EClinicalMedicine 38 (2021) 101038

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research paper

A prospective observational safety study on ChAdOx1 nCoV-19 corona virus vaccine (recombinant) use in healthcare workers- first results from India

Upinder Kaur[a], Bisweswar Ojha[a], Bhairav Kumar Pathak[a], Anup Singh[b], Kiran R. Giri[a], Amit Singh[a], Agniva Das[a], Anamika Misra[b], Ashish Kumar Yadav[c], Sangeeta Kansal[d,**], Sankha Shubhra Chakrabarti[b,*]

[a] Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India
[b] Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India
[c] Center for Biostatistics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India
[d] Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

ARTICLE INFO

Article History:
Received 1 June 2021
Revised 5 July 2021
Accepted 6 July 2021
Available online 23 July 2021

Post-approval
AEFI
India
Risk
Thyroid
COVID-19

ABSTRACT

Background: We provide the first post-approval safety analysis of COVISHIELD in health care workers (HCWs) in northern India.

Methods: This continuing prospective observational study (February 2021 to May 2022) enrolled participants ≥18 years receiving COVISHIELD vaccination. Primary outcome was safety and reactogenicity. Categories (FDA toxicity grading) and outcomes of adverse events following immunization (AEFIs) were recorded, causality assessment performed, and risk factors analysed.

Findings: We present the results of an interim analysis of 804 participants. AEFIs following first dose were reported in 321 (40%; systemic involvement in 248). Among 730 participants who completed a 7-day follow-up post second dose, AEFIs occurred in 115 (15.7%; systemic in 99). Majority of AEFIs were mild-moderate and resolved spontaneously. Serious AEFIs, leading to hospitalization was noticed in 1 (0.1%) participant with suspicion of immunization stress related response (ISRR). AEFIs of grade 3 severity (FDA) were recorded in 4 participants (0.5%). No deaths were recorded. Regression analysis showed increased risk of AEFIs in younger individuals, a two times higher odds in females, those with hypertension or with history of allergy; and three times higher odds in individuals with hypothyroidism.

Interpretation: COVISHIELD carries an overall favourable safety profile with AEFI rates much less than reported for other adenoviral vaccines. Females, those with hypertension, individuals with history of allergy and hypothyroidism may need watchful vaccine administration. This being an interim analysis and based on healthcare workers who may not reflect the general population demographics, larger inclusive studies are warranted for confirming the findings.

Funding: No funding support.

1. Introduction

COVID-19 is an infectious respiratory illness caused by a novel beta corona virus, SARS-CoV-2. The course of COVID-19 can be unpredictable and mortality as high as 26% has been observed in the elderly population and those with co-morbidities [1]. Deaths due to COVID-19 are often because of respiratory failure, septic shock, disseminated intravascular coagulation, and sometimes myocardial injury [2]. The treatment of COVID-19 at present relies on supportive therapies such as prophylactic anticoagulants, oxygen supplementation and parenteral steroids [3,4]. In the absence of definitive anti-SARS-CoV-2 therapy, immunization against viral disease or at least against severe form of illness may offer an attractive means of curtailing the epidemic. This unmet need spurted the development of vaccines which are being manufactured using pre-existing and novel platforms and are in various preclinical and clinical phases. Some of these vaccines

* Corresponding author at: Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP 221005, India
** Co-corresponding author at: Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP 221005, India
E-mail addresses: sangeetakansalbhu@gmail.com (S. Kansal), sankha.geriatrics@gmail.com (S.S. Chakrabarti).

https://doi.org/10.1016/j.eclinm.2021.101038

Research in context

Evidence before this study

COVISHIELD, based on Oxford-AstraZeneca's simian adenovirus platform and coding for the S protein of SARS-CoV-2, was the first vaccine to be given emergency use authorization in India in early January 2021. The first phase of vaccination was targeted towards front line workers such as health care workers (HCWs). Though favorable safety, immunogenicity and efficacy profile has been demonstrated in ChAdOx1 based clinical trials, real-world data on vaccine safety is scarce and no study so far has suggested the potential risk factors of occurrence of adverse events following immunization (AEFIs), making a detailed post approval surveillance necessary.

Added value of this study

This is the first post approval prospective observational safety study of ChAdOx1 based COVID-19 vaccine (COVISHIELD, Serum Institute of India) in HCWs. The preliminary results show reactogenicity rates of 40% after first dose, further reduced to 16% after second dose. These rates are lower than previous reported rates with other adenoviral vector vaccines. Grade 3 AEFIs (FDA) were also less frequent (0.5%) compared to 9-20% rates observed with other adeno virus-based vaccines. Regression analysis shows that younger individuals, females, those with history of allergy to any known stimuli, individuals with hypertension and those with hypothyroidism are at increased risk of AEFIs.

