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Overview of COVID-19 Vaccine Adverse Events Following Immunization in Bali

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ABSTRACT

Adverse event following immunization (AEFI) is undesired medical events that occur post-vaccination without considering whether there is a cause-and-effect relationship with the use of the vaccine or not. COVID-19 vaccination is an ongoing vaccination but the AEFI research is still limited, especially in Bali. This study aimed to report the overview of COVID-19 vaccine AEFI in Bali during January 2021 – December 2022. This was a descriptive study with cross-sectional approach by using the recapitulation data of the COVID-19 vaccine AEFI reports from the Bali Provincial Health Service. Of 958 cases, AEFI cases of COVID-19 vaccine were dominated by females (61.38%), age group of 18 – 29 years (38.73%), and domiciled in Denpasar (38.62%). The majority of adverse reaction reports were obtained from the hospital (53.34%), post vaccination of Sinovac (41.34%), and after the first dose (68.72%). The most frequently reported COVID-19 vaccine AEFI cases were non-serious AEFI (94.57%) with the most common symptoms in the local reaction group was pain at the injection site (9.65%), in the systemic reaction group was fever (17.77%), and in the other reaction group was shortness of breath (1.79%). In conclusion, AEFI of COVID-19 vaccine in Bali was dominated by females, age 18 – 29 years, and domiciled in Denpasar with most reports obtained from hospitals, post-vaccination of Sinovac, and after the first dose. The most reported AEFI cases were non-serious AEFIs where the most common symptoms were pain at the injection site for local reactions, fever for systemic reactions, and breathing difficulty for other reactions.

Keywords: COVID-19 vaccine, AEFI, side effect, adverse event

INTRODUCTION

Pandemic is a situation where an epidemic spreads in massive numbers and extends globally, usually related to an infectious disease. In 2019, the world was faced with a new pandemic which known as Coronavirus disease 19 (COVID-19).[1] Coronavirus disease 19 is a respiratory tract infection caused by a new virus species, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[2] This SARS-CoV-2 virus can mutate and transmit very quickly through droplets (aerosol), air, or surface which caused a significant increase in cases.[3]

Based on World Health Organization (WHO) data on the 23rd of October 2022, COVID-19 prevalence in the world has reached 623.893.894 confirmed cases.[4] Currently, Indonesia is in the 20th world rank with a prevalence that has reached 6.469.276 confirmed cases.[5] This condition initiates researchers to develop vaccines to prevent the spread of the virus.[6]

Vaccine is a biological product that triggers the body to form immunity against a particular disease by imitating infection mechanism.[7,8] Several COVID-19 vaccines have been used in Indonesia such as

Sinovac, AstraZeneca, Biofarma, Moderna, Pfizer, Sinopharm, etc. The COVID-19 vaccine is divided into four doses consisting of two primary doses and two booster doses. Based on WHO data on the 18th of October 2022, a total of 12.814.704.622 doses have been injected into people around the world.[4] By the 23rd of October 2022, COVID-19 vaccination in Indonesia had injected 205.091.868 first dose vaccine, 171.786.632 second dose vaccine, 64.780.128 third dose vaccine, and 659.486 fourth dose vaccine.[9] Based on the COVID-19 vaccination report by the Committee for Handling COVID-19 and National Economic Recovery, COVID-19 vaccination in Bali in 2021 – 2022 has reached 7.461.927 first dose vaccine, 6.788.080 second dose vaccine, dan 2.193.883 third dose vaccine.[10]

In several conditions, vaccination can cause unexpected events called adverse events following immunization (AEFI). This is a medical event that occurs directly after vaccination or until one month post-vaccination period without considering whether the is a cause-and-effect relationship with the use of the vaccine.[11] This incident generally happens as a hypersensitivity reaction to the vaccine which can occur due to various causal factors including vaccine product-related reaction, vaccine quality defect reaction, immunization error-related reaction, immunization anxiety-related reaction, and coincidental event.[7,11,12]

