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Does ChAdOx1-S and BNT162b2 heterologous prime-boost vaccination trigger higher rates of vaccine-related adverse events?

Alhan Haji[a], Abdallah Alkattan[b,c,*], Nagla Mahmoud[a,**], Elfadil Elkagam[a], Mustafa Hassanein[a], Amal Alfaifi[a], Jaffar A. Al-Tawfiq[d,e,f], Khaled Alabdulkareem[a,g], Hani Jokhdar[h], Nashwa Radwan[a,i]

[a] Department of Training, Research and Development, Assisting Deputyship for Primary Health Care, Ministry of Health, Riyadh, Saudi Arabia
[b] Department of Research and Development, General Directorate of School Health, Ministry of Health, Riyadh, Saudi Arabia
[c] Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia.
[d] Specialty Internal Medicine and Quality Patient Safety Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[e] Infectious Diseases Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
[f] Infectious Diseases Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[g] Department of Family Medicine, College of Medicine, Al-Imam Mohammad bin Saud Islamic University, Riyadh, Saudi Arabia
[h] Deputyship of Public Health, Ministry of Health, Riyadh, Saudi Arabia
[i] Department of Public Health and Community Medicine, Faculty of Medicine, Tanta University, Egypt

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ABSTRACT

Background: There has been significant international interest in heterologous prime-boost COVID-19 vaccination. However, it is linked with different intensity and frequency of adverse events. This study aimed to assess the safety of ChAdOx1-S and BNT162b2 vaccines when given as heterologous prime-boost vaccination in Saudi Arabia.
Methods: A cross-sectional study was conducted during the period October 2021 to March 2022. The study included two groups of people based on the type of vaccination regimen. The first group (heterologous) was subjected to different prime-boost vaccination schedules irrespective of the prime and boost vaccine types. The second group included people vaccinated with the same type of COVID-19 vaccine (homologous).
Results: The overall sample included 334 participants. Those included in the heterologous group were at about 1.5 fold -increased risk for developing local and systemic adverse events compared to the homologous group. Fever, headache, and vomiting were significantly more frequent among the heterologous group compared to the homologous group (p-value<0.05). In both groups, more than half of the recorded adverse events were mild/moderate in severity.
Conclusion: Heterologous prime-post vaccination is associated with a slightly increased risk for the development of local and systemic adverse events compared to the homologous regimen. However, most of these adverse events are mild/moderate in nature and recede within two days with no serious adverse events documented.

Background

Since the first quarter of 2021, several official health authorities have approved various types of COVID-19 vaccines globally [1]. The homologous vaccination was the typically used method [2,3]. However, there was a significant international interest in heterologous prime-boost COVID-19 vaccination to mitigate against supply shortages. Besides, heterologous vaccination regimens were suggested to trigger stronger and more robust immune responses [4]. Several countries recommend mRNA vaccine to be given as a booster dose after primary COVID-19 vaccination, regardless of the type of vaccine received earlier [5].

Some advantages and disadvantages were anticipated for the heterologous COVID-19 vaccination regimen [6]. A previous systematic review showed that heterologous COVID-19 vaccination may provoke a higher stimulation of T-cells immunological reactions and could protect people from several SARS-CoV-2 variants. Nevertheless, this vaccination regimen may result in a higher risk of adverse effects; fortunately, these effects were probably mild to moderate and not life threatening [7]. Disadvantages of this regimen were published by a British study, which concluded that people who received heterologous vaccination experienced higher rates of common vaccine-related side effects, such as fever [8].

* Corresponding author: Abdullah Alkattan Tel. 00966540745588
** Corresponding author: Nagla Mahmoud: Tel. 00966550853708
E-mail addresses: abdullahalkattan@gmail.com (A. Alkattan), nagla114@gmail.com (N. Mahmoud).