Implications of all the available evidence

COVISHIELD (Serum Institute of India) carries a favorable safety profile and was tolerated well in HCWs of northern India. We attribute the lower reactogenicity rates to probable pre-existing immunity to adenoviruses in the Indian people. Watchfulness may be advised while administering the vaccine in individuals with hypothyroidism, hypertension, and past history of allergy to any stimuli. Since this study has a limited participant population of healthcare workers who may not reflect general population demographics and this being an interim analysis, larger long-term studies with better representation of people with co-morbidities and diverse ethnicities are warranted. Higher occurrence of AEFIs in individuals with hypothyroidism needs to be investigated in future research.

such as Moderna's mRNA-1273, Pfizer's mRNA based BNT162b2, Oxford university-Astra Zeneca's vaccine based on the simian adenovirus have been given emergency use authorization status in various countries [5,6]. In India, COVISHIELD (Serum Institute of India (SII)) and COVAXIN (Bharat Biotech) were the first to be approved for emergency use. COVISHIELD is based on a replication-deficient simian adenoviral vector coding the whole length spike glycoprotein (S) of SARS-CoV-2 while COVAXIN is based on inactivated SARS-CoV-2 platform [7]. The vaccines have been rolled out pan-India and are being administered to all individuals $\geq$ 18 years of age other than those with a history of allergy to one of its components. The first phase of vaccination was directed towards health care workers and front-line workers (police, sanitary workers etc) who are at increased risk of acquiring COVID-19, and who consented to receiving the vaccines [7]. However, the type of vaccine allocated for a particular center (COVISHIELD or COVAXIN) is at the discretion of the government and based on availability status and logistic concerns. Both the vaccines are being provided free of cost by the government of India, through state government health systems and utilising an elaborate and well-designed micro plan of vaccinating every front-line worker [8]. Pre-approval COVID-19 vaccine trials have been done largely in healthy population under controlled settings, have limited inclusion of diverse ethnicities and are limited by short duration of follow up with merging of various phases of clinical trials. Such studies therefore may not detect all safety-related issues that arise when vaccines are intended for marketing in general population [9]. The main objective of this observational study is to carry out a detailed long term safety analysis of COVISHIELD use in the Indian population. Here we present the first interim safety analysis of use of COVISHIELD in health care workers in three vaccination centres in the city of Varanasi (Uttar Pradesh) in north India. COVISHIELD was the designated vaccine for these centres and hence the focus of our study.

2. Materials and methods

2.1. Study design and setting

Ours is a continuing prospective observational study which started from 5th February 2021 and is expected to be continued till May 2022 with at least one year follow up of all the recipients enrolled. The study is being conducted at three sites in Varanasi: Sir Sunderlal hospital which is one of the largest tertiary care teaching and research hospitals of north India, SVM hospital which is a government hospital, and urban community health centre (UCHC), Durgakund. Here we report the first results of a subset of participants who have been followed up for at least seven days post second dose of vaccination. The authors UK and SSC had access to the complete data.

2.2. Study participants

All the individuals who received vaccines, in the above-mentioned centres, and who provided consent to participate were enrolled in the study. In the current analysis, all enrolled participants are healthcare workers. The study involves follow up of the enrolled individuals for at least one year.

2.3. Safety analysis

Adverse events following immunization (AEFIs) were recorded at prespecified intervals and the following detailed data for safety analysis were extracted.

- Incidence of AEFIs
- Type and pattern of AEFIs (Medical dictionary for regulatory activities, MedDRA low level terms and system organ class terminology used)
- Distribution of AEFIs with respect to age and gender
- Outcomes of AEFIs
- Interventions done to manage AEFIs
- Seriousness of AEFI as per WHO definition
- Severity of AEFIs for local AEs (adverse events), systemic AEs, and vital signs. These were recorded as per FDA severity grading scales of individual AEFIs
- Causality assessment of AEFIs using WHO Scale
- AEFIs resulting in hospitalization.
- Any vaccine-disease interaction resulting in AEFI
- Any vaccine-drug interaction resulting in AEFI

2.4. Vaccination procedure and enrolment in study

As per government policy, COVISHIELD is being administered to health care workers and frontline workers, in the centres of the current study. The vaccine is administered in a dose of 0.5 mL in a two-

dose schedule, with the doses given at interval of 4-6 weeks (now revised to 8-12 weeks), intramuscularly in the deltoid. Each mL of the dose administered contains 5×10^{10} simian adeno-viral particles produced in genetically modified human embryonic kidney (HEK) 293 cells. All recipients are routinely monitored at study sites for 30 minutes post vaccine administration, as a part of standard operating procedure for vaccination. All participants who gave consent to participate in our study were enrolled and are being contacted on phone after 24 hours of vaccination, at day 7, day 14, day 28, day-90 and thereafter 3-monthly for a total period of one year. A support phone number is provided to each participant to contact for reporting, at times of emergency or in case of any doubts. For safety analysis, individuals are specifically questioned about local site symptoms such as pain, erythema, swelling, tenderness, and degree of limitation of physical activity. They are also questioned about systemic symptoms such as fever, fatigability, myalgia, arthralgia, headache, nausea, vomiting, diarrhoea, rash, chest tightness and dyspnoea. Biochemical tests are not done routinely in all the vaccine recipients but are planned in case of persistence or severe form of AEFIs. Individuals are informed about the clinical features of COVID-19 and are instructed for RT-PCR based nasal or oropharyngeal swab test for SARS-CoV-2 in any event of developing COVID-19 like symptoms. However, since the study is focused on safety analysis only, testing was not compulsory and only at the discretion of the participants.

