Original article

Adverse Events Following Immunization (AEFI) with CoronaVac COVID-19 Vaccine among Clinical Clerkship Students at the Faculty of Medicine, Syarif Hidayatullah State Islamic University, Jakarta, Indonesia

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Abstract:

Objective: Clinical clerkship students, as adolescent health workers, have been first recipients of the COVID-19 vaccination programme. The success rate and trust of recipients in the program have been impacted by adverse events following immunization (AEFI). This study aims to determine the AEFI of the CoronaVac vaccine among clinical clerkship students at the Faculty of Medicine, State Islamic University, Jakarta. ***Material and Methods:*** This study used cross sectional methods with a total of 225 subjects completing a questionnaire. The *CoronaVac* vaccine was administered twice with 2 week interval. AEFI was evaluated after 30 minutes, 24 hours, and on the third day. ***Results and discussion*****:** 73.3% of the participants were female, 20-25 years old. AEFIs were found in 57.8 % of all participants in the first and second doses vaccination. The most common local AEFI was pain at the site injection, accounting 27.1 % which occurred 30 minutes after second dose vaccination. The most common systemic AEFI was drowsiness, accounting for 18 % which occurred 24 hours after first dose vaccination. Other systemic AEFIs were headache, fatigue, and chills. There was significant association between AEFIs and females but no significant association with history of allergy, comorbidities, and history of previous COVID-19 . AEFIs were mild, no special treatment or hospitalization were required. ***Conclusion:*** The AEFIs of the CoronaVac vaccine among students were mild and had significant association with females. The study is expected to increase the public's confidence in the COVID-19 vaccination program and to create awareness of its safety.

Keywords: Adverse Events Following Immunization (AEFI); COVID-19; Clinical Clerkship Students;CoronaVac Vaccine; Vaccine Safety

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Introduction:

In late December 2019, the Coronavirus disease-19 (COVID-19) caused by a novel coronavirus called SARS-CoV-2 was first reported in Wuhan, China. The World Health Organization (WHO) declared it to be a global pandemic on March 11, 2020[1]. Several management and health protocols were implemented to limit the spread of the virus. Some

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treatments have been developed, but they are not all effective to cure critical cases[2,3]. The development of a COVID-19 vaccine is required to create new hope for communities[4]. Vaccination programmes must be implemented with consideration of their effectiveness, immunogenicity and safety.

Around 170 vaccines have been developed up to phase 3 clinical trials and a few are already being used[5,6] The Beijing-based pharmaceutical company Sinovac Ltd produced the third vaccine called CoronaVac. The main ingredient of the vaccine is the inactivated SARS-CoV-2 virus[7]. It was approved by Brazil, Chile, Turkey, and Indonesia after clinical trials, and received Emergency Use Authorization (EUA) on May 7, 2021 from SAGE (Strategic Advisory Group of Experts) at WHO[5,6]. Preliminary reports show the CoronaVac vaccine is well tolerated and able to activate humoral immunity to eliminate the virus. Study results from Turkey, Chile, and Brazil showed an efficacy of 84 %, 67 %, and 50.7 % respectively[7,8,9]. The third phase of the clinical trial in Indonesia showed 65.3% of efficacy[10]. The EUA of the CoronaVac vaccine was announced by the Food and Drug Supervisory Agency (BPOM) on January 13, 2021 and it also received a Halal Fatwa from the Indonesian Ulema Council (MUI)[11,12].

Vaccines are products using modern biotechnology that build specific antibodies against infection. Vaccines should be good quality, safe and effective, although they may have adverse events. Therefore, the implementation of the vaccine needs evaluation of adverse events following immunization (AEFI)[13]. AEFI is any untoward medical event which takes place after immunization and does not have a causal relationship with use of the vaccine. The classification of AEFI includes vaccine product-related reactions, vaccine procedural errors, vaccine quality defects, immunization-anxiety reactions or coincidental events. AEFI could be common, mild, or severe with serious symptoms, accounting for 10% and <0.01% of cases, respectively. Management of mild AEFI is based on the symptoms present, while severe cases require specific medical treatment or hospitalization[13,14]. AEFI is divided into local and systemic symptoms that occurred quickly or slowly[13]. Many studies have shown AEFI from the CoronaVac vaccine were mild, such as pain, redness and swelling at the injection site as local symptoms meanwhile headache, fatigue, drowsiness, myalgia, chills, fever, nausea, and vomiting as systemic symptoms [15-23].

