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Assessment of the severity of COVID-19 symptoms after vaccination among the Saudi population suffering from chronic conditions

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ABSTRACT

Since the emergence of COVID-19 disease, more than 600 million people have been affected. However, the severity and the risk of mortality of the disease were shown to depend on whether the infected individual was suffering from any other comorbidities. The present study is designed to determine a group of people with comorbidities who are more susceptible to developing severe symptoms after infection with COVID-19. We also aim to compare the side effects of different COVID-19 vaccines in the Saudi population. Here we report a statistically significant difference between the chronic medical condition of the participants and their COVID-19 status (p = 0.03). We also observed a statistically significant difference between vaccine status and COVID-19 infection, as more than 70% of the participants (n=195) were unvaccinated when they tested positive for COVID-19. In our study, most of the participants (n=856, 77.5%) took the Pfizer-BioNTech vaccine, while 14.7% (n=162) and 4.5% (n=50) of the participants took Oxford–Astra Zeneca and Moderna Vaccines, respectively. There were also statistically significant differences in the severity of side effects between different vaccines (p=0.001). In conclusion, severe side effects were reported after the Oxford-AstraZeneca vaccine. In addition, the side effects, including fever, tiredness, headache, nausea, chills, pain, swelling at the injection site, body pain, and muscle pains, were reported more frequently after the vaccine's first dose, and participants with either one or more comorbidities.

Keywords: COVID-19, vaccination, comorbidities, severity of the disease

1. INTRODUCTION

The world has been fighting a global health problem since the first case of the newly discovered Coronavirus strain in Wuhan, China, on December 31, 2019, has been reported. The coronavirus disease has quickly spread across various

countries, causing death and taking down the economies of many countries (Zhu et al., 2020). The SARS-CoV-2 viruses are transmitted primarily by respiratory droplets with a reproduction number of around ~2.2 (Li et al., 2020). Since the rapid spread of the virus across the world and according to the World Health Organization (WHO) data, till August 2022, there have been nearly six hundred million confirmed cases and more than six million deaths (WHO 2021).

Persons with COVID-19 have symptoms ranging from mild to critical conditions. Milder symptoms are usually non-specific and include fever, fatigue, cough (with or without sputum), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, diarrhea, nausea, vomiting, and headache without abnormal chest imaging findings. In contrast, persons with moderate infections have chest images showing pneumonia manifestation. A critical patient has rapid disease progression due to respiratory failure, which might require mechanical ventilation. Children under the age of 10 years were also affected but their symptoms were milder than in adults. In addition, persons with no clinical symptoms after infection with SARS-CoV-2 require no hospital visits or treatment (WHO, 2020). Since the treatment of the patients usually depends upon the symptoms, it is crucial to understand and classify the risk factors for severe outcomes. Stratifying the infected persons based on their symptoms and associated risk factors will help better treatment intervention strategies, thus decreasing the hospital burden and mortality rates in those patients.

The COVID-19 pandemic has established its effect on many aspects internationally. An immediate response to COVID-19 was needed to reduce the burden of the disease. Therefore, several possible vaccine candidates against SARS-CoV-2 have been developed, but only a few were authorized for emergency use authorization (Dal-Re et al., 2021). Immunization is a safe and effective process to protect against infections, as it enhances the immune system to form antibodies. Given how easily and quickly the coronavirus can spread, the importance of these vaccines lies in decreasing the burden of the disease by allowing the body to develop an immune response against the coronavirus safely. Currently, in Saudi Arabia (as of August 2021), three vaccine candidates have been approved by the Saudi food and drug administration (SFDA), which are Pfizer BioNTech (BNT162b2 mRNA), Oxford AstraZeneca (ChAdOx1 nCoV-19), and Moderna (mRNA-1273) (Saudi CDC, 2021).

