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Adverse events following immunization (AEFIs) in health workers who receive COVID-19 vaccination at Academic Hospital Universitas Gadjah Mada, Yogyakarta

Ade Febrina Lestari[1,2], Mei Neni Sitaresmi[2], Anjarsari Haspitaningrum[1], Kusuma Ayu Rachmasari[1], Ratih Wulandari[1], Shinta Kusumalarna Sari[1], Firda Ridhayani[3]

[1]Academic Hospital Universitas Gadjah Mada, Yogyakarta, [2]Child Health Department, DR Sardjito Hospital, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, [3]Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia

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ABSTRACT

COVID-19 is a new viral infection that has become a global pandemic, resulting in extremely high mortality and morbidity rates worldwide, including in Indonesia. Vaccination is one of the strategies for preventing COVID-19 infection promoted by the World Health Organization (WHO) to reduce COVID-19 morbidity and mortality. The Indonesian government supports the implementation of vaccination and conducts mass vaccination as a strategy to overcome the pandemic in Indonesia. The high immunization coverage resulted in increased use of vaccines, and events following immunization (AEFI) also increased. Reports on follow-up AEFI are needed as government policy references and information for the public. This study aims to describe the following events after the COVID-19 vaccine immunization and the incidence of the infection post vaccination. The study design was a cross-sectional study using primary and secondary data. The data were analyzed descriptively and statistically using the Chi Square method by identifying an association between demographic data and AEFI incidence. A total of 131 respondents were included. Most respondents experienced AEFI after giving the first (77.1%) or second (71.9%) vaccine with the Sinovac vaccine. However, all reported mild AEFI. Most reported AEFIs were pain (48.8% and 49.6%), hungry (37.4% and 10.0%), and drowsiness (32.1% and 23.7%) after the first and the second vaccine. In conclusion, the prevalence of AEFI in the first and the second dose of inactivated COVID-19 vaccine is higher than that reported in the clinical trial study, although all AEFIs are considered as mild.

ABSTRAK

COVID-19 merupakan infeksi virus baru yang menjadi pandemi global, mengakibatkan angka motalitas dan morbiditas sangat tinggi di seluruh dunia, termasuk di Indonesia. Vaksinasi merupakan salah satu tindakan pencegahan yang digalakkan oleh *World Health Organization* (WHO) untuk menurunkan morbiditas dan mortalitasnya. Pemerintah Indonesia melaksanaan vaksinasi masal untuk penanggulangan pandemik di Indonesia. Cakupan imunisasi yang tinggi meningkatkan penggunaan vaksin dan kejadian ikutan pasca imunisasi (KIPI). Laporan tindak lanjut KIPI diperlukan sebagai dasar pengambilan kebijakan pemerintah dan informasi bagi masyarakat. Penelitian ini bertujuan untuk mendata KPI vaksin COVID-19 dan kejadian infeksi COVID-19 pasca vaksinasi. Rancanan penelitian ini adalah potong lintang menggunakan data primer dan data sekunder. Data dianalisis secara deskriptif dengan menganalisis data sosiodemografi (jenis kelamin, usia, dan riwayat penyakit), serta durasi munculnya gejala. Total diperoleh 131 responden. Sebagian besar responden mengalami KIPI setelah menerima vaksin pertama (77,1%) atau kedua (71,9%) menggunakan vaksin Sinovac, namun semuanya merupakan KIPI ringan. Laporan KIPI terbanyak yaitu nyeri (48,8% dan 49,6%), rasa lapar (37,4% dan 10,0%), dan mengantuk (32,1% dan 23,7%) setelah vaksinasi pertama dan kedua. Dapat disimpulkan bahwa prevalensi terjadinya KIPI pada vaksinasi COVID-19 dosis pertama dan kedua lebih tinggi dibanding laporan pada uji klinik meskipun KPI yang terjadi seluruhnya dikategorikan ringan.

