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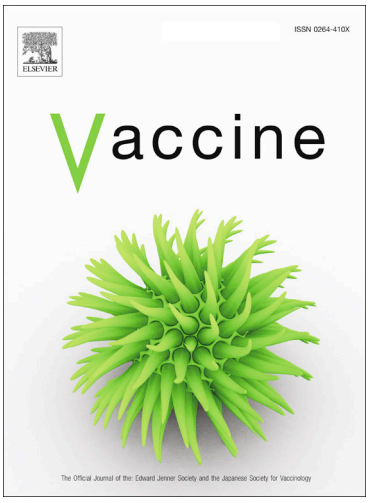

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Yousif A. M. Hassan, Mohammad Daud Ali, Rawan Rashad Al-Eid, Fatimah Ali Al Ghuraya, Zainab Essa Alqasimi, Ayaz Ahmad, Zainab Eltrafi, Sherihan Ahmad Ghosn

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A Retrospective Evaluation of Side-Effects Associated with the Booster Dose of Pfizer-BioNTech/BNT162b2 COVID-19 Vaccine among females in Eastern Province, Saudi Arabia

Yousif A. M. Hassan[a], Mohammad Daud Ali[a,*], Rawan Rashad Al-Eid[a], Fatimah Ali Al Ghuraya [a], Zainab Essa Alqasimi[a], Ayaz Ahmad[a], Zainab Eltrafi[a], Sherihan Ahmad Ghosn[a]

***Correspondence**
Dr. Mohammad Daud Ali, Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Abdulrazaq Bin Hammam Street, Al Safa, Dammam 34222, Saudi Arabia.
Email: dali.niper@gmail.com, mohammadd@machs.edu.sa

Dr. Yousif A. M. Hassan
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences
Abdulrazaq Bin Hammam Street, Al Safa, Dammam 34222, Saudi Arabia.
Email: yousifa@machs.edu.sa
ORCID iD: https://orcid.org/0000-0003-4227-5849

Dr. Mohammad Daud Ali
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: dali.niper@gmail.com, mohammadd@machs.edu.sa
ORCID iD: https://orcid.org/0000-0003-3752-2331

Ms.Rawan Rashad Al-Eid
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: 2018100143@machs.edu.sa

Ms.Fatimah Ali Al Ghuraya
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: 2018100141@machs.edu.sa

Ms.Zainab Essa Alqasimi
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: 2018100030@machs.edu.sa

Dr. Ayaz Ahmed
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: ayaza@machs.edu.sa
ORCID iD: https://orcid.org/0000-0003-3137-637X

Mrs.Zainab Eltrafi
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: zainaba30@machs.edu.sa
ORCID iD: https://orcid.org/0000-0001-8944-6831

Mrs. Sherihan Ahmad Ghosn
[a]Department of Pharmacy, Mohammed Al-Mana College for Medical Sciences, Dammam 34222, Saudi Arabia. Email: sherihang@machs.edu.sa

ORCID iD: https://orcid.org/0000-0003-4423-0126

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Institutional Review Board Statement

Prior to conduction of the study and the data collection, the proposed study has been ethically approved by the Ethical Committee of Mohammed Al-Mana College for Medical Sciences (MACHS) with approval number SR/RP/81. Furthermore, any information disclosing respondent identity was excluded from the tool. Before participating in the study, an online consent was also obtained from the respondents who took part in the study subject to assure all rights of privacy and secrecy of all registered data. Moreover, this study com-plies with the ethical rules of the 64th World Medical Association Declaration, General Assembly, Helsinki (2013).

Informed Consent Statement

Informed consent was obtained from all the respondents participated in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

All the author(s) declare none conflict of interest.

Author's Contributions

Writing of the first draft: M.A., Z.E. and S.G. (Mohammad Daud Ali, Zainab Eltrafi and Sherihan Ahmad Ghosn). Data analysis: M.A. (Mohammad Daud Ali). Con-cept, and design of the study: M.A. Participated review the manuscript, concept, and editing, writing and review, and revised the manuscript: M.A. and Y.H. (Yousif A. M. Hassan). Construc-tion of Questionnaire: M.A., R.E. (Rawan

Rashad Al-Eid). F.G., (Fatimah Ali Al Ghuraya), Z.A. (Zainab Essa Alqasimi) Review the manuscript: Y.H., and A.A.(Ayaz Ahmad) Data collection: R.E., F.G. and Z.A.. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

A Retrospective Evaluation of Side-Effects Associated with the Booster Dose of Pfizer-BioNTech/BNT162b2 COVID-19 Vaccine among females in Eastern Province, Saudi Arabia

Abstract

Backgrounds: The development of several types of vaccines to avert COVID-19 has taken place. Despite several reports of undesirable reactions noted post-COVID-19 vaccine administration, later remains one of the best prevention and management tools in fighting the spread of the virus and its variants and reducing the harshness of this viral attack. The purpose of the current paper was to explore the side-effects experienced by the females in the Eastern Province of Saudi Arabia directly after receiving the booster dose of the Pfizer-BioNTech/BNT162b2 COVID-19 vaccine.

Methods: A descriptive cross-sectional study among adults living in the East-ern Province, Saudi Arabia was applied. A survey link was, distributed through WhatsApp, SMS, or e-mail to community members. Respondent's demographic information was acquired, as well as information about any local and systemic side-effects reported following booster dose of BioNTech/BNT162b2 COVID-19 vaccine.

Results: A total of 72.36% (432/597) of the respondents who participated in this study reported at least one side-effect. Pain and redness at the injection site (75.93%), myalgia (71.99%), headache (53.24%), fever (33.56%), and fatigue (43.78%) were the highest frequently stated side-effects. Furthermore, 9.25% of the respondents had to see a physician due to side effects, plus merely four participants were admitted to the hospital. The respondents working in the non-healthcare-related sector had a 1.677-fold more possibility of side effects in comparison with the other respondents (adjusted odds ratio = 1.677; 95% CI = 1.363, 2.064).

Conclusions: All reported side-effects were mild to moderate. These findings might persuade pessimists and refusers to get the COVID-19 vaccine. Myalgia and pain or redness at the site of injection were the most common reported side-effects in our study.

Keywords: COVID-19 vaccine; side-effects; Female; Booster dose, Eastern province; Saudi Arabia.