Pfizer-BioNTech was the first COVID-19 vaccine to get FDA emergency use authorization in December 2020 (US-FDA, 2021). In August 2021, it was also the first COVID-19 vaccine to receive full FDA approval for ages 16 and older (US-FDA, 2021). It is an mRNA-lipid nanoparticle encoding the viral spike glycoprotein of SARS-CoV-2 (WHO, 2021). The vaccine is administered in two doses of 30 μg each with an interval of 21-28 days. Its efficacy against symptomatic disease is about 91% at six months post the second dose (Liu et al., 2021). The Moderna vaccine was authorized for emergency use by the FDA in December 2020, about a week after the Pfizer-BioNTech vaccine (Self et al., 2021). Moderna and Pfizer-BioNTech vaccines share the same mRNA technology with similar efficacy rates at preventing symptomatic disease (WHO, 2021). Its effectiveness against symptomatic disease can reach 91.9% after one dose and 94.1% after two doses given in two doses that contain a 100 μg mRNA, 28 days apart (WHO, 2021).

Oxford-AstraZeneca is a viral vector COVID-19 vaccine. It is a recombinant simian adenovirus vector expressing S glycoprotein with a tissue plasminogen activator (tPA) leader sequence. It is administered as 2.5–5 × 1010 viral particles, taken in 2 doses, 4-12 weeks apart. It has an efficacy of 76% against symptomatic disease after 22 days from the first dose (WHO, 2021). Longer dose intervals are associated with greater vaccine efficacy. The second dose efficacy is about 81% with more than 12-week interval and 55% with less than 6-week interval (WHO, 2021).

All these vaccines have proven their safety and efficacy in clinical trials (Polack et al., 2020; Baden et al., 2021; Voysey et al., 2021) and are beneficial in reducing the morbidity and mortality of the disease (Swan et al., 2021). During the clinical trials of these vaccines, mild to moderate local and systemic post-vaccination adverse effects have been documented (Polack et al., 2020; Baden et al., 2021; Voysey et al., 2021). The present study is designed to investigate the severity of symptoms after COVID-19 infection among the Saudi population suffering from chronic conditions and to determine the group of people with comorbidities who are more susceptible to developing severe symptoms after COVID-19 infections. The study also aims to compare the side effects of each vaccine in the Saudi population.

2. METHODOLOGY

Research survey design and target population

The present research is a cross-sectional study design and is conducted between December 2021 and March 2022 in Saudi Arabia. The general city population, medical and dental students, and faculty members of the University of Hail are included as study participants.

Sampling technique, sample size, and study variables

The participants are selected through a convenient sampling technique. For determining the sample size, Raosoft Inc software is used. (http://www.raosoft.com/samplesize.html). Parameters for sample size calculation are a margin of error of 5%, 95% confidence of interval, and 50% response distribution. The minimum sample size required for this study is 1104. The dependent variable is the patient's status as COVID-19 positive or negative.Independent variables are age, gender, education level, smoking status, chronic medical condition, COVID-19 vaccine status, side effects, and vaccine type.

Data collection

Data is collected using an online self-administered questionnaire. The structured questionnaire consisted of respondents' demographic info and focused on questions related to their experience of COVID-19 disease and the side effects after being administered with various COVID-19 vaccines. The questionnaire was designed using Google Forms, and its link was shared through social media apps. The questionnaire is prepared in English and Arabic languages.

Study questionnaire

The e-survey questionnaire is grouped into two sections: socio-demographic information of the respondents and their experience of COVID-19 vaccines' side effects. While answering the questionnaire, age, gender, nationality, residence, occupation, educational level, monthly family income, and past smoking history are acquired in the demographic section. In the COVID-19 vaccines section, 12 questions are included. The questions inquire about the comorbidities, the symptoms of COVID-19 disease, and the side effects experienced by the respondents for each vaccine, whether it is Pfizer BioNTech, Oxford AstraZeneca, or Moderna with each dose.

Statistical analysis

The data is analyzed by Microsoft Excel and IBM SPSS V.23 software. Descriptive statistics are presented as mean scores, standard deviations, or medians. Histogram and Kolmogorov–Smirnov test was used to determine the normal distribution of data. Inferential statistical analysis (Chi-square test) is used to test the association strength between COVID-19 vaccines' side effects and comorbidities. A P-value of <0.05 was considered statistically significant.