*corresponding author: adefebrina@ugm.ac.id

INTRODUCTION

In Wuhan, China, cases of pneumonia with an unknown cause were discovered, which led to the discovery of the COVID-19 infection. A pandemic was declared by the World Health Organization (WHO) on March 11, 2020, after the WHO classified it as an exceptional occurrence on December 31, 2019, due to its rapid spread.[1,2] Indonesia reported two confirmed cases of COVID-19 for the first time on March 2, 2020. In 2022, WHO reported more than 6 million deaths from COVID-19 infection worldwide. Health workers are reported to have the highest mortality in the world due to COVID-19 outbreak. More than 180 thousand deaths in health workers in the world were reported by WHO, while in Indonesia, it was reported that more than 2,000 health workers died due to COVID-19, especially the professions of doctors, nurses, and midwives.[1,2]

Vaccination is an active effort to induce immunity in the body against a specific disease. Vaccination or immunization has been recognized as the best effort to prevent infectious diseases and improve public health status through the herd immunity mechanism.[3,4,5] Indonesia makes the implementation of the COVID-19 vaccine as part of the pandemic response to protect the public from SARS-Cov-2 infection which can cause illness and death. Based on the Decree of the Minister of Health Number HK.01.07/Menkes/12758/2020, the types of COVID-19 vaccines that can be used in Indonesia are; vaccines produced by Bio Farma, Sinovac (CoronaVac), AstraZeneca, Sinopharm, Moderna, Novavax, and Pfizer.[6] The implementation of vaccination in Indonesia is carried out in 4 stages. Phase I had been held in January – April 2021 with the target of health workers, support staff, and students undergoing the medical profession. At this stage, the type of vaccine used is Sinovac. Even though the Sinovac vaccine was still in the clinical trial stage of phase 3 when vaccination was carried out in Indonesia for the first time, it has already obtained permission from BPOM in the form of an Emergency Use of Authorization (EUA)[7] for use and permitted by The Indonesian Religious Council (MUI) as a halal vaccine to use.[8]

The most important factor that must be considered in manufacturing and using vaccines is the balance between the immunity to be achieved and the adverse reactions that may arise. It is hoped that the vaccine used has an antigen that is effective in stimulating the immune response but does not cause severe side effects.[11] The high immunization coverage resulted in increased use of vaccines, and adverse events following immunization (AEFI) also increased. The occurrence of AEFIs is caused by several factors, such as reactions related to vaccine products, reactions due to vaccine quality defects, incorrect immunization procedures, or coincidental events.[12] Research related to clinical trials of the CoronaVac vaccine showed an AEFI incidence rate of 8% to 38%, while in phase 2, almost 18% to 35% of research respondents experienced AEFI.[7]

As one of the main vaccines in the prevention of COVID-19, so it is essential to know their security after being adopted in a larger population. Therefore, evaluating patients' AEFI risk variables following COVID-19 vaccination is also crucial. The study aims to determine the incidences of AEFI and COVID-19 infection after receiving the Sinovac vaccine among health workers in Academic Hospital, Universitas Gadjah Mada, Yogyakarta. Hopefully, this research can help the community's decision to accept or reject the vaccine. Vaccine refusal contributes to reduced vaccine coverage and diminished herd immunity, leading to outbreaks.

MATERIALS AND METHODS

Design

This research was conducted at the Academic Hospital Universitas Gadjah Mada (RSA UGM). The research's design was a cross-sectional study, using primary and secondary data. Primary data comes from questionnaires and secondary data in the form of vaccine data through the national health system including a history of COVID-19 vaccination. The data of this study were analyzed descriptively by identifying demographic data (gender, age, and disease history) and symptoms that occur along with the duration of symptoms. Chi Square analysis was used to describe the association between each variable (gender, age, and comorbidities) and AEFI incidence. The vaccine used is Sinovac Biotech Ltd under the name CoronaVac; containing an inactivated virus in a single dose of 1 vial of 0.5 mL. This vaccine is injected into the left upper 1/3 of the arm or the arm that is not actively used, in 2 doses with an interval of 14-28 days. An AEFI was defined as a vaccine adverse reaction that the subject experienced up to 4 weeks post-vaccination. Ethical clearance was submitted and approved by the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia with document number KE/FK/0827/EC/2021.

