Research Article

Study on the adverse events following immunization (AEFI) of ChAdOx1 nCoV-19 vaccine in a group of Sri Lankan medical officers

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Sri Lankan Journal of Infectious Diseases 2022 Vol. 12(1):E11 1-11

*DOI: http://dx.doi.org/*10.4038/sljid.v12i1.8423

Abstract

Introduction: Amidst a rapid outbreak of COVID-19, ChAdOx1 nCoV-19 vaccine was initially administered to health care workers in Sri Lanka.

Objective: The aim of this study was to investigate adverse events following immunization (AEFI) after the first dose of ChAdOx1 nCoV-19 vaccine in a group of Sri Lankan medical officers from 5th February to 7th March 2021.

Methods: A retrospective survey was conducted using a pretested Google form questionnaire designed to gather demographic data, medical history, AEFI and their management. The questionnaire was shared among a convenience sample of medical officers through online apps (Facebook, Imo, Viber, WhatsApp). Responses to the questionnaire were collected and the quantitative and categorical data and their associations were analyzed statistically.

Results: Of 836 participants (male/female ratio = 0.92; mean age = 39.6±7.9 years), the majority, 738 (88.3%) experienced AEFI. Commonest AEFI were body ache (80.7%), lethargy (76.1%), local site reactions (72.4%) fever (70.1%), chills (68.7%) and headache (61.5%). The most severe AEFI was body ache (35.6%). The mean time of onset of AEFI was 11.3±7.5 hrs.

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Received 27 October 2021 and revised version accepted 3 March 2022. Published on 29.4.22

AEFI lasted for a mean duration of 36.3±24.3 hrs. Occurrence of AEFI was significantly associated with age and, individuals below 40 years were more likely to experience AEFI (Pearson Chi-Square =5.13; P=0.02). Moderate to severe AEFI was also significantly associated with age where a high proportion of younger individuals (≤40 years) experienced moderate to severe AEFI (Pearson Chi-Square 5.31, P=0.02). A proportion of females (80.7%) had AEFI. The occurrence of AEFI was significantly associated with the females (Pearson Chi-Square 10.34, P=0.01). A significant association between poor physical exercise and the incidence of AEFI (Pearson Chi-Square 11.15, P=0.004) was also observed. Those who had no regular exercise (79%) were more prone to get AEFI than those who had regular exercise (72.5%). Paracetamol was used prophylactically by 56.1% vaccinees prior to vaccination. Paracetamol was taken by 52.8% vaccinees (1g, 6-8 hourly for 2-3 days) therapeutically for AEFI as self-medication. However, 4 (0.005%) sought medical advice on further management and 7 (0.008%) got hospitalized.

Conclusions: A high incidence (88%) of AEFI was observed in our study population. The commonest AEFI were body ache, lethargy, local site reactions, fever, chills and headache, while the most severe AEFI was body ache. AEFI associated in ChAdOx1 nCoV-19 vaccine lasted about 1-2 days. Occurrence of AEFI was significantly associated with females below 40 years and with low physical exercise. The majority took self medication with paracetamol either prophylactically or therapeutically. Medical consultation and hospitalization for AEFI were low. AEFI of ChAdOx1 nCoV-19 vaccine was observed to be tolerable and responded to self medication with paracetamol. Surveillance studies on AEFI are feasible using online apps.

Key words: *Adverse events following immunization, ChAdOx1 nCoV-19 vaccine, Health care workers, SARS CoV2, Vaccination*

Introduction

COVID-19 is caused by the novel coronavirus, SARS-CoV-2. Due to the rapid transmission of SARS-CoV-2 and the emergence of its variants causing high morbidity and mortality, several COVID-19 vaccines have been introduced worldwide. Vaccines to control the spread of SARS-CoV-2 and its emerging variants were accepted as an essential global intervention to control the COVID-19 pandemic.[1,2] Some of these vaccines as named by the manufacturers include AstraZeneca's Covishield vaccine, Moderna vaccine, Pfizer BioNtech vaccine, Sputnik V vaccine and Sinopharm vaccine. They are administered in two doses for optimum immune response. Such vaccines against SARS-CoV-2 may contain inactivated or attenuated virus, viral like particles, viral vector DNA, and encapsulated mRNA along with other additives.[3]

