

Original Article

Comparative analysis of COVID-19 incidence and neutralizing antibody response after primary COVID-19 vaccination and heterologous booster doses in adolescents vs. adults: the Indonesian experience

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Abstract

Background The Indonesian COVID-19 immunization program has provided primary doses of a COVID-19 vaccine to adolescents and adults, while booster doses were given to adults only. Evaluation of this program is crucial to determine if boosters should be recommended for adolescents.

Objective To compare COVID-19 incidence and SARS-CoV-2 IgG neutralizing antibody levels after COVID-19 vaccination in adolescents given a primary dose vs. adults given a primary dose and a booster.

Methods In this cross-sectional study, participants were given questionnaires on their COVID-19 history and evaluated for SARS-CoV-2 IgG neutralizing antibody titers. We included healthy individuals aged 12 years or older who resided in Jakarta and consented to participate, had received primary COVID-19 vaccine doses, and for adults, booster doses. Participants were stratified into two age groups, adolescents (12-17 years) and adults (18 years and above). We compared the incidence of COVID-19 and SARS-CoV-2 antibody titers between the two age groups.

Results Out of 419 participants who met the inclusion criteria, 159 had blood specimens drawn for measurement of SARS-CoV-2 antibody titers. Before the widespread administration of the vaccine, the incidence of COVID-19 in was 4.9% in adolescents vs. 10.2% in adults ($P=0.036$). After widespread vaccination, the incidence of COVID-19 remained lower in adolescents than in adults (2.2% vs. 8.8%, respectively; $P=0.005$). The median SARS-CoV-2 antibody titer post-COVID-19 vaccination was 97.85 (range 46.46-98.23) U/mL in adults vs. 96.78 (range 22.08-98.23) U/mL in adolescents ($P<0.05$).

Conclusion While the incidence of COVID-19 was significantly lower in vaccinated adolescents than in vaccinated adults, titers of SARS-CoV-2 IgG neutralizing antibody in adolescents were significantly lower compared to that of adults. [Paediatr

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The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred worldwide and impacted global health and economics since its emergence at the end of 2019.¹ By March 2020, the *World Health Organization* (WHO) reported 4,995,996 confirmed cases and 327,821

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deaths. SARS-CoV-2 is transmitted from infected people through inhalation of or direct contact with droplets, and has an incubation period ranging from 2 to 14 days. The virus spread rapidly worldwide, as some people may be asymptomatic due to good immunity or herd immunity, but infectious to others, leading to a fatality rate of 3 to 4%.² Indonesia was affected by the first COVID-19 cluster in March 2020, followed by multiple waves of SARS-CoV-2 infections.³ Several public health measures were implemented to mitigate the spread of the virus.⁴ Various vaccine platforms, including inactivated virus, adenovirus-based, nucleic acid-based (mRNA and DNA), and protein-based vaccines were developed to prevent COVID-19 and subsequently received approval. After worldwide immunization, COVID-19 transmission, disease severity, and mortality rate decreased dramatically.⁵ Vaccination has been a cornerstone of Indonesia's strategy to control the pandemic, aiming to achieve herd immunity, reduce transmission rates, and prevent severe disease outcomes. Safety and immunogenicity of nine COVID-19 vaccine candidates' phase II/III trial results were reviewed for immediate use and distribution in Indonesia, while COVID-19 cases continued to rise.⁶

When the Indonesian national immunization program started administering the COVID-19 vaccination, different age groups were prioritized based on vulnerability, transmission dynamics, and vaccine availability. On 13 January 2021, an inactivated COVID-19 vaccine (*CoronaVac*®) was included in the Indonesian national COVID-19 vaccination program, with a schedule of two 0.5-mL doses given four weeks apart.⁷ The first targeted population was adults, who experienced the most severe case.⁸ The vaccine had not yet been approved for adolescents (clinical trial research was still ongoing for adolescents, therefore, the timing of vaccine administration was different). The COVID-19 vaccination program was carried out in four stages, starting from the most prioritized as follows: the first stage focused on health professionals; the second stage included the elderly; the third stage consisted of the general public who were susceptible to economic, social or geospatial pressures; and the fourth stage covered other general public.⁴ On July 1, 2021, the Indonesian government initiated the COVID-19 vaccination program, targeting adults (aged 18 years and above)