AEFI can be classified into several classifications. The first classification is based on the level of seriousness as serious and non-serious AEFI. Serious AEFI is an adverse event that may cause death, hospitalization or extended hospitalization, disability, life-threatening conditions, congenital abnormalities, and/or other serious medical events. Non-serious AEFI is a temporary adverse event with mild to moderate intensity and does not cause any severe risk to the individual's health.[13,14] Other AEFI classifications may be based on the reaction and symptoms, it can be classified into local reaction AEFI, systemic reaction AEFI, and other AEFI reactions. Local reactions are reactions that occur at the site of injection with local symptoms such as pain, redness, and swelling. Systemic reactions are reactions that occur throughout the body with systemic symptoms such as fever, myalgia, arthralgia, malaise, headache, nausea, vomiting, fatigue, etc. Other AEFI reactions that may occur post-vaccination are anaphylactic, syncope, or allergic reactions.[11,15,16]

Based on the description above, considering that the AEFI of the COVID-19 vaccine is still a new issue and the research regarding the AEFI of the COVID-19 vaccine is still limited, especially in Bali, this study aims to find out the nature of AEFI COVID-19 vaccine in Bali.

MATERIALS & METHODS

Study Design

This research was a descriptive study with a cross-sectional approach. Data was collected retrospectively by looking at AEFI reports summary in Bali from January 2021 until December 2022 which was obtained from the Bali Provincial Health Service. The research was conducted in January – July 2023.

Samples

Samples of this study were data on AEFI cases reported by the vaccination provider health workers to the Bali Provincial Health Service. In total, there were 1.456 AEFI cases which number of samples that met the inclusion criteria was 958 cases. The inclusion criteria in this study include data with individuals who experienced AEFI after receiving the COVID-19 vaccine in Bali in the period January 2021 – December 2022 and had been reported by the vaccination provider health workers to the Bali Provincial Health Service. The exclusion criteria in this study are incomplete AEFI patient information data and incomplete AEFI report data.

Data Collection

Sampling in this study used total sampling method where all subjects who fulfill the inclusion and exclusion criteria will be sampled in the research. The variables from samples are then recorded in a data processing matrix which includes gender, age, regency domicile, vaccination provider health service facility, COVID-19 vaccine manufacturers, COVID-19 vaccine doses, seriousness level of AEFI, reactions and symptoms of AEFI.

STATISTICAL ANALYSIS

Data processing was done by using the Microsoft Office Excel 2019 application. The statistical analysis design in this study used univariate analysis by describing the frequency distribution of each variable. The results will be presented in the form of frequency distribution tables.

RESULT & DISCUSSION

1. AEFI of COVID-19 Vaccine in Bali Based on Gender

The research result shows that more COVID-19 vaccine AEFI cases in Bali in the period of January 2021 – December 2022 occurred in women than men which can be seen in **Table 1**. Of 958 samples, women experienced AEFI in 588 cases (61,38%), while 370 cases (38,62%) were men.

Table 1 Frequency Distribution Based on Gender

Gender	Frequency (n=958)	Proportion (%)
Women	588	61,38
Men	370	38,62
Total	958	100

Abbreviation: n = number of samples

This result was congruent with the research by Al-Qazaz et al. (2022) towards health works in Iraq. From a total sample of 843 people, it was found that 628 of them experienced adverse effects, of which 512 people (81,53%) were female and 116 people (18,47%) were male.[17] A research by Wibowo et al. (2022) involving 311 participants from 33 provinces in Indonesia also obtained results that women experience more short-term adverse events.[18] This may be related to hormonal and psychological factors. Women have more estrogen hormone, especially estradiol, which can induce the immune system thereby increasing immune response and antibody formation. On the other hand, men have more testosterone hormone, which has the opposite mechanism from estrogen, so it can reduce immune response and simultaneously increase the possibility of men being infected with a disease. Psychologically, stereotypes (masculinity and femininity) also have an impact on case data collection because women tend to request more treatment from health workers compared to men who tend to pay less attention to their health.[17,19]

2. AEFI of COVID-19 Vaccine in Bali Based on Age

The research results in **Table 2** show that COVID-19 vaccine AEFI cases in Bali in the period of January 2021 – December 2022 mostly occurred in the age group of 18 – 29 years old with a total of 371 cases (38,73%), while the least occurred in 12 – 17 years age group with a total of 20 cases (2,09%).

