Reactogenicity to ChAdOx1 nCoV-19 vaccine in health care workers: A multicenter observational study in Sri Lanka

Chandimani Undugodage[1], Upul Dissanayake[2], Hemantha Kumara[3], Bodhika Samarasekera[4], Lakmini Yapa[5], Osanda Dissanayake[1], Daminda Domingoarachchi[5], Dilshan Priyankara[2], Kanishka Seneviratne[5], Ranjan Ganegama[5], Widanagamage Kumara Wickramasinghe[2],Samiddhi Samarakoon[2], Pradeep Wijesinghe[6], Upuli Wijemanne[6], Ulluwishewage Chaminda Sandaruwan[6], Rajalingam Neranjan[6], Palinda Thenuwara[6], Gamhewa Arachchige Amashakya[1], Hasarah Dasanayake[1], Sumaalya Jayasooriya[7], Binuri Kalubandara[7] Nimthara Madurawala[1], Thushanthy Prasath[6], Nilanka Perera[1]

(Index words: COVID-19, SARS-CoV-2, ChAdOx1 nCoV-19, vaccine, reactogenicity)

Abstract

Introduction: The acceptability of a vaccine is an important factor during mass vaccination programs and this is largely dependent on the symptoms of local and systemic reactogenicity. There is paucity of data on the systemic and local reactions experienced by COVID-19 vaccine recipients in South Asia.

Objectives: To identify the early local and systemic reactogenicity of ChAdOx1 nCoV-19 vaccine.

Method: A multicenter observational study was performed to identify the reactogenicity to ChAdOx1 nCoV-19 vaccine in healthcare workers following the first dose.

Results: There were 4478 participants with a median age of 42 years (IQR 34-51) and 2863 (63.9%) were females. At least one symptom of reactogenicity was reported by 4151 (92.7%). Local reactions were reported by 2612 (58.3%). Systemic reactions were bodyache (3244,72.4%), fatigue (2379, 53.1%), headache (2277, 50.8%), fever (2290, 51.1%), feverishness (1912, 42.7%) and chills (2295, 51.3%). Lower age (p<0.0001) and female gender (p 0.002) were associated with a higher frequency of developing systemic reactions. There was no association between reactogenicity and comorbidities. There were 342 (7.6%) reports of palpitations and one case of ventricular bigeminy. There was one report of anaphylaxis and hospital admissions were reported by 24 (0.5%). One vaccine recipient was managed for possible aseptic meningitis.

Conclusion: This study demonstrates that early systemic and local reactions are common. Systemic reactions were more frequent in females and in the younger population. Most symptoms were self-limiting and did not require medical attention or hospital admission. ChAdOx1 nCoV-19 vaccine appears safe in the studied population.

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has spread globally, infecting more than 150 million people since its first identification in December 2019 [1]. A safe and effective vaccine is the best strategy to combat this pandemic and research community leaped into vaccine design using different platforms including lipid nano-particle mRNA [2,3] and adenovirus vectors [4,5,6,7]. In order to emerge victorious in the battle against SARS-CoV-2 and to return to the "old normal", mass vaccination of the global population is needed. Despite the dire need to be vaccinated, there is a trend to refuse the vaccine due to the fear of systemic and local reactions (reactogenicity). Reactogenicity, the physical manifestations of the inflammatory response to vaccination [8], plays a decisive role in the acceptability of a vaccine.

