


## RESEARCH ARTICLE

# Safety of COVID-19 vaccines

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## Abstract

This study is aimed to identify the adverse effects associated with three types of coronavirus disease 2019 vaccines. Approximately 1736 individuals agreed to participate in this study. The participants involved in the study were individuals who had received the first dose or full course (two doses) of the vaccine at least 30 days before the survey. A direct and interactive web-based system interview with a paper and electronic version of the questionnaire was used for all participants. A total of 1736 randomized individuals were identified. The reactogenicity of the vaccines including pain, redness, urticaria, and swelling at the site of the injection was reported in 34.56% of the participants. Local site reaction was reported in more individuals who had Pfizer and AstraZeneca vaccines than those who received the Sinopharm vaccine. The systemic events were more common with AstraZeneca and Pfizer vaccines, symptoms reported were fatigue, body pain, headache, muscle pain, fever, and gastrointestinal side effects. There were no correlations between age or gender, and the duration of the adverse effects for the three vaccines. Swelling and severe allergic reaction of the eyelids, severe hypotension, generalized body aches, shortness of breath, weakness and numbness on the injected arm, acute hyperglycemia, severe chest pain, and fever more than 39°C were among the unusual signs and symptoms reported by the participants. Pfizer, AstraZeneca, and Sinopharm vaccines were found to be safe and Sinopharm vaccine showed a lower prevalence of adverse effects compared with the other vaccines. The duration and severity of adverse effects were not affected by age or gender. Unusual side effects should be closely monitored to establish determine they are linked to the immunization.

## KEYWORDS

AstraZeneca vaccine, COVID-19, Pfizer vaccine, Sinopharm vaccine, vaccine

## 1 | INTRODUCTION

The United States has approved the use of two coronavirus disease 2019 (COVID-19) vaccines.<sup>1</sup> The Food and Drug Administration granted an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020, and on December 18, 2020, for the Moderna COVID-19 vaccine; both

are to be given in a two-dose sequence.<sup>2</sup> According to Reuters, Phase III trials for the Sinopharm shot took place in 10 countries around the world in September 2020. China and some other countries, including Jordan, have approved the Sinopharm vaccine.<sup>3</sup> These vaccines have been modeled in different development approaches, therefore they have diversity in some characteristics like efficacy and storage conditions.<sup>4</sup> The Pfizer

and Moderna vaccines are nucleic acid vaccines that use genetic materials such as messenger RNA, or mRNA, a technology that gets part of genetic code into the human cells. Sinopharm, on the other hand, is BBIBP-CorV, an inactivated coronavirus vaccine.<sup>5</sup> The immune response is triggered to produce antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus by BBIBP-CorV. Antibodies bind to viral proteins like the spike proteins that stud the virus's surface. Safety monitoring for these vaccines is an essential Phase IV clinical study despite thousands of participants were involved in the clinical Phase II and III trials. At the time of writing, the number of people vaccinated was 411.61 million and 93,343,417 are fully vaccinated globally.<sup>6</sup>

For a good reason, vaccine production is a lengthy and time-consuming process. Vaccines are typically given to large groups of healthy people to avoid infection rather than to give them to sick people to help them recover. Therefore, a new vaccine's protection threshold must be very high and apply to the entire target population, regardless of age, gender, color, or ethnicity.<sup>7</sup> Individuals would not consider taking a vaccine because of its side effects when it is meant to protect them from contracting the infection. The careful and deliberate method of vaccine's production and testing is guided by this central emphasis on protection. Phase 4 trials, which include hundreds of thousands of people and concentrate on vaccine's safety (how well the vaccine performs in the real world), as well as monitoring for rare adverse effects, are done after the vaccine has been licensed.<sup>8</sup>

There was no evidence of a causal association between COVID-19 vaccines and death, this was based on records collected from death certificates, autopsy reports, psychiatric history, and clinical descriptions from VAERS reports and healthcare providers. Only a few cases of anaphylaxis have been identified after receiving Pfizer-BioNTech and Moderna COVID-19 vaccines (4.5 reported cases per million doses administered).<sup>9</sup> Reactions registered to the v-safe system by people who had received the Pfizer-BioNTech vaccine were more common after administering the second dose than after the first. The two COVID-19 vaccines currently in use did not show any signs of unexpected significant adverse effects in their original post-authorization protection profiles.<sup>10</sup> These findings provide reassurance and insights on what healthcare providers and vaccinated individuals should predict after vaccination.