1. Introduction

The pandemic impulse created by the virus SARS-CoV-2 resulted in millions of people getting infected and around six million deaths globally [1-2]. As of March 14th, 2022, there were 749,044 cases reported and 9,021 deaths in the kingdom of Saudi Arabia due to SARS-CoV-2 [2]. SARS-CoV-2 viral infection symptoms ranged from minor illnesses like fever, chills, cough, and difficulty breathing to major, Cutaneous, Neurological and Oral manifestations, life-threatening symptoms that led to ICU admissions, ventilator use, and multi-organ damage. Millions of infections and deaths pressurized the pharmaceutical companies to accelerate vaccine development, whether by using old technologies or developing an innovative technology rapidly [3-6].

Vaccination could be one of the lifesavers from the COVID-19 pandemic. Overall, until today, 5.5 billion people have been administered with COVID-19 vaccine world-wide. The first COVID-19 vaccine developed was Pfizer-BioNTech/BNT162b2 with the aim of holding off the pandemic. It was developed in a very short time and was given FDA (US Food and Drug Administration) approval after just 7 months following its phase I/II trial that took place in May 2020. It was granted EUA (emergency use authorization) in December 2020. It received the full FDA approval on August 23rd, 2021, after passing all efficacy and safety requirements [7,8]. It showed 95% efficacy against moderate-to-severe disease [9]. Initially, there was uncertainty among Middle Eastern people about taking the vaccine during the pandemic [10].

The Pfizer-BioNTech/BNT162b2 vaccine is an mRNA vaccine that works by encoding the SARS-CoV-2 spike glycoprotein with its nucleoside mRNA and is prepared as a lipid-based nanoparticle drug delivery system for its efficient extravasation into host cells [9]. The Pfizer-BioNTech/BNT162b2 COVID-19 vaccine is approved as two doses with an interval of 21 to 28 days for all people 12 years of age and older. With the rise of new variants of the Corona virus, such as "Omicron", "Delta", and "Mu", there is a worry that the decline in immunity over time will reduce the potency of the vaccine and require a booster dose to help stimulate immunity against the new strains [11].

After FDA approval, the CDC (Center for Disease Control and Prevention) recommended a booster dose for all people aged 65 and above, and later eligibility was expanded to other groups. The World Health Organization is also promoting the importance of obtaining a third booster dose of the vaccine in order to emphasize immunization efforts in order to decrease the death rates and reduce the severity of dis-ease, so as to protect the health care system in general [12].

Among Saudi Arabia's women, the average age of menopause is 48.98 years [13]. There is a higher likelihood of sore arms, fever, fatigue, and myalgia following COVID-19 vaccination, according to UK's Medicines and Healthcare Products Regulatory Agency (MHRA) [9]. Primary care clinicians and those who work in reproductive health regularly receive inquiries from people who have experienced changes to their periods or unexpected vaginal bleeding shortly after vaccination. As of the 2nd September 2021 reporting period, more than 30000 of these adverse drug reactions had been submitted to the MHRA's yellow card surveillance program [9]. The current COVID-19 vaccines failed to take into account the effects of the vaccine on women's menstrual cycles post-vaccination [14].

In Saudi Arabia, on 26th April 2022 announced a booster dose was recommended for all people over 16 years of age and who had completed their 2 doses of vaccine. The Ministry of Health Saudi Arabia created awareness of a booster dose of the COVID-19 vaccine through a campaign called "Maintain Your Level with Booster Shot" so as to achieve maximum immunity among the community [15].

While the clinical trial demonstrated the vaccine's efficacy and safety, it did have limitations, including a few participants and a healthy sample compared to what a real-world sample would have. The result may be misidentification of less common ad-verse events [16]. The development of the vaccine in a short span and the use of new technology led to a rise in concern among people regarding its safety. Post-marketing evaluation is necessary to increase the public trust in vaccines and encourage them to accept the vaccine [17-19]. Keeping the limitations of clinical trials in mind, further epidemiological studies are imperative to assess the short term COVID-19 vaccine side-effects and to increase public trust in the safety and efficacy of the current vaccine, likely requiring additional boosting.

To the best of author's knowledge, no study has been performed to investigate prevalence of mild and moderate side-effects only in female population associated with booster dose of Pfizer-BioNTech/BNT162b2 COVID-19 vaccine in Eastern Province of Saudi Arabia. However, few study has been conducted in other region of Saudi Arabia to assess first and second dose side-effects of Pfizer-BioNTech/BNT162b2 COVID-19 vaccine among both genders.

Therefore, the present descriptive cross-sectional study was aimed to assess Prevalence of mild and moderate side-effects associated with booster dose of Pfizer-BioNTech/BNT162b2 vaccine among females of Eastern Province, Saudi Arabia.

2. Materials and Methods

2.1 Study Settings

A descriptive, cross-sectional study was carried out in the Eastern Province of Saudi Arabia using a self-administrated online survey to look for adverse reactions reported by females aged 18–50 years who had received the booster dose of the Pfizer-BioNTech/BNT162b2 vaccine. All vaccinated respondents who had received their booster dose of Pfizer-BioNTech/BNT162b2 vaccine were requested for online surveys where the respondents were requested to self-report any mild-to-moderate symptoms that they developed post vaccination. The target populations of the present study (aged 16–50 years) were residents of the Eastern Province, Saudi Arabia. The entitled respondents were to have taken their booster dose of the COVID-19 vaccine prior to participating and filling in the survey questionnaire. Respondents who had not taken booster doses as well as those aged more than 50 years were excluded from the study. The female survey team identified the female member community of Eastern Province. Information was collected about those who were eligible and willing to participate in the survey.

2.2 Sample Size

A convenience sampling technique was applied for the study sample selection. The sample size was calculated using raosoft.com [20]. The Eastern Province population (around 4.9 million) was used as the population size. To determine the sample size, a margin of error of 5%, a 50% response rate, and a 95% confidence interval for a population of 4.9 million people were used. Therefore, it was determined that 385 responses were sufficient in this study. However, as this study was based on an online questionnaire distributed via social media, it was decided to reduce the sampling bias in our method. However, we included 770 participants to increase the significant power of this study. During the study period, 787 eligible respondents participated in the survey.

