RESEARCH ARTICLE

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SARS-CoV-2 Antibody Level after Homologous and Heterologous Booster Vaccines: an 18-month Longitudinal Observational Cohort Study in Indonesia

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Abstract:

Background: Recently, there have been reports of the rise of COVID-19 cases in several sites. The effectiveness of the COVID-19 vaccine was reported elsewhere. There are still questions on how the kinetics of antibody response during relatively long periods, the need for additional doses, and the effect of homologous and heterologous boosters. The study was conducted to analyze the kinetics of antibody response after the primary dose and the third dose of the ChAdOx1 vaccine in individuals previously receiving two doses of the ChAdOx1 (homologous) and CoronaVac (heterologous) COVID-19 vaccines.

Methods: The study population comprised 52 men and 98 women, divided into CoronaVac Recipients and ChAdOx1 Recipients for the first two doses according to the recommended schedule by the Ministry of Health of Indonesia (MoH).Six months after the second dose, the third dose of ChAdOx1 was administered as a homologous and heterologous booster. COVID-19 antibody levels were measured by the CMIA method before the first dose (time-point or TP1), two weeks after the first dose (TP2), before the second dose (TP3), 1 month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months (TP6) after the second dose administration. Six months after the second dose, the third dose of ChAdOx1 was administered as a homologous and heterologous booster. Along with these, several epidemiological data were collected from subjects on TP1.

Results: A total of 153 serum samples were collected from subjects who had received the third dose, and the antibody response was measured. On TP1, COVID-19 antibody reactivity (the level was >50 AU/mL) was detected on 100 (66,67%) of subjects, indicating a possible previous exposure to SARS-CoV-2. On TP2, the sharp increase in antibody level was documented in the ChAdOx1 group. However, in the following data during the cohort, the gap was narrowing, and on the TP6, the antibody levels showed no significant difference between groups (p>0.05). Likewise, no significant differences were shown between groups with or without a history of COVID-19 antibody reactivity on TP1 (p>0.05). Considering epidemiological characteristics, no significant differences were documented based on sex, age groups, and BMI level.

Conclusion: This study provides a deeper understanding of the kinetics of antibody levels longitudinally among those with and without previous history of SARS CoV-2 infection, among the recipients of different vaccines, and the recipients of homologous and heterologous boosters. It is necessary to elucidate further in the next study how the level of antibody reflects the neutralizing antibody level as an indicator of protection against the infection risk.

Keywords: SARS-CoV-2, Antibody response, Homologous and heterologous booster, COVID-19, Infection, Serum samples.

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1. INTRODUCTION

The COVID-19 pandemic swept the globe and changed the paradigms of public health and healthcare systems [1, 2]. The global battle against COVID-19 has witnessed fluctuating trends, with periods of decline often followed by resurgences in cases. Recently, the rise of COVID-19 cases was again reported in December 2023 [3] even during May 2024 in Singapore [4] and June 2024 in the United States [5].

Positive cases and deaths from new COVID-19 strains continue to occur even after three years, as evidenced by wastewater monitoring and clinical diagnosis. In addition, some common detrimental mutations are found in SARS-CoV-2 genomes from deceased COVID-19 patients from different continents. It highlights that the risk of COVID-19 is still present; thus, care and preparedness should never be abandoned [6-8].

During pandemic times, COVID-19 vaccination was initiated in December 2020 [9]. ChAdOx1, a non-replicating adenovirus vector encoding the SARS-CoV-2 viral spike protein, is one of the most widely used vaccines. ChAdOx1 appears to be a viable preventive measure against COVID-19 disease based on early clinical trials; however, concerns remain regarding the long-term immune response and the need for repeated doses to maintain protection [10, 11].

Meanwhile, several nations have integrated the CoronaVac vaccine—which uses the inactivated SARS-CoV-2 virus as an antigen—into their immunization regimens. According to a preliminary investigation, there may be a correlation between age and specific health factors and the effectiveness of CoronaVac in avoiding severe COVID-19 disease. As with previous vaccinations, further study is required to comprehend the immune response that grows over time after receiving the first and second doses of CoronaVac [12, 13].

In this situation, the administration of additional doses (booster doses) has been suggested as a strategy to strengthen and sustain the immune response to SARS-CoV-2. There are now two different methods of administering booster shots: homologous boosting, which uses the same vaccine platform for both the primary series and the booster, and heterologous boosting, which uses a separate vaccine platform [14].

Utilizing the same vaccine platform as the primary series, homologous booster vaccines have been extensively researched and put into practice. These vaccinations have proven to be effective in boosting immune responses and offering heightened defense against COVID-19, including its evolving variations. Conversely, heterologous boosting has drawn interest as a possible tactic to expand the immune response and maybe provide improved protection [15].

According to recent research, heterologous boosting might be more successful at eliciting a stronger immune response overall, which could provide greater defense against SARS-CoV-2 subtypes [16]. This strategy might benefit from the distinct immunological pathways and modes of action triggered by multiple vaccination platforms, resulting in a more varied and all-encompassing immune response [17]. The long-term effectiveness of this strategy is currently being assessed despite the encouraging potential benefits of heterologous boosting [18, 19].

Meanwhile, in the general population of previous recipients of two doses of ChAdOx1 nCoV-19, the third dose of ChAdOx1 nCoV-19 (Vaxzevria, Cambridge, Astra Zeneca, UK) demonstrated significant immunogenicity for both the humoral and cellular arms of the immune response [20, 21].

Nevertheless, it is still unknown how the extra dose would impact the immune response in those who have already received the vaccine's primary two doses. Moreover, the effect of ChAdOx1 as a heterologous booster to other vaccines, mainly CoronaVac, is still unclear.