The COVID-19 pandemic has placed substantial pressures on the health care systems delivering care for patients with COVID-19 and, on the other hand, disrupting non-COVID-19 health care provision. Considering the strain created upon the health care system and the economy by COVID-19, Sri Lanka opted for vaccination of front line health care workers as an initial step with a ChAdOx1 nCoV-19 vaccine (AstraZeneca Covishield) which is a non-replicating viral vector DNA vaccine by the end of January 2021. Currently, the COVID-19 vaccination

campaign has been extended to many categories of persons to cover the whole population of Sri Lanka.

An AEFI is defined as "any untoward medical occurrence which follows vaccination, and which does not necessarily have a causal relationship with the usage of the vaccine".[4] AEFI regarding COVID-19 vaccines have not been fully understood because all the vaccines came into existence along accelerated timelines. There is a low tolerance within the public for potential adverse effects following immunization (AEFI) that exerts massive impacts, resulting in vaccine hesitancy.[5] AEFI with regard to ChAdOx1 nCoV-19 vaccine (AstraZeneca) have been already studied by several groups of researchers. According to Jeon *et al*.[6] the most commonly reported AEFI of ChAdOx1 nCoV-19 vaccine were tenderness at the injection site (94.5%), fatigue (92.9%), pain at the injection site (88%), and malaise (83.8%) in Korean health care workers. Similarly, a survey among health care workers in Nepal after the first dose of ChAdOx1 nCoV-19 vaccine showed that 85.04% vaccinees experienced AEFI, as either minor (84.9%), severe (0.02%) or serious (0.05%).[7] Another study which assessed Somalian health care workers following ChAdOx1 nCoV-19 vaccine showed that 75.8% of the participants got AEFI, particularly as pain at the injection site.[8] While the foregoing studies demonstrated high incidence rates of AEFI, other studies have reported low rates of AEFI following ChAdOx1 nCoV-19 vaccine. A study of 804 healthcare workers in northern India reported that only 321 (40%) of vaccinees who received the first dose of ChAdOx1 nCoV-19 vaccine developed AEFI, with the majority of reactions being mild to moderate in severity.[9] Correspondingly, Sultana *et al.* found that the incidence of AEFI was 50.88% in a survey among Bangladesh health care workers following ChAdOx1 nCoV-19 vaccine.[10] .

Even though many frontline healthcare workers and the general population have been immunized up to now with a ChAdOx1 nCoV-19 vaccine in Sri Lanka, there have been no large-scale studies on AEFI in the Sri Lankan population. Despite surveillance on AEFI by the Epidemiology unit of the Ministry of Health, Sri Lanka, there might be an under-reporting of AEFI among vaccine recipients due to various reasons. Considering the scarcity of local studies on AEFI of ChAdOx1 nCoV-19 vaccine, this study aimed to investigate the same after the first dose of ChAdOx1 nCoV-19 vaccine in a group of Sri Lankan medical officers.

Methods

Study design and instrument

A retrospective study was undertaken on the AEFI associated with the first dose of the ChAdOx1 nCoV-19 vaccine. An online survey was performed among a convenience sample of Sri Lankan medical officers who received the first dose of ChAdOx1 nCoV-19 vaccine from 5th February to 7th March 2021. Systemic and local adverse events during the first seven days following the vaccination were recorded using a self-administered questionnaire developed in accordance with previous literature and recent information regarding the adverse effects following COVID-19 vaccines.[4,11,12] The questionnaire contained closed and open ended questions focused on the demographic details, medical history, AEFI and their management. The questionnaire was pretested among 20 medical officers and improved based on their responses. In order to maintain

confidentiality, the questionnaire was made anonymous and identification details such as email address or contact number were not collected. Ethical clearance was obtained from the Ethics review committee of the National Hospital, Kandy (21/2021).