2.5. Ethical permission

The study started after obtaining permission from the Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, and written informed consent was taken from all the participants.

2.6. Data sources/measurement

Data pertaining to demography, medical history including history of SARS-CoV-2 positivity at any time in the past, existing co-morbidities, concurrent drug history and history of allergy to any known stimuli was recorded in a pre-designed case report form. Information regarding development of AEFIs, severity of AEFIs, interventions required for management of AEFIs, outcomes of AEFIs, time to complete recovery, and causality of AEFIs was also collected. Causality assessment was done by the investigators of the study. (**Supplementary files- case report form and telephonic message**)

2.7. Sample size

So far, the trials analysing the safety and reactogenicity of COVID-19 vaccines have reflected inconclusive evidence on the rates of occurrence of adverse events of clinical significance. Clinically significant AEFIs have been seen to occur in 1-20% of COVID-19 vaccine recipients. In view of lack of India-specific data and assuming an average rate of occurrence of clinically significant AEFIs to be 10% and margin of error of 2.5%, the expected sample size for this study was calculated to be 576. After clinical and feasibility considerations, we decided to include at least 1400 vaccine recipients for detailed analysis. Considering a drop-out rate of 15%, it was planned to enroll at least 1650 individuals.

2.8. Statistical analysis

Results were recorded as frequencies as well as percentages for data such as incidence, types, severity, and outcomes of AEFIs. Independent t test was used to compare the quantitative variables such as age, between the group developing AEFIs and that without AEFIs. Chi square test was applied for dichotomous variables such as gender, presence of co-morbidities and co-medications to find association between various factors and development of AEFIs. Variables with statistically significant association ($P<0.05$) on bivariate analysis or deemed to be clinically relevant were incorporated in final regression model. We conducted two separate regression analyses- one for all enrolled vaccine recipients, and another one for the subset of vaccine recipients who could be contacted telephonically up to 7 days after receiving their second dose, i.e. those with at least 7 day follow-up post-second dose. We also conducted regression analysis with interaction variables, incorporating those variables with statistically significant association in bivariate analysis (for the set of n=804). Results were analyzed using SPSS version 16.

2.9. Role of funding source

This study had no funding support.

3. Results

Fig. 1 (as per STROBE guidelines) represents the enrolment of vaccinated individuals in the present study. A total of 1666 individuals were screened of whom 16 refused to participate in the study. Of the included 1650 participants, 846 and 804 participants were visiting the centres for their first and second dose of vaccine respectively. At the time of analysis, a significant percentage of the subset who were enrolled while receiving the first dose was yet to receive their second dose, as timing of second dose had been changed from 4 weeks to 12 weeks, after initiation of our study. Since this is an ongoing study and including the 846 participants in this interim analysis would result in variable follow-up duration of different individuals, and also inappropriate regression analysis, they were not included in this interim analysis. These individuals shall be included for safety and effectiveness analysis in the future. For the other 804 individuals who were enrolled in the study while receiving the second dose of vaccine, detailed enquiry was made about any AEFIs during their first dose of vaccine as per protocol described in methods section. They were subsequently followed up after their second dose. Total period of follow-up was calculated starting from their day of receiving first dose and up to 12th March 2021. Median (Q1,Q3) follow up period was 42 (36,43) days. Of these 804, two participants were considered ineligible for the second dose of vaccine by the vaccination programme authorities due to possible AEFI concerns. The investigators of the current study had no role in determining this ineligibility for vaccination. The remaining 802 individuals received the second dose of vaccine. 72 recipients who did not respond to telephonic messages as well as three attempts at telephonic calls at follow-up were considered lost to follow up and a total of 730 individuals were included for the main regression analysis. The baseline characteristics of the study participants are mentioned in Table 1.

3.1. AEFIs after first dose of vaccine

Of the 804 vaccine recipients, AEFIs were reported in 321, giving an AEFI incidence rate of 40% (Table 2). Systemic AEFIs with or without local (injection site) involvement was seen in around 31% participants and only local site involvement was observed in 9% individuals. Among systemic AEFIs, fever, headache and dizziness were the commonly reported AEFIs, seen respectively in 15.2%, 6.2% and 3.7% individuals. Other individual AEFIs and MedDRA SOCs are mentioned in Table 2 and Fig. 2 **a** & b. Severity wise, 70.4% AEFIs were classified as 'mild' and 28.7% were of 'moderate' category. Two AEFIs (0.6%) were of grade 3 severity and one AEFI (0.3%) was 'serious' and led to hospitalization. Causality assessment was not performed for mild-moderate AEFIs developing in recipients after first dose owing to recall bias related considerations. However, it was performed for all serious AEFIs and severe AEFIs. Both AEFIs of grade 3 severity shared 'probable' association with the vaccine and the only serious AEFI was attributed a 'possible' association and with suspicion of immunization

