Research Article

Factors Affecting Adverse Events Following SARS-CoV-2 Vaccine among Indonesian Ear, Nose, and Throat Specialist, and Residences

Susyana Tamin,[1]* Jenny Bashiruddin,[1] Indra Zachreini,[2] Harim Priyono,[1] Ika D. Mayangsari,[1] Respati Ranakusuma,[1] Natasha Supartono,[1] Khoirul Anam,[1] Anggina Diksita,[3] Yussy A. Dewi,[4] Sagung R. Indrasari,[5] Nyilo Purnami,[6] TSH Haryuna,[7] Juliandi Harahap,[7] Eka Savitri,[8] Tjandra Manukbua[9]

[1]Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo General Hospital, Jakarta
[2]Faculty of Medicine, Malikussaleh University – Cut Meutia Hospital, North Aceh
[3]Proklamasi Ear, Nose, and Throat – Head and Neck Surgery, Jakarta
[4]Faculty of Medicine, Padjajaran University – Hasan Sadikin General Hospital, Bandung
[5]Faculty of Medicine, Gajah Mada University – Sardjito General Hospital, Yogyakarta
[6]Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital, Surabaya
[7]Faculty of Medicine, University of Sumatera Utara – H. Adam Malik General Hospital, Medan
[8]Faculty of Medicine, Universitas Hasanuddin / Wahidin Sudirohusodo Hospital, Makassar
[9]Lakipadada District Hospital, Makale, Tana Toraja

*Corresponding author: usyana@yahoo.com
Received 6 April 2022; Accepted24 August 2022
http://doi.org/10.23886/ejki.10.165.129

Abstract

This study's objectives were to investigate factors affecting the adverse events of the COVID-19 vaccine in Indonesia among health care workers and compare adverse events following SARS-CoV-2 vaccine using CoronaVac as the first and second dose and Moderna used as the booster third dose. A cross-sectional study was conducted using the Self-reporting Online Survey Platform (Google Form) from August to October 2021. Subjects included in the study were ENT specialists and residents all over Indonesia who had been vaccinated with both doses of CoronaVac COVID-19 vaccine and Moderna COVID-19 vaccine as a booster dose. Among a total of 1394 participants, 51.2% and 43.7% of subjects experienced adverse events following the first and second dose of the CoronaVac vaccine. Adverse events are significantly higher following the third dose of Moderna vaccine (95.3%) with p-value <0.001, odds ratio (OR) 26.63 (95% CI 19.87-35.7). Adverse events following the CoronaVac vaccine were significantly higher in females and individuals with comorbidities in the first dose (p=0.002 and p=0.04), and the second dose (p=0.008 and p=0.042). Adverse events following the Moderna vaccine were significantly higher in females (p=0.01) and lower in individuals ≥40 years of age (p=0.017). Comorbidity status did not affect adverse events following the Moderna vaccine.

Keywords: *adverse events, SARS-CoV-2, COVID-19, vaccine, otorhinolaryngology.*

Faktor yang Mempengaruhi Efek Samping Vaksin SARS-CoV-2 terhadap Dokter Spesialis dan Residen Telinga, Hidung, dan Tenggorok di Indonesia

Abstrak

Penelitian ini bertujuan untuk mengetahui faktor-faktor yang mempengaruhi efek samping vaksin COVID-19 di Indonesia pada petugas kesehatan dan membandingkan efek samping setelah vaksin SARS-CoV-2 menggunakan CoronaVac sebagai dosis pertama dan kedua dan Moderna sebagai booster dosis ketiga. Studi potong lintang dilakukan dengan menggunakan self-reporting survei online (Google Form) dari Agustus-Oktober 2021. Subjek yang termasuk dalam penelitian adalah dokter residen dan spesialis THT di Indonesia yang telah divaksinasi dengan kedua dosis vaksin CoronaVac COVID-19 dan vaksin Moderna COVID-19 sebagai dosis tambahan. Dari total 1394 peserta, 51,2% dan 43,7% subjek mengalami efek samping setelah dosis pertama dan kedua vaksin CoronaVac. Efek samping secara signifikan lebih tinggi setelah dosis ketiga vaksin Moderna (95,3%) dengan p-value <0,001, rasio odds (OR) 26,63 (95% CI 19,87-35,7). Efek samping setelah vaksin CoronaVac secara signifikan lebih tinggi pada wanita dan individu dengan penyakit penyerta pada dosis pertama (p=0,002 dan p=0,04), dan dosis kedua (p=0,008 dan p=0,042). Efek samping setelah vaksin Moderna secara signifikan lebih tinggi pada wanita (p=0,01), dan lebih rendah pada individu ≥ 40 tahun (p=0,017). Status komorbiditas tidak mempengaruhi efek samping setelah vaksin Moderna.