3. RESULTS

Characteristics of the participants included in the study

A total of 1104 individuals participated in the present study. The socio-demographic profiles of the survey cohort are shown in Table 1. Around 98% of the participants were Saudi nationals. Nearly 60% of the study participants are males (59.3) in the present study. More than 50% of the study participants are in the age group of 35-70 years (50.2%) and are married (55.2%). Most participants have higher education (75.6%), while 35.8% are government and private companies' employees, and only 21.2% were ever smokers. 31.5% of participants had either one or multiple chronic medical problems; diabetes (30.3%), obesity (21.6%), hypertension (14.1%), and chronic lung diseases (11%) constituted more than 75% of the diseases reported by the participants (Figure 1a).

Table 1 Socio-Demographic Characteristics of Study Participants. (n=1104)

S.No	Characteristics	Frequency n (%)
1.	Age (Years) (Mean ±SD)	
	15-34	550 (49.8)
	35-70	554 (50.2)
2.	Gender	
	Male	655 (59.3)
	Female	449 (40.6)
3.	Marital Status	
	Single	495 (44.8)
	Married	609 (55.1)
4.	Nationality	
	Saudi	1083 (98)
	Non-Saudi	21 (2)

5.	Education level	
	Basic Education	270 (24.5)
	Higher Education	834 (75.5)
6.	Occupation	
	Healthcare worker	97 (8.8)
	Employee(Government and Private sector)	396 (35.8)
	Students	243 (31)
	Others[#]	269 (24.3)
7.	Smoking	
	Ever	233 (21.2)
	Never	871 (78.8)
8.	Monthly income (SAR)	
	Less than 15000	604 (54.8)
	More than 15000	500 (45.2)
9.	Chronic Medical Condition	
	No	757 (68.6)
	Yes	347 (31.4)
10.	Infection with Covid-19	
	No	833 (75.5)
	Yes	271 (24.5)

[#] un-employed, disabled

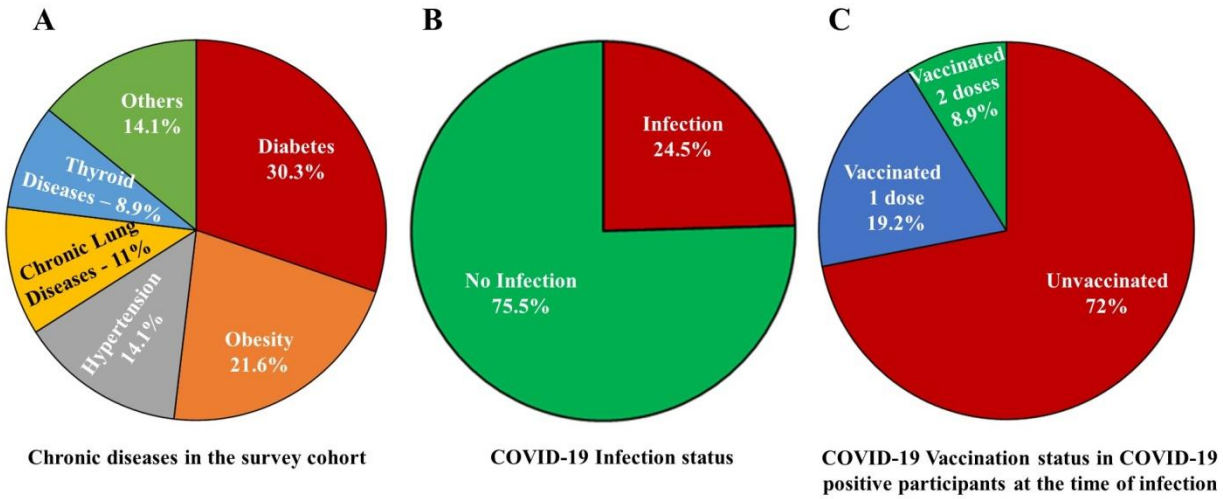

Figure 1 A) Chronic diseases in the survey cohort, B) COVID-19 infection status, and C) COVID-19 Vaccination status in COVID-19 positive participants at the time of infection

Correlation between socio-demographic variables and COVID-19 infection status

In our study, a quarter of the participants (271, 24.5%) were previously infected with COVID-19 (Table 1). Most of them were not vaccinated (n=195, 72%) at the time of infection, and only 19.2% and 8.9% of participants were vaccinated with one dose (n=52) and doses (n=24), respectively, at the time of infection (Figure 1b). The correlation of socio-demographic variables with COVID-19 infection status was also investigated. There were no statistically significant differences between age, gender, educational level, occupation, and smoking status with COVID-19 infection status ($p > 0.2$, Table 2). However, there was a statistically significant difference between the chronic medical condition of the participants and their COVID-19 status ($p = 0.03$, Table 2). We also observed that more than 70% of the participants (n=195) were unvaccinated when they tested positive for COVID-19 (Figure 1c). In contrast, more than 92% of the participants (n=770) who took the vaccine were negative for COVID-19, and this difference between vaccine status and COVID-19 infection was statistically significant ($p<0.000$, Table 2).

