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Safety comparison of mRNA, viral vector, and inactivated Covid-19 vaccines: incidence of adverse events following primary and booster doses among medical professionals in Malaysia

Rekha Prabhu[1], Girish Prabhu[2], Mila Nu Nu Htay[3,5], Ashwathy Varadarajan Thundakattil[1], Soe Moe[3] and Sabyasachi Das[1,4*]

Abstract

Background This study aimed to examine adverse events following first, second, and booster doses of Covid-19 vaccines in Malaysia.

Methods This was a prospective longitudinal cohort study conducted between September 2021 to September 2022. Recipients who received different Covid-19 vaccines (Comirnaty, Vaxzevria, and CoronaVac) completed a self-report questionnaire of adverse events on days 1, 2, 4, and 7 following their primary (first and second) and booster (third) vaccinations.

Results A total of 1283 respondents had completed the questionnaire survey. The most frequent adverse events among Comirnaty recipients ($n=271$) following the first dose were pain (87.4%), fatigue (56.9%), myalgia (37.2%), and fever (17.5%), which further increased to 92.1%, 72.8%, 51·2%, and 48%, respectively, following the booster. The most frequent adverse events following the first dose of Vaxzevria ($n=90$) were pain (84.4%), fever (76.7%), headache (58.9%) and myalgia (53.3%). Adverse events were reduced after the second dose of Vaxzevria but sharply increased after the booster. The most common adverse events among CoronaVac recipients (1st dose) were pain at the injection site (69.1%), fatigue (49.1%) and increased hunger (34.5%). However, adverse events subsequently decreased after the second and booster doses. The average number of adverse events was highest for Vaxzevria after the first dose ($n=6$) and booster dose ($n=6$) and lowest for CoronaVac after the first ($n=3$), second ($n=2$) and booster doses ($n=2$).

Conclusion The incidence of adverse events following the first dose of the Covid-19 vaccine was highest among Vaxzevria recipients. Adverse events following Comirnaty vaccine increased gradually from primary to booster dose, whereas recipients with CoronaVac showed subsequent lesser adverse events following primary and booster doses.

*Correspondence:
Sabyasachi Das
sabyasachi.das@um.edu.my; sdas.vu@gmail.com

Full list of author information is available at the end of the article

Keywords Covid-19 vaccines, Adverse events, Booster dose, mRNA vaccine, Viral vectored vaccine, Inactivated viral vaccine, Vaccine safety, Comparative study

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the Covid-19 pandemic, resulted in considerable morbidity and mortality [1]. The Covid-19 pandemic triggered an unprecedented worldwide response, resulting in the rapid development and deployment of numerous vaccines [2, 3]. Like many other nations, Malaysia had implemented a multi-vaccine approach to immunize the majority of the population. Millions of Malaysians received primary and secondary vaccinations, including booster shots of viral vector vaccines (Vaxzevria), inactivated virus vaccines (CoronaVac), and mRNA vaccines (Comirnaty) [4]. Despite the remarkable efficacy of Covid-19 vaccinations in averting serious illness, hospitalization, and death, concerns regarding their safety and potential hazards had emerged [5, 6]. Understanding the types, frequency, and severity of adverse events associated with Covid-19 vaccination is crucial for making informed decision and implementing public health interventions. Adverse events could be significantly impacted by the type of vaccine, individual demographics, and existing medical conditions. Since previous research had demonstrated that the incidence and types of side effects differ across vaccination types, a comprehensive analysis was required to assess the safety of these vaccines in the Malaysian context [7, 8]. These evaluations strengthened the public confidence in immunization programs while also improving the surveillance of vaccine safety.

The National Pharmaceutical Regulatory Agency (NPRA) received many reports of adverse events when the Covid-19 vaccine was introduced. In order to evaluate the immunogenicity and safety of approved homologous and heterologous Covid-19 vaccination combinations, a post-marketing surveillance program was crucial [9]. The severity of these reports varied, ranging from mild symptoms like fatigue and fever to more severe conditions like myocarditis and allergies [10]. Worldwide research on post-vaccination adverse events has demonstrated that vaccines like mRNA (Comirnaty) were associated with a higher incidence of certain acute adverse events than vaccinations utilizing viral vectors (Vaxzevria) or inactivated virus vaccines (CoronaVac) in various nations, including Hong Kong, Canada, and Pakistan [8, 11–13]. Research conducted in the UK indicated that systemic adverse effects were more prevalent with heterologous vaccines compared to homologous vaccines [14]. These variances emphasized the need for customize research that considers Malaysia's heterogeneous population and healthcare landscape. In addition, the introduction of booster doses had made the assessment of vaccine safety even more crucial. Early research suggested that the booster doses might have resulted in diverse immune responses and negative side effects compared to the primary vaccinations, raising serious questions about their effectiveness and long-term safety [13–16]. Previous studies also revealed gender differences in adverse outcomes after receiving the Covid-19 vaccination. Expression of IFN γ and innate immune responses were elevated in females after vaccination, which were influenced by ChrY gene polymorphisms and X chromosome-linked genes mutation [17, 18]. The vaccine's ability relies on to block viral docking onto the angiotensin-converting enzyme 2 (ACE2) receptor, while the ACE 2 gene was found on the X chromosome, may have contributed to an increased immune response and a higher risk of vaccine-associated adverse events in females [19]. Studies also reported relatively greater adverse events following Covid-19 vaccine in people with common chronic diseases like hypertension, diabetes mellitus (DM), coronary artery disease (CAD), chronic respiratory disease (CRD), obesity, and cancer [20, 21]. A comparative analysis of the side effect associated with various Covid-19 vaccine and booster variants was crucial to inform future vaccine campaigns and policy making.

Therefore, the purpose of this study was to compare the adverse events associated with various types of Covid-19 primary and booster vaccinations among the healthcare professional and medical students in Malaysia. The outcomes of this study will help the public, policymakers, and medical professionals make decisions regarding the development of new vaccines for other diseases as well as the Covid-19 vaccination by improving knowledge of adverse events in the Malaysian population.

Methodology

Study setting and design

A prospective longitudinal cohort study was conducted between September 2021 to September 2022 to elucidate the adverse event of different vaccine of Covid-19. The Covid-19 vaccination was introduced to frontline healthcare workers in Malaysia in February 2021 [4]. This was Malaysia's inaugural introduction of a distinct Covid-19 vaccination for its people. The study population comprised of healthcare professionals and medical students, from Manipal University College Malaysia (MUCM) (both Melaka campus and Muar facility) and University of Malaya (UM). Being frontline healthcare worker all of them were prioritized for the Covid-19 vaccine and almost everyone received the first dose of vaccine on the

same day of October 2021 and the recipients were considered as vaccine exposure group. However, the introduction to Covid-19 mRNA vaccine was considered as a unique exposure since mRNA vaccine had never been used in humans in Malaysia. Since the Ministry of Health (MOH), Govt. of Malaysia, made vaccination mandatory for all federal government employees and health care professionals in September 2021 [22, 23], we were unable to recruit unvaccinated individuals (non-exposure group) in our study population.

Study population

Sample size calculation

There was no prior research to use for prevalence because the Covid-19 vaccination project was still in its infancy. However, we took into account the Covid-19 incidence rate based on real-time global information from Worldometer [24]. In order to determine the sample size, we utilized the Raosoft online sample size calculator (Raosoft, Seattle, WA, US), as previously mentioned by Elnaem et al. in 2021 [25]. Taking into account the 34.28 million people that lived in Malaysia in 2021, the necessary sample size for this study was 385, assuming a 50% response distribution, a 95% confidence level, and a 5% margin of error.

Sampling method

We employed universal sampling. We anticipated a high percentage of dropouts and non-responding recipients due to survey fatigue, a large number of hospitalized patients with coronavirus infections, and extended medical school vacations followed by work from home. The purpose of universal sampling was to remove sampling bias and produce the most accurate representation of the population. Moreover, among the disadvantages of longitudinal studies, we encountered a significant number drop out during the follow-up. The response rate was lower, with about 24% of recipients provided informed consent and taking part in the study.

Inclusion criteria

Recipients had to meet the following criteria: they had to be healthcare professionals or medical students at MUCM and UM, residents of Malaysia (including foreign nationals), older than eighteen, have a body temperature below 37.5 °C at the time of vaccination, and not been infected with COVID-19 in the past three months.

Exclusion criteria

Pregnant women and the recipients below age of 18 years were excluded from the study. Individuals who were hospitalized due to serious adverse events within 7 days following vaccination were not included. Additionally, those who developed Covid-19 infection within seven days of receiving their immunization were not allowed to participate. recipients with different kinds of autoimmune disorders, including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, Crohn's disease, multiple sclerosis, and inflammatory bowel disease, were excluded from the study as they were on immunosuppressive medications which may altered the incidence of adverse events following vaccination [26]. Additionally, recipients who did not complete the questionnaire or who provided an incomplete questionnaire were eliminated from the study. The study also excluded recipients with complex physical illnesses, as well as those who were unable to use the smart devices or the internet.

Data collection

This study employed online questionnaires in Google form platform to obtain data from people who got various Covid-19 vaccinations (Comirnaty, Vaxzevria, and CoronaVac).