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The Kingdom of Saudi Arabia (KSA) was one of the first countries around the globe to introduce COVID-19 vaccination and to have an effective vaccination program [9]. Previous studies conducted in Saudi Arabia examined the adverse events of homologous COVID-19 vaccination of ChAdOx1-S and BNT162b2 vaccines [10–13]. Globally, there are several data published about the safety of heterologous vaccination, while fewer studies focused on this topic in Saudi Arabia. Thus, this study aimed to assess the safety of ChAdOx1-S and BNT162b2 vaccines when given as heterologous prime-boost COVID-19 vaccination in Saudi Arabia.

Material and methods

Study design and participants

A cross-sectional study was conducted during the period October 2021 to March 2022 utilizing the National Vaccination Registry (NVR) in Saudi Arabia. The study included two groups of people based on the type of vaccination regimen. The first group (heterologous) was subjected to different prime-boost vaccination schedules irrespective of the prime and boost vaccine types (BNT162b2→ChAdOx1-S or ChAdOx1-S→BNT162b2). The second group (homologous) included people vaccinated with the same type of COVID-19 vaccine (BNT162b2→BNT162b2, ChAdOx1-S→ChAdOx1-S). Subjects vaccinated with mRNA-1273, Ad26.COV2.S, BBIBP-CorV, or other types of COVID-19 vaccines were excluded.

The sample size was calculated using the formula: n= Z2 (pq)/d2, where p , hypothesized as the frequency of adverse events following heterologous vaccination, was about 50% [14], Z=1.96, d= 5%. Therefore, the estimated sample size was about 384. To ensure good community presentation of the sample, a systematic random sampling technique was utilized to select the participants from the NVR data and their phone numbers were obtained for contact.

Questionnaire, data collection, and statistical analysis

A predesigned phone questionnaire was used to collect data after at least 7 days from receiving the second dose. An official unified system for phone calls provided by the Saudi Ministry of Health was used to contact the participants through data collectors (health care providers), and verbal consent was obtained before starting the questionnaire. The questionnaire includes data related to participants' background variables, the presence of local and systemic adverse events, including injection site pain/swelling, fever, fatigue, headache, vomiting, diarrhea, myalgia, and joint pain). The data regarding adverse events' onset, duration, and severity were also collected.

Based on FDA's "toxicity assessment scale", the severity of adverse events was categorized into mild (does not interfere with daily activity), moderate (some interference with daily activity), severe (prevents daily activity), and life threatening (usually requiring an emergency room visit or hospitalization) [15].

The background variables and frequency of adverse events reported in both study groups were analyzed and compared using Chi-square and Fisher's exact tests. The risk for their occurrence was determined using Odds ratio with 95%. The duration of adverse events was shown as mean and the differences between study groups (heterologous vs. homologous vaccination) was performed using Mann-Whitney U test. The onset of adverse events at first day and the intensity of adverse events reported in study groups were shown in graphs with percentages, and the related nominal data were compared using Chi-square test. The SPSS package version 28 was used for the data analysis , and a p-value of < 0.05 was considered statistically significant.

Ethical consideration

The study was reviewed and approved by the Central Institutional Review Board (IRB) at the Saudi Ministry of Health (IRB Log Number: 22 – 40 M). The confidentially and anonymity of the participants' data were preserved.

Results

The study included 334 participants, taking into consideration that 87% was the response rate to the phone questionnaire. Forty-seven percent (47%, N = 157) of the included participants were vaccinated with homologous COVID-19 prime-post schedules, while the remaining 53% (N = 177) received heterologous vaccinations. About two-thirds (74%) of the included participants were below 40 years of age.