The study evaluated the kinetics of antibody levels during the primary doses and for 18 months after the second dose administration with CoronaVac and ChAdOx1 based on the recommended schedule [22]. It also observes the difference between one with or without a possible previous infection as well as between one receiving a homologous and heterologous third dose as a booster. The understanding will be part of the strategy for monitoring post-pandemic COVID-19 cases. Moreover, it will contribute to developing more tailored and effective vaccination regimens in response to the possible challenges posed by SARS-CoV-2 after the pandemic.

2. METHODS

2.1. Study Design and Participants

The study is a longitudinal cohort design conducted from August 2021 until May 2023, along with the Indonesian Ministry of Health (MoH) vaccination program. The types of vaccines and study sites in the two cities

were based on the recommendations of the MoH and the local government [22].

All participants met the inclusion criteria, were 18-59 years old, were not pregnant, and had no record of a formal report or self-report of previous symptomatic infection of COVID-19. The criteria referred to technical guidelines for pre-COVID-19 vaccination recipient screening issued by the Indonesian MoH [23].

The participants represented a range of age groups and demographic backgrounds. The participants were then divided into two groups: CoronaVac Recipients and ChAdOx1 Recipients. The selection of participants into each group was based on the vaccine availability and policy of MoH and local government [24].

The author passively observes the selection with no decisive role in the process of participant screening. The study design was explained and discussed fairly 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 subjects of the study.

For the two groups, two doses of the CoronaVac and ChAdOx1 vaccines were administered respectively according to the recommended schedule by the Ministry of Health of Indonesia [22]. Initially, the study was designed to monitor the antibody level during 18 months after second dose administration. Antibody levels were measured just before the first dose (time-point or TP1), two weeks after the first dose (TP2), just before the second dose (TP3), 1 month after the second dose (TP4), 12 months after the second dose (TP5), and 18 months (TP6) after the second dose (Fig. **1**).

Meanwhile, during 6-12 months after the second dose, the MoH released a policy to implement booster administration [25]. The subjects were then administered with a third dose based on vaccine availability and local government policy. The third dose that was administered was ChAdOx1 as a homologous booster (for the previous two doses of ChAdOx1 recipients) as well as a heterologous booster (for the previous two doses of
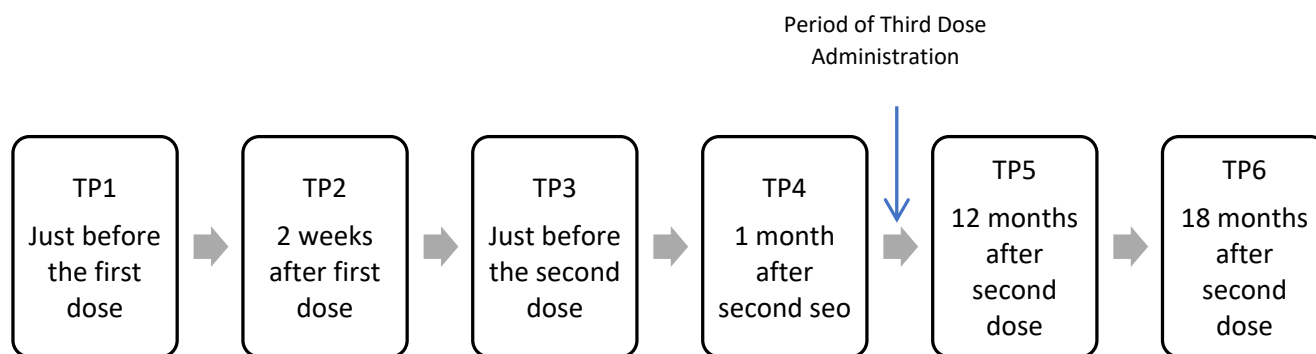
CoronaVac recipients). The antibody levels in the 12 months and 18 months after the second dose were measured as initially designed.

The total sampling method was implemented based on the number of participants on the site during the cohort period. Lost follow-ups were anticipated during the 18 months, and coordination with stakeholders and intensive preparation were implemented intensively to minimize the number. This study focused on the subjects that followed all the designated TP and were administered with ChAdOx1 as the third dose before antibody level measurement on TP5 to analyze the antibody level among homologous and heterologous booster groups.

2.2. Data Collection

A blood sample was drawn from the subject on every designed time-point (TP1-TP6). A blood sample was taken using conventional sampling techniques. The CMIA method was used to measure the antibody response. Accredited clinical laboratories measure by the instrument's use guidelines. The SARS-CoV-2 IgG II quantitative assay technique was used for antibody testing Chemiluminescent microparticle immunoassay (CMIA) technology was used to quantitatively and qualitatively identify IgG antibodies to SARS-CoV-2. Reactivity to COVID-19 antibody was set on the cut-off of 50 AU/mL as declared by the guideline of the kit [26].

Along with the blood sample collection, sex, age, and BMI were collected to determine the subjects' characteristics. Beyond that, the study recognized that scheduling of vaccination, economic aspects and the rise and down of COVID-19 cases, were among the uncontrolled variables influencing the subject during the cohort study. Microsoft Excel packages and SPSS v25.0 software (SPSS Inc., Chicago, IL) were used for data analysis. The data of subjects were verified to be valid in all TP1 to TP6 for analysis. For any missing data, the related subject) data were excluded from the analysis. An independent t-test or Wilcoxon test was used to compare antibody responses between the two groups after the third vaccination dose.

Period of Third Dose
Administration

| TP1 Just before the first dose | TP2 2 weeks after first dose | TP3 Just before the second dose | TP4 1 month after second seo | TP5 12 months after second dose | TP6 18 months after second dose |

Fig. (1). The time-point during 18 months cohort after the second dose administration.