The first dose of the non-replicating simian adenovirus-based ChAdOx1 nCoV-19 vaccine was administered to 500,000 individuals in Sri Lanka in January 2021. Despite the availability of trial data in non-Asian

[1]*University of Sri Jayewardenepura, Nugegoda, Sri Lanka,* [2]*National Hospital of Sri Lanka,* [3]*Base Hospital Panadura, Sri Lanka,* [4]*District General Hospital, Gampaha, Sri Lanka,* [5]*Teaching Hospital Anuradhapura, Sri Lanka,* [6]*Colombo South Teaching Hospital, Sri Lanka,* [7]*University of Ruhuna, Sri Lanka.*

Correspondence: NP, *e-mail: <nilanka@sjp.ac.lk>.* *Received 15 September 2021 and revised version 10 December 2021 accepted 15 December 2021*

populations, there is paucity of information on the systemic and local reactions experienced by vaccine recipients in South Asia. Reports of unusual site venous thrombosis [9,10] have further caused anxiety among vaccine recipients. Real world data on post vaccination reactions are helpful to reassure people requiring vaccination. Thus, we report the early manifestations of reactogenicity following the first dose of ChAdOx1 nCoV-19 vaccine in a large population of healthcare workers in Sri Lanka. This is the largest post vaccination study conducted in South Asia.

Methods

An observational study was performed to identify the reactogenicity of ChAdOx1 nCoV-19 vaccine in healthcare workers of five major hospitals in Sri Lanka. The study was conducted to include participants who were vaccinated during the first vaccine roll-out program over 4 days from 29.01.2021 to 02.02.2021. Healthcare workers of all categories were included in the study. A standard dose of ChAdOx1 nCoV-19 vaccine containing $5x10^{10}$ viral particles were administered to healthcare workers. National Hospital of Sri Lanka (NHSL) is the largest hospital in the country with 4721 vaccine recipients during the study period. Therefore, half of the vaccine receivers from NHSL were selected randomly as study participants. All vaccine recipients from the other four sites namely, 2190 vaccine recipients from Colombo South Teaching Hospital (CSTH), 2314 from Teaching Hospital Anuradhapura (THA), 1200 from District General Hospital Gampaha (DGHG) and 624 from Base Hospital Panadura (BHP) were selected for the study (Figure 1).

Participants were recruited and data obtained during the first two months following vaccination. All selected vaccine recipients were administered either a self-administered paper-based questionnaire or an online form to record the local and systemic symptoms experienced during the post-vaccination period. All participants were provided a participant information leaflet (both online and paper based) and a consent form. Study participants were advised to record symptoms that occurred up to eight days following the first dose of the vaccine. Aim of the study was to identify early manifestations during the first 8 days following vaccination comparable to the phase 2/3 trial of ChAdOx1 nCoV-19 vaccine by Ramasamy *et al.* [11]. Vaccine recipients who were unable to fill the above forms were contacted via telephone by a team of dedicated research investigators to record the symptoms. The participants that were recruited via a telephone call were informed of the contents of the patient information leaflet and were recruited upon verbal consent. All vaccine recipients who consented to participate in the study were recruited. There were 4650 responders (53.5% from vaccine recipients selected for the study). A total of 172 participants were removed due to incomplete data.

Data were entered into a MS EXCEL sheet and analyzed using IBM SPSS statistics version 22 and GraphPad Prism version 9. Shapiro-Wilk test was used to identify normal distribution of the data. Frequencies were expressed as a number and percentage. Median and

