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Mixed and Matched Covid-19 Vaccination in Saudi Arabia: Adverse Effects, Hospitalization, and Infection

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KEYWORDS
COVID-19, Mixed and matched, Adverse effects, Pfizer vaccine, AstraZeneca vaccine, Saudi Arabia.

ABSTRACT:

Vaccination has been conserved as an essential mechanism in the fight against SARS-CoV-2. Preliminary data have demonstrated that both the Pfizer–BioNTech and the Oxford–AstraZeneca vaccines have been significantly effective in reducing the number of COVID-19 infections and protecting older persons from severe disease.

The study aimed to investigate mixed and matched COVID-19 vaccination (Pfizer–BioNTech and Oxford–AstraZeneca) in terms of adverse effects, hospital admissions, and COVID-19 infections post-vaccination in Saudi Arabia.

An observational, analytical, cross-sectional, community-based study was conducted in Saudi Arabia within the period July–December 2022, and it included adult participants who received either two doses of the AstraZeneca or two doses of the Pfizer COVID-19 vaccines and who received one dose each of the AstraZeneca and the Pfizer vaccines. Data were collected via direct interviews using an interactive web-based interview system with an electronic version of the questionnaire after obtaining participant consent. Ethical guidelines and permissions were obtained from the relevant authorities, and data were collected, prepared, and analyzed using the SPSS software version 28.0

This study covered 424 adult participants with a mean age of 38.6 ± 16.4 years and a male-to-female ratio of 1:2.8. More than half of participants (243, 57.3%) were obese, while 60 (14.2%) were smokers and 63 (14.9%) had comorbidities, such as respiratory disease (29, 46%) and endocrine disorders (12, 19%). Concerning the vaccination regimen, the result revealed that of the 311 participants (73.7%) who received two doses of the same vaccine, 262 (61.8%) received the Pfizer vaccine and 49 (11.6%) the AstraZeneca vaccine, while 113 (26.7%) received a mix (one dose each of the Pfizer and AstraZeneca vaccines). In total, 362 (85.4%) reported post-vaccination symptoms, such as body pains (208, 57.5%), muscle pain (207, 57.2%), and headaches (180, 49.7%). Nearly half (178, 49.2%) reported a symptom duration of 1–3 days, while hospitalization was reported in 10 (2.4%), ICU admission in 1 (0.2%), and COVID-19 infection post-vaccination in 63 (14.9%). The analysis found that symptoms were significantly higher among participants who received a mix of vaccines, compared with the participants who received two doses of the same vaccine (94.7% versus 82% respectively, and $p = 0.001$). Thus, the occurrence of symptoms was significantly higher among participants who received a mix of vaccines, compared with the participants who received two doses of the Pfizer or the AstraZeneca vaccine (94.7%, 82.8 and 79.6%, respectively and $p = 0.004$). Further, there was no significant effect between the vaccine regimen and the rate of hospitalization or COVID-19 infection post-vaccination (p values > 0.05 in all).

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The study concluded that symptom occurrence after the second vaccination against COVID-19 was significantly higher among people who received one dose each of two different vaccines compared to those who received two doses of the same vaccine (Pfizer or AstraZeneca), though the rates of hospitalization and infection with COVID-19 post-vaccination were unaffected.

1. INTRODUCTION

COVID-19, a viral respiratory syndrome that was firstly appeared in Wuhan, China, in a group of patients suffer from severe respiratory infection. COVID-19 is caused by a novel corona virus which was scientifically named severe acute respiratory syndrome coronavirus 2 (SARS -COV-2) [1]. It has been worrying features of spreading rapidly among populations, causing a severe form of the disease in older adults and in patients with underlying medical condition [2].

The outbreak of infectious disease such as SARS, MERS and COVID-19 and the consequences (disease – related fear, threat and anxiety) are indisputable stressors .Although COVID-19 is a new strain of Corona viruses, it is known to cause disease ranging from cold to more severe illness such as SARS and MER [3].