and adolescents (aged 12-17 years), with two doses of primary vaccination. Starting January 12, 2022, adults were given a third dose as booster, at least six months after the second dose. This staggered approach reflected the evolving scientific evidence on vaccine efficacy, waning immunity, and the need for booster doses to sustain protective antibody levels, especially in populations at higher risk of severe disease.

Understanding the differential impacts of varying vaccine doses across age groups is important to develop the vaccination strategies to be implemented in Indonesia. SARS-CoV-2 IgG neutralizing antibodies play a crucial role in protecting against infection by inhibiting viral entry into host cells. Measuring these antibody levels provides insight into the immunogenicity of vaccines and the potential need for additional doses to sustain protective immunity. Comparative studies examining antibody responses and infection rates between different dosing regimens and age groups are essential for the basis of public health policies to ensure the effectiveness of vaccination programs. Therefore, we aimed to evaluate the incidence of COVID-19 and titers of SARS-CoV-2 IgG neutralizing antibodies in adolescents (12-17 years) who received the primary vaccine (two doses) compared to adults (18 years and above) who received the primary vaccine and a booster dose (third dose). This comparison may provide insights into the efficacy of different vaccination strategies and potential need for booster vaccinations in adolescents.

Methods

This cross-sectional study was performed between June and August 2022 at five primary health centers located in the Senen, Jatinegara, Koja, Tambora, and Pasar Minggu sub-districts of Jakarta, Indonesia. This study was done simultaneously with a study evaluating the effectiveness of a vaccine against dengue ten years after its administration; the incidence of COVID-19 and antibody response to the COVID-19 vaccine were assessed in the same set of subjects. The questionnaire-based results of previous history of COVID-19 stratified with dengue vaccination have been published elsewhere.⁹

Starting July 1, 2021, both adolescents and adults received the primary inactivated COVID-19

vaccine, administered as two doses four weeks apart. Beginning on January 12, 2022, adults were given booster doses, thus a third dose, that differed from the primary vaccine. We compared the COVID-19 incidence and SARS-CoV-2 IgG neutralizing antibody titers following COVID-19 vaccination between adolescents and adults, without taking into account their dengue vaccination history.

Inclusion criteria were healthy subjects aged 12 to 27 years who were willing to complete questionnaires on previous history of COVID-19, had received COVID-19 vaccination, agreed to be part of the subset tested for SARS-CoV-2 antibody titers, and lived in the Jakarta Special Capital Region. Subjects were asked for written informed consent prior to their participation in the study; for adolescents, consent was sought from their parents. Participants were stratified into two different age groups: adolescents (12-17 years) and adults (18 years and above). Subjects were excluded if they had an acute infection within seven days before study recruitment, had been diagnosed with an immune system disorder, had received corticosteroid treatment for >14 days, or were uncontactable.

A structured questionnaire was used to collect data from all participants. The questionnaire captured demographic information, history of COVID-19 exposure, symptoms experienced, and dates of COVID-19 vaccination and type of COVID-19 vaccines used for the second and third doses. A subset of 30% of the total participants was fulfilled by consecutive sampling; these subjects provided blood specimens so that we could measure SARS-CoV-2 IgG neutralization antibody titers. Blood specimens for antibody titer measurement were collected from adolescent subjects approximately 6 months after the second vaccine dose and from adult subjects 6-12 months after the booster dose.

The SARS-CoV-2 IgG neutralizing antibody titers were measured using GenScript cPass SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (GenScript, Nanjing, China). The sVNT measures the ability of antibodies to inhibit the interaction between the SARS-CoV-2 spike protein receptor-binding domain (RBD) and the angiotensin-converting enzyme 2 (ACE2) receptor on host cells. The sVNT measures the neutralizing antibody to SARS-CoV-2 RBD, with a threshold of >30 units per milliliter

(U/mL) considered to indicate protective immunity. The median and interquartile range (IQR) of antibody levels were calculated for each age group.