Table 2 Frequency Distribution Based on Age

Age Group (years old)	Frequency (n=958)	Proportion (%)
< 12	32	3,34
12 – 17	20	2,09
18 – 29	371	38,73
30 – 39	258	26,93
40 – 49	166	17,33
50 – 59	79	8,25
≥ 60	32	3,34
Total	958	100

Abbreviation: n = number of samples

According to the age grouping by the Ministry of Health of the Republic of Indonesia, COVID-19 vaccine AEFI cases in this study mostly occurred in the productive age group.[20] This is congruent with the Republic of Indonesia Health Minister Regulation No. 84 of 2020 which states that in the early phases COVID-19 vaccines are prioritized for people aged 18 – 59 years old and working as health workers, health worker assistants, public service officers, etc.[16] The results of this study can also be related to the analysis of Xiong et al. (2021) where researchers used AEFI reports data on the Vaccine Adverse Event Reporting System (VAERS) in the United States. From 8.976 reported cases, AEFI was mostly reported by adults between ages 18 – 64 years old with 8.207 cases, while the elderlies (≥ 65 years old) had only 769 cases. Most of the elderly group experienced more serious AEFI compared to adults. This may be due to greater exposure of the COVID-19 vaccine to the productive age group so the chances of AEFI in the productive age group are higher.[21] A study by Elnaem et al. (2021) in Malaysia also stated that the young adult age group (18 – 30 years old) had a 7,4 times higher risk of experiencing side effects from the COVID-19 vaccine than the elderly group (≥ 60 years old).[22] Wang et al. (2021) explained that young adults have better immunogenicity which made their immune system more responsive and sensitive. This causes young adults to be more likely to experience AEFI due to immune reactions to vaccines which are considered foreign objects to the body. The lower incidence of AEFI in the elderly groups can also be related to the immunosenescence phenomenon, which is defined as a gradual decline of the immune system by the increasing of age. This causes the effectiveness of the vaccine to be less optimal inside the body.[23]

3. AEFI of COVID-19 Vaccine in Bali Based on Regency

Based on regency in Bali, most COVID-19 vaccine AEFI cases happened in Denpasar City with 370 cases (38,62%), followed by Badung Regency with 224 cases (23,38%), and Buleleng Regency with 155 cases (16,18%) (**Table 3**).

Table 3 Frequency Distribution Based on Regency in Bali

Regency	Frequency (n=958)	Proportion (%)
Denpasar City	370	38,62
Badung Regency	224	23,38
Buleleng Regency	155	16,18
Gianyar Regency	93	9,71
Klungkung Regency	67	6,99
Jembrana Regency	23	2,40
Tabanan Regency	15	1,57
Karangasem Regency	11	1,15
Bangli Regency	0	0,00
Total	958	100

Abbreviation: n = number of samples

Until today, there has been no similar research that explains the relationship between someone's domicile and AEFI incidence, especially in Bali. Based on the Ministry of Health of the Republic of Indonesia data and the COVID-19 vaccination reports by the Committee for Handling COVID-19 and National Economic Recovery, Denpasar City is at the highest rank in the number of COVID-19 vaccine administrations where the first dose has reached 1.813.392 doses, the second dose has reached 1.654.157 doses, and the third dose has reached 553.844 doses.[10] The high total of vaccine recipients in Denpasar City may cause a greater probability of AEFI in Denpasar City than in other districts. Other studies state that factors such as knowledge level differences, lack of AEFI reporting procedures socialization, and lack of health infrastructure can also contribute to the data

collection process on AEFI cases.[24,25]

4. AEFI of COVID-19 Vaccine in Bali Based on Vaccination Provider Health Service Facilities

In this study, eleven types of health service facilities reported COVID-19 vaccine AEFI cases to the Bali Provincial Health Service, which consist of hospitals, primary health care (puskesmas), immunization centers, schools, national immunization week posts, port health offices, supporting community health centers (pukesmas pembantu), village maternity cottages (pondok bersalin desa / polindes), clinics, homes, and integrated service posts (posyandu). Based on the data obtained, most COVID-19 vaccine AEFI cases were reported from hospitals with 511 cases (53,34%), followed by primary health care (puskesmas) with 198 cases (20,67%), and immunization centers with 131 cases (13,67%) (**Table 4**).