Table 2 Relationship between Socio-demographic characteristics and COVID-19 status

Characteristics	Covid-19 Positive	Covid-19 Negative	p-value
Age			
15-45	140 (51.7%)	410 (49.2%)	0.529
46-70	131 (48.3%)	423 (50.8%)	
Gender			
Male	163 (60.1%)	492 (59.1%)	0.205
Female	108 (39.9%)	341 (40.9%)	
Education level			
Basic Education	67 (24.8%)	203 (75.2%)	0.935
High Education	204 (24.6%)	630 (75.4%)	
Smoking			
Ever	51 (21.8%)	183 (78.2%)	0.231
Never	221 (25.4%)	650 (74.6%)	
Chronic Medical Condition			
No	184 (67.9%)	573 (68.8%)	0.030 *
Yes	87 (32.1%)	260 (31.2%)	
Vaccine Status at the time of COVID-19 infection			
Unvaccinated	195 (72.0%)	63 (7.6%)	0.000 **
Vaccinated	76 (28%)	770 (92.4%)	
Severity of side-effects after vaccine second dose			
Mild	79 (29.2%)	224 (26.9%)	0.000 **
Moderate	72 (26.6%)	241 (28.9%)	
Severe	44 (16.2%)	58 (7.0%)	
No side effects	76 (28%)	310 (37.2%)	

Vaccine status, type and its side effects

At the time of this survey, almost all the participants (99.3%) were vaccinated with two doses of the vaccines. The majority of the participants (n=856, 77.5%) were administered the Pfizer-BioNTech vaccine, while 14.7% (n=162) and 4.5% (n=50) of the participants took Oxford–AstraZeneca and Moderna Vaccines, respectively. 2.5% of the participants were not sure about the vaccine type they took (Table 3, Figure 2a). At the time of this survey, more than 90% of the participants did not take their booster dose, as only 9.9% were administered with a booster dose (Table 3). More than 60% of the participants had side effects after vaccination. These side effects were fever, tiredness, headache, nausea, chills, pain, swelling at the site of injection, body pain, and muscle pains (data not shown). After the first dose, 68.7% of the participants experienced some side effects, whereas 65.1% experienced side effects after the second dose. Though this difference is slight, it was statistically significant ($p<0.000$, Figure 2b). Moreover, most of these vaccine side effects were observed among participants with comorbidity (62%, Figure 2c).

Table 3 Type of vaccine administered at the time of the survey

Vaccine type	First Dose	Second Dose	Booster Dose
No Vaccine	5 (0.5%)	8 (0.7%)	995 (90.1%)
Pfizer-BioNTech	894 (81%)	856 (77.5%)	98 (8.9%)
Oxford-AstraZeneca	174 (15.8%)	162 (14.7%)	0
Moderna	6 (0.5%)	50 (4.5%)	2 (0.2%)
Not sure which vaccine	25 (2.3%)	28 (2.5%)	9 (0.8%)
Total	1104	1104	1104