Table 1 presents the recorded adverse events following homologous and heterologous vaccination. The most commonly recorded systemic adverse events among both studied groups were fever, fatigue, headache, myalgia, and joint pain (>17%). Compared to the homologous prime-post vaccination group, the heterologous group developed more local (51.59% vs. 66.67%, OR = 1.38, 95% CI 1.11-1.73, p-value = 0.005) and systemic (48.41% vs. 66.10%, OR = 1.46, 95% CI 1.16-1.83, p-value = 0.001) adverse events. In particular, systemic adverse events, namely fever, headache, and vomiting were significantly more frequent adverse events among the heterologous group (p-value $<$ 0.05). Other adverse events were not significantly different between the two groups.

Table 2 presents the possible factors associated with the development of vaccine adverse events in the heterologous schedule. The development of adverse events was equally distributed among the different variables including males (68.22%), females (60.42%), employed (65.66%), unemployed (66.67%), age >40 years (68.22%), age ≤ 40 years (60.42%), and among subjects with and without chronic diseases (70.59% and 65.63%, respectively). Moreover, these underlying variables were not significant risk factors affecting the development of ad-

Table 1
Adverse events following administration of homologous and heterologous prime-post vaccination among studied participants.

Adverse events	Homologous (n=157)		Heterologous (n=177)		Total (n=334)		p-value	OR	95% CI
	Frequency	%	Frequency	%	Frequency	%			
Local AE	81	51.59	118	66.67	199	59.58	0.005	1.38	1.11-1.73
Systemic AE	76	48.41	117	66.10	193	57.78	0.001	1.46	1.16-1.83
Fever	47	29.94	89	50.28	136	40.72	0.001	1.61	1.24-2.09
Fatigue	46	29.30	69	38.98	115	34.43	0.063	1.54	0.98-2.44
Headache	38	24.20	63	35.59	101	30.24	0.024	1.36	1.03-1.80
Diarrhea	3	1.91	7	3.95	10	2.99	0.274[b]	2.11	0.54-8.32
Myalgia	38	24.20	57	32.20	95	28.44	0.106	1.49	0.92-2.41
Joint Pain	28	17.83	45	25.42	73	21.86	0.094	1.57	0.92-2.67
Vomiting	0	0	5	2.82	5	1.50	0.034[b]	1.04	0.67-1.59

[b] Fisher's exact test is usedAE: Adverse events. OR: Odds ratio. CI: Confidence interval.

Table 2
Risk factors for the development of systemic adverse events following heterologous vaccination.

Heterologous vaccination		No systemic AE (n=60)		Systemic AE (n=117)		Total (n=177)	p-value	OR (95% CI)
	Variable	N	%	N	%			
Age	>40	19	39.58	29	60.42	48	0.33	1.13 (0.87-1.46)
Sex	Male	34	36.17	60	63.83	94	0.497	1.16 (0.76-1.75)
Occupation	Unemployed	26	33.33	52	66.67	78	0.888	1.03 (0.68-1.56)
Education	Low education	37	39.36	57	60.64	94	0.081	1.04 (0.67-1.59)
Chronic Diseases	Yes	5	29.41	12	70.59	17	0.681	1.17 (0.67-1.29)

AE: Adverse events. OR: Odds ratio. CI: Confidence interval.