Symptoms of CORONAVIRUS infection include Fever, Chills, Cough, Sore throat, new loss of taste or smelling, myalgia, Nausea and Vomiting, and diarrhea, Men with history of underlying diseases are more likely to be infected with the virus and would experience worse outcomes [4]. To combat the disease spread, huge vaccination campaigns have been launched worldwide, with 3.9 billion serum doses provided to date. The efficiency of (food and Drugs Administration) FDA -approved COVID-19 vaccines has been prepared in controlled clinical trials and real-world clinical investigations [5].

Vaccination has been viewed as a critical instrument in the fight against COVID-19, despite the fact that deployment has several problems compared to other vaccination programs . Briefly, infection and vaccination rates are in a competing , with the latter now constrained by supply and logistic issues and the former spreading rapidly regardless [6]. Because SARS-CoV-2 is related to the extremely pathogenic SARS-CoV and MERS-CoV, vaccine development for other Beta coronaviruses may aid in the development of COVID-19 vaccines [7].

To stop a pandemic, considerable efforts have been made to produce COVID-19 vaccines, and the majority of the vaccine candidates under development use the S-protein of SARS-CoV-2 [8]. Vaccines to prevent COVID-19 infection are critical to achieve an effective worldwide pandemic response. In total, 50 COVID-19 candidate vaccines were under clinical evaluation and 162 were in preclinical development as of October 2020, out of 212 Corona virus candidate vaccines were being developed globally [7-s9 There were a variety of vaccines available, including 72 protein subunit vaccines, 27 RNA-based vaccines, 26 vaccines using non-replicating viral vectors, 18 vaccines using replicating viral vectors, 17 vaccines using DNA, 16 vaccines using virus-like particles (VLPs), 14 inactivated shots, and four vaccines using live attenuated strains. Additionally, eight inactivated vaccines are undergoing clinical trials, and six RNA-based vaccines [7-10].

The current vaccines represent a significant technological success, as they have been shown to elicit significant immune responses, as well as provide ample disease protection [11].

Preliminary data proved that both the Pfizer–BioNTech and the Oxford–AstraZeneca vaccines are significantly effective in reducing the number of COVID-19 infections and protecting older persons from severe disease [12].

A considerable number of studies have been conducted on efficiency of COVID-19 Vaccine for instance the analysis of four randomized controlled trials conducted in the United Kingdom, South Africa, and Brazil, a report on the efficacy results of the Oxford–AstraZeneca vaccine suggested an overall vaccine efficacy of 70.4% (95% confidence interval [CI] 54.8–80.6), with a greater efficacy of 90% (95% CI 67.4–97.0) in those who received a small dose (2.2×1,010 viral particles per dose) followed by a standard dose (5×1,010 viral particles per dose) and a vaccine efficacy of 62.1% (95% CI 41.0–75.7) among those who obtained two standard doses (four weeks apart [13].

COVID-19 vaccinations have been mixed in numerous countries due to vaccine shortages, particularly in underdeveloped countries, the advent

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of novel variations of concern (VOCs) that have shown some resistance to existing vaccines, and the prevalence of adverse effects [14]. This method has had a great deal of success, as studies have shown that combining vaccinations from different brands can increase IgG and neutralizing antibodies as well as the cellular immune response [15]. Moreover, it has been proved that using heterologous COVID-19 vaccines is more effective in better neutralizing antibody levels against VOCs compared to homologous vaccines, based on this result, the methods of vaccination were adopted not only with countries with economic cries but, also were used by industrialized once hoping to be given to wide great numbers of their citizens to prevent COVID-19 spreading [15]. Research and trails on vaccines showed that , the new vaccines have been promising due to the the efficiency of mixing vaccines in immune response , Consequently, this approach can enhance vaccine efficacy and aid in solving vaccine shortages in poor regions.

Study aim

This study aims to compare adverse effects between two doses of either the Pfizer–BioNTech or Oxford–AstraZeneca SARS-CoV-2 vaccine or a combination of one dose each of the Pfizer–BioNTech and the Oxford–AstraZeneca vaccines.

Objectives

- To investigate the adverse effects of two doses of the AstraZeneca vaccine or the Pfizer vaccine against COVID-19 symptoms in comparison to a combination of one dose each of the AstraZeneca and the Pfizer vaccines.
- To investigate the effect of two doses of the AstraZeneca vaccine or the Pfizer vaccine in comparison with a combination of one dose each of the AstraZeneca and the Pfizer vaccines against COVID-19 regarding hospital admission.
- To investigate the rate of COVID-19 infection post-vaccination following each vaccination regimen.