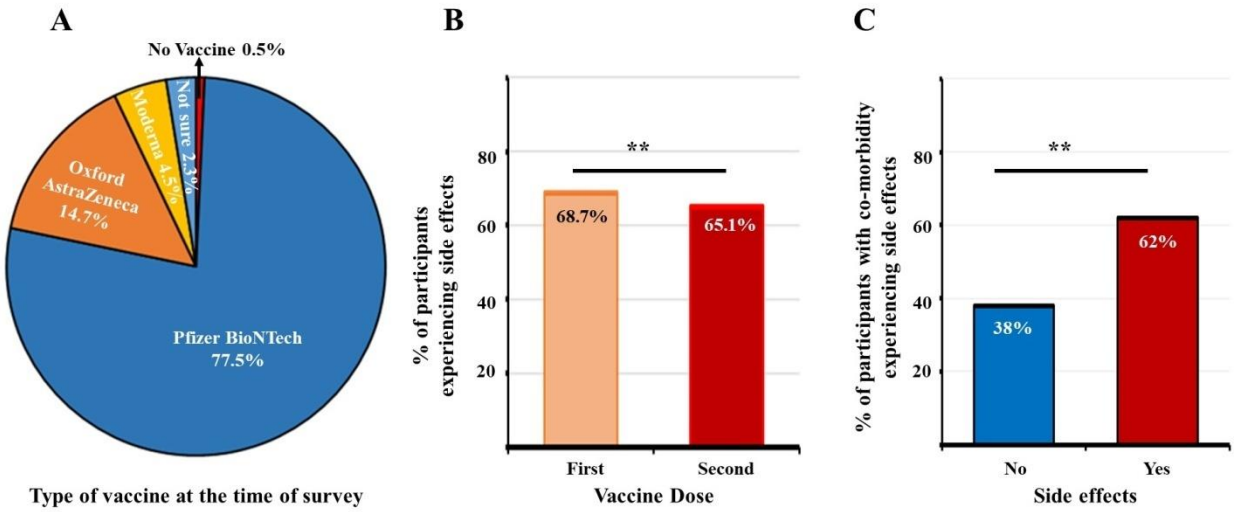

Figure 2 A) Type of vaccine at the time of the survey, B) percentage of participants experiencing side effects after the first and second dose of the vaccine, C) the percentage of participants with comorbidity experiencing side effects after vaccination.

The severity of the side effects after the vaccine's second dose was also evaluated. We observed that9.2% of the participants experienced severe side effects, and 27.4% and 28.4% experienced mild and moderate side effects. At the same time, 35% of the study participants did not report any side effects after the vaccine's second dose (Figure 3a). We also investigated if different types of vaccines would have different effects on the severity of the side effects. In our study, 77.5% of the participants were administered with Pfizer-BioNTech vaccine as the second dose. After the double dose with the Pfizer-BioNTech vaccine, only 7.4% of the participants complained about the severe side effects. In comparison, 28.5% and 29.3% of the participants reported mild and moderate side effects after the second vaccination dose (Figure 3b). In contrast, the corresponding numbers for severe, mild, and moderate side effects were 13.6%, 27.8%, and 21.0%, respectively, after the Oxford-AstraZeneca vaccine (Figure 3c). These differences in the severity of side effects between different vaccines were statistically significant (p=0.001).