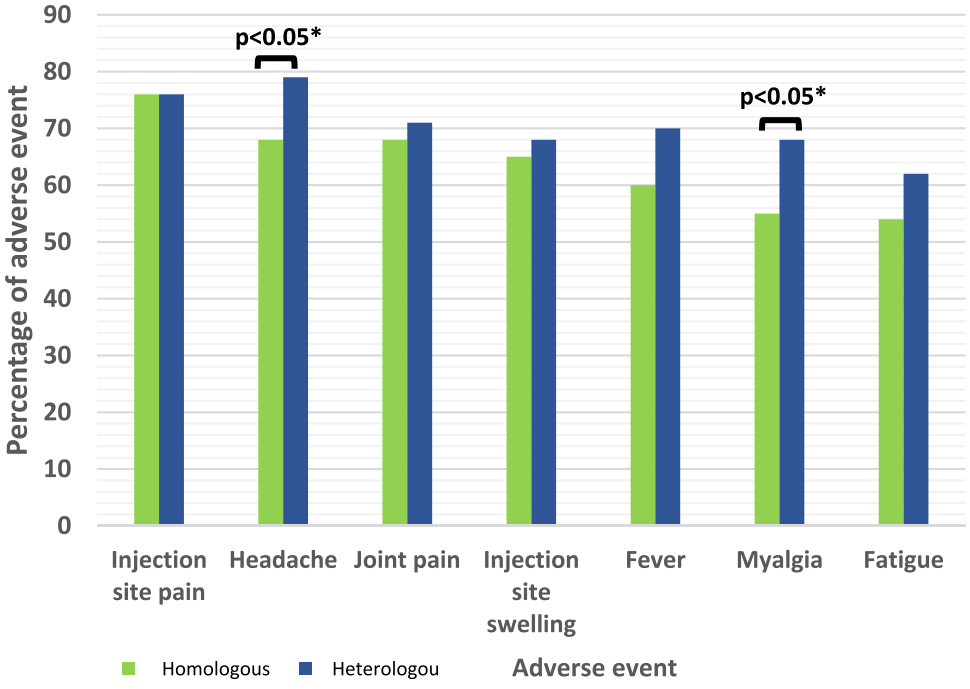

Figure 1. Adverse events reported in the first day of receiving homologous or heterologous vaccinations.
* Chi-square test performed.

verse events following heterologous vaccination among studied subjects (P>0.05).

Figure 1 shows the adverse events reported on the first day following the homologous and heterologous COVID-19 prime-post vaccinations. More than 50% and 60% of those who received homologous and heterologous vaccination schedules, respectively, developed adverse events within the first day. Headache and myalgia appeared on the first day among 68% and 55% of the participants in the homologous group compared to 79% and 68% of those in the heterologous group ($p < 0.05$).

Figure 2 presents the severity of adverse events following both heterologous and homologous vaccination. More than 80% of the adverse events were mild/moderate in severity in both homologous and heterologous groups. Severe fever, headache, joint pain, and myalgia adverse events were recorded among 9-15% and 11-18% of participants in the heterologous and homologous groups, respectively. Severe cases of fatigue were not reported among the homologous group, while 12% of those who received heterologous vaccination stated that they visited hospitals to manage their severe fatigue events. There were no life-threatening adverse events reported in both study groups.

Table 3 shows the mean duration of adverse events following homologous and heterologous vaccination. Most of the adverse events resolved within 2-3 days in both homologous and heterologous groups. The mean duration of the adverse events ranged from 1.98 ± 1.00 to 3.29 ± 1.90 days among heterologous group compared to 2.09 ± 1.40 to 3.35 ± 1.85 days in the homologous group with no significant difference recorded between both study groups ($p > 0.05$). In both studied groups, local adverse events such as injection site pain and swelling lasted for more than 3 days.

Discussion

Prime and boost heterologous COVID-19 vaccination have been implemented by several countries, including Saudi Arabia. This study was conducted to determine whether this heterologous schedule induces a higher rate of adverse reactions compared to the initial homologous vaccine schedule.

The study showed that subjects vaccinated with the heterologous vaccines, irrespective of the type of prime and boost vaccines, were at about a 1.5 fold-increased risk for developing local and systemic adverse events compared to those vaccinated with the homologous schedule. Moreover, background variables and underlying chronic illness were not significant risk factors for developing these adverse events.