## 2 | PATIENTS AND METHODS

This study involved 1736 participants with the age range of 18–86 years. The participants included in the study were people who had taken the first dose or full course of vaccine (two doses) a minimum of 30 days before the study. Moreover, participants subgrouped into those who had taken either Pfizer, AstraZeneca, or Sinopharm vaccine. A trained research assistant conducted a direct interview with a paper version of the questionnaire and an interactive web-based

system interview with an electronic version of the questionnaire for the participants. The questionnaire collected information such as the participants' demographic data (age, gender, weight, and smoking); comorbidities (cardiovascular, respiratory, kidney, liver, immunological, and endocrine diseases); type of vaccine received, number of vaccine doses; and the symptoms the individuals presented with after the vaccination and the duration of these symptoms. The prevalence of these adverse reactions was analyzed and assessed to determine what symptoms are the most common and to what type of vaccine could be associated with.

## 2.1 | Statistical analysis

Statistical analysis and figures were conducted using SPSS software (version 23.0; SPSS) and Prism 8 for OS X (version 8.4.3 GraphicPad Software, LLC).

The prevalence of signs and symptoms were expressed as a number and percentage and mean  $\pm$  SD was used to describe the continuous variables. Analysis of variance test used to compare the dependent variables. Hazard ratio and 95% confidence interval used to determine the risk of age and gender with the duration and prevalence of the signs and symptoms.

## 3 | RESULTS

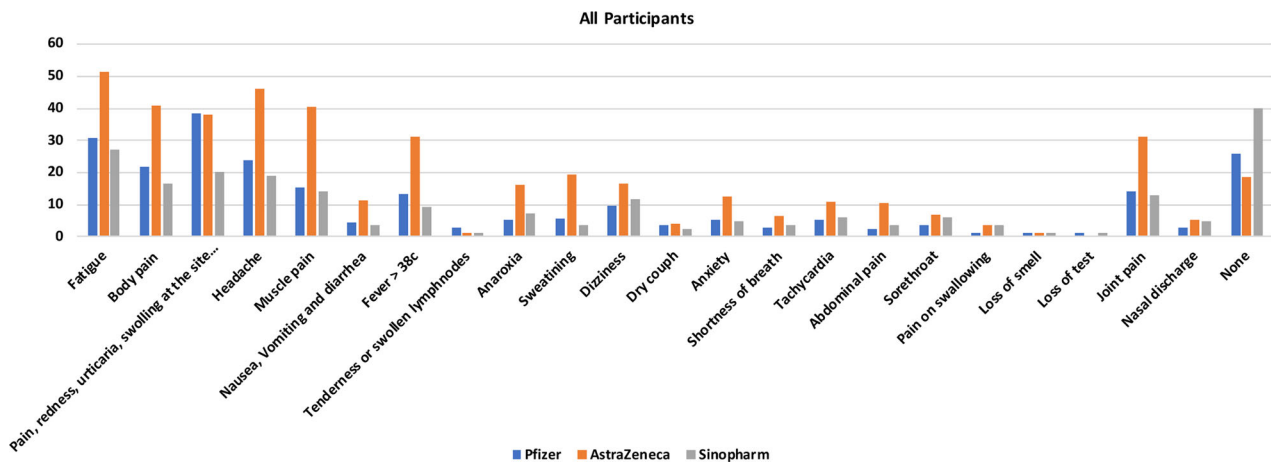
For the period from January 1, 2021 to April 10, 2021, a total of 1736 randomized participants from Iraq and Jordan have been identified for the study, of whom 700 received Pfizer (BioNTech) vaccine, 696 received AstraZeneca (AZD1222), and 340 received Sinopharm (BBIBP-CorV). The demographic data for these participants were illustrated in Table 1. Participants' age range was between 18 and 86 years (median age 49 years [interquartile range, IQR, 26–74]; males formed 51.61% of the total number of the participants and 19.64% received two doses of vaccines).