Statistical analyses were performed with SPSS version 26 software (IBM, Armonk, New York). The demographic characteristics of the study population are shown descriptively in tables. The COVID-19 incidence between age group was calculated before and after vaccination and compared using chi-square tests. The distribution of SARS-CoV-2 IgG neutralizing antibody levels was compared between age groups using the Mann-Whitney U test. A P value of <0.05 was considered statistically significant. The study protocol has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

Results

Four-hundred nineteen subjects were included in the study, consisting of 233 (55.6%) adolescents and 186 (44.4%) adults. Among the adolescent subjects, 48.5% were male; in adults, 50.5% were male. The median (IQR) age of participants was 15 (12-17) years in adolescents, and 20 (18-27) years in adults. Most participants had good nutritional status (79% in adolescents and 78.1% in adults). No significant differences in gender and nutritional status distribution were found between the two age groups.

Before receiving the COVID-19 vaccine, the incidence of COVID-19 was 4.9% in adolescents, which was significantly lower than the incidence of 10.2% in adults ($P=0.036$). After vaccination, the incidence of COVID-19 further decreased to 2.2% in adolescents compared to 8.8% in adults ($P=0.005$). **Table 1** shows the difference between adolescents and adults in the incidence and severity of COVID-19 before and after vaccination.

Both before (**Figure 1**) and after (**Figure 2**) COVID-19 vaccination, adolescents reported fewer signs and symptoms of COVID-19 than did adults. Profiles of the median SARS-CoV-2 IgG neutralizing antibody titers between the two age groups after the COVID-19 vaccine were significantly different overall and after two doses, as shown in **Table 2**. Overall, adults had significantly higher antibody titers than adolescents, regardless of the number of

doses received ($P=0.003$). In those who received only one dose, antibody titers did not differ significantly between adolescents and adults. However, in those who received two doses, adults had significantly higher titers than adolescents ($P=0.021$).

The adolescent and adult groups who received two doses of inactivated CoronaVac had similar antibody titers (96.79 vs. 97.89 u/mL, respectively), as shown in **Table 3**. Adults who received a heterologous booster (third dose) using a different COVID-19 vaccine type had median titer values ranging from 88.50-97.94 U/mL.

Discussion

We found that COVID-19 incidence was significantly lower in adolescents compared to adults, both before and after vaccination. Prior to COVID-19 vaccination, the reported incidence was 4.9% in adolescents vs. 10.2% in adults ($P=0.036$); after COVID-19 vaccination, it decreased to 2.2% in adolescents vs. 8.8% in adults ($P=0.005$). These results indicate a reduction in COVID-19 incidence post-vaccination, particularly in the younger age group. Although the SARS-CoV-2 IgG neutralization

Table 1. Analysis of COVID-19 illness and severity between age groups

Variables	Adolescent (12-17 years)	Adult (≥ 18 years)	P value
Had COVID-19 before COVID-19 vaccination, n (%)	(n=233)	(n=186)	0.036**
Yes	11 (4.7)	19 (10.2)	
No	222 (95.3)	167 (89.8)	
Had COVID-19 after COVID-19 vaccination, n (%)	(n=233)	(n=186)	0.005**
Yes	5 (2.2)	15 (8.8)	
No	228 (97.8)	171 (91.2)	
COVID-19 severity before COVID-19 vaccine, n (%)	(n=11)	(n=19)	0.862**
No symptoms	2	2	
Mild	6	14	
Moderate	3	3	
COVID-19 severity after COVID-19 vaccine, n (%)	(n=5)	(n=15)	0.402**
No symptoms	2	4	
Mild	3	9	
Moderate	0	2	
Median length of stay of subjects hospitalized for COVID-19	(n=5)	(n=15)	0.063*
Before COVID-19 vaccine (range), days	8.5 (3-13)	14 (2-17)	
After COVID-19 vaccine 19 (range), days	0	9 (NA)	

