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Cutaneous adverse reactions to coronavirus vaccines: A Saudi nationwide study

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Abstract

The coronavirus vaccine was developed to help overcome the COVID-19 crisis. This study aimed to identify the cutaneous side effects secondary to Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines in the general population of Saudi Arabia and to list the risk factors for the development of cutaneous side effects. This cross-sectional study was conducted in 2021, self-administered surveys were distributed electronically through social media, and telephonic interviews were conducted with a sample size of 1000 participants. Data analysis was performed using Statistical Package for the Social Sciences. A total of 1021 patients (229 male and 722 female) aged 12 years or older were included. While 833 participants were medically free, 188 had chronic illnesses. While 802 participants were not taking any medications, 219 were taking medications regularly. Oxford-Astra Zeneca and Pfizer BioNTech vaccines were administered to 319 and 702 participants, respectively. One-hundred and twenty-five participants previously had COVID-19 infection and 407 were exposed to a PCR positive case of COVID. Six hundred and fifty-nine patients (64.5%) reported experiencing injection site reactions: 606 (59.4%) had injection site pain, 168 (16.5%) had injection site swelling, and 107 (10.5%) had injection site redness. Only 51 patients (5%) experienced cutaneous side effects after injection. A significant association was found between chronic illnesses and cutaneous side effects post-vaccine (9% vs. 4.1%; p value = 0.005). Patients on medications showed a higher rate of symptoms (8.2% vs. 4.1%; p value = 0.005). Age, gender, vaccine types, and history of COVID-19 infection were not significantly associated with cutaneous side effects post-vaccine.

KEYWORDS
COVID-19, cutaneous adverse reactions, injection site reaction, Oxford Astra-Zeneca, Pfizer/BioNTech (BNT162b2)

1 | INTRODUCTION

In December of 2019 the world reported the first known case of the coronavirus disease (COVID-19) (caused by the SARS-CoV-2 virus) in Wuhan city, China,[1] which was the start of a new pandemic that took many human lives. COVID-19 is contagious in nature, which partially explains its rapid spread globally. To overcome this pandemic crisis, a vaccine for COVID-19 was developed in December of 2020.[2] Clinical

trials of the Pfizer–BioNTech COVID-19 vaccine began in April of 2020; by November of 2020, the vaccine entered Phase III clinical trials.[3] Studies for the Oxford–AstraZeneca COVID-19 vaccine were carried out in 2020, and on December 30, 2020, the vaccine was first approved for use in the UK vaccination program.[4]

A total of four vaccines have been approved in Saudi Arabia so far, these include the Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Janssen vaccines.[5] Side effects have been listed, but most of these reports has been distributed by manufacturer-funded studies that have been observed by third parties and are in agreement with the parameters set by the drug authorities.[6] Thus, there is a shortage of independent studies on the safety of the vaccines, which may influence the vaccine acceptance by people and affect the uptake of the vaccine. To get away from this vicious cycle of the COVID-19 virus and its variants, we have to accelerate the vaccination process.[7] Vaccinations are critical for the prevention of infectious diseases; however, vaccines have side effects, many of which are cutaneous. Cutaneous adverse events reported in clinical and post-authorization trials include local injection-site reactions and local or generalized reactions beyond the injection site. Local injection-site reactions, both immediate or delayed (4 days after vaccination), are the most frequent manifestation.[8] Less frequent cutaneous reactions have been described including urticaria, maculopapular or morbilliform rash, pityriasis rosea-like rash, chilblain-like lesions, facial dermal filler reactions, reactivation of varicella-zoster virus, lichen planus, erythema multiforme, and non-specific hypersensitivity eruptions.[9]

The objectives of our study are to identify the cutaneous side effects secondary to the Pfizer-BioNTech and Oxford-AstraZeneca COVID-19 vaccines among the general population of Saudi Arabia and to list the risk factors for the development of cutaneous side effects.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This cross-sectional study was conducted from June 1, 2021, to September 30, 2021, to estimate the prevalence of cutaneous side effects of the COVID-19 vaccine among the general population of Saudi Arabia. Male and female adults and adolescents aged 12 years or older who were vaccinated with the Pfizer–BioNTech or AstraZeneca COVID-19 vaccine in Saudi Arabia were included. Participants who did not complete the questionnaire and those who did not approve the informed consent were excluded.