All the data supporting the findings of the article are available within the article. Data were analyzed as groups of CoronaVac and ChAdOx1 recipients, between with or without antibody reactivity on TP1, and based on the characteristics of sex, age groups, and BMI.

2.3. Ethical Consideration

The research Ethical approval was granted by the Ethics Committee of the National Institute of Health Research and Development, Ministry of Health, Indonesia (MoH No.: LB.02.01/2/KE. 431/2021).

3. RESULTS

A total of 153 subjects completed the study period, comprising 87 subjects in the ChAdOx1 group and 66 subjects in the CoronaVac groups, who were enrolled and actively participated during 18 months of the cohort. Those two types of vaccines were among the dominant types used in the Indonesian COVID-19 Vaccination Program.

The serum samples of each subject were collected from TP1 through TP6. On TP1, serum samples were drawn just before the first dose administration. Table **1** shows the characteristics of subjects and the number of subjects with or without positive reactivity to COVID-19 Antibody on TP1 (baseline data).

Most of the subjects were female (64.05%) in two groups. The dominant number of females was not by design and was not parallel with the proportion of male and female citizens of Indonesia. It was related to vaccine availability and local government policy. Most subjects were aged between 36 and 59 years (72,55%), with an average age of 41.91 years. The age grouping was based on the guidelines of the Indonesian MoH [27]. Also, based on body mass index (BMI), the majority of the subjects showed normal BMI (47.06%) and were overweight

(28,76%).

There were 66 subjects in the CoronaVac group, with 3 of them being>60 years old. Considering the small number, then the following analysis excluded these subjects and only included the 63 subjects. The total number of subjects added to the ChAdOx1 group was 150.

On TP1, immediately before the first dose administration, a blood sample was taken. COVID-19 antibody reactivity was detected in 100 (66.67%) of the subjects. The relatively high number indicated the high prevalence of asymptomatic COVID-19 infection, mainly during the highest toll in June-August 2021.

The data of single or multiple sessions of previous infection were out of the study coverage. Among the two groups, the difference proportion of subjects with COVID-19 antibody reactivity was not by design since the occurrence was random, while the division into groups was based on vaccine availability and local government policy.

The BMI showed no simple conclusion to draw on the relationship with COVID-19 antibody reactivity. Even in the subjects with normal BMI, the proportion of previous infection was high, as in the overweight subjects. In contrast, it was relatively low in the subjects who were underweight or obese.

Overall, regarding age groups and BMI, the study did not document a significant differentiation antibody level between CoronaVac and ChAdOx1 groups during TP1 to TP6 (p>0,05 in all measured variables, Table **1**).
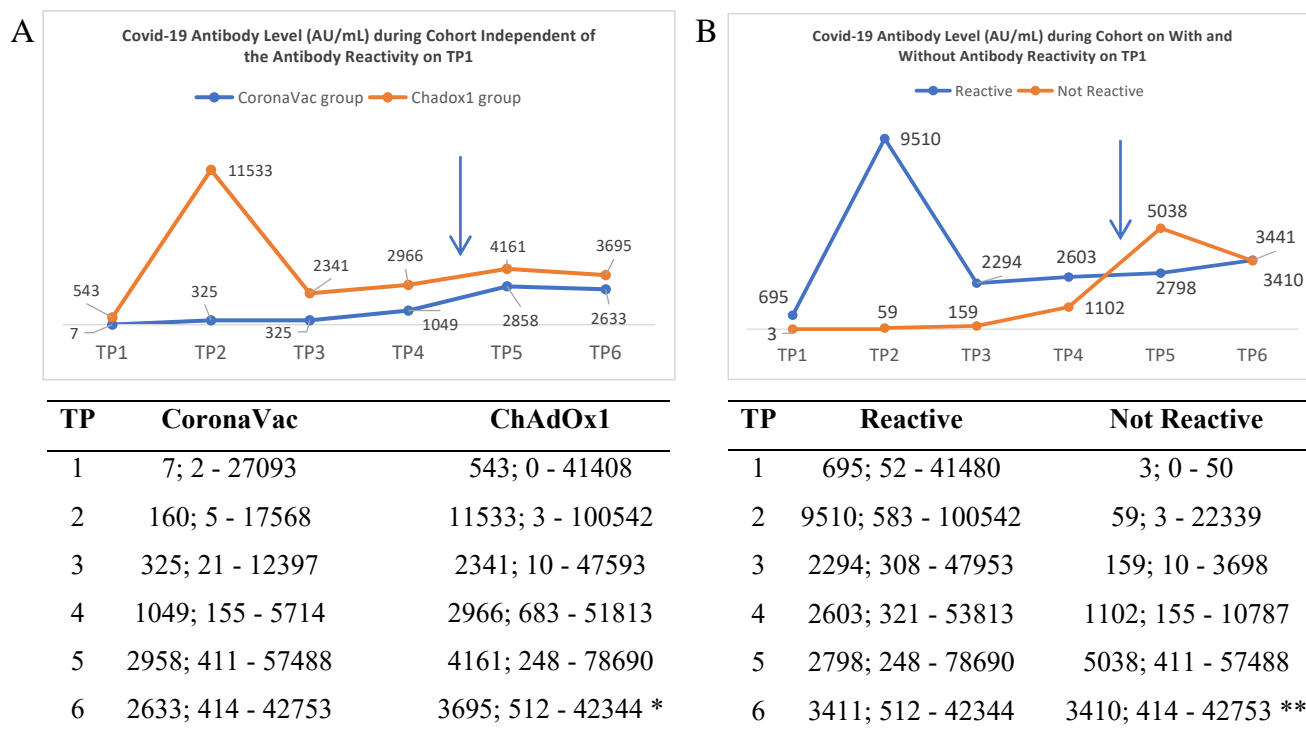
Fig. (**2**) shows the kinetic of COVID-19 antibody levels during the cohort of TP1 through TP6 as designed in detail in the method section. These kinetics were independent of (part A) or based on the antibody reactivity status on TP1 (part B).