2.3 Instrument and Data Collection

A review of literature, including PubMed, Medline, Google Scholar, and other databases, was conducted with the goal of identifying short-term and potential side-effects that might occur after the Pfizer-BioNTech/BNT162b2 vaccination [7, 21–24]. The questionnaire was designed using Google Forms and was written in English and Arabic. The final versions were reviewed by four different experts in the field to check for face and content validity. It was initially distributed to a pilot sample consisting of 10 participants to check for any technical misunderstandings or contraindications. Final data analysis did not include the pilot survey response. The survey was made as short in length as possible. It was clarified that the information would be used only for medical research purposes, as the participants were not identified and had the right to withdraw at any stage. Multiple sections were included in the questionnaire. A brief description of the purpose of the study is contained in the first section, along with contact details for the investigators, and an agreement for participants to consent to participate. The second section of the questionnaire was designed for the purpose of gathering general information about the respondents, including age, sex (only female in option), marital status, educational qualification, occupation, chronic diseases such as hypertension, diabetes mellitus, asthma, and others, in addition to whether they had a previous infection history with SARS-CoV-2 infection. The third section of the study focused on the COVID-19 vaccine, specifically the side-effects

experienced after the Pfizer-BioNTech's/BNT162b2 COVID-19 vaccine, their timing, and duration. Participants were able to leave the box unchecked if no symptoms were reported. There is a section with a list of the most frequently reported side effects from other studies [7, 21–24], such as pain or redness at the injection site, myalgia, fatigue, fever, chills, delayed menstruation, headaches, allergies, nausea, and vomiting. Moreover, a section was provided for reporting other possible unlisted side effects. The study participants may have experienced Further-more, participants were asked to report visits to doctors and any hospitalizations after vaccination, as well as any medications taken after vaccination. The target group for this study is citizens and residents aged 16–50 years in the Eastern Province of Saudi Arabia. The survey team identified the community for the survey. The survey's link was disseminated to the respondents via WhatsApp, SMS, or email and in person to set an appointment. Survey/data collection has been performed from February 7, 2022 to March 9, 2022. All participants were asked to respond to the survey; thus, the survey team members communicated with those who did not respond to identify and verify their responses. Survey responses were provided by eligible participants based on their willingness to participate in the research.

Data for only those who had taken a booster dose of the Pfizer-BioNTech/ BNT162b2 vaccine, respondent's adherence with the inclusion and exclusion criteria and submitted a complete questionnaire. Out of 787 participants, 121 (15.37%) individuals were excluded due to incomplete survey. 69 (8.76%) participants received the Moderna COVID-19 vaccine; and were excluded from this study. 597 (75.85%) respondents were included in the final analysis.

2.4 Ethical Approval

Ethical approval for conducting this study was obtained from the standing ethical approval committee at Scientific Research Unit at Mohammed Al-Mana College for Medical Sciences (reference number; SR/RP/81). Consents were obtained from all participants prior to their participation in the study. The study excluded responses with no informed consent, incomplete responses, age greater than 50 years,

those who failed to take a booster dose, and those who received a COVID-19 vaccine other than the Pfizer-BioNTech/BNT162b2 vaccine.

2.5 Statistical Analysis

Statistical analysis was conducted using the data exported from Google Forms (Mountain View, California, USA) and Microsoft Excel (Version 2016), and then ex-ported into Statistical Package for Social Sciences (SPSS) version 26.0 (IBM, Inc., Ar-monk, NY, USA). To depict the distribution of categorical variables, we used descriptive statistics such as frequency, proportion, and mean ± standard deviation (SD), and to represent quantitative variables, we used median (interquartile range, IQR), respectively. Shapiro-Wilk tests were performed before the analysis to determine the normality of all quantitative variables. We used Pearson's chi-square (χ^2) or Fisher's exact test as applicable for examining the connotation amongst COVID-19 post-vaccination side-effects and the independent variables (demographics and background characteristics). The Mann-Whitney U-tests and Kruskal-Wallis tests were used to assess the number of COVID-19 post-vaccination adverse effects reported by the respondents as an ordinal dependent variable corresponding to the independent variables.

Additionally, multivariate logistic regression analysis was conducted to determine the factors associated with a complaint about side-effects following administration of the Pfizer–BioNTech/BNT162b2 COVID-19 vaccine, which was coded as a replica de-pendent on variable (yes = 1 and no = 0). A multivariate ordinal logistic regression exploration was conducted to determine whether certain factors are associated with side-effects following vaccination. A multivariate logistic regression model was created based on all variables that were associated with $p \leq 0.25$ in univariate analyses [25]. Odds ratios were calculated and intervals of confidence were calculated for all analyses. P-values were corrected for multiple comparisons using the sequential Bonferroni method (Bonferroni-Holm). Statistical significance was defined as p-values less than 0.05 [26].

3. Results

3.1 Respondent's General characteristics

General demographic characteristics of 597 vaccinated females with the booster dose of Pfizer-BioNTech/BNT162b2 vaccine was shown in table 1. The mean ± SD age of the participants was 26.45 ± 7.99 (the reason behind division of the age group in two group only is that mean result in which till 26 years group respondents comes under ≤26 age group similarly, more than 26 years age categorized as >26 group); more than halve (59.8%, n=357) of them were married, and 31.66% were unmarried. Non-Healthcare related accounted for the majority of group at 52.6% (n=341), followed by House wife (39.03%, n=233). Participants who infected with COVID-19 before taking booster dose made up 23.45% (n=140). Only 11.73% (n=70) of participants had reported to be suffering from a chronic disease.

3.2 Side-effects reported by female respondents for booster dose of COVID-19 vaccine.

The results of this study demonstrated that 72.36% (432/597) of the participants reported at least one COVID-19 post-vaccination side-effect. Fig.1 describes that most participants reported three side-effects (22.69%, 98/432), (20.83%, 90/432) re-ported two side-effects, and (12.96%, 56/432) reported four side-effects, while (9.26%, 40/432), (5.79%, 25/432), (4.40%, 19/432), (1.85%, 8/432) and (2.3%, 10/432), participants reported five, six, seven, eight, and nine side effects, respectively.

Among the 432 females who developed COVID-19 post-vaccination side-effects, Fig. 2 displays that pain and redness at the site of injection (75.93%) and myalgia (71.99%) were the most frequently reported side-effects, followed by headache (53.24%), delayed menstruation (39.12%) and fever (33.56%). However, the least frequently reported side-effects were allergy at 3.7%, joint or bone pain, dizziness, at 22.69% each, fatigue (21.99%), chills (20.83%), and nausea or vomiting 13.19% among all the respondents.