Population and research

The study population was all health workers and supporting health workers who received vaccinations with the Sinovac vaccine at the RSA UGM from January to July 2021 who met the inclusion and exclusion criteria. The Sampling method is a total sampling technique. The inclusion criteria are as follows: (1) Health workers aged over 18 years and elderly health workers, and health support personnel; (2) Have received vaccinations/vaccinated with the Sinovac vaccine type 2 times. The exclusion criteria for this study were: (a) Cannot be contacted to obtain primary data; (b) Did not complete the questionnaire. The questionnaire contains two section, first section includes demographic data of respondents, presence or absence of comorbid diseases, history of covid vaccination, and whether or not they have been infected with COVID-19. The second section of the questionnaire asks about types of AEFI, severity, and duration of AEFI. Questionnaire validation was carried out by consultation with a team of vaccine experts at our hospital. Questionnaires were sent to a private number of the subject by permission before.

RESULTS

A total of 131 respondents were involved in this study. Most of the respondents (87%) were females, and 42% were in rage age of 20-30 years old. Most vaccinators (58.8%) were given by midwives. The majority of participants got the location of the vaccine injection on the left arm (96.2%) according to government instructions. Around 30.6% of respondents had comorbidities: hypertension (3.8%), asthma (8.4%), tuberculosis (1.5%), and autoimmunity (1.5%), respectively. A total of 33 respondents (25.2%) in this study had been infected with COVID-19 before getting the first vaccination (TABLE 1).

TABLE 1. Characteristics of subjects

Subject characteristics	n (%)
Sex	
• Male	17 (13)
• Female	114 (87)
Age	
• 20 – 30 years	55 (42)
• 31 – 40 years	51 (39)
• 41 – 50 years	25 (19)
Vaccinator	
• Doctor	9 (6.9)
• Nurse	45 (34.4)
• Midwives	77 (58.8)
Injection site	
• Right arm	5 (3.8)
• Left arm	126 (96.2)
Comorbidities	
• Hypertension	5 (3.8)
• Asthma	11 (8.4)
• Tuberculosis (TBC)	2 (1.5)
• Autoimmune disease	2 (1.5)
• Others	7 (5.4)
History of COVID-19 infection	
• Yes (been infected)	33 (25.2)
• No (never)	98 (74.8)

A total of 101 respondents (77%) were experienced AEFI after the first vaccination and the remaining of 37 respondents (28.2%) experienced after the second vaccination. The majority of respondents complained of pain at the injection site after the first vaccine (48.8%), and after the second vaccine (49.6%), respectively. Other complaints felt by respondents were sleepiness after the first vaccination (32.1%), after the second vaccination (23.7%), and feeling hungry after the first vaccination (37.4%), and after the second vaccination (16%). Other complaints felt by respondents included redness, swelling at the injection site, dizziness, fever >37.5°C, muscle aches throughout the body (myalgia), joint pain (arthralgia), weakness, headache,

nausea and vomiting, weakness in body parts, itching all over the body, flu. Besides that, there were respondents who did not feel any complaints after the first vaccine by 22.9% and after the second vaccine by 28.2% (TABLE 2). Data from respondents found that there were no respondents who were hospitalized due to post-vaccination complaints.

The factors associated with AEFTs were also evaluated (TABLE 3). Comorbidities were significantly associated with the AEFIs in the first vaccination (p=0.015), but not in the second vaccination. Furthermore, injection site was associated with the AEFIs in the second vaccination (p=0.006), but not in the first vaccination.

TABLE 2. Adverse events following immunization (AEFIs)

Type of AEFIs	Vaccine 1st n (%)	Vaccine 2nd n (%)
Local reaction		
• Pain	64 (48.8)	65 (49.6)
• Redness	4 (3.1)	2 (1.5)
• Swelling	1 (0.8)	3 (2.3)
Systemic reactions		
• Headache	8 (6.1)	8 (6.1)
• Fever > 37.5 °C	1 (0.8)	1 (0.8)
• Myalgia	3 (2.3)	1 (0.8)
• Arthralgia	3 (2.3)	3 (2.3)
• Weakness	2 (1.5)	3 (2.3)
Other reaction		
• Feel hungry	49 (37.4)	21 (16)
• Drowsiness	42 (32.1)	31 (23.7)
• Anaphylaxis	0 (0)	0 (0)
• Faint or unconscious	0 (0)	0 (0)
• Body rash and itch	1 (0.8)	0 (0)
• Vomit and dyspepsia	1 (0.8)	0 (0)
• Diarrhea	0 (0)	0 (0)
• Weakness part of the body	1 (0.8)	0 (0)
• Cough	0 (0)	1 (0.8)
No AEFIs	30 (22.9)	37 (28.2)

