Adverse events following immunisation of COVID-19 vaccine among health care workers in the first phase of vaccination

Norhayati Rahmat, MD[1], Leelavathi Muthupalaniappen, MMed Fam Med[2], Wan Fadhilah Wan Ismail, MMed Fam Med[1]

[1]Klinik Kesihatan Mahmoodiah, Ministry of Health Malaysia, Johor Bahru, Johor, Malaysia, [2]Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Bandar Tun Razak, Cheras, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: The new COVID-19 vaccine was met with worldwide overwhelming uncertainties pertaining to its safety profile, effectiveness, and potential adverse reactions when it was first introduced. This led to vaccine refusal and delay in vaccine uptake in many countries including Malaysia. The objective of this study was to determine the Adverse Events Following Immunization (AEFI) to the COVID-19 vaccine.

Materials and methods: A retrospective cross-sectional study was conducted among healthcare workers who received the COVID-19 vaccine during the first phase of immunisation from eight public primary clinics in Johor Bahru district. Data were collected between May and September 2021 using a self-administered questionnaire.

Results: A total of 240 healthcare workers participated and all of them received the Pfizer Messenger RNA vaccine. Our study found that a large majority of vaccine recipients (87.5%, n=210) experienced AEFI to COVID-19 vaccine for either the first, second, or both doses. More than 80% of them experienced more than one type of AEFI. The most common AEFI reported during the first and second dose was localised symptom such as pain at injection site (60–68%), pain on the injected arm (52–61%), and swelling at injection site (32–33%). Common systemic symptoms were fever (22–57%), myalgia (20–45%), and dizziness (24–26%). Although a large majority experienced AEFI, these reactions were mostly of mild to moderate severity (47.3–73.6%). The mean duration of AEFI onset was within 30 minutes to about 1 day (0.33–22.5 hours) of injection and lasted between 30 minutes and 2.5 days. There was no association between demographic characteristic of participants and severity of AEFI to COVID-19 vaccine. Mean duration of fever was significantly (p=0.005) longer after the second dose (34.2 hours) of vaccine compared to first (20.6 hours)

Conclusion: This study shows that a large majority of COVID-19 vaccine recipients experienced AEFI; however, these reactions were mostly of mild to moderate severity and lasted between 30 minutes and 2.5 days. A large majority experienced more than one type of AEFI. The most common AEFI was localised reactions consisting of pain and swelling at the injection site and pain on the injected arm. The most common systemic reactions were fever, myalgia, and dizziness. Duration of fever was significantly longer after the second dose.

KEYWORDS:
Adverse events, immunization, COVID-19, COVID-19 vaccines, injection site reaction

INTRODUCTION

COVID-19 became a pandemic and affected more than 120 countries, causing millions of deaths and affected the global economy.[1] Given the seriousness of the disease, many pharmaceutical companies joined the rat-race in developing a safe and effective vaccine to combat the COVID- 19 disease. In November 2020, Food and Drug Administration authorised the emergency use of the Pfizer-BioNTech COVID-19 to curb the spread of COVID-19.[2]

Immunisation has been recognized as one of the advanced preventive measures in public health.[3] If used correctly, all vaccines in the national immunisation programs are safe and effective. However, no vaccine is free from risk, and adverse reactions may occasionally occur after immunisation. Adverse events may range from mild side effects to serious reactions. These events may cause public concern about the safety of vaccines and affect vaccine acceptability.[4] An adverse event following immunisation is any untoward medical occurrence which follows immunisation and which may not necessarily have a causal relationship with the usage of the vaccine.[5]

In Malaysia, the Ministry of Health (MOH) implemented the first phase of the National COVID-19 vaccination programme in February 2021. The target was to vaccinate 25.6 million populations nationwide. This vaccination programme was carried out in three phases starting with medical and non-medical front line workers in phase one, high risk population in phase two and the rest of the population in phase three.[6]

Some of the concerns regarding the COVID-19 vaccine were pertaining to the safety, efficacy, and side effects as this was a new vaccine which was developed in a short span of time. Early studies have shown that one of the reasons for vaccine