**TABLE 1** Age of participant and duration of symptoms

Type of vaccine	Age (years)	Duration of sign and symptoms (days)	p value
Pfizer	18–35	1.286 $\pm$ 1.328	0.31345
	36–55	1.903 $\pm$ 2.128	
	>55	1.747 $\pm$ 1.969	
AstraZeneca	18–35	1.861 $\pm$ 2.304	0.24551
	36–55	1.663 $\pm$ 1.657	
	>55	2.343 $\pm$ 2.617	
Sinopharm	18–35	1.733 $\pm$ 1.258	0.19957
	36–55	1.405 $\pm$ 0.916	
	>55	2.080 $\pm$ 2.120	

Type of vaccine	Gender	Duration of symptoms (mean ± SD)/day	p value
Pfizer	M	1.524 ± 1.505	0.158
	F	1.942 ± 2.288	
AstraZeneca	M	1.652 ± 2.016	0.116
	F	2.159 ± 2.218	
Sinopharm	M	1.485 ± 1.688	0.153
	F	1.952 ± 1.229	

**TABLE 2** Gender of participant and duration of symptoms



**FIGURE 1** Prevalence of adverse effect reported by all participants

### 3.1 | Prevalence of signs and symptoms associated with COVID-19 vaccines

The reactogenicity of vaccines including pain, redness, urticaria, and swelling at the site of the injection was reported by 34.56% of participants. Overall, Pfizer and AstraZeneca recipients reported more local reactions at the site of the injection than those who received Sinopharm vaccine with an average duration of 2 days (Table 2 and Figure 1).

The systemic events were reported more often in participants who received AstraZeneca and Pfizer vaccines compared with Sinopharm vaccine. The most commonly reported systemic effects were fatigue, body pain, headache, muscle pain, fever, and gastrointestinal effects (nausea, vomiting, anorexia, and diarrhea). Tenderness or swollen lymph nodes was more frequently noted in participants who received Pfizer vaccine compared with other types of vaccine. Sweating, dizziness, dry cough, anxiety, shortness of breath, tachycardia, abdominal pain, sore throat, joint pain, and nasal discharge were more common adverse effects associated with AstraZeneca vaccine. Whereas loss of smell and loss of taste shared relatively the same percentage among the three vaccines.

The percentage of participants who did not report any signs and symptoms represented by 40% for those who received Sinopharm vaccine, 25.71% who received Pfizer vaccine, and 18.39% who had AstraZeneca vaccine (Table 2 and Figure 1).

Signs and symptoms after the first dose of AstraZeneca vaccine were more prevalent compared with other vaccines, followed by Pfizer and less adverse reaction associated with Sinopharm vaccine (Table 3 and Figure 2).

Despite the fact that a small number of participants received a second dose of AstraZeneca vaccine, the signs and symptoms were more prevalent with the second dose compared to Pfizer and Sinopharm vaccines (Table 3 and Figure 3). The duration of signs and symptoms was not affected by age and gender in the three types of vaccines (Tables 1 and 2).