3.3 COVID-19 vaccine side-effects distribution

The dissemination of different side-effects according to contributors' age group was investigated among females who developed COVID-19 post-vaccination undesirable effect (Table 2).

The results displayed that female older than 26 years had a significantly higher frequency of side-effects of myalgia (90.59% vs. 55.65%; $\chi2=9.72$; p=0.001), pain or redness at the site of injection (89.11% vs. 64.35%; $\chi2= 3.21$; p=0.007) and chills (27.72% vs. 14.78%; $\chi2=5.37$; p=0.020) compared to females younger than 26 years. On the other hand, the females younger than 26 years had a higher frequency of dizziness (25.65% vs. 19.31%; $\chi2=4.08$; p=0.043) compared to the other groups.

3.4 Associations of the reported COVID-19 vaccine side-effects among the respondents

Table 3 illustrates the associations of COVID-19 vaccine side-effects with the demographic and health background characteristics of the participants. The findings revealed no statistically significant difference in the frequency of side effects based on respondent age, with (73.71%) for the age group ≤ 26 years old compared to (70.87%) > 26 years old. The side-effects were significantly more frequent among unmarried participants (83.59%, 158/189) compared to others marital status (p<0.001). Healthcare workers had a significantly higher frequency of side-effects than non-healthcare workers (92.0% vs. 79.61%; p<0.001).

Interestingly, middle school participants reported a lower frequency of side-effects (31.42 %) compared to other groups. The side-effects were significantly more frequent among females who had a history of comorbidities such as DM (Diabetes Mellitus), HTN (Hypertension), asthma, and any other chronic disease (82.85%, 58/70) compared to females without a history of comorbidities (70.96%, 374/527) (p<0.001).

Table 4 displays differences in COVID-19 post-vaccination side-effects reported by participants according to independent variables. A Mann–Whitney U test displayed that the number of side-effects was found to be meaningfully more common amongst females who had a history of comorbidities

such as DM, HTN, asthma, and any other chronic disease (median = 2; IQR = 1, 3) compared to females without a history of comorbidities (median = 4; IQR = 4, 3) (U = 4002; p = 0.001).

The Kruskal-Wallis tests, however, did not show any substantial differences in the number of side-effects between age groups (H = 1.0; p = 0.317). Similarly, differences in side-effects between the different variables were not significant ($p \leq 0.05$).

An analysis of multivariable factors associated with the reported side-effects of the COVID-19 vaccination.

According to Table 5, the factors associated with reporting side-effects following a booster dose of the COVID-19 vaccine amongst female respondents are multivariate logistic regression analyses. A test of inferential goodness-of-fit was used to determine whether the model fit the data ($\chi2= 74.289$; p = 0.001), which showed that all variables that indicated associations with $p \leq 0.25$ in the univariate analysis displayed in Table 3. The results revealed that respondents working in non-healthcare related sectors had a 1.677-fold amplified risk of side effects compared to those working in healthcare related sectors (aOR =1.677; 95% CI =1.363, 2.064). Furthermore, respondents with at least one child were less likely to report COVID19 post-vaccination side effects than those without children (aOR = 0.809; 95% CI = 0.15, 0.673, 0.973). In the multivariate analysis, however, the significant association of chronic diseases with side effects was not retained (p = 0.142).

Moreover, the following table 6 displays the multivariate ordinal logistic regression analysis results for the factors that influenced how many female respondents reported COVID-19 side-effects from this vaccine. The univariate analysis presented in Table 4 showed that all variables with $p \leq 0.25$ had associations. The model was of Goodness-of-Fit and was statistically significant ($\chi2 = 46$, $p < 0.001$). The number of reported side-effects was found to be significantly prejudiced by the marital status, and occupation of the respondents. According to the results, healthcare-related respondents reported fewer side-effects in comparison to the other respondents when other variables were held constant

(aOR = 0.732; 95% CI = 0.128–1.172; p = 0.015). Likewise, unmarried respondents reported a lower number of side-effects than married respondents (aOR = 0.191; 95% CI = 0.165, 0.201; p = 0.018).

3.5 The onset, duration, and management of COVID-19 vaccine side-effects

53.94% (233/432) of the females who developed COVID-19 post-vaccination side-effects experienced them on the day of vaccine administration (Day 0). In contrast, 22.22%, 12.73%, and 11.11% of reported side effects occurred on the first, second, and third post-vaccination days, respectively. According to those who reported side effects, 40.28% (n = 74) said they lasted 1–2 days, 25.0% (n = 108) said they lasted 3–5 days, and 12.5% (n = 54) said they lasted longer than 5 days. On the other hand, 9.25% (n = 40) of those who experienced side-effects visited a doctor, and medication for post-vaccination side-effects was taken by 63.19% (n = 276). Only eight (3.48.31%) females aged 26 years old were admitted to the hospital for less than 24 hours out of ten (2.31%), while only two (0.86%) were admitted for more than 24 hours (Table 7).

4. Discussion

Despite the fact that the vaccine is available for the Saudi Arabian population, people are still hesitant to get vaccinated. Some reasons may be because these vaccines were developed in a short time compared to the previously approved vaccines, which normally take years to be approved. Another reason for the hesitance could be associated with the emergent technique for some of the COVID-19 vaccines; mRNA vaccines [27, 28, 29]. These two key features may raise the concern among some individuals about latent or severe post-vaccination side-effects. Therefore, we evaluated the short-term side-effects of the booster dose of the Pfizer-BioNTech/BNT162b2 vaccine among 16–50-year-old females of Eastern Province of Saudi Arabia. The statistics revealed that the vaccine is well tolerated with variances in the reactogenicity amongst individuals in the Eastern Province. The findings revealed similar side-effects among groups on the first day and were comparable to previously reported findings among individuals [30].