Data collection and analysis

Participants were invited to complete the Google form questionnaire which was shared among a convenience sample of medical officers to cover the whole country through online apps (Facebook, Imo, Viber, WhatsApp). The opening screen of the questionnaire form clearly provided the basic information and instructions regarding the study and the statement on informed consent. Participants were informed that their participation was voluntary and to provide accurate facts during the first seven days following the receipt of the first dose of the vaccine. Quantitative and categorical data were analyzed with regard to measures of central tendency, dispersion, and proportions respectively. Associations were analyzed using Chi-Square test. Statistical significance was set at $P < 0.05$.

Results

Sociodemographic details

Table1. Demographic data and the medical history of the study population

Demographic factor/medical history		Number	%
Sex	Male	404	48.3
	Female	431	51.6
Age	41-75 years	322	38.5
	25-40 years	514	61.5
Engagement in physical exercise	Daily	60	7.2
	Frequently (every other day)	209	25.0
	No regular exercise	567	67.8
History of allergy	Drugs including vaccines	51	12
	Foods	162	13.5
	Other products such as rubber, nickel, etc.	55	6.6
	None	568	67.9
Intake of prophylaxis	Antihistamine only	35	4.2
	NSAID only	367	43.8
	Antihistamines and NSAIDs	67	8.1
	Antihistamines, NSAIDs and some other medication	15	1.8

A total of 836 medical officers (mean age of 39.6±7.9 years) responded to the survey and their demographic data and the medical history are summarized in Table 1. They represented almost equal proportions of either sex (male/female ratio = 0.92). When the age was categorized, 61.5% were below 40 years and the rest (38.5%) were above 40 years. When the overall physical activity of the study population was considered, 32.2% engaged in physical exercise daily or every other day while 67.8% did not engage in such physical activity. Importantly, 32.1% of the study population had past history of allergy to drugs, vaccines, food or other substances, while 67.9% had no history of allergy.

Adverse effects following immunization (AEFI)

Table 2. Severity of AEFI as perceived by the vaccinees

AEFI	Frequency	%
Body ache	263	35.6
Fever	131	17.7
Chills / feeling feverish	115	15.6
Headache	68	9.2
Lethargy	62	8.4
Rigors	37	5.0
Injection site reaction	35	4.7
Feeling dizzy	10	1.4
Nausea	7	0.9
Other	7	0.9
Abdominal pain	2	0.3
Decreased appetite	1	0.1
Total	738	100

Among the 836 participants, 738 (88.3%) reported that they experienced AEFI, while 98 (11.7%) had not experienced any side effects (Table 2). The commonest AEFI experienced was body ache (80.7%) followed by lethargy (76.1%), local site reactions (72.4%) and fever (70.1%) (Table 3). Moderate proportions reported chills (68.7%) and headache (61.5%). The intensity of those local and systemic AEFI ranged from mild to severe and 35.6% participants rated body ache as the most severe AEFI. In addition, 17.7% and 15.6% rated fever and chills as severe AEFI respectively (Table 2). The mean onset time of AEFI was 11.3±7.5 hrs., and the mean duration of the AEFI was 36.3±24.3 hrs.

Table 3. Intensity of the local and systemic AEFI

AEFI	Number of individuals				
	Mild	Moderate	Severe	Total	%
Body ache	159	346	170	675	80.7
Lethargy	168	314	154	636	76.1
Local site reaction	255	272	78	605	72.4
Fever	206	231	149	586	70.1
Chills	158	242	174	574	68.7
Headache	168	226	120	514	61.5
Rigors	97	127	120	344	41.1
Low appetite	147	121	39	307	36.7
Nausea	173	96	26	295	35.3
Dizziness	146	109	32	287	34.3
Abdominal pain	77	42	4	123	14.7
Faintishness	98	3	1	102	12.2
Diarrhoea	51	18	4	73	8.7
Other	19	9	7	35	4.2
Vomiting	19	10	5	34	4.1
Skin itching	20	4	7	31	3.7
Skin rash	3	6	4	13	1.6