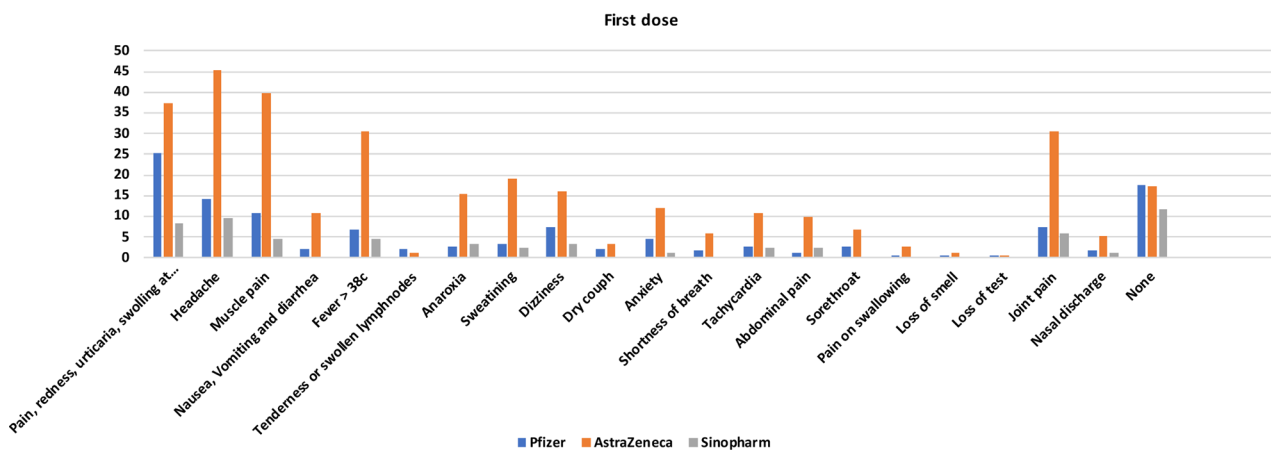
### 3.2 | Unusual symptoms

Table 3 summarizes the unusual symptoms expressed by the participants after vaccination. Two participants reported swelling and severe allergic reaction of their eyelids on the day of vaccination by Pfizer vaccine, the allergic reaction lasted up to 3 days. Six cases (four received Pfizer and two received AstraZeneca vaccine) were admitted into the hospital due to severe hypotension, generalized body aches, shortness of breath, and fever more than 39°C. Weakness and numbness of the hand on the injected side was reported by one participant and lasted for 13 days after Sinopharm vaccine administration. In two cases, severe chest pain for 6 days was reported; acute hypertension, four cases (with blood pressure exceeded 210/105 mm Hg) with a duration of 5 days and one case had

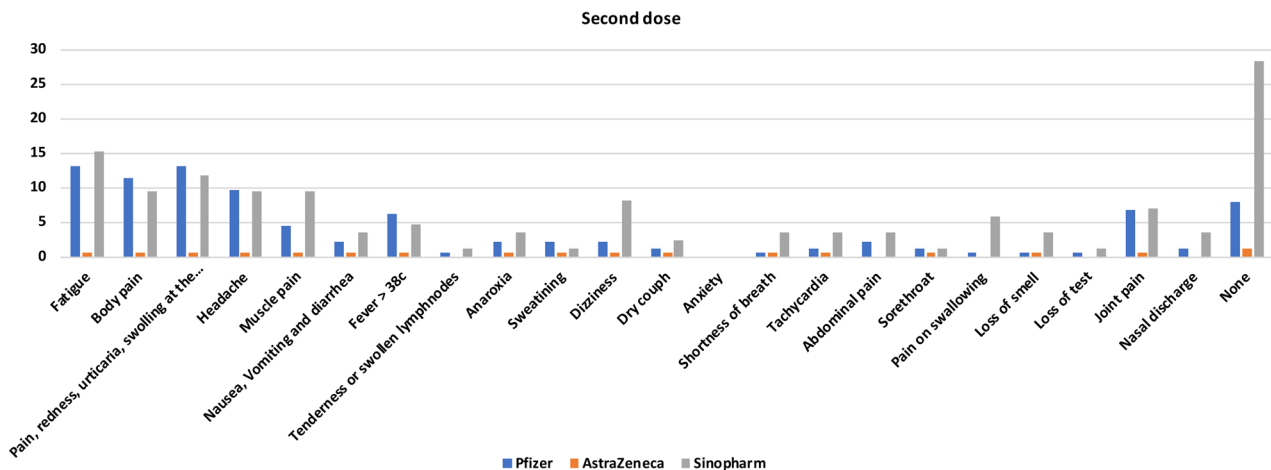
**TABLE 3** Unusual symptoms reported by the participants

Unusual symptoms	Number of cases	Type of vaccine	Average duration of symptoms (days)
Swelling and severe allergic reaction of eyelids	2	Pfizer	3
Hospital admission due to positive result of COVID-19 infection	4	Pfizer	7
	2	AstraZeneca	
Weakness and numbness of the hand, the site of injection	1	Sinopharm	13
Severe chest pain	3	Pfizer	6
	1	AstraZeneca	
Nasal bleeding	1	AstraZeneca	2
Acute hypertension, over 210/105 mm Hg	2	Pfizer	5
Acute hyperglycemia (FBS > 170 mg/dL)	1	Pfizer	2

Abbreviations: COVID-19, coronavirus disease 2019; FBS, fasting hyperglycemia.



