# S-RBD Antibody Titers Following the First and Second Doses of Inactivated SARS-CoV-2 Vaccination (CoronaVac) in Native Participants: A Prospective Cohort Study in Bali, Indonesia

by Universitas Warmadewa Admin

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# S-RBD Antibody Titers Following the First and Second Doses of Inactivated SARS-CoV-2 Vaccination (CoronaVac) in Native Participants: A Prospective Cohort Study in Bali, Indonesia

**Sri Masyeni[1,2]\*, I Made Indrawijaya[3], I Made Wisnu Wardhana[3], Harapan Harapan[4,5,6], Agus Santosa[3] and Erni J Nelwan[7]**

[1]Department of Internal Medicine, Faculty of Medicine and Health Sciences Universitas Warmadewa, Denpasar, Bali 80235, Indonesia.
[2]Department of Internal Medicine, Sanjiwani Hospital, Gianyar, Bali 80235, Indonesia.
[3]Faculty of Medicine and Health Sciences, Universitas Warmadewa, Denpasar, Bali 80235, Indonesia.
[4]Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia.
[5]Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia.
[6]Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia.
[7]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
\*Corresponding author Email: masyeniputu@yahoo.com

Vaccination has been recognized as an additional option, besides the health protocols practices to control the coronavirus disease 2019 (COVID-19) pandemic, especially with the unknown specific treatment for the disease. This study sought to evaluate the immunogenicity of CoronaVac among the general population in Bali province, a popular tourist spot in Indonesia. As many as 422 volunteers were recruited from the three vaccination centers, of which 230 volunteers were seronegative and included in the study. CoronaVac was used as vaccine with dose of 0.5 mL or $3\,\mu g$ at each administration. Blood samples were drawn before vaccination, 21 days after the first dose, and 56 days after second dose, where the interval between the first and second dose vaccination was 28 days. Vaccine immunogenicity was evaluated by the anti-spike receptor-binding domain (anti-S-RBD) IgG titer which was measured using the electrochemiluminescence immunoassay technique. The mean anti-S-RBD levels at 21 days after first dose, and 21 days after the second dose of vaccination are $25.25 \pm 59.74$ U/mL and $138.77 \pm 90.93$ U/mL, respectively. The result of the Friedman test was $p < 0.001$ which means that there are significant differences in anti-S-RBD levels between 21 days after first dose and 21 days after second vaccination. Post hoc analysis with the Wilcoxon test also showed significant difference among the three-testing point ($p < 0.001$). The seroconversion rate from the first dose of CoronaVac was 69.7% and it increased to 99.4% (171/172) on after the second dose. Although the protective level was not totally reached on the first vaccination, the immunogenicity was considered rapid 3 weeks after the first vaccination.

**Keywords:** COVID-19, vaccination, CoronaVac, anti-S-RBD, immune response.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has impacted the lives of individuals worldwide.[1,2] Types of COVID-19 vaccines have been developed and entered clinical trials, with some have received the

approval to be used in the community.[3] In addition, several oral therapies such as molnupiravir and ritonavir-boosted nirmatrelvir which are thought to turn the tide of the pandemic are currently under investigation in clinical trials.[4, 5] With vaccination program along with improved healthcare capacity and the enforcement of COVID-19 prevention protocols, the end of the pandemic has been predicted with multiple scenarios.[6] Nonetheless, the challenge of controlling the SARS-CoV-2 infection still remains as it shift into endemic state.[6] Moreover, several countries face vaccine hesitancy issues which are associated with the perceived efficacy and side effects.[7, 8] Therefore, monitoring vaccine efficacy in inducing the immune system and its adverse reactions is important.

