECT i2000SR Immunoassay Analyzer (Abbott Core of Laboratory System, Illinois, USA). After adding 150 microliters of participants' serum into the sample tube, the analyzer runs automatically, and the BAb level will be displayed on the monitor in AU/mL [33].

The SARS-CoV-2 Spike RBD inhibition rate of NAb was assessed using a Surrogate Virus Neutralization Test (SVNT) employing the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript Biotech, Singapore) following the manufacture protocol. The rate of inhibition was measured by the optical density (OD) of the microplate at 450 nm employing the MP96 Microplate Reader (SAFAS, Monaco). The inhibition rate was calculated using the formula: (1 – (OD value of the sample/OD value of the negative control) ×100%) [34].

Statistical analysis

Continuous data were presented as mean, standard deviation, or median, and minimal-maximal and categorical data as percentages. Meanwhile, antibody responses were compared using an independent Student t-test, Chi-Squares test, or Mann-Whitney test based on the data type and the Saphiro-Wilk and Kolmogorov-Smirnov normality test result. SPSS version 25.0 software (IBM SPSS, Chicago, Illinois, USA) was employed for data analysis, with $p<0.05$ considered statistical significance.

Results

Participants Characteristics

A total of 121 participants were enrolled and did not miss the six time points measurement during the study: 49 persons in the CoronaVac group and 72 persons in the ChAdOx1 group. The participants' number fulfilled the required minimum sample size as calculated in the method section. The following results data will be analyzed in a sequence of participants' characteristics, analysis based on the vaccine type and the infection history.

The participants' characteristics and BAb reactivity at TP1 are presented in **Table 1**. Most participants were female (69.4%), not by design, but rather due to vaccine availability and local policy, and between 45–59 years old (75.2%), with an average age of 41.9 years old. Approximately 44.6% of participants had normal BMI, while 30.6% were overweight. At TP1, BAb reactivity was found in 85 participants (70.2%), indicating a high prevalence of asymptomatic infection mainly during the high pandemic wave from June to August 2021 (**Table 1**).

Table 1. Participants' characteristics and binding antibody (BAb) reactivity at TP1

Variables	Number, n (%)	CoronaVac group		ChAdOx1 group		*p*-value
		Reactive, n (%)	Not-reactive, n (%)	Reactive, n (%)	Not-reactive, n (%)	
Total	121	49		72		
Sex						0.10
Male	37 (30.6)	7 (14.3)	8 (16.3)	14 (19.4)	8 (11.1)	
Female	84 (69.4)	19 (38.8)	15 (30.6)	45 (62.5)	5 (6.9)	
Total		26 (53.1)	23 (46.9)	59 (81.9)	13 (18.1)	
Age (years)						0.12
18–44	30 (24.8)	9 (18.4)	7 (14.3)	9 (12.5)	5 (6.9)	
45–59	91 (75.2)	17 (34.7)	16 (32.7)	50 (69.4)	8 (11.1)	
Body mass index						0.10
Underweight	9 (7.4)	1 (2.0)	2 (4.1)	2 (2.8)	4 (5.6)	
Normal	54 (44.6)	16 (32.7)	7 (14.3)	25 (34.7)	6 (8.3)	
Overweight	37 (30.6)	5 (10.2)	11 (22.4)	20 (27.8)	1 (1.4)	
Obese	21 (17.4)	4 (8.2)	3 (6.1)	12 (16.7)	2 (2.8)	

Antibody response in CoronaVac and ChAdOx1 groups

The BAb level indicated broad variation among the participants. Statistical analysis showed a non-normal distribution of data. Meanwhile, data on the NAb inhibition rate showed a normal distribution. The analysis results were then displayed accordingly, depending on whether the data distribution was normal or non-normal.

The broad variation in BAb levels among participants during the time points is described in **Table 2**. Also, overlapping data of BAb levels and NAb inhibition rates indicated diverse humoral responses to the vaccine, potentially influenced by other factors. However, no significant differences in antibody response were observed between CoronaVac and ChAdOx1 groups based on sex, age, or BMI from TP1 to TP6 ($p>0.05$ for all variables).