Table 1. Characteristics of Study Participants and Antibody COVID-19 Reactivity on TP1.

Variables	CoronaVac					ChAdOx1					N	%	p
	N	Reactive*		Not Reactive*		N	Reactive*		Not Reactive*				
		N	%	N	%		N	%	N	%			
Sex													>0.05
Male	18	7	10.61	11	16.67	34	27	31.03	7	8.05	52	33.99	
Female	45	17	25.76	28	42.42	53	49	56.32	4	4.60	98	64.05	
Total	63	24	36.36	39	59.09	87	76	87.36	11	12.64	150		
Age group (years)													>0.05
18-35	20	9	38.09	11	61.91	19	13	87.36	6	12.64	39	25.49	
36-59	43	15	34.88	28	65.12	68	63	92.65	5	7.35	111	72.55	
60+	3**												
Body Mass Index													>0.05
Underweight	3	1	1.52	2	3.03	6	4	4.60	2	2.30	9	5.88	
Normal weight	33	15	22.73	18	27.27	39	34	39.08	5	5.75	72	47.06	
Overweight	17	6	9.09	11	16.67	27	26	29.89	1	1.15	44	28.76	
Obesity	10	2	3.03	8	12.12	15	12	13.79	3	3.45	25	16.34	

* Reactive or Not Reactive: with or without reactivity of COVID-19 antibody on TP1.

** As too small number of elderly subjects, the data are excluded from the following analysis.

A

Covid-19 Antibody Level (AU/mL) during Cohort Independent of the Antibody Reactivity on TP1

B

Covid-19 Antibody Level (AU/mL) during Cohort on With and Without Antibody Reactivity on TP1

TP	CoronaVac	ChAdOx1
1	7; 2 - 27093	543; 0 - 41408
2	160; 5 - 17568	11533; 3 - 100542
3	325; 21 - 12397	2341; 10 - 47593
4	1049; 155 - 5714	2966; 683 - 51813
5	2958; 411 - 57488	4161; 248 - 78690
6	2633; 414 - 42753	3695; 512 - 42344 *

TP	Reactive	Not Reactive
1	695; 52 - 41480	3; 0 - 50
2	9510; 583 - 100542	59; 3 - 22339
3	2294; 308 - 47953	159; 10 - 3698
4	2603; 321 - 53813	1102; 155 - 10787
5	2798; 248 - 78690	5038; 411 - 57488
6	3411; 512 - 42344	3410; 414 - 42753 **

* and ** p>0.05

- Data displayed as median, minimal, and maximal as data were not normally distributed

- Blue arrow: timepoint of third dose administration

Fig. (2). Kinetics of COVID-19 antibody level during cohort (part **A**) independently from the reactivity and (part **B**) based on the reactivity status on TP1.

Of note, considering the mean and standard deviation of antibody level, it was indicated that the response varied broadly among the subjects. Statistical analysis showed a non-normal distribution of data. The results and analysis were then displayed as median and minimal-maximal values.

On TP2, two weeks after the first dose, subjects receiving ChAdOx1 averagely showed a high increase in antibody level that was very significantly different from the CoronaVac group. It is worth noting that, the median, minimal, and maximal values, even on TP2, had an overlap of antibody levels between groups. It indicated the variety of humoral responses to vaccines that might be related to other factors.

The rise was followed by a sharp decrease in TP3 just before the second dose was administered, which was still significantly different but in a narrower gap with the average level in the CoronaVac group. On TP4, one month after the second dose administration, there was just a slight increase in the two groups while keeping the narrow gap between both. During the time between TP4 and TP5, a portion of subjects were administered with the third dose. The types of which were in variety. The study focuses on the portion of the subject that was being administered with ChAdOx1 as the third dose.

On TP5, there was a rise in the antibody level of two groups, with the gap narrowing. Eventually, on the TP6, the level slowly decreased with the gap was more narrowing and showed no significant difference between the two groups.

Considering the reactivity status of TP1, in Fig. (**2**) Part B, there was a high increase in TP2 among the reactive groups. It was then followed by a sharp decrease and a narrowing gap with the antibody level of the group that was not reactive. The interesting trend was on the TP5 that after being administered with the booster, the group that was not reactive showed an increase even more than the antibody level of the reactive group. It was suspected as a temporary reaction since the levels were becoming very close on TP6, and no significant differences were documented.

4. DISCUSSION

Early reports of patients with cough, lung ground glass opacities, and symptoms progressing to severe pneumonia suggested that SARS-CoV-2 could be transmitted through the respiratory system. Direct transmission by respiratory droplets is confirmed by productive SARS-CoV-2 replication in both the upper and lower respiratory tracts (LRT), as well as the rising number of cases demonstrating

human-to-human transfer among close contacts exhibiting vigorous coughing [28].

Accurate virus detection through RT-PCR is a first step toward containing the COVID-19 pandemic. Lapses jeopardize public safety by allowing illness to spread, helped by misleading negative test findings. Serological testing complements virus detection by indicating prior infection, which could be used for therapeutic gain [29]. Dealing with the risk, during the examination of a suspected COVID-19-infected patient, a modification was made to minimize the risk of transmission as well as radiation exposure [30-32].

Given the burden of containing the pandemic, the reasonably successful preventive method was to keep both physical and social isolation. Even in the past, artificial intelligence has proven to be a promising solution to everyday life problems. The required prototype will be provided with some instructions on using Python, CV, and deep learning to keep track of people and their distance [33].

