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Rates, types, and associated factors of acute adverse effects after the first dose of ChAdOx1 nCoV-19 vaccine administration in Thailand

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ABSTRACT

Objectives: Effective vaccines are prioritized to curtail the transmission and burden of coronavirus disease 2019. Nevertheless, monitoring the safety of vaccines is crucial. As Thailand began the ChAdOx1 nCoV-19 vaccination, our study examined the acute adverse effects and associated factors after the first dose of vaccination.

Methods: A mobile self-report questionnaire was employed to assess the rates and types of different side-effects within 3 days of the first dose of ChAdOx1 nCoV-19 vaccine administration. The risk factors associated with these side-effects were analyzed.

Results: In total, 774 participants were included in the survey, with a mean (± standard deviation) age of 49.5 (± 17.2) years. The majority (57.8%) were females, and 59.1% were anxious before the vaccination. Side-effects after the vaccination were a common occurrence (65.2%), but most (42.6%) were mild. Side-effects were significantly associated (odds ratio [95% confidence interval]) with younger age (4.32 [2.26–8.23]; $p < 0.001$; age < 30 years vs ≥ 60 years), female sex (1.66 [1.19–2.30], $p = 0.003$), anxiousness (2.10 [1.06–4.13]; $p = 0.033$; moderate–severe anxiousness vs none), and allergic disease (2.60 [1.07–6.31]; $p = 0.035$).

Conclusions: After the ChAdOx1 nCoV-19 vaccination, most acute adverse effects were mild and often noted among participants with younger age, female sex, anxiousness, and allergic disease.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was declared a pandemic by WHO on March 11, 2020 (World Health Organization, 2020), resulting in devastating medical, economic, and social consequences worldwide. Safe and effective vaccines are therefore very crucial and urgently needed in order to contain the pandemic. Because COVID-19 spreads swiftly, newer vaccine platforms, including mRNA and adenovirus vector-based, were quickly developed and distributed worldwide. In Thailand, the Food and Drug Administration (FDA) granted emergency use approval for the ChAdOx1 nCoV-19 (AstraZeneca) vaccine from January 2021, and the country's mass COVID-19 vaccination program began in June 2021.

Following the introduction the ChAdOx1 nCoV-19 vaccine, there have been variable rates of vaccine acceptance in many parts of the world (Sallam, 2021), and uncertainty about vaccine safety (Lin et al., 2020; Megget, 2020). Since public acceptance of vaccination appears to have a decisive role in successful pandemic control, a study that determines and provides reassurance regarding a new vaccine's safety is highly desirable. Our study aimed to explore the rates and types of acute adverse effects after the first dose of ChAdOx1 nCoV-19 vaccine in Thailand. It also analyzed the factors associated with acute adverse effects (AAEs) after vaccination.

Materials and methods

Participant and data collection

Adults ≥ 18 years of age who were healthy, or had stable chronic medical conditions, were included in the study. These participants were scheduled to receive the first dose of the ChAdOx1 nCoV-19 vaccine between June 8, 2021, and July 8, 2021, at two vaccination sites. One site

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was hosted by Praram 9 Hospital, Bangkok, Thailand, and another was cooperated by Praram 9 Hospital, The Street Ratchada, and the Bangkok Metropolitan Administration. Individuals with a history of severe allergic reactions to the components of the COVID-19 vaccine were excluded. Before the vaccination, all participants were educated about the possible side-effects after the vaccination. The vaccine was then administered according to the manufacturers' instructions. Participants were also observed at the site for 30 minutes after the vaccination procedure, and then asked to record any adverse events, using an electronic survey, over the 3-day (acute) follow-up period. The survey was designed to collect data regarding the participants' demography, underlying diseases/chronic medical conditions, and clinical symptoms after the vaccination.