**FIGURE 2** Prevalence of adverse effect reported by participants administered the first dose



**FIGURE 3** Prevalence of adverse effect reported by participants administered the second dose

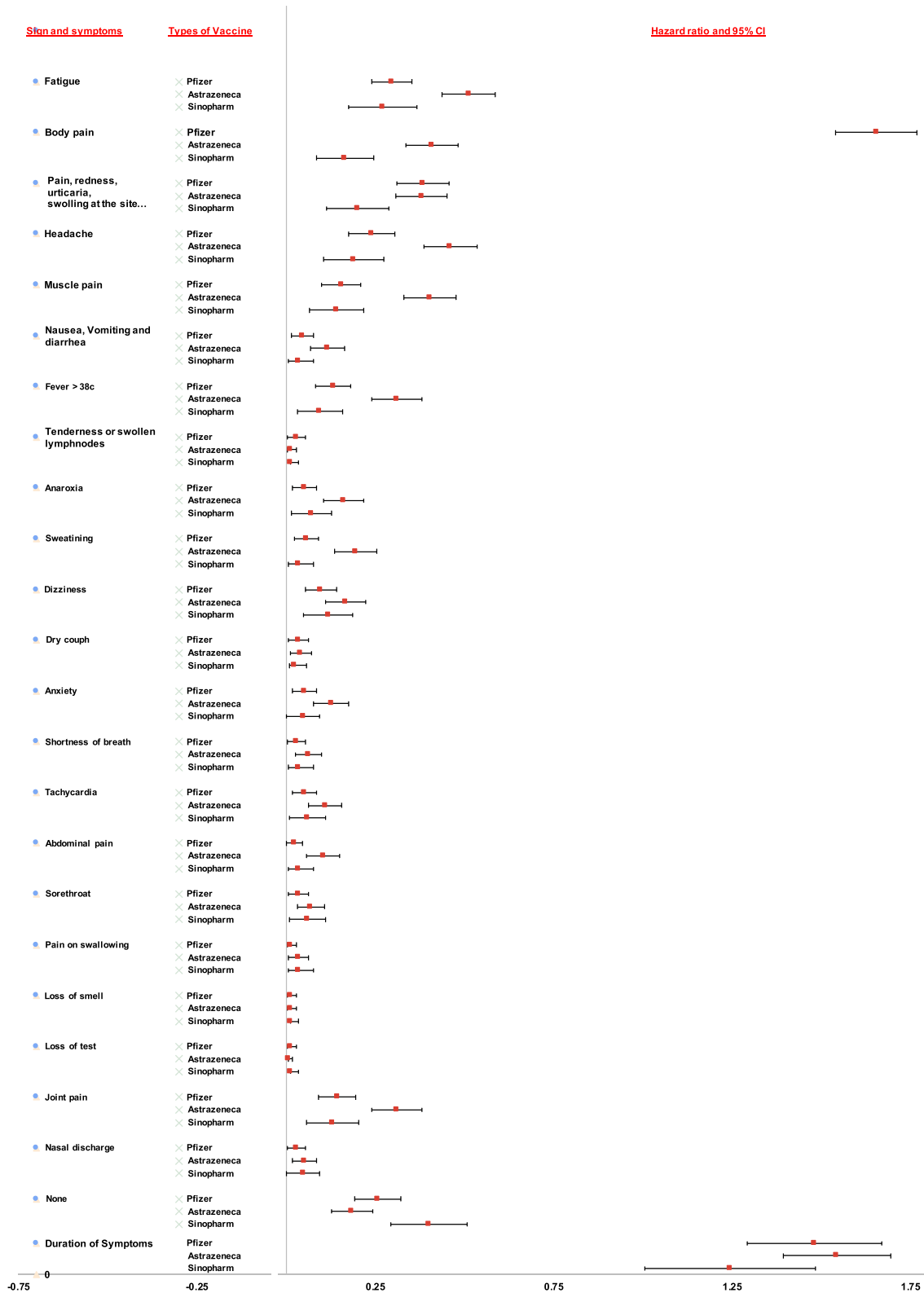


FIGURE 4 Hazard ratio associated with the three types of vaccines

acute hyperglycemia, (FBS > 170 mg/dL) for 2 days were reported by Pfizer vaccine. Whereas one recipient of AstraZeneca vaccine reported severe chest pain for up to 6 days and one case reported intermittent nasal bleeding for 2 days (Table 3).

Figure 4 showed that AstraZeneca vaccine was associated with higher risk and longer duration of postvaccination signs and symptoms compared to Pfizer and Sinopharm vaccines.

## 4 | DISCUSSION

Even though the year 2020 had been a tough year for all, 58 vaccines against the SARS-CoV-2 have been developed and are in clinical trials 1, with some vaccines currently achieving over 90% effectiveness against COVID-19 in clinical trials.<sup>11</sup> This extraordinary accomplishment comes at a time when COVID-19 events are at an all-time peak on a regular basis around the world. The development of coronavirus vaccines happened in a short period when it is essential for the regulatory and medical decisions to focus on benefit and risk estimates, identifying the stakes and possible checkpoints.<sup>12</sup> Delivering a conformationally accurate protein is crucial for any vaccine that aims to induce antibody-mediated immunity. The safety of vaccinations provided to otherwise healthy people is a top priority, and there's a possibility that vaccination could make SARS-CoV-2 infection worse.<sup>13</sup> Identifying, quantifying, and weighing proven and possible safety risks against potential advantages are important aspects of designing any vaccine.<sup>14</sup> One of the concerns posed during the production of the COVID-19 vaccine was whether the immune responses evidenced by the vaccine will help or prejudice SARSCoV-2 transmission as infection could happen after vaccination.<sup>15</sup>