The Indonesian government has the responsibility to ensure that immunization coverage reaches around 70% of the population, called herd immunity. Therefore, vaccination of 189 million out of the 270 million Indonesian population is needed[2,14]. Information about AEFI had an impact on public confidence in terms of benefits and support for the programme's implementation. Elnaem, et al study showed uncertainty regarding vaccine safety was the most common reported reason for vaccine hesitancy[16]. Generally, a lack of vaccine knowledge especially the benefits and risks leads to refusal or delay in terms of vaccination[14]. A study in Indonesia found that the majority neither supported nor rejected the mass vaccination programme[24].

The immunization programme covered approximately 1 million Indonesians in January- February 2021[15]. Health workers and older people were first priority while adolescents who have better immunity and low risk of comorbidity are next priority[25]. Meanwhile clinical clerkship students as adolescent health workers represent an ideal population group could take part in the vaccination program and to provide information about the vaccine's benefits and the safety of the community and environment, due to their high level of health literacy and scientific interest[15]. Therefore, this study aims to determine the adverse events of COVID-19 vaccination in clinical clerkship students at the Faculty of Medicine, State Islamic University, Syarif Hidayatullah, Jakarta, Indonesia.

Material and Methods:

The study was cross sectional that conducted between February and March 2021. The collection of data made using a validated questionnaire that covered the subjects characteristics and adverse events after administration of the vaccine. The inclusion criteria were clinical clerkship students from the Faculty of Medicine, State Islamic University in Jakarta, who had received two doses of the CoronaVac vaccine and completed the questionnaire. The vaccine was administered twice, with an interval 2 weeks[17]. Adverse events were evaluated after 30 minutes, 24 hours, and on the third day after the administration of the two doses. The data were analysed statistically using Microsoft Excel 2019 and SPSS 24.0. The Chi-square statistical analysis test was used to determine association between AEFIs and sex, history of allergy, comorbidities and history of COVID-19 previous 3 month , which p-value < 0.05 were

statistically significant. The questionnaire included the reason and benefits of the study also informed consent document.

Ethical clearance: Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine, Syarif Hidayatullah State Islamic University, with registry number B-027/F12/KEPK/TL.00/04/2021. All the research data were used solely for the study and remained confidential.

Results:

A total of 225 students who met the inclusion criteria comprised 73.3% females within the age range of 20 to 25. There were 35. 6 % had a history of allergy history and 5.8 % had history of COVID-19 positive in the previous 3 months as shown in Table 1.

Table 1. Respondent characteristics (n=225)

Characteristic	Description	N = total (%)
Gender	Male	60 (26.7)
	Female	165 (73.3)
Comorbidities	Allergies	80 (35.6)
	Asthma	8 (3.6)
	Gastritis	4 (1.7)
	History of COVID-19 in the previous 3 months	13 (5.8)

There were 57.8 % participants had AEFIs after first dose and second dose vaccination, while 51,1 % participants experienced AEFIs at first dose vaccination. Moreover this study showed 17.3% participants had local symptoms, 18.7 % had systemic symptoms and 15.1% felt local and systemic symptoms at first dose vaccination. At second dose vaccination, only 44 % participant had experienced AEFIs. Participants had local symptoms increased to 23.1 % but participants experienced systemic symptoms decreased to 9.3%. After 2 doses vaccination, 19.6 % participants had local symptoms and 23.1 % had local and systemic symptoms as shown in Table 2.