Clinical parameters were included in the questionnaire, with AAEs divided into two types — mild and severe. Mild AAEs included any of the following symptoms: local site reactions (injection site pain, tenderness, warmth, redness, swelling, induration, and itch), feverishness (i.e. a self-reported feeling of having a fever), headache, nausea/vomiting, and fatigue. Severe AAEs included: palpitation, high-grade fever, chills, chest tightness, severe headache, facial weakness, limb weakness, skin lesion (i.e. spots/bleb/blister), bleeding spots, facial/body swelling, muscle ache, joint pain, ≥ 3 episodes of vomiting, diarrhea, altered mental status, and seizure. During the morning and evening of every day, data submitted via the mobile survey regarding the participants' side effects were reviewed. The study was approved by the Institutional Review Board (IRB) of Praram 9 Hospital. Written or verbal consent from the participants was waived because the study was observational, and patient identifiers were concealed before the analysis.

Statistical analysis

All data were entered into Microsoft Excel and cross-checked for the presence of any errors to ensure their accuracy. Descriptive statistics were used to present and summarize the categorical variables by frequency (*n*) and percentage (%). Inferential statistics were performed to assess the associations between factors and side effects, using the chi-squared test (χ^2), while logistic regression analysis was conducted to identify statistically significant factors associated with different outcome variables (any side-effects). A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the STATA software package, version 16.1 (StataCorp, College Station, TX, USA).

Results

Demographic data and acute adverse effects

Between June 8, 2021, and July 8, 2021, 774 participants who received the first dose of the ChAdOx1 nCoV-19 vaccine were identified. Their mean (range) age was 49.5 (18–91) years, and they included 447 (57.8%) females. Most (65.1%) of the participants did not have an underlying disease, while the majority (59.1%) were anxious before the vaccination. Comparing participants who did experience AAEs with those did not (Table 1), the group with AAEs were predominantly (62.6 %) female and were younger than the group without AAEs (46.5 ± 15 vs 55.1 ± 15.6 years old; $p < 0.001$). The rate of AAEs was higher among patients with allergic disease compared with those without (8.7% vs 2.2%; $p < 0.001$), while the rate was lower among participants with diabetes mellitus compared with the non-diabetic group (7.9% vs 13.8%; $p = 0.010$). Among the group with allergic disease, common AAEs were arm pain (84.1%), low-grade fever (52.3%), fatigue (52.3%), headache (47.7%), joint/muscle pain (20.5%), chills (18.2%), and high-grade fever (13.6%). Less common symptoms were numbness (4.5%) and palpitation (4.5%). One (2.3%) reported a skin lesion. The rate and intensity of anxiousness differed between participants who had and did not have AAEs ($p = 0.001$). AAEs (Table 2) after vaccination were common occurrences (65.2%), and ranged from mild (42.6%) to severe (22.6%). Common symptoms included arm pain (48.2%), low-grade fever (30.9%), fatigue (27.5%), headache (27.4%), chills (10.7%), and joint/muscle pain (9.4%). Severe AAEs that were considered serious seldom occurred. These included muscle weakness (0.5%), limb weakness (1.0%), skin lesions (0.6%), and multiple bleed spots (0.3%). There was no case of concurrent bleeding spots and limb weakness, and no re-

Table 1
Characteristics of participants who did or did not have acute adverse effect(s) after the first dose of ChAdOx1 nCoV-19 administration

Clinical parameters	Presence of side-effect(s)		*p*-value
	Yes (*n* = 505)	No (*n* = 269)	
Age (years old)	46.0 ± 14.8	53.9 ± 15.2	< 0.001
< 30	77 (15.2)	14 (5.2)	< 0.001
30–39	103 (20.4)	37 (13.8)	
40–49	120 (23.8)	49 (18.2)	
50–59	91 (18.0)	50 (18.6)	
≥ 60	114 (22.6)	119 (44.2)	
Female sex	316 (62.6)	131 (48.7)	< 0.001
Underlying disease (*n*, %)			
Chronic respiratory disease	1 (0.2)	3 (1.1)	0.124
Cardiovascular disease	34 (6.7)	26 (9.7)	0.146
Chronic kidney disease	16 (3.2)	13 (4.8)	0.246
Cerebrovascular disease	7 (1.4)	2 (0.7)	0.427
Obesity	17 (3.4)	11 (4.1)	0.608
Cancer	9 (1.8)	11 (4.1)	0.054
Diabetes mellitus	40 (7.9)	37 (13.8)	0.010
Kidney transplant	17 (3.4)	16 (5.9)	0.090
Hypertension	47 (9.3)	29 (10.8)	0.512
Allergy	44 (8.7)	6 (2.2)	< 0.001
Autoimmune disease	2 (0.4)	2 (0.7)	0.613
Anxiousness before vaccination (*n*, %)			
No	164 (33.1)	113 (47.1)	0.001
Mild	281 (56.8)	114 (47.5)	
Moderate–severe	50 (10.1)	13 (5.4)	