In Malaysia, the vaccine was given in two required primary doses, followed by booster shots. The second dosage of the Comirnaty and CoronaVac vaccine were given 21 days following the first dose while the second dose of Vaxzevria was given 8–12 weeks after the first dose [4]. All three groups were eligible for booster following the administration of the second dosage for a minimum of three months [4]. Each of the three vaccines is injected intramuscularly, usually into the deltoid muscle. In a longitudinal way, repetitive data of short-term (acute) adverse events were routinely gathered on days 1, 4, and 7 following their primary (first and second) and booster (third) doses of vaccinations We assessed the acute and short-term adverse effects of the Covid-19 immunization from 24 h to 7 days, as previously stated by Shapiro et al. [27]. Data sheets in Microsoft Excel were downloaded and kept on password-protected institutional devices. While we did not closely monitor recipients response toward filling their questionnaire, we routinely reviewed the online Google form and contacted individual recipients if they failed to submit their responses within a specified timeframe and check about their respective response on adverse events as an act of online supervision. If recipients had any concerns about the side effects of vaccinations or were suspicious of any minor or temporary symptoms, they were advised to get in touch with the research team at any time by phone or social media. The access to data was limited only for the research team.

Preparation and validation of the questionnaire

We developed our adapted questionnaire after making significant changes to the WHO's coronavirus disease 2019 (Covid-19) vaccine and Covid-19 Recipient Vaccination Questionnaire, by NC Department of Health and

Human Services, United Nations 2021 [28, 29]. After consulting with experts, the questionnaire's content was validated to assess the questions' applicability to the target audience as well as its simplicity, clarity, intelligibility, specificity, and relevance to the topic. Six experts provided qualitative feedback on 30 questions pertaining to recipients demographics, lifestyle, comorbidities, and acute adverse events. As recommended by the content expert, the questionnaire was revised prior to field application. A pre-test of the revised questionnaire was conducted on 30 recipients prior to the start of the final study to ensure that it was comprehensive. Furthermore, the Cronbach's alpha test was used for predicting the questionnaire's reliability and internal consistency. With a Cronbach alpha value of 0.851, the survey validation revealed strong internal consistency for every question. This number suggests a greater degree of interrelatedness in the questionnaire's evaluation. The demographic characteristics of the recipients including age, sex, ethnicity, and nationality were collected. Additionally, information on smoking status, dietary patterns (vegetarian or non-vegetarian), and comorbidities (such as hypertension, diabetes, overweight/obesity, asthma, coronary heart disease, and fatty liver) was collected to assess their associations with short-term adverse events following Covid-19 vaccination. The recipients were advised to report all minor and major adverse events following Covid-19 vaccination and to categorize them via the questionnaire. Questionnaires on days 1, 4, and 7 following doses 2 and 3 were identical (Supplementary data).

Outcome

The outcomes of the study were self-reported adverse events following vaccination. Local adverse effects, such as pain at the site of injection; redness; swelling; and systemic adverse effects, like fever, chills, fatigue, myalgia, dizziness, headache, blur vision, nausea, loss of appetite, increased appetite, diarrhea, breathlessness, palpitation, and sleep disturbances, were recorded. Binary "yes" or "no" responses were collected for each adverse event.

The onset of adverse events of pain, fever, and fatigue following each dose of vaccines were recorded. The following responses were gathered: fever (onset < 6 h, 6–12 h, 12–24 h, > 24 h, not applicable); fatigue (onset < 6 h, 6–12 h, 12–24 h, > 24 h, not applicable); and pain (immediately after injection, ≥ 1 h after injection, 1–3 h after injection, 3–5 h after injection, > 5 h after injection, not applicable).

Data analysis

The data was analyzed via SPSS (version 27) and Epi Info statistical software. This study utilized primarily descriptive statistics. We employed frequency percentages for the socio-demographic analysis. We determined the prevalence of each adverse event by calculating the percentage of recipients who reported their adverse occurrences. For socio-demographic analysis, we employed frequency and percentage, with the exception of age, which was recorded as a complete value in years (continuous data). The majority of the data was categorical; therefore, we utilized frequency and percentage. The connection between adverse effects among various vaccines was analysed using the chi-square test, with a significance level set below 0.05. Bonferroni corrected family wise error rate was performed among the adverse event to find out the type I error. Multivariate logistic regression analysis with odd ratio were performed to compare different types of vaccines and having at least one adverse event following dose 1, dose 2 and dose 3 of vaccination. If the predicted frequency in any cell of the table was less than 5 for chi-square calculation, we utilized Fisher's exact test.

Ethical consideration

This research was performed in compliance with the ethical guidelines outlined by the Declaration of Helsinki. Participation was voluntary, and informed consent was obtained from all individual recipients included in the study. The institutional ethics committee assessed and approved our adapted questionnaires (MUCM/FOM/Research Ethics Committee– 5/2021).

Results

Demographic characteristics of the study population

We invited 10,451 vaccine recipients from public and private health universities of Malaysia and sent them a questionnaire during three distinct vaccine doses. A total of 2514 effective responses (24.05%) were received. Among the effective responses, 687 (27.32%) respondents were removed due to Covid-19 infection within 7 days of vaccination. Because their questionnaire was considered incomplete, 472 additional respondents (18.77%) were eliminated. An additional 18 (0.71%) recipients were disqualified because they experienced serious side effects after vaccination that required hospitalization. Furthermore, another 41 (1.63%) recipients were eliminated due to different autoimmune disease. Figure 1 demonstrated the selection of research participants as well as the specific justifications for their exclusion. The questionnaire was successfully completed by 1283 recipients. In Table 1, the demographic details of the recipients who received three vaccination doses are displayed. The following were among the subjects who completed questionnaire: Dose 1 ($n = 416$), Dose 2 day 1 ($n = 137$), Dose 2 day 4 ($n = 120$), Dose 2 day 7 ($n = 105$), Dose 3 day 1 ($n = 196$), Dose 3 day 4 ($n = 167$), and Dose 3 day 7 ($n = 142$). In all seven groups, the recipients' mean age varied from 22.15 (± 4.06) to 36.23 (± 15.09) years. Regardless of the vaccine

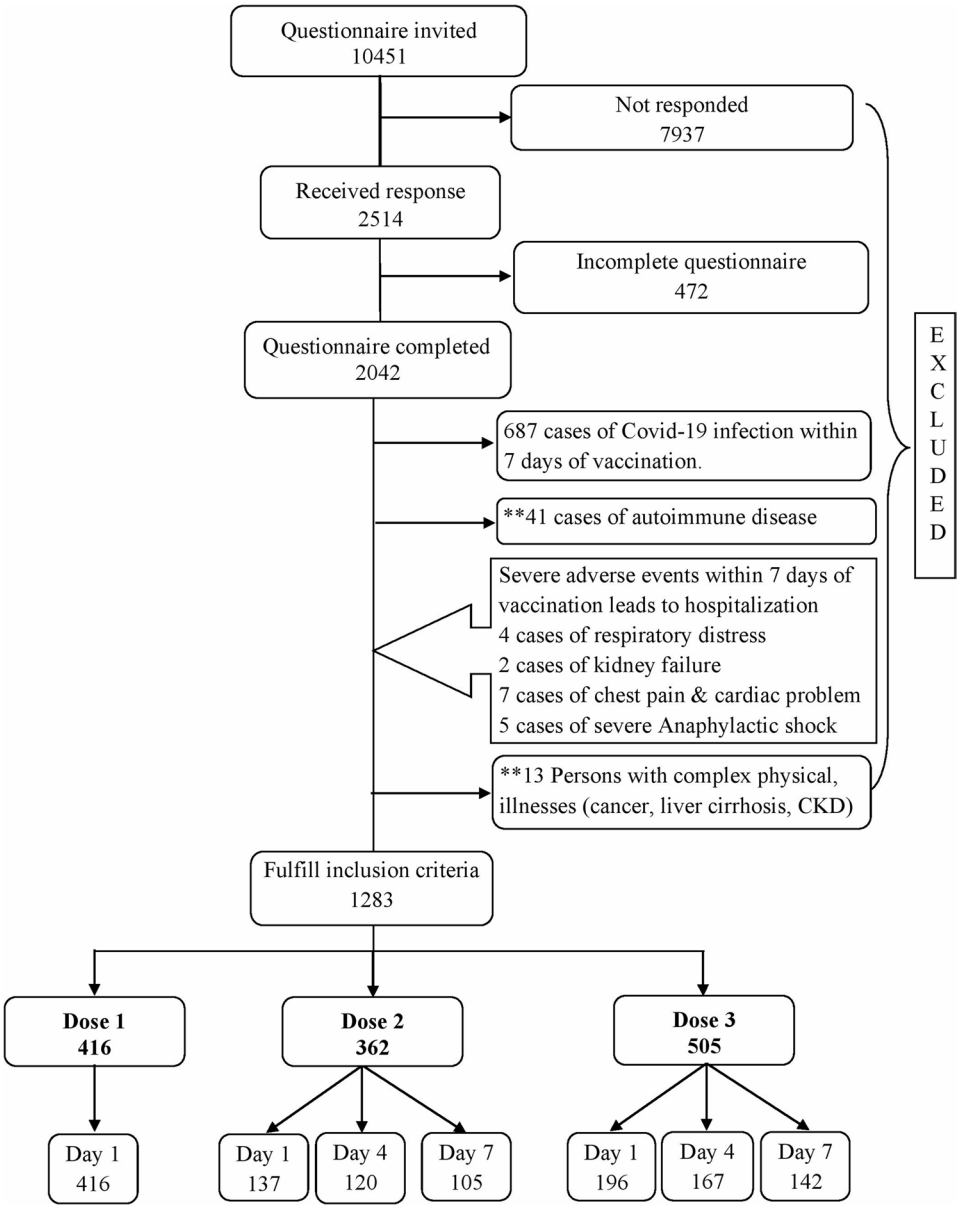

Fig. 1 A strobe flowchart of study planning and selection of subject. 7937 (75.94%) individuals had not responded the questionnaire. Only 2042 (19.54%) individuals had completed the questionnaire. Out of 18 severe adverse events, Chest pain and cardiac complications were the most commonly reported adverse events followed by anaphylactic shock, respiratory distress and kidney failure. Of the 41 recipients, 11, 5, 2, 7, 1, 6, and 9 had rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, Crohn's disease, multiple sclerosis, and inflammatory bowel disease, respectively. In addition, 8, 3, and 2 recipients were eliminated due to significant clinical conditions such as cancer, liver cirrhosis, and chronic kidney failure (CKD). Ultimately, 1283 individuals had successfully finished the questionnaires for doses 1, 2, and 3 (booster) of various COVID vaccines on days 1, 4, and 7

