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Adverse Effects Following the First and Second Dose in Individuals Receiving the Pfizer/BioNTech COVID-19 Vaccine: A Cohort Study

Running Title: Side Effects Following the First and Second Dose of COVID-19 Vaccination

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Abstract The FDA-approved vaccine against the novel coronavirus developed by Pfizer and BioNTech became widely popular in Iraq. The study aims to evaluate the incidence of vaccine adverse reactions, and severity after first and second doses and to link some of the demographic criteria of recipients. This study included 850 adults (16 years and older), and the sample was collected from a randomly selected vaccination center in Baghdad, Iraq for the period January to March 2022. Study Participants were directly interviewed while taking the first dose. Later on, phone calls were used to monitor participants' self-reported local or systemic adverse reactions for one week after the first dose and second dose. The participants' age range was (19-76 years) with a mean of (46.2 ± 15.8) years. 59.9% were males. The mean body mass index (BMI) was (27.7 ±2.9). The incidence of vaccine adverse reactions after first and second doses were: first dose (local 17%, systemic 27%), second dose (local 27%, systemic 35%). Ordinal logistic regression analysis after adjusting for age, sex, and past medical history (PMHx) showed a higher incidence and severity in females and those with PMHx in nearly all the types of reactions except for chills (second dose) and PMHx (two doses), muscle or joint pain (two doses). Spearman's Rank test showed an insignificant correlation with any type of reaction. The vaccine is generally safe and adverse reactions are mild and tolerable in the majority of cases.

Keywords Pfizer, Vaccine, Adverse Reaction, First and Second Dose

1. Introduction

Coronavirus disease 2019 (COVID-19) is a viral illness caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Disease severity ranges from a mild, self-limited illness to severe infection with life threatening complications like respiratory and multi-organ failure requiring hospital admission and even may lead to death [1,2]. People of all ages are at risk of acquiring the

infection, although those aged 14 years or younger are at lower risk [3,4]. Safety measures when adopted by individuals with personal hygiene, social distancing along with vaccination against covid-19 are now the most effective method of stopping disease spread [5,6]. BNT162 is an mRNA-based FDA-approved vaccine developed by Pfizer and BioNTech and marketed as Comirnaty for the prevention of COVID-19 (in those aged 5 and above) and is administered intramuscularly as a series of 2 doses (0.3 ml each) 3 weeks apart [7]. According to Pfizer Biontech vaccine package insert, the clinical studies reported the most common adverse reactions being pain and swelling at the injection site, fatigue, headache, muscle pain, joint pain, fever and chills in participants aged 16-55 years following any vaccine dose [7]. Acute allergic reactions, myocarditis and pericarditis, although uncommon, were also reported [7-9]. A study showed that anaphylactic reactions occurred mostly in individuals with a history of hypersensitivity reaction to known allergens (like certain medications, foods or insect venoms) [10].

According to Phase I/II trials, most of adverse effects (both local like injection site pain, or swelling and systemic like fever), peak 48 hours and are generally resolved within 1 week after vaccination [11]. In the form of severity, adverse reactions were generally mild to moderate, with older individuals experiencing milder and less frequent reactions. In the form of frequency, adverse effects following the second dose of the vaccine were similar to (particularly local reactions) or more than those reported following the first dose (particularly systemic reactions) [11,12]. A history of COVID-19 infection was associated with the occurrence of side effects following the first dose [13].

To date, more than 10 million COVID-19 vaccines'' doses have been administered in Iraq, Pfizer BioNTech was the administered vaccine in the majority [14]. The rationale for this study is to evaluate the adverse effect of BNT162 mRNA-based Pfizer vaccine, severity and associated demographic characteristics.

2. Methods

This study enrolled 850 adults (16 years and older) out of initial 900 participants who just received the first dose of Pfizer/BioNTech vaccine and agreed to participate in the study, [twelve participants lost to follow up (not answering the phone), 27 were not wishing to take the second dose and 21 were diagnosed as confirmed COVID-19 cases few days after the first dose]. The sample was collected from a randomly selected vaccination center in Baghdad, Iraq for the period January to march 2022. Those who are on chronic use of steroids or analgesics (non-steroidal anti-inflammatory drugs or paracetamol) were excluded from the study.

Study participants were directly interviewed about demographic data, previous medical history, weight and height, blood pressure measurement, all filled in a specifically designed questionnaire.