Table 2
Descriptions of the types and rates of acute adverse effects after the first dose of ChAdOx1 nCoV-19 administration

Side-effect	Frequency	%
Mild side-effect		
No	282	36.4
Yes	492	63.6
Total	774	100.0
Low-grade fever	239	30.9
Arm pain	373	48.2
Headache	212	27.4
Nausea	31	4.0
Fatigue	213	27.5
< three episodes of vomiting	14	1.8
Total	774	100.0
Severe side-effect		
No	599	77.4
Yes	175	22.6
Total	774	100.0
Palpitation	16	2.1
High-grade fever	38	4.9
Chills	83	10.7
Severe headache	21	2.7
Diarrhea	18	2.3
Joint pain/muscle pain	73	9.4
Local numbness	12	1.6
Others[a]	28	3.6
Total	774	100.0

[a] Included chest tightness (5, 0.6%), muscle weakness (4, 0.5%), limb weakness (8, 1.0%), spots/bleb/blister (5, 0.6%), ≥ 3 episodes of vomiting/day (4, 0.5%), multiple bleeding spots (2, 0.3%)

Table 3
Comparisons of clinical characteristics between participants with no, mild, or severe acute adverse effect(s) after the first dose of ChAdOx1 nCoV-19 administration

Variables	Intensity of side-effect		
	No (n = 269)	Mild (n = 330)	Severe (n = 175)
Age, mean ± SD (years old)	55.1 ± 15.6	48.8 ± 15.1	42.3 ± 13.8
< 30	14 (5.2)	40 (12.1)	37 (21.1)
30–39	37 (13.8)	55 (16.7)	48 (27.4)
40–49	49 (18.2)	82 (24.8)	38 (21.7)
50–59	50 (18.6)	62 (18.8)	29 (16.6)
≥ 60	119 (44.2)	91 (27.6)	23 (13.1)
Female, n (%)	131 (48.7)	194 (58.8)	122 (69.7)
Underlying disease, n (%)	98 (36.4)	121 (36.7)	51 (29.1)
Chronic respiratory disease	3 (1.1)	0	1 (0.6)
Cardiovascular disease	26 (9.7)	26 (7.9)	8 (4.6)
Chronic kidney disease	13 (4.8)	10 (3.0)	6 (3.4)
Cerebrovascular disease	2 (0.7)	6 (1.8)	1 (0.6)
Obesity	11 (4.1)	12 (3.6)	5 (2.9)
Cancer	11 (4.1)	8 (2.4)	1 (0.6)
Diabetes mellitus	37 (13.8)	28 (8.5)	12 (6.9)
Kidney transplant	16 (5.9)	13 (3.9)	4 (2.3)
Hypertension	29 (10.8)	32 (9.7)	15 (8.6)
Allergy	6 (2.2)	31 (9.4)	13 (7.4)
Autoimmune disease	2 (0.7)	1 (0.3)	1 (0.6)
Anxiousness before vaccination, n (%)			
No	113 (47.1)	106 (32.8)	58 (33.7)
Mild	114 (47.5)	188 (58.2)	93 (54.1)
Moderate–severe	13 (5.4)	29 (9.0)	21 (12.2)

ports of facial weakness, alteration of consciousness, or seizure. Local numbness (1.6%) was always transient.

Table 3 describes and compares characteristics between the participants who had mild, severe, or no AAEs. The mean age (years old ± standard deviation) of participants with no side effects was highest, followed by the group with mild AAEs and those with severe AAEs (55.1 ± 15.6 vs 48.8 ± 15.1 vs 42.3 ± 13.8, respectively). The female proportion was highest in the group with severe AAEs, followed by mild AAEs and no AAEs (69.7% vs 58.8% vs 48.7%). The highest rate of severe AAEs (12.2%) was observed among the participants who had moderate to severe anxiousness before vaccination. The highest rate of participants who did not have AAEs (47.1%) was among those without anxiousness.