type, the proportion of female responses was higher than that of male respondents across all doses (53.3–75.4%). The female: male ratio was found to be the highest on Day 4, Dose 3, at 3.07:1, followed by Day 1, Dose 3, at 2.62:1, and on Day 7, Dose 3, at 2.38:1. Among the ethnic categories, the Chinese (ranging from 26.3 to 39.4%) and Indian (18.1–36.5%) populations accounted for the majority of responders across all vaccine doses, followed by the Malay population (13.3–23%). A considerable number of other ethnic groups, including Sabahan, Kadazan, Bisaya, Javanese, Sudanese, and Sinhalese, had response rates ranging from 9.6 to 39.2%. A total of 96.2% of the respondents from dose 1 and 98% of the respondents from subsequent doses were nonsmokers. Obesity and overweight were the most often reported comorbidities, with prevalence rates varying from 5.1 to 12.4% followed by hypertension (0 to 11.4%) and diabetes (0 to 5.7%) (Table 1).

Table 1 Demographic characteristics of the respondents

Variable	Dose 1	Dose 2			Dose 3		
	Day 1 (*n* = 416)	Day 1 (*n* = 137)	Day 4 (*n* = 120)	Day 7 (*n* = 105)	Day 1 (*n* = 196)	Day 4 (*n* = 167)	Day 7 (*n* = 142)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age (mean, SD)	29.08 (12.95)	34.64 (14.72)	36.23 (15.09)	35.49 (15.22)	23.65 (4.74)	22.15 (4.06)	22.29 (4.22)
Gender							
Male	149 (35.8)	54 (39.4)	56 (46.7)	43 (41)	54 (27.6)	41 (24.6)	42 (29.6)
Female	267 (64.2)	83 (60.6)	64 (53.3)	62 (59)	142 (72.4)	126 (75.4)	100 (70.4)
Ethnicity							
Malay	67 (16.1)	19 (13.9)	16 (13.3)	18 (17.1)	45 (23.0)	31 (18.6)	23 (16.2)
Chinese	122 (29.3)	36 (26.3)	34 (28.3)	30 (28.6)	66 (33.7)	59 (35.3)	56 (39.4)
Indian	134 (32.2)	27 (19.7)	23 (19.2)	19 (18.1)	56 (28.6)	61 (36.5)	44 (31.0)
Others	93 (22.4)	41 (29.9)	47 (39.2)	38 (36.2)	21 (10.7)	16 (9.6)	19 (13.4)
Nationality							
Malaysian	317 (76.2)	82 (59.9)	68 (56.7)	66 (62.9)	184 (93.9)	162 (97.0)	130 (91.5)
NonMalaysian	99 (23.8)	55 (40.1)	52 (43.3)	39 (37.1)	12 (6.1)	5 (3.0)	12 (8.5)
Smoking status							
Yes	16 (3.8)	2 (1.5)	4 (3.3)	4 (3.8)	3 (1.5)	2 (1.2)	1 (0.7)
No	400 (96.2)	135 (98.5)	116 (96.7)	101 (96.2)	193 (98.5)	165 (98.8)	141 (99.3)
Diet							
Non-vegetarian	393 (94.5)	124 (90.5)	105 (87.5)	98 (93.3)	189 (96.4)	165 (98.8)	140 (98.6)
Vegetarian	23 (5.5)	13 (9.5)	15 (12.5)	7 (6.7)	7 (3.6)	2 (1.2)	2 (1.4)
Comorbidities							
Hypertension	25 (6.0)	11 (8.0)	10 (8.3)	12 (11.4)	3 (1.5)	0	0
Diabetes	14 (3.4)	7 (5.1)	6 (5.0)	6 (5.7)	0 (0)	0	0
Overweight/Obesity	38 (9.1)	13 (9.5)	11 (9.2)	13 (12.4)	10 (5.1)	12 (7.2)	10 (7.0)
Asthma	13 (3.1)	5 (3.6)	6 (5.0)	3 (2.9)	3 (1.5)	5 (3.0)	5 (3.5)
Coronary heart disease (CHD)	3 (0.7)	0 (0)	2 (1.7)	1 (1.0)	0 (0)	0	0
Fatty Liver	1 (0.2)	2 (1.5)	1 (0.8)	1 (1.0)	0 (0)	0	0

Adverse events following vaccination

The prevalence rates of adverse events following the first dose of Comirnaty, Vaxzevria, and CoronaVac were depicted in Fig. 2. Individuals received Vaxzevria at the first dose reported more adverse events than those receiving other vaccines. The most frequent short-term adverse events among recipients who received first dose of Comirnaty were pain (87.4%), fatigue (56.9%), myalgia (37.2%), headache (25.3%), and swelling at the injection site (24.2%). Among those who got the Vaxzevria vaccine following the first dose, the most frequent adverse events were pain (84.4%) and fever (76.7%), followed by headache (58.9%) and myalgia (53.3%). However, pain (69.1%), fatigue (49.1%), increased hunger (34.5%), headache (25.5%), and myalgia (18.2%) were the most common adverse events among the recipients of 1st dose of the CoronaVac vaccine (Fig. 2A). Compared to Vaxzevria and Comirnaty vaccines, the percentage of adverse events following CoronaVac vaccination was considerably ($p < 0.05$) lower (Table 2).

In contrast to the first dose, recipients of the Comirnaty experienced a subsequent rise in the incidence of adverse events after the second dose. Pain was the most common adverse effect (88.1%) associated with the second dose of the Comirnaty vaccine, followed by fatigue (62.4%), headache (32.7%), myalgia (46.5%), fever (44.6%), and sleep difficulties (28.7%) (Fig. 2B). The second dosage of the Comirnaty vaccine caused a substantial 2.45- and 2.41-fold increase in fever and sleep disturbances as compared to the first dose. Following the second dose of the Comirnaty vaccine, episodes of myalgia, headache, nausea, and chills increased 1.73, 1.65, 1.29, and 1.25 times, respectively (Table 2). However, the responders reported fewer adverse events following a second dosage of the CoronaVac and Vaxzevria vaccinations. Nevertheless, swelling increased from 9.1 to 23.1% after the second dosage of the CoronaVac vaccination.

Compared to CoronaVac vaccine, both Comirnaty and Vaxzevria had more adverse events following the booster (third) dose. The frequency of adverse events following the Comirnaty booster was elevated. Following booster, pain climbed from 87.4 to 92.1%. After the booster dose, the incidences of fatigue, myalgia, and fever rose from 56.9%, 37.2%, and 17.5–72.8%, 51.2%, and 48%, respectively (Fig. 2A and C). Following booster shot of Vaxzevria, commonly reported adverse events were pain (81.8%) and fatigue (81.8%), followed by headache (63.6%), fever (54.5%), chills (45.5%), and myalgia