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Corresponding Author: Leelavathi Muthupalaniappen
Email: drleelaraj@gmail.com

hesitancy, was due to concerns about the safety of COVID-19 vaccine pertaining to Adverse Events Following Immunization (AEFI).[7] Although experiences from other countries have shown that the AEFI related to the COVID-19 vaccine was low, there is a need to report and describe the vaccine experience in our local setting. Hence the aim of this study was to determine the incidence, type, severity, and factors affecting adverse events of COVID-19 vaccine among phase one recipients who were the first to receive this vaccine in Malaysia. The study also sought to determine the difference in AEFI severity between the first and the second doses of the vaccine. This data will be useful to study the local response to the vaccine and help dissipate fears regarding the side effects of COVID-19 in Malaysia.

MATERIALS AND METHODS

This is a retrospective cross-sectional study conducted among healthcare workers from eight public primary care clinics in Johor Bahru district between May and September 2021. Clinics were randomly selected using the ballot box method. Participants included doctors, pharmacist, medical assistant, dental assistants, pharmacist assistant, matron, nurse, health care assistants, medical laboratory technologist, administrative officer, ambulance driver and essential service, defence, and security personnel. Participants who were 18 years and above and completed two doses of the vaccine were approached using convenient sampling method. The main tool used in this study was a self-administered paper-based questionnaire developed from literature research.[8] An expert panel consisting of the researcher and two family medicine specialists, looked the suitability, and content validity of the questionnaire. The questionnaire was then translated forwards and backwards by two linguists to Bahasa Melayu and subjected to face validity among 20 participants from a health clinic of a similar setting. One item was suggested to be edited by the participants where the option for the initial response after the injection from "after 30 minutes" to "within 30 minutes" as some of them experienced reactions within this time frame. Some minor language adjustments were also made as suggested by the participants to facilitate an easy understanding of the questionnaire.

The questionnaire had two sections A and B. Section A contained demographic information such as age, gender, ethnicity, occupation health status of participant, such as previous history of COVID-19 infection, past medical, and drug allergy history. Participants were also asked if they had been informed regarding the possible side effects of the vaccine. The answers for this section were selected from the options provided or written in by the participants.

Section B contained 23 statements which describe the details of both the first and second vaccination such as dates, type of reaction, onset, overall perceived severity of the reaction, duration, and whether the reactions were reported, warranted treatment, required sick leave, or hospitalisation.

Severity of AEFI, was classified as mild, moderate, and severe based on participants self-report on how these events affected their daily activities. Mild adverse events were defined as events which did not interfere with their daily activity, moderate adverse events were those which interfered with their daily activity while severe adverse events were those which limited or restricted their daily activity.[5,9] For each question, participants either selected from the list of options provided or wrote in their responses.

Sample size was calculated using Open Epi programme calculator based on previous reported AEFI prevalence of 0.2% using the formula n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)] taking 95% confidence level and 20% added for incomplete response requiring a total of 238 participants.[8,10]

This study was approved by Universiti Kebangsaan Malaysia Research Ethics Committee and Institute of Medical Research Ethics Committee. This project was registered with the National Medical Research Registration (NMRR-21-1025-59179). Data were analysed using SPSS version 27 descriptive statistics and associations using Chi-square test and T-test (Mann–Whitney U test)

RESULTS

A total of 240 health front-line workers agreed to participate in this study. The median age of participants was 32 years with the youngest being 24 and the oldest being 55 years of age. Majority were females (87.5%, n=201), worked as nurses (32.1%, n=77) and belonged to the Malay ethnic group (77.1%, n=185). All participants received the Pfizer Messenger RNA vaccine for the first and second dose, while only one participant received Sinovac for the second as he developed anaphylaxis with the first dose of Pfizer mRNA vaccine. Most (80.3%, n=191) of them did not have any previous history of drug allergy and did not have any underlying medical conditions (86.1%, n=205). Almost all participants (98.8%, n=237) received information regarding possible vaccine-related adverse reaction prior to vaccination.