TABLE 3. Factors associated with AEFIs

Variable	Vaccine 1st		p*	Vaccine 2nd		p*
	AEFI n (%)	No AEFI n (%)		AEFI n (%)	No AEFI n (%)	
Gender						
• Male	12 (70.6)	5 (29.4)	0.493	11 (64.7)	6 (35.3)	0.392
• Female	89 (78.1)	25 (21.9)		85 (74.6)	29 (25.4)	
Age group						
• Geriatric	0	0	-	0	0	-
• Non geriatric	101 (77.1)	30 (22.9)		94 (93.0)	37 (7)	
Vaccinator						
• Doctor	6 (66.7)	3 (33.3)		6 (66.7)	3 (33.3)	
• Nurse	33 (73.3)	12 (26.7)	0.490	28 (62.2)	17 (37.8)	0.079
• Midwives	62 (80.5)	15 (19.5)		62 (80.5)	15 (26.7)	
Injection site						
• Right arm	3 (60.0)	2 (40.0)	0.354	1 (20.0)	4 (80.0)	0.006
• Left arm	98 (77.8)	28 (22.2)		95 (75.4)	31 (24.6)	
Comorbidities						
• Yes	14 (58.3)	10 (41.7)	0.015	17 (70.8)	7 (29.2)	0.764
• No	87 (81.3)	20 (18.7)		79 (73.8)	28 (26.2)	
History**						
• Yes	23 (69.7)	10 (30.3)	0.242	25 (75.8)	8 (24.2)	0.710
• No	78 (79.6)	20 (20.4)		71 (72.4)	27 (27.6)	

Chi-Square test p <0.05; **History of COVID-19 infection before vaccination

Respondents who felt post-vaccination complaints said that their complaints disappeared after 30 min until the 7th d after vaccination. The majority of respondents said that complaints disappeared in less than 24 h in the first vaccine 59.8% and in the second vaccine by 48.5%. Only 2% of respondents experienced complaints about 3 to 7 d after vaccination (TABLE 4). Respondent data shows that 3 respondents were infected with COVID-19 less than 1 mo after the first vaccination. After the second vaccination, there were 30 respondents infected with COVID-19 in the second mo to the sixth mo.

On average, the respondents were infected after 4.4 mo after vaccination (TABLE 5). Only 3 subjects had COVID-19 infection after the first dose of vaccination and total of 32 subjects had COVID-19 infection after the second dose of vaccination.

TABLE 4. Duration of AEFIs

Duration of AEFIs	Vaccine 1st n (%)	Vaccine 2nd n (%)
> 30 min	18 (17.6)	22 (22.7)
> 24 h	61 (59.8)	47 (48.5)
> 2 x 24 h	14 (13.7)	18 (18.2)
> 3 x 24 h	7 (6.9)	8 (8.2)
3-7 d	2 (2)	2 (2)
> 7 d	0 (0)	0 (0)

TABLE 5. Onset of COVID-19 infection after vaccination

Onset infection after vaccination	Vaccine 1st n (%)	Vaccine 2nd n (%)
< 1 mo	3 (100)	0
> 2 mo	0	2 (6.6)
> 3 mo	0	5 (16.7)
> 4 mo	0	9 (30.0)
> 5 mo	0	8 (26.7)
> 6 mo	0	6 (20.0)

DISCUSSION

This study was conducted to evaluate the AEFIs incidences after vaccination using Sinovac vaccine as one of the COVID-19 vaccine options in Indonesia. This vaccine has high efficacy in preventing COVID-19 infection. The Sinovac vaccine efficacy value is based on research from several countries: Brazil (50.4%),[9] Turkey (91.25%),[10] and Indonesia (65.3%).[7] This value already surpasses the minimum standard of WHO >50%.[4]

The result of this study reported that most of the respondents experienced AEFI after the first or second vaccination with the Sinovac vaccine (72-77%). This result is significantly different from the study conducted in China which is only 17-38% of respondents experienced AEFIs.[13] The significant difference due to the number of AEFIs has not been reported before, such as feeling hungry that occurred in more than one of third of the respondents.