Among 11 vaccines approved in Indonesia, the one commonly administered is an inactivated whole-virion SARS-CoV-2 vaccine, CoronaVac, developed by Sinovac Life Sciences (Beijing, China).[9] The vaccine is based on inactivated SARS-CoV-2 (CZ02 strain) and added with aluminum hydroxide as its adjuvant.[3, 10] One of the most significant features of this vaccine is its easy transportation after freeze-dried and only require 2—8°C storing temperatures.[11] In terms of its efficacy, a phase 3 placebo-controlled clinical trial from Turkey revealed two doses of CoronaVac injection reached 83.5% against PCR-confirmed symptomatic COVID-19, where no serious adverse reactions were observed.[12] The efficacy, however, was found lower (50.7%) in a clinical trial among Brazilian healthcare professionals.[13] In Chile, the vaccine efficacy to prevent the infection was 65.9%, hospitalization 87.5%, ICU admission 90.3%, and mortality 86.3%.[14]

To investigate vaccine efficacy, levels of antibody such as anti-spike receptor-binding domain (S-RBD) antibody could be used as it correlates with symptomatic COVID-19 incidence.[15, 16] Spike protein of SARS-CoV-2 RBD is responsible for the viral entry through angiotensin-converting enzyme 2 (ACE2) and it could induce the neutralizing antibodies.[17] A single dose of CoronaVac (3 ìg) among Chinese population (18-59 years old) yield 92% seroconversion for neutralizing antibodies on day 14 and 97% on day 28.[15] Meanwhile, in Chilean population (n=397, 18—59 years old), two doses of CoronaVac resulted in 86.67% seroconversion for anti-S-RBD IgG.[18] Despite data have been gathered around the world regarding the vaccine efficacy, studies in Bali, province a tourism hotspot in Indonesia with high air travel frequency, are scarcely reported.[19] Herein, we present data on the CoronaVac immunogenicity and its adverse reaction following the first and second vaccinations among Balinese population.

## METHODS

### Study design

A prospective cohort study involving 422 Balinese volunteers was conducted between July 10th and December 30th, 2021 to identify the immunogenicity of the inactivated virus vaccine (Sinovac Biotech, CoronaVac). One hundred and seventy-two healthy subjects were recruited based on the data provided by the three vaccination centers in Bali. Blood samples were collected three times on each individual: before the vaccination and after the first and second shots, respectively.

### Recruitment and sampling

Volunteers (n=422) were recruited from the vaccination centers in Bali Province, Indonesia, from July 10th to December 30th, 2021. Individuals aged e"18 years old were considered eligible. Data of age, gender, body mass index (BMI), and side effects of the vaccination were collected. BMI was measured from the length and body weight of each volunteer. For each time, three mL of venous blood samples from participant was collected and centrifuged to separate the sera. Blood sampling was performed three times: pre-vaccination, 21-days post-1st shot and 56-days post-2nd shot. The interval between the 1st and 2nd shot was 28 days.

The S-RBD titer of the pre-vaccination blood samples was measure and those who were seropositive were excluded from the study. Participants who did not return after the first sampling or confirmed SARS-CoV-2 positive based on the real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) were dropped out from the study. A schematic diagram depicting how the participants were included in this study is presented in Figure 1.

### Electrochemiluminescence immunoassay (ECLIA)

All sera were analyzed with electrochemiluminescence immunoassay (ECLIA) using Elecsys® anti-SARS-CoV-2 S quantitative

assay kit (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) to determine the total anti S-RBD neutralizing antibody titer. The analysis was carried out on automatic Roche cobas® e601 immunoassay analyzer (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). A double-antigen sandwich assay approach was used by the system utilizing recombinant protein representing the RBD of the S antigen. The analysis was conducted following the manufacturers' instruction. The detectable antibody titer ranged between 0.4 U/mL and 250 U/mL and a titer of e" 0.8 U/mL was classified as positive possessing antibody against SARS-CoV-2 S-RBD.

**Statistical analysis**

SPSS Version 25 (SPSS Inc., Chicago, IL) was used to statistically analyses the data that

were collected. A probability value of P d" 0.05 was considered statistically significant. Repeated ANOVA or Friedman test was used as comparison analysis according to data distribution. If there were significant differences, subsequent post hoc analysis using paired wise comparison or Wilcoxon test was done.

**Ethical clearance**

Ethical clearance for this study obtained from the Ethical Committee of the Faculty of Medicine and Health Sciences, Universitas Warmadewa on 8 July 2021 (68/Unwar/FKIK/EC-KEPK/VII/2021). A written informed consent was obtained from all volunteers.

**RESULTS**

**Characteristics of the subjects and vaccine reactogenicity**

Characteristics of volunteers participating in this study are presented in Table 1. Most of the volunteers were d" 29 years old (65/172, 37.8%) and male (124/172, 60.5%) with mean BMI of 23.19 ± 4.45. Systemic adverse reactions experienced by the participants after the first vaccination included fever (8/172, 4.7%), sleepiness (2/172, 1.2%), dizziness (2/172, 1.2%), hunger (1/172, 0.6%), and weakness (1/172, 0.6%), whilst 2.9% (5/172) volunteers experienced the injection-site pain. As many as 153 (89%) volunteers did not experience any adverse reaction. On second vaccination, the number of adverse reactions dramatically reduced to almost none (only 1 volunteer felt hunger after the second shot).

**S-RBD antibody titers post CoronaVac vaccination**

S-RBD titers of each volunteer were measured before and after the first and second dose. All volunteers were seronegative before the vaccination and more than half became seropositive 21 days after first dose. The mean antibody titers at 21 days after the first dose of CoronaVac was

**Table 1.** Demographics data of the subjects and vaccination side effects (n=172)

| Variables | n (%) |
|---|---|
| Age, years old | |
| ≤ 29 | 65 (37.8) |
| 30-39 | 41 (23.8) |
| 40-49 | 31 (18) |
| 50-59 | 20 (11.6) |
| >59 | 15 (8.7) |
| Gender | |
| Male | 124 (60.5) |
| Female | 48 (39.5) |
| Body mass index, mean ± SD | 23.19 ± 4.45 |
| Vaccination side effect | |
| 1st dose vaccination | |
| No side effect | 153 (89.0) |
| Fever | 8 (4.7) |
| Injection-site pain | 5 (2.9) |
| Sleepiness | 2 (1.2) |
| Dizziness | 2 (1.2) |
| Hunger | 1 (0.6) |
| Weakness | 1 (0.6) |
| 2nd dose vaccination | |
| No side effect | 171 (99.4) |
| Hunger | 1 (0.6) |

**Table 2.** Friedman test of anti-S-RBD IgG levels in each testing point

| Anti S-RBD IgG level (U/ml) | n | Median | Mean | $p$ |
|---|---|---|---|---|
| Pre vaccination | 172 | 0 | 0 | < 0.001 |
| 21 days after 1st dose | 172 | 2.7 (0-251) | 25.25 ± 59.74 | |
| 56 days after 2nd dose | 172 | 128 (0-251) | 138.77 ± 90.93 | |

$25.25 \pm 59.74$ U/mL. The mean titers increased to $138.77 \pm 90.93$ U/mL 56 days after the second dose. Seroconversion rate 21 days after the first dose of CoronaVac was 69.7% (120/172) and increased to 99.4% (171/172) 56 days after the second dose.

Only one patient was still seronegative after second dose of CoronaVac.

     The study analyzes the titers of anti-S-RBD pre-vaccine, at 21 days after first dose and 56 days after second dose vaccination. Statistical
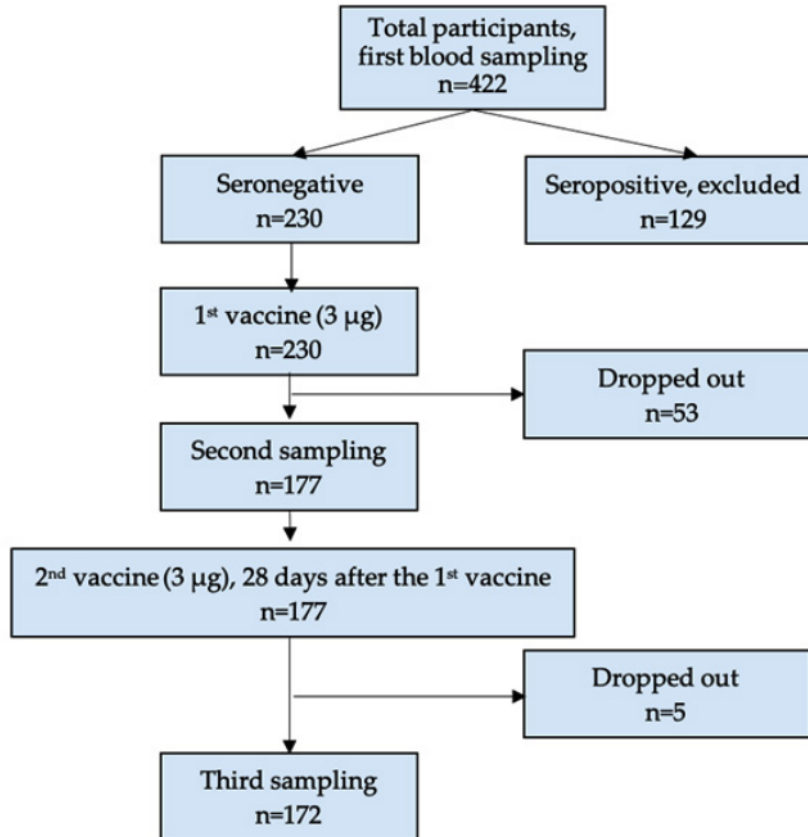


**Fig. 1.** Sampling flowchart

**Table 3.** Post hoc analysis of anti-S-RBD IgG levels between all testing point

| Anti S-RBD IgG level (U/mL) | n | Median | Mean | *p* |
|---|---|---|---|---|
| Pre vaccine vs 21 days after 1st dose | | | | |
| Pre vaccination | 172 | 0 | 0 | < 0.001 |
| 21 days after 1st dose | 172 | 2.7 (0-251) | $25.25 \pm 59.74$ | |
| Pre vaccine vs 56 days after 2nd dose | | | | |
| Pre vaccination | 172 | 0 | 0 | < 0.001 |
| 56 days after 2nd dose | 172 | 128 (0-251) | $138.77 \pm 90.93$ | |
| 21 days after 1st dose vs 56 days after 2nd dose | | | | |
| 21 days after 1st dose | 172 | 2.7 (0-251) | $25.25 \pm 59.74$ | < 0.001 |
| 56 days after 2nd dose | 172 | 128 (0-251) | $138.77 \pm 90.93$ | |

analysis showed that the data distribution was not normal *p* <0.05 and Friedman test was used to compared anti-S-RBD levels before, and after the first and second vaccination. The results reveal the titers of anti S-RBD were significantly difference among the three-testing point (Table 2). The Friedman test result was *p* <0.001 which means that there are significant differences of anti-S-RBD levels in at least at two-testing point.

Post hoc analysis was done using Wilcoxon test to find out which measurement had different anti-S-RBD titers. Wilcoxon test was done between pre vaccination and 21 days after first dose, pre vaccination and 56 days after second dose, and between 21 days after first dose and 56 days after second dose. The result was *p* < 0.001 for all group (Table 3).

## DISCUSSION

Our study provides the data of the S-RBD antibody titers measured on day 21 after first dose and 56 days after second dose of CoronaVac. The mean of the antibody titers increased from 0 to 25.25 IU/mL at 21 days after the administration of the first dose and further increased to 138.77 IU/mL 56 days after the second dose. The protective effect (based on >15 U/mL cut-off), also followed with rapid seroconversion was observed as early as 21 days following the vaccination. Our previous study employing a smaller number of participants (n=60) suggests the mean antibody titers could reach a seroconversion rate of 91.6% with a mean value of 63.62±82.57 IU/mL.[20] Our findings are in line with a previously reported study investigating the Thai population, where mean value of S-RBD antibody titers of 1.98 IU/mL was obtained after the first dose of CoronaVac.[21] After the second dose, the mean titer increased to 92.9 IU/mL on day-30 and decreased to 49.4 IU/mL on day-90, though the seroconversion rate persisted at 100%.[21] A study conducted in Banten of Indonesia also supported the immunogenicity of the CoronaVac vaccine after the second dose, where the median of the antibody titers was 38.7 IU/mL.[22] Inactivated virus vaccine has been suggested to be suitable for emergency use due to its rapid immunogenicity (14 days post-injection).[15] Regardless the immunogenicity, the protective level of CoronaVac vaccine against SARS-CoV-2 infectivity is low. In a published report investigating Indonesian health care workers, the recipients of two doses [1] CoronaVac were reported to remain at risk for SARS-CoV-2 infection.[23]