Associated factors for AEFI

Occurrence of AEFI was significantly associated with age and those who were below 40 years were more likely to have AEFI (Pearson Chi-Square 5.13; P=0.02). Severity of AEFI was also significantly associated with age where a high proportion of younger individuals (79.6% of ≤40 age group) experienced moderate or severe AEFI such as body ache, lethargy, local site reactions, fever, chills and headache (Pearson Chi-Square 5.31, P=0.02). Intriguingly, 80.7% of females had AEFI and the occurrence of AEFI was significantly associated with them (Pearson Chi-Square 10.34, p=0. 0.01).

There was a significant association between poor physical exercise, with moderate to severe AEFI occurring in 78.2% of participants without frequent exercise in contrast to 60% who had frequent exercise (Pearson Chi-Square 11.15, P=0.004). Those who had less, or no regular physical exercise (79%), were more prone to get AEFI than those who engaged in regular exercise (72.49%). Summary of the statistical analysis regarding the associations of AEFI and other variables are shown in Table 4.

Table 4. Associations between the demographic characteristics and AEFI (*significantly associated)

Demographic characteristic		Presence of moderate to severe AEFI		Absence of moderate to severe AEFI		P value
		Number	%	Number	%	
Age*	<40 years	409	79.6	105	20.4	0.02
	>40 years	234	72.7	88	27.3	
Sex*	Female	348	80.7	83	19.3	0.006
	Male	295	73.0	109	27.0	
Body weight	Underweight	25	89.3	3	10.7	0.2
	Optimal	316	77.8	90	22.2	
	Overweight	229	76.6	70	23.4	
	Obese	57	70.4	24	29.6	
Physical exercise*	No regular exercise	448	79.0	119	21.0	.004
	Regular exercise	195	72.5	74	27.51	
History of allergy	Present	205	76.5	63	23.51	.94
	Absent	438	77.1	130	22.9	
Comorbidities	Present	244	82.1	53	17.8	0.24
	Absent	499	78.1	140	21.9	
Prophylaxis	Yes	370	76.4	114	23.6	0.71
	No	273	77.6	79	22.4	

Management of AEFI

Details regarding prophylaxis that had been taken by the participants prior to vaccination revealed that the majority (56.1%) took some form of prophylaxis. Paracetamol was the commonest medication used by 441 (52.75%) participants as a prophylactic agent alone or in combination with other drugs such as antihistamines. Numerous measures have been followed by the medical officers for the management of AEFI (Table 5).

Table 5. Management of AEFI by the vaccinees

Actions taken for management of AEFI	Frequency	%
Did nothing	144	17.2
Self-medication (NSAID, antihistamine etc.)	685	81.9
Sought medical advice	04	0.005
Admitted to hospital	07	0.008
Total	836	100

Remarkably, it was found that 685 (81.9%) participants took self-medication, predominantly paracetamol (52.8%), subsequent to vaccination although 144 (17.2%) participants took no medication. Only 4 (0.005%) participants sought medical advice on further management and 7 (0.008%) got hospitalized due to high fever (n=3), dizziness and feeling faint (n=2), itching and generalized skin rash (n=1) and vomiting and diarrhea (n=1).

Discussion

ChAdOx1 nCoV-19 vaccine is based on a simian adenovirus platform and coding for the spike (S) protein of SARS-CoV-2, was the first vaccine to be administered to frontline health care workers in Sri Lanka during the COVID-19 pandemic. Since adverse events following immunization (AEFI) directly influence public trust in the vaccination programme, triggering vaccine hesitancy, surveillance of AEFI is part and parcel of all immunization campaigns. This preliminary study based on online technology targeted medical officers, considering that they were the first group of persons in Sri Lanka to receive the vaccine. Moreover, their awareness of AEFI was assumed to be satisfactory compared to the general public owing to their medical background.[13] On the other hand, collection of data was supported immensely by their satisfactory level of English language, IT skills and the use of digital devices and platforms.