Table 4 Frequency Distribution Based on Vaccination Provider Health Service Facilities

Health Service Facilities	Frequency (n=958)	Proportion (%)
Hospitals	511	53,34
Primary Health Care (Puskesmas)	198	20,67
Immunization Centers	131	13,67
Schools	56	5,85
National Immunization Week Posts	40	4,18
Port Health Offices	6	0,63
Supporting Community Health Centers	5	0,52
Village Maternity Cottages (Polindes)	4	0,42
Clinics	3	0,31
Homes	3	0,31
Integrated Service Posts (Posyandu)	1	0,10
Total	958	100

Abbreviation: n = number of samples

A study by McNeil et al. (2013) who observed the use of the Vaccine Adverse Event Reporting System (VAERS) in health service facilities in the United States showed that more AEFI reports were obtained from hospitals than from public health service facilities. This study also showed that 594 health facilities (37%) had identified at least one AEFI case, but only 276 of them (17%) reported the case to VAERS. This condition can occur due to a lack of knowledge about VAERS. It is proven from the same study where the results show that 86% of AEFI reporting used paper methods and only 6% of AEFI reporting used internet-based methods via the VAERS website.[26]

5. AEFI of COVID-19 Vaccine in Bali Based on COVID-19 Vaccine Manufacturers

This research obtained AEFI reports on nine types of COVID-19 vaccine manufacturers shown in **Table 5**, including Sinovac, AstraZeneca, Biofarma, Moderna, Pfizer, and Sinopharm. The most reported AEFI cases of COVID-19 vaccine were Sinovac with 396 cases (41,34%), followed by AstraZeneca with 272 cases (28,39%), Biofarma with 148 cases (15,45%), Moderna with 132 cases (13,78%), Pfizer with 7 cases (0,73%), and Sinopharm with 3 cases (0,31%).

Table 5 Frequency Distribution Based on COVID-19 Vaccine Manufacturers

COVID-19 Vaccine Manufacturers	Frequency (n=958)	Proportion (%)
Sinovac	396	41,34
AstraZeneca	272	28,39
Biofarma	148	15,45
Moderna	132	13,78
Pfizer	7	0,73
Sinopharm	3	0,31
Total	958	100

Abbreviation: n = number of samples

These results were in line with research by Desnita et al. (2022) involving 95 respondents in Padang where 73,70% of respondents complained of AEFI after being given Sinovac.[27] Another study by Riad et al. (2021) stated that the most frequent AEFI that appeared after Sinovac vaccination were pain at the site of injection, fatigue, headaches, myalgia, and arthralgia with higher symptoms incidence in women ($p < 0,001$).[28] The higher number of AEFI reports after the Sinovac vaccination can also be related to the number of Sinovac doses used which dominates in Indonesia considering that Sinovac was the first COVID-19 vaccine that is permitted in Indonesia so the chance of AEFI incidence is higher.[29]

6. AEFI of COVID-19 Vaccine in Bali Based on COVID-19 Vaccine Dose

The results showed that the most AEFI cases of COVID-19 vaccine were reported after administering the first primary dose with 654 cases (68,27%), followed by the second primary dose with 155 cases (16,18%), and the first booster dose with 149 cases (15,55%) (**Table 6**).

Table 6 Frequency Distribution Based on COVID-19 Vaccine Dose

COVID-19 Vaccine Dose	Frequency (n=958)	Proportion (%)
First Primary Dose (First Dose)	654	68,27
Second Primary Dose (Second Dose)	155	16,18
First Booster Dose (Third Dose)	149	15,55
Total	958	100

Abbreviation: n = number of samples

Research by Gee et al. (2021) in the United States who observed AEFI in the use of Pfizer obtained results where AEFI cases were higher after administering the first primary dose with 5.428 cases, while AEFI after the second primary dose was 193 cases.[30] Similar results were found by Supangat et al. (2021) in Jember where symptomatic AEFI frequency was higher at the primary dose with 55 cases compared to the booster dose with 51 cases.[31] Another study also reported that there were 757 cases after the first primary dose vaccination and 715 cases after the second primary dose vaccination.[32] Opposite results were obtained from research by Maruyama et al. (2022) where AEFI incidence is higher after the second primary dose vaccination compared to the first primary dose vaccination.[33] Goda et al. (2022) explained that someone who experiences AEFI after the first primary dose vaccination is significantly more potentially to experience AEFI again after the second primary dose vaccination.[34] Research results by Izumo et al. (2021) also showed that only 35% of participants had positive antibody titers after the first primary dose vaccination, whereas all participants had positive results after the second primary dose vaccination. These results indicate that administering two doses of vaccination produces higher effectiveness in preventing COVID-19.[32,35]