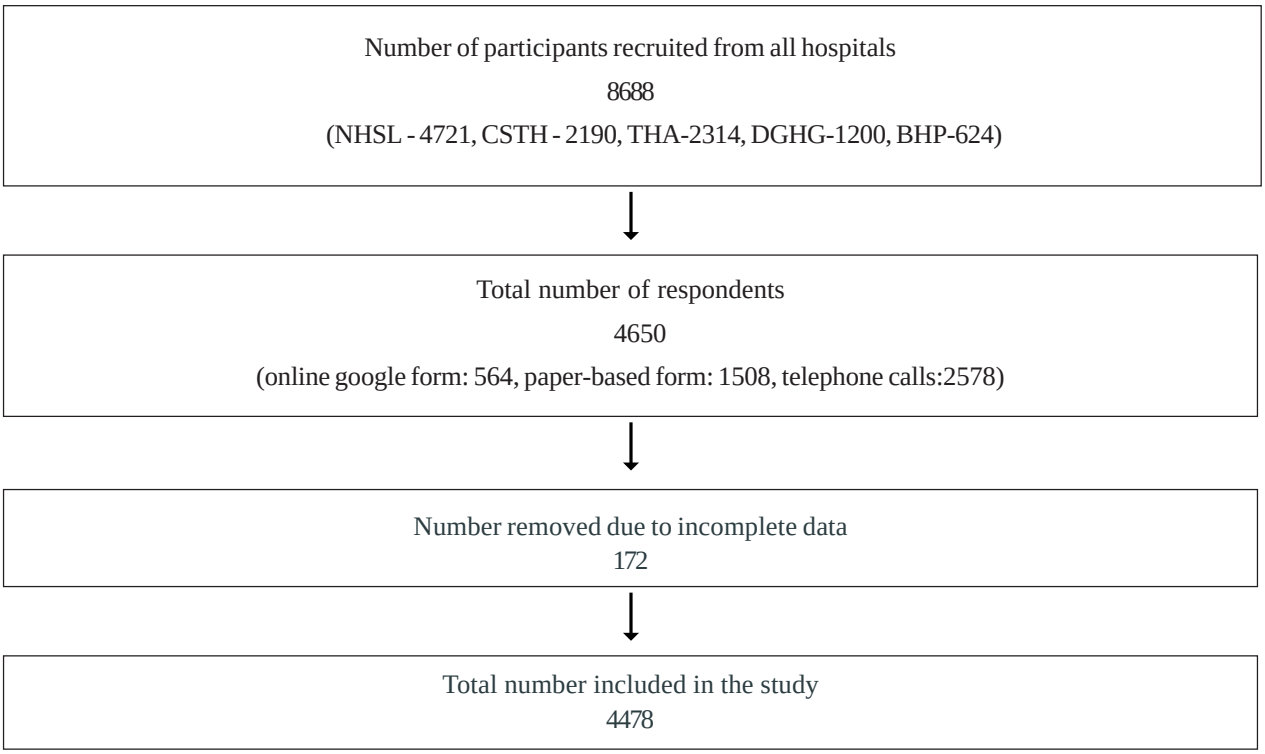

Figure 1. **Flow chart depicting participant recruitment of the study.**

interquartile range were used to describe continuous data with a skewed distribution. Categorical data were compared using chi-square test and continuous data were compared among groups using the non-parametric Mann-Whitney U test or Kruskal-Wallis test as appropriate. A p value <0.05 was considered statistically significant.

Results

There were 4478 participants with a median age of 42 years (IQR 34-51) and 3869 (86.4%) were less than 55 years of age. Females constituted two third of the study population (n=2863, 63.9%). Diabetes (n=412, 9.2%) and hypertension (n=377, 8.4%) were the commonest comorbidities reported and other illnesses such as hypothyroidism, dyslipidaemia, rhinitis and gastritis were reported by 392 (8.7%) participants.

Reported systemic reactions during the first eight days following ChAdOx1-nCoV-19 vaccination

At least one symptom of reactogenicity was reported by 4151 (92.7%) participants in the study population (Table 1). Most frequent symptom was body ache (n=3244, 72.4%) followed by fatigue (n=2379, 53.1%). The symptoms were more frequent during the first 72 hours following vaccination with a peak at 48 hours after the vaccine (Figure 2). Chills were reported by 2295 (51.3%) of participants and the highest frequency was reported within the first 24 hours of vaccination (Figure 2).