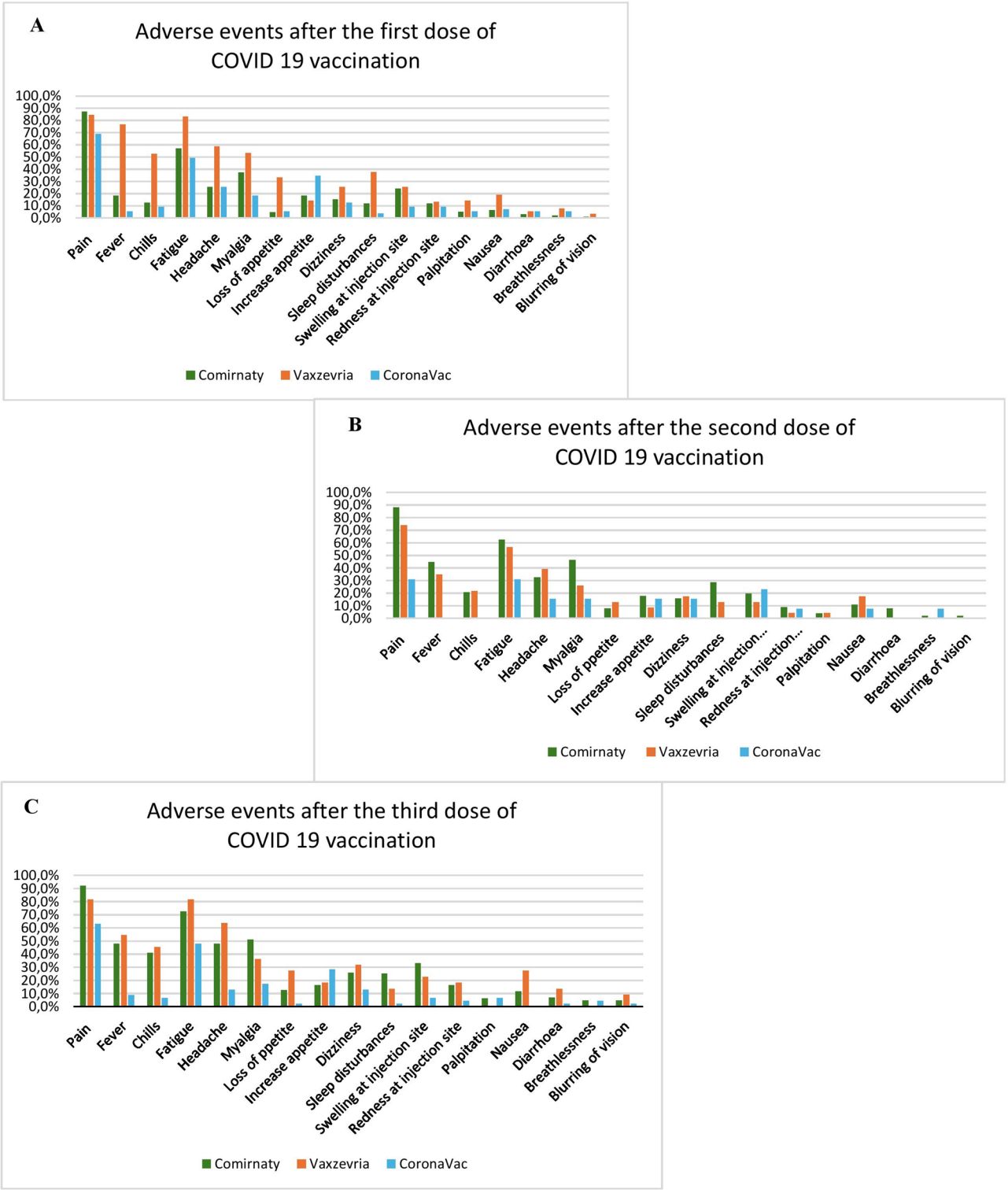

Fig. 2 Short-term adverse events following Covid-19 vaccination: Panels **A**, **B**, and **C** represent the prevalence of self-reported adverse events associated with the Comirnaty, Vaxzevria, and CoronaVac vaccines following the first, second and third (booster) doses, respectively

(36.4%). These side effects were almost identical to the first dose of vaccination (Fig. 2C). Recipients with CoronaVac booster reported significantly ($P < 0.003$) less pain (63%) and fatigue (47.8%) than those who received the Comirnaty and Vaxzevria vaccinations (Table 2). The risks of fever (8.7%), headache (13%), and myalgia (17%)

Table 2 Prevalence of adverse events after the vaccination with Comirnaty,Vaxzevria, and CoronaVac vaccines

Adverse events	Dose 1 (*n* = 416)				Dose 2 (*n* = 137)				Dose 3 (*n* = 196)			
	Comirnaty	Vaxzevria	Corona Vac	*P*	Comirnaty	Vaxzevria	Corona Vac	*P*	Comirnaty	Vaxzevria	Corona Vac	*P*
	n = 271 (65.1%)	*n* = 90 (21.6%)	*n* = 55 (13.2%)		*n* = 101 (73.7%)	*n* = 23 (16.8%)	*n* = 13 (9.5%)		*n* = 127 (64.8%)	*n* = 22 (11.2%)	*n* = 47 (24.0)	
Pain at injection site	235 (87.4)	76 (84.4)	38 (69.1)	0.003	89 (88.1)	17 (73.9)	4 (30.8)	< 0.001*	117 (92.1)	18 (81.8)	29 (63.0)	< 0.001
Redness	32 (11.9)	12 (13.3)	5 (9.1)	0.749	9 (8.9)	1(4.3)	1 (7.7)	0.874*	21 (16.5)	4 (18.2)	2 (4.3)	0.094
Swelling	65 (24.2)	23 (25.6)	5 (9.1)	0.039	20 (19.8)	3 (13.0)	3 (23.1)	0.714*	42 (33.1)	5 (22.7)	3 (6.5)	0.002
Fever	49 (18.2)	69 (76.7)	3 (5.5)	< 0.001	45 (44.6)	8 (34.8)	0 (0)	0.006	61 (48.0)	12 (54.5)	4 (8.7)	< 0.001
Chills	34 (12.6)	47 (52.2)	5 (9.1)	< 0.001	21 (20.8)	5 (21.7)	0 (0)	0.188*	52 (40.9)	10 (45.5)	3 (6.5)	< 0.001
Fatigue	153 (56.9)	75 (83.3)	27 (49.1)	< 0.001	63 (62.4)	13 (56.6)	4 (30.8)	0.086	92 (72.4)	18 (81.8)	22 (47.8)	0.003
Myalgia	100 (37.2)	48 (53.3)	10 (18.2)	< 0.001	47 (46.5)	6 (26.1)	2 (15.4)	0.030	65 (51.2)	8 (36.4)	8 (17.4)	< 0.001
Dizziness	41 (15.2)	23 (25.6)	7 (12.7)	0.054	16 (15.8)	4 (17.4)	2 (15.4)	1.00	33 (26.0)	7 (31.8)	6 (13.0)	0.142
Headache	68 (25.3)	53 (58.9)	14 (25.5)	< 0.001	33 (32.7)	9 (39.1)	2 (15.4)	0.330	61 (48.0)	14 (63.6)	6 (13.0)	< 0.001
Blurr vision	3 (1.1)	3 (3.3)	0 (0)	0.192	2 (2.0)	0 (0)	0 (0)	1.00*	6 (4.7)	2 (9.1)	1 (2.2)	0.370*
Nausea	17 (6.3)	17 (18.9)	4 (7.3)	0.002	11 (10.9)	4 (17.4)	1 (7.7)	0.663*	15 (11.8)	6 (27.3)	0 (0)	0.001*
Loss of appetite	13 (4.8)	30 (33.3)	3 (5.5)	< 0.001	8 (7.9)	3 (13.0)	0 (0)	0.430*	16 (12.6)	6 (27.3)	1 (2.2)	0.007*
Increase appetite	49 (18.2)	13 (14.4)	19 (34.5)	0.008	18 (17.8)	2 (8.7)	2 (15.4)	0.585*	21 (16.5)	4 (18.2)	13 (28.3)	0.233
Diarrhoea	8 (3.0)	5 (5.6)	3 (5.5)	0.469	8 (7.9)	0 (0)	0 (0)	0.368*	9 (7.1)	3 (13.6)	1 (2.2)	0.168*
Breathlessness	6 (2.2)	7 (7.8)	3 (5.5)	0.046	2 (2.0)	0 (0)	1 (7.7)	0.325*	6 (4.7)	0 (0)	2 (4.3)	0.871*
Palpitation	14 (5.2)	13 (14.4)	3 (5.5)	0.014	4 (4.0)	1 (4.3)	0 (0)	1.00*	8 (6.3)	0 (0)	3 (6.5)	0.720*
Sleep disturbances	32 (11.9)	34 (37.8)	2 (3.6)	< 0.001	29 (28.7)	3 (13.0)	0 (0)	0.031	32 (25.2)	3 (13.6)	1 (2.2)	0.002

Level of significance was analysed by Chi square test. In '*' Fisher's Exact Test was used

Table 3 Chances of getting type I error or false positive results among the different adverse events following vaccination

Adverse events	Bonferroni corrector α = significance level (α)/number of test (*n*)	Family wise error rate (FWER) = [1-(1-α)^n][a]	Chance of type I error or false positive result
Pain at injection site	0.0003	0.003	0.3%
Redness	0.0936	0.5455	54.55%
Swelling	0.0048	0.0378	3.78%
Fever	0.0001	0.001	0.1%
Chills	0.0001	0.001	0.1%
Fatigue	0.0001	0.001	0.1%
Myalgia	0.0001	0.001	0.1%
Dizziness	0.0067	0.0524	5.24%
Headache	0.0001	0.001	0.1%
Blur vision	0.024	0.1767	17.67%
Nausea	0.0002	0.0016	0.16%
Loss of appetite	0.0008	0.0064	0.64%
Increase appetite	0.0291	0.2105	21.05%
Diarrhoea	0.0586	0.3832	38.32%
Breathlessness	0.0057	0.0448	4.48%
Palpitation	0.09	0.5298	52.98%
Sleep disturbances	0.0001	0.001	0.1%

[a]α denoted the original significance level, $n = 8$, represented the number cooperative test

were lowest among those who received the CoronaVac booster, in contrast to Comirnaty and Vaxzevria booster recipients (Fig. 2C) (Table 2). Only 2.2% of recipients reported experiencing loss of appetite after receiving CoronaVac booster, compared to 25% who had it after receiving a Vaxzevria booster dose. 25% of recipients had sleep disturbances after taking the Comirnaty booster dosage, compared to 2.2% of recipients who took the CoronaVac booster (Table 2). We found that a number of acute adverse events, including pain at injection site, swelling, fever, chills, fatigue, myalgia, headache, nausea, loss of appetite, and sleep disruptions, were within the acceptable range for a Type 1 error of 5% after vaccination (Table 3). Type 1 error across the different adverse events were varied from 0.1 to 54.55%.