2.2 | Sampling technique and Instrument

The convenience sampling technique was conducted by a combined method using self-administered surveys that were distributed electronically through social media platforms (WhatsApp and Twitter) and telephonic interviews with a sample size of 1000 participants. The questionnaire was categorized into four main sections: (i) demographic data including gender, age, and region; (ii) medical comorbidities and current medications; (iii) COVID-19-related history, including vaccination type, date and the number of doses, exposure to infected cases and previous infection; and (iv) vaccine side effects.

2.3 | Ethical considerations

The study was reviewed and approved by the Ethical Committee of the Imam Mohammad Ibn Saud Islamic University on June 1, 2021 (Project number: 81-2021). All participants provided informed consent and were able to decline participation at any stage. The data was kept confidential with the primary investigator and was used only for the purposes described in the study objectives. Participants have been anonymized by numerical listing.

2.4 | Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) 23rd version (SPSS Inc, IL). Frequency and percentages were used to display categorical variables. The Chi-square test was used to assess the presence of an association between categorical variables where the p-value of 0.05 was considered significant.

3 | RESULTS

A total of 1021 participants were included in this study. Table 1 displays the socio-demographic profile of the participants. Ninety-five (9.3%) of the participants were 12–18 years old, 886 (86.8%) of the participants were 19–60 years old, and 40 (3.9%) of the participants were older than 60 years old. As for the gender, 229 (29.3%) of the

TABLE 1 Demographic characteristics ($n = 1021$)

Demographical characteristics	*n*	%
Age		
12–18 years	95	9.30
19–60 years	886	86.80
>60 years	40	3.90
Gender		
Male	299	29.30
Female	722	70.70
Region		
Central	557	54.60
Eastern	116	11.40
Northern	45	4.40
Southern	85	8.30
Western	218	21.40

participants were males, and 722 (70.7%) of the participants were females. As for the region, 557 (54.6%) of the participants were from the central region, 116 (11.4%) were from the eastern region, 45 (4.4%) were from the northern region, 85 (8.3%) were from the southern region, and 218 (21.4%) were from the western region.

Table 2 presents the medical history of the participants. About 833 (81.6%) of the participants were medically free, while 188 (18.4%) had a chronic disease. The most commonly observed chronic diseases were diabetes 53 (5.2%), asthma 52 (5.1%), and hypertension 41 (4%). As for the medication history, 802 (78.6%) of the participants were not taking any medication regularly, while 219 (21.4%) of the participants were using some medication regularly. The most commonly used medication were antidepressants 31 (3%), antihistamine 29 (2.8%), and antibiotics 24 (2.4%).

Table 3 shows the vaccination and COVID-19 profile of the participants. Only 442 (43.3%) of the participants received the second dose, while 579 (56.7%) did not. 319 (31.2%) of the participants received Oxford-Astra Zeneca vaccine, while 702 (68.8%) received Pfizer BioNTech. Only 125 (12.2%) of the participants had a history of being diagnosed with COVID-19, while 407 (39.9%) of the participants had a history of being exposed to a PCR-confirmed COVID-19 case.

Figure 1 demonstrates the incidence of injection site symptoms post-vaccination. About 659 (64.5%) of the participants reported experiencing injection site symptoms, while 362 (35.5%) did not report experiencing injection site symptoms.

Figure 2 illustrates injection site symptoms post-vaccination. Six hundred and six (59.4%) patients reported experiencing injection site pain, 168 (16.5%) reported experiencing injection site swelling, and 107 (10.5%) reported experiencing injection site redness. It is worth mentioning that 499 (48.9%) patients experienced only pain, 98 (9.6%) experienced pain and swelling, and 62 (6.1%) experienced pain, swelling, and redness.

Figure 3 demonstrates the incidence of cutaneous symptoms post-vaccination. Fifty-one (5%) patients reported experiencing cutaneous manifestation post-vaccination, while 970 (95%) did not report experiencing cutaneous manifestation.