Table 2. Frequency of AEFIs

	First Dose Vaccination N (%)	Second Dose Vaccination N (%)	1st and 2nd Dose Vaccination N (%)
Local symptoms	39 (17.3)	52 (23.1)	44 (19.6)
Systemic symptoms	42 (18.7)	21 (9.3)	34 (15.1)
Local and Systemic symptoms	34 (15.1)	26 (11.6)	52 (23.1)
All AEFIs	115 (51.1)	99 (44)	130 (57.8)
No AEFIs	110 (48.9)	126 (56)	95 (42.2)

Based on these results local symptoms happened more after second dose vaccination, but participants had systemic symptoms decreased after second dose vaccination. Participants had both local and systemic symptoms also decreased after second dose vaccination.

Study also showed that 24.4 % of the participants experienced local AEFIs such as pain at the site of the injection after 30 minutes of the first vaccination and 8.4 % of the participants still felt pain on the third day. 64.9 % of the participants had no AEFIs during the first 30 minutes, 66,7 % felt no AEFIs after 24 hours, and 88 % felt no AEFIs on third day, as shown in Table 3

Table 3 also showed the most common systemic AEFI was drowsiness accounting 18 % after 24 hours, but on the third day only 4 % of the participants continued to experience this symptoms. Other systemic AEFIs happened more in participants 24 hours after vaccination , such as fatigue 5.3 %, headache 2.3 % and chills 1.8 %

At the second vaccination dose, 27.1 % of the participants had local symptoms after 30 minutes, more increase than first dose , but this fell to 9.7 %

Table 3. AEFI after first and second vaccination doses (n=225)

Adverse Event	First vaccination dose (%)			Second vaccination dose (%)		
	30 minutes	24 hours	3 days	30 minutes	24 hours	3 days
No adverse event	64.9	66.7	88.0	67.1	72.9	88
Pain at site of injection	24.4	20.4	8.4	27.1	16.4	9.7
Drowsiness	13.3	18	4	8	8.4	2.7
Fatigue	4.9	5.3	1.3	5.3	5.3	2.2
Headache	1.8	2.2	0.9	1.3	1.3	0.4
Chills	0.0	1.8	1.3	0.0	0.0	1.3

by the third day. The most common systemic AEFI in the second dose was drowsiness, accounting for 8.4% after 24 hours, before falling to 2.7 % by the third day. Fatigue was common symptoms at the second dose accounting 5.3 %, at 30 minutes and 24 hours. Headache was also a systemic symptom accounting 1.3 % after 30 minutes and 24 hours while chills only happened on the third day accounting 1.3%.

Table 4 showed that systemic AEFI occurred more in the female than the male participants, accounting 41.2 % of female and 23.3 % of male at both vaccination, respectively. Despite this, there was significant association between sex and systemic AEFI at first dose and two doses CoronaVac vaccination ($p<0.05$) as

Table 4. Association between sex and systemic AEFIs

Sex 1st dose vaccination	Systemic AEFIs						
	Yes		No		Total		*p*-value
	N	%	N	%	N	%	
Females	63	38.2	102	61.8	165	100	**0.025**
Males	13	21.7	47	78.3	60	100	
2nd doses							
Females	39	23.6	126	76.4	165	100	0.096
Males	8	13.3	52	86.7	60	100	
1st and 2nddoses							
Females	68	41.2	97	58.8	165	100	**0.018**
Males	14	23.3	46	76.7	60	100	

Table 5. Association between history of allergy and systemic AEFIs

History of allergy 1st dose vaccination	Systemic AEFIs						
	Yes		No		Total		*p*-value
	N	%	N	%	N	%	
Yes	30	37.5	50	62.5	80	100	0.462
No	46	31.7	99	68.3	145	100	
2nd dose vaccination							
Yes	20	25	60	75	80	100	0.302
No	27	18.6	118	81.4	145	100	
1st and 2nd dose vaccination							
Yes	32	40	48	60	80	100	0.47
No	50	34.5	95	65.5	145	100	