Number of adverse events following vaccination

Among the vaccines, the average number of adverse events was found to be highest for Vaxzevria after the first dose ($n = 6$) and booster dose ($n = 6$). Following the first, second, and booster doses of the Comirnaty vaccine, an increasing average number of adverse events ($n = 3$, $n = 4$, $n = 5$) was observed. In contrast, fewer adverse events were reported on average ($n = 3$, $n = 2$, $n = 2$) after the first, second, and booster doses of the CoronaVac vaccine. On day 1 after receiving the Comirnaty vaccine, 96.3% of recipients reported experiencing at least one adverse event which was subsequently increased during doses 2 and 3, eventually reached 100% following the booster vaccine. In contrast, 87.3% of recipients of the CoronaVac vaccine reported of having at least one adverse event at dose 1 day 1 which was further decreased to 69.2% in the second dose and again increased to 85.1% after the booster dose. Approximately 95.6% of the people who received the first dose or booster dose of Vaxzevria reported at least one adverse event following vaccination (Table 4).

Gender and age stratification with at least one adverse event following vaccination

Overall vaccination exposure and adverse event outcomes after doses 1, 2, and 3 were found to be statistically significant ($p < 0.05$). There was no association between the genders and the adverse events following 1 st dose of vaccination. Following the second dose of vaccination, male gender stratified by vaccine exposure exhibited a significant association with adverse outcomes ($p = 0.003$). Subsequent to the booster (third dose) vaccination, both male and female genders demonstrated a strong correlation between adverse events and vaccine exposure (males $p = 0.012$, females $p = 0.005$) (Table 4). Gender modification effect was positive, i.e. the combination of male and female were found significant in producing at least one adverse event after dose 1 of vaccination. Gender could be a confounding factor in this case as individual male and female data were not significant. In case of dose 3 gender is not a confounding factor while in dose 2 male effect was masked the female response.

A significant higher proportion of younger adults (18–24 years) reported to have significant higher adverse events compared to older adults (25 years and above) following the 1 st dose of vaccine ($p = 0.032$). In contrast,

Table 4 Gender stratification for association between different types of vaccines and having at least one adverse event

Exposure	Having at least one adverse event		Fisher's exact test	*P*
	Yes, *n* (%)	No, *n* (%)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	259 (96.3)	10 (3.7)	6.50	0.031
Vaxzevria	86 (95.6)	4 (4.4)		
CoronaVac	48 (87.3)	7 (12.7)		
Male gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	91 (93.8)	6 (6.2)	4.98	0.069
Vaxzevria	31 (96.9)	1 (3.1)		
CoronaVac	15 (78.9)	4 (21.1)		
Female gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	168 (97.7)	4 (2.3)	3.70	0.126
Vaxzevria	55 (94.8)	3 (5.2)		
CoronaVac	33 (91.7)	3 (8.3)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	98 (97.0)	3 (3.0)	13.18	< 0.001
Vaxzevria	19 (82.6)	4 (17.4)		
CoronaVac	9 (69.2)	4 (30.8)		
Male gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	42 (97.7)	1 (2.3)	11.88	0.003
Vaxzevria	6 (75.0)	2 (25.0)		
CoronaVac	1 (33.3)	2 (66.7)		
Female gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	56 (96.6)	2 (3.4)	4.83	0.074
Vaxzevria	13 (86.7)	2 (13.3)		
CoronaVac	8 (80.0)	2 (20.0)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	127 (100)	0 (0)	17.15	< 0.001
Vaxzevria	21 (95.5)	1 (4.5)		
CoronaVac	40 (85.1)	7 (14.9)		
Male gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	38 (100)	0 (0)	8.15	0.012
Vaxzevria	4 (100)	0 (0)		
CoronaVac	9 (75.0)	3 (25.0)		
Female gender stratified for vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	89 (100)	0 (0)	9.44	0.005
Vaxzevria	17 (94.4)	1 (5.6)		
CoronaVac	31 (88.6)	4 (11.4)		

Table 5 Age stratification for association between different types of vaccines and having at least one adverse event

Exposure	Having at least one adverse event		Fisher's exact test	*P*
	Yes, *n* (%)	No, *n* (%)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	259 (96.3)	10 (3.7)	6.50	0.031
Vaxzevria	86 (95.6)	4 (4.4)		
CoronaVac	48 (87.3)	7 (12.7)		
Age (18–24 years) stratified for vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	152 (97.4)	4 (2.6)	6.19	0.032
Vaxzevria	53 (96.4)	2 (3.6)		
CoronaVac	35 (87.5)	5 (12.5)		
Age (25 years and above) stratified for vaccine exposure and having adverse event of outcomes (after Dose 1)				
Comirnaty	107(94.7)	6 (5.3)	1.85	0.409
Vaxzevria	33 (94.3)	2 (5.7)		
CoronaVac	13 (86.7)	2 (13.3)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	98 (97.0)	3 (3.0)	13.18	< 0.001
Vaxzevria	19 (82.6)	4 (17.4)		
CoronaVac	9 (69.2)	4 (30.8)		
Age (18–24 years) stratified for vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	26 (92.9)	2 (7.1)	3.22	0.231
Vaxzevria	11 (73.3)	4 (26.7)		
CoronaVac	9 (81.8)	2 (18.2)		
Age (25 years and above) stratified for vaccine exposure and having adverse event of outcomes (after Dose 2)				
Comirnaty	71 (98.6)	1 (1.4)	14.67	0.002
Vaxzevria	8 (100)	0 (0)		
CoronaVac	0 (0)	2 (100)		
Overall vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	127 (100)	0 (0)	17.15	< 0.001
Vaxzevria	21 (95.5)	1 (4.5)		
CoronaVac	40 (851)	7 (14.9)		
Age (18–24 years) stratified for vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	99 (100)	0 (0)	14.32	< 0.001
Vaxzevria	18 (94.7)	1 (5.3)		
CoronaVac	32 (84.2)	6 (15.8)		
Age (25 years and above) stratified for vaccine exposure and having adverse event of outcomes (after Dose 3)				
Comirnaty	28 (100)	0 (0)	3.80	0.300
Vaxzevria	3 (100)	0 (0)		
CoronaVac	8 (88.9)	1 (11.1)		

substantial higher proportion of older adults reported to have significant adverse events compared to young adults following 2nd dose of vaccination ($p = 0.002$). Short term adverse events following booster vaccination was found more frequently in young adults ($p < 001$) compared to older age groups (Table 5). In case of dose 1 and dose 3

Table 6 Comparison of having at least one adverse event after taking booster dose compared to the first and second doses of COVID-19 vaccine

Doses	Having at least one adverse event	Did not have adverse event	OR (95%CI)	*P*
Dose 3 (booster dose)	188 (95.9)	8 (4.1)	1.26 (0.55, 2.89)	0.591
Dose 1	393 (94.9)	21 (5.1)		
Dose 3 (booster dose)	188 (95.9)	8 (4.1)	2.05 (0.80, 5.24)	0.126
Dose 2	126 (92.0)	11 (8.0)		

Table 7 Comparison of different types of vaccines and having at least one adverse event

Vaccines	Having at least one adverse event *n* (%)	Did not have adverse event *n* (%)	Adjusted OR (95%CI)	*P*[a]
Dose 1				
Comirnaty	259 (96.3)	10 (3.7)	Reference	
Vaxzevria	86 (95.6)	4 (4.4)	0.49 (0.13, 1.89)	0.303
CoronaVac	48 (87.3)	7 (12.7)	0.18 (0.05, 0.62)	0.006
Dose 2				
Comirnaty	98 (97.0)	3 (3.0)	Reference	
Vaxzevria	19 (82.6)	4 (17.4)	0.11 (0.01, 1.86)	0.125
CoronaVac	9 (69.2)	4 (30.8)	0.16 (0.02, 1.44)	0.102
Dose 3				
Comirnaty	127 (100)	0 (0)	Reference	
Vaxzevria	21 (95.5)	1 (4.5)	-	-
CoronaVac	40 (85.1)	7 (14.9)	-	-

[a]Multivariate logistic regression analysis: the model is adjusted for age, gender, ethnicity, nationality, smoking status, having comorbidities such as hypertension, diabetes mellitus, overweight, asthma, coronary heart diseases, fatty liver, and diet pattern)

early adults were masked the response of elderly people while in case of dose 2 elderly people masked the effect of early adults. Therefore, age might not be a confounding factor in exerting side effects.

There was no substantial difference in experiencing at least one adverse event after the booster dose compared to the first ($p = 0.591$, odd ratio 1.26 (0.55, 2.89) and second doses ($p = 0.126$, odd ratio 2.05 (0.80, 5.24) (Table 6).

Multivariate model after adjusted for age, gender, ethnicity, nationality, smoking status, having comorbidities such as hypertension, diabetes mellitus, overweight, asthma, coronary heart diseases, fatty liver, and diet pattern Corona vac was significantly lower ($p = 0.006$) odds of having at least one adverse event compared to Comirnaty after the first dose. Following dose 2 and dose 3 vaccination there were no statistically significant comparisons of different types of vaccines and having at least one adverse event (Table 7).