Table 1. Reported symptoms of reactogenicity of the vaccine in the study participants

Reported symptoms following vaccination	*Total N=4478*
Experienced one or more symptoms	4151 (92.7)
None	327 (7.3)
Reported symptoms	
Bodyache	3244 (72.4)
Fatigue	2379 (53.1)
Headache	2277 (50.8)
Fever (temp>38.4°C)	2290 (51.1)
Feverishness (temp<38.4°C or not measured)	1912 (42.7)
Chills	2295 (51.3)
Joint pain	2059 (46)
Sore throat	468 (10.5)
Vomiting	464 (10.4)
Shortness of breath	377 (8.4)
Cough	352 (7.9)
Palpitations	342 (7.6)
Hypotension	336 (7.5)
*Any other symptoms**	925 (20.6)
Nausea	261 (5.8)
Anorexia	209 (4.7)
Back pain	73 (1.6)
Diarrhoea	54 (1.2)
Dizziness/giddiness	47 (1.0)
Abdominal pain or discomfort	36 (0.8)

All values are given as frequency (percentage)

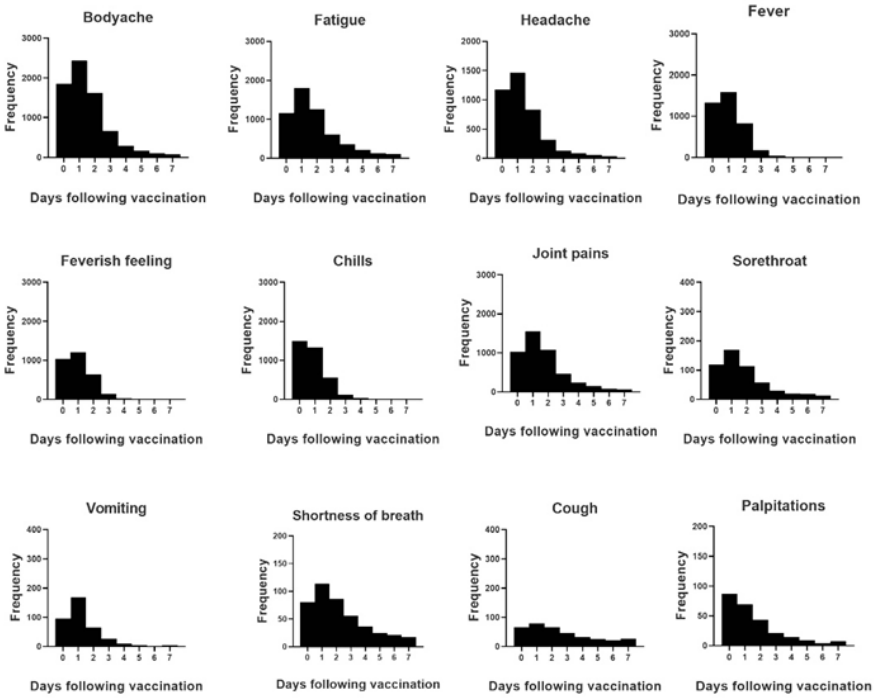

Figure 2. **Reported symptoms in the vaccine recipients throughout the first eight days following ChAdOx1-nCoV-19 vaccine.**

(a) frequency of adverse effects throughout the eight days following vaccination is shown in this figure. (b)-(m) figures show the frequency of individual symptoms during the 8 days following vaccination. Number of vaccine recipients who specified the days of symptoms: bodyache 3213, fatigue 2338, headache 2051, Palpitations 159, fever 2245, feverish feeling 1821, chills 2231, joint pains 2004, sorethroat 284, cough 167, shortness of breath 195, vomiting 281 are included in the figures (b)-(m).

Neurological symptoms

Headache

There were 2277(50.8%) vaccine recipients with headache. The intensity of the headache was graded using a numeric rating scale (NRS) ranging from 0-10 as reported previously [12]. Minor headache (score 1-3) was reported by 858 (37.7%), moderate headache (score 4-6) by 761 (33.4%) and severe headache (score 7-10) by 355 (15.6%) vaccine recipients. Intensity was not reported by 303 (13.3%) participants.

Severe headache was more common among females (263, 16.6%) than males (92, 13.3%) and the difference was statistically significant (p 0.002). The median age of the participants with minor headache (42 years) was significantly higher compared to moderate (40 years) and severe headache (40 years) in the study (p<0.0001).