Kata kunci: *efek samping, SARS-CoV-2, COVID-19, vaksin, otorinolaringologi.*

Introduction

COVID-19 pandemic had led the global socioeconomic into a severe condition since its early cases were found in Wuhan by the end of 2019, as well as morbidity and mortality throughout the world.[1,2] United Nations Development Programme (UNDP) reported around ten million jobs and livelihoods have been lost.[2] Thus, the pandemic should be controlled as soon as possible to prevent further casualties. To control the pandemic, herd immunity, known as the indirect protection from an infectious disease that occurs when a significant proportion of a population is immune, should be achieved, either through vaccination or immunity developed through the previous infection.[3] Vaccination was considered to be effective and promising to control the pandemics as this plays a crucial role in breaking the transmission chain of SARS-CoV-2 infections.[1,3] Several vaccines had been manufactured on different modalities, such as mRNA, viral vectors, peptide-based, live attenuated, and inactivated virus.[3]. By early 2021, there are several SARS-CoV-2 vaccines available for public; Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and CoronaVac. These vaccines have undergone phase I and II trials, and based on their safety and efficacy, it was subjected to emergency use approval in many countries, including Indonesia. Still one of the major concerns regarding the COVID-19 vaccine was its safety, and vaccine side effects can increase hesitancy levels among individuals.[4,5]

In January 2021, Indonesia started its first SARS-CoV-2 vaccine program, starting with health care workers and the elderly being prioritized in the first phase. Health care workers are prioritized based on their risk of exposure. The first available vaccine in Indonesia is the CoronaVac vaccine (Sinovac Life Sciences, Beijing, China). With the emerging COVID-19 second wave of infection in Indonesia back in July 2021, some health care workers are still being transmitted with COVID-19 after vaccination, causing an increase in health care workers died due to COVID-19.[6,7] A study by Yigit et al[8] found that about one-fifth of the healthcare workers were seronegative in 2 months after the second dose of CoronaVac vaccine. Applying a booster dose after two doses of CoronaVac is recommended to preserve the continuity of herd immunity, especially in risk groups, including healthcare workers.[8] The Indonesian Health Ministry decided to start the SARS-CoV-2 vaccine booster program using Moderna, prioritized for healthcare workers back in August 2021. This program aimed to minimize transmission and reduce COVID-19 mortality among Indonesian health care workers.[6,7]

This study's primary objective was to investigate the factors affecting the adverse events of the COVID-19 vaccine in Indonesia among health care workers. The secondary objective was to compare adverse events following the SARS-CoV-2 vaccine using CoronaVac as the first and second dose and Moderna used as the booster third dose.

Methods

A cross-sectional study was conducted from August 2021 to October 2021. We gathered data from Ear, Nose, and Throat (ENT) Specialists and Residents all over Indonesia using the Self-reporting Online Survey Platform (Google Form). The self-reported questionnaire consisted of 30 multiple-choice questions, divided into three main sections: participant's identity, SARS-CoV-2 vaccine status (including time and place of vaccination, vaccine type, the interval between doses), and vaccine adverse events. The questionnaire was created and had been validated and adapted socio-culturally.

Subjects included in the study were ENT specialists and residents who had been vaccinated with both doses of CoronaVac COVID-19 vaccine and Moderna COVID-19 vaccine as a booster dose. All subjects included in this study are Indonesian, working as health care workers in various types of hospitals in Indonesia. Informed consent was obtained from all participants. Participants were unwilling to participate in the research, and participants with ambiguous questionnaire answers were excluded from the analysis. The study was conducted and reported following the recommendations stated in the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria for a cross-sectional study. This study was approved by the Committee of Medical Research Ethics of the Faculty of Medicine Universitas Indonesia (No: KET-188/UN2.F1/ETIK/PPM.00.02/2022), with regard to the protection of human rights and welfare in medical research. The participants provided written informed consent before study participation.