TABLE 2 Medical history ($n = 1021$)

Demographical characteristics	*n*	%
Medical history		
Medically free	833	81.60
Diabetes	53	5.20
Asthma	52	5.10
Hypertension	41	4.00
Cardiac disease	17	1.66
Blood disease	13	1.30
Rheumatoid arthritis	13	1.30
Bone disease	12	1.20
Bowel disease	9	0.90
Cancer	3	0.30
Renal diseases	3	0.30
COPD	1	0.10
Others	38	3.70
Medication history		
None	802	78.60
Antidepressants	31	3.00
Antihistamine	29	2.80
Antibiotics	24	2.40
Immunosuppressants	19	1.90
Analgesics	14	1.40
Antiepileptics	4	0.40
Others	127	12.40

TABLE 3 Participants vaccination and COVID-19 profile ($n = 1021$)

Question	*n*	%
Q1/Have you taken the second dose		
Yes	442	43.3
No	579	56.7
Q2/Vaccine type		
Oxford-Astra Zeneca	319	31.2
Pfizer BioNTech	702	68.8
Q3/Have you ever been diagnosed with COVID-19		
Yes	125	12.2
No	896	87.8
Q4/Have you been exposed to PCR-confirmed COVID-19 cases		
Yes	407	39.9
No	614	60.1