As distancing was a temporary strategy, numerous vaccine platforms have been developed to elicit a potent immune response and protect people from severe COVID-19. Vaccination is one of the most important methods of stopping the spread of the virus and protecting the general public from the harmful effects of COVID-19 infection [34, 35]. Even recently, there was still peoples' mistrust in the COVID-19 vaccine monitored through social media [36].

CoronaVac is a vaccine that is currently widely used in several countries, and it works by stimulating the immune system with an inactivated virus. The preliminary study suggests that CoronaVac vaccination significantly reduces the risk of contracting COVID-19, becoming seriously ill, and dying from the virus. However, other studies have shown that the level of protection varies depending on the vaccination and demographic context. Studies in many countries show that effectiveness rates in preventing serious illness or death vary from fifty percent to more than eighty percent [37-39].

Meanwhile, ChAdOx1, which uses a modified adenovirus vector to deliver the viral spike protein gene into the body, is one of the most widely used vaccines in the world today. Clinical trials suggest that the ChAdOx1 vaccine is reasonably effective in reducing the risk of severe illness, hospitalization, and mortality associated with COVID-19. Concerns have been raised in some countries about the extremely rare possibility of blood clots forming following this vaccination, although the risk is very low [40, 41].

Booster doses can be administered using the same type of vaccine as the previous dose (homologous booster) or a different type of vaccine (heterologous booster). Population studies in Northern Cyprus, Turkey, have shown that administration of a third single booster dose of both Pfizer and CoronaVac vaccines can increase the level of anti-spike RBD IgG antibodies in elderly populations. In this study, a booster dose was administered to recipients of a complete two-dose CoronaVac/CoronaVac vaccine regimen. Although both vaccines increased antibody levels, subjects who received a Pfizer booster (a heterologous booster) had an 8-fold increase in antibody levels [42].

A study conducted in Thailand compared groups receiving only two doses of CoronaVac with those receiving an additional dose of AstraZeneca (a heterologous booster). The results of the study showed a more than 80-fold increase in antibody level in the group receiving an AstraZeneca booster (6.763 BAU/mL; 4.626-11.525 BAU/mL; p < 0.0001) compared to the group receiving only one dose of CoronaVac (60.97 BAU (binding antibody unit)/mL, 47.95-127.9 BAU)/mL). The study also found that the group that received an additional dose of Pfizer (21.457 BAU/ml; 15.571-34.266 BAU/mL; p<0.0001) also had an increase in antibody level that reached more than 200 times that of the group that did not receive an additional dose [43].

A study conducted in Botswana evaluated the immune response following administration of AstraZeneca's vaccine in the 1 dose, 2 dose, and booster groups. The results of the study showed that the group given a booster dose had anti-SARS CoV-2 level, remained awake, and increased from 28.4 GMC (95% CI 14.1-57.4) to 35.3 GMC (95% IC 23.2-53.6) on day 182 after dose 1 compared to before the booster dose (day 170 after the first AZ dose). The limitation of this study was the lack of data on antibody levels in a group that received only two doses of the vaccine on days 170 and 182 after the first dose. However, on these two days, a small proportion of the population in the two-dose group was still found to be seropositive [44].

The study showed that the kinetics of average COVID-19 antibody levels among the subjects were dynamically different between the CoronaVac and ChAdOx1 groups. Independent of antibody reactivity status, the difference in the kinetics was very significant for TP2. This is in coherence with the understanding that there were different responses between types of COVID-19 vaccine, mainly between inactivated whole-virus and viral vector vaccines, as also reported previously [45].

The rise in TP2 was followed by a decrease that was sharp in ChAdOx1 groups and slight in CoronaVac groups. This is in coherence with the understanding of short response after the first dose, that the immune system was well-informed for a long effect after the second dose administration on TP3. The slight increase towards TP4 indicated a gradual increase of antibody levels toward long-term effect as targeted with vaccination as a reflection of long-term IgG antibody product [46].

A slight increase was also noted after the third dose of ChAdOx1, with the gap narrowing between the two groups. It was noted that even on the previous recipients' CoronaVac subject, the increase was like that previously being administered with ChAdOx1. It indicated that there was no significant difference between homologous and heterologous boosters. The relatively mature IgG was

expected to respond similarly in the two groups upon homologous and heterologous boosters. It was even more strongly shown on TP6 that the gap was narrowing and became not significantly different [47].

It was interesting that the antibody level of the reactive group steadily increased from TP3 to TP6, indicating that a longer period from the previous infection led to a maturity of humoral response than the non-reactive group. Nevertheless, the most important point is that homologous and heterologous provide no different antibody levels during an 18-month cohort.

In addition to the antibody response, the effect of the third dose of the ChAdOx1 vaccine on defense against COVID-19 infection and disease should also be considered. Effective protection involves not only the antibody response but also the cellular immune response and other elements. The antibody response is an important signal of adaptive immunity. In populations with heterologous boosters, further studies with long-term follow-up are needed to assess the efficacy of the third dose of the ChAdOx1 vaccine in preventing severe COVID-19 disease and SARS-CoV-2 infection [40, 48].

Other research suggests that the type of previous immunization may have an impact on the immunological response to a third dose of the COVID-19 vaccine [49, 50]. Furthermore, response to the third dosage of the ChAdOx1 vaccine might be affected by age, gender, and prior immunization status. While elderly people or those with deteriorating health conditions may have fewer antibody responses, younger people often show stronger antibody responses. These results bolster the significance of taking immunological and demographic variables into account when designing COVID-19 immunization programs, particularly when multiple doses are involved [40, 50].

The study documented no significant difference among the subjects based on sex, age, and BMI. Among the possible explanations, the subjects were enrolled based on the policy of sites and the availability of vaccines on the sites. It is one of the drawbacks of the study. The broader scale of study on a more varied number of sites and randomly selected subjects is necessary to adjust and analyze the effect more properly.