7. AEFI of COVID-19 Vaccine in Bali Based on Seriousness Level of AEFI

Based on the level of seriousness, the most common AEFI that occurred was non-serious AEFI with a total of 906 cases (94,57%), while the serious AEFI reports were 52 cases (5,43%) (**Table 7**).

Table 7 Frequency Distribution Based on Seriousness Level of AEFI

Seriousness Level of AEFI	Frequency (n=958)	Proportion (%)
Non-Serious	906	94,57
Serious	52	5,43
Total	958	100

Abbreviation: n = number of samples

Similar results were found in research by Gee et al. (2021) in the United States where non-serious AEFI was reported in a total of 6.354 cases (90,9%), while serious AEFI

was reported in a total of 640 cases (9,2%).[30] Research by Hartutik et al., (2022) in Surakarta also showed 99 out of 100 respondents had non-serious AEFI and only 1 respondent experienced serious AEFI which had to be hospitalized.[36] This might happen because non-serious AEFIs generally have mild to moderate symptoms which will not cause a serious risk and are normal in the population as an immune response to vaccines so it does not require any serious medical intervention and the data collection process will be easier.[13,14] Furthermore, vaccines that have been developed have certainly passed clinal trial phases so it can be ensured that the doses are safe to be injected into almost all populations. It also minimizes side effects so the potential for serious AEFIs to occur is low.[37]

8. AEFI of COVID-19 Vaccine in Bali Based on AEFI Reactions and Symptoms

With a sample size of 958 cases, the total of AEFI symptoms reports that was received by the Bali Provincial Health Service was 1.564 symptoms. These symptoms are then grouped into three types of AEFI reactions which are local reactions, systemic reactions, and other reactions. Overall, the results of this study showed that the most frequent AEFI symptoms were fever which occurred in 278 cases (17,77%), followed by drowsiness in 171 cases (10,93%), myalgia/arthralgia in 158 cases (10,10%), and local pain in 151 cases (9,65%) (**Table 8**).

Table 8 Frequency Distribution Based on AEFI Reactions and Symptoms

AEFI Reactions and Symptoms	Frequency (n=958)	Proportion (%)
Local Reaction		
Pain at the injection site	151	9,65
Swelling	41	2,62
Erythema / Redness	16	1,02
Others	31	1,98
Systemic Reaction		
Fever	278	17,77
Drowsiness	171	10,93
Myalgia / Arthralgia	158	10,10
Headache	129	8,25
Malaise / Fatigue	121	7,74
Nausea	110	7,03
Dizziness	72	4,60
Vomiting	54	3,45
Itching on the Body	43	2,75
Cough / Cold	38	2,43
Diarrhea	15	0,96
Others	44	2,81
Other Reaction		
Breathing Difficulty	28	1,79
Syncope	14	0,90
Anaphylaxis	6	0,38
Death	6	0,38
Seizures	4	0,26
Allergy	1	0,06
Others	33	2,11
Total	1564	100

Abbreviation: n = number of symptoms reports

Based on AEFI reactions, this research showed that the most frequently reported local reaction is pain at the injection site with 151 cases. This result is congruent with research by Riad et al. (2021) where 731 of 877 people (89,80%) experienced pain at the injection site.[28] Research by Desnita et al. (2022) in Padang using 95 samples obtained similar results where the most common COVID-19 vaccine AEFI symptom in the local reaction group was pain at the injection site which was experienced by 70 people (73,70%) after the first primary dose vaccination and 65 people (69,00%) after second primary dose vaccination.[27] The research results by

Supangat et al. (2021) in Jember also showed that the most common local symptom of AEFI was pain at the injection which was experienced by 25 people (45%) after the first primary dose vaccination and 34 people (67%) after second primary dose vaccination.[31] Pain at the injection site arises because of vaccine liquid being injected intramuscularly, which can stretch the muscle fibers, thereby triggering an immune reaction in the form of inflammation. This inflammation is characterized by local pain which is usually accompanied by swelling and redness/erythema at the injection site.[38,39] Complaints of pain after vaccination can also arise as a physiological stress response from a vasovagal reaction which is not necessarily caused by the injected vaccine liquid, but rather due to tissue injury during the vaccine injection process.[40]

Table 9 Frequency Distribution Based on Reactions and Systems of AEFI and Types Of COVID-19 Vaccine Manufactures

AEFI Reactions and Symptoms	COVID-19 Vaccine Manufactures			
	Sinovac	AstraZeneca	Biofarma	Moderna
Local Reaction				
Pain at the injection site	103	5	8	34
Swelling	13	4	5	18
Systemic Reaction				
Fever	38	125	33	77
Drowsiness	153	2	11	5
Other Reaction				
Breathing Difficulty	8	14	4	2
Syncope	2	8	4	0
Total	317	158	65	136

Abbreviation: n = number of symptoms reports

The most frequently reported systemic reaction was fever with 278 cases. Fever can occur due to the existence of exogenous pyrogens (substances that cause fever) in the form of an immune reaction that stimulates leukocytes to produce endogenous pyrogens in the form of cytokines (IL-1, IL-6, IFN, dan TNF-α). These pyrogens stimulate the hypothalamus to produce prostaglandins which increase the thermostat benchmark in the hypothalamic thermoregulatory center so the hypothalamus will assume that the current temperature is lower than the latest thermostat standards. Compensation is carried out by increasing heat production thereby increasing body temperature to reach the newest thermostat standards.[41] These results are in line with research by Komici et al. (2023) in Italy where the most common systemic reaction was a fever experienced by 44 out of 460 people who had received the first dose vaccination and 17 out of 365 people who had received the second dose vaccination.[42] Research by Hartutik et al. (2022) in Surakarta also found that 37 out of 100 respondents (37%) experienced fever, which is the most common symptom.[36] Different results were found in research by Djanas et al. (2021) in Padang involving 840 respondents. It was found that the most common systemic AEFI symptom was myalgia which was experienced by 333 people.[43] Research by Menni et al. (2021) regarding the use of AstraZeneca and Pfizer in the UK also showed different results where the most common systemic AEFI symptom was a headache with 160.844 reported cases.[44] Differences in results can be influenced by many factors, such as differences in the dominant type of vaccine used between research locations. Although AEFI is most reported after administering Sinovac, most of the fever symptoms are reported after administering AstraZeneca (**Table 5** and **Table 9**). This might happen because AstraZeneca has quite high efficacy and is a viral vector vaccine, which makes it possible for the immune system to also react to its viral vector.[45] These results differences make it necessary to carry out further research to determine the

relationship between types of vaccines, doses, and AEFIs.

Another reaction that was frequently reported was breathing difficulty with 28 cases. Research by Abu-Hammad et al. (2021) in Jordan also got results that the most common reaction was breathing difficulty which was experienced by 19 people (4,6%).[46] Similar results were also obtained in a research by Alkhalifah et al. (2023) in Saudi Arabia where from a total sample of 28.031 people, there were 1.736 people (6,19%) who experienced breathing difficulty.[47] Breathing difficulty can occur as an immune response. Another source states that breathing difficulty could be related to immunization stress-related responses (ISRRs), which is one of the AEFIs that is not caused by the components contained in the vaccine, but rather by the vaccination process itself.[48]

CONCLUSION

Adverse events following immunization of COVID-19 vaccine in Bali in the period of January 2021 – December 2022 were mostly experienced by women, aged 18-29 years, and domiciled in Denpasar. The majority of AEFI reports were received from hospitals, after the Sinovac vaccination, and after the first primary dose vaccination. The most frequently reported AEFI was non-serious AEFI with the most common symptoms were pain at the injection site for local reactions, fever for systemic reactions, and breathing difficulty for other reactions.

Declaration by Authors

Ethical Approval: This research was approved by the Ethics Committee of the Faculty of Medicine Udayana University (No: 240/UN14.2.2.VII.14/LT/2023).

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