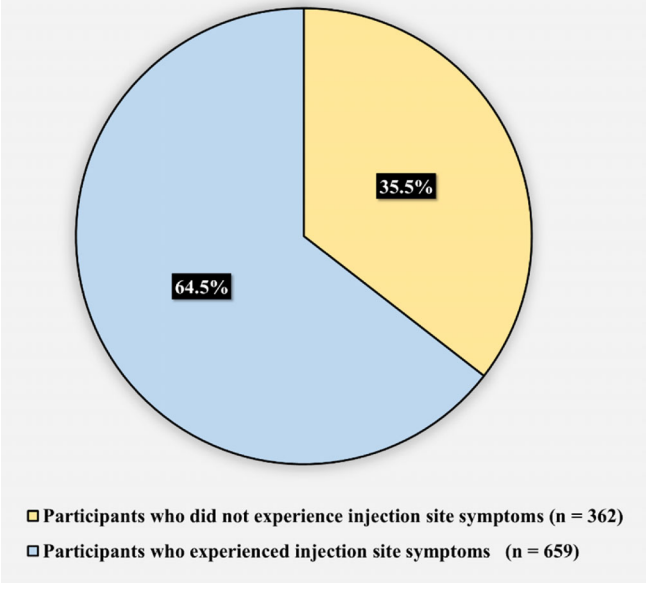

FIGURE 1 Incidence of injection site symptoms post-vaccination

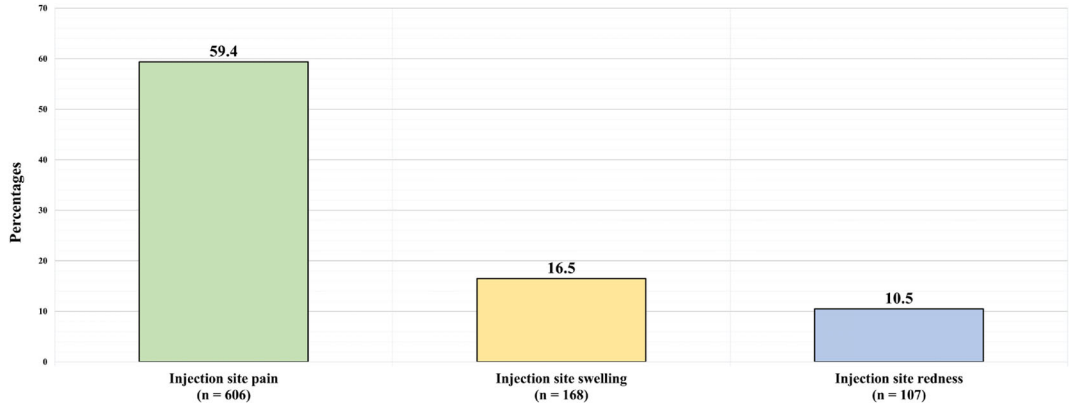

FIGURE 2 Injection site symptoms post-vaccination

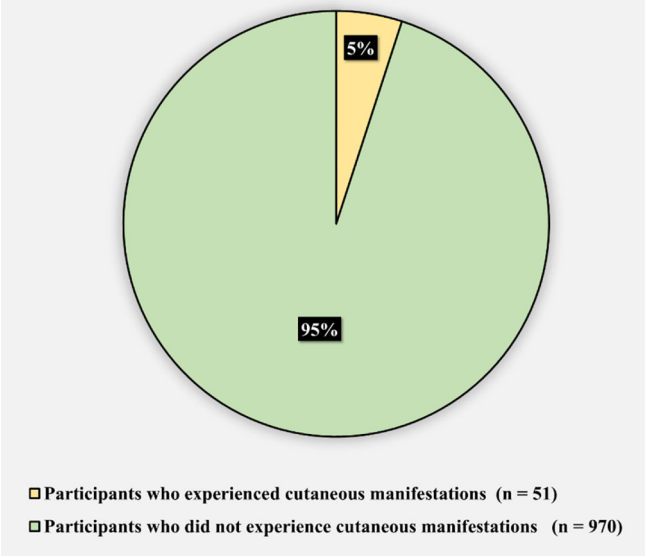

FIGURE 3 Incidence of cutaneous manifestations post-vaccination

Figure 4 illustrates the cutaneous manifestation post-vaccination. Twenty-nine (2.8%) reported experiencing maculopapular rash, 12 (1.2%) reported experiencing urticaria, 6 (0.6%) reported experiencing itching, 4 (0.4%) reported experiencing acne, 3 (0.3%) reported experiencing angioedema, and 8 (0.8%) reported experiencing other skin manifestations. It is worth mentioning that 41 (4%) had only one cutaneous manifestation, 9 (0.9%) had two cutaneous manifestations, and 1 (0.1%) had three cutaneous manifestations.

Table 4 presents the profile of injection site symptoms and cutaneous manifestation post-vaccination. The majority experienced injection site reaction symptoms for 3 days 348 (52.8%), while a minority 19 (2.9%) experienced the symptoms for more than 1 week and even a lower number 12 (1.8%) experience the symptoms for more than 1 month. As for the onset of cutaneous symptoms, 21 (41.2%) reported experiencing symptoms after 1–3 days, 9 (17.6%) reported experiencing the symptoms within the first week, 6 (11.8%) reported experiencing the symptoms within the second week, 7 (13.7%) reported within the third week, and 8 (15.7%) reported within the fourth week. The duration of these cutaneous symptoms ranged from 1 day to more than 1 month. 15 (29.4%) reported it lasted for more than 1 week, and 13 (25.5%) reported it lasted for more than 1 month. As for the affected site in participants who experienced rash, urticaria, or angioedema, 14 (36.8%) reported it was on the chest/trunk, 3 (7.9%) reported it was on the face, 10 (26.3%) reported it was on the lower limb, and 11 (28.9%) reported it was on the upper limb.

Table 5 shows the factors associated with the incidence of cutaneous manifestation post-vaccination. A significant association is found between having a chronic disease and the incidence of cutaneous manifestations post-vaccination ($p = 0.005$). It is observed that those with chronic diseases had a notably higher rate of developing cutaneous reactions post-vaccination, compared to those who were medically free (9% vs. 4.1%). Moreover, regular use of medication is also significantly associated with the incidence of cutaneous reactions post-vaccination ($p = 0.013$). It is noted that regular use of medication had a notably higher rate of cutaneous reactions compared to those who were not using any medication regularly (8.2% vs. 4.1%). Age, gender, region, vaccine type, a history of COVID-19 are all not significantly associated with the incidence of cutaneous manifestation post-vaccination.

4 | DISCUSSION

As of January 28, 2022, COVID-19 has infected more than 364 million people and taken more than 5.6 million lives.[10] Vaccination, which is the cornerstone to contain such a global pandemic, was available as early as December of 2020, and soon afterward, several vaccine types have been made available. In Saudi Arabia, vaccines were available by the end of December of 2020. The two vaccines that were approved the earliest were the Pfizer-BioNTech and Oxford-AstraZeneca vaccines, which have been evaluated in this study for cutaneous side effects.

The most common cutaneous adverse reactions reported in the clinical trial for the Pfizer-BioNTech included erythema, swelling, and pain. No serious side effects were reported.[3] In the clinical trial for the Oxford-AstraZeneca vaccine, erythema, swelling, tenderness, pain, induration as well as pruritus were reported. One case each of