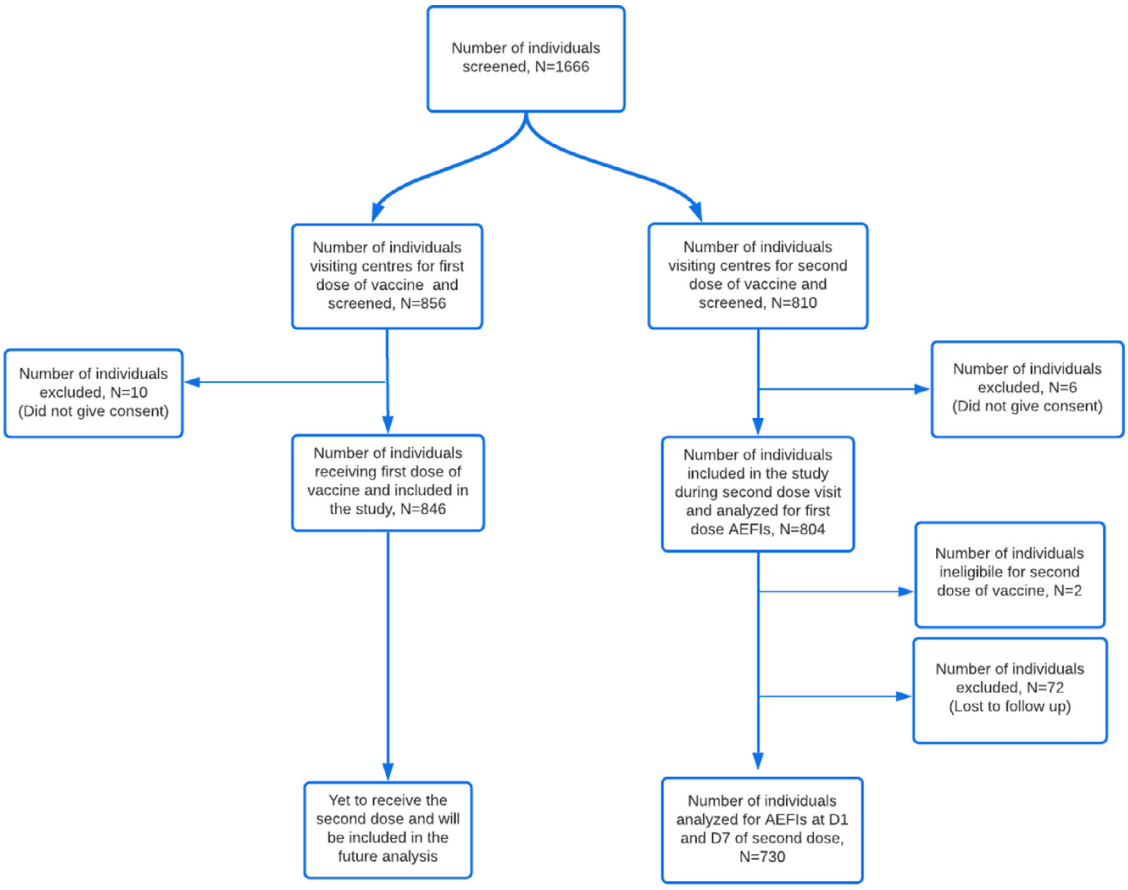

Fig. 1. STROBE flow diagram depicting enrollment of participants in the safety study.

A total of 1666 individuals were screened out of which 16 did not give consent for study participation. Of the 1650 individuals enrolled, 804 were visiting for their second dose of the vaccine and 846 for their first dose of vaccine. The 846 participants have not yet received their second dose and their data would be analyzed later. Of the 804 participants, 2 were judged ineligible for second dose by vaccine administrators. The remaining 802 participants were followed up for 30 minutes following vaccination as per standard protocol. 72 of these 802 participants were subsequently lost to follow-up (could not be contacted). The remaining 730 participants were included in final regression model. A separate regression analysis of total enrolled participants (n=804) was also performed.

stress related response (ISRR). Details of these participants are mentioned in **Table 3**. Median time of complete recovery from AEFIs was 1 day (Q1,Q3 1,2). 91 participants with AEFIs needed interventions of which paracetamol was used in 82 cases, anti-histaminics in 7 cases, and tramadol, proton pump inhibitors and systemic steroids in 2 cases each.

3.2. AEFIs within 30 minutes of second dose

Out of total 802 participants, AEFIs were observed in seven individuals (0.9%). Three recipients developed systemic AEFIs while only local involvement was seen in four participants. All seven AEFIs were of 'mild' severity and shared a 'probable' association with the vaccine. Median time to complete recovery was 2 days.