Side effects are natural reactions to foreign drug injection, these include symptoms such as fever, muscle pain, and inflammation at the site of injection. They are mediated by the innate immune system. When the body's neutrophils or macrophages detect vaccine molecules, they release cytokines, which are chemical signals that trigger immune responses expressed as fever, chills, nausea, and muscle pain. This cytokines' reaction is expected to occur when a foreign agent is inserted into the bloodstream.<sup>16</sup> About half of people aged 16–55 who got a SARS-CoV-2 vaccine experienced a headache after the second dose according to trials when neither the recipients nor the researchers had the knowledge of who got a placebo and who got the mRNA vaccine. This reaction may relate to the vaccine.<sup>17</sup> Blood clots, which lead the United States to halt the AstraZeneca vaccine, are a very unusual occurrence, reportedly occurring one in a million times. Blood clots are currently being investigated as a possible side effect of the vaccine, yet a link to be found, they will be an incredibly unlikely complication.<sup>18</sup> According to scientists, there is no connection between the initial inflammatory reaction and the long-term defensive response. There is no scientific indication that those with more noticeable vaccine side effects are better protected from COVID-19. There's no reason to think that an exaggerated innate response will help the adaptive response.<sup>19</sup>

This study was not designed to assess the efficacy of these vaccines, the study focused primarily on reporting the postvaccination signs and symptoms expressed by the participants and comparing them between the three vaccines. Overall, the three types of vaccines were found to be safe, a direct conclusion according to the severity of the side effects the individuals experienced postvaccination when the signs and symptoms were mild or moderate. The postauthorization safety profiles for Pfizer, BioNTech, and Sinopharm COVID-19 vaccines are reassuring after the administration of 1736 doses to the public within the first month of the vaccination program.