*Mann-Whitney test; **Pearson's Chi-square test; NA=not available

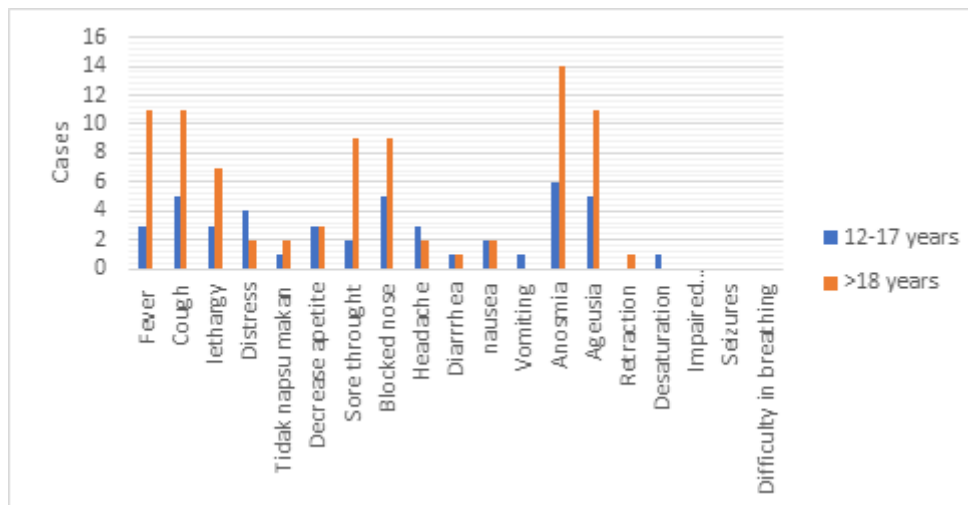


Figure 1. Clinical manifestations of COVID-19 infection before COVID-19 vaccination by age group

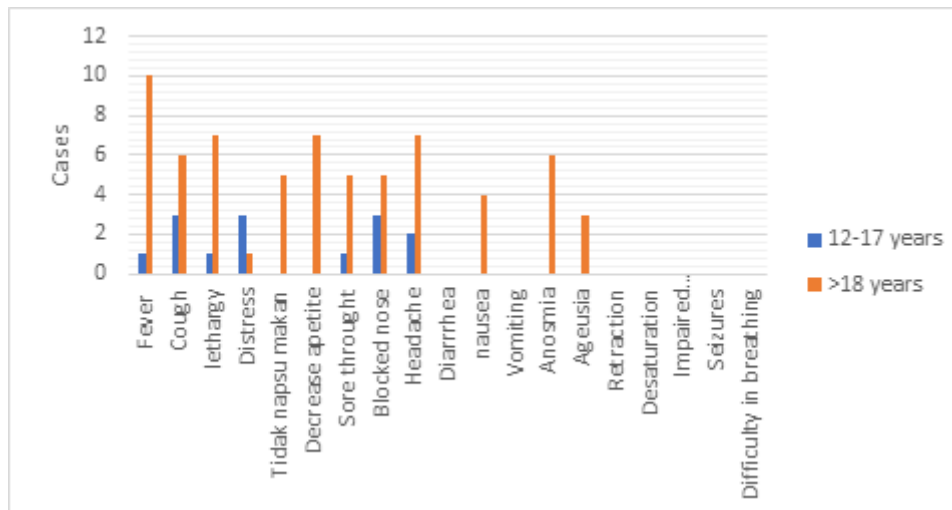


Figure 2. Clinical manifestations of COVID-19 infection after the COVID-19 vaccination by age group

Table 2. SARS-CoV-2 neutralizing antibody titers after COVID-19 vaccination by age group