The overall incidence of AEFI (for either first or second dose) of COVID-19 vaccine was 87.5 % (n=210) meaning the majority who received the vaccine experienced some form of AEFI. Majority (> 80%) of the vaccine recipients also reported more than one type of AEFI. The most common AEFIs reported during the first and second dose were pain at injection site (60–68%), pain on the injected arm (52–61%), and fever (57%). The AEFIs experienced for the first and second doses of the COVID-19 vaccine were almost similar. Only three participants required hospital admission, out of which one was due to anaphylactic shock. But all three had a complete recovery and were discharged well (Table I).

Although a large majority of participants experienced AEFI to COVID-19 vaccine, these reactions were mostly reported as mild (47.3–73.6%), did not require sick leave (94.8%) or hospital admission (98.2%). About 60% took self-medication after the second dose of vaccine. Only 13.5 to 23.0% reported severe reaction. Only half of the participants (53.4%, n=93) reported the AEFIs at the MySejahtera Application (Table II).

The mean duration for onset for AEFI to COVID-19 vaccine ranged from, within 30 minutes of injection to about 1 day (0.33 to 22.5 hours) and lasted between 30 minutes and 2.5

Table I: Frequency and type of AEFI for 1st and second doses of COVID-19 vaccine

Types of AEFI reported			
1st dose		2nd dose	
AEFI	% (n)	AEFI	% (n)
Pain at injection site	68.9 (120)	Pain at injection site	60.0 (104)
Pain on the entire arm	60.9 (107)	Fever	57.2 (99)
Swelling at injection site	33.7 (59)	Pain on the entire arm	52.3 (91)
Dizziness	24.0 (42)	Myalgia	44.8 (78)
Fever	22.2 (39)	Chills	39.1 (68)
Myalgia	19.4 (34)	Swelling at injection site	32.2 (56)
Chills	16.0 (28)	Arthralgia	30.1 (52)
Headache	14.2 (25)	Headache	27.0 (47)
Arthralgia	12.0 (21)	Dizziness	25.7 (44)
Nausea	10.3 (18)	Nausea	9.7 (17)
Vomiting	1.7 (3)	Vomiting	4.0 (7)
Rashes	1.1 (2)	Diarrhoea	1.1 (2)
Fainted	0.5 (1)	Rashes	0.6 (1)
Anaphylactic shock	0.5 (1)	Fainted	0 (0)
Diarrhoea	0 (0)	Anaphylactic shock	0 (0)
Others	4.5 (8)	Others	6.9 (12)

Table II: Severity and reporting of AEFI to COVID-19 vaccine

1st Dose	% (n)	2nd Dose	% (n)
Severity level (self-reported)		**Severity level (self-reported)**	
Mild	73.6 (126)	Mild	47.3 (78)
Moderate	12.9 (22)	Moderate	29.7 (49)
Severe	13.5 (23)	Severe	23.0 (38)
Took self-medication for AEFI		**Took self-medication for AEFI**	
Yes	37.8 (65)	Yes	60.2 (103)
No	62.2 (107)	No	39.8 (68)
Took sick leave for AEFI		**Took sick leave for AEFI**	
Yes	5.2 (9)	Yes	15.8 (27)
No	94.8 (163)	No	84.2 (144)
AEFI requiring hospital admission		**AEFI requiring hospital admission**	
Yes	1.8 (3)	Yes	0.6 (1)
No	98.2 (167)	No	99.4 (170)
Reporting of AEFI (to doctor/ MySejahtera)		**Reporting of AEFI (to doctor/ MySejahtera)**	
Yes	53.4 (93)	Yes	60.2 (103)
No	46.6 (81)	No	39.8 (68)

Table III: Onset and duration of AEFI to COVID-19 vaccine in mean hours for 1st and 2nd dose