Table 2. Binding antibody, neutralizing antibody, and the percentage of participants with reactive binding antibody (BAb) and positive neutralizing antibody (NAb) with the administration of CoronaVac and ChAdOx1

Time point	BAb level* (AU/mL)					NAb inhibition rate** (%)		Percentage of participants with reactive BAb (%)	Percentage of participants with positive NAb (%)
	Mean	SD	Median	Min	Max	Mean	SD		
CoronaVac group									
TP1	561	1,053	107	0	5,805	62.2	14.2	53.1	100
TP2	1,437	2,228	647	4	10,574	81.5	14.6	79.6	100
TP3	1,247	1,801	751	18	9,035	74.4	15.1	89.8	100
TP4	1,282	967	1,068	155	4,599	86.5	12.9	100	100
TP5	3,970	5,955	1,996	12	33,190	86.5	12.9	95.9	100
TP6	4,999	7,349	2,597	52	42,752	84.5	22.9	100	100
ChAdOx1 group									
TP1	2,679	5,096	684	0	24,663	40.3	35.5	81.9	54.2
TP2	13,957	12,067	11,079	25	53,500	96.2	7.3	98.6	100
TP3	3,842	5,900	2,360	10	47,592	91.1	11.7	98.6	100
TP4	4,426	6,554	2,824	683	53,812	96.1	8.0	100	100
TP5	10,517	14,682	5,771	44	78,690	96.5	8.3	86.1	100
TP6	6,978	11,751	3,639	41	80,260	94.1	12.8	84.7	100

Time points: before the first dose (TP1); two weeks after the first dose (TP2); before the second dose (TP3); one month after the second dose (TP4); 12 months after the second dose (TP5); and 18 months after the second dose (TP6).
*Data was not normally distributed
**Data was normally distributed

Antibody responses in CoronaVac vaccinated participants

The kinetics of BAb levels and NAb inhibition rates from TP1 to TP6 in participants receiving the CoronaVac vaccine are described in **Figure 1**. The BAb level and NAb inhibition rate were relatively low at TP1, followed by a gradual increase towards TP6. At TP1, 53.1% of participants were reactive BAb and 100% were positive NAb with a mean inhabitation rate of 62.2±14.2%, as illustrated in **Figure 2**. Interestingly, it suggested that a portion of participants might inhibit infection even without detectable BAb, indicating a past infection. At the following TP2 to TP6, the proportion of participants with reactive BAb revealed fluctuations, with a slight decrease at TP5 (95.9%) and re-increased at TP6 (100%). Of note, at TP6, the BAb level still showed an increase while the NAb inhition rate showed a decrease. However, all the participants were positive NAb during the period of study.

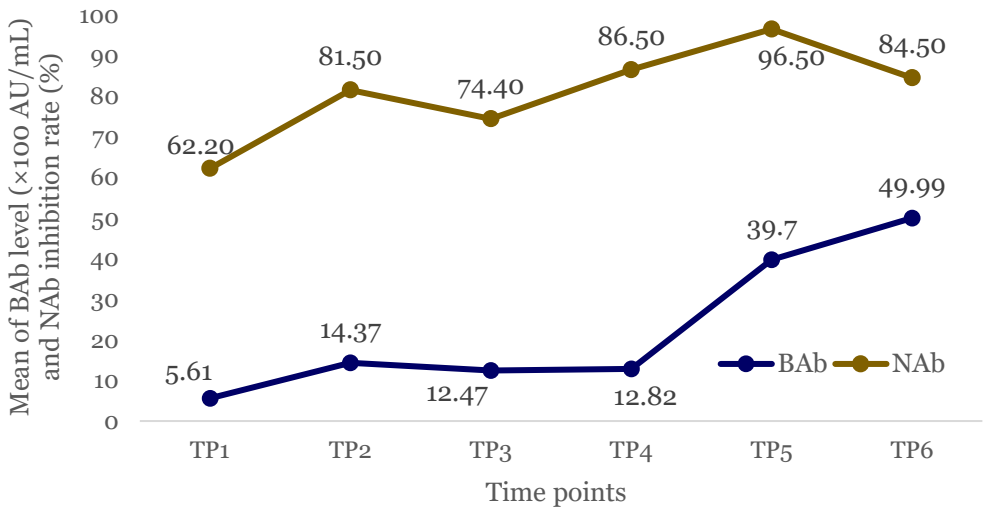

Figure 1. BAb level (×100 AU/mL for simple display on the graph) and NAb inhibition rate (%) in the group receiving CoronaVac. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