Number of vaccine doses received	Adolescent	Adult	P value*
Median SARS-CoV-2 IgG neutralizing antibody level (range), U/mL			
Overall	(n=75) 96.78 (22.08-98.23)	(n=84) 97.85 (46.46-98.23)	0.003
1 dose	(n=5) 97.84 (89.37-98.13)	(n=5) 97.13 (76.29-98.08)	0.602
2 doses	(n=64) 96.87 (39.06-98.23)	(n=51) 97.85 (52.92-98.23)	0.021
3 doses	N/A	(n=23) 97.94 (46.46-98.18)	N/A

Table 3. SARS-CoV-2 IgG neutralizing antibody titers by age group, type of COVID-19 vaccine, and number of dosis given

Vaccine doses	Adolescents			Adults			P value
	Vaccine types	n	Median SARS-CoV-2 IgG neutralizing antibody titer (range), U/mL	Vaccine types	n	Median SARS-CoV-2 IgG neutralizing antibody titer (range), U/mL	
First dose	Inactivated	68	86.87 (39.06-98.23)	Inactivated	66	97.87 (52.92-98.18)	0.003
First and second doses	Inactivated vaccine	63	96.79 (39.06-98.23)	Inactivated	61	97.89 (52.92-98.18)	0.077
				Viral vector	7	98.04 (97.32-98.18)	
				Protein subunit	5	92.19 (46.46-98.23)	
Booster	Not administered			mRNA (BNT162b2)	9	97.96 (92.60-98.13)	N/A
				mRNA (mRNA-1273)	5	97.91 (97.80-98.18)	
				Viral vector	5	97.94 (97.32-98.18)	
				Protein subunit	4	88.50 (46.46-98.18)	

antibody titer was significantly higher in adults who received three vaccine doses compared to adolescents who received two doses, the lower antibody levels in adolescents are likely to be sufficient to provide

immunity against SARS-CoV-2,7 apparent from the lower incidence of COVID-19 in adolescents compare to adults (Table 1).

The lower incidence of COVID-19 in adolescents

may be attributed to several factors beyond antibody-mediated adaptive immunity.¹⁰ Adolescents typically exhibit a more robust innate immune response, which facilitates rapid viral clearance and results in milder clinical manifestations. This innate immunity likely complements the adaptive immune response elicited by vaccination, enhancing overall protection even with lower antibody titers.¹⁰ Fewer signs and symptoms in adolescents may have been due to a more active innate immune response, healthier respiratory tracts due to lower cumulative exposure to air pollution or cigarette smoke, and fewer comorbidities.¹¹ Furthermore, trained immunity may have played a role,¹² as other vaccine types, such as live-attenuated vaccines can lead to innate immune memory development. BCG, measles, mumps, and rubella vaccination can produce nonspecific immunity against SARS-CoV-2.^{13,14} Having a complete inactivated diphtheria-pertussis-tetanus vaccination history before the age of 12 years alongside vaccination with CoronaVac produces stronger immune responses of SARS-CoV-2-specific T cells, which protect against novel pathogens, through heterologous immunity.¹⁵ More explanations proposed were the possibility of higher antibody levels in children developed by cross-reactivity with other human coronaviruses, such as human coronavirus OC43 and HKU1.¹⁶

In contrast to our findings, a previous study showed that adolescents produced higher levels of median SARS-CoV-2 IgG, total antibody (TAB), surrogate neutralizing antibody (SNAb) activity, and antibody binding avidity compared to adults. Adolescents also exhibited higher median TAB levels, IgG levels, and SNAb activity than young adults.¹⁷

In Table 3, adults who had received three vaccine doses had significantly higher antibody levels and more sustained adaptive immune responses; therefore, a booster dose for adults is crucial. The booster dose is needed due to the greater risk of severe disease in adults from increased natural waning of immunity over time. The booster dose in adults appears to increase antibody-mediated protection, aligning with global observations that additional vaccine doses enhance immunity, especially in populations at higher risk.¹⁸

Our findings are consistent with studies indicating that younger populations generally experience milder signs and symptoms of COVID-19 and may require fewer vaccine doses to achieve protective immunity.