A further subgroup analysis was performed on participants with headache (n= 2277) to identify factors associated with headache of 9-10/10 severity. This group was labelled as "very severe" headache. There were 188 (4.2%) participants who developed headache of 9-10/10 in the scale (Table 2). Results revealed that very severe headache was commonly seen among vaccine recipients of less than 45 years of age. The frequency of very severe headache was 5.7% and 5% among vaccine recipients of age less than 34 years and 35-44 years compared to 2.6% and 2.8% vaccine recipients of 45-54 years or more than 55 years of age (Table 2).

Other neurological symptoms

Vaccine recipients reported other neurological symptoms such as drowsiness (n=9, 0.2%), confusion (n=6, 0.13%) and photophobia (1, 0.02%). One healthcare worker had severe headache associated with drowsiness and confusion.

Cardiovascular symptoms

There were cardiovascular symptoms reported by vaccine recipients such as palpitations (342, 7.6%), chest pain (13, 0.29%) and transient hypertension (n=8, 0.18%). There was one vaccine recipient who developed ventricular bigeminy immediately after vaccination. He was a 53-year-old male without underlying cardiac disease. He was observed in the coronary care unit and was treated with intravenous verapamil. Another participant developed transient ST elevations in the ECG with a negative troponin.

Other reported symptoms

Gastrointestinal symptoms reported were nausea, anorexia, diarrhoea, abdominal pain or discomfort (table 1) and gastro-oesophageal reflux symptoms. There were sleep related symptoms such as insomnia, nightmares and increased sleepiness. Rashes were noted by 6 (0.12%) participants and some of the less commonly reported adverse effects included neck pain, muscle cramps, taste disturbances and increased thirst.

Local injection site reactions

Injection site pain and/or swelling was reported by 2612 (58.3%) vaccine recipients and two participants have received antibiotics for injection site infection. Lymph node enlargement was noticed by 9 (0.2%) study participants. There were two participants who noticed enlargement of the posterior auricular lymph nodes.

Use of analgesics

Majority of participants (n=3751, 83.9%) have taken analgesics either regularly or occasionally following vaccination. Participants with symptoms of reactogenicity were more likely to have consumed analgesics than participants without symptoms (3706, 89.3% vs 50, 15.3%, p<0.0001).

Allergy

There was one report of anaphylaxis and 2 (0.02%) reports of urticaria following vaccination among the study participants.

Hospitalization

There were 24 (0.5%) hospital admissions following vaccination. There was no association between age or gender and hospitalization. Reasons for admission included anaphylaxis, severe headache with confusion, severe vomiting, syncope, severe abdominal pain, leg pain, high fever and diarrhoea. One study participant required intensive care unit admission for possible aseptic meningitis as described above. The vaccine recipient who developed tachycardia and ventricular bigeminy was managed in a high dependency unit for cardiac observation.

Association of reactogenicity with the age and gender of vaccine recipients

The frequency of symptoms of reactogenicity were higher in the younger age groups compared to older vaccine recipients (table 3). This association was seen for headache (p 0.001), fatigue (p 0.001), joint pains (p<0.0001), bodyache (p<0.0001), chills (p<0.0001) and fever (p<0.0001). Further analysis revealed that females reported

Table 2. Association of age category with very severe headache

Age category (years)	*Very severe headache (NRS 9-10/10) n=188 (4.2%)*	*Mild-moderate-severe headache (NRS 1-8/10) n=2089 (46.7%)*	*No headache n=2201 (49.2)*	*Total N=4478*	*Significance*
≤34	67 (5.7)	560 (47.9)	543 (46.4)	1170	p<0.0001
35-44	71 (5.0)	668 (46.9)	685 (48.1)	1424	
45-54	33 (2.6)	608 (47.7)	634 (49.7)	1275	
≥55	17 (2.8)	253 (41.5)	339 (55.7)	609	