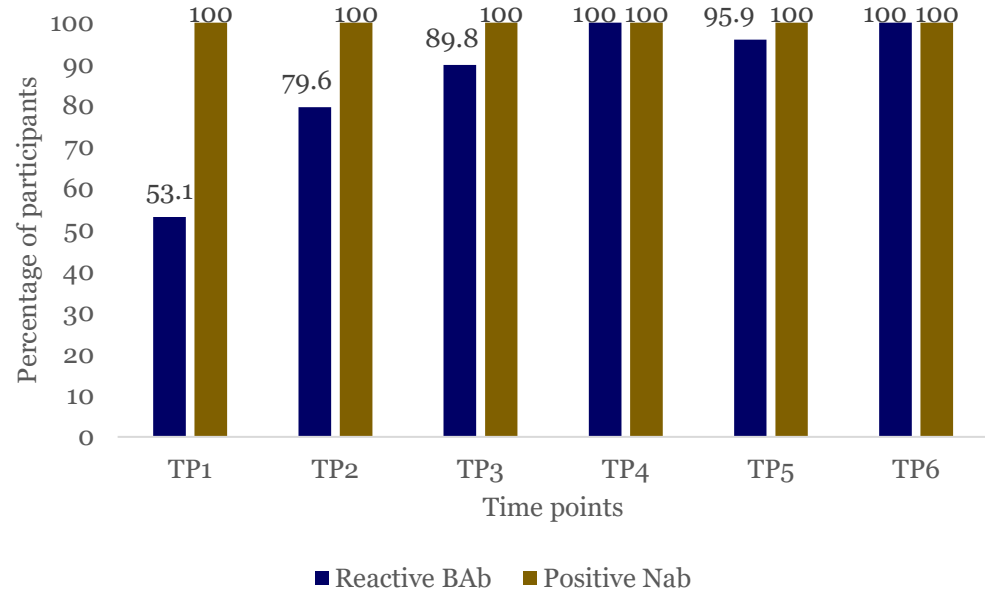

Figure 2. Percentage of participants with reactive BAb and positive NAb in the group receiving CoronaVac. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

Antibody responses in ChAdOx1 vaccinated participants

The BAb levels and NAb inhibition rates kinetics from TP1 to TP6 in ChAdOx1 recipients are described in **Figure 3**. At TP1, a relatively high mean BAb level was revealed while the mean NAb inhibition rate was 40.3±35.5%, suggesting recent SARS-CoV-2 infections in some participants. These recent infections produced high IgG BAb levels with low maturity, resulting in a lower NAb inhibition rate. While at TP2, both BAb level and NAb inhibition rate levels sharply increased, with all participants showing high inhibition rates (96.2±7.3%).

At TP3 and TP4, the BAb level decreased while the NAb inhibition rate was steadily high. Of note, at TP5, BAb level peaked and then decreased at TP6. The mean NAb inhibition rate also presented a modest decrease during the period of TP5 to TP6. However, 100% of participants were positive NAb at TP5 and TP6.