Research Problem

The rapid creation of SARS-CoV-2 vaccines, which have been demonstrated to elicit significant immune responses and provide significant disease protection, has been lauded around the world. The Pfizer–BioNTech and Oxford–AstraZeneca vaccines are both extraordinarily successful in reducing the number of COVID-19 infections and protecting older persons from severe disease. Given the necessity of establishing high levels of protection in the population, identifying the optimal interval between doses has become a critical issue.

While some countries' vaccination programs are moving forward, a multitude of challenges, ranging from suspicion to safety considerations, are preventing them from reaching the aim. Combining multiple COVID-19 vaccinations has been suggested as a possible solution to these issues, but some factors must be studied and compared between these two protocols (two doses of a single vaccine or one dose each of two vaccines) to evaluate real-world effectiveness: the symptoms of COVID-19 infection, hospital admission rates, and COVID-19 morbidity and mortality. In addition, a low number of countries have applied this combination of two vaccines (one dose of Pfizer and one dose of AstraZeneca); therefore, the researcher sought to conduct this study to evaluate combination effectiveness in Saudi Arabia.

Research Importance

The significance of the study stems out from the fact that the COVID-19 pandemic is still in its early stages, so there is an urgent need to identify efficient medications for severe cases and effective vaccinations in general [16]. The whole world is seeking the most effective vaccination regimen that provides the best immunity against COVID-19 infection. Some researchers aimed to study the impact of mixing two vaccines, suggesting this may boost immunity [17]. However, these researches were insufficient and there is a scarcity of data on their efficacy, hence the importance of the research providing evidence of the efficiency of mixing two vaccinations. Therefore, this study could offer hope via potential immunity against the COVID-19 virus, and it has the potential to enhance efforts to save billions of people facing unforeseen side effects.

Methodology
Patients and Study Design

In total, 424 participants were enrolled in this study who received either two doses of the AstraZeneca or two doses of the Pfizer COVID-19 vaccine and who received one dose each of the AstraZeneca and the Pfizer vaccines. Their ages ranged from 18 to 60 years.

Study Design

This study was an observational, analytical, cross-

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sectional study that compared the participants who received two doses of the AstraZeneca or two doses of the Pfizer COVID-19 vaccine with those who received one dose each of the AstraZeneca and the Pfizer vaccines.

Data Collection and Technique

A direct interview was conducted with the participants using an interactive web-based interview system with an electronic version of the questionnaire, which included such demographic data as the participants' age, sex, weight, and smoking habits, as well as their comorbidities (respiratory, cardiovascular, liver, kidney, immunological, and endocrine disorders), vaccination type and number of doses received, symptoms experienced after vaccination and how long they lasted, hospitalization linked to vaccination and the time of admission, and admission to the intensive care unit (ICU). The prevalence of adverse responses was investigated and examined to understand which symptoms are the most common and to which vaccines they may be linked, and the COVID-19 infection rate post-vaccination was also investigated.

Statistical Analysis

The SPSS Statistical Package for Social Sciences' software was used for statistical analysis. For continuous quantitative variables, data were given as the mean ± standard deviation (SD), and significance was considered as a P-value <0.05. The prevalence of signs and symptoms was described as the mean ± SD and percentage, and the dependent variables were compared using the analysis of variance.

Study's Overall Structure

Stage 1	**5 months**	**- Distributing the questionnaire to persons who received COVID-19 vaccination according to the types of vaccines under study (AstraZeneca and Pfizer vaccines).** **- Collecting data from the patients' answers on the questionnaire.** **-Dividing the patients' answers according to the study objectives.**
Stage 2	1–3 months	-Statistical analysis of the collected data.
Stage 3	2–3 months	-Writing thesis.