All data gathered were recorded electronically, and measures were taken to ensure the non-disclosure of participants' information. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS). The data were evaluated using the descriptive statistical method and presented by frequency and percentage. Bivariate statistics were carried out to evaluate factors affecting vaccine adverse events using the Chi-squared test, with a confidence level of 95% and a significance level of $p \leq 0.05$. Bivariate analysis data were presented

in a table using frequency, percentage, p-value, odds ratio, and confidence interval. Variables with a significance level of ≤ 0.25 were then included in the multivariate analysis to generate a model of adverse events predictor following the SARS-CoV-2 vaccine.

Table 1. Demography Characteristics of the Subjects (n=1394)

Characteristics	Frequency (%)
Sex	
Female	759 (54.4)
Male	635 (45.6)
Age	
<40 years old	749 (53.7)
≥ 40 years old	645 (46.3)
Work Status	
Resident	424 (30.4)
Specialist	970 (69.6)
Vaccine Place	
Hospital	1304 (93.5)
Primary Care	81 (5.8)
Clinic	9 (0.6)
Previous COVID-19 infection	
Before 1st Vaccine	184 (13.1)
Between 1st and. 2nd Vaccine	18 (1.2)
Between 2nd and 3rd Vaccine	191 (13.7)
Never Been Infected	1001 (71.8)
Number of Comorbidities	
0	1060 (76)
1	274 (19.7)
2	48 (3.4)
3	9 (0.6)
4	3 (0.2)
Comorbidity	
Cardiovascular Disease	42 (13.0)
Asthma	90 (72.8)
Kidney Disease	9 (2.8)
Hypertension	162 (50)
Liver Disease	8 (2.5)
Diabetes	61 (18.8)
Autoimmune Disease	16 (4.9)
Hypercoagulation	10 (3.1)
Pregnancy	11 (3.3)
Vaccine Dose	
First Dose (CoronaVac)	1394 (100)
Second Dose (CoronaVac)	1394 (100)
Third Dose (Moderna)	1170 (83.9)

Results

Demographic Characteristics of Participants

This study recruited 1394 participants for final analysis. Out of all participants, 54.4% were females, and 53.7% were below 40 years old. The majority of participants lived and worked as health care workers in Jakarta (11.2%) and North Sumatra (10.6%), and the others were distributed among 32 provinces.

Table 2. Adverse Events Following the First, Second, and Third Dose of Vaccine

Adverse Events	Frequency (%)
Each dose	
Adverse Events Following First Dose (CoronaVac)	713(51.2)
Adverse Events Following Second Dose (CoronaVac)	609 (43.7)
Adverse Events Following Third Dose (Moderna)	1116 (95.3)
Adverse Events Following First Dose (CoronaVac) Duration	
No Adverse Events	681 (48.9)
<24 hours	385 (27.6)
24-48 hours	276 (19.8)
48-62 hours	32 (2.3)
>62 hour	20 (1.4)
Adverse Events Following Second Dose (CoronaVac) Duration	
No Adverse Events	785 (56.3)
<24 hours	384 (25)
24-48 hours	219 (15.7)
48-62 hours	25 (1.8)
>62 hour	17 (1.2)
Adverse Events Following Third Dose (Moderna)	
No Adverse Events	54 (4.6)
<24 hours	79 (6.8)
24-48 hours	674 (57.6)
48-62 hours	290 (24.8)
>62 hour	73 (6.2)

Table 1 shows that 93.5% of respondents received vaccines at the hospital where they worked. Three hundred ninety-three out of 1394 (28%) participants were previously infected with COVID-19, with the most being infected before receiving the first vaccination (13.1%) and after receiving both vaccines (13.7%). Only 1.2% were infected after the vaccination.

Three hundred thirty-four out of 1394 (23.9%) participants have ≥1 comorbidities, including asthma (72.8%) and hypertension (50%), also Cardiovascular, kidney, liver, autoimmune disease, and Diabetes with a smaller percentage. All participants had received two doses of the SARS-CoV-2 vaccine, and 1170 out of 1394 participants (83.9%) had received a booster dose (Table 1).

Post SARS-CoV-2 Vaccine Adverse Events

Seven Hundred thirteen (51.2%) and 609 (43.7%) out of 1394 participants experience adverse events following the first and second dose of the CoronaVac vaccine. Adverse events are significantly higher following the third dose of Moderna vaccine (95.3%) with p-value <0.001, odds ratio (OR) 26.63 (95% CI 19.87-35.7).