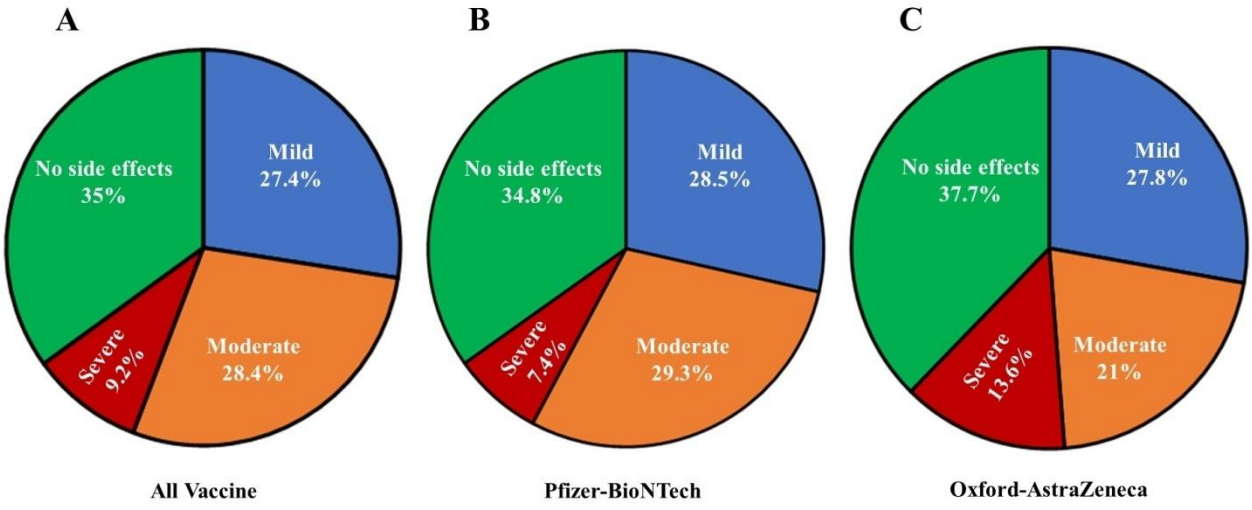

Figure 3 Severity of side effects after different vaccine administration

Prior COVID infection and severity of the side effects

Next, we evaluated the severity of COVID-19 side effects in those participants who had earlier tested positive for the virus. We found that severe vaccine side effects were present in 16.2% of those participants who were earlier positive for COVID-19 compared to 7% in earlier COVID-19 negative participants. Moreover, no side effects were reported in 37.2% of the COVID-19 negative

participants compared to 28% of COVID-19 positive participants, and these differences between the COVID-19 side effects and prior COVID-19 infection were statistically significant ($p < 0.000$, Table 2).

4. DISCUSSION

COVID-19 vaccinations are intended to elicit an immunological response, boosting neutralizing antibodies against the SARS-CoV-2's spike protein. In the present research survey, we performed a cross-sectional, community-based survey of more than 1100 individuals with or without chronic conditions and investigated the side effects they experienced after the COVID-19 vaccination. Our study cohort included male and female participants from different age groups and educational backgrounds. The side effects were evaluated after being administered with any of the three vaccines currently in use in KSA: Pfizer BioNTech (BNT162b2 mRNA), Oxford AstraZeneca (ChAdOx1 nCoV-19), and Moderna (mRNA-1273). Several vaccines, including mRNA and adenoviral-vectored, have shown effectiveness in phase III clinical trials, and many have been given emergency permission in several countries. Ministry of Health in KSA has approved BNT162b2 mRNA (Pfizer-BioNTech/), mRNA-1273 (Moderna), and ChAdOx1 nCoV-19 (University of Oxford-AstraZeneca) vaccines for use (as of September 2021) (Saudi CDC, 2021). All these vaccines have proven their safety and ability to prevent or reduce COVID-19 symptoms.

In the present study, nearly a quarter of the participants had contacted the SARS-CoV2 virus earlier. We found that participants with diabetes, hypertension, obesity, chronic lung diseases, and thyroid diseases were more prone to get COVID-19 infection than those without comorbidities. This result is in line with several other studies on patients with comorbidities (Yadav et al., 2021; Zhou et al., 2020; Ahmad Malik et al., 2022; Wang et al., 2020). Ahmed Malik et al., (2022) noticed that persons with comorbidities, including diabetes, obesity, cardiovascular disorders, and chronic lung diseases, were more likely to get COVID-19 infections. Another study by Radha Yadav et al., (2021) reported that persons over 60 years of age, suffering from diabetes and hypertension, had a significantly higher risk of infection with the SARS-CoV2virus (Yadav et al., 2021). This association between the SARS-CoV2 virus and hypertension can be explained by the virus entering the cells by interacting with ACE2 receptors, critical in regulating blood pressure, wound healing, and inflammation processes. Some studies have shown that administration of antihypertensive drugs like ACE inhibitors (Ferrario et al., 2005) and angiotensin receptor blockers (Klimas et al., 2015) may be involved with enhanced ACE2 receptor expression at the cell membrane, so it supplies SARS-COV-2 with an increased number of entrances to infect the cells.

In our study, more than 70% of the COVID-19-positive participants were unvaccinated at the time of infection. In contrast, 19.2% of COVID-19-positive participants were vaccinated with one dose of the vaccine, and8.9% were vaccinated with two doses of the vaccine at the time of COVID-19 infection, indicating that the vaccine has a protective role against the SARS-CoV2 virus infection, as shown in several other studies earlier (Cohn et al., 2022; Hall et al., 2022). In our study, most participants took the Pfizer-BioNTech vaccine, followed by Oxford-AstraZeneca and Moderna vaccines. This may be due to the wider availability of the Pfizer-BioNTech vaccine compared to the other two vaccines. This can also be due to the dissimilar distribution and online accessibility of the questionnaire.