The inactivated whole-virus type of vaccine (CoronaVac) was most frequently used in Indonesia's COVID-19 vaccination program during the pandemic. The viral vector vaccine (ChAdOx1) was the second. The study indicated that both vaccines showed different kinetics during a short period but eventually induced no significant difference in antibody response in the cohort until 18 months. It is imperative that nowadays, the product of the inactivated whole virus vaccine is regulated to be dominantly administered during the post-pandemic COVID-19 vaccination in Indonesia [51, 52].

Consideration of vaccination policy and defense strategies during the transition period requires consideration of economic, logistical, and etiological factors. The dosage and distribution of vaccines must take into account the most urgent needs of the population and the availability of daily supplies for COVID-19. It is also important to consider ethical guidelines for resource distribution and ease of access to ensure that public sector efforts reach each segment of the community equitably [53].

The type of vaccine was based on local availability and government policy. Those were the two dominant types being used in the Indonesian COVID-19 Vaccination Program. The study was not authorized to analyze other type of vaccines. The participants' selection was also based on government policy. Overall, the above-mentioned were the limitations of the study.

It is also a drawback that the study only d had a very small number of elderly people, which renders it difficult to conduct a proper analysis. However, for the general population, the results showed no significant difference between homologous and heterologous groups at 12 months after the third dose and 18 months after the second dose. It widens the opportunity to have a booster vaccine without constraint on the same type of vaccine availability.

It is also imperative to note that the level of antibodies does not merely reflect the protection level of the COVID-19 infection. The neutralizing antibody should be measured to more precisely indicate the protection level. Further study was necessary to elucidate the neutralizing level of the reported antibody level to more precisely reflect the protective level of COVID-19 infection.

CONCLUSION

Overall, this study has provided information on the immunological response to the COVID-19 vaccine, particularly concerning homologous and heterologous boosters. The information should be important to build, maintain, and strengthen the strategy to prepare the public for the possible threat of COVID-19. Further study is necessary to elucidate deeper information on humoral immunity protection levels against infection as well as severe illness and death caused by COVID-19.

AUTHOR'S CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

MoH = Ministry of Health

CMIA = Chemiluminescent Microparticle Immunoassay

BMI   = Body Mass Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Research Ethical approval was granted by the Ethics Committee of the National Institute of Health Research and Development, Ministry of Health, Indonesia (MoH No.:

LB.02.01/2/KE. 431/2021).

REFERENCES

[1]   Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506.
http://dx.doi.org/10.1016/S0140-6736(20)30183-5   PMID: 31986264

[2]   Sallam M. COVID-19 vaccine hesitancy worldwide: A concise systematic review of vaccine acceptance rates. Vaccines (Basel) 2021; 9(2): 160.
http://dx.doi.org/10.3390/vaccines9020160 PMID: 33669441

[3]   WHO South-East Asia. As COVID-19 cases rise, WHO asks countries to scale up surveillance and protective measures. Available   from:
https://www.who.int/southeastasia/news/detail/24-12-2023-as-covi
d-19-cases-rise-who-asks-countries-to-scale-up-surveillance-and-
protective-measures accessed on 10 June 2024

[4]   Singapore MoH. Update on COVID-19 situation. Available from:
https://www.moh.gov.sg/news-highlights/details/update-on-covid-1
9-situation accessed on 10 June 2024

[5]   CDC United States. Center for Forecasting and Outbreak Analytics Current Epidemic Growth Status (Based on R) for States   and   Territories.   Available   from:
https://www.cdc.gov/forecast-outbreak-analytics/about/rt-estimate
s.html accessed on 10 June 2024

[6]   Islam MA. A review of SARS-CoV-2 variants and vaccines: Viral properties, mutations, vaccine efficacy, and safety. Infect Med 2023; 2(4): 247-61.
http://dx.doi.org/10.1016/j.imj.2023.08.005 PMID: 38205179

[7]   Islam MA, Marzan AA, Arman MS, *et al.* Some common deleterious mutations are shared in SARS-CoV-2 genomes from deceased COVID-19 patients across continents. Sci Rep 2023; 13(1): 18644.
http://dx.doi.org/10.1038/s41598-023-45517-1 PMID: 37903828

[8]   Islam MA, Rakib SH, Bhattacharya P, Jakariya M, Haque MM, Tiwari A. Integrated strategy: Identifying SARS-CoV-2 strains in communities *via* wastewater monitoring and clinical diagnosis. Sci Total Environ 2024; 912: 168617.

[9]   WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes the need for equitable global access. Available   from:
https://www.who.int/news/item/31-12-2020-who-issues-its-first-em
ergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-
need-for-equitable-global-access

[10] Ramasamy MN, Minassian AM, Ewer KJ, *et al.* Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020; 396(10267): 1979-93.
http://dx.doi.org/10.1016/S0140-6736(20)32466-1   PMID: 33220855

[11] Tanriover MD, Doğanay HL, Akova M, *et al.* Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021; 398(10296): 213-22.
http://dx.doi.org/10.1016/S0140-6736(21)01429-X   PMID: 34246358

[12] Kumar S, Saikia D, Bankar M, *et al.* Efficacy of COVID-19 vaccines: A systematic review and network meta-analysis of phase 3 randomized controlled trials. Pharmacol Rep 2022; 74(6): 1228-37.
http://dx.doi.org/10.1007/s43440-022-00429-1 PMID: 36342658

[13] Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397(10269): 99-111.
http://dx.doi.org/10.1016/S0140-6736(20)32661-1   PMID: 33306989

[14] World Health Organization. Interim statement on the use of additional booster doses of Emergency Use Listed mRNA vaccines against   COVID-19.   2022.   Available   from:
https://www.who.int/news/item/17-05-2022-interim-statement-on-t
he-use-of-additional-booster-doses-of-emergency-use-listed-mrna-
vaccines-against-covid-19