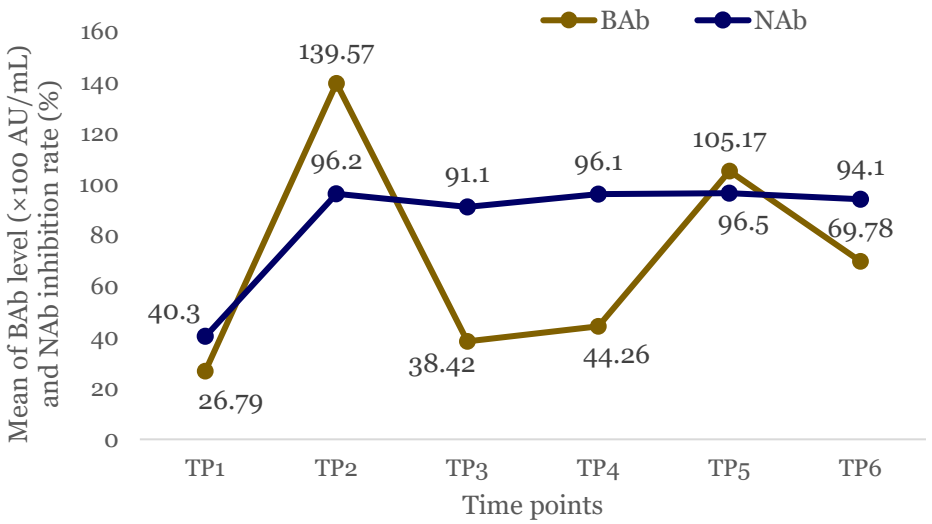

Figure 3. BAb level (×100 AU/mL) and NAb inhibition rate (%) among ChAdOx1 recipients. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

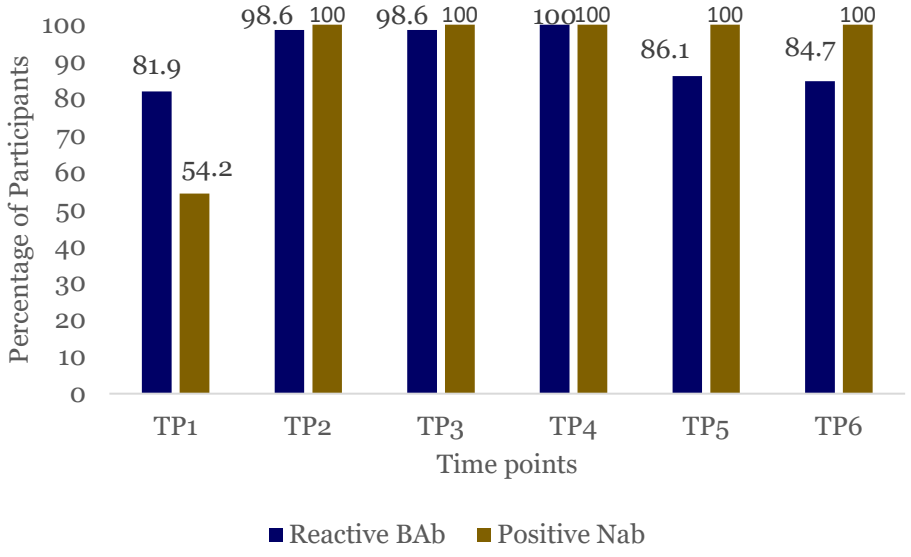

Figure 4. Percentage of participants with reactive BAb and positive NAb in the group receiving ChAdOx1. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

At TP1, reactive BAb was found in 81.9% of participants, with only 54.2% of participants showing positive NAb, as demonstrated in **Figure 4**. The data was different from the result of the CoronaVac group, which showed that 53.1% of participants were reactive BAb and 100% of participants were positive NAb. Nevertheless, considering the broad distribution of BAb level data, it again suggested that a proportion of participants were positive NAb with potential infection inhibition even with undetected BAb. In the following TP2 to TP4, the proportion of participants with reactive BAb fluctuated, however, all the participants were still positive NAb. At TP5 towards TP6, the mean BAb levels decreased (10,517 AU/mL and 6,978 AU/mL, respectively, see **Figure 3**), and the proportion of participants with reactive BAb decreased (86.1% and 84.7% respectively). However, all the participants were still positive NAb.

Role of the previous infection on the kinetics of antibody responses

The kinetics of BAb levels, based on the vaccine types, with and without BAb reactivity at TP1, marking their SARS-CoV-2 infection history, are presented in **Figure 5** and **Figure 6**. Most participants had a history of past or recent asymptomatic infection, as illustrated in **Figure 2** and **Figure 4**. In the group receiving CoronaVac, **Figure 5** reveals a higher BAb level at TP2 on the participants with BAb reactivity at TP1, suggesting the prime response of existing BAb towards the vaccine, followed by a decrease towards TP4. Meanwhile, in the participants without reactive BAb at TP1, the BAb levels gradually increased towards TP4. At TP5 and TP6, those participants demonstrated relatively higher BAb levels compared to participants with reactive BAb at TP1. Of note, even both participants with and without reactive BAb at TP1 demonstrated higher BAb levels at TP6, **Figure 1** illustrated that the NAb inhibition rate started to decrease in the participants receiving CoronaVac.