Expected Findings

The study is expected to find out the effectiveness of mixing and matching COVID-19 vaccines (Pfizer–BioNTech and Oxford–AstraZeneca vaccines), moreover it evaluates the effect of receiving one dose of the Pfizer vaccine and one dose of the AstraZeneca vaccine, which is expected to be greater than the effect of receiving two doses of either the Pfizer or AstraZeneca vaccine and recognize the rate of COVID-19 infection post-vaccination, which is expected to be lower with a combination of two vaccination types than with one vaccination type.

Results

This study covered 424 adult participants who received two COVID-19 vaccination doses in Saudi Arabia in 2022. The study found that most of the participants (297, 70%) were younger than 40 years, with a mean age of 38.6 ± 16.4 years; a female gender predominance (312; 73.6%); and a male-to-female ratio of 1:2.8, as in Table 1.

More than half (243, 57.3%) were overweight or obese, 60 (14.2%) were smokers, and 63 (14.9%) had comorbidities, such as respiratory diseases (29, 46%) and endocrine disorders (12, 19%), as in Table 2.

Concerning the vaccination regimen, the study revealed that 311 (73.7%) participants received two doses of the same vaccine, including 262 (61.8%) who received the Pfizer vaccine and 49 (11.6%) the AstraZeneca vaccine, while 113 (26.7%) received a mix of vaccines (one dose each of the Pfizer and AstraZeneca vaccines, as detailed in Table 3).

The study showed that 362 (85.4%) participants

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reported post-vaccination symptoms, such as body pains (208, 57.5%), muscle pain (207, 57.2%, headaches (180, 49.7%), (fullness) all symptoms (159, 43.9%), and injection site redness (156, 43.1%), as detailed in Table 4.

Nearly half of participants (178, 49.2%) reported a symptom duration of 1–3 days, while hospitalization was reported in 10 (2.4%) cases, ICU admission in 1 (0.2%), and post-vaccination COVID-19 infection in 63 (14.9%), as in Table 5.

In this study, cross-tabulation was conducted to assess the possible association between the vaccination regimen received and the overall effect in terms of post-vaccination symptoms, hospitalization, and COVID-19 infection using the chi-square statistical test. The analysis found that symptom occurrence was significantly higher among participants who received a mix of vaccines compared with the participants who received two doses of the same vaccine (94.7% versus 82%, respectively, and p = 0.001). There was no significant effect between the vaccine regimen and the rate of hospitalization or post-vaccination COVID-19 infection (p values > 0.05 in all), as detailed in Table 6. Lastly, the analysis found that symptom occurrence was significantly higher among participants who received mixed vaccines, compared with the participants who received two doses of the Pfizer or AstraZeneca vaccine (94.7%, 82.8, and 79.6%, respectively and p = 0.004). There was no significant effect between the vaccine regimen and the rate of hospitalization or post-vaccination COVID-19 infection (p values > 0.05 in all), as detailed in Table 7.

Demographic characteristics

Table (1) Distribution of participants according to their demographical characteristics (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Demographical characteristics		Frequency	Percent (%)
Age (years)	**18–30**	171	40.3
	31–40	126	29.7
	41–50	80	18.9
	51–60	47	11.1
Gender	**Male**	112	26.4
	Female	312	73.6

Clinical characteristics

Table (2) Distribution of the participants according to clinical characteristics (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Clinical characteristics	Frequency	Percent (%)

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Body mass index (kg/m^2)	**Underweight**	32	7.5
	Normal	149	35.1
	Overweight	105	24.8
	Obese	138	32.5
Smoking	**Yes**	60	14.2
	No	364	85.8
Comorbidities	**Yes**	63	14.9
	No	361	85.1
Type of chronic disease (n = 63)	**Respiratory diseases**	29	46.0
	Endocrine disorders	12	19.0
	Immunological disorders	6	9.5
	Cardiovascular disease	5	7.9
	Renal disease	2	3.2
	Liver disease	2	3.2
	Others	7	11.1

Vaccination regimens

Table (3) Distribution of participants according to the vaccination received (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Vaccination regimens		
Vaccination type (study groups)	**Frequency**	**Percent (%)**

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Same vaccine (*)	**Pfizer**	262	61.8
(n = 311, 73.7 %)	**AstraZeneca**	49	11.6
Mix of vaccines (**)		113	26.7
Total		**424**	**100.0**