Associated factors of acute adverse effects

The significance of clinical parameters associated with AAEs after vaccination was also analyzed (Table 4). Ages (years old) were further categorized into five groups: < 30, 30–39, 40–49, 50–59 and ≥ 60. Participants ≥ 60 years old were used as a reference group for univariate and multivariate analysis. Diabetes mellitus showed an association with the occurrence of AAEs after vaccination only in univariate analysis. From the multivariate analyses (Table 4), associated factors (adjusted odds ratio [95% confidence interval]) of AAEs after the vaccination included younger age (4.32 [2.26–8.23]; $p < 0.001$ for age group < 30, 2.30 [1.43–3.72]; $p = 0.001$ for age group 30-39, 2.23 [1.43–3.48]; $p < 0.001$ for age group 40-49, and 1.72 [1.08–2.72]; $p = 0.022$ for age group 50-59), sex (1.66 [1.19–2.30]; $p = 0.003$), allergic disease (2.60 [1.07–6.31]; $p = 0.035$), and anxiousness before vaccination (1.49 [1.06–2.09]; $p = 0.021$ for mild degree and 2.10 [1.06–4.13], $p = 0.033$ for moderate-to-severe degree). The crude odds ratios for all AAEs increased with every 10 years' reduction in age, while the crude odds ratio [95% CI] was highest (5.59 [3.09–10.11]) in the < 30 years old group.

Discussion

Our study reported the types and rates of acute side effects among Thais who received their first dose of the ChAdOx1 nCoV-19 vaccine. With global COVID-19 vaccination a priority for ending the pandemic, such information is crucial. Doubt or uncertainty about vaccine safety is a major contributing factor to vaccine hesitancy, which negatively impacts public health. Our study re-emphasizes that the benefits of COVID-19 vaccination outweigh the risks of AAEs.

Our results showed that side-effects were a common occurrence, especially in younger adults, but most of the symptoms were mild. Our finding of higher rates of side-effects among females and younger participants was in agreement with previous studies (Bae et al., 2021; Ramasamy et al., 2021). Although severe symptoms were noted in about one-fifth of our cases, most of these were not serious (chills, joint/muscle

Table 4
Univariate and multivariate analysis of clinical parameters associated with side-effects after the first dose of ChAdOx1 nCoV-19 vaccine

	Univariate		Multivariate	
	OR_{crude} (95% CI)	p-value	OR_{adj} (95% CI)	p-value
Age group				
< 30	5.76 (3.07–10.72)	< 0.001	4.32 (2.26–8.23)	< 0.001
30–39	2.91 (1.84–4.58)	< 0.001	2.30 (1.43–3.72)	0.001
40–49	2.56 (1.68–3.89)	< 0.001	2.23 (1.43–3.48)	< 0.001
50–59	1.90 (1.24–2.92)	0.003	1.72 (1.08–2.72)	0.022
≥ 60	Reference			
Sex				
Female	1.76 (1.31–2.38)	0.001	1.66 (1.19–2.30)	0.003
Male	Reference			
Diabetes mellitus				
Yes	0.54 (0.34–0.87)	0.011		
No	Reference			
Allergy				
Yes	4.18 (1.76–9.95)	0.001	2.60 (1.07–6.31)	0.035
No	Reference			
Degree of anxiousness				
No	Reference			
Mild	1.70 (1.23–2.35)	0.001	1.49 (1.06–2.09)	0.021
Moderate–severe	2.65 (1.38–5.10)	0.004	2.10 (1.06–4.13)	0.033

CI: confidence interval; OR_{crude}: crude odds ratio; OR_{adj}: adjusted odds ratio

pains, and high-grade fever), and most were subsequently resolved in a few days (Bae et al., 2021; Ramasamy et al., 2021). Although symptoms compatible with serious AAEs were rare, two cases of multiple bleeding spots and eight cases of limb weakness were self-reported. It was unclear whether such reports were subsequently confirmed as clinically significant, while the underlying etiologies among these cases remained unknown. It was therefore uncertain if these symptoms occurred as a result of bleeding or clotting disorders.