Table 6. Association between comorbidities and systemic AEFIs

Comorbidities 1st dose vaccination	Systemic AEFIs						
	Yes		No		Total		*p*-value
	N	%	N	%	N	%	
Yes	5	41.7	7	58.3	12	100	0.545
No	71	47.1	142	66.7	213	100	
2nd dose vaccination							
Yes	4	33.3	8	66.7	12	100	0.28
No	43	20.2	170	79.8	213	100	
1st and 2nd dose vaccination							
Yes	6	50	6	50	12	100	0.362
No	76	35.7	137	64.3	213	100	

Table 7. Association between history of COVID-19 infection with systemic AEFIs

COVID-19 History	Systemic AEFI						
	Yes		No		Total		*P*-Value
1st dose vaccination	N	%	N	%	N	%	
Yes	4	30.8	9	69.2	13	100	1.000
No	72	34	140	66	212	100	
2nd dose vaccination							
Yes	3	23.1	10	76.9	13	100	0.737
No	44	20.7	168	79.2	212	100	
1st and 2nddose vaccination							
Yes	4	30.8	9	69.2	13	100	0.773
No	78	36.8	134	63.2	212	100	

Meanwhile, tables 5,6 and 7 showed that the systemic AEFI had no significant association with history of allergies, comorbidities and history of COVID-19 previous 3 month (all *p*-values > 0.05).

Discussion:

AEFIs were observed after two doses of the vaccine with an interval 2 weeks. This is in line with the WHO recommendations that all individuals should receive two doses intramuscularly in the deltoid muscle at intervals of 2 to 4 weeks[5,19-20].

This study showed 57.8 % of AEFI cases in both first and second doses vaccination, accounting 19.6 % participants only experienced local symptoms such as pain and redness at the injection site, 15.1 % only had systemic symptoms such as drowsiness, fatigue, headache and chills, while 23.1 % had both local and systemic symptoms. This is in line with 2 studies in Turkey conducted in health workers. Tosun et al, reported that the most common local and systemic symptoms after the COVID-19 vaccine were pain at the injection site, headaches, fatigue and drowsiness[20]. The proportions of each symptoms were higher than our study, with headaches being the most common systemic symptom. Meanwhile Kaya et al., reported 33.2% of subjects had AEFIs and the most common systemic symptoms was headache that happened after 24 hours and up to the third day, followed by drowsiness, fatigue, nausea and vomiting. Drowsiness and fatigue only occurred within the first 24 hours. Due to the fact that their study was conducted among healthcare workers, the intense working conditions might have affected the frequency of fatigue[23]. Moreover, Riad et al in Czech Republic found a high prevalence of CoronaVac AEFI among health workers (62.5%). Injection site pain was the most common local AEFI, while fatigue and headaches were the common systemic AEFIs. In most cases, the AEFIs persisted one to three days. The time AEFI occurred and its average duration were similar to our study at 1-3 days.

A study in Indonesia by Supangat et al, also conducted to clinical clerkship students, reported that the most common AEFI was localized pain at the injection site, followed by fatigue. Other symptoms, such as headaches, fever, chills, drowsiness, nausea, dysphagia, and colds, were also reported[19]. Supangat et al study is similar to three clinical trials in China, where 16,671 recipients of CoronaVac reported pain at the injection site, fatigue and headaches[6,30]. Bueno et al., stated that CoronaVac vaccination with an interval 2 weeks in Chilean adults aged ≥18 years was safe, mostly mild, local symptoms, activated T cells and secretion of IFN-γ upon stimulation with SARS CoV-2 antigens[17]. All studies in Chile, Czech, China, and Jember, Indonesia showed that fatigue was the most common systemic symptom this differs from our study, which drowsiness was the most common systemic AEFI. Another study by Benjamanukul et al., in Thailand found myalgia was the most common systemic adverse event , with no serious adverse events observed. A study in Bangladesh found that 39.48% out of 1180 participants reported at least one side effect after receiving their COVID-19 vaccine. Injection-site pain, redness, swelling at the injection site, fever, headache, and fatigue were the most commonly reported adverse events, but all were mild and only lasted 1-3 days. The lowest percentage of side effects were found among people who received Sinovac accounting 21.05% comparing with Pfizer-BioNTech (80.46%) , Moderna (76.63%) and Oxford Astra Zeneca (67.72%) vaccines. Beg et al in Pakistan reported the first dose of vaccine has resulted

in significantly local symptoms as compared to the second dose of vaccine that similar with our study.