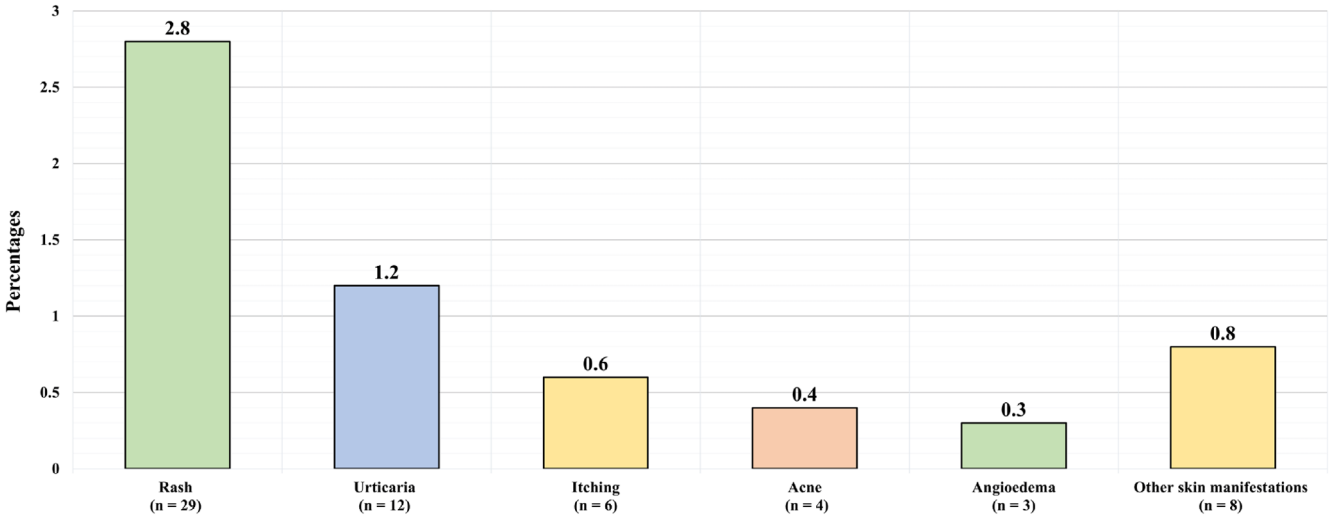

FIGURE 4 Cutaneous manifestations post-vaccination

TABLE 4 Profile of injection site symptoms and cutaneous manifestations post-vaccination

Question	*n*	%
Injection site symptoms post-vaccination profile ($n = 659$)		
Duration of injection site symptoms		
1 day	125	19
3 days	348	52.8
5 days	85	12.9
1 week	70	10.6
>1 week	19	2.9
>1 month	12	1.8
Cutaneous manifestations post-vaccination profile ($n = 51$)		
Q1/When did the skin symptoms emerge?		
1–3 days after vaccination	21	41.2
During 1st week after vaccination	9	17.6
During 2nd week after vaccination	6	11.8
During 3rd week after vaccination	7	13.7
During 4th week after vaccination	8	15.7
Q2/Duration of skin symptoms		
1 day	1	2
3 days	9	17.6
5 days	4	7.8
1 week	9	17.6
>1 week	15	29.4
>1 month	13	25.5
Q3/In the case of rash, urticaria, or angioedema, please select the affected site		
Chest/trunk	14	36.8
Face	3	7.9
Lower limb	10	26.3
Upper limb	11	28.9

psoriasis, vitiligo, Raynaud phenomenon, and severe cellulitis were reported.[4]

Several cutaneous reactions have been reported after COVID-19 vaccination such as injection site reaction, exanthematous rash, urticaria, vesicular eruption, chilblain-like lesions, erythromelalgia, angioedema, erythema multiforme-like lesion, and zoster.[9,11–13] Similar results were found in our local registry. However, our study found a lower incidence of cutaneous adverse reactions affecting only 5% of the population that could either be explained by the separate calculation of injection site reactions including pain, swelling, and redness from other cutaneous reactions or by the fact that there was an actual lower incidence in the Saudi population. Additionally, we found that 0.6%, 0.4%, and 0.3% reported persistent generalized itching, acne eruption, and angioedema, respectively, post-vaccination. Anaphylaxis was not reported in our study, but with urticaria, angioedema, and generalized pruritus being reported, health care providers must pay meticulous attention to the possibility of immediate hypersensitivity reactions in the form of anaphylaxis. Other skin conditions affected 0.8% of our sample; these included one case each of generalized xerosis and generalized macular purpura, and two cases of exacerbated atopic dermatitis, exacerbated psoriasis, and herpes zoster.

Klugar et al.[13] studied the side effects of specific COVID-19 vaccines available among health care workers in Germany. This study concluded that mRNA-based vaccines are associated with a higher prevalence of local side effects, while viral vector-based vaccines are associated with a higher prevalence of systemic side effects. Female and younger age groups were more prone to side effects of both vaccines. However, our data suggest that age, gender, and vaccine type are not significantly associated with cutaneous adverse events post-vaccination.