In early 2021, after the rollout of the ChAdOx1 nCoV-19 vaccine, concern about an increased thrombosis risk led many European countries to temporarily suspend this vaccine (Wise, 2021). A recent study on a cohort of 1.7 million ChAdOx1 nCoV-19 vaccinees in Scotland revealed an increased risk of idiopathic thrombocytopenic purpura and arterial thromboembolic events at 0–27 days after vaccination (adjusted rate ratio [aRR] 5.77, 95% confidence interval [CI] 2.41–13.83, and 1.22, 95% CI 1.12–1.34, respectively). For hemorrhagic events, the aRR was 1.48,95% CI 1.12–1.96 at 0–27 days after vaccination (Simpson et al., 2021). The statistical significance of these rate ratios was noticed after day 7 of vaccination. Another study on 19.6 million first-dose ChAdOx1 nCov-19 vaccinees in England reported increased risks of thrombocytopenia and of venous thromboembolism at 8–14 days after ChAdOx1 nCoV-19 vaccination (incidence rate ratio 1.33, 95% CI 1.19–1.47, and 1.10, 95% CI 1.02–1.18, respectively). Importantly, the study also showed a greater and prolonged increased risk of hematological events after SARS-CoV-2 infection than after vaccination (Hippisley-Cox et al., 2021). An increased risk of cerebral venous thrombosis after ChAdOx1 nCoV-19 was seen at 8–14 days after vaccination (Hippisley-Cox et al., 2021; Hwang et al., 2021a). Later, a European Medicines Agency (EMA) investigation concluded that this blood disorder following the vaccination was deemed a very rare adverse event (Mahase, 2021).

In Thailand, during the preparation of this manuscript, four cases (one definite and three probable) of vaccine-induced immune thrombotic thrombocytonenia (VITT) were reported after vaccination with more than 35 million doses of ChAdOx1 nCoV-19 (Department of Disease Control, Ministry of Public Health, 2021). Of these, two cases with probable VITT died. Albeit extremely rare, this adverse event should be included in advice presented to the vaccinees, while those diagnosed with VITT should be closely monitored and evaluated, in order to provide timely treatment (Hwang et al., 2021b).

A limited number of studies have found an association between allergic disease and adverse reactions (Kaur et al., 2021). Almost all of the side-effects that occurred in our allergic disease group were not serious. Only one had skin lesions and joint/muscle pain.

The ChAdOx1 nCoV-19 vaccine is based on replication-deficient chimpanzee adenovirus vector ChAdOx1, containing the gene that encodes the glycoprotein spike (S) antigen of SARS-CoV-2. It also contains polysorbate 80, which can trigger an allergic reaction. Although this allergic reaction can occur, recent studies have noted that the incidence is rare. The only contraindication for administering this vaccine is a previous history of allergic reactions to any component contained in the vaccine (Novak et al., 2021; Sokolowska et al., 2021).

Taken together, the above results support our conclusion that the benefits of ChAdOx1 nCoV-19 vaccination still outweigh the risks of adverse events. A strength of our study was the use of a mobile self-report questionnaire to assess the side-effects within 3 days following vaccination; this approach could avoid both interviewer and recall biases. However, there were some limitations to our study. First, the data relating to types and severity of adverse reactions may have been biased (overestimated or underestimated) due to the nature of the self-reporting survey. Second, the final diagnoses among cases with acute adverse effects — especially those with severe symptoms — were not determined. Third, any adverse effects that occurred later — especially VITT — were unknown, because the self-reporting occurred only within an acute period (3 days) after the vaccination.

Conclusion

Acute adverse effects after one dose of ChAdOx1 nCoV-19 vaccination were common occurrences, but these were primarily mild and unlikely to be serious. Adverse reactions were more commonly reported in females, those in the younger age groups, those who reported anxiousness, and those with allergic diseases. However, the possibility of rare but sometimes fatal adverse effects, especially VITT, should be advised to ChAdOx1 nCoV-19 vaccinees for the sake of vigilance.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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Ethical approval

This study was approved by the Institutional Review Board (IRB) of the Praram 9 Hospital.

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