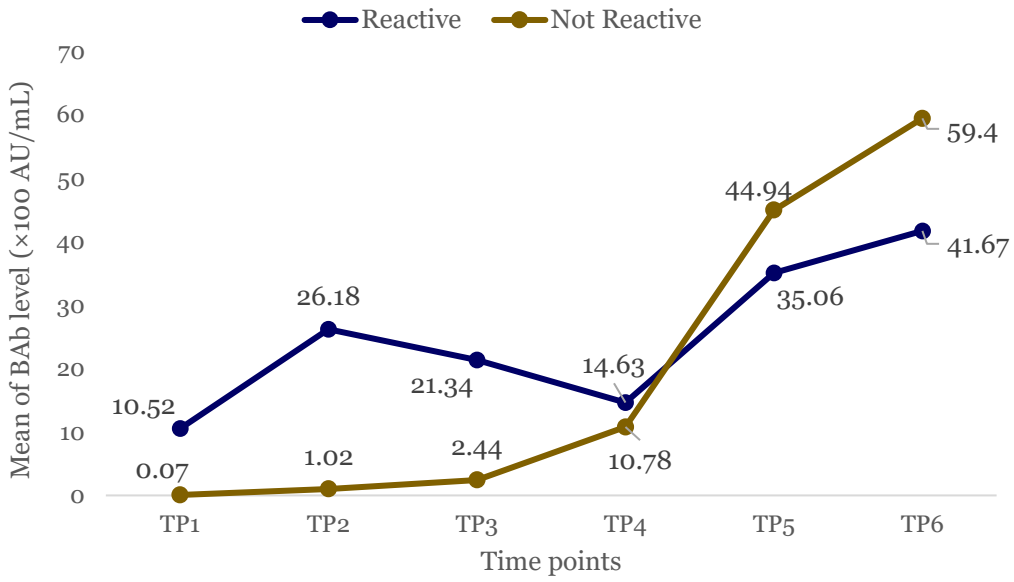

Figure 5. BAb level (×100 AU/mL) on participants with or without reactive BAb at TP1 in the group receiving CoronaVac. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

In the group receiving ChAdOx1, **Figure 6** reveals fluctuating BAb levels. At TP2, a sharp increase was shown in the participants with reactive BAb at TP1, indicating the prime responses to the administered vaccine. It then followed by a decrease towards TP3 and TP4. While on the participants without reactive BAb at TP1, it showed a gradual at TP2 to TP3, followed by a decrease at TP4. Both groups showed an increase at TP5 followed by a decrease at TP6. Combined with **Figure 3** and **Figure 4**, participants receiving ChAdOx1 showed a decrease in BAb level and NAb inhibition rate, even all participants were positive NAb at TP6. However, it suggested a trend of decrease in antibody response during the longer duration beyond 18 months.

The increase in BAb levels at TP5 in all participants receiving both types of vaccines may not only be due to primary doses. During the time of the study, the government released a policy to provide boosters in the period between TP4 and TP5. Thus, the presence of reactive BAb 1 at TP1 might not solely predict the antibody kinetics until 18 months later. The booster administration, as well as possible re-exposure during the 18 months, might also played a significant role. As the booster was enforced by the government to all participants at the same time, it suggested that the effects applied equally to all participants, regardless of the type of vaccine and whether they have a history of previous infection. Thus, the booster effect in more detail needs to be elucidated in further studies.