Remarkably, the incidence of AEFI in the present study was 88.3% with only 11.7% experiencing no AEFI. In a dose-escalation, open-label, non-randomized, clinical trial regarding the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine, Zhu *et al.*[12] reported that the incidence rate of AEFI remained at 75-83%. In another preliminary report of a phase 1/2, single-blind, randomized controlled trial regarding the safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine, Folegatti *et al.*[11] demonstrated that even though the local and systemic AEFI were common in recipients of ChAdOx1 nCoV-19 vaccine, many were reduced by use of prophylactic paracetamol, including pain, fever, chills, muscle ache, headache, and malaise. Our finding of incidence of AEFI in the Sri Lankan medical officers as high as nearly 88% in spite of prophylaxis with paracetamol is comparable with that of the community studies on health care workers elsewhere.[6-8] In contrast, some investigators from India have reported a reduced incidence rate of AEFI as low as 40% in health care workers who had received ChAdOx1 nCoV-19 vaccine.[9] Similarly, Sultana *et al.*[10] who investigated AEFI in a group of ChAdOx1 nCoV-19 vaccine recipients from Bangladesh found that AEFI occurred in 50.88% of their study group.[10] Therefore, further studies using bigger samples representing different geographical settings are warranted to explore the exact rates of AEFI affecting diverse communities.

Clinical trials have shown that ChAdOx1 nCoV-19 vaccine produced pain and tenderness at the injection site, fatigue and headache, myalgia, malaise and fever as common side effects.[11,12] Jeon *et al*.[6] found that the most commonly reported AEFI after the first dose of the ChAdOx1 nCoV-19 vaccine were fatigue, malaise, tenderness, and pain at the injection site. The majority of the ChAdOx1 nCoV-19 vaccine recipients in a group of people from Bangladesh reported swelling followed by pain at the injection site and fever as commonly experienced AEFI.[10] Another study involving Ethiopian health care workers showed that tiredness and headache are the commonest adverse effects following ChAdOx1 nCoV-19 vaccine.[8] The commonest AEFI in the present study were body ache, lethargy, local site discomfort and fever, and chills and headache which are comparable with previous studies.[6,10-12] Collectively, it is reasonable to conclude that body ache, lethargy and local site discomfort and fever followed by chills and headache are some of the general AEFI associated with ChAdOx1 nCoV-19 vaccine. Meanwhile, the intensity of AEFI ranged from mild to severe and 35.6% rated body ache as the most severe form of AEFI followed by fever (17.7%) and chills (15.6%) in our study sample.

It was interesting to note that the occurrence of AEFI was significantly associated with age, female sex and the level of engagement in physical exercise. AEFI were common in females below 40 years of age who were poorly engaged in regular physical exercise. This is comparable with Jeon *et al*.[6] who reported that the severity and number of AEFI were less in the older age (>40 years) group. Supporting these observations Kaur *et al*.[9] also identified a high incidence of AEFI among younger individuals with, two times higher odds in females. It is therefore likely that AEFI of ChAdOx1 nCoV-19 vaccine occur more frequently among younger female population with low physical activities.

In a clinical trial regarding the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine, Zhu *et al*.[12] reported that at least one AEFI occurred within the first 7 days after vaccination. Therefore, the participants of the current study were invited to respond to the questionnaire on the 7th day following immunization. Solomon *et al*.[8] have reported that most AEFI peaked within the first 24 hrs. and lasted for 1-3 days in a group of Ethiopian health care workers. In the current study, mean onset time for the AEFI was 11.3 hrs., and the mean duration of the AEFI was 36.3 hrs., indicating that AEFI became evident and disappeared in a much shorter duration in our study group compared to previous reports.[8,12]

When the drugs taken as prophylaxis prior to vaccination were analyzed, it was found that 56.1% had taken antihistamines, NSAIDs, or both, while 43.9% had no prophylaxis indicating that more than half of the participants had prophylactic drugs expecting some AEFI. This may have been due to the fact that 32.1% of the study population had a previous history of allergy to drugs, vaccines, food or other substances. On the other hand, it may be that the medical officers have taken extra precautionary steps expecting some untoward effects from the first COVID-19 vaccine used in the Sri Lankan population.