3.3. AEFIs within 24 hours and till day 7 post-second dose

After excluding 72 individuals who were lost to follow up, a total of 730 individuals were included for analysis of AEFIs occurring within 24 hours and till seven days of vaccination, but not within 30 mins post vaccination. Of these, 93 vaccine recipients (12.7%) developed AEFIs within 24 hours and 22 (3%) developed AEFIs after day 1 and till day 7 post-vaccination, respectively. AEFIs were thus observed in a total of 115 recipients till day seven. Systemic involvement with or without local site reaction was seen in 99 (13.6%) and only local involvement was seen in 16 (2.2%). Severity wise, among 93 individuals developing AEFIs within 24 hours, 66 (78%) had AEFIs of mild grade, 26 (21%) of moderate grade and one recipient developed AEFI of grade 3 severity (details in **Table 3**). For 22 recipients developing AEFIs after 24 hours and till day-seven of second dose, 13 (59.1%), 8 (36.4%) and one (4.5%) had AEFIs of moderate, mild and severe grade (**Table 2**). No serious AEFIs or deaths were reported in this subset of 730 recipients. On performing causality assessment, AEFIs belonged to 'probable', 'possible' and 'unclassifiable' category in 105 (91.3%), 3 (2.6%) and 7 (6.1%) cases, respectively. Median time to complete recovery was 2 days for AEFIs developing within and after 24 hours of vaccination. Interventions were required in 41 individuals of which paracetamol was taken by 36, antibiotics by five, proton pump inhibitors by four and antihistaminic by two (**Table 2**).

3.4. Risk factors for occurrence of AEFIs

Bivariate analysis followed by logistic regression analysis was conducted for two population sets. The first set comprised of all the enrolled vaccinated participants whose data was available till 30 mins post second dose. The second set included the 730 recipients with complete follow-up up to 7 days post second dose.

3.5. Results of bivariate analysis for AEFI risk in 804 participants

Occurrence of AEFIs after the first dose of vaccine was considered as the dependent variable for risk factor analysis of the full set of 804 participants. Significant difference in age was seen between the group developing AEFIs (mean age ± SD: 36.9 ±9.8 years) and that

Table 1
Baseline characteristics of study participants

Vaccinated individuals enrolled (N)	804
Age (years); Mean (± SD)	38.44 (± 11.47)
Gender (Male/Female)	573/231
Body mass index (kg/m^2); Mean (± SD)	24.68 (± 3.68)
History of laboratory confirmed COVID-19 at any time before vaccination; N (%)	56 (7)
Blood Group	N (%)
B^+	252 (31.3)
O^+	225 (28)
A^+	132 (16.4)
AB^+	66 (8.2)
B^-	13 (1.6)
O^-	7 (0.9)
AB^-	4 (0.5)
A^-	4 (0.5)
No details	101 (12.5)
Individuals with diabetes mellitus; N (%)	66 (8.2)
On antidiabetic drugs; N (%)	51 (6.3)
Individuals with hypertension; N (%)	73 (9)
On anti-hypertensive drugs; N (%)	70 (8.7)
Individuals with hypothyroidism; N (%)	28 (3.5)
On thyroxine; N (%)	27 (3.3)
Individuals with asthma or COPD; N (%)	10 (1.2)
On inhaled beta agonists; N (%)	6 (0.7)
On inhaled steroids; N (%)	3 (0.4)
Individuals with coronary artery disease; N (%)	5 (0.6)
Individuals on antiplatelet drugs or anticoagulants; N (%)	4 (0.5)
Individuals on statins; N (%)	3 (0.4)
Individuals with self-described allergy to any agent (environmental; household; medications etc); N (%)	51 (6.3)
Individuals with past history of or active tuberculosis; N (%)	5 (0.6)
On anti-tubercular therapy; N (%)	4 (0.5)
Individuals with epilepsy; N (%)	2 (0.2)
On antiepileptic drugs; N (%)	2 (0.2)
Individuals with skin diseases; N (%)	3 (0.4)
Individuals with rheumatoid arthritis; N (%)	3 (0.4)
Individuals currently receiving other drugs	N (%)
Non-steroidal anti-inflammatory drugs	6 (0.7)
Antibiotics	2 (0.2)

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease. All percentages in brackets are out of total enrolled vaccine recipients (N=804).

without AEFIs (Mean age ± SD: 39.4 ±12.4 years) (P=0.003). Among other variables, female gender (P<0.001), hypothyroid status (P<0.001), and past history of allergy (P=0.004) were observed as significant predictors of high risk of AEFI occurrence (**Supplementary Table 1**). Other variables such as body mass index and history of asthma did not show statistical significance. The number of participants with other comorbidities namely, seizure disorder (epilepsy), rheumatoid arthritis, viral hepatitis, tuberculosis, and chronic skin diseases were small (<10) and hence we did not evaluate them for statistical significance.

3.6. Results of bivariate analysis for AEFI risk in 730 participants

Occurrence of AEFIs at any time after the second dose of vaccine (within 30 minutes, within 24 hours, or within 7 days) was chosen as the dependent variable for AEFI risk factor analysis in the 730 participants who were followed up till 7 days post-second dose. Significant difference in age was seen between the group developing AEFIs (n=730) (Mean age ± SD: 36.9 ± 10.0 years) and that without AEFIs (Mean age ± SD: 39.9 ± 12.5 years) (P=0.001). Further when age was categorized into 18-39 years and ≥ 40 years groups, 1.4 times higher odds of AEFIs was observed in the 18-39-year age group (P < 0.05). Among other variables, female gender (P<0.001), hypothyroid status (P=0.003), and past history of allergy (P=0.03) were observed as significant predictors of high risk of AEFIs similar to the analysis of 804 vaccine recipients (**Supplementary Table 2**).