In this study, it was observed that there was a high incidence of side-effects after taking the booster dose, around 72.36% (432/597), which is unlikely to be related to what was reported before and after the first and second doses of Pfizer-BioNTech's/BNT162b2) COVID-19 Vaccine. Compared to a previous study for first and second dose in which we looked at short-term side-effects of Pfizer-BioNTech/BNT162b2 in individuals aged 18–70 years old, fewer overall side-effects (40%, n = 208) were noted [31]. According to our study, the majority of side-effects related to vaccination were reported by unmarried individuals that are 83.59%, while a study conducted in Ethiopia reveals only 44% among unmarried individuals [32]. In comparison with their older counterparts [9, 33,34], the younger population has reported more side-effects. Pain and redness at the injection site (75.93%), myalgia (71.99%), headache (53.24%), fever (33.56%), fatigue (43.78%), and equal number of respondents shows dizziness and joint or bone pain (22.69%), were the most commonly reported side-effects by the participants (Fig. 2 despite the findings of the current study, that of clinical trials, as well as those of other world studies [7,16,17,30,33], are consistent a phase 3 clinical trial with the Pfizer-BioNTech/BNT162b2 vaccine revealed that injection site pain was the most common complication (71-83%), fatigue was the second (34-47%), and headache was the third (25-42%). Delayed menstruation one of the leading side-effects also reported by the 39.12% of the respondents which is higher than previously reported (4.3%) study conducted by Alison et al in USA [34], In the existing study, 53.94% of the side-effects happened on vaccination day (0 day), and 40.28% of the symptoms lasted for 1-2 days, which is in agreement with the results voiced in other comparable studies [31, 35]. In the present investigation, around 63.19% of participants took medication (mainly analgesics) to relieve the side-effects. Analgesics are commonly used by Saudi Arabians, both those currently working in healthcare and those not in healthcare, to ease the COVID-19 vaccine's side-effects [36]. Moreover, only 9.25% of the respondents needed to see a physician owing to side-effects from the vaccines, and only 3.93% of the respondents were hospitalized. Collectively, taking into consideration the safety parameters of the vaccine (duration, onset, self-medication for prevention of AE, visiting a hospital & hospitalization) based on our analysis, the results have shown

non-significance, which means strongly supported towards more safety of COVID-19 vaccine. Females have a higher prevalence of side effects than males, and people aged 55 years or younger have a lower prevalence of side effects than those older than 55 years [7, 16, 17, 30, 33]. However, our data showed that in respondents less than and more than 26 years old, nearly the same percentage of the appearance of side-effects with slight variation, which reflects the findings of Alhazmi et al., who reported a greater prevalence of side-effects in females. Pfizer-BioNTech's/BNT162b2 COVID-19 vaccine, on the other hand, caused more side-effects in younger patients than in older patients, according to a study in south-western Saudi Arabia [37]. The number of side-effects was also greater among people with past exposure to SARS-CoV-2 compared to individuals without previous expo-sure (Table 3). Both of these findings are consistent with previous research that found more side effects after the second dose and in people who had previously been exposed to COVID-19 infection [7, 33, 35, 38]. This observation could be interpreted on the basis of the immune system's response. For instance, emerging real-world evidence indicates that the humoral immunity in individuals with prior SARS-CoV-2 infection following a single dose of the vaccine is equal to or stronger than that found in SARS-CoV-2- naïve individuals following the second dose [39]. Such improved immunity may induce the production of cytokines that may have an inflammatory effect on muscles, blood vessels, and other tissues, mediating more systemic adverse effects post second doses or following doses in individuals who have previously been infected with SARS-CoV-2 [40]. Although it remains to be tested, this increased reactogenicity may indicate increased immunogenicity and vaccine effectiveness. However, as our work in this study is observational, we cannot directly comment on the effectiveness of the given vaccine.

To date, a few research studies have been conducted in Saudi Arabia to measure the safety and efficacy of the Pfizer-BioNTech/BNT162b2 COVID-19 vaccine. We have demonstrated that the current study participants only reported common side-effects that have been reported previously in several studies. In particular, our study participants were provided with a choice to report any other side-effects which were not listed in the survey. However, none of the study participants have

reported any other adverse effects except delayed menstruation, indicating that our data is in strong agreement with the types of unfavorable effects that were reported from the phase 3 clinical study. The data of the current study showed that individuals with a history of previous exposure to the SARS-CoV-2 virus had a greater likelihood of reporting side-effects. However, A respondents who given correct response on delayed mensuration, further details are required from respondents, to know detail history regarding delayed mensuration and to find out association between delayed mensuration and Pfizer-BioNTech/BNT162b2 COVID-19 vaccine.

As reported by prior studies, a gender-based difference in reporting adverse events following various viral and bacterial vaccines has been recorded [35, 41]. It was detected that there were stronger inflammatory, antibody, and cell mediated immune responses to vaccines in females as opposed to males, which could explain the gender based variances in reactions and immunogenicity toward vaccinations [42]. Behavioral, genetic, and hormonal factors may contribute to gender differences in adverse events following vaccination [41-43]. As well, a few studies have concluded a major association between the occurrence of post-vaccination side-effects and advancing age. Studies among healthcare workers in Jordan [44], Germany [45], and Slovakia [46] found that young adult respondents had a pointedly greater prevalence of COVID-19 vaccine side-effects in comparison to their older age counterparts, and this has been due to the fact that immune responses gradually decline with age. This study, however, did not notice such an association with the same results as certain studies conducted in Saudi Arabia [8] and elsewhere [47].

As a result of the present study, we can add more public confidence in the safety profile of the COVID-19 Pfizer-BioNTech/BNT162b2 vaccine, which may aid in accelerating the process of vaccine coverage. However, our study is not without limitations. First of all, participants were enrolled by convenience sampling from a large region in Eastern Province, Saudi Arabia; thus, the generalizability of our findings may be limited. Moreover, a self-administered online questionnaire was used to collect the data, which could result in a report bias. We chose to conduct the study as a web-based study because we