This first and second dose adverse events were experienced mostly for less than 24 hours following the injection (27.6% in the first dose, and 25% in the second dose). On the other hand, the adverse events following the third Moderna dose are mostly experienced between 24-48 hours after vaccine injection (57.6%) (Table 2).

The most common adverse events were muscle pain in the injection site from either CoronaVac (56.3%) in the first dose, 61.4% in the second dose, or Moderna vaccine (92.7%). The next most common adverse events following the CoronaVac vaccine are severe drowsiness (42.8% in the first dose, and 26.8% in the second dose) and fatigue (18.7% in the first dose, and 14.6% in the second dose). Following the Moderna vaccine, the next most common adverse events are fever ≤39°C (57.8%), myalgia (49.6%), arthralgia (35.8%), and headache (32.4%) (Table 3).

Table 3. Symptoms of Adverse Events Following the First, Second, and Third Dose of Vaccine among Indonesian Health care Workers

Symptoms	Frequency* (%)		
	First Dose	Second Dose	Third Dose
Pain in the injection site	401 (56.3)	374 (61.4)	1034 (92.7)
Swollen injection site	7 (1.0)	10 (1.6)	391 (35)
Redness in the injection site	14 (2.0)	11 (1.8)	226 (20.3)
Itchiness in the injection site	6 (0.8)	5 (0.8)	114 (10.2)
Headache	54 (7.6)	45 (7.4)	362 (32.4)
Myalgia	77 (10.8)	63 (10.3)	553 (49.6)
Arthralgia	46 (6.5)	34 (5.6)	399 (35.8)
Shiver	12 (1.7)	11 (1.8)	371 (33.2)
Severe Drowsiness	305 (42.8)	163 (26.8)	142 (12.7)
Nausea and Vomiting	17 (2.4)	14 (2.3)	112 (10)
Swollen Axillary Area	8 (1.1)	-	54 (4.8)
Fatigue	133 (18.7)	89 (14.6)	293 (26.3)
Hunger	245 (17.6)	131 (21.5)	94 (8.4)
Dizziness	37 (5.2)	26 (4.3)	158 (14.2)
Fever < 39^0 C	58 (8.1)	28 (4.6)	645 (57.8)
Fever ≥ 39^0 C	2 (0.3)	4 (0.7)	172 (15.4)
Tachycardia	5 (0.7)	4 (0.7)	25 (2.2)
Syncope	-	-	-
Seizure	-	-	-
Dyspnea	2 (0.3)	-	2 (0.2)
Swollen face and neck	-	2 (0.3)	3 (0.3)
Whole body Rash	-	2 (0.3)	1 (0.1)
Unilateral Tinnitus	2 (0.3)	-	-
Bilateral Tinnitus	1 (0.1)	1 (0.2)	2 (0.2)
Unilateral Hearing Loss	-	-	-
Bilateral Hearing Loss	2 (0.3)	-	-
Anosmia	-	-	-
Ageusia	1 (0.1)	-	3 (0.3)

Table 4. Factors Affecting Adverse Events Following The CoronaVac Vaccine

Characteristics	AE n (%)	No AE n (%)	p-value	cOR (95% CI)	AdjOR (95% CI)
First Dose					
Sex					
Female	417 (54.9)	342 (45.1)	0.002	1,36 (1,13-1,72)	1.44 (1.16-1.789)
Male	296 (46.6)	339 (53.4)			
Age					
<40 years	387 (51.7)	362 (48.3)	0.67	1,046 (0,84-1,29)	
≥40 years	326 (50.5)	319 (48.5)			
Work Status					
Residents	206 (48.6)	218 (51.4)	0.206	0,86 (0,68-1,08)	
Specialists	507 (52.3)	463 (47.7)			
Vaccine Place					
Hospital	673 (51.6)	613 (48.4)	0.188	1,33 (0,86-2,04)	
Primary Care and Clinic	40 (44.4)	50 (55.5)			
COVID-19 infection history before first dose					
Yes	94 (51.1)	90 (48.9)	0.986	0,99 (0,73-1,36)	
No	619 (51.2)	591 (48.8)			
Comorbidity					
Yes	187 (56)	147 (44)	0.04	1,29 (1,0-1,65)	1.36 (1.06-1.75)
No	526 (49.6)	534 (50.4)			
Second Dose					
Sex					
Female	356 (46.9)	403 (53.1)	0.008	1.334 (1.077-1.651)	
Male	253 (39.8)	382 (60.2)			
Age					
<40 years	330 (44.1)	419 (55.9)	0.763	1.033 (0.836-1.278)	
≥40 years	279 (43.3)	366 (56.7)			
Work Status					
Residents	182 (42.9)	242 (57.1)	0.704	0.956 (0.760-1.204)	
Specialists	427 (44)	970 (56)			
Vaccine Place					
Hospital	575 (44.1)	729 (55.9)	0.243	1.299 (0.837-2.017)	
Primary Care and Clinic	34 (37.8)	56 (62.2)			
COVID-19 infection history before first dose					
Yes	80 (39.6)	122 (60.4)	0.206	0.822 (0.606-1.114)	
No	529 (44.4)	663 (55.6)			
Comorbidity					
Yes	162 (48.5)	172 (51.5)	0.042	1.292 (1.009-1.653)	1.395 (1.12-1.73)
No	447 (42.2)	613 (57.8)			
Interval Between 1st and 2nd Dose					
>1 month	165 (41.5)	233 (58.5)	0.289	0.880 (0.696-1.114)	
≤ 1 month	444 (44.6)	552 (55.4)			