Phone calls were used to monitor participants' self-reported local or systemic adverse reactions for one week after both doses. The adverse reactions were classified into local (redness, swelling and pain at injection site) and systemic (fever, chills, fatigue, headache, diarrhea, nausea or vomiting and muscle or joint pain), and severity were prepared with reference to the severity of the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

3. Statistical Analysis

Wilcoxon's signed rank test was used to compare adverse reactions after the first and second doses and chi square test used to calculate numbers and percentages. McNemar chi square was used to examine differences in frequencies. Ordinal logistic regression model was performed using age, sex and PMHx as Covariates. Spearman rank correlation test was used to address the relationship between age and severity of each adverse reaction. Data were entered and analyzed using IBM SPSS Statistics version 24, p value < 0.05 was considered significant.

4. Ethical Consideration

The study was approved by the institutional review board of the college of Medicine/ Al-Nahrain University (IRB). Participants who were invited to participate in the study, were told about the research purpose, procedures, and an oral consent was obtained. Confidentiality about patients' information, keeping anonymity, securing privacy and sharing results were insured.

5. Results

The participants' age range was (19 to 76 years) with a mean of (46.2 ± 15.8) years. Males were 59.9%. The mean BMI was (27.7 ±2.9) (Table 1). 26% have previous chronic illness and the most frequent diseases were: Hypertension (14.2%), diabetes (6.5%), ischemic heart disease (3.5%) and asthma (1.8%). 10.5% had previous COVID-19 infection.

No one experienced grade 4 or 5 severity score in all types of reactions.

The frequency of vaccine adverse reactions after first and second doses was shown in Figures 1 and 2, respectively. 17% developed local reactions (vs 27% following second dose) while systemic reactions were 21% (vs 35% in second dose). Pain at injection site was the commonest local reactions following both doses, while

fatigue (and headache in second dose) was the most common systemic reaction.

Following the second dose, all adverse reactions were more severe and statistically significant than the first dose except for headache (Table 2) and usage of over the counter drugs was also more than following the first dose (McNemar chi square: 95%CI=1.32, 2.52, OR=1.82, P<0.001). Pain at injection site was the most severe local reaction following both doses, while chill (and muscle or joint pain in second dose) was the most sever systemic reaction (Figure 3).

Ordinal logistic regression analysis after adjusting age, sex and PMHx as shown in Table 3 showed higher incidence and severity in females (except for chills in second dose) and those with PMHx (except for muscle or joint pain in both doses) in nearly all the types of reaction. Spearman rank test (Table 4) showed an insignificant correlation of age with any type of reactions. McNemar chi square showed significant use of over the counter drugs following the first dose (95% CI (1.32, 2.52), OR=1.8, P<0.001) (Table 5).

Table 1. Demographic characteristics of the studied sample

Variable	No.	%
Male	509	59.9
Smoking	257	30.2
Alcohol	52	6.1
PMHx	221	26.0
Previous infection	89	10.5
Age	46.2 ±15.8 years*	
BMI	27.7 ±2.9*	
SBP	130.4 ±11.7*	
DBP	80.2 ±5.9*	

*= Mean ± Sd (PMHx: past medical history, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure)

Table 2. Adverse reaction after first and second vaccine dose

Adverse Reactions**	Non*	grade 1*	grade 2*	grade 3*	P value
Redness	613(72.1)/658 (77.4)	82(9.6)/91 (10.7)	138(16.2)/86 (10.1)	17(2.0)/15 (1.8)	0.001
Swelling	280(32.9)/514 (60.5)	80(9.4)/230 (27.1)	454(53.4)/91 (10.7)	36(4.2)/15 (1.8)	<0.001
Pain at injection site	156(18.4)/415 (48.8)	51(6.0)/218 (25.6)	287(69.1)/154 (18.1)	56(6.6)/36 (7.4)	<0.001
Fever	462(54.4)/389 (45.8)	71(8.4)/375 (44.1)	285 (33.5)/66 (7.8)	32(3.8)/20 (2.4)	<0.001
Chills	400(47.1)/617 (72.6)	124(14.6)/158 (18.6)	261 (30.7)/47 (5.5)	65(7.6)/28 (3.3)	<0.001
Fatigue	365(42.9)/504 (59.3)	84(9.9)/124 (14.6)	338 (39.8)/190 (22.4)	63(7.4)/32 (3.8)	<0.001
Headache	462(54.4)/389 (45.8)	71(8.4)/375 (44.1)	285 (33.5)/66 (7.8)	32(3.8)/20 (2.4)	0.36
GIT	609(71.6)/710 (83.5)	146(17.2)/49 (5.8)	75(8.8)/61 (7.2)	20(2.4)/30 (3.5)	0.007
Muscle or joint pain	374(44.0)/560 (65.9)	104(12.2)/81 (9.5)	354 (41.6)/146 (17.2)	18(2.1)/63 (7.4)	<0.001