3.7. Results of logistic regression analysis

Tables 4a and **4b** show the findings of the logistic regression analyses performed on all 804 enrolled vaccine recipients and on the 730 recipients who completed 7 day follow up post-second dose, respectively. For both the regression models, the independent variables selected were age (as continuous variable), gender, history of COVID positivity in past, presence of diabetes mellitus, hypertension, hypothyroidism, and history of allergy. Increasing age was associated with lower risk of development of AEFIs with statistical significance in both models. Females compared to males, recipients with hypertension compared to those with normal blood pressure, and recipients with history of allergy compared to those without, were each observed to have 2 times higher odds of developing AEFIs (P <0.05 for each). Hypothyroid patients had three times higher odds of developing AEFIs compared to those with normal thyroid status (P<0.05). Except for history of allergy, all other risk factors were consistent in both the analyses. In regression analysis using interaction terms (age-gender, hypertension-hypothyroidism, allergy-hypothyroidism, allergy-hypertension), no statistical significance was obtained in any case.

4. Discussion

The results of this interim analysis show that ChAdOx1 vaccine (Serum Institute of India) has a generally favourable safety profile. Around one half of vaccine recipients developed adverse events at any time post vaccination with majority of reactions being mild to moderate in severity. AEFIs were seen in 40% participants after first dose and around 16% participants after second dose. This observed reactogenicity is much less compared to 60-88% reactogenicity observed in phase 1 and phase 2/3 clinical trials of Oxford-AstraZeneca's ChAdOx1vaccine in the UK based population (AZD1222) [10,11]. Further, a decrease in reactogenicity and severity of AEFIs was evident in the second dose which was consistent across AEFI types and SOC categories. Systemic involvement with or without local site involvement was seen in nearly one third of vaccine recipients after first dose and in more than 13% vaccine recipients after second dose. Fever, injection site pain and headache were the commonly observed AEFIs. Fever occurred in 15% individuals after first dose and in 5% participants on second dose. Frequency of other events such as malaise, and headache remained lower than 10% overall. Previously, these events have been shown to occur in 30-70% UK based recipients of Oxford-AstraZeneca's ChAdOx1 vaccine, 40-50% Chinese recipients of recombinant Ad5 based vaccine manufactured by CanSino Biologics and in 20-40% US and Belgium based individuals receiving recombinant Ad26 based vaccine of Janssen Pharmaceuticals [10–13]. In our study, the frequency of AEFIs decreased with age, with around 1.4 times higher odds of developing AEFIs in those 18-39 years of age compared to those ≥ 40 years of age, on bivariate analysis. That increasing age is associated with lesser risk of AEFIs is in concordance with the published clinical trials analysing various viral vector-based vaccines [11,13,14]. Other than age, other significant predictors of AEFIs were gender, thyroid status, history of allergy and hypertension status. Females, people with hypertension, and those with any history of allergy were found to have a 2 times higher odds of developing AEFIs compared to males, participants who were normotensive, and those without any history of allergy. Likewise, compared to those with normal thyroid function, three times higher odds of developing AEFIs was observed in individuals suffering from hypothyroidism. It is worth noting that all patients of hypothyroidism except one were on thyroxine treatment. Whether AEFI risk is because of vaccine-disease interaction or vaccine-thyroxine interaction needs to be explored in future. The link between thyroid and immunity or inflammation has been suggested in some studies with thyroxine having a stimulatory action on neutrophils, natural killer cells and

Table 2
AEFIs developing in recipients of vaccine after first dose and second dose