The present study showed a significant higher frequency of fever and headache following the heterologous vaccination regimen . Other systemic adverse events, namely fatigue, diarrhea, myalgia, joint pain, and vomiting were more or less similar in both vaccination schedules (P>0.05). This was in line with Shaw et al. who recorded comparable higher increase in systemic adverse events (fever, chills, fatigue, headache, joint pain, malaise, and myalgia) after the booster dose of heterologous vaccine schedule in comparison to homologous vaccine schedule among people aged 50 years and older [8]. They indicated that fever was reported among 34% of recipients of ChAdOx1-S vaccine

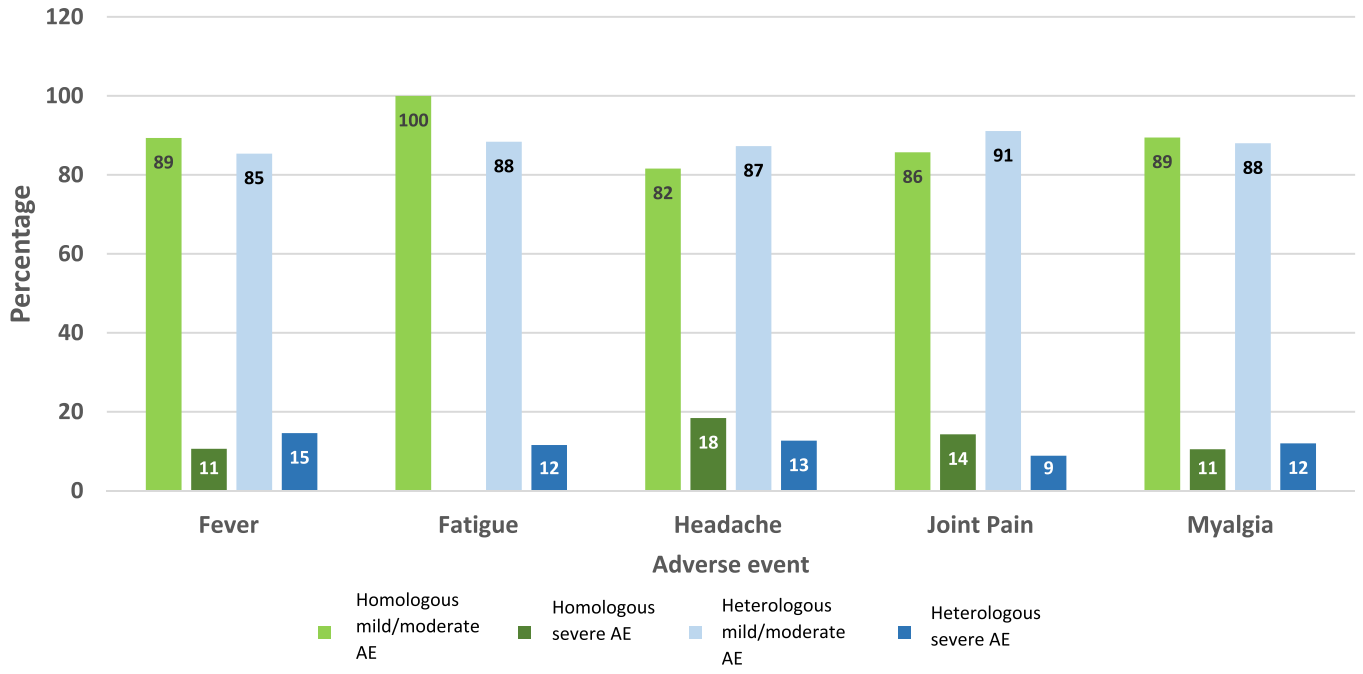

Figure 2. Mild/moderate and severe (non-life-threatening) adverse events following homologous and heterologous vaccinations. AE: Adverse events.

Table 3
Mean duration (days) of adverse events following homologous and heterologous vaccination.