AEFI	Onset of AEFI (in mean hours)				Duration of AEFI (in mean hours)			
	1st dose	2nd dose	t statistics *(df)*	*p* value	1st dose	2nd dose	t statistics *(df)*	*p* value
Pain at injection site	17.7	18.2	-0.47 (71)	0.963	48.2	49.7	-0.103 (60)	0.918
Swelling	20.3	21.1	0.52 (39)	0.605	52.9	52.6	0.686 (32)	0.498
Dizziness	12.0	9.2	1.8 (20)	0.081	17.3	23.4	-0.682 (20)	0.503
Fever	20.6	20.4	-0.66 (23)	0.515	20.6	34.2	-3.1 (2.2)	0.005
Myalgia	19.5	21.5	1.59 (15)	0.132	38.4	50.3	-1.699 (15)	0.110
Chills	19.1	18	-1.7 (12)	0.116	21.1	26.5	-0.99 (33)	0.338
Headache	15.7	11.8	-0.01 (7)	0.991	35.1	15.2	1.022 (4)	0.365
Arthralgia	18.3	21.1	-0.18 (7)	0.991	41.3	56.3	-1.17 (8)	0.276
Nausea	12.8	14.7	-1.19 (5)	0.286	33.4	24.6	0.364 (5)	0.730
Vomiting	13.0	17.2	-	-	16.2	24.2	-	-
Rashes	168.0				732			
Fainted	1.0				0.5			
Anaphylactic shock	0.33				24			
Pain on arm injected arm	19.6	22.5	1.8 (51)	0.075	46.9	52.9	-0.910 (51)	0.367

Table IV: Association between demographic factors and AEFI to COVID-19 vaccine

Demographic data	AEFIs (dose 1 + dose 2)		Test	*p* value
	Yes % (n)	No % (n)		
Age group				
< 40 years	87.9 (182)	12.1(25)	c^2	
≥40years	84.8 (28)	15.2(5)	0.246	0.577
Gender				
Male	20 (6)	80 (24)	c^2	
Female	88.6 (186)	11.4 (24)	1.763	0.232
Ethnic group				
Malay	88.6 (164)	11.4(21)	c^2	
Non-Malay	83.6 (46)	16.4 (9)	0.974	0.324
Previous COVID-19 infection				
Yes	80 (16)	20 (4)	c^2	
No	88.6 (194)	11.4 (25)	1.267	0.279
Previous allergy (any)				
Yes	85.1 (40)	14.9 (7)	c^2	
No	88.5 (169)	11.5 (22)	0.385	0.535
Medical problems (any)				
Yes	81.8 (27)	18.2 (6)	c^2	
No	88.8 (182)	11.2 (23)	1.288	0.256

Table V: Association between demographic factors and severity of AEFI to COVID-19 vaccine

Participant Character	AEFI severity 1st dose		Test	*p* value	AEFI severity 2nd dose		Test	*p* value
	Mild & Moderate % (n)	Severe % (n)			Mild & Moderate % (n)	Severe % (n)		
Age group								
< 40 years	87.2 (130)	12.8 (19)	c^2		77.4 (113)	22.6 (33)	c^2	
≥40years	81.8 (18)	18.2 (4)	0.486	0.486	73.7 (14)	26.3 (5)	0.131	0.718
Gender								
Male	83.3 (15)	16.7 (3)	c^2		73.3 (11)	26.7 (4)	c^2	
Female	86.9 (133)	13.1 (20)	0.179	0.672	77.3 (116)	22.7 (34)	0.123	0.726
Ethnic group								
Malay	87.1 (115)	12.9 (17)	c^2	0.695	76.2 (99)	23.8 (31)	c^2	
Non-Malay	84.6 (33)	15.4 (6)	0.162		80 (28)	20 (7)	0.230	0.631
Previous COVID-19 infection								
Yes	90.9 (10)	9.1 (1)	c^2		83.3 (10)	16.7 (2)	c^2	
No	86.3 (138)	13.8 (22)	0.192	0.661	76.5 (117)	23.5 (36)	0.296	0.587
Previous allergy (any)								
Yes	87.5 (28)	12.5 (4)	c^2		68.8 (22)	31.3 (10)	c^2	0.227
No	86.3 (120)	13.7 (19)	0.031	0.861	78.8 (104)	21.2 (28)	1.458	
Medical problems (any)								
Yes	84.25 (16)	15.8 (3)	c^2		66.7 (12)	33.3 (6)	c^2	
No	86.8% (131)	13.2% (20)	0.093	0.76	78.1% (114)	21.9% (32)	1.173	0.279