wanted to ensure participants' safety due to the COVID-19 pandemic, SARS-CoV-2 viruses, and the recommendation to continue social distancing as a precaution measure in Saudi Arabia. In addition, conducting community-based surveys would be difficult during this pandemic. Thus, we collected our data online through a self-reported survey, and it was distributed based on the authors' networks. Another limitation of the current study is that it monitored the vaccine's short-term side-effects (immediately after injection). Vaccine effects on our cohort are still un-known in both the short- and long-term. However, for the side-effects related to the fertility factor, reproductive hormonal changes as well as delayed menstruation, we did not give focus due to observational and short-term assessment of the side-effects of the respondent. In the right circumstances, mRNA vaccines can induce a robust immune response, which could temporarily affect the hypothalamic-pituitary-ovarian axis. Regulating T cells have been demonstrated to be affected by the menstrual cycle and modulated during the 4-week cycle. Chronic diseases affecting female reproductive age patients may be affected particularly by these fluctuations. It could be the possible reason for alteration of the menstrual cycle [48, 49]. Similarly, another observed mRNA vaccin against human papillomavirus (HPV) has also been associated with menstrual changes [50]. Likewise, side-effects subsequent to the booster dose of the vaccine were investigated, whereas the side-effects post the first and second dose of the vaccine were not studied. Additionally, the participants were mostly Pfizer-BioNTech/BNT162b2 recipients, with only a few Moderna vaccine recipients. It is likely that this is the result of the shortage of Moderna vaccine throughout the study period and the quite small sample size; therefore, more multi-centered investigations with bigger sample sizes are necessary to confirm the different COVID-19 vaccine safety profiles permitted in the country, as well as a forthcoming study to assess other rare events such as thromboembolic profiles and myocarditis is also important [51]. One study also describes a strategy to reduce the adverse events without reducing the immunologic response to SARS-CoV-2 vaccination, such as the use of immunostimulants like pidotimod [52]. So, healthcare policymakers in Saudi Arabia should also think about the implementation of different evidence-based strategies to minimize the frequency of occurrence of post booster dose vaccination of COVID-19 vaccine such to foster the

reporting of side-effects associated with Pfizer-BioNTech/BNT162b2 COVID-19, sensitization of community reading Pfizer-BioNTech/BNT162b2 COVID-19 as well as proper patient counselling regarding pre and post COVID-19 vaccination.

Finally, follow-up study for long term side-effects not been investigated to avoid an excessive length of the questionnaire as well as long study duration. However, this is the first study showed a prevalence of side-effects about Pfizer-BioNTech/BNT162b2 COVID-19 vaccine in females from Eastern Province, Saudi Arabia. Moreover, the study enrolled a statistically significant number of females in a short period of time, while a wide debate on second booster dose of vaccination policies and mandatory use of health passports is underway. Therefore, our results are of practical significance for the design and implementation of health programs for the female population, not only targeted to the implementation of the preventive measures against COVID-19, but also to contribute to their acceptance of booster dose and long-lasting immunity against SARS COV-2 infection. Further multi-centric studies are needed to confirm these data and deepen the related factors to plan effective health promotion interventions as well as to identify long-term side-effects and immunity associated with booster dose.

5. Conclusions

The current research comes up with relevant information regarding the side-effects that can occur post COVID-19 vaccine administration amongst females in the Eastern Province of Saudi Arabia. Myalgia and pain or redness at the site of injection were the most reported side-effects in our study. Moreover, reported delays in menstruation have been observed among participants, which required a follow-up study to further investigate any significant association between delayed menstruation and the COVID-19 vaccine. Consequently, the existing study's findings reinforce the vaccine's safety and offer main standard facts to raise healthcare workers' and the general community's awareness of the predictable side effects of subsequent COVID19 vaccines. This may persuade those who are hesitant, refuse, or are pessimistic about receiving the COVID19 booster dose.

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Institutional Review Board Statement

Prior to conduction of the study and the data collection, the proposed study has been ethically approved by the Ethical Committee of Mohammed Al-Mana College for Medical Sciences (MACHS) with approval number SR/RP/81. Furthermore, any information disclosing respondent identity was excluded from the tool. Before participating in the study, an online consent was also obtained from the respondents who took part in the study subject to assure all rights of privacy and secrecy of all registered data. Moreover, this study com-plies with the ethical rules of the 64th World Medical Association Declaration, General Assembly, Helsinki (2013).

Informed Consent Statement

Informed consent was obtained from all the respondents participated in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

All the author(s) declare none conflict of interest.

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Table 1. Socio-demographics and general characteristics of study participants (n= 597).

Characteristics		n (%)
Age (years) (Mean± SD: 26.45±7.99)	≤26	312 (52.26)
	>26	285 (47.74)
Marital status	Unmarried	189 (31.66)
	Married	357 (59.80)
	Widow	24 (4.02)
	Separated	27 (4.04)
Educational Qualification	Middle School	105 (17.59)
	High School	114 (19.10)
	Diploma or post high school	115 (19.26)
	Bachelor	239 (40.03)
	Master/Ph.D.	24 (4.02)
Occupation	Non-Healthcare related	314 (52.60)
	Healthcare related	50 (8.38)
	House wife	233 (39.03)
How many children	One	97 (16.25)
	Two	145 (24.29)
	More than two	143 (23.95)
	None	212 (35.51)
Suffering from any chronic disease such as HTN, DM and Asthma or others	Yes	70 (11.73)
	No	527 (88.27)
History of COVID-19 infection before taking booster dose	Yes	140 (23.45)
	No	457 (76.55)

Table 2. Distribution of COVID-19 vaccine side-effects reported amongst the participants according to the age group (n =432).

Outcome	≤26 Years old (n = 230)	>26 Years old (n = 202)	Total (n =432)	χ2 (p)
Myalgia	128 (55.65)	183 (90.59)	311 (71.99)	9.72 (0.001)
Pain or redness at the site of injection	148 (64.35)	180 (89.11)	328 (75.93)	3.21 (0.007)
Fatigue	40 (17.39)	55 (27.23)	95 (21.99)	2.37(0.123)
Fever	67 (29.13)	78 (38.61)	145 (33.56)	0.83 (0.360)
Chills	34 (14.78)	56 (27.72)	90 (20.83)	5.37 (0.020)
Headache	114 (49.57)	116 (57.43)	230 (53.24)	0.02 (0.895)
Joint or bone pain	44 (19.13)	54 (26.73)	98 (22.69)	1.02 (0.312)
Nausea or vomiting	31 (13.48)	26 (12.87)	57 (13.19)	3.98 (0.046)
Delayed menstruation	93 (40.43)	76 (37.62)	169 (39.12)	1.71 (0.190)
Allergy	6 (2.61)	10 (4.95)	16 (3.70)	1 (0.317)
Dizziness	59 (25.65)	39 (19.31)	98 (22.69)	4.08 (0.043)

χ2: Chi-square test. Significant difference between the two groups (unadjusted $p \leq 0.05$).

Table 3. Associations of the reported COVID-19 vaccine side-effects with the respondents' background features (n = 597).