[15] Jafari A, Danesh Pouya F, Niknam Z, Abdollahpour-Alitappeh M, Rezaei-Tavirani M, Rasmi Y. Current advances and challenges in COVID-19 vaccine development: from conventional vaccines to next-generation vaccine platforms. Mol Biol Rep 2022; 49(6): 4943-57.
http://dx.doi.org/10.1007/s11033-022-07132-7 PMID: 35235159

[16] Mackey K, Ayers CK, Kondo KK, *et al.* Racial and Ethnic Disparities in COVID-19–Related Infections, Hospitalizations, and Deaths. Ann Intern Med 2021; 174(3): 362-73.
http://dx.doi.org/10.7326/M20-6306 PMID: 33253040

[17] Chavda VP, Patel AB, Vaghasiya DD. SARS-CoV-2 variants and vulnerability at the global level. J Med Virol 2022; 94(7): 2986-3005.
http://dx.doi.org/10.1002/jmv.27717 PMID: 35277864

[18] Chagla Z. In adults, the Oxford/AstraZeneca vaccine had 70% efficacy against COVID-19 >14 d after the 2nd dose. Ann Intern Med 2021; 174(3): JC29.
http://dx.doi.org/10.7326/ACPJ202103160-029 PMID: 33646835

[19] Flaxman A, Marchevsky NG, Jenkin D, *et al.* Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet 2021;

398(10304): 981-90.
http://dx.doi.org/10.1016/S0140-6736(21)01699-8 PMID: 34480858

[20] Munro APS, Janani L, Cornelius V, *et al.* Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021; 398(10318): 2258-76.
http://dx.doi.org/10.1016/S0140-6736(21)02717-3 PMID: 34863358

[21] Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384(5): 403-16.
http://dx.doi.org/10.1056/NEJMoa2035389 PMID: 33378609

[22] Minister of Health Regulation Number 10 of 2021 concerning Implementation of Vaccinations in the Context of Overcoming the 2019 Corona Virus Disease (COVID-19) Pandemic. 2021. Available from:
https://peraturan.bpk.go.id/Download/162786/Permenkes%20Nomor%2010%20Tahun%202021.pdf

[23] Decree of the Minister of Health Number HK.01.07/MENKES/4638/2021 concerning Technical Instructions for Implementing Vaccination in the Context of Overcoming the 2019 Corona Virus Disease (Covid-19) Pandemic. 2021. Available from:
https://peraturan.bpk.go.id/Download/164806/Kepmenkes%20HK.01.07-Menkes-4638-2021.pdf

[24] Presidential Decree. Presidential Regulation (Perpres) Number 99 of 2020 concerning Procurement of Vaccines and Implementation of Vaccinations in the Context of Overcoming the 2019 Corona Virus Disease (Covid-19) Pandemic. 2020. Available from:
https://peraturan.bpk.go.id/Download/139877/Perpres%20Nomor%2099%20Tahun%202020.pdf accessed on 10 June 2024

[25] Circular Letter for Implementing Booster Vaccination in All Regions. 2022. Available from:
https://sehatnegeriku.kemkes.go.id/baca/rilis-media/20220113/45391 accessed on 10 June 2024

[26] English E, Cook LE, Piec I, Dervisevic S, Fraser WD, John WG. Performance of the Abbott SARS-CoV-2 IgG II Quantitative Antibody Assay Including the New Variants of Concern, VOC 202012/V1 (United Kingdom) and VOC 202012/V2 (South Africa), and First Steps towards Global Harmonization of COVID-19 Antibody Methods. J Clin Microbiol 2021; 59(9): e00288-21.
http://dx.doi.org/10.1128/JCM.00288-21

[27] Minister of Health Regulation Number 25 of 2016 concerning the National Action Plan for Elderly Health for 2016-2019. 2016. Available from:
https://peraturan.bpk.go.id/Download/104006/Permenkes%20Nomor%2025%20Tahun%202016.pdf accesses on 10 June 2024

[28] Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol 2020; 41(12): 1100-15.
http://dx.doi.org/10.1016/j.it.2020.10.004 PMID: 33132005

[29] Kevadiya BD, Machhi J, Herskovitz J, *et al.* Diagnostics for SARS-CoV-2 infections. Nat Mater 2021; 20(5): 593-605.
http://dx.doi.org/10.1038/s41563-020-00906-z PMID: 33589798

[30] Diwakar M, Singh P, Karetla GR, *et al.* Low-Dose COVID-19 CT Image Denoising Using Batch Normalization and Convolution Neural Network. Electronics (Basel) 2022; 11(20): 3375.
http://dx.doi.org/10.3390/electronics11203375

[31] Diwakar M, Singh P, Swarup C, *et al.* Noise suppression and edge preservation for low-dose COVID-19 CT Images Using NLM and method noise thresholding in shearlet domain. Diagnostics (Basel) 2022; 12(11): 2766.
http://dx.doi.org/10.3390/diagnostics12112766 PMID: 36428826

[32] Singh P, Diwakar M, Pandey NK, *et al.* Low-dose COVID-19 CT image denoising using CNN and its method noise thresholding. Curr Med Imaging Rev 2023; 19(2): 182-93.
http://dx.doi.org/10.2174/1573405618666220404162241 PMID: 35379137

[33] Nimje S, Ahmad M, Thakur R, *et al.* COVID protocols adherence detection in multi-people interaction using deep learning YOLO V3 algorithm for COVID prevention. AIP Conf Proc 2023; 2771(1): 020015.
http://dx.doi.org/10.1063/5.0152401

[34] Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res 2020; 288: 198114.
http://dx.doi.org/10.1016/j.virusres.2020.198114 PMID: 32800805

[35] Ewer KJ, Barrett JR, Belij-Rammerstorfer S, *et al.* T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med 2021; 27(2): 270-8.
http://dx.doi.org/10.1038/s41591-020-01194-5 PMID: 33335323

[36] Vatsa D, Yadav A, Singh P, Diwakar M. An analytical insight of discussions and sentiments of Indians on omicron-driven third wave of COVID-19. SN Computer Science 2023; 4(6): 791.
http://dx.doi.org/10.1007/s42979-023-02269-z

[37] Al Kaabi N, Zhang Y, Xia S, *et al.* Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults. JAMA 2021; 326(1): 35-45.
http://dx.doi.org/10.1001/jama.2021.8565 PMID: 34037666

[38] Vandebosch A, Sadoff J, Douoguih M. Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med 2021; 385: 288.