* Two doses of the same vaccine

** One dose of the Pfizer vaccine and one dose of the AstraZeneca vaccine

Vaccination effect assessment

Table (4) Distribution of participants according to the presented symptoms post-vaccination (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Vaccination effect assessment			
Symptoms		**Frequency**	**Percent (%)**
Yes		362	85.4
No		62	14.6
Symptoms (n = 362)	**Body pains**	208	57.5
	Muscle pain	207	57.2
	Headache	180	49.7
	Fullness	159	43.9
	Injection site redness	156	43.1
	Fever (> 38 degrees)	108	29.8
	Dizziness	61	16.9
	Sweating	35	9.7

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	Shortness of breath	28	7.7
	Loss of appetite	27	7.5
	GI disturbances	27	7.5
	Abdominal pain	24	6.6
	Palpitation	23	6.4
	Anxiety	20	5.5
	Sore throat	18	5
	Lymph node enlargement	16	4.4
	Dry cough	11	3
	Loss of taste	10	2.8
	Loss of smell	9	2.5
	Others	7	1.9

Table (5) Distribution of participants according to the vaccination effect (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Effect of vaccination		**Frequency**	**Percent (%)**
Symptom duration (n = 362)	**< 1 day**	96	26.5
	1 - 3 days	178	49.2
	3 - 7 days	83	22.9
	> 1 week	5	1.4

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Hospitalization	**Yes**	10	2.4
	No	414	97.6
ICU admission	**Yes**	1	0.2
	No	423	99.8
COVID-19 infection	**Yes**	63	14.9
	No	361	85.1

Cross-tabulation

Table (6) Comparison of the effects of different vaccination regimens (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Cross tabulation								
Effects of vaccination		**Vaccination regimen (2 doses)**						**P value**
		Matched vaccine (*) (n = 311)		**Mixed vaccines (**) (n = 113)**		**Total (n = 424)**		
Symptom occurrence	**Yes**	255	**82.0**	107	**94.7**	362	85.4	**0.001**
	No	56	18.0	6	5.3	62	14.6	
Hospitalization	**Yes**	6	1.9	4	3.5	10	2.4	0.334
	No	305	98.1	109	96.5	414	97.6	
COVID-19 infection	**Yes**	42	13.5	21	18.6	63	14.9	0.194
	No	269	86.5	92	81.4	361	85.1	

* Two doses of the same vaccine
** One dose of the Pfizer vaccine and one dose of the AstraZeneca vaccine

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Table (7) Comparison of the effects of different vaccination regimens (n = 424 adult participants who received two doses of COVID-19 vaccination in Saudi Arabia in 2022)

Vaccination effects		Vaccination regimen								P value
		AstraZeneca - 2 doses (n = 49)		Pfizer - 2 doses (n = 262)		Mixed vaccines (*) (n = 113)		Total (n = 424)		
Symptom occurrence	**Yes**	39	**79.6**	216	**82.4**	107	**94.7**	362	85.4	**0.004**
	No	10	20.4	46	17.6	6	5.3	62	14.6	
Hospitalization	**Yes**	2	4.1	4	1.5	4	3.5	10	2.4	0.349
	No	47	95.9	258	98.5	109	96.5	414	97.6	
COVID-19 infection	**Yes**	8	16.3	34	13.0	21	18.6	63	14.9	0.358
	No	41	83.7	228	87.0	92	81.4	361	85.1	

* One dose of the Pfizer vaccine and one dose of the AstraZeneca vaccine

Discussion

Since the COVID-19 outbreak, dozens of countries have been mixing vaccines, aiming to increase their effectiveness and protection. In this context, the current study examined the perceptions and experiences of a large representative sample of participants who received an initial two-dose combination of the Saudi government-approved COVID-19 vaccines (Pfizer–BioNTech and Oxford–AstraZeneca) in comparison with those who received a combination of one dose each of the two vaccines.