We also investigated the side effects in the participants after being administered different vaccines. Mild to moderate side effects are not uncommon after vaccination. However, experiencing severe side effects will undermine the value of COVID-19 vaccination. A larger number of participants reported severe side effects with the Oxford-AstraZeneca vaccine compared to the Pfizer-BioNTech vaccine after the second dose. The adverse effects of all the COVID-19 vaccines are quite similar; the most reported post-vaccination adverse effects were headache, fever, myalgia, fatigue, pain at the injection site, and chills (Hatmal et al., 2021; Kadali et al., 2021; Kadali et al., 2021; Riad et al., 2021; Abuqudairi et al., 2022). Although adverse effects have been reported on both doses, it has been found that participants who received BNT162b2 and mRNA-1273 vaccines reported more adverse effects on the second dose compared to the first dose (Chapin-Bardales et al., 2021). But for the ChAdOx1 nCov-19 vaccine, the first dose has reported more adverse effects than the double dose (Jeon et al., 2021). Also, both vaccines, BNT162b2 and mRNA-1273, can cause various adverse effects, but these reactions that have been reported are found to be less frequent in the BNT162b2 vaccine compared to the mRNA-1273 COVID-19 vaccine (Meo et al., 2021). Participants after the first dose of the ChAdOx1 nCov-19 vaccine have reported significantly more adverse effects than the first dose of the BNT162b2 vaccine (Andrzejczak-Grzadko et al., 2021).

Many self-reported studies have been performed on the extent of side effects experienced in the surveys. A prospective observational self-reported study has been made to evaluate the adverse effects of BNT162b2 mRNA and ChAdOx1 nCoV-19 vaccines (Menni et al., 2021). Around 25% of vaccinated individuals reported one or more systemic adverse effects. In addition, 66.2% have reported one or more local side effects. Fatigue and headache were the most common systemic side effects, whereas tenderness and local pain around the injection site were the most common local side effects. Systemic adverse effects were higher in

individuals receiving one dose of the ChAdOx1 nCov-19 vaccine than those receiving one dose of the BNT162b2. Participants who received the two doses of the BNT162b2 vaccine reported more systemic and fewer local adverse effects than the first dose. A study from Saudi Arabia by Alhazmi Abdulaziz et al., (2021) also reported similar data in a retrospective, cross-sectional survey for both Pfizer-BioNTech and Oxford-AstraZeneca adverse effects. The most reported adverse effects were fatigue, pain at the injection site, fever, and headache. Moreover, the individuals who received the two doses had more adverse effects on the second dose. The adverse effects reported by the participants who received the ChAdOx1 nCoV-19 vaccine are higher than those who received the BNT162b2 vaccine.

Similar findings were found in another study by Adam et al., (2021). Another study showed that individuals with chronic diseases are more prominent to have adverse effects (Alghamdi et al., 2021). Also, several studies regarding BNT162b2 and ChAdOx1 have reported more side effects in females (Alghamdi et al., 2021; El-Shitany et al., 2021) and previously infected individuals (El-Shitany et al., 2021).

Study limitations and conclusions

We used self-reported data, which can produce bias. Also, the subjective judgment of how severe the side effects were, and the recall of the vaccine's side effects may lead to inaccurate data. In conclusion, the most common side effects of COVID-19 vaccines were fever, tiredness, headache, nausea, chills, pain, swelling at the injection site, body pain, and muscle pains. These side effects were reported more frequently after the first dose and participants with either one or more comorbidities. Moreover, severe side effects were reported among the participants who received the Oxford-AstraZeneca vaccine.

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Author Contributions

Conception and study design: ASSK. Data collection: MA, HA, and IA. Data analysis and interpretation: ASSK and MZ. Manuscript drafting: MA, HA, IA, and ASSK. Manuscript revision: ASSK, MS. All authors approved the final version of the manuscript.

Informed Consent

Obtaining written informed consent is difficult inonline surveys. However, we included a consent question at the beginning of the online questionnaire, taking respondents' consent. The responses were collected from only those participants who agreed to take part in the study. The participants had the option to either agree or decline to participate in this survey.

Ethical approval

The study was performed after approval by the Medical Ethics Committee of the University of Hail (Ethical approval code.H-2020-649-23749).

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This study has not received any external funding.

Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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