	AEFI after first dose (n=804)	AEFI after second dose		
		Within 30 minutes (n=802)	Within 24 hours (n=730)	After 24 hours and till D7 (n=730)
AEFIs	321 (40)	7 (0.9)	93 (12.7)	22 (3)
Systemic AEFIs with/without local, n (%)	248 (30.8)	3 (0.4)	99 (13.6)[#]	
MedDRALLT				
Fever	122 (15.2)	1 (0.1)	29 (3.9)	8 (1.1)
Injection site pain	96 (12)	4 (0.5)	24 (3.3)	3 (0.4)
Headache	50 (6.2)	0	23 (3.1)	6 (0.8)
Dizziness	30 (3.7)	1 (0.1)	4 (0.5)	1 (0.1)
Malaise	20 (2.5)	0	11 (1.5)	3 (0.4)
General body pain	24 (3)	0	7 (0.9)	0
Weakness	17 (2.1)	0	13 (1.7)	3 (0.4)
Fatigue	5 (0.6)	0	3 (0.4)	0
Myalgia	16 (2)	1 (0.1)	4 (0.5)	1 (0.1)
Shivering	10 (1.2)	0	1 (0.1)	0
Rhinitis	6 (0.7)	0	2 (0.3)	1 (0.1)
Itching	4 (0.5)	0	0	0
Cold	8 (1)	0	1 (0.1)	0
Arthralgia	8 (1)	0	2 (0.3)	1 (0.1)
Throat sore	2 (0.2)	0	0	1 (0.1)
Nausea	8 (1)	0	1 (0.1)	1 (0.1)
Drowsiness	5 (0.6)	0	1 (0.1)	0
Diarrhoea	7 (0.9)	0	1 (0.1)	4 (0.5)
Abdominal pain	0	0	3 (0.4)	2 (0.3)
Anxiety	5 (0.6)	1(0.1)	0	0
Palpitation	6 (0.7)	0	1 (0.1)	1 (0.1)
Hypertension	4 (0.5)	1(0.1)	1 (0.1)	0
Tachycardia	4 (0.5)	0	0	0
Loss of appetite	3 (0.4)	0	1 (0.1)	0
Eye symptoms	4 (0.5)	0	0	1 (0.1)
Taste altered	2 (0.2)	0	0	0
Rash	2 (0.2)	0	2 (0.3)	1 (0.1)
Vomiting	2 (0.2)	0	1 (0.1)	1 (0.1)
Bleeding	1 (0.1)	0	2 (0.3)	0
Tingling	3 (0.4)	0	1 (0.1)	0
Isolated local AEFI (including pain/tenderness/ erythema/limitation of activity of involved limb)	73 (9.1)	4 (0.5)	16 (2.2)[#]	
MedDRASOC involved, n (%)				
General disorders & administration site conditions	245 (30.5)	5 (0.6)	74 (10.1)	14 (1.9)
Nervous system disorders	85 (10.6)	1 (0.1)	29 (4)	6 (0.8)
Musculoskeletal & connective tissue disorders	24 (3)	0	6 (0.8)	2 (0.3)
Respiratory, thoracic & mediastinal disorders	16 (2)	0	4 (0.5)	2 (0.3)
Skin & subcutaneous tissue disorders	7 (0.9)	0	2 (0.3)	1 (0.1)
Cardiac disorders	10 (1.2)	0	1 (0.1)	1 (0.1)
Vascular disorders	4 (0.5)	1 (0.1)	2 (0.3)	0
Psychiatric disorders	6 (0.7)	1 (0.1)	0	0
Gastrointestinal disorders	17 (2.1)	0	5 (0.7)	6 (0.8)
Eye disorders	4 (0.5)	0	0	1 (0.1)
Reproductive system and breast disorders	1 (0.1)	0	1 (0.1)	0
Severity (FDA)^	(n=321)	(n=7)	(n=93)	(n=22)
Grade 1 (mild), n (%)	226 (70.4)	7 (100)	66 (71)	8 (36.4)
Grade 2 (moderate), n (%)	92 (28.7)	0	26 (28)	13 (59.1)
Grade 3 (severe), n (%)	2 (0.6)[*]	0	1 (1)[##]	1 (4.5)[###]
Grade 4 (very severe), n (%)	1 (0.3)[**]	0	0	0
Serious (WHO)	1 (0.3)[**]	0	0	0
Time to Recovery (days) [Median (Q1,Q3)]	1 (1,2)	2 (0.625,2)	2 (1,2)	2 (2,3)
Interventions required, n (%)^	91 (28.3)	0	41 (35.6)[$]	
Paracetamol	82		36	
Antibiotics (norfloxacin, metronidazole, tinidazole)	1		5	
Anti-histaminics	7		2	
PPI	2		4	
IVF	1		1	
Antihypertensive (amlodipine)	1		0	
Antianxiety (propranolol)	1		0	
Systemic steroids	2		0	
Systemic opioids	2		0	

[**Abbreviations:** AEFI: Adverse event following immunization, IVF: Intra venous fluid, LLT: Low level term, MedDRA: Medical dictionary for regulatory activities, PPI: Proton pump inhibitor, SOC: System Organ Class

[#]The figure is total of AEFIs developing within 24 hours and those occurring after 24 hours and till 7 days of second dose of vaccination

All percentages for AEFIs, systemic AEFIs, MedDRA LLT, isolated local AEFIs, MedDRA SOC are expressed with respect to total participants observed for same ^All percentages for severity and interventions required are expressed out of participants developing AEFIs

[*] Both of 'Probable' causal association, [**] 'Possible' causal association, [##] 'Unclassifiable' causal association, [###] 'Probable' causal association, [$]Interventions for AEFIs occurring within 24 hours and those from 24 hours till 7 days following second dose of vaccination, presented together]