Factors Affecting Post CoronaVac Vaccine Adverse Events

Adverse events following the CoronaVac vaccine were significantly higher in females, compared to males in the first dose (p=0.002, OR 1.36 95% CI 1.13-1.172), and second dose (p=0.008, OR 1.33 95% CI 1.07-1.65). Adverse events were significantly higher in individuals with comorbidities in the first dose (p=0.04, OR 1.29, 95% CI 1.00-1.65)), and second dose (p=0.042, OR 1.29, 95% CI 1.00-1.65). Other variables such as age, work status, vaccine place and the COVID-19 infection history before the first dose did not show a statistically significant relationship. (p>0.05) (Table 4). These two factors were then included in the multivariate analysis alongside with health care centre where the vaccine was administered, and work status (residents or specialists). In the final multivariate analysis, other factors are not significant (Table 4).

Factors Affecting Post Moderna Vaccine Adverse Events

Adverse events following the Moderna vaccine were also significantly higher in females compared to males (p=0.01, OR 2.07 95% CI 1.17-3.64), and significantly lower in individuals ≥40 years of age (p=0.017, OR 0.5 95% CI 0.28-0.89). Unlike the analysis in the CoronaVac vaccine, comorbidity status did not affect adverse events following the Moderna vaccine. Other variables included in the multivariate analysis are work status (residents or specialists), and comorbidity, but both factors are not significant (Table 5).

Discussion

In this large national scale study, we have been able to investigate the adverse events following the first, second, and third dose of the SARS-CoV-2 vaccine using CoronaVac and Moderna. Our study subjects consisted of Indonesian health care workers with a proportionate amount of female and male participants, aged below and above forty years old. Jeskowiak et al[9] in their study found there is a visible advantage of women (1301) over men (355), which is generally due to the quantitative advantage of women employed in the health care sector compared to men.[9]

Based on the vaccine coverage, all our participants have been vaccinated with the first and second dose of CoronaVac, and 83.9% had received a third booster dose of Moderna. This result is in accordance with the national vaccine coverage report on November 2021, showing that 100% of Indonesian health care workers have received first and second-dose vaccines and 79.29% had received third-dose boosters.[10]

Back on January 13th, 2021, the Indonesian National Agency of Drug and Food Control (BPOM), released an Emergency Use Authorization (EUA) for the CoronaVac vaccine to be used in Indonesia, to

Table 5. Factors Affecting Adverse Events Following Moderna Vaccine

Characteristics	AE n (%)	No AE n (%)	p-value	OR (95% CI)	AdjOR (95% CI)
Sex					
Female	613 (96.8)	20 (3.2)	0.01	2.07 (1.17-3.64)	2,00 (1.13-3,53)
Male	503 (93.7)	34 (6.3)			
Age					
<40 years	517 (93.8)	34 (6.2)	0.017	0.50 (0.28-0.89)	0.52 (0.29-0.92)
≥40 years	599 (96.8)	20 (3.2)			
Work Status					
Residents	336 (95.5)	16 (4.5)	0.94	1.02 (0.56-1.86)	
Specialists	780 (95.4)	38 (4.6)			
Vaccine Place					
Hospital	1059 (95.2)	53 (4.8)	0.51	0.35 (0.04-2.58)	
Primary Care and Clinic	57 (98.3)	1 (1.7)			
COVID-19 infection history before first dose					
Yes	115 (94.3)	7 (5.7)	0.53	0.77 (0.34-1.76)	
No	1001 (95.5)	47 (4.5)			
Comorbidity					
Yes	247 (93.9)	16 (6.1)	0.19	0.67 (0.37-1.23)	
No	869 (95.8)	38 (4.2)			