Characteristic	Participants with Side Effects, n=432	Participants with no Side Effects, n=165	ORs (95% CI)	p-Value #
Age, years				
≤26 (n=312)	230 (73.71)	82 (26.28)	1.15 (1.14, 1.65)	0.464
>26 (n=285)	202 (70.87)	83 (29.12)	0.65 (0.44, 0.95)	0.034*
Marital status				
Unmarried (n=189)	158 (83.59)	31 (16.40)	2.50 (1.61, 3.85)	<0.001*
Married (n= 357)	247 (69.18)	110 (30.81)	0.66 (0.45, 0.97)	0.039
Widow (n= 24)	19 (70.16)	5 (20.83)	1.47 (0.55, 4)	0.491
Separated (n=27)	8 (29.62)	19 (70.37)	0.15 (0.06, 0.34)	<0.001*
Occupation				
Non-Healthcare related (n=314)	250 (79.61)	64 (20.38)	2.16 (1.502, 3.12)	<0.001*
Healthcare related (n=50)	46 (92)	4 (8)	4.79 (1.69, 13.54)	0.001*
House wife (n=233)	136 (58.36)	97 (41.63)	0.32 (0.22, 0.46)	1.220
Highest educational qualification				
Middle School (n= 105)	33 (31.42)	72 (68.57)	0.10 (0.07, 0.17)	1.591
High school (n= 114)	95 (83.33)	19 (16.66)	2.16 (1.27, 3.67)	0.003*
Diploma or post high school (n= 115)	93 (80.86)	22 (19.13)	1.78 (1.07, 2.95)	0.027*
Bachelor (n= 239)	193 (80.75)	46 (19.24)	2.08 (1.41, 3.08)	0.001*
Master/Ph.D. (n=24)	18 (75)	6 (25)	1.15 (0.44, 2.95)	0.822
Number of children				
One (n= 97)	78 (80.41)	19 (15.58)	1.69 (0.98, 2.89)	0.062*
Two (n= 145)	68 (46.89)	77 (53.11)	1.43 (0.83, 2.47)	0.198
More than two (n= 143)	114 (79.72)	29 (20.27)	1.68 (1.06, 2.64)	0.024*
No children (n= 212)	172 (81.11)	40 (18.86)	2.06 (1.37, 3.09)	0.001*
History of comorbidities such as DM/HTN/Asthma or others				
Yes (n= 70)	58 (82.85)	12 (17.14)	1.97 (1.03, 3.78)	0.022*
No (n=527)	374 (70.96)	153 (29.04)	0.51 (0.26, 0.96)	0.045*
History of COVID-19 infection before booster dose				
Yes (n=140)	126 (90)	14 (10)	4.39 (2.48, 7.75)	5.45
No (n=457)	307 (66.95)	150 (33.04)	4.50 (0.13, 0.42)	0.24

ORs: Odds ratio; CI: Confidence interval. Significant association (unadjusted p ≤ 0.05). * Significant association (using the Fisher exact test correction for multiple comparisons).

Table 4. Number of side-effects reported by the respondents following the booster dose of COVID-19 vaccine rendering to the respondents' background features (n =432).

Characteristic	No. of Reported Side-Effects	Statistics	*p*
	Median (IQR)		
Age, years		H=1.0	0.317
≤26 (n=312)	3 (4,2)		
>26 (n=285)	2 (1,2)		
Marital status		H=3.0	0.391
Unmarried (n=189)	3 (2,3)		
Married (n= 357)	3 (4,3)		
Widow (n= 24)	2 (1,2)		
Separated (n=27)	1 (2,1)		
Occupation		H=2.0	0.367
Non-Healthcare related (n=314)	2 (4,3)		
Healthcare related (n=50)	1 (1,2)		
House wife (n=233)	3 (3,2)		
Highest educational qualification		H=4.0	0.406
Middle School (n=105)	3 (1,4)		
High school (n= 114)	1 (2,1)		
Diploma or post high school (n= 115)	2 (3,2)		
Bachelor (n=239)	4 (4,3)		
Master/Ph.D. (n=24)	3 (1,3)		
History of comorbidities such as DM/HTN/Asthma or others		U=4002	0.001
Yes (n= 70)	2 (1,3)		
No (n=527)	4 (4,3)		
History of COVID-19 infection before taking booster dose		U=38556	0.001
Yes (n=140)	2 (1,2)		
No (n=457)	3 (4,2)		

IQR: Interquartile range; U: Mann–Whitney U statistic; H: Kruskal–Wallis test statistic. Significant difference (unadjusted p ≤ 0.05). * Significant difference (using the Bonferroni correction for multiple comparisons).

Table 5. Multivariate analysis of factors related with reporting of side-effects following COVID-19 vaccine amongst the participants (n = 432).

Variable	AORs	95% CI	*p*
History of chronic diseases	1.641	0.848, 3.178	0.142
Occupation (Non-Healthcare related	1.677	1.363, 2.064	0.001*
Children (One)	0.809	0.673, 0.973	0.025*

AORs, adjusted odds ratio; CI, confidence interval. * Significant association of COVID-19 vaccine side-effects ($p \leq 0.05$).

Table 6. Results of ordinal logistic regression for the factors associated with the number of reported side-effects following COVID-19 vaccine (n = 432).

Variable	AORs	95% CI	*p*
Age (year) More than 26 years	0.189	0.034, 0.965	0.350
Marital status (Unmarried)	0.191	0.165, 0.201	0.018*
Occupation (Healthcare related)	0.732	0.128, 1.172	0.015*
Educational Qualification (Bachelor)	0.540	0.968, 1.149	0.867

AORs, adjusted odds ratio; CI, confidence interval. * Significant association of COVID-19 vaccine side-effects ($p \leq 0.05$).

Table 7. The onset, length, and management of COVID-19 vaccine side-effects reported amongst the respondents in the study (n = 432).