Values are expressed as frequency and percentage of n/N

Table 3. Reactogenicity of study participants by age categories and gender

Characteristic	*Reactogenicity present n=4151 (92.7%)*	*Reactogenicity absent n=327 (7.3%)*	*Total N=4478*	*Significance*
Age category (years)				
≤34	1108 (94.7)	62 (5.3)	1170	p<0.0001
35-44	1328 (93.3)	96 (6.7)	1424	
45-54	1176 (92.2)	99 (7.8)	1275	
55-64	521 (88.9)	65 (11.1)	586	
≥65	18 (78.3)	5 (21.7)	23	
Gender				
Male	1471 (91.1)	144 (8.9)	1615	p 0.002
Female	2680 (9.6)	183 (6.4)	2863	

Values are expressed as frequency and percentage of n/N

a higher frequency of adverse effects (93.6%) compared to males (91.1%) as given in table 3. All the individual symptoms except feverishness (temperature <38.4°c) were commoner among females than males and the difference was statistically significant (all p<0.05).

Discussion

The acceptability of a vaccine is an important factor during mass vaccination programs and rare reports of vaccine induced serious adverse effects have created doubts in the minds of vaccine recipients which could inadvertently affect the number of people opting to receive the second dose of the ChAdOx1 nCoV-19 vaccine. These data in large populations could help to identify rare reactions and help authorities to educate the public to ease anxiety. The main objective of our study was to identify the reactogenicity of the vaccine which although self-limiting, significantly affects the recipient's perception of the vaccine side effects. Knowledge of the potentially alarming systemic reactions following the first dose of the vaccine in our population is important for the health authorities to be vigilant and to conduct active surveillance during the roll-out of the second dose of the vaccine.

Life-threatening reactions were rare following vaccination and occurrence of minor symptoms were consistent with the results observed in other populations in the vaccine studies [5,11,13]. The frequency of most of the above symptoms in our study was similar to data from UK [5,11] and South Korea [13] (Table 4). The presence of fever was higher in our study population (51.1%) compared to published data. Most of the symptoms were recorded the day after the vaccine and these symptoms were minimal after 72 hours. Symptoms requiring hospitalization were not common with only 24 (0.5%) vaccine recipients seeking hospital admission. Increased age was associated with reduced frequency of adverse effects experienced by the vaccine recipients, similar to findings from other studies [11,5]. Females were more likely to develop systemic reactions except in the age category of more than 65 years.

Table 4. Comparison of the systemic reactions reported following the first dose of ChAdOx1 nCoV-19 vaccine in literature

Systemic reaction	*Current study n=4478*	*Folegatti et al.* [5] *n=543*	*Ramasamy et al.*[11]* *n=128*	*Kim et al.* [13] *n=1431*
Bodyache	3244 (72.4)	321 (59.1)#	46 (35.9)#	866 (60.5)#
Fatigue	2379 (53.1)	380 (70)	72 (56.2)	726 (50.7)
Headache	2277 (50.8)	365 (67.2)	67 (52.3)	678 (47.4)
Fever (temp>38°C)	2290 (51.1)	96 (17.7)	12 (9.4)	517 (36.1)
Feverishness (temp<38°C or not measured)	1912 (42.7)	270 (49.7)	29 (22.7)	-
Chills	2295 (51.3)	287 (52.9)	22 (17.2)	589 (41.2)
Joint pain	2059 (46)	166 (30.6)	28 (21.9)	381 (26.6)
Sore throat	468 (10.5)	-	-	-
Vomiting	464 (10.4)	-	-	53 (3.8)
Shortness of breath	377 (8.4)	-	-	-
Cough	352 (7.9)	-	-	-
Palpitations	342 (7.6)	-	-	-
Hypotension	336 (7.5)	-	-	-
Nausea	261 (5.8)	133 (24.5)	21 (16.4)	327 (23.2)
Anorexia	209 (4.7)	-	-	-
Back pain	73 (1.6)	-	-	-
Diarrhoea	54 (1.2)	-	-	-
Dizziness/giddiness	47 (1.0)	-	-	-
Abdominal pain or discomfort	36 (0.8)	-	-	