Ahsan et al.[14] conducted a cross-sectional survey on health care professionals in the Jazan province of Saudi Arabia to evaluate post-vaccination adverse events. It was found that 35.9% of participants who were on regular medications developed vaccine-related side

TABLE 5 Factors associated with the prevalence of cutaneous manifestations post-vaccination

Factor	Experienced cutaneous manifestations post-vaccination		*p*-value
	Yes	No	
Age			0.071
12–18 years	1 (1.1%)	94 (98.9%)	
19–60 years	46 (5.2%)	840 (94.8%)	
>60 years	4 (10%)	36 (90%)	
Gender			0.119
Male	10 (3.3%)	289 (96.7%)	
Female	41 (5.7%)	681 (94.3%)	
Region			0.296
Central	26 (4.7%)	531 (95.3%)	
Eastern	5 (4.3%)	111 (95.7%)	
Northern	0 (0%)	45 (100%)	
Southern	7 (8.2%)	78 (91.8%)	
Western	13 (6%)	205 (94%)	
Medical history			0.005*
Medically free	34 (4.1%)	799 (95.9%)	
Have chronic disease	17 (9%)	171 (91%)	
Medication history			0.013*
Not using any medication	33 (4.1%)	769 (95.9%)	
Have history of chronic medication use	18 (8.2%)	201 (91.8%)	
Vaccine type			0.772
Oxford-Astra Zeneca	15 (4.7%)	304 (95.3%)	
Pfizer BioNTech	36 (5.1%)	666 (94.9%)	
Have you ever been diagnosed with COVID-19			0.915
Yes	6 (4.8%)	119 (95.2%)	
No	45 (5%)	851 (95%)	

*Significant at level 0.05.

effects. A similar observation is found in our study where 8.2% of participants on chronic medication developed cutaneous adverse events post-vaccination, compared to 4.1% among participants who were not taking any medications. Unlike Ahsan et al., our study found a significant association between the history of chronic diseases and incidence of adverse cutaneous reactions (9%) compared to 4.1% in medically free individuals.

Limitations of our study include the possibility of morphologic misclassification as well as a lack of clear evaluation of the recurrence of adverse cutaneous events after the second dose.

Awareness of the cutaneous adverse reactions to COVID-19 vaccines can help health care providers to identify and manage these conditions This analysis is reassuring to dermatologists counseling their patients about the safety of COVID-19 vaccinations and its unlikely impact on their skin conditions. Further evaluation of newly approved vaccines, evaluation in the pediatric population, and recurrence of adverse events after second and third doses, will all help in better scientific understanding of the COVID-19 vaccinations and their safety. Such knowledge will promote public health, awareness, and the acceptance of vaccination programs worldwide.

5 | CONCLUSION

We report a spectrum of cutaneous reactions to Pfizer BioNTech (BNT162b2) and Oxford-AstraZeneca COVID-19 vaccines. Injection site reaction was observed in 64.5% of the patients. The prevalence of cutaneous reactions was 5% in the Saudi population. Chronic diseases history is associated with a notable higher occurrence (9% vs. 4.1%). In addition, people on chronic medications were two times more prone to develop cutaneous reactions (8.2% vs. 4.1%). Unlike other studies, we did not find a difference in occurrence between the different types of vaccines evaluated. Age and gender were not significantly associated with incidence. Further larger-scale studies are required to assess other newly approved vaccines as well as the effects on the pediatric population.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS CONTRIBUTIONS

Abrar E. Bukhari is the primary investigator, who came up with the project's main concept, supervised literature review, data collection, and analysis. As the primary investigator, she wrote most parts of the manuscript and is in charge of submitting the article as the corresponding author. Malak M. Almutlq and Alhanouf A. Bin Dakhil are active co-authors who participated in work conception, proposal writing, data collection, data analysis, and drafting the manuscript. Sulaiman K. Alfouzan, Mohammed A. Alqahtani, Abdullah A. Aljalfan, Mohammed A. Almutawa, and Fahad S. Alsubaie are co-investigators who participated in proposal writing, data collection, and data analysis. Abdulaziz N. Madani and Ghadah I. Alhetheli are co-authors in charge of Critical revision of the manuscript and proofreading.

DATA AVAILABILITY STATEMENT

The primary investigator states that all data used in this study including: raw data, clean data, and figures are stored safely after participants' deidentification and are available upon requests.

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