Adverse event	Homologous (n=157)		Heterologous (n=177)		p-value[b]
	N	($\bar{x}$ ± SD)	N	($\bar{x}$ ± SD)	
Fever	47	2.09 ±1.40	89	1.98 ± 1.0	0.894
Fatigue	46	2.7 ± 1.84	69	2.86 ± 1.93	0.586
Headache	38	2.18 ± 1.49	63	2.24 ± 1.43	0.694
Myalgia	38	2.61 ± 1.94	57	2.98 ± 1.88	0.146
Joint pain	28	2.86 ± 2.12	45	3.11 ± 2.11	0.51
Injection site pain	80	3.35 ± 1.85	118	3.29 ± 1.90	0.734
Injection site swelling	23	3.3 ± 1.80	37	3.51 ± 2.10	0.901

[b] Mann-Whitney U test.

for prime and BNT162b2 for boost dose compared to 10% of recipients of ChAdOx1-S vaccine for both prime and boost doses [8].

On the other hand, Benning et al. recorded significantly higher percentages of systemic adverse reactions in homologous BNT162b2 vaccinated group compared to individuals with ChAdOx1-S homologous and heterologous vaccinations [16]. Hillus et al. conducted a prospective study among German healthcare workers and recorded more frequent systemic adverse events (including fatigue, myalgia, headache, chills, and fever) following homologous BNT162b2 vaccination compared to BNT162b2→ChAdOx1-S heterologous vaccination [14]. Nevertheless, comparable to our findings, they found a slightly higher frequency of local reactions (most commonly pain and tenderness) after heterologous vaccination in comparison to the homologous doses. An additional study compared the occurrence of adverse events after a booster dose and showed no difference between those who received two doses of mRNA or ChAdOx1-S followed by a booster dose of mRNA vaccine [17]. One study, however, showed that heterologous vaccination had slightly higher local reactions compared to homologous BNT162b2 [18].

With respect to the onset and severity of the adverse events, the present study reported no serious systemic adverse events following both homologous and heterologous vaccination schedules. Additionally, the majority of these events were mild/moderate in nature and appeared in subjects within 2 days following both vaccination schedules. Local adverse events (pain and swelling at the injection site) receded after more than 3 days after the vaccination in both groups. GroB et al. and Shaw et al. found that heterologous (ChAdOx1-S→BNT162b2) (BNT162b2→ChAdOx1-S) and homologous vaccination were not associated with serious adverse events [8,19]. Additionally, pain and swelling at the injection site (50% and 10% respectively) receded after more than 2 days in 5% of subjects with heterologous vaccination [8,19].

Incongruously, Hillus et al. recorded severe systemic adverse events following homologous BNT162b2→BNT162b2 vaccination schedule compared to heterologous vaccination schedule [14]. Similarly, Shaw

et al. reported the onset of the systemic adverse events after the boost dose of heterologous vaccine schedules within 48 hours [8]. Hillus et al. observed vaccine reactions in one and three days and receded after seven days following both vaccination schedules [14].

The study provided insight on the adverse events following heterologous vaccination schedule, which may have an implication on the future vaccination strategies in Saudi Arabia. However, the self- reported adverse events are the main limitation of this study.

In summary, a heterologous prime-post vaccination regimen is associated with a slightly increased risk for the development of local and systemic adverse events compared to the homologous regimen. However, most of these adverse events are mild/moderate in nature and recede within two days with no serious adverse events documented. Further prospective studies in Saudi Arabia with a large sample size are recommended to investigate the long-term adverse events following heterologous vaccination schedule.

Declarations

Ethical approval and consent to participate

The study was reviewed and approved by the Central Institutional Review Board (IRB) at the Saudi ministry of health (IRB Log Number: 22–20 M). The confidentially and anonymity of the participants' data were preserved.

Consent for participation

Consent for participation was taken.

Consent for publication

Not applicable.

Competing interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Authors' contributions

A.H, A.K, N.R, and N.M contributed to the study conception and design. Data cleaning and data analysis were performed by A.K, N.R, E.K, M.H. The first draft of the manuscript was written by A.K, N.R, A.F, J.T, H.J, N.M and K.A contributed in writing—review and editing. A.K, N.R, and M.H contributed in resources. All authors commented on previous versions of the manuscript. All authors read, review, and approved the final manuscript.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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