days (30 min to 56 hours). Pain at the injection site which was the most common AEFI, was usually experienced after 17–18 hours of injection and lasted for about 2 days. There was no significant difference in the onset of the AEFI between the first and second doses but the duration of fever experienced after the second dose was significantly longer (p=0.005)(Table III).

There was no association between demographic characteristic of participants and AEFI to COVID-19 vaccine (Table IV).

Analysis for association between demographic characteristic of participants and severity of AEFI to COVID-19 vaccine also showed no significance (Table V).

DISCUSSION

There has been much apprehension and hesitation for the COVID-19 vaccination acceptance as it is a new vaccine and was developed over a short period of time to fight the pandemic. Hence, there is much emphasis on monitoring the efficacy and possible AEFIs related to the COVID-19 vaccines. Our study found that a large majority (87.5 %) of recipients developed AEFI to the COVID-19 vaccine (Pfizer BioNTech) and most (>80%) of them experienced more than one type of reaction. This was similar to the findings from a metanalysis which showed that adverse events related to the COVID-19 vaccines ranged between 21 and 90% with higher percentage of reactions with mRNA vaccines. In Malaysia, almost 25,000 adverse events related to the COVID-19 vaccine were reported by The National Pharmaceutical Regulatory Agency (NPRA) by the end of January 2022.[11]

This study found that the most common (50–70%) AEFI to the Pfizer mRNA COVID-19 vaccine were localised symptoms such as pain at injection site, pain on the injected arm, and swelling at injection site. Similarly, a study in Ontario found that the most common reported adverse events were allergic skin reaction and injection site pain or swelling, 31.6% and 21.2%, respectively.[12] These findings are also similar to the common AEFIs recorded by CDC (Centres for Disease control and Prevention) and NPRA which are pain at injection site and muscle ache.[11,13] Pain at the injection site was also the most common reaction followed by headache and fatigue reported worldwide.[14] The common adverse event reported for Pfizer-BioNTech COVID-19 vaccine were injection site pain, swelling and redness, tiredness, headache, muscle pain, chills, joint pain, fever, nausea, feeling unwell, and lymphadenopathy.[13,15] However, the localised symptoms experienced by our study participants were not associated with recipient characteristics. There is inconsistency in the available literature pertaining to the relationship between the adverse events experienced and participant characteristics. The CDC reported that younger recipients (age 18–55 years) experienced pain more frequently compared to older participants (>55 years) for both first and the second dose of vaccine.[13] However, a study in Indonesia found that age, gender, previous COVID-19 infection, previous allergy, and past medical history did not affect AEFI occurrence whether the participants were vaccinated with either Pfizer-BioNTech, Sinovac, or Oxford–AstraZeneca vaccine (Covishield).[16]

The most common systemic adverse events of the vaccine reported in our study was fever, dizziness, and myalgia for both first and second dose vaccine. These systemic adverse events also did not show any association with recipient characteristics. The common systemic adverse events recorded by CDC to this vaccine were fatigue, headache, and new or worsened generalised muscle pain which was more among the younger age group and after the second dose.[13] Common systemic adverse events reported in Malaysia by the NPRA were fever, headache, and Immunisation Stress-Related Response (ISRR).[11] ISSR is a response to the stress that individuals may feel regarding getting an injection which includes vasovagal reaction, fainting, hyperventilation, or non-epileptic seizures. These reactions were previously known as "AEFI arising from anxiety about the immunisation").[17]