The findings of the study revealed that symptoms occurrence were significantly higher among participants who received mixed vaccines than among those who received two doses of the Pfizer or the AstraZeneca vaccine (94.7%, 82.8, and 79.6%, respectively, and p = 0.004),but without a difference in the rate of hospitalization or COVID-19 infection. The study in the line with recent studies which have shown that mixing the Oxford–AstraZeneca and Pfizer–BioNTech vaccines triggers an immune response similar to or even more significant than that of two doses of matched vaccines, with a lesser appearance of side effects, especially severe ones [18-15-19]. For instance , a study by Barros et al. showed that those who received one dose of the AstraZeneca vaccine and received a second dose of the Pfizer vaccine were 11.5 times higher than in those who received two doses of the AstraZeneca vaccine, and the humoral immune response was also significantly high . It also significantly reduced the need for hospital admission due to serious side effects [20]. Further, similar to our findings, a second trial phase of a Spanish study that was conducted by Borobia et al. revealed that complaining vaccination with the Oxford–AstraZeneca vaccine as the initial dose and the Pfizer–BioNTech vaccine as the second one improved antibody levels by 150 times by two

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weeks after the second dose compared with a control group that received only the first dose, and it reduced side effects as well [15].

Furthermore, Liu *et al*. issued a Com-COV trial at Oxford University with more than 800 participants, they found out that mixing the Oxford–AstraZeneca and Pfizer–BioNTech vaccines resulted in much more effective immune response, which is reflected in the level of side effects that appear after receiving the second dose [21]. Similarly, in a study issued by Lewis et a l in Spain their study revealed that no severe side effect were appeared in mix and match trials moreover,448 participants who had the Oxford–AstraZeneca vaccine for the initial dose and the Pfizer–BioNTech vaccine for the second presented lesser side effects, moreover, their blood tests reveal that a coarse antibody response two weeks after the second dose [22]. In the same line the study disagree with Lewis et al. findings , who found out that side effects of mix-match vaccines were not worse than those of two injections of the same type of vaccination. Nevertheless, the Com-COV study shows that complaining vaccines could cause more side effects than prescribing two doses of the same vaccine [22]. Moreover, Elgallal et al. added that there have been successful attempts at mixing COVID-19 vaccines. The use of the Pfizer vaccine as the first dose and AstraZeneca as the second in mice showed that not only did this mixture not cause any problems, but it also resulted in higher immunity [23].

Many researches and trials on complaining the available COVID-19 vaccines were promising, as this mixing has been associated with an advanced immune response without a significant increase in adverse reactions, hospitalization, or COVID-19 infection. Hence, this strategy can help improve vaccine efficiency, as well as aid in overcoming vaccine scarcity in poor areas.

The limitation of the current study may due to the nature of the data in which it depends on the participants' self-report that they might be biased in their responses, moreover, their response might be affect by news, social media platforms and socialization. For instance, in some cases of the participants might not be able to differentiate between COVID-19 symptoms and vaccine side effects. Also, the study is limited to 424 adult Saudi Arabian participants due to the convenience of gathering individuals immunized with a mix of COVID-19 vaccines. However, this research could be replicated in other.

Conclusion and Recommendations

The study concludes that symptom occurrence after the second vaccination against COVID-19 was significantly higher among people who received one dose each of two different vaccination product in comparison to those who received two doses of the identical vaccine (Pfizer or AstraZeneca vaccines), while it does not affect the rate of hospitalization or COVID-19 infection.

Recently, the Omicron variability has become a main strain and a cause of the fourth wave of the COVID-19 pandemic. Accordingly, preliminary research has suggested that all currently available vaccines provide efficacy and protection against serious illness from Omicron. However, the Pfizer–BioNTech and Oxford–AstraZeneca vaccines should be tested when mixed and matched in the context of stopping the spread of Omicron. Due to the fast spread of Omicron—or perhaps of other new strains—across the world, the importance of a third booster shot and the consequences of mixing and matching vaccinations will be vital to explore in Saudi Arabia.

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Author Contributions

The principal author’s role was to propose the research idea, prepare the proposal, and design the study. The co-authors contributed to collecting the necessary data for the research. The main author continued to prepare the rest of the research with statistical analysis and to write the rest of the research manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Informed consent was obtained from all participants involved in the study.

Data Availability Statement

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

Conflicts of Interest

The authors declare that they have no conflicts of

interest.

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