Wilcoxon's signed rank test, *=Frequency (Percentages), **=first dose/ second dose, (GIT: gastrointestinal tract)

Table 3. Ordinal logistic regression for adverse reaction after first and second vaccine dose

Adverse Reactions**	Age	Sex	PMHx
Redness	0.99(0.98, 1.00)*/1.01 (0.1, 1.02)	0.20(0.15, 0.28)*/ 4.90(3.18, 7.55)*	0.29(0.21, 0.40)*/ 1.77(1.14, 2.75)*
Swelling	0.99(0.99, 1.00)/ 1.00(0.99, 1.01)	3.71(2.75, 4.99)*/ 3.86(2.82, 5.29)*	0.10(0.07, 0.14)*/ 0.43(0.32, 0.59)*
Pain at injection site	0.99(0.98, 1.00)/ 0.99(0.99, 1.01)	13.54(9.32,19.67)*/ 2.92(2.20, 3.86)*	0.38(0.27, 0.54)*/ 0.47(0.35, 0.63)*
Fever	1.00(0.99, 1.01)/ 1.00(0.99, 1.00)	13.83(9.61,19.91)*/ 1.79(1.36, 2.35)*	1.58(1.10, 2.35)*/ 0.48(0.36, 0.65)*
Chills	1.00(0.99, 1.01)/ 0.10(0.10, 1.01)	29.30(19.94,43.03)*/ 1.14(0.84, 1.56)	0.88(0.60, 1.03)/ 1.11(0.78, 1.58)
Fatigue	1.00(0.99, 1.01)/ 0.99(0.98, 0.99)*	12.49(8.94, 17.44)*/ 2.29(1.71, 3.07)*	0.75(0.53, 1.06)*/ 0.49(0.36, 0.66)*
Headache	1.00(0.99, 1.01)/ 0.99(0.99, 1.01)	4.12(3.01, 5.64)*/ 1.94(1.46, 2.59)*	0.56(0.41, 0.77)*/ 0.60(0.45, 0.81)*
GIT	0.99(0.98, 1.01)/ 0.10(0.99, 1.01)	5.94(4.00, 8.82)*/ 0.63(0.43, 0.92)*	0.24(0.17, 0.35)*/ 0.25(0.17, 0.36)*
Muscle or joint pain	0.99(0.99, 1.01)/ 1.0(0.99, 1.01)	35.66(24.11,52.72)*/ 1.89(1.40, 2.56)*	0.93 (0.62, 1.40)/ 0.79(5.80, 1.09)

Sex entered as female to male ratio, PMHx (past medical history) as ratio of having any past medical condition, *= P value < 0.05, **= first dose/ second dose, OR (95%CI), (GIT: gastrointestinal tract)

Table 4. Correlation between age (years) and severity of adverse reactions

Adverse Reactions	First dose**	Second dose**
Redness	0.09*	-0.06
Swelling	0.04	-0.03
Pain at injection site	0.05	0.02
Fever	0.01	0.03
Chills	0.01	0.03
Fatigue	-0.03	0.08
Headache	0.01	0.05
GIT	0.04	0.02
Muscle or joint pain	0.01	0.00

**=Rs value, *= P value < 0.05, (GIT: gastrointestinal tract)

Table 5. McNemar chi square for the use of over the counter drugs following first and second dose*