Onset of major adverse events after Covid-19 vaccination

Our research has led us to identify three main adverse events following vaccination: pain, fever, and fatigue (Table 8).

Pain at the injection site

The most commonly observed time period for the onset of pain after the initial dose of the Comirnaty vaccine was > 5 h (26.8%), followed by 1–3 h (24.5%) and 3–5 h (19.3%). Similar to Comirnaty recipients, Vaxzevria vaccine recipients experienced pain most often at > 5 h (25.6%), followed by 3–5 h (16.5%), and immediately after the vaccination (15.6%). In contrast, 29.1% of the CoronaVac vaccine recipients reported no pain. However, individuals who reported pain did so shortly after the injection (23.65%), followed by one-hour post-immunization. The majority of CoronaVac recipients (69.2%) reported no pain after the second dose. Among the Comirnaty recipients who reported pain, 22.8% experienced pain after three to five hours, and 24.8% experienced pain after more than five hours of vaccination. Recipients of the Vaxzevria vaccine most commonly experienced pain within one hour (34.8%) and between one and three hours (26.1%).

After the Comirnaty booster dose, the recipients reported pain within 1 h (20.5%), at 1–3 h (27.6%) and > 5 h (26.8%). In contrast, among recipients of the Vaxzevria booster dose, pain was most frequently reported within 1 h (27.3%), followed by 1–3 h (22.7%), and 3–5 h (18.2%). However, 31.9% of the CoronaVac booster dose recipients experienced no pain. Among those who experienced pain, 34% did so within the first hour of injection, and 14.9% did so an hour after immunization (Table 8).

Fever

After 6–12 h of the first dose of Vaxzevria, fever was most frequently detected (43.3%), followed by 12–24 h (21.1%) of vaccination. Fever was rarely developed (< 4%) following any dose of CoronaVac. However, among the dose 1 Comirnaty recipients, 7.8% and 6.7% of individual developed fever after 12–24 h and 6–12 h following vaccine respectively. After the Comirnaty booster dose, fever started to appear usually at 6–12 h (21.3%) followed by 12–24 h (15.7%). Similarly, among Vaxzevria recipients, fever was reported between 6 and 12 h (22.7%) or 12–24 h (18.2%) following booster shots.

Fatigue

Fatigue was commonly reported 6–12 h after the first dose of Vaxzevria (44.4%) followed by 24–36 h (24.4%)

Table 8 Onset of adverse events (pain, fever, and fatigue) following vaccination

Adverse events after vaccine	Dose 1			Dose 2			Dose 3		
	Comirnaty (*n* = 269)[a]	Vaxzevria (*n* = 90)	CoronaVac (*n* = 55)	Comirnaty (*n* = 101)	Vaxzevria (*n* = 23)	CoronaVac (*n* = 13)	Comirnaty (*n* = 127)	Vaxzevria (*n* = 22)	CoronaVac (*n* = 46)[b]
Pain starts									
Immediately	17 (6.3)	14 (15.6)	13 (23.6)	9 (8.9)	1 (4.3)	2 (15.4)	11 (8.7)	0	16 (34.0)
Within 1 h	37 (13.8)	13 (14.4)	10 (18.2)	16 (15.8)	8 (34.8)	0 (0)	26 (20.5)	6 (27.3)	7 (14.9)
1–3 h	66 (24.5)	12 (13.3)	9 (16.4)	18 (17.8)	6 (26.1)	1 (7.7)	35 (27.6)	5 (22.7)	2 (4.3)
3–5 h	52 (19.3)	15 (16.7)	4 (7.3)	23 (22.8)	2 (8.7)	0 (0)	12 (9.4)	4 (18.2)	2 (4.3)
> 5 h	72 (26.8)	23 (25.6)	3 (5.5)	25 (24.8)	0 (0)	1 (7.7)	34 (26.8)	3 (13.6)	4 (8.5)
Not applicable	25 (9.3)	13 (14.4)	16 (29.1)	10 (9.9)	6 (26.1)	9 (69.2)	9 (7.1)	4 (18.2)	15 (31.9)
Fever starts									
< 6 h	7 (2.6)	8 (8.9)	1 (1.8)	10 (9.9)	2 (8.7)	0 (0)	4 (3.1)	3 (13.6)	1 (2.1)
6–12 h	18 (6.7)	39 (43.3)	1 (1.8)	15 (14.9)	5 (21.7)	0 (0)	27 (21.3)	5 (22.7)	2 (4.3)
12–24 h	21 (7.8)	19 (21.1)	2 (3.6)	15 (14.9)	0 (0)	0 (0)	20 (15.7)	4 (18.2)	1 (2.1)
25–48 h (> 24 h)	6 (2.2)	3 (3.3)	0 (0)	5 (5.0)	1 (4.3)	0 (0)	11 (8.7)	0	0
Not applicable	217 (80.7)	21 (23.3)	51 (92.7)	56 (55.4)	15 (65.2)	13 (100.0)	65 (51.2)	10 (45.5)	42 (89.4)
Fatigue starts									
< 6 h	57 (21.2)	12 (13.3)	13 (23.6)	29 (28.7)	6 (26.1)	2 (15.4)	15 (11.8)	4 (18.2)	6 (12.8)
6–12 h	57 (21.2)	40 (44.4)	9 (16.4)	15 (14.9)	3 (13.0)	0 (0)	40 (31.5)	11 (50.0)	10 (21.3)
12–24 h	42 (15.6)	22 (24.4)	5 (9.1)	20 (19.8)	4 (17.4)	2 (15.4)	28 (22.0)	2 (9.1)	4 (8.5)
> 24 h	0	0	0	0	0	0	14 (11.0)	1 (4.5)	2 (4.3)
Not applicable	113 (42.0)	16 (17.8)	28 (50.9)	34 (33.7)	9 (39.1)	9 (69.2)	30 (23.6)	4 (18.2)	24 (51.1)

[a]Missing value = 2, [b]missing value = 1

of vaccination. In contrast, following first dose of Comirnaty vaccine fatigue was frequently experienced by recipients within 6 h (21.2%) and 6–12 h (21.2%) of vaccination. However, a substantial proportion of CoronaVac vaccine users (50.9%, 69.1%, and 51%) reported no fatigue following doses 1, 2, and 3, respectively. After the Comirnaty booster dose, fatigue frequently appeared 6–12 h (31.5%) or 12–24 h (22%) of vaccination. Similarly, after receiving booster doses, Vaxzevria recipients commonly experienced fatigue within 6–12 h (50%) or less than 6 h (18.2%) of vaccination (Table 8).

Two recipients of the first-day Comirnaty vaccine and one recipient of the third-day CoronaVac vaccine failed to respond when adverse effects started. As a result, those data were missing.

Duration of adverse events following Covid-19 vaccination

The self-reported durations of adverse events associated with different vaccines were presented in Fig. 3. Adverse events were not reported after the second dose of the CoronaVac vaccine. However, after the booster dose, the majority of adverse events lasted 24 h.

In 28% of recipients, increased appetite was also reported to persist until day 3 after the booster (Fig. 3A). The duration of adverse events following the second dose of the Comirnaty vaccine was short, with the majority of adverse events resolving within 2 days. Muscle pain, fatigue, swelling, and breathlessness lasted longer, up to 2–3 days for some individuals (Fig. 3B). The self-reported durations of adverse events after the booster dose of the Comirnaty vaccine were short (within 2 days) for itchiness, dizziness, redness, nausea, breathlessness, headache, and fever. Some adverse events, such as pain (at site of injection), muscle pain (myalgia), and sleep disturbances, lasted 2 to 3 days (Fig. 3C).

The adverse events following the second dose of Vaxzevria extended up to day 3, except for sleep disturbances, which were reported to be resolved by < 24 h (Fig. 3D). After the booster dose of the Vaxzevria vaccine, itching, sleep disturbances, increased appetite, fever, and swelling were reported to last less than 2 days. The other adverse events, such as muscle pain (myalgia), dizziness, nausea, pain (at the injection site), generalized muscle pain, fatigue and headache, lasted up to 3–4 days (Fig. 3E).

Discussion

The Ministry of Health, Malaysia, has introduced mRNA, viral vectors, and inactivated viral vaccines to control the spread of the Covid-19 pandemic [4]. The adverse events associated with primary and booster doses of this vaccine in Malaysia have yet to be elucidated. In this study, we investigated the prevalence of adverse events following primary and booster doses of the Comirnaty, Vaxzevria, and CoronaVac vaccines. Our study revealed significant variation in the short-term adverse events reported by vaccine recipients depending on the type of Covid-19 vaccine they received. The most common adverse event

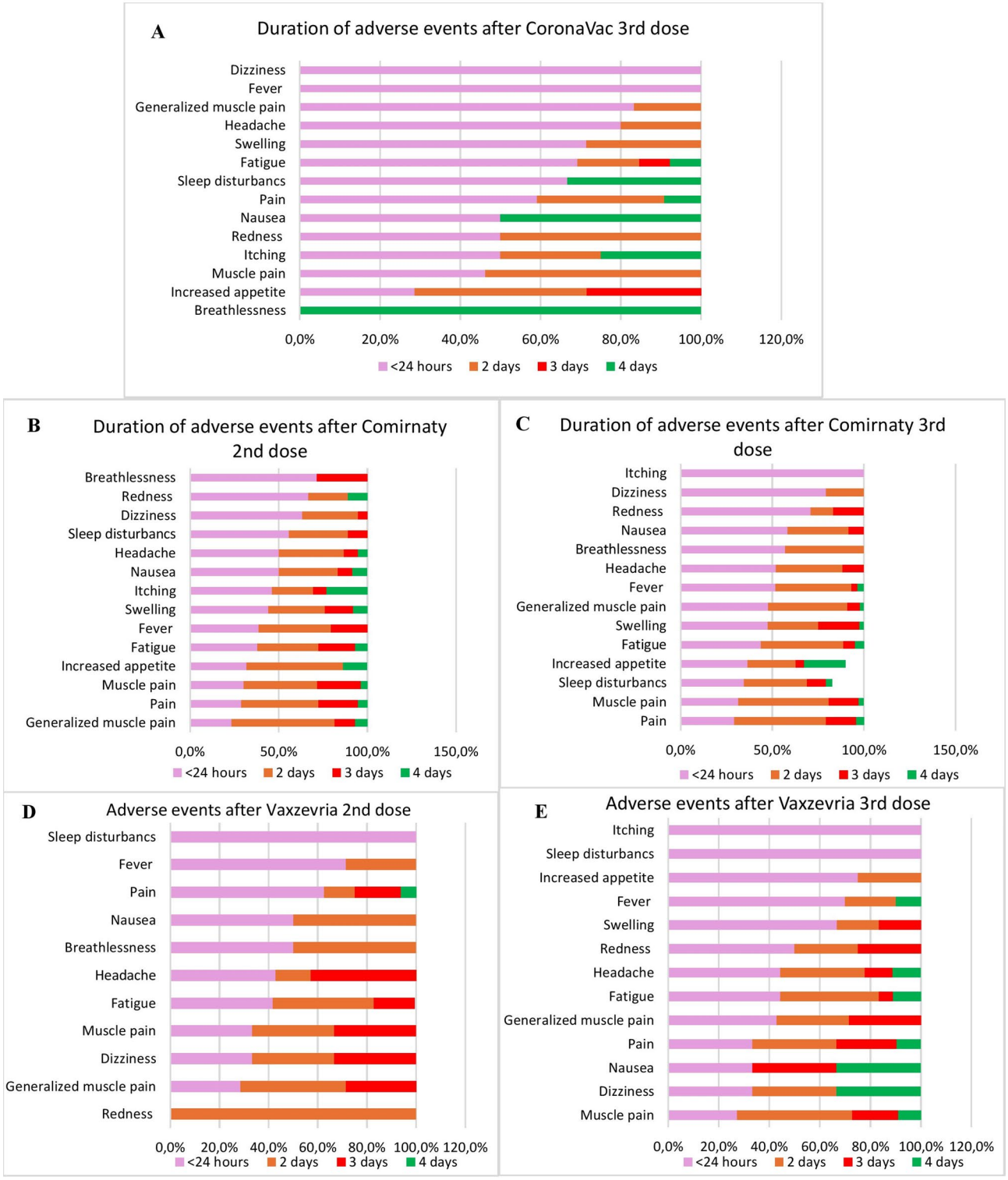

Fig. 3 Duration of adverse events associated with Covid-19 vaccines. Figure 3**A**: Duration of adverse events following booster administration of the CoronaVac vaccine. Figure 3**B** and 3**C** show the duration of adverse events following the 2nd and 3rd doses of Comirnaty. vaccine. Figure 3**D** and 3**E** shows the duration of adverse events following the 2nd and 3rd doses of the Vaxzevria vaccine

reported consistently among all types and doses of the Covid-19 vaccine was pain at the injection site. However, its magnitude differed. Following the first dose, pain was common in Comirnaty recipients (87.4%), followed by Vaxzevria (84.4%) and CoronaVac vaccine recipients (69.1%). This finding was consistent with a previous study conducted among healthcare workers in the Czech Republic who received the Pfizer–BioNTech vaccine, in which injection site pain was most prevalent in among < 55-year-old individuals [30]. The differences in occurrence of pain at the injection site with different Covid-19 vaccines could attributed to immune or inflammatory responses to the antigens. Comirnaty and Vaxzevria were mRNA and recombinant viral vaccines, respectively, and usually developed more localized inflammation at the site of injection than CoronaVac (an inactivated viral vaccine). Lipid nanoparticles, which were used in an mRNA vaccine, were linked to enhanced local inflammation and may hence exacerbate injection site pain [31]. Fatigue (56.9%) and myalgia (37.2%) were the next most common adverse events following the first dose of Comirnaty. Fatigue was the most commonly reported side effects in VAERS) and V-safety studies conducted in USA following first dose of Comirnaty [32].

We observed occurrence of fever following Comirnaty vaccination subsequently increased from dose 1 to dose 3. In UK, less than 5% of recipients experienced fever after first doses of Comirnaty vaccine [33]. Comirnaty was linked to increased IgG against the S1 protein antibody titre and Ig RBD neutralizing antibody activity thereby it triggered more systemic side effects such fever, myalgia, and headache [34]. Activation of the immune system resulted in the transient production of pro-inflammatory cytokines that also caused inflammation in muscles, blood vessels, respiratory tract and other tissues [35]. Activation of toll-like receptors by adjuvants used in mRNA vaccine might further elevated the systemic adverse effects as fever, headache, flu-like symptoms, and breathlessness [35, 36]. In order to provide targeted protection against the Covid-19 infection, vaccines contain antigens that trigger an immune response. Following Comirnaty vaccine, mRNA was internalized and quickly translated by antigen-presenting cells (APC) in draining lymph nodes as well as at the injection site, where it triggered strong in vivo adaptive as well as humoral immune responses by activating more $CD8^+$ T-cells and generating more RBD-specific and neutralizing antibodies in humans [37]. In contrast, Vaxzevria was a recombinant non-replicating viral vector vaccine that stimulates a robust humoral and innate immunological response by causing host cells to produce the S protein [38]. The most frequent adverse events following the first dose of Vaxzevria were pain at the injection site (84.4%), fatigue (83.3%), fever (76.7%), headache (58.9%), and myalgia (53.3%). The incidence of adverse events following the first dose was greater among Vaxzevria recipients than those who received Comirnaty or CoronaVac due to greater humoral immune response. These results were in line with a study done on Danish citizens that showed higher side effects following first dose of Vaxzevria than those who got mRNA vaccine [39]. Prior report suggested that viral vector vaccines provide a pro-inflammatory milieu, which increased the production of type-I IFN. These cytokines primarily triggered by the transcription factors NF-kB, IRF7, and IRF3 [40]. Following Vaxzevria vaccination, proinflammatory cytokines like interleukin-6 (IL-6) and tumour necrosis factor (TNF-α) were released as a result of macrophage activation which further elevated the helper T-cell differentiation [41, 42]. Furthermore, helper T-cells released IL-4 and IL-6 cytokine which in turn activated B-cells. Activation and proliferation of B-cells elicited humoral immune response and elevated pro-inflammatory cytokines also attributed to the strong innate immune response following Vaxzevria vaccination [43].

Similar to earlier reports, we noticed, the incidence of systemic adverse events like pain, fatigue, headache, myalgia, fever, and insomnia were higher in recipients of second dose of Comirnaty vaccination than in those who received the Vaxzevria and CoronaVac vaccines [37, 44]. The molecular complexity and immunogenicity of second-dose of Comirnaty were probably linked to these increases in adverse events [34]. In contrast, following the second dose of the CoronaVac vaccination swelling at the injection site was the major adverse event. The primed expansion of dendritic cells and T cells into resident memory cells in the skin was the probable reason for the local reaction after intramuscular administration of inactivated vaccinations [45].

Our study also revealed that the incidence of adverse events following the second dose of Vaxzevria was lower than the first and booster doses. These results were in line with a study done in South Korea where health workers had less systemic and local adverse effects following second dosage of the Vaxzevria vaccine [46]. Another cross-sectional study by Haider et al., revealed that most adverse events considerably decreased after the second dose [13]. These findings contradicted those of another Canadian study that found adverse events were more common following the second dose than the first [11]. The exact reason of decreased adverse events was unknown, but extrinsic and intrinsic factors might influence the reactogenicity profile, tolerability and immunogenicity of vaccines.

In the third dose (booster vaccine), recipients of the Comirnaty and Vaxzevria vaccines reported significantly greater adverse events (fever, chills, fatigue and pain at the injection site) than did those receiving the CoronaVac

vaccine. Both mRNA and adenovirus vector vaccines activate longer-lived memory B cells and $CD4^+$ T cells, which ultimately evoke the production of serum IgA and IgG antibodies against anti-S antibody and anti-RBD (receptor binding domain)-neutralizing antibodies [47]. Pain and tenderness at the injection site were the most frequent adverse events following third dose of COVID-19 vaccination. This finding corroborates with the studies conducted globally in Brazil, South Africa and UK [48], Czech Republic [30], US [32], and Vietnam [49] which also showed a high incidence of pain at the injection site to Comirnaty and Vaxzevria vaccination. In contrast to our study, fever was less frequently reported in the UK following administration of Comirnaty vaccine [33] Higher incidences of fatigue, myalgia, and headache were reported in the study conducted in the US [32] which was similar to the findings of our study. The variations in the frequency of adverse events across different regions might attributed to the genetic and ethnic differences and the differences in the adverse event reporting systems.