Local and systemic AEFI occur because vaccines contain antigens that recognised as potential pathogens which found on peripheral circulating immune cells resulting in the synthesis and release of pyrogenic cytokines such as interleukin (IL)-1, IL-6, TNF-α, prostaglandin-E2, and chemokines. These inflammatory events lead to the development of symptoms at the injection-site, such as pain, redness and swelling within the first hours after administration. Pain sensation is transmitted through fast-conducting myelinated neurons. Those components may enter the bloodstream and produce systemic symptoms such as fatigue, headaches, myalgia and drowsiness. Intracerebral prostaglandin E2 activates neuronal circuits, which create autonomic and behavioural responses, such as metabolic heat production, chills and elevated body temperature[29].

Our study showed females had significant association with AEFIs than males, that was similar with Riad et al, reported females were more likely to have vaccine-related side effects, apart from fever, which slightly more common in males[19]. Kaya et al, showed that females complained more of severe adverse events than males because they have stronger immune responses and less susceptible to viral infection however there were no significant differences in the adverse events found between males and females[23]. But Supangat study found that AEFIs was not correlated with gender[19]. Our study showed the systemic AEFI had no significant association with history of allergies, comorbidities and history of COVID-19 previous 3 month which similar with Beg et al found no relationship between the previous COVID-19 infection, comorbidities and systemic AEFI[36]. Meanwhile Tosun study reported history of allergy had a higher rate of AEFIs [20]. A case series study identifying individuals who had been infected with COVID-19 showed that there was no increase in the risk of myocarditis/pericarditis, Bell's Palsy, stroke, or myocardial infarction in the 21 days following either dose of the CoronaVac vaccine, apart from arrhythmia[35]. The study was also similar to the Indonesia Ministry of Health report that adverse events after the CoronaVac vaccine were mild, with no history of anaphylactic shock[23].

This study showed pain at the site injection being the most common local symptom and most systemic reactions were felt 24 hours after vaccination which similar with other studies. All symptoms were mild and none needed specific treatment or hospitalization.

Implementation of the vaccination programme is intended to protect people from the high risk of infection, especially health workers. Furthermore, the target group was clinical clerkship students, an adolescent group who were expected to spread information about the benefits and safety of the vaccination to the community.

This study had the limitations that the respondents were homogenous, and that it only assessed up to three days after the vaccinations. Long-term follow-up is needed to assess late symptoms of vaccination.

Conclusion:

The most common local AEFI after administering the CoronaVac vaccine in the clinical clerkship students at the Faculty of Medicine Syarif Hidayatullah State Islamic University Jakarta was pain at the injection site after 30 minutes while the most common systemic AEFI was drowsiness after 24 hours of the first and second doses vaccination. Other common adverse events were fatigue, chills and headache. There were significant association between females and AEFIs, but no significant differences history of allergy, comorbidities and history of COVID previous 3 month. Generally, the AEFIs were mild and people were released without any specific treatment or hospitalization. Clinical clerkship students, represent an adolescent population group to take part in active surveillance studies due to their high level of health literacy and scientific interest. Therefore, this study is expected to increase public confidence in the vaccination program and create awareness of its safety. Future studies of the AEFI of CoronaVac vaccination should explore more of its risk factors.

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Data gathering and idea owner of this study: FNA, HH

Study design: FNA, HH

Data gathering: FNA, HH, RT, NNF

Data analysis and consultation: FNA, HH, RT

Writing and submitting the manuscript: FNA, RT, NNF

Reference:

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