Second dose / First dose	Yes	No
Yes	167	67
No	356	260

*95% CI (1.32, 2.52), OR=1.8, P<0.001

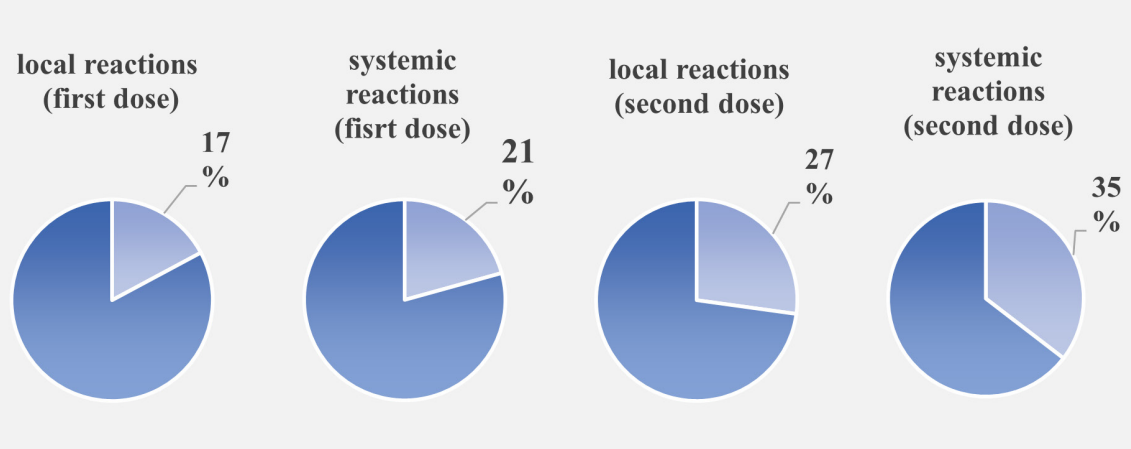

Figure 1. Incidence of adverse reactions in first and second dose

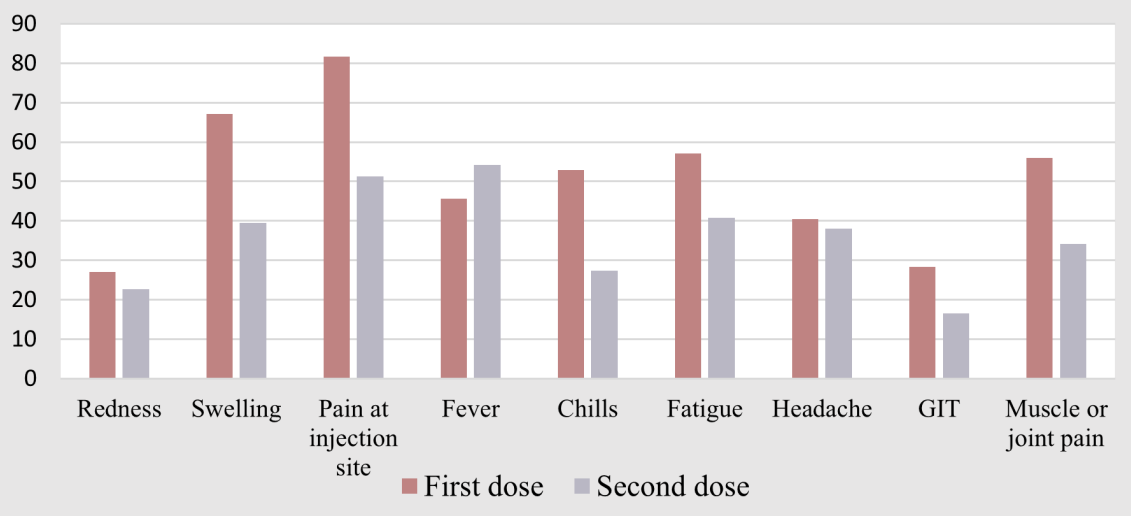

Figure 2. Frequency of adverse reactions following the first and second doses, (GIT: gastrointestinal tract)