One in four people experienced sleep difficulty following a booster dose of Comirnaty. The recipients who received the Vaxzevria booster experienced loss of appetite. Studies have shown that the injection of Covid-19 vaccines results in the production of proinflammatory cytokines such as IL-1b, IL-6, and IFN γ by microglia of the brain and in the circumventricular organs (CVOs) and choroid plexus. These cytokines projected to hypothalamic nuclei that regulate food intake and sleep [50]. The underlying mechanisms of sleep disturbances and changes in food intake associated with each type of Covid-19 vaccine remain poorly understood.

Similar to previous study, we found that demographic variables like age, gender, and underlying medical conditions had an impact on adverse events that happened after vaccination [51]. We controlled for potential confounders, such as age and gender, by stratification. We found that young age was an independent risk factor for at least one adverse event following the 1 st dose of vaccine. Being old or male, were both significantly associated with higher adverse events following the 2nd dose of vaccine. Aging was associated with immune-senescence that resulted in diminished humoral and cellular immune responses [52]. Age-associated decreased in TLR function had been previously reported to affect vaccine immunogenicity as it decreased the levels of proinflammatory cytokines following vaccination [53, 54]. In a longitudinal study, both Comirnaty and Vaxzevria exhibited significantly lower anti-trimeric spike IgG levels and neutralizing antibody titres in older adults compared to younger adults [55]. These physiological responses helped to explain why younger people experienced noticeably more adverse events after their first vaccination than older people did. Studies had shown a lower prevalence of adverse events after Comirnaty or Vaxzevria vaccination in recipients aged 50 years or older [33].

The number of respondents who experienced at least one adverse event on Day 1 was highest among those who received the Comirnaty vaccination at all doses and lowest among those who received the CoronaVac vaccination. Irrespective of gender, and age distribution following booster adverse events and their severity was found to be increased while after second dose of vaccine older age males represented more severe adverse events. These findings were consistent with the results of a study conducted among healthcare workers in South Korea, where most recipients experienced at least one adverse reaction during days 0–7 following Vaxzevria vaccination [56]. The average number of adverse events was highest for Vaxzevria following both the first and booster doses. In contrast, Comirnaty exhibited a progressive increase in the average number of adverse events across the first, second, and booster doses as similar to the reports found in USA following mRNA-1273 vaccine with multiple doses [57]. Reactogenicity tends to be greater with Vaxzervria and Comirnaty vaccines due to more immune memory activation.

Increased reactogenicity leads to release of pro-inflammatory cytokines [58]. Prior reports indicated that viral vector vaccines typically demonstrated an enhanced memory B cell (IgM and IgG) and T cell response, in addition to a robust antibody response [59]. Vaxzevria showed increased release of Th1 cytokines, including IL-2, TNF-α, and IFN-γ, produced by CD4 + T cells [60]. This dominating Th1 response could be the reason of increased adverse events.

The average number of adverse events was lower after first dose, second dose and the booster dose following CoronaVac vaccine. Similar to earlier study our finding suggested that CoronaVac might linked to roughly five times lesser side effects than the Comirnaty or Vaxzevria vaccines [61]. Following the second dose of the CoronaVac vaccine, no adverse events were reported. However, after the booster dose of the CoronaVac vaccine, most adverse events occurred within a brief duration (< 24 h). The decrease in the number of adverse events with CoronaVac can be attributed to its inactivated nature and to its antibody titer, which diminishes over time. The duration of adverse events after vaccination differed based on the type and dose of the vaccine. Adverse effects may vary in onset and durability due to the different immunogenic processes of mRNA-based vaccinations, viral vector vaccines, and inactivated vaccines. Furthermore, most adverse events imply very little type I error (≤ 5%), indicating that the study was more reliable.

Strengths

I. **Comparison of adverse events across different vaccine platforms**: Our study of post-vaccination adverse events compared how various vaccine platforms like mRNA (Comirnaty), viral vector (Vaxzevria), and inactivated (CoronaVac) vaccines could trigger distinct immunological physiological responses.Comparison of adverse events across different vaccine platforms: Our study of post-vaccination adverse events compared how various vaccine platforms like mRNA (Comirnaty), viral vector (Vaxzevria), and inactivated (CoronaVac) vaccines could trigger distinct immunological physiological responses.

II. **Dose-Dependent Reactogenicity**: We investigated the putative role of immune priming in vaccine reactogenicity by comparing the frequency and severity of adverse events following first, second, and booster doses.Dose-Dependent Reactogenicity: We investigated the putative role of immune priming in vaccine reactogenicity by comparing the frequency and severity of adverse events following first, second, and booster doses.

III. To our knowledge, no other study has compared the adverse events associated with different vaccines following primary and booster doses of Covid-19 vaccination in Malaysia. This knowledge across different vaccine platforms might help in the design of vaccines for other diseases in the future.To our knowledge, no other study has compared the adverse events associated with different vaccines following primary and booster doses of Covid-19 vaccination in Malaysia. This knowledge across different vaccine platforms might help in the design of vaccines for other diseases in the future.

Limitations

This study relied on self-reported symptoms, which may be subjected to recall bias. Recipients might underreported transient symptoms or inaccurately recalled the timing or severity of events, particularly if there was a delay between symptom onset and survey completion. Moreover, we did not independently validate severe symptom reports (e.g., breathlessness) with clinical assessments or medical records, which may affect the precision of symptom classification. While self-reporting is a pragmatic and widely used method in population-based research, especially under pandemic-related constraints, these limitations should be considered when interpreting the findings. A low response rate raises the possibility of non-response bias, which could jeopardize the study's external credibility and make it challenging to extrapolate results to the intended audience. The low participation rate could be attributed to a number of factors including survey fatigue, a lack of financial or non-monetary incentives, and huge Covid-19 patient load in hospitals and prolonged university holidays followed by work from home. Recipients were recruited from different medical schools and were predominantly volunteers. This may create a potential selection bias. A key limitation of this study is the absence of an unvaccinated control group, which resulted from government health mandates that required vaccination for all federal government employees and healthcare professionals. This limitation restricts the ability to draw direct causal inferences regarding the effect of vaccination compared to unvaccinated individuals. However, the internal consistency of our data and alignment with findings from other studies that included unvaccinated cohorts support the validity of our conclusions. Future studies with broader participant inclusion may help to address this gap. There was an unequal distribution of vaccine recipients by age category, with a higher percentage of younger medical students, lecturers, and medical professionals in the 18–45 years age range than those over 45 years. There were fewer recipients in some vaccine groups (CoronaVac, Vaxzevria) after the second dose. This study was a self-reported study based on recipients' perceptions of adverse events, which were not clinically evaluated or confirmed. Given the online nature of the study, not all the recipients responded to all the surveys. We were unable to observed the severity of the adverse events. A graded severity scale of mild, moderate or severe would have offered a comprehensive understanding of patterns of adverse events. Our study focused on short-term adverse events following COVID-19 vaccination. Long post-vaccination side effects tracking could provide information about the vaccine safety.

Suggestions for future research

1. Long-term safety monitoring beyond 7 days is desirable in future research studies to assess the possibility of delayed adverse events, especially for booster doses and different vaccine combinations.
2. Participation can be increased by using a streamlined, clear, and easy-to-use questionnaire and offering financial or other incentives. The rate of participation may be raised by sending out individualized invitations, sending out several personalized reminders, ensuring anonymity and confidentiality regarding data protection procedures, and scheduling events during less demanding times.
3. Immune response, genetic predisposition, and demographic factors associated with vaccine reactogenicity and severity of the adverse events may provide further insights into individual variability.

4. Comparisons of different vaccine platforms in diverse populations will further help refine vaccine safety and policy recommendations.

Conclusion

In conclusion, pain at the injection site, fatigue, fever and headache were the most frequently reported adverse events across all vaccine types. Compared with Comirnaty and CoronaVac recipients, individuals who received Vaxzevria had the highest rate of adverse events following the first dose of the Covid-19 vaccine, which decreased after the second dose but again significantly increased after the booster dose. The higher rate of adverse events observed with Vaxzevria may be attributed to activation of pro-inflammatory pathways triggering a strong innate immune response by adenoviral vector vaccines. Adverse events after getting the Comirnaty vaccine steadily increased following the primary and booster doses; however, adverse events following the CoronaVac vaccine subsequently decreased from primary to booster vaccinations.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

SD, RP, and GP helped to create and conceptualize the manuscript. SD, RP, GP, and AVT created the questionnaires. Online data collection and processing were performed by SSD, RP, AVT and MNNH. MNNH, SM, and RP analyzed and interpreted the data. SD, RP, MNNH, and AVT wrote the manuscript. The manuscript was proofread by GP and SM. All the authors have approved the final version of the manuscript.

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Data availability

According to the institutional regulations of the ethics committee, data representing sensitive patient information are restricted; our data involving clinical data of vaccine recipients are not freely available in a public repository. However, the data are available upon request

Declarations

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Physiology, Faculty of Medicine, Manipal University College Malaysia, Melaka, Malaysia
[2]Department of Biochemistry, Faculty of Medicine, Manipal University College Malaysia, Melaka, Malaysia
[3]Department of Community Medicine, Faculty of Medicine, Manipal University College Malaysia, Melaka, Malaysia
[4]Department of Physiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
[5]Department of Social and Preventive Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

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