help control SARS-CoV-2 transmission. CoronaVac is effective and safe in phase I through III clinical trials. Hong Kong SAR on CoronaVac reported that the most common local adverse events following the CoronaVac vaccine are injection site pain.[11] The report is in accordance with our study result that shows injection site pain occurs in 56.3% of patients following the first dose, and 61.4% of patients following the second dose. Injection site pain is the most common local adverse event compared to other possible local adverse events such as swelling (1% following the first dose, and 1.6% following the second dose) and redness (2% following the first dose, and 1.8% following the second dose). This result is also supported by local research done in East Java, Indonesia, that shows localized injection site pain occurs in 45% of patients.[12]

This study shows that the most common systemic adverse events after the CoronaVac vaccine are drowsiness and fatigue. This is also supported by the previous smaller study in Indonesia, showing that drowsiness occurs in 15% of patients after CoronaVac, and fatigue in 36% of patients.[12] Based on Hongkong SAR on CoronaVac, the most common systemic adverse events are headache and fatigue.[11]

In the analysis of factors affecting the occurrence of adverse effects following the first and second dose of whole inactivated vaccine, we found that gender and comorbidity played a significant role in resulting adverse effects, both first and second dose. A previous study by Lai et al[3] found that the adverse effect following both first and second doses occurred more frequently in women, with the most common systemic adverse reactions post-vaccination were muscle pain, fatigue, headache, and/or dizziness. However, a study by Ramlabeevi et al[13] showed that comorbidities, such as cardiac disease, diabetes mellitus, hypertension, bronchial asthma, and immunological disorder were not significantly associated with adverse events following the first or second dose of the COVID-19 vaccine.[13]

On the other hand, our current study found that mRNA COVID-19 vaccine given as a third booster dose showed a higher occurrence of adverse events as well as the duration of symptoms. Most of our participants experienced local adverse events, especially pain at the injection site. This local adverse event finding is in accordance with Wu et al[14], who stated mRNA vaccine significantly showed a higher risk of the local adverse event, 2.5 times higher than systemic adverse events.[14] Similar results shown by Lai et al[3], stated that local symptoms are more common in mRNA vaccine, compared to systemic events. In addition, from 21 December 2020 to 10 January 2021, ten cases of anaphylactic reaction out of 4,041,396 first doses of Moderna vaccines were detected in the USA.[15] A study by Hause et al[16] showed that local side effects were reported more frequently after the third dose than the second dose of Moderna. Besides, systemic side effects were less frequent after the third dose compared to the second dose of Moderna.[16]

As shown in Table 5, we analyzed the factors affecting the occurrence of adverse effects following a third booster dose using the mRNA vaccine. A bit different from the first and second doses of whole inactivated vaccine, the result showed age also had a significant role in resulting the adverse effect following the third booster dose. However, after we adjusted the factors using multivariate analysis, we found that gender and age plays role in resulting adverse event following the third booster dose using mRNA vaccine as aggravating factor and protecting factor respectively, while comorbidity showed no significant effect on adverse event following third booster dose using mRNA vaccine. A study by Xiong et al[17] found that older adults aged 65 years or older reported fewer adverse events following COVID-19 vaccination compared to younger adults aged 18 to 64 years. However, older adults were more likely to report serious adverse events, permanent disability, hospitalization, and death following COVID-19 vaccination. The predominance of death in older adults might be associated with serious underlying health conditions, polypharmacy, and their higher all-cause death rate.[17] The age disparities in adverse events of the COVID-19 vaccine might be associated with the lower ability to create an effective response to vaccination in older adults.[18]