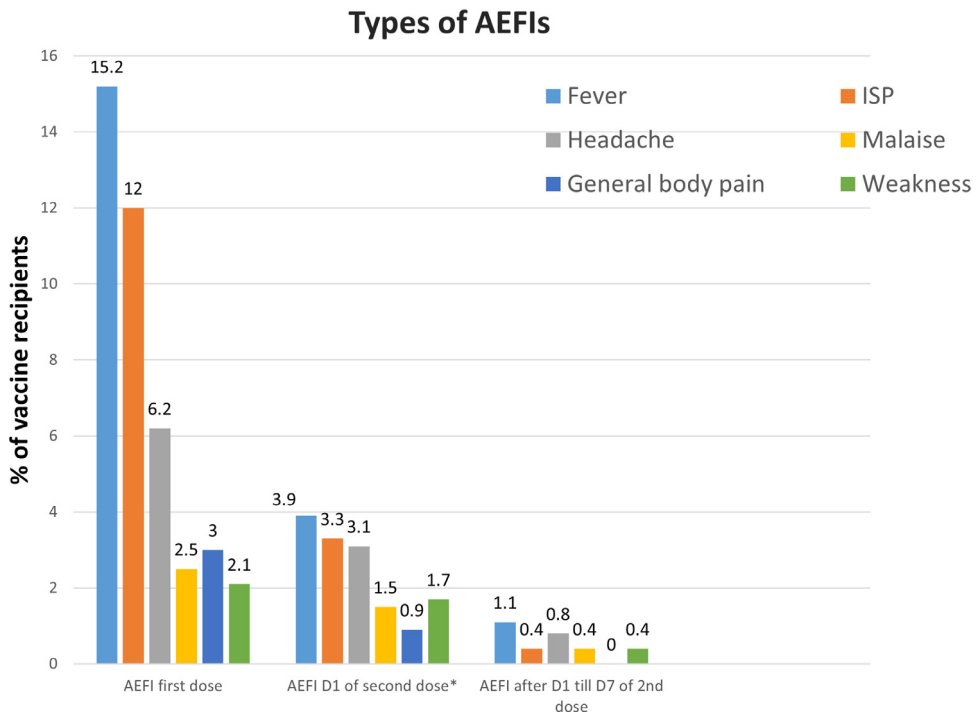

Fig. 2. (a) Types of AEFIs observed after first and second dose of vaccine in study participants.
[*AEFIs occurring after 30 minutes of vaccination up to 24 hours; AEFI: Adverse event following immunization, ISP: Injection site pain]. (b) Common MedDRA SOCs of AEFIs in vaccine recipients.
[*AEFIs occurring after 30 minutes of vaccination up to 24 hours; AEFI: Adverse event following immunization]

macrophages, implying a more robust immune response [15]. Apart from the simian adeno virus or the S protein, adjuvants of the vaccine including polysorbate and EDTA can also interact with thyroxine or the hypothyroid state. Though possibly unrelated to our finding, it is interesting to note that COVID-19 may have an adverse course in patients with hypothyroidism [16]. No significant association of AEFI risk was seen with lab confirmed diagnosis of COVID-19 in past. Likewise, co-morbidities such as diabetes mellitus and asthma or COPD did not have any statistically significant association with AEFIs. The findings should be interpreted with caution as majority of vaccine recipients enrolled in the study were healthy individuals and co-morbidities were present in only a minority.

Severity wise, four participants developed grade 3 AEFIs, assessed by the Food and Drug Administration (FDA) toxicity grading scale. Two of these vaccine recipients developed symptoms after second dose and two after the first dose. One of the latter two was considered ineligible for second dose by the vaccination programme nodal officers. Three grade 3 events were rated as 'probable' and one as 'unclassifiable' by the investigators using the WHO scale of causality assessment. One patient developed serious (grade 4) AEFI leading to emergency room visit followed by in-patient ward admission. The patient was discharged within 2 days with a final diagnosis of COVID-19 vaccination reaction. A possibility of immunization stress related response (ISRR) existed in the case and the reaction was scored under 'possible' category by the investigators. The lady refused second dose of vaccination and was also considered ineligible for second dose by the vaccination programme nodal officers. Four of these five patients developing AEFIs of $\geq$ 3 grade were females and three were diagnosed case of hypothyroidism and were taking thyroxine supplements. EDTA present in the COVISHIELD vaccine (also present in Oxford's ChAdOx1 vaccine) can cause cardiovascular disturbances such as tachycardia and arrythmias and by increasing cardiac load can raise blood pressure in susceptible individuals, as observed in three out of these five vaccinees [17,18].

Overall, the frequency of systemic events of severity grade 3 was 0.5% and is much less than the reported rates of 9-20% with rAd5 and rAd26 based vaccines [13,14]. The interim analysis of clinical trials investigating ChAdOx1 in UK, South Africa and Brazil showed a 0.7% rate of occurrence of serious adverse events. The corresponding rate in our study was 0.1%. No deaths were reported in the vaccine recipients in our study during the study period.

Low reactogenicity rates with COVISHIELD (Serum Institute of India) compared to Oxford-AstraZeneca's ChAdOx1 vaccine and other adenovirus-based vaccines can be explained to a certain extent by pre-existing immunity against human and chimpanzee adenoviruses in the Indian population by virtue of exposure to such viruses in the past. Human adenoviruses, known to cