



Effectiveness of CoronaVac Vaccine in Health Workers in Indonesia: A Case-Control Study

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Abstract. Despite various platforms, vaccines are expected to be an essential effort to control COVID-19. Phase 3 clinical trials for CoronaVac, one of the inactivated virus vaccines, in Indonesia showed a promising efficacy of 65.3%. This study aimed to assess CoronaVac effectiveness in health workers against symptomatic COVID-19 and its severity after the vaccination program started on 13 January 2021. It was a case-control study with a ratio of 1 case: 4 controls. Data collection was conducted from August to October 2021 in several hospitals and primary health centers in 14 cities/regencies of Indonesia. Cases were health workers with symptomatic COVID-19, confirmed by RT-PCR or antigen rapid test in the period of 13 January 2021 to the data collecting time. Controls were health workers never been diagnosed with COVID-19. Hospitalized subjects' data were extracted from medical records and input by an enumerator into LimeSurvey, an online survey tool. Non-hospitalized subjects and non-COVID-19 subjects filled the questionnaire by themselves in LimeSurvey. A total of 913 cases and 3342 controls met the criteria. CoronaVac effectiveness was analyzed and adjusted for gender, age, and comorbidity. Fully vaccinated gave 92.1% (95% CI 90.0–93.8; $p = 0.0001$) effectiveness in preventing symptomatic COVID-19; 96.4% (95% CI 95.3–97.3; $p = 0.0001$) for moderate/severe cases and 70.3% (95% CI 56.9–79.6; $p = 0.0001$) for mild cases. Partially vaccinated only gave 27.5% (95% CI 0.11–47.4; $p = 0.049$) effectiveness in preventing symptomatic COVID-19 incidence. It concludes that 2 doses of CoronaVac are effective to prevent symptomatic and moderate to severe cases in health workers.

Keywords: case-control · effectiveness · CoronaVac · COVID-19 · health worker

1 Introduction

Corona Virus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 or SARS-CoV-2. It was first found in Wuhan China on December 29, 2019 and become a pandemic on March 11, 2020 [1, 2]. It caused significant morbidity, mortality worldwide and affected hugely to education and economic sectors. As of January 13, 2021, 223 countries were affected 91,823,722 confirmed cases and 2,095,965 deaths globally [3]. The first case in Indonesia was on March 2, 2020 in Depok city then spread to 34 provinces. Globally, public health and social measures, contact tracing, and treatment had been taken to limit the spread of COVID-19. Simultaneously, the scientific and medical community worked on various platforms of vaccines, starting with inactivated, live attenuated, nucleic acid, subunit and vectored vaccines with rapid speed. Vaccines are believed to be one of the best options to control COVID-19. Hundreds of clinical trials were conducted to assess the vaccine efficacy. Through Presidential Decree number 99 in 2020, the Indonesian government determined the need for vaccination acceleration to control COVID-19 [4]. As the front line force of health care, the health workers at high risk of acquiring and transmitting infection were prioritized as the stage 1 target population for vaccination [5]. During the early phase of the pandemic, many health workers were infected and died. A systematic review of the literature undertaken up to May 8, 2020 to estimate COVID-19 infections and deaths in healthcare workers worldwide showed that most COVID-19 cases and deaths were reported in the 50–59 age range but the highest case fatality rate was in aged over 70 years group (37.2 deaths/100 infections). Infections were mainly in women (71.6%, $n = 14058$) and nurses (38.6%, $n = 10706$) but deaths were mainly in man (70.8%, $n = 550$) and doctors (51.4%, $n = 525$) (6). The first vaccine that obtains emergency use authorization (EUA) from The National Agency of Drug and Food Control (NA-DFC), Indonesia was CoronaVac, an inactivated virus vaccine from Sinovac, China. A phase 3 clinical trial was conducted in Indonesia with an interim analysis showed 65.3% (95% CI 20.0–85.1%) efficacy [7, 8]. Other phases 3 clinical trials in Brazil and Turkey found that CoronaVac was 50.7–83.5% effective against symptomatic COVID-19, 83.7% against moderate cases, and 100% against severe cases [9, 10]. How CoronaVac will protect the health workers from COVID-19 in the real world is still a concern. The Ministry of Health, Republic of Indonesia conducted 7 studies to evaluate the implementation of COVID-19 vaccination since it started on 13 January 2021 including the logistic management, the disease transmission, vaccine effectiveness, duration protection, seroprevalence, people acceptance, and waste management. This study aimed to assess the CoronaVac effectiveness in health workers against symptomatic COVID-19 and its severity.

2 Materials and Methods

This was an unmatched case-control study with a ratio of 1 case: 4 controls. The sample size was calculated using the formula of estimating an odds ratio with specified relative precision (95% confidence level) [11]

$$n = \frac{Z_{1-\alpha/2}^2}{[\log_e(1 - \epsilon)]^2} \left[\frac{1}{P_1(1 - P_1)} + \frac{1}{P_2(1 - P_2)} \right] \quad (1)$$

With 95% confidence level (α 5%), 20% relative precision (ϵ), anticipated probability of exposure given no disease based on the coverage of vaccination (P_2) = 80%, and anticipated odds ratio of 0.347 based on the efficacy of CoronaVac from an interim analysis of phase 3 clinical trial in Indonesia [7, 8], the ratio of case and control = 1: 4, the minimum case and control subjects should be 500 and 3200 respectively. Data collection was conducted from August to October 2021 in 39 hospitals and 41 primary health centers in 14 cities/regencies, and seven provinces of Indonesia. Cases were health workers aged 18 years and over with symptomatic COVID-19, confirmed by RT-PCR or antigen rapid test in the period of 13 January 2021 to the data collecting time, and domiciled in the study location or its surroundings. Controls were health workers aged 18 years and over, never been diagnosed with COVID-19 since the vaccination program started, and domiciled in the study location or its surroundings. Cases and controls were selected by systematic random sampling from the health workers list provided by hospitals and primary health care. Data were collected using a structured questionnaire with an online survey tool called LimeSurvey. Enumerators extracted data from hospitalized cases' medical records and input the data into LimeSurvey while non-hospitalized cases filled the questionnaire in LimeSurvey by themselves as well as the control subjects. Subjects vaccinated by other than CoronaVac were excluded. Fully vaccinated was defined as 14 days after the second dose while partially vaccinated was defined as 14 days after the first dose, haven't got a second dose, or less than 14 days after the second dose. We used binary and multinomial logistic regression to calculate the effectiveness of CoronaVac against symptomatic COVID-19 and its severity with adjustment for gender, age, and presence of comorbidity. COVID-19 severity was assessed by the doctor in charge based on the guidelines from 5 health professional organizations in Indonesia. Symptomatic COVID-19 is categorized as mild if there are mild symptoms without pneumonia; as moderate if there are pneumonia symptoms and $SpO_2 \geq 93\%$; as severe if there are severe pneumonia and $SpO_2 < 93\%$ or respiratory rate > 30 x/minute; and as critical if there are acute respiratory distress syndrome and sepsis [12]. Comorbidity includes hypertension, diabetes mellitus, asthma, obesity, allergy, heart disease, renal disease, liver disease, other respiratory disease, cancer, and autoimmune. Effectiveness is assumed as 1 minus the corresponding odds ratio. This study had received ethical approval number LB.02.01/2/KE.237/2021 dated 05 May 2021 and protocol amendment approval number LB.02.01/2/KE.391/2021 dated 05 July 2021 from the Health Research Ethics Committee, National Institute of Health Research and Development, Ministry of Health, Indonesia.

3 Results

The process of subject screening and recruitment is shown in Fig. 1. A total of 4255 health workers met the criteria with 913 cases and 3342 controls.

Table 1 shows the characteristics, severity, and vaccination status of both case and control subjects. Among 601 health workers having comorbidity, there were 237 with hypertension, 121 with asthma, 93 with obesity, 67 with diabetes mellitus, 63 with allergy. A total of 665 (72.8%) cases had received 1 dose of CoronaVac and 654 (71.6%) had received 2 doses while in the control group 3212 (96.1%) had received 1 dose and 3194 (95.6%) had received 2 doses of CoronaVac.

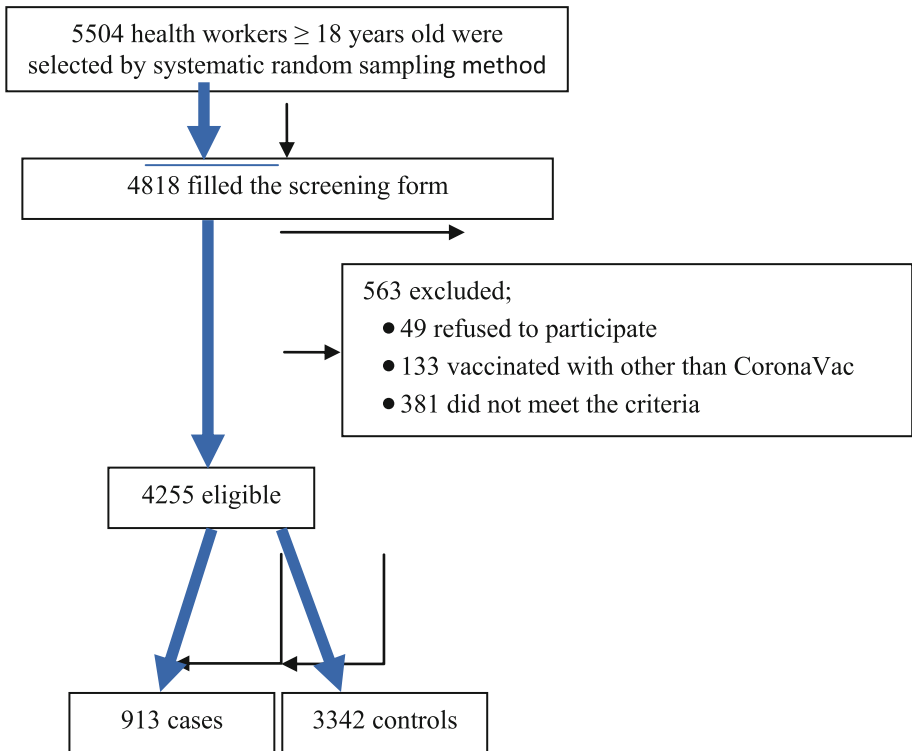


Fig. 1. Diagram of case and control subject screening

Table 1. Distribution of case and control subjects by demography, comorbidity, severity, and vaccination status in health workers

Characteristic	Case (n = 913)	Control (n = 3342)
Gender		
Male	262 (28.7%)	923 (27.6%)
Female	651 (71.3%)	2419 (72.4%)
Age (year)		
Min-max	19—71	19—72
18 – 39	614 (67.3%)	2319 (69.4%)
40 – 59	287 (31.4%)	1005 (30.1%)
60 +	12 (1.3%)	18 (0.5%)
Comorbidity		
Yes	163 (17.9%)	438 (13.1%)
No	722 (79.1%)	2754 (82.4%)
Unknown	28 (3.1%)	150 (4.5%)
Severity		
Not ill	0	3342 (100%)
Mild	457 (50.1%)	0
Moderate	439 (48.1%)	0
Severe	16 (18%)	0
Critical	1 (0.1%)	0
Vaccination status ¹		
Fully vaccinated	485 (53.1%)	3086 (92.3%)
Partially vaccinated	174 (19.1%)	123 (3.7%)
Unvaccinated	254 (27.8%)	133 (4.0%)

¹Fully vaccinated: ≥ 14 days after the second dose

Partially vaccinated: ≥ 14 days after the first dose till < 14 days after the second dose

Unvaccinated: has not been vaccinated or < 14 days after the first dose

Table 2 showed the effectiveness of CoronaVac either fully vaccinated or partially vaccinated against symptomatic COVID-19 and its severity. The CoronaVac effectiveness was higher in fully vaccinated health workers especially against symptomatic COVID-19 incidence and moderate to critical disease than in partially vaccinated health workers.

Table 2. CoronaVac effectiveness against symptomatic COVID-19 incidence and severity in health workers

Outcome	CoronaVac Effectiveness			
	Fully vaccinated ¹ vs unvaccinated ³		Partially vaccinated ² vs unvaccinated ³	
	Crude % (95% CI); p-value	Adjusted ⁴ % (95% CI); p-value	Crude % (95% CI); p-value	Adjusted ⁴ % (95% CI); p-value
Symptomatic COVID-19	91.8 (89.6—93.5); p < 0.001	92.1 (90.0—93.8); p < 0.001	25.9 ((-1.2)—45.8); p = 0.059	27.5 (0.1—47.4); p = 0.049
<u>Severity</u>				
Mild	69.8 (56.6—79.0); p < 0.001	70.3 (56.9—79.6); p < 0.001	(-184.2) (-85.2)—(-336.1); p < 0.001	(-181.0) (-80.0)—(-336.5); p < 0.001
Moderate/Severe/ Critical	96.2 (95.1—97.1); p < 0.001	96.4 (95.3—97.3); p < 0.001	68.7 (54.5—78.5); p < 0.001	69.4 (54.9—79.2); p < 0.001

¹Fully vaccinated: \geq 14 days after the second dose

²Partially vaccinated: \geq 14 days after the first dose till < 14 days after the second dose

³Unvaccinated: has not been vaccinated or < 14 days after the first dose

⁴Adjusted for gender, age, and comorbidity

4 Discussion

Effectiveness Against Symptomatic COVID-19

The mean anti-S antibodies level at day 14 after 2 doses of CoronaVac in health workers was 73.2 U/ml, SD 68 U/mL (cutoff value for a positive result is > 0.80 U/mL) but it decreased significantly by day 42 post-vaccination (55.2 U/mL) and persisted for up to 98 days (54.1 U/mL). Vaccinated health workers with prior SARS-CoV-2 infection had significantly higher, stable levels of anti-S antibodies compared with vaccinated health workers without prior SARS-CoV-2 infection (day 14: 73.2 vs 219.9 U/mL) [20]. The receptor-binding domain of the S protein can block virus entry, thus preventing infection and transmission [21] and its level correlates strongly with the level of protective neutralizing antibodies [22]. In this study, we did not consider the variant of SARS Cov-2. SARS Cov-2 Delta variant was found in early May 2021 in Indonesia and the COVID-19 surged in July 2021. A matched test-negative case-control study in healthcare workers in Manaus, Brazil where the SARS-Cov-2 Gamma variant was dominant showed 49.4% (95% CI 13.2 to 71.9) effectiveness at preventing COVID-19 but it found no significant effectiveness of two-dose CoronaVac (adjusted VE 36.8%, 95%CI -54.9 to 74.2) [23]. It suggests bias from unmeasured confounding. Another study in Chile to assess the CoronaVac effectiveness among people aged 16 years and older found the vaccine effectiveness in fully vaccinated people was 65.9% (95% CI 65.2 to 66.6%) in

preventing COVID-19 [24]. A survey to investigate the protective effect of CoronaVac on health workers in Turkey compared the cases before vaccination with the breakthrough cases in terms of demographic and clinical features. It indicated that CoronaVac provides protection against COVID-19. The rate of breakthrough cases after being vaccinated was 7% but the hospitalization rate was similar between the breakthrough cases and cases before the CoronaVac vaccination [25]. It seems that vaccine effectiveness in health workers was higher than in the general population. It is reported that VE against infection in the general population aged 16 years and older was 86.1% (95% CI 77.8—94.4%), in the elderly 83.8% (95% CI 77.1—90.6%), and in the health workers was 95.3% (95% CI 92.0—98.6%). Compared to other types of vaccines, the CoronaVac effectiveness for those fully vaccinated against infection was 65.7%, lower than the Pfizer-BioNTech (91.2%), and the Moderna (98.1%) (26).

Effectiveness Against COVID-19 Severity

The adjusted vaccine effectiveness against mild COVID-19 in fully vaccinated health workers is 70.3% (95% CI 56.9—79.6%) and 96.4% (95% CI 95.3—97.3%) against moderate to critical COVID-19. It is similar to the CoronaVac effectiveness found in a prospective observational cohort study in Chile which was 87.5% (95% CI 86.7 to 88.2%) in preventing hospitalization, and 90.3% (95% CI 89.1 to 91.4) in preventing ICU admission, and 86.3% (95% CI 84.5 to 87.9%) for prevention of COVID-19 related death [24]. Earlier studies in clinical trial settings in Turkey and Brazil showed the efficacy of two doses of CoronaVac in reducing hospitalization and severe cases were 100% [9, 10]. Further study in Turkey, 7.5 months after the COVID-19 vaccination program started, showed no significant difference in hospitalization rate between the breakthrough cases and cases before CoronaVac vaccination in health workers. The decision to be hospitalized is not always based on the disease severity but also to protect the household from being infected [25].

The health workers' protection from COVID-19 is crucial for any country to handle the surge of patients and overcome this pandemic. Vaccine effectiveness does not depend only on the vaccine itself but also on the population vaccinated. To protect the health workers, other populations should also be vaccinated. In Indonesia, one month following vaccination for health workers, the elderly, and public service workers were targeted, continued to the other vulnerable population and then all populations including children aged ≥ 6 years with 10 types of vaccine authorized. The task force worked very hard to achieve the target of 70% population vaccination. This success may increase the vaccine's effectiveness in preventing symptomatic COVID-19 and its severity. As of 16 June 2022, persons fully vaccinated with the last dose of primary series per 100 population in Indonesia is 61.36/100 population (global 60.58) or 168,183,942 from the target of 208,265,720. Total cumulative cases is 6,063,251 (global 534,495,291) with 156,670 cumulative total deaths (global 6,311,088) [3, 27]. High vaccine effectiveness should not lead to loosening preventive and control measures. Public health and social measures are still important factors to fight against COVID-19 along with vaccination programs although COVID-19 tends to become milder. The 2-dose vaccination still

needs to be continued and expanded to achieve the determined targets to deal with the COVID-19 pandemic.

Study Limitation

We did not conduct COVID-19 RT PCR or rapid antigen testing on the control group so the control group may include symptomatic COVID-19. No question about the history of COVID-19 before the implementation of vaccination was collected and we did not consider the variant of SAR CoV-2. Although fully vaccinated gave high effectiveness against symptomatic COVID-19 and disease severity, we need to know how long the protection lasts and also the effectiveness against a new variant of SARS-COV-2. This could be a potential further study.

5 Conclusion

This study concludes that two doses of CoronaVac are effective to prevent symptomatic and moderate to critical COVID-19 in health workers.

6 Contributors

D, N, SI, HH, LW, and IUT conceptualized the study. D, N, SI, HH, LW, IUT, HS, TAJ, NAR, AKS, NP, DA, ME, and TU contributed to the data collection instrument and data accuracy. NAF, SW, DY, SA, HS, TAJ, YR, RA, AKS, NP, YDC, EIN, and MDS contributed to data collection and data cleaning. D, N, SI, and HH contributed to data analysis and prepared the manuscript draft. All authors participated in data interpretation, revised the manuscript, and approved the final manuscript. D, N, HH, SI, LW, and IUT were shared as main contributors.

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