The most respondents complaints in this study was pain at the injection site after the first vaccine (48.8%), and after the second vaccine (49.6%). This result is comparable to a study on the safety of the Sinovac vaccine in China which reported that most post-immunization complaints were mild, the most common complaint being pain at the injection site.[13] Other complaints that are often felt are drowsiness after the first vaccination (32.1%), after the second vaccination (23.7%), and feeling hungry after the first vaccination (37.4%), and after the second vaccination (16%). Other studies have shown the same results, another systemic effect that often appears after COVID-19 immunization is fatigue.[10] In addition, some respondents also felt complaints such as redness, swelling at the injection site, dizziness, fever >37.5°C, and muscle aches. whole body (myalgia), joint pain (arthralgia), weakness, headache, nausea and vomiting, weakness of body parts, itching all over the body, and flu.

Interestingly, this study reported AEFI symptom that is not stated in the manual brochure of the Sinovac vaccine, such as hungry found after the first and second vaccination, around 37% and 16%, respectively. Several researchers from Indonesia have already captured this finding, especially for the Sinovac and CoronaVac vaccine recipients.[14] Hunger may be explained by the immunological response that the vaccine generated, such as stress-related modulation of cytokine release by activated T cells that may exacerbate an inflammatory reaction to the vaccination-induced hypothalamic response.[14] Inflammation is hypothesized to affect the homeostatic and non-homeostatic mechanisms of appetite, which are predominately controlled by dopamine signaling in the hypothalamus and mesolimbic zone. Therefore, the control of hunger feeling, and body weight is more dependent on inflammatory mediators on central production.[15]

We found an association between

comorbidities and AEFI on first dose of COVID-19 vaccination (p=0.015). The presence of comorbidities becomes a major factor that associate with AEFI. When compared to people without comorbidities, people with any comorbidities had a 2.08-times higher risk of having AEFI.[16] Those with comorbidities should be vaccinated with caution.

The type of AEFI felt by all respondents in this study (100%) was classified as mild AEFI. After vaccination, mild adverse reactions are typical. Local reactions, including pain, redness, and swelling at the injection site, as well as systemic reactions, like fever, malaise, and dizziness, can manifest as symptoms.[10] Severe reaction is uncommon. In most cases, it doesn't result in long-term issues, but it can be incapacitating and rarely life-threatening. Seizures, anaphylaxis, thrombocytopenia, periods of hypotonic hyporesponsiveness, and persistent, unrelenting screams are just a few of the severe reactions that may occur.[10,13] Research conducted by Tanriover *et al*.,[10] stated that the majority of side effects complained of were mild and occurred within 7 days after immunization. This is similar to the results of research conducted, respondents said that the side effects of the vaccine were disappear after 30 minutes to 7 days after immunization. There were no respondents who experienced hospitalization in the hospital due to the complaints they felt. As many as 25% of respondents were infected with COVID-19 after being vaccinated. After vaccination, a person still has the possibility to be infected with the COVID-19 virus but with mild severity. In the study, Ranzani *et al*.,[9] reported that vaccination after the second dose at an interval of 14 days had an effectiveness rate of 55.5% in preventing a person from being hospitalized and preventing a mortality rate of 61.2%.

This study found that 30 respondents (22.9%) were infected with COVID-19 2-6 mo after receiving 2 complete doses of vaccination. In June-August 2021 in Indonesia, there was an increase in COVID-19 cases because of the entry and spread of the Delta variant of the virus. This Delta variant is twice more infectious than the previous virus variant. This variant can infect people who have been fully vaccinated. Some experts say the Delta variant can cause more severe disease in people who have not been vaccinated.[17] On average, these respondents were infected with COVID-19 after 4.4 months after vaccination. Meanwhile, immunogenicity data for some vaccines show that antibodies persist for at least 6 mo.[18]

There are limitations to this study. It was cross-sectional and based on self-reported data, which means that the participant's prior prejudice and misunderstanding about vaccine adverse events could have an impact on the research results. There may be recall bias regarding symptoms of vaccination adverse events. Moreover, only observational studies were used in this study, which is prone to flaws such confounding, information, and selection bias.

CONCLUSION

Most of the respondents experienced mild AEFIs after administering the first or second vaccine with the Sinovac vaccine are pain at the injection site, drowsiness, and feeling hungry that have various duration, disappearing after 30 min to 7 d after COVID-19 immunization. The prevalence of AEFI in the first and the second dose of inactivated COVID-19 vaccine is higher than that reported in the clinical trial study although the all AEFIs are considered as mild.

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