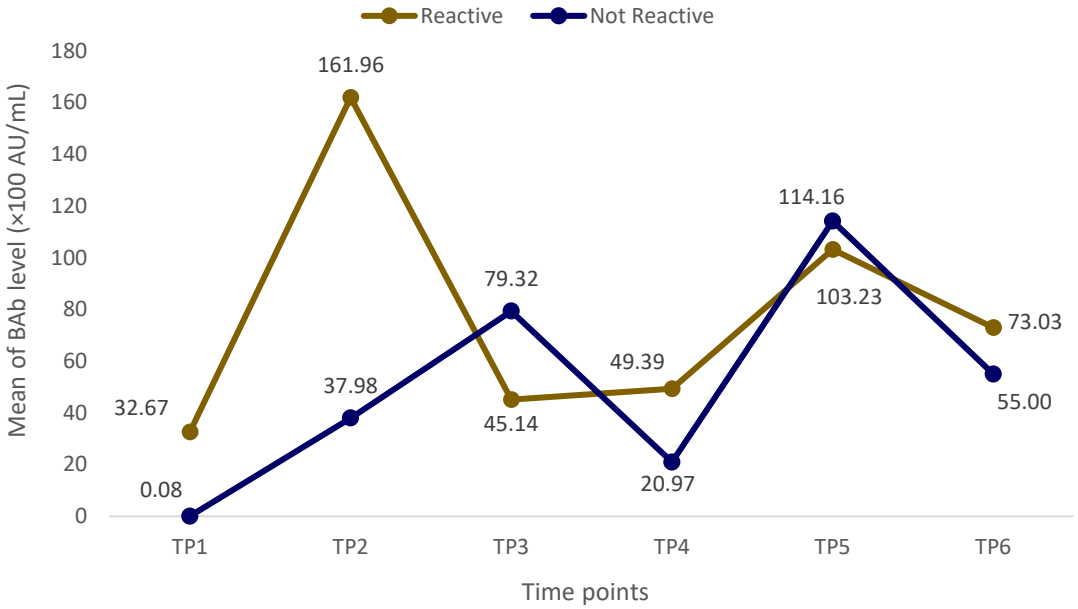

Figure 6. BAb level (×100 AU/mL) on participants with or without reactive BAb at TP 1 in the group receiving ChAdOx1. Time points: before the first dose (TP1), two weeks after the first dose (TP2), before the second dose (TP3), one month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months after the second dose (TP6).

Discussion

Briefly, the study showed fluctuating BAb levels among both vaccine groups, as well as, those with or without a history of SARS-CoV-2 infection. The NAb inhibition rates were also fluctuating, however, all participants were positive NAb during the 18 months post-second dose. Also, sex, age, and BMI did not show a significant influence on the antibody response during the study. Beyond those convincing results, it is imperative to note a trend of decrease in antibody response was suggested at the 18-month time point.

Binding antibodies and neutralizing antibodies are essential in immunology and vaccination and each plays distinct roles in combating pathogens such as SARS-CoV-2 [13,19]. Binding antibodies assist pathogen recognition and indicate destruction by immune cells such as phagocytes. Meanwhile, neutralizing antibodies bind to pathogen antigens and block infection of host cells [35,36]. Its process depends on the level of antibody's affinity and avidity towards SARS-CoV-2. Only antibodies with high avidity will strongly bind the pathogen and neutralize it to block the infection. If the antibody were just partially specific to the pathogen, the process would not be induced efficiently [13,37].

COVID-19 vaccination initially induces robust antibody responses, particularly to neutralizing antibodies, yet antibody levels may decline over time, affecting the long-term immunity [38,39]. Continuous monitoring of antibody levels may be necessary to sustain protection against SARS-CoV-2 [40]. A previous study found that following two CoronaVac doses and a booster dose, antibody levels significantly increased. However, in individuals who did not receive a booster dose, antibody titers drastically decreased seven months after vaccination [41].

Similarly, a recent study demonstrated increased seropositivity of binding antibodies at four weeks after the first dose and two weeks after the second dose of the AstraZeneca vaccine, mirroring the pattern observed for neutralizing antibodies [42]. Furthermore, a similar result came from a study observing the elevated binding antibodies one month after the first and second doses of AstraZeneca vaccines [18]. Moreover, the seropositivity rate decreased from 100% one month after the second dose to 97% at four months post-second administration, a trend similarly occurring in neutralizing antibodies [43].

Recently, a study found persistent seropositivity levels from a week after the first administration of the AstraZeneca vaccine to six months post-second dose. The study also noted an initial increase in seropositivity of neutralizing antibodies up to a month followed by a decline by three months, both after the first dose [44]. Meanwhile, another study on Sinovac vaccine recipients demonstrated rising seropositivity of binding antibodies around the second dose and up to 28 days' post-vaccination. Conversely, neutralizing antibody seropositivity shrunked by 28 days after the second dose [45].