Onset and Length of Side Effects	≤26 Years old (n = 230)	>26 Years old (n = 202)	Total (n =432)	χ^2 (p)
Duration of the side effect symptom				7.29 (0.063)
One day	57 (24.78)	39 (19.31)	96 (22.22)	
From 1-2 days	95 (41.30)	79 (39.11)	174 (40.28)	
From 3-5 days	58 (25.22)	50 (24.75)	108 (25)	
More than 5 days	20 (8.70)	34 (16.83)	54 (12.50)	
Time of the side effects started to appear				0.35 (0.948)
Day 0	115 (50)	118 (58.42)	233 (53.94)	
Day 1	45 (19.57)	51 (25.25)	96 (22.22)	
Day 2	25 (10.87)	30 (14.85)	55 (12.73)	
After 2 days	23 (10)	25 (12.38)	48 (11.11)	
Taking medication to alleviate side effects	133 (57.82)	140 (69.30)	273 (63.19)	0.179 (0.671)
Visiting a hospital due to side effects	12 (5.21)	28 (13.86)	40 (9.25)	6.4 (0.011)*
Hospitalization because of side effects				4.54 (0.103)
Less than 24 Hours	8 (3.48)	2 (0.99)	10 (2.31)	
24-36 Hours	1 (0.43)	2 (0.99)	3 (0.69)	
More than 36 Hours	1 (0.43)	3 (1.49)	4 (0.93)	

χ^2: Chi-square test. *Significant association of COVID-19 vaccine side-effects ($p \leq 0.05$)

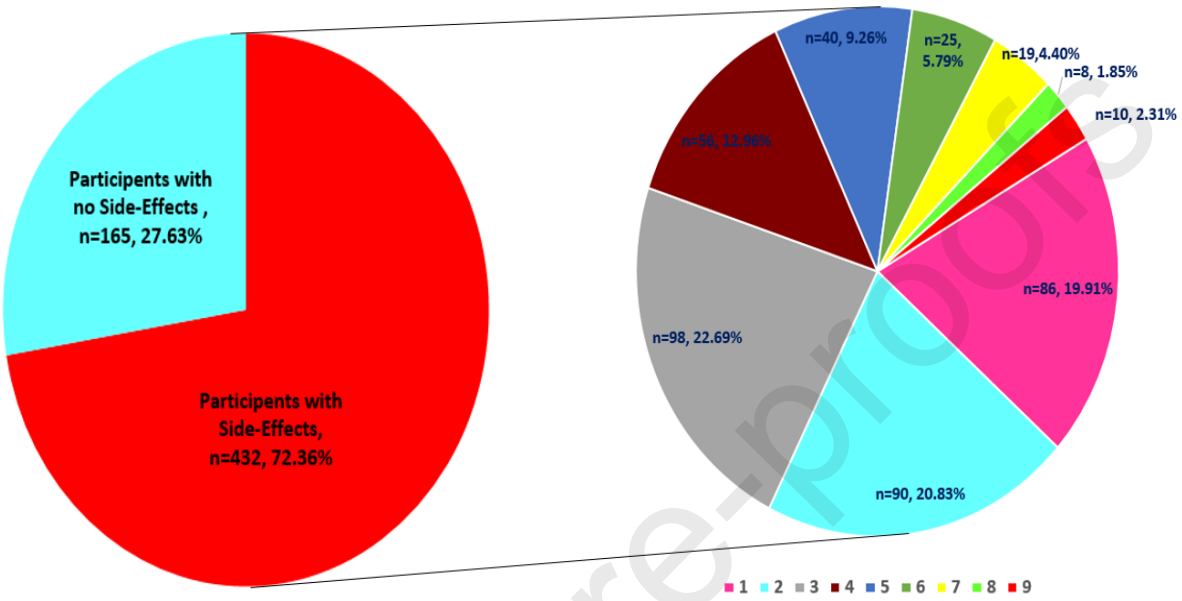

Fig. 1. Total number of COVID-19 vaccine side-effects reported amongst the participants.

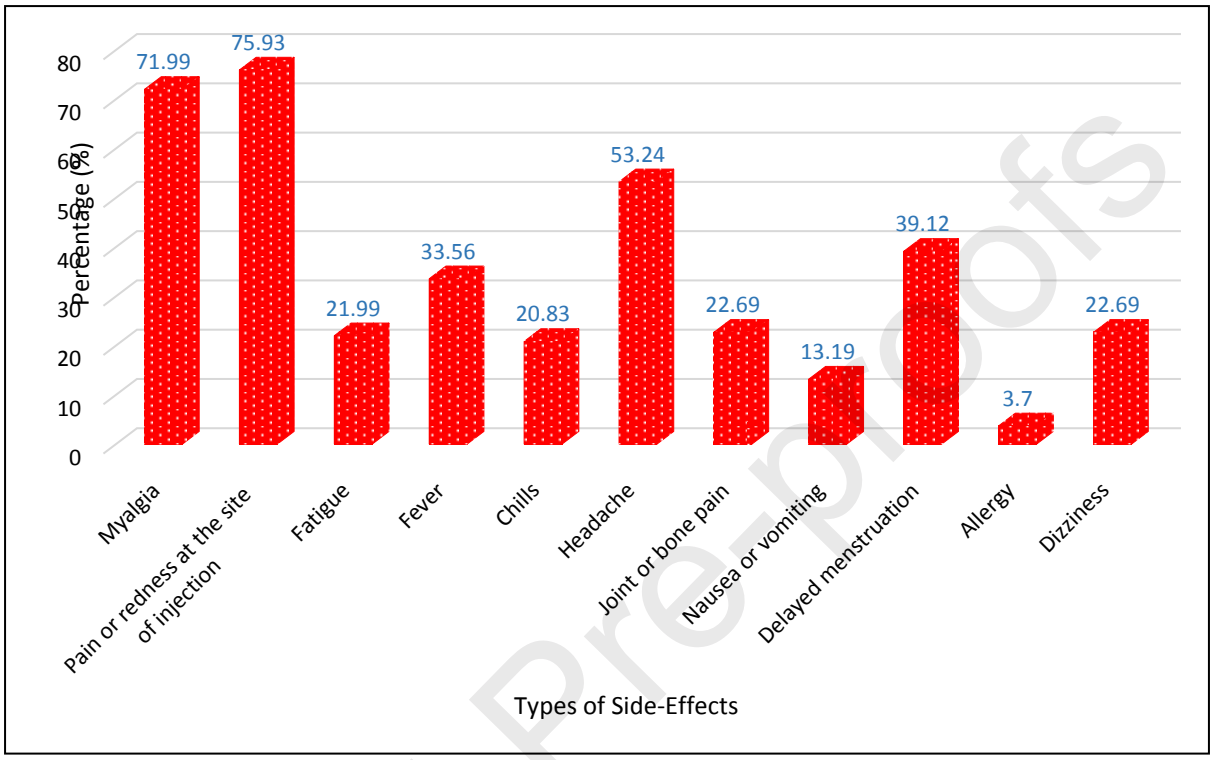

Fig. 2. The frequency of COVID-19 vaccine side-effects reported amongst the respondents (n = 432).

Declaration of interest

None.