Comparing other COVID-19 vaccines, such as the inactivated virus, Sinovac life sciences Co, the localised symptom such as pain at the injection site was also the most common localised AEFI. While the most common systemic AEFI with this vaccine was malaise.[16] AEFI due to another widely used vaccine, the Oxford–AstraZeneca recombinant vaccine, Covishield, affecting about 50% of recipients with majority (37%) experiencing localised symptoms of swelling and pain at the injection site and fever (25%) as the main systemic symptoms.[18] Among the more serious AEFIs, anaphylaxis is a life-threatening response that requires emergency treatment. Fortunately, only one recipient in our study developed anaphylaxis with the first dose and was given Sinovac vaccine (inactivated virus) for the second dose. Although rare, continued monitoring of the anaphylaxis AEFI due to Pfizer-BioNTech COVID-19 is essential for further research and development.[10]

Although a large majority of vaccinated individuals in our study experienced some type of AEFI, most of these reactions were reported as mild (47.3–73.6%) to moderate (12.9–29.7%) hence not requiring sick leave, hospital admission, or causing severe limitation of activity. Similarly, other studies looking at the COVID-19 mRNA vaccine also showed that that most of the local or systemic adverse reactions were non-severe with about only 2–22% of cases being severe.[12,19,20,21] Most of the recipients of the Oxford–AstraZeneca vaccine (Covishield) in a study from Bangladesh also reported mild to moderate severity of the AEFI.[18] Similarly, in Ontario, 99.0% of AEFI reported were non-serious.[12]

The mean duration for onset for AEFI to COVID-19 vaccine in our study, ranged within 30 minutes and about 1 day (0.33–22.5 hours) and reactions mostly lasted between 30 minutes and 2.5 days. Pain at the injection site, which was the most common AEFI was commonly experienced after 12 hours of receiving the vaccine and lasted for about 2.5 days. The median time of local reaction onset recorded by CDC was from the day of vaccine receipt, up to 2 days and lasted between 1 and 2 days.[13] Another study by Chen et al. also found a similar presentation.[19] The median interval for symptom onset of non-anaphylactic adverse reactions for the Pfizer-BioNTech COVID-19 vaccine in an earlier local study was similar to our findings.[10] Shimabukuro et al. found that the median interval for anaphylactic reaction was 13 minutes.[22] Our study also found that the mean duration of fever experienced after the second dose vaccine was significantly longer compared to the first dose. In general, the severity of AEFI to vaccines is anticipated to be more with the second dose; however, these reactions may be unpredictable. This is because there are multiple factors affecting AEFIs due to the complex immune system activation which gets triggered when the vaccine is instituted into the system.[23]

LIMITATIONS

This study was based on self-reported adverse reaction to the vaccine hence other possible causes for the symptoms could not be verified. Recall bias cannot be excluded, as data were collected between 2 weeks after the first dose up to the following 5 months during which the participants received their second dose. Most vaccine recipients probably anticipated to experience AEFI as almost all (98.8%, n=237) of them received information regarding possible vaccine-related adverse events. This heightened awareness could have influenced the self-reported symptoms related to ISRR. Convenience method of sampling could have contributed to selection bias; hence the findings may not be generalisable.

CONCLUSION

This study shows high rates (87.5%) of AEFI with the COVID-19 mRNA vaccine (Pfizer-BioNTech) and the majority of recipients experienced more than one reaction. However, it is reassuring that most of these reactions were reported as mild to moderate severity. A large majority of these reactions

started within 1 day of the injection and were transient, lasting between 30 minutes and about 2.5 days. Pain at injection site, pain on the injected arm, and swelling at injection site were the most common localised symptoms while fever, myalgia, and dizziness were the most common systemic symptoms. Duration of fever was significantly longer after the second dose of vaccine compared to the first.

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This study was self-funded, and we declare no conflicts of interest.

ETHICAL APPROVAL

The ethical approval was obtained from Medical Research & Ethics Committee's (MREC), Ministry of Health Malaysia, and Research Ethics Committee of Universiti Kebangsaan Malaysia

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