The current study revealed that nearly 82% of the study population took self medication for AEFI and the popular drug used as a therapeutic or prophylactic agent was paracetamol. Folegatti *et al*.[11] in their clinical trials also reported that local and systemic reactions were more

common in ChAdOx1 nCoV-19 vaccinees and many adverse effects including pain, fever, chills, muscle ache, headache, and malaise were reduced by paracetamol. However, the rate of using self medication in our study is higher than that of Shreshta *et al*.[7] who reported that only 55.6% vaccinees resorted to self medication.

A small number of vaccinees (17%) had no medication for AEFI. Medical advice on extra management (0.005%) and hospital admission (0.008%) were sought by a minority of vaccinees. This may be attributed to medical officers' knowledge, clinical experience, and practice with regard to management of AEFI at the early stage. However, the observations could be different in a non-medical sample. Supporting our observations, Jeon *et al*.[6] also reported that there were no serious events requiring hospitalization, and most AEFI improved within a few days. According to Kaur *et al*.[9], serious AEFI leading to hospitalization were reported in 0.1% of health care workers immunized with ChAdOx1 nCoV-19 vaccine in India. . Similarly, only 0.76% among a group of health care workers from Nepal sought medical advice for AEFI due to ChAdOx1 nCoV-19 vaccine.[7] This collective data suggests that serious AEFI associated with ChAdOx1 nCoV-19 vaccine is low and supports the observations of Voysay *et al*.[14] who have admired the ChAdOx1 nCoV-19 vaccine for an acceptable safety profile and its efficacy in clinical trials conducted in Brazil, South Africa and the UK. Nonetheless, it is important to conduct long-term population-level surveillance studies to further define the safety profile of COVID-19 vaccines, even though they have shown acceptable short-term safety as pointed out by Wu *et al*.[15] in a comprehensive rapid review of the safety profiles of the COVID-19 vaccines.

Conclusions

Common AEFI due to ChAdOx1 nCoV-19 vaccine include body ache, lethargy, local site reactions and fever whereas the most severe AEFI was body ache in the current study. Occurrence of AEFI was significantly associated with females below 40 years who had low physical exercise. The majority of the participants took self medication with paracetamol either prophylactically or therapeutically. Medical consultation and hospitalization for AEFI were very low. The AEFI associated with ChAdOx1 nCoV-19 vaccine lasted about 1-2 days and the majority responded to self medication with paracetamol. Hence, vaccinees should be educated on the expected AEFI following vaccination. Surveillance studies on AEFI appear to be feasible online and may be useful to ameliorate the concerns about AEFI.

Declaration

- Acknowledgements: Authors would like to thank all the medical officers who have participated in the study
- Funding: Personal
- Conflict of Interest statement: The authors declare that there is no conflict of interest
- Ethics statement: Informed consent was obtained prior to completing the questionnaire form from the study participants. Ethical clearance was obtained from the Ethics review committee of the National Hospital, Kandy (21/2021).
- Author contributions

1. Jayatilake JAMA – Conceived the research idea, conducted the literature search and prepared the proposal, Contributed data collection, data analysis and interpretation, preparation of the manuscript.
2. Karunaratne HMAH - Conceived the research idea, conducted the data collection, data analysis and interpretation.
3. Perera KYD - Conducted the data collection, data analysis and interpretation.
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5. Dileka WSC - Conducted the data collection, data analysis and interpretation.
6. Weerasinghe IE - Data analysis and interpretation, contributed to preparation of proposal and manuscript.
7. Jayatilake JAMS - Contributed to preparation of proposal, data analysis, interpretation, and preparation of the manuscript.

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