

Article

Immunogenicity and Reactogenicity of CoronaVac: A Cohort Study

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Abstract: The ongoing COVID-19 pandemic remained a major public health concern despite a large-scale deployment of vaccines. One of the vaccines is CoronaVac, an inactivated vaccine. The efficacy of the vaccine was estimated at 50.7–83.5% in clinical trials. However, the real-world efficacy often differed. This study described CoronaVac post-vaccination reactogenicity and immunogenicity. Serum was collected on days 0, 28, 56 and 84 from participants who received CoronaVac in March–May 2021. Anti-SARS-CoV-2 Spike receptor binding domain was measured using an Elecsys[®] quantitative assay. Participants were interviewed for adverse events (AEs) one week after vaccination. Reported AEs were fatigue, fever, runny nose, headache, muscle pain, pain at injection site, and paresthesia. Females reported more incidents than males. However, the frequency was similar between immunologically naïve and pre-immune participants. In the naïve group, the antibody titer was 61.7 ± 84.2 U/mL (mean \pm SD) on day 28 and increased to 99.3 ± 91.9 U/mL on day 56. The titer peaked on day 56 across all age groups, but a reduction of 18.0–26.3% was observed on day 84. A titer-boosting effect was observed in pre-immune participants with a baseline titer of 139.0 ± 101.0 U/mL, which increased to 206.7 ± 77.4 U/mL on day 28, and remained steady until day 84. Hence, CoronaVac elicited an antibody response in naïve and pre-immune participants, with mild AEs.

Keywords: CoronaVac; inactivated vaccine; SARS-CoV-2; spike RBD



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1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 virus, has strained public health systems and inflicted severe socio-economic problems globally. Controlling the spread of the virus through well-planned vaccination programs could accelerate the path to pandemic recovery. CoronaVac (Sinovac Biotech, Beijing, China), an inactivated vaccine, was the first licensed vaccine in Indonesia. The vaccine's efficacy in clinical trials varied between sites, ranging from 50.7% to 83.5% [1–3]. Trial efficacy, however, often differed from real-world efficacy, due to the large scale deployment in a highly diverse population and field conditions [4]. Thus, post-licensure studies could provide complementary data to pre-licensure clinical trial data. In two test-negative case-control studies of high-risk groups in Brazil, the CoronaVac vaccine efficacy was estimated to be 36.8% in healthcare workers and 46.8% in the ≥ 70 year-old group, during a high prevalence of the Gamma variant [5,6]. A nationwide study in Chile with 10.2 million

participants estimated a higher efficacy at 65.9% [7]. Despite a lower observed efficacy, the vaccine remained effective in preventing hospitalization and death, including those in high-risk groups [6–9]. Following a deployment to larger and diverse populations, the vaccine was noted to have acceptable side effects and immunogenicity [10–14], although a lower immunogenicity was observed in immunocompromised individuals with autoimmune rheumatic diseases [15], immune-mediated diseases [16] and malignant diseases [17]. Immunogenicity of the vaccine was also reported to be reduced with increasing age [18]. Our study aims to describe post-vaccination adverse events and immunogenicity of the CoronaVac vaccine in an Indonesian population.

2. Materials & Methods

2.1. Subject Recruitment and Sample Collection

A prospective study was conducted at two vaccination centers in Bali, Indonesia: Warmadewa Clinic and Wantilan Regional House of Representatives for Bali Province, from March 2021 to May 2021. The Ethical Committee of Universitas Warmadewa (Ethics approval number 47/Unwar/FKIK/KEPK/III/2021) approved the study.

Written informed consent was explained and collected from 101 volunteer adult participants, aged ≥ 18 years, who received the COVID-19 CoronaVac vaccine. The vaccination regimen, following the Indonesian Ministry of Health guidelines, was 2 weeks apart from the first vaccine dose for participants aged 18–59 years, and 4 weeks apart for participants aged >59 years. 3 mL of blood was drawn aseptically in a clot activator collection tube on days 0, 28, 56 and 84. Blood was allowed to clot at room temperature, and serum was extracted following blood centrifugation. Subjects were interviewed by phone for post-vaccination side effects one week after receiving the first vaccine dose.