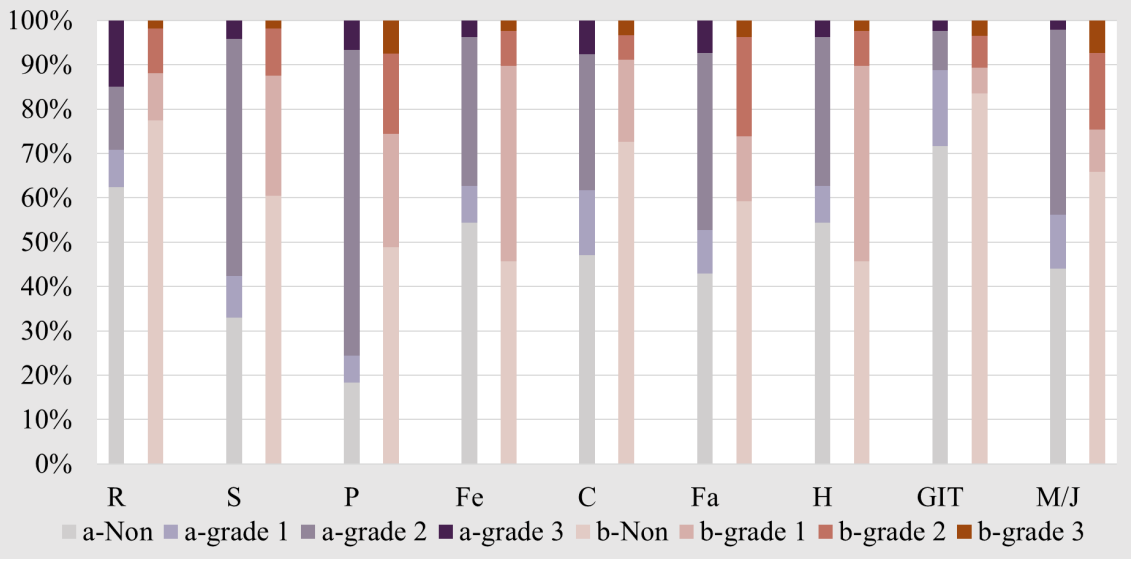

Figure 3. Severity grading for the first (a) and second (b) adverse reactions following the first and second doses. (R=redness, S=swelling, P=pain at injection site, Fe=fever, C=chills, Fa=fatigue, H=headache, GIT= gastrointestinal tract, M/J=muscle or joint pain)

6. Discussion

The mRNA vaccines induce an immune reaction and immunity against the virus develops without actually causing an illness and these reactions are signs that the immune system is working [15]. Pfizer BioNTech vaccine's adverse reactions as described by the recipients and documented in clinical trials and many studies are not harmful by themselves, thus, outlining these reactions helps expand knowledge and reject myths about the vaccine. Some real evidences exist that refusal to take the vaccine among general population being caused by little knowledge about these reactions [16].

In this study, all recipients experienced at least one adverse effect after receiving any dose of the Pfizer BioNTech vaccine and this was also seen in other studies with at least 60% experienced one side effect [17]. Furthermore, no participant experienced grade 4 or 5 severity score in all types of reactions indicating the general safety of the vaccine.

Our results were generally similar to what were documented in other studies, with injection site pain being the most common local adverse effect following both vaccine doses [18]. Injection site pain was also the most commonly reported adverse effect to the intra-muscular administration of other vaccines (influenza vaccine, Pneumococcal Polysaccharide Vaccines) [19,20]. In another study, generalized weakness/fatigue was the most commonly reported side effect [21]. The finding that more females experienced adverse effects following any vaccine dose goes with the documented fact that a relationship coexists between sex steroids and antibody response to vaccination or infection, with females having higher neutralizing antibody responses than males do [22]. Having a chronic health condition was significantly associated with individuals experiencing more severe adverse effects following the second dose. Individuals with chronic underlying health conditions were not included in phase I/II trials, however, in one study in Slovakia, there was a slightly higher adjusted ratio for systemic reactions in those with prior medical illnesses [23].

Comparing the two doses, all local and systemic adverse reactions were more severe (but less common) following the second dose (except for fever). This goes with the findings of phase I/II trials conducted in United States. However, if some differences do exist, they may be due to differences in immunological background influenced by many individual or demographic-related factors.

More participants were used over the counter drugs following the first dose as adverse reactions were more common with the first dose or maybe due to preconceived ideas and fear of being vaccinated. Two of the most important limitations of this study were: first, the adverse effects were described by vaccine recipients and hence they were amenable to subjective assessment. Nevertheless, obtaining an objective form of these adverse effects in order to precisely document the vaccine's effects is not easy, but unlike other studies in which recipient-filled questionnaires were used, phone calling made the information obtained more accurate. Second, the duration of follow-up for adverse effects for one week might be short, however, it was documented that most adverse reactions to the vaccine peak 48 hours and were generally resolved within one week after vaccination [11], besides, studying late-onset adverse effects was not the scope of this study.

7. Conclusions

Vaccine adverse reactions will be experienced after any dose of Pfizer BioNTech vaccine but they are generally mild, tolerable and self-limited or relieved using over the counter prescriptions.

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