Furthermore, another study revealed a sharp decrease in seropositivity rates from 4 weeks post-second dose of Sinovac vaccine to 132 days after vaccination, with binding antibodies level falling from 100% to 54.10% and neutralizing antibodies inhibition rate from 91.80% to 19.67% [46]. Stable seropositivity levels of binding antibodies were studied in another study, however, with a declining trend in neutralizing antibodies over time. By the fourth and ninth months post-second dose vaccination, the binding antibody seropositivity rates were 83.9% and 76.3%, respectively, while neutralization rates were 48.7% and 20.5%, respectively [47].

The study showed different antibody responses between CoronaVac and ChAdOx1 recipients. This may be attributed to the vaccine types that CoronaVac is an inactivated whole virus vaccine, while ChAdOx1 is a viral-vector vaccine. CoronaVac induces a slower and weaker immune response but primes antibodies against multiple parts of the virus, explaining the steady increase in binding antibodies and neutralizing antibody levels in recipients. Any re-exposure to the virus further boosts neutralizing antibody levels. In contrast, ChAdOx1 induces a robust and specific antibody response against the spike protein of the virus, leading to initially higher binding antibody and neutralizing antibody levels. However, binding antibody levels decrease more rapidly compared to CoronaVac recipients [48].

Following the increase occurring two weeks after the first dose, there was a notable decline in the ChAdOx1 groups and a slight drop in the CoronaVac groups. This is consistent with the notion that the immune system was prepared for a prolonged effect following the administration of the second dose, given the brief response observed following the first dose. As a reflection of the long-term IgG antibody product, the modest rise towards one-month post-second dose suggested a progressive increase in antibody levels towards the long-term effect as targeted with vaccination [49].

In addition to the binding antibody response, the vaccine effect in fighting against SARS-CoV-2 infection and disease should also be considered. The antibody response is an essential signal of adaptive immunity. However, adequate protection involves not only the antibody response but also the cellular immune response and other elements [12-14].

This study presented that the NAb inhibition rate was averagely above the cutoff even when the BAb levels varied during the 18-month cohort. In the CoronaVac group, 53.1% of participants were reactive BAb just before the first dose administration. In comparison, 100% of participants were positive NAb suggesting that participants could inhibit infection without any detectable binding antibodies. This implies that all participants had a history of asymptomatic SARS-CoV-2 infections at different times. Recent infections induced detectable binding antibodies before the first dose, while earlier infections might not, probably due to low or rapidly declining antibody levels. Of note, even without detectable IgG, NAb inhibition rates remained ≥30%.

The rise in NAb inhibition rate two weeks post-first dose, followed by a fall towards the second dose administration, indicates a priming response. Notably, neutralizing antibodies might include IgM and IgA, not just IgG. The priming response induces IgM and IgA which might be included beside IgG in neutralizing antibodies, along with non-specific immune factors, contributing to inhibition. IgG levels significantly rose post-second dose administration, while

IgM and IgA lowered. Since the BAb test measured specific IgG, it presented a steady growth both in binding and neutralizing antibodies from the second dose administrations onward.

One month after the second dose, 100% of participants were reactive BAb and positive NAb. On 12 months post-second dose, the mean and median of BAb level climbed, but the proportion of participants with reactive BAb slightly diminished. On 18 months after the second dose, the mean and median of BAb level decreased but the proportion of participants with reactive BAb reached 100% again, suggesting that some participants experienced declined IgG levels over time, but the NAb inhibition rate was relatively stable. Any re-exposure to the SARS-CoV-2 virus during the period probably boosted the IgG BAb level and NAb inhibition rate. The IgG BAb that was produced during 18 months after the second dose is expected to be mature with high avidity supporting the power of neutralization [49,50].

In the ChAdOx1 group, the BAb levels fluctuated with an increase two weeks after the first dose suggesting a primary response. It was then followed by a decrease before being increased at 12 months post-second administration but fell at 18 months. The proportion of participants with reactive BAb also diminished from 12 to 18 months after the second dose. The rise and fall were probably due to several participants being re-exposed to the SARS-CoV-2 virus during the periods of one to 12 months after the second dose vaccination, leading to an increase in BAb levels by 12-month time point. Another possibility is that booster doses were administered per government policy six months after the second dose, contributing to the rise seen at the 12-month time point. It was then followed by a fall over the next six months towards the 18-months' time point, as the possible effect of re-exposure as well as booster already diminished. However, these fluctuations did not significantly affect the NAb inhibition rates.