Following the initiation of these vaccinations, reports of anaphylaxis have been submitted. During the analytic era, the incidence of

anaphylaxis after receiving COVID-19 vaccines was within the range for the data recorded after receiving inactivated influenza vaccine, pneumococcal polysaccharide vaccine, and live attenuated herpes zoster vaccine; successful medications for anaphylaxis are available.<sup>9</sup> Reactogenicity was generally mild or moderate, and reactions were less common and milder in participants who had Sinopharm vaccine compared to Pfizer and AstraZeneca vaccine. In a double-blind, randomized, placebo-controlled clinical trial performed in Henan Province, China, the average cumulative adverse events recorded after 7 days of Sinopharm vaccine for Phases 1 and 2 were 15%.<sup>20</sup> In our study, overall Sinopharm vaccination's adverse effect was ranged between 1.18% with loss of smell and test to 27.06% with a headache.

Fatigue, headache, body pain, and muscle pain were among the most common adverse effects associated with the three vaccines. AstraZeneca was associated with higher prevalence; this is compatible with other studies.

One of the study limitations was the number of participants who administered the second dose of vaccine. Generally, the first dose of the vaccine showed a higher prevalence of adverse effects with AstraZeneca vaccine, followed by Pfizer and was less with Sinopharm. Despite a small number of participants received the second dose of AstraZeneca vaccine, the adverse effect was still higher compared with the other two vaccines. Though, fatigue, body pain, and reactogenicity were higher prevalent after the second dose of Pfizer vaccine. This, however, requires further investigation with large-scale participants.

Although age was not significantly shown to affecting the duration and severity of the adverse effect of the three types of vaccines, the duration was longer in participants over 55 years old who received AstraZeneca and Sinopharm vaccine. With regards to the Pfizer vaccine, the duration was relatively higher in participants aged between 36 and 55. This conclusion could be resulted from the small number of elderly participants recruited for the study who administered Pfizer vaccine. Furthermore, females suffered from adverse effects with longer duration compared to male counterparts after receiving one of the three vaccines.

In this study we reported unusual events that could be related to the vaccines like swelling and severe allergic reaction of eyelids, hospital admission due to positive results for COVID-19 infection, weakness and numbness of the hand of the injected arm, severe chest pain, nasal bleeding, acute hypertension with blood pressure over 210/105 mm Hg, and acute hyperglycemia (FBS > 170 mg/dL). These events were most evident with Pfizer and AstraZeneca vaccines and only one case was reported with Sinopharm vaccine. Since untoward cases might occur independently of vaccination, we must closely review any case of adverse effect after vaccination, paying particular attention to the "base incidence" of that event in the community before vaccination.

## 5 | CONCLUSION

Pfizer, AstraZeneca, and Sinopharm vaccines were found to be safe according to the observation of the mild to moderate postvaccination signs and symptoms. Sinopharm vaccine showed a lower prevalence of adverse effects compared with Pfizer and AstraZeneca

vaccine after first and second dose respectively. Age and gender were not significantly affecting the duration and severity of adverse effects. Unusual adverse effects should be monitored carefully to determine whether they are related to the vaccine or not.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## ETHICS STATEMENT

All participants enrolled in the study signed their written consent forms before participating in the study and give an agreement to use their results. The study was approved by the ethical committee of Medical city, Baghdad, Iraq with ID: 6218 on 17-12-2020.

## AUTHOR CONTRIBUTIONS

**Qutaiba Ahmed Al Khames Aga** conceived the research idea, data analysis, manuscript writing and review; **Waseem Hashim Alkhaffaf** conceived the research idea, manuscript review; **Tagreed Hamood Hatem** conceived the research idea, manuscript writing and review; **Kawthar F Nassir** participant interview and data collection, data analysis; **Yazan Batineh** conceived the research idea, manuscript review; **Luma Ahmed Al Khames Aga** manuscript writing and review, data analysis; **Manhal Yasseen Rijab Agha** manuscript writing and review, data analysis; **Abdullah Tahseen Dahham** participant interview and data collection; **Dimah Shaban** participant interview and data collection, **Muaamar Traqchi** participant interview and data collection.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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