According to our study, gender showed a consistent effect in resulting adverse events following the vaccination, despite the type of vaccine. A study by Xiong et al[17] showed that more females reported adverse events than males and most of the adverse events occurred within 1 week after the first dose of vaccination. The onset of side effects was faster in females than males.[19] However, males were more likely to report serious adverse events, death, and hospitalization compared to females.[17] The female predominance of adverse events was found on inactivated virus vaccines and mRNA-based vaccines.[4,20,21] A study by Alghamdi et

al. found that females have significantly more side effects after administration of the viral vector-based vaccine.[19] Viral vector-based vaccine significantly impacts females than mRNA-based vaccine.[19] The gender disparities in the adverse events of the COVID-19 vaccine might be caused by the difference in the immune response to antigens, innate, and adaptive immune response between males and females.[22] In addition, males have a relative cellular immune suppression of the specific immune system compared to females.[23] The role of gender in adverse events following immunization could be hormonal. Sex hormones regulate immune cells, such as B cells. Estrogen's immune-suppressive effects at higher levels and immune-stimulant activity at lower levels are different from testosterone, which suppresses innate immune responses. In terms of genetics, females have two X chromosomes which carry many genes related to immune mechanisms, while males just have one. Angiotensin-converting enzyme 2 (ACE2), a functional receptor for SARS-CoV-2, is encoded by its homologous gene (ACE2), which maps on chromosome X. The angiotensin-converting enzyme-2 (ACE2) receptor is an essential part of cell entry for the spike (S) protein of SARS-CoV-2. It has been reported that estrogen inhibits ACE2 activity, while androgen upregulating.[3,4]

In our knowledge, our study was the first study that correlate vaccine place and work status with adverse events of the COVID-19 vaccine. There was no significant correlation between vaccine place and work status with adverse events of the vaccine. In addition, our study did not find a significant relationship between adverse events and COVID-19 infection history. Our results were in line with the study by Remlabeevi et al[13] that showed no association between previous COVID-19 infection and adverse events following vaccination.[13]

The strength of this study is the large and dispersed sample size, able to represent almost all Indonesian provinces. Also, the availability of two vaccine types, allows us to do the inter-vaccine comparison. However, this study has several key limitations; the study was conducted using a self-reported questionnaire in a retrospective manner, increasing the probability of recall bias. Moreover, adverse events reported in this study were subjective and collected several months after a vaccine injection, further increasing recall bias. To address this limitation, we recommend future studies be done prospectively. Participants involved in this study were ENT specialists and residents therefore it might not be representative of the general health care workers population.

Conclusion

From this Indonesia national scale study, we can conclude that both minor local and systemic adverse events following Moderna third dose is significantly more common than CoronaVac first and second dose SARS-CoV-2 vaccine among Indonesian health care workers. Adverse events in both vaccines are significantly more common in females compared to males. Aside from sex, the existence of comorbidity also affects adverse events following the CoronaVac vaccine. The individual below 40 years old has a higher risk of experiencing Moderna adverse events. However, more serious adverse events including dyspnea, seizure, and anaphylactic reaction rarely occur.

References

1. WHO. Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac developed by Sinovac [Internet]. 2021;1-7 [cited 1 April 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-2021.1
2. United Nations, Asian Development Bank, United Nations Development Programme. Responding to the COVID-19 Pandemic: leaving no country behind [Internet]. 2021 [cited 2 April 2022]. Available from: https://www.adb.org/publications/responding-covid-19-pandemic
3. Lai CC, Chen IT, Chao CM, Lee PI, Ko WC, Hsueh PR. COVID-19 vaccines: concerns beyond protective efficacy and safety. Expert Rev Vaccines. 2021;20:1013–25. doi: 10.1080/14760584.2021.1949293.
4. Riad A, Sağıroğlu D, Üstün B, Pokorná A, Klugarová J, Attia S, Klugar M. Prevalence and risk factors of coronavac side effects: An independent cross-sectional study among healthcare workers in turkey. J Clin Med. 2021;10:1–13. doi: 10.3390/jcm10122629.
5. Shrestha S, Khatri J, Shakya S, Danekhu K, Khatiwada AP, Sah R, et al. Adverse events related to COVID-19 vaccines: the need to strengthen pharmacovigilance monitoring systems. Drugs Ther Perspect. 2021;37:376-82. doi: 10.1007/s40267-021-00852-z.
6. Chintia A, Darmawan ES. Management of Jakarta Metropolitan Medical Center Hospital in Preventing Burnout in Nurses during the Covid-19 Pandemic. BJI. 2021;7:551-16.doi: 10.32539/BJI.v7i3.581.
7. Adelina M, Dwijayanti F. The Infection of COVID-19 among Health Care Workers in Dharmais Cancer Hospital. IJoC. 2021;15:1-3. doi: 10.33371/ijoc.v15i1.823.

8. Yigit M, Ozkaya-Parlakay A, Cosgun Y, Ince YE, Bulut YE, Senel E. Should a third booster dose be scheduled after two doses of CoronaVac? A single-center experience. J Med Virol. 2022;94:287-90. doi: 10.1002/jmv.27318.
9. Jęśkowiak I, Wiatrak B, Grosman-Dziewiszek P, Szeląg A. The Incidence and Severity of Post-Vaccination Reactions after Vaccination against COVID-19. Vaccines (Basel). 2021;9:502. doi: 10.3390/vaccines9050502.
10. Ministry of Health of the Republic of Indonesia. Vaksinasi COVID-19 Nasional [Internet]. 2021 [cited 2 April 2022]. Available from: https://vaksin.kemkes.go.id/#/vaccines
11. Food and Health Bureau (FHB). Report on Evaluation of Safety, Efficacy, and Quality of CoronaVac COVID-19 Vaccine (Vero Cell) Inactivated [Internet]. 2021 [cited 2 April 2022]. Available from: https://www.fhb.gov.hk/download/our_work/health/201200/e_evaluation_report_CoronaVac.pdf
12. Supangat, Sakinah EN, Nugraha MY, Qodar TS, Mulyono BW, Tohari AI. COVID-19 Vaccines Programs: adverse events following immunization (AEFI) among medical Clerkship Student in Jember, Indonesia. BMC Pharmacol Toxicol. 2021;22:58. doi: 10.1186/s40360-021-00528-4.
13. Remlabeevi A, Mathew T, Nair G, Rajasekharan Nair G, Alex M. Adverse events and their association with comorbidities after first and second doses of Covishield vaccination among healthcare workers of Government owned medical colleges in Kerala [Preprint]. MedRxiv. 2021. doi: 10.1101/2021.05.19.21257317.
14. Wu Q, Dudley MZ, Chen X, Bai X, Dong K, Zhuang T, et al. Evaluation of the safety profile of COVID-19 vaccines: a rapid review. BMC Med. 2021;19:173. doi: 10.1186/s12916-021-02059-5
15. Centers for Disease Control and Prevention. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine—United States, December 21, 2020–January 10, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:125–129. doi: 10.15585/mmwr.mm7004e1.
16. Hause AM, Baggs J, Gee J, Marquez P, Myers TR, Shimabukuro TT, et al. Safety Monitoring of an Additional Dose of COVID-19 Vaccine - United States, August 12-September 19, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1379-84. doi: 10.15585/mmwr.mm7039e4.
17. Xiong X, Yuan J, Li M, Jiang B, Lu ZK. Age and Gender Disparities in Adverse Events Following COVID-19 Vaccination: Real-World Evidence Based on Big Data for Risk Management. Front Med (Lausanne). 2021;8:1-5. doi: 10.3389/fmed.2021.700014.
18. Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. J Allergy Clin Immunol. 2020;145:1309-21. doi: 10.1016/j.jaci.2020.03.017.
19. Alghamdi A, Ibrahim A, Almutairi R, Joseph M, Alghamdi G, Alhamza A. A cross-sectional survey of side effects after COVID-19 vaccination in Saudi Arabia: male versus female outcomes. J Adv Pharm Educ. 2021;11:51-6. doi: 10.51847/bCwca2qGfP.
20. Riad A, Pokorná A, Attia S, Klugarová J, Koščík M, Klugar M. Prevalence of COVID-19 Vaccine Side Effects among Healthcare Workers in the Czech Republic. J Clin Med. 2021;10:1-18. doi: 10.3390/jcm10071428.
21. El-Shitany NA, Harakeh S, Badr-Eldin SM, Bagher AM, Eid B, Almukadi H, et al. Minor to Moderate Side Effects of Pfizer-BioNTech COVID-19 Vaccine Among Saudi Residents: A Retrospective Cross-Sectional Study. Int J Gen Med. 2021;14:1389-401. doi: 10.2147/IJGM.S310497.
22. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626-38. doi: 10.1038/nri.2016.90.
23. Bouman A, Schipper M, Heineman MJ, Faas MM. Gender difference in the non-specific and specific immune response in humans. Am J Reprod Immunol. 2004;52:19-26. doi: 10.1111/j.1600-0897.2004.00177.x.