2.2. Anti SARS-CoV-2 Antibody Quantification

Within two hours of the sample processing, the serum was tested for the total antibody against SARS-CoV-2 Spike receptor-binding domain (RBD) using the Elecsys® Anti-SARS-CoV-2 S quantitative assay kit in the cobas e601 automated electrochemiluminescence sandwich immunoassay system (Roche, Basel, Switzerland), following the manufacturer's instruction and quality control. The detectable antibody titer was 0.4–250 U/mL. A titer of ≥ 0.8 U/mL was considered positive for an antibody against SARS-CoV-2 Spike RBD.

2.3. Data Analysis

Subjects who were lost to follow up were excluded from the data analysis. An antibody titer <0.4 U/mL was interpreted as 0.0 U/mL, and >250.0 U/mL was interpreted as 251.0 U/mL. The data was analyzed using Prism 8.

3. Results

A total of 101 volunteer participants were recruited to study the immunogenicity of the CoronaVac vaccine. Only 91 participants were included in the analysis, due to losing ten participants during the follow up. The cohort consisted of 51 (56.6%) male and 40 (44.4%) female participants. The median age was 50.2 (IQR: 29.6–57.1) and 33.2 (26.6–51.7) years in males and females, respectively. 7.7% (7/91) of the participants were above 59 years old. Males had a slightly higher median body mass index at 26.1 (24.2–28.0) kg/m² than females at 23.6 (21.4–25.9) kg/m². Of the 91 participants, three presented with comorbidities: malignancy with hypertension, autoimmune disease, and hypertension. Following the first dose, participants reported adverse events (AEs) of fatigue, fever, runny nose, headache, muscle pain, pain at injection site, and paresthesia. No serious AE was reported. Fatigue and pain at injection site were the most common AEs reported in males, whereas those for females were fatigue and headache. Overall, female participants reported higher AE incidents than males at 42.5% and 31.3%, respectively (Table 1).

Table 1. Participants' demography and adverse events after receiving the first vaccine dose.

Parameter	Overall	Male	Female
Gender, <i>n</i> (%)	91 (100%)	51 (56.6%)	40 (44.4%)
Age, median (IQR)	42.9 (28.1–55.4)	50.2 (29.6–57.1)	33.2 (26.6–51.7)
BMI ¹ , median (IQR)	25.4 (22.5–27.5)	26.1 (24.2–28.0)	23.6 (21.4–25.9)
Comorbidity, <i>n</i> (%)			
Autoimmune Disease	1 (1.1%)	1 (2.0%)	0 (0.0%)
Hypertension	2 (2.2%)	0 (0.0%)	2 (5.0%)
Malignancy	1 (1.1%)	0 (0.0%)	1 (2.5%)
Adverse Events, <i>n</i> (%)			
Any symptom	33 (36.3%)	16 (31.3%)	17 (42.5%)
Fatigue	21 (23.1%)	13 (25.5%)	8 (20.0%)
Fever	3 (3.3%)	1 (2.0%)	2 (5.0%)
Runny nose	1 (1.1%)	0 (0.0%)	1 (2.5%)
Headache	7 (7.7%)	1 (2.0%)	6 (15.0%)
Muscle pain	3 (3.3%)	1 (2.0%)	2 (5.0%)
Pain at Injection site	2 (2.2%)	2 (3.9%)	0 (0.0%)
Paresthesia	1 (1.1%)	1 (2.0%)	0 (0.0%)

¹ BMI: Body Mass Index, kg/m².

Blood serum was collected before (day 0) and after receiving the first dose (days 28, 56 and 84). Prior to vaccination, 73 participants had no antibody against SARS-CoV-2 Spike RBD, and 18 had pre-existing antibody. Antibody was detected in the immunologically naïve group at 61.7 ± 84.2 U/mL (mean \pm SD) on day 28, although only 66 (90.4%) participants seroconverted. By day 56, all participants seroconverted, and the titer was increased to 99.3 ± 91.9 U/mL. However, it decreased by 22.0% to 77.5 ± 78.5 U/mL on day 84. Interestingly, immunologically naïve males had lower average antibody titers than females on days 28, 56, and 84, albeit the difference was not statistically significant (Student's *t*-test, $p > 0.05$). Moreover, participants with pre-existing antibody had titers of 139.0 ± 101.0 U/mL on day 0. The level was boosted to 206.7 ± 77.4 U/mL after 28 days and remained steady until day 84. Average antibody titers were similar between males and females from day 0 to day 84 in pre-immune participants (Table 2).

Data were further stratified by age groups of 18–29, 30–39, 40–49, 50–59 and 60–65. Antibody titers of immunologically naïve vaccinees were increased to 69.9 ± 85.5 , 89.1 ± 92.9 , 117.9 ± 119.9 , and 32.1 ± 51.9 (mean \pm SD), respectively, on day 28. Antibody titer peaked on day 56 across all age groups of 18–59, except for the 30–39 age group which remained similar at 87.8 ± 81.0 U/mL. Antibody titer in the 50–59 age group was the lowest among the remaining 18–59 age groups, only peaking at 50.1 ± 65.0 U/mL on day 56. However, a titer reduction of 18.0–26.3% was observed across all age groups of 18–59 on day 84. On the other hand, a boosting effect was observed in participants with pre-existing antibody across the 18–59 age groups on day 28. The effect was more pronounced in participants with low baseline titers. The titers of days 56 and 84 remained at a similar level to the titer of day 28 across the different age groups of 18–59 (Table 2). In the 60–65 age group, the vaccination regimen was instead four weeks apart between doses. One month after receiving the second dose, the antibody titer ($n = 4$) was 142.9 ± 85.9 U/mL, and was decreased to 105.3 ± 101.3 U/mL in the second month. On the other hand, three individuals with pre-existing antibody had a titer of 247.9 ± 5.4 U/mL before vaccination. The maximal titers from the effect of boosting could not be determined, as it was beyond the assay detection level of 250 U/mL.

Table 2. Antibody titer in participants with different pre-existing antibody statuses, blood collection days, genders, and age groups.

	Overall	Gender		Age Group			
		Male	Female	18–29	30–39	40–49	50–59
Spike RBD Ab (–) Before Vaccination							
<i>n</i>	73	39	34	21	11	10	27
Day 0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Day 28	61.7 ± 84.2	54.8 ± 79.8	69.6 ± 89.6	69.9 ± 85.5	89.1 ± 92.9	117.9 ± 119.9	32.1 ± 51.9
Day 56	99.3 ± 91.9	76.1 ± 79.0	125.8 ± 99.3	133.2 ± 92.9	87.8 ± 81.0	155.9 ± 109.0	50.1 ± 65.0
Day 84	77.5 ± 78.5	57.9 ± 69.8	100.0 ± 82.8	103.8 ± 84.2	70.2 ± 69.9	127.9 ± 98.2	37.2 ± 42.7
Spike RBD Ab (+) Before Vaccination							
<i>n</i>	18	12	6	7	3	1	4
Day 0	139.0 ± 101.0	139.4 ± 102.3	138.1 ± 108.1	127.6 ± 107.0	37.2 ± 29.8	111.7	160.4 ± 104.7
Day 28	206.7 ± 77.4	201.8 ± 87.7	216.6 ± 57.1	210.8 ± 59.1	159.4 ± 103.8	251.0	190.8 ± 120.5
Day 56	209.7 ± 79.6	205.0 ± 83.4	219.1 ± 78.0	206.8 ± 70.8	184.4 ± 115.4	251.0	192.6 ± 116.9
Day 84	207.2 ± 81.0	199.2 ± 88.3	223.1 ± 68.4	203.4 ± 66.7	178.9 ± 124.9	251.0	191.5 ± 119.0

Note: Antibody titer, mean ± SD in U/mL.

Lastly, the AE frequency was similar between immunologically naïve and pre-immune participants. Between age groups, the frequency was similar at a rate of 42.9–45.5%, except for the 50–59 age group which expressed almost a two times lower frequency at 22.6% (Table 3).

Table 3. Frequency of reported adverse events according to pre-existing antibody status and age group.

Adverse Events	Pre-Existing Antibody		Age Group				
	Positive	Negative	18–29	30–39	40–49	50–59	60–65
Sample Size	18	73	28	14	11	31	7
Count, <i>n</i> (%)	7 (38.9%)	26 (35.6%)	12 (42.9%)	6 (42.9%)	5 (45.5%)	7 (22.6%)	3 (42.9%)

4. Discussion

Our study described the post-vaccination adverse events and immunogenicity of CoronaVac, an inactivated virus vaccine. The vaccination regimen, following the Indonesian Ministry of Health guidelines, involved having two weeks between doses for participants aged 18–59 years, and four weeks between them for participants aged >59 years. Fatigue, fever, and muscle pain were the most common reported systemic AEs in the previous studies [2,10,12,19,20], similar to those observed in our study. The incident rate of AEs was similar to a phase 1/2 clinical trial [20] and a study on healthcare workers [11]. Lower incidents were reported in a phase 3 clinical trial, with a rate of 18.9% [2], and in a study on healthcare workers at 15.6% [12]. Contrary to this, other studies on healthcare workers and phase 3 clinical trials in Brazil and Indonesia reported much higher AE incidences at rates of 62.5% [10], 65.5% [3], and 54.3% [1], respectively. In addition, female participants reported a higher incidence of AEs at a rate of 42.5%, than males at 31.3%, a trend that has been observed in earlier works [10,12]. We noted a similar rate of AEs across age groups, except for the 50–59 age group, which had AEs that were twice less frequent. Older age groups receiving CoronaVac had a tendency to have fewer AEs [10,12,19,20]. The 60–65 age group in our study reported a similar rate of AEs to the younger age groups, likely due to a small sample size.

All naïve participants in our study seroconverted after receiving the second dose. The vaccine also produced a titer-boosting effect in participants with pre-existing antibody.

We observed that immunologically naïve females had slightly higher and more persistent antibody titers than their male counterparts. At day 84, the average antibody titer of the females remained much higher than on day 28, whereas males dropped to a level similar to the day 28 titer. A similar trend was not observed in pre-immune participants. Gender-based titer differences had been noted before in CoronaVac recipients [2,10,21], although in our study, age could be the main contributor [2,14,16,21], with the median age of females at 33.2 years and that of males at 50.2 years. In addition, immunologically naïve participants in the 50–59 age group produced the lowest antibody titer compared to other age groups within the 18–59 age bracket. Coincidentally, this age group also reported the fewest AE incidents. However, correlations between AE incidents and antibody titers were reported to be weak in the previous Spike mRNA-based vaccine studies [22–24].

We observed that pre-immune participants had an increased antibody titer following two doses of CoronaVac and that the level of antibody persisted until the end of the study (Day 84 after the first vaccine dose), similar to a previous report [13]. In immunologically naïve participants, the average antibody titer was measured at 61.7 U/mL, two weeks after the second vaccine dose. Titers continued to rise on day 56 at 99.3 U/mL and later decreased to 77.5 U/mL on day 84. Previously, a higher average titer of 73.2 U/mL was reported two weeks after receiving the second dose [13]. However, the titer decreased by almost 25% on day 56 to 55.2 U/mL and remained at a similar level throughout the study until the last time point of 112 days [13]. Despite the standardization effort by the WHO, comparing the antibody titer between assays remains a challenge due to an imperfect correlation and sensitivity [25,26], consequently, limiting our comparison with other published data on CoronaVac immunogenicity. Nevertheless, our study only described antibody titers up to day 84. Therefore, further investigation into the longevity of antibody responses is warranted.

Antibody titer in blood could be used as a surrogate marker in predicting protection against SARS-CoV-2 infection. A high level of neutralizing antibodies (NABs) is associated with protection against symptomatic COVID-19, although the link between NABs and vaccine efficacy remains disputed [27,28]. To infect a cell, SARS-CoV-2 needs to gain access through interaction between the virus Spike RBD and the host ACE2 receptor. Hence, antibody against Spike RBD is often used as a proxy to NABs [29]. The Roche Elecsys® Anti-SARS-CoV-2 S quantitative assay kit used in our study has a moderate agreement with live virus [30] and pseudovirus [31] neutralizing tests, and a good agreement with the surrogate Spike RBD-based neutralizing test [32]. Even without a perfect agreement, antibody against Spike RBD could serve as an alternative marker to NABs.

There were several limitations in our study. First, we did not perform a further serum dilution to determine the antibody end titer for samples with titer >250 U/mL. Our data may not have captured the true titer distribution in participants with high antibody titers. Second, the participants were not tested for SARS-CoV-2 infection during the study, amidst a high prevalence of the Delta variant throughout Indonesia. Although none of the participants reported COVID-19 symptoms, we were unable to rule out infection and that the changes in antibody titers were solely due to vaccination. Third, our study has limited participants, especially older people, which is the population that would benefit most from the COVID-19 vaccine. Thus, an expansion to a larger study cohort would allow for drawing more robust conclusions.

5. Conclusions

CoronaVac, an inactivated vaccine, was observed to be able to elicit an antibody response in both immunologically naïve and pre-immune participants. All participants reported relatively mild adverse events and seroconverted after receiving the second vaccine dose.

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administration: N.R.K.D.; Funding acquisition: A.A.G.B. and SM. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data is presented in this manuscript. No publicly available data was used in the writing of manuscript.

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