Considering the Correlate of Protection, a formula should be applied to calculate the results into BAU/mL. The present study showed a relatively high rate of neutralizing antibodies even with fluctuating levels of binding antibodies. Nevertheless, until recently, there has not been an agreement on the cutoff of BAb level for protection from SARS-CoV-2 infection. Thus currently, the BAb level does not yet accurately represent the Correlate of Protection [51].

The present study found divergent trends between the level of BAb and the rate of NAb. Specifically, the CoronaVac vaccine demonstrated a relatively prolonged antibody response compared to the ChAdOx1 vaccine. Participants in the CoronaVac receiving group showed a trend of increase of BAb level during 18 months. As for the NAb inhibition rate, it showed a trend of initial increase before starting to decrease after 12 months, but all participants were positive NAb during the 18 months. While participants in the ChAdOx1 group showed a decrease in BAb reactivity starting on 12 months after the second dose, however, 100% of participants were still positive NAb during the study.

During the pandemic, the inactivated whole-virus type of vaccine (CoronaVac) was most frequently used in Indonesia within the COVID-19 vaccination program. The viral vector vaccine (ChAdOx1) was next in line. The study indicated that both vaccines showed different kinetics during a short period but eventually induced no significant difference in antibody response during the cohort until 18 months. It is imperative that nowadays, the product of inactivated whole virus vaccine is regulated to be dominantly administered in the post-pandemic COVID-19 vaccination in Indonesia [52].

Sex, age, gender, and previous immunization status may have an impact on how the body reacts to the vaccine. Younger individuals frequently exhibit more robust antibody responses, whereas older adults or those with worsening medical conditions may have lesser antibody responses. These findings emphasize the importance of considering the immunological and demographic factors when developing COVID-19 vaccination programs, especially when several doses are required [53].

The study showed non-significant differences in antibody levels by sex, age, and BMI. Among the possible explanations, the selection of participants was based on the policy of sites and the availability of vaccines on the sites. It is one of the study's drawbacks, as selection bias might be the case. The broader scale of study on the more variety of sites and randomly selected participants is necessary to adjust and analyze the effect more appropriately.

It is also crucial to remember that binding antibody levels do not merely represent the level of protection against SARS-CoV-2 infection. To determine the level of protection more precisely,

the neutralizing rate should be quantified. In the course of massive daily practice, and to more accurately depict the protective level against SARS-CoV-2 infection, more studies were required to determine the neutralizing rate and correlate of protection of the reported antibody level.

Conclusion

This study presented the trend in kinetics as well as functional humoral response upon COVID-19 vaccination. Aside from any history of SARS-CoV-2 infection along with the types of received vaccines, whether the inactivated whole virus or viral vector type of vaccines, the binding antibody level was fluctuating. However, a high inhibition rate of neutralizing antibodies was indicated within the 18-month cohort. This ensures the use of the vaccine in helping to optimize the vaccination strategies to effectively combat the pandemic and protect public health during the post-pandemic era.

Ethics approval

The protocol of the present study was reviewed and approved by the Ethical Committee of the Indonesia National Institute of Health Research and Development (approval number: LB.02.01/2/KE. 431/2021). The study design was explained and discussed with the allocated participants before informed consents were provided and enrolled as the subject of the study. Participants without formal informed consent were not enrolled as participants in the study.

Acknowledgments

The authors thank the National Institute of Health Research and Development, Indonesia Ministry of Health, Indonesia National Research and Innovation Agency, Provincial and City/Regency Health Services, and Primary Health Care at the study sites for their valuable support. Also, we are grateful to the Universitas Sebelas Maret (UNS) Institute for Research and Community Service (LPPM).

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study was partially supported by the Universitas Sebelas Maret (UNS) Institute for Research and Community Services (LPPM) grant with no 349.1/UN27/HK/2021.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

How to cite

Ardyanto TD, Khariri K, Agus TP, Soebandrio A. Post COVID-19 vaccination binding and neutralizing antibody with or without previous infection: An 18-month longitudinal study in Indonesia. Narra J 2024; 4 (2): e1071 - http://doi.org/10.52225/narra.v4i2.1071.

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