Studies have shown that adolescents possess a more resilient innate immune system, which can contribute to more effective viral clearance and reduce reliance solely on vaccine-induced antibodies.¹⁹ Children and adolescents have an innate immune response to SARS-CoV-2 which works faster and stronger than that in adults, especially in the nasal mucosa, controlling the virus more rapidly. In contrast, adults may have overactive, dysregulated, and weaker effective innate responses, leading to uncontrolled pro-inflammatory cytokine production and tissue injury. Children and adolescents who encounter new exposures to other viruses and receive routine vaccines may have stronger protective cross-reactive antibodies and T cells against SARS-CoV-2.¹⁰

Conversely, studies in adult populations have demonstrated the benefits of booster doses in maintaining high levels of neutralizing antibodies and reducing breakthrough infections.^{18,20} However, some studies have reported varying antibody responses based on factors such as vaccine type, interval between doses, and individual health status.¹⁷ In our study, blood specimens were drawn from adolescents about 6 months after the second dose, whereas blood specimens were collected from adults approximately 6-12 months after the booster (third) dose, therefore, waning immunity may have occurred similarly in both age groups. Our study adds new evidence specifically in the Indonesian setting, highlighting the effectiveness of tailored vaccination strategies across different age groups.

The differences in COVID-19 incidence and antibody response between adolescents and adults underscores the importance of age-specific vaccination strategies. In adolescents, the administration of two vaccine doses appears sufficient to maintain protective immunity against COVID-19,²¹ potentially simplifying vaccination campaigns and reducing logistical burdens. In contrast, the need for a third, booster dose in adults highlights the necessity of ongoing vaccine administration to sustain immunity, particularly in populations at higher risk of severe disease.²² These findings can inform policymakers as they optimize vaccination schedules, ensuring that resource allocation aligns with the immunological needs of different age groups. Additionally, sustained antibody levels above protective thresholds in both groups emphasize the overall effectiveness of the

vaccination program in Indonesia, contributing to the broader goal of pandemic control.

Several limitations of this study should be kept in mind when interpreting the results. Firstly, the cross-sectional design limits the ability to determine causal relationships between vaccine doses and reported incidence rates. Longitudinal studies would provide more robust evidence on the temporal dynamics of antibody levels and infection rates. Secondly, the sample size, particularly for the subset of participants who provided blood specimens, may limit the extrapolation to general settings for antibody responses. Another limitation was that incidence rates were based on self-reporting. Participants may not have reported illness, may have been unaware of having an illness, or may have reported an illness other than COVID-19. Other potential confounders that may influence the incidence of COVID-19 and antibody response, such as underlying health conditions, behavioral factors, and exposure risks, were not comprehensively controlled for.²³

Future studies should adopt a longitudinal approach to monitor changes in antibody levels and infection rates over time, providing a clearer picture of the durability of vaccine-induced immunity. Increasing the sample size and including different populations across various regions can enhance the generalizability of the study results. Furthermore, investigating the cellular immune response, such as T-cell immunity,¹⁵ alongside antibody levels would offer a more comprehensive understanding of the immune protection conferred by vaccines. Exploring the impact of different COVID-19 vaccine types, dosing intervals, and newly-occurring SARS-CoV-2 variants on antibody responses and infection rates could also inform more varied vaccination strategies.²⁴ Lastly, assessing the long-term clinical outcomes in vaccinated individuals, including the severity of breakthrough infections, would provide valuable insights into the real-world effectiveness of the vaccination program.

In conclusion, our study revealed that adolescents exhibit a smaller COVID-19 incidence compared to adults both before and after receiving COVID-19 vaccinations. While SARS-CoV-2 IgG neutralizing antibody titers are significantly higher in adults who received three vaccine doses compared to adolescents who received two doses, antibody titers in both age

groups exceed protective thresholds, indicating effective immune protection. These findings support the current vaccination strategy, emphasizing the adequacy of primary vaccination with two doses in adolescents and the necessity of booster doses in adults to sustain immunity. The decision to administer a booster dose to adolescents will depend on the current epidemiological study of COVID-19 in Indonesia.

Conflict of interest

None declared.

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