*All values are given as frequency and percentage. *Frequency of symptoms in the SD/SD group after prime vaccination was used for the table. #Frequency of muscle pain as a symptom was used*

The 30-year-old healthcare worker who required hospitalization had severe headache, vomiting associated with high fever on day 0 of vaccination and treated as aseptic meningitis by the treating physician. Other neurological signs such as drowsiness (n=9, 0.2%), confusion (n=6, 0.13%) and photophobia (1, 0.02%), although reported by few, would require surveillance. The commonest reported cardiac symptom was palpitations which had highest frequency on day 0 of vaccination. Although self-limiting in most, it is an alarming symptom for vaccine recipients. To our knowledge, palpitations has not been identified as a significant symptom of systemic reactogenicity following ChAdOx1 nCoV-19 vaccination. There was one report of atrial flutter and one case of a complete atrioventricular block among 12021 participants in the vaccine group of the multicenter randomized controlled trial by Voysey *et al.* [16]. One report each of palpitations, supraventricular tachycardia and second degree atrioventricular block was also noted in the control group among 11724 participants [16]. However, given the high frequency of palpitations reported in our study, it is important to be vigilant about cardiac arrhythmias during the post vaccination period. There was one report of anaphylaxis in the vaccine recipients. This is an expected adverse effect of any vaccine and the lower frequency of reported severe or minor allergies following vaccination is reassuring.

One of the main limiting factors of this study was the self-reporting nature of data collection. There could be reporting bias when filling the forms and we have used the most appropriate language (English, Sinhala or Tamil) to minimize any reporting errors. We could expect the reliability of reporting to be good as our study population was healthcare workers with a good understanding of medical symptoms. Another limitation was the response rate of participants was 53.2%. We took several measures to increase the response rate such as contacting the vaccine recipients by telephone in addition to deriving information by the paper-based form and the google form. However, the study sample size was adequate and there was satisfactory representation from all tires of age categories. Our objective was to identify reactogenicity of the vaccine and thus, we recorded symptoms during the first 8 days of vaccination. Some of the systemic

symptoms reported by vaccine recipients such as palpitations and headache were not investigated further. Adverse effects such as unusual site venous thrombosis [9,10], transverse myelitis and Guillain-barre syndrome [17] are late presentations due to the immunological nature of these manifestations. Therefore, these adverse effects could have been missed in our study population.

In conclusion, this multicenter observational study demonstrates that early systemic and local reactions are common. However, most symptoms were self-limiting and did not require medical attention or hospital admission. Reactogenicity was less frequent with increasing age and in males. ChAdOx1 nCoV-19 vaccine appears safe in the studied population.

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Author contributions

CU and NP conceived the study and are the Chief Investigators and contributed equally to the manuscript. CU, NP, UD, HK, BS, LY, OD, DD, DP, KS, RG, WKW, SS, KW, WW, US, RN, PI, HT and TP contributed to the design of the study. CU, NP, UD, HK, BS, LY, OD, DD, DP, KS, RG, WKW, SS, KW, WW, US, RN, PI, HT and TP, GA, HD, DJ, BK and MM contributed to the implementation of the study or data collection. NP did the statistical analysis. NP and CU contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration

Ethical approval and consent to participate

This study was approved by the Ethics Review Committee of University of Sri Jayewardenepura, Sri Lanka (COVID 02/21) and informed consent was obtained from all participants.

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This study did not receive any funding.

Conflicts of interests

All authors do not declare any conflict of interest.

Availability of the data/pre-print

A pre-print of the article is available at https://dx.doi.org/10.2139/ssrn.3845379. Data is available from the authors on reasonable request.

Abbreviations:

BHP	: Base Hospital Panadura,
CSTH	: Colombo South Teaching Hospital,
DGHG	: District General Hospital Gampaha,
NHSL	: National hospital of Sri Lanka,
NRS	: Numeric rating scale,
SARS-CoV-2	: Severe acute respiratory syndrome coronavirus-2,
THA	: Teaching Hospital Anuradhapura.

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