[39] Top KA, Chen RT, Levy O, *et al.* Advancing the science of vaccine safety during the Coronavirus Disease 2019 (COVID-19) pandemic and beyond: Launching an international network of special immunization services. Clin Infect Dis 2022; 75 (Suppl. 1): S11-7.
http://dx.doi.org/10.1093/cid/ciac407 PMID: 35680552

[40] Lopez Bernal J, Andrews N, Gower C, *et al.* Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021; 385(7): 585-94.
http://dx.doi.org/10.1056/NEJMoa2108891 PMID: 34289274

[41] Strukcinskiene B, Valotkiene Z, Jurgaitis J, Grigoliene R, Genowska A. Immune response to COVID-19 vaccination in frontline healthcare workers. Vaccines (Basel) 2024; 12(2): 199.
http://dx.doi.org/10.3390/vaccines12020199 PMID: 38400182

[42] Barin B, Kasap U, Selçuk F, Volkan E, Uluçkan Ö. Comparison of SARS-CoV-2 anti-spike receptor binding domain IgG antibody responses after CoronaVac, BNT162b2, ChAdOx1 COVID-19 vaccines, and a single booster dose: A prospective, longitudinal population-based study. Lancet Microbe 2022; 3(4): e274-83.
http://dx.doi.org/10.1016/S2666-5247(21)00305-0 PMID: 35165669

[43] Phumisantiphong U, Chunhakan S, Manomaipiboon A, *et al.* Comparison of antibody responses before and after booster doses with the Pfizer-BioNTech or Oxford–AstraZeneca vaccines in healthcare workers in Thailand. Vaccine X 2023; 13: 100277.
http://dx.doi.org/10.1016/j.jvacx.2023.100277 PMID: 36845212

[44] Makhema J, Shava E, Izu A, Gaolathe T, Kuate L, Walker A. Safety of AZD1222 COVID-19 vaccine and low Incidence of SARS-CoV-2 infection in Botswana following ChAdOx1(AZD1222) vaccination: A single-arm open-label interventional study - final study results. IJID Reg 2024; 10: 35-43.

[45] Lazarus R, Querton B, Corbic Ramljak I, *et al.* Immunogenicity and safety of an inactivated whole-virus COVID-19 vaccine (VLA2001) compared with the adenoviral vector vaccine ChAdOx1-S in adults in the UK (COV-COMPARE): Interim analysis of a randomised, controlled, phase 3, immunobridging trial. Lancet Infect Dis 2022; 22(12): 1716-27.
http://dx.doi.org/10.1016/S1473-3099(22)00502-3 PMID: 36075233

[46] Brisotto G, Muraro E, Montico M, *et al.* IgG antibodies against SARS-CoV-2 decay but persist 4 months after vaccination in a cohort of healthcare workers. Clin Chim Acta 2021; 523: 476-82.
http://dx.doi.org/10.1016/j.cca.2021.10.035 PMID: 34755649

[47] Dehgani-Mobaraki P, Wang C, Floridi A, Floridi E, Dawoodi S, Zaidi AK. Long-term persistence of IgG antibodies in recovered COVID-19 individuals at 18 months post-infection and the impact of two-dose BNT162b2 (Pfizer-BioNTech) mRNA vaccination on

the antibody response: Analysis using fixed-effects linear regression model. Virology 2023; 578: 111-6.
http://dx.doi.org/10.1016/j.virol.2022.12.003 PMID: 36516688

[48]   Lopez Bernal J, Andrews N, Gower C, *et al.* Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021; 373(1088): n1088.
http://dx.doi.org/10.1136/bmj.n1088 PMID: 33985964

[49]   Cao Y, Wang J, Jian F, *et al.* Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature 2022; 602(7898): 657-63.
http://dx.doi.org/10.1038/s41586-021-04385-3 PMID: 35016194

[50]   Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E. Spike-antibody waning after the second dose of BNT162b2 or ChAdOx1. Lancet 2021; 398: 385-7.

http://dx.doi.org/10.1016/S0140-6736(21)01642-1

[51]   Shrotri M, Fragaszy E, Nguyen V, *et al.* Spike-antibody responses to COVID-19 vaccination by demographic and clinical factors in a prospective community cohort study. Nat Commun 2022; 13(1): 5780.
http://dx.doi.org/10.1038/s41467-022-33550-z PMID: 36184633

[52]   Regulation of the Minister of Health of the Republic of Indonesia Number 7 of 2023 concerning Procurement of Vaccines and Implementation of Vaccinations in the Context of Overcoming the 2019 Corona Virus Disease (Covid-19) Pandemic. 2023. Available from:
https://peraturan.bpk.go.id/Details/249131/permenkes-no-7-tahun-2023 accessed on 10 June 2024

[53]   Rosenberg ES, Dorabawila V, Easton D, *et al.* Covid-19 Vaccine Effectiveness in New York State. N Engl J Med 2022; 386(2): 116-27.
http://dx.doi.org/10.1056/NEJMoa2116063 PMID: 34942067