In addition to the immunogenicity, our findings suggest the safety of the CoronaVac with 11.04% adverse reaction incidence after the first dose, and almost all volunteers (171/172) reported no side effects after the second dose. None of life-threatening adverse reaction was observed after each shot, where most of the participants felt feverish after the first dose. In previous reports, the most co[1]mon short-term side effects observed after the injection of either the first or the second dose of CoronaVac included fatigue, muscle pain, fever, and headache.[24, 25] The side effects frequency obtained in this present study is fewer as compared with that obtained previously (35.6%) who employed a smaller number of seronegative participants (n=73).[19] Apart from the different number of participants, the gender ratio was also different between this present study and the previous study[19], which might play a role in the different adverse reaction frequencies. In fact, several previous studies have witnessed that being female is associated with higher adverse reaction frequency, yet could induce higher immunogenicity.[26, 27]

It is worth-mentioning that the waning efficacy of inactivated virus vaccine has been highlighted by previous studies, in particular during the emergence of SARS-CoV-2 variants.[28, 29] Moreover, a previous study also found the anti-S-RBD antibody titers were higher in naturally infected individuals as compared with those vaccinated using CoronaVac[21]. Third dose vaccination might be required to improve the protective effect of the vaccine. A longitudinal study comparing the third immunization using CoronaVac and BNT162b2 vaccines suggests that heterogenous booster could induce higher antibodies against SARS-CoV-2.[30] A study even reported the absence of inhibition effect of CoronaVac vaccine-induced antibodies against Omicron variant (strains HKU691 and HKU344-R346K).[31] Hence, despite the rapid immunogenicity and low adverse reaction frequency, third dose vaccination with mRNA-based vaccine might require for those who received two doses of CoronaVac.

There are some limitations of this study that need to discussed. We did not perform sera dilution for samples with concentration > 250 U/mL, suggesting that the antibody titers could have higher concentration for those who had >250 U/mL. The number of male and female volunteers was not equal in our study of which more dominated by male volunteers and this might cause bias. We did not investigate the change of antibody titers in the following months after the second dose, and therefore we are unable to monitor the length of the vaccine protective time. Regardless the stated limitations, our study could describe the rapid immunogenicity of CoronaVac vaccine following the first and second dose. Rapid immunogenicity is essential during the early time of pandemic, especially in population that are at risk due to high intensity of international mobility such as Bali.

## CONCLUSION

CoronaVac could induce rapid seroconversion of at least 21 days following the first shot. Moreover, CoronaVac cause low adverse reactions, where none are life-threatening. Further studies are recommended with higher number of participants to assess the dynamic of specific anti-SARS-CoV-2 S-RBD antibody concentration following the second or even booster dose.

### Data sharing

The underlying dataset containing deidentified participants of this article is available from the corresponding author (SM) upon reasonable request and accompanied by IRB approval.

### Author Contributions

Conceptualization, S.M; Data curation, S.M., I.M.I, I.M.W.W., Investigation, I.M.I, I.M.W.W; Methodology, S.M., E.J.N; Resources, S.M.; Validation, S.M., I.M.I, H.H.; Writing – original draft, S.M., H.H.; Writing – review & editing, S.M., H.H., E.J.N.

### Source of Funding

This study was funded by International Society of Travel Medicine to SM. Grant no. is 1330/Unwar/FKIK/PD-13/2022

### Conflict of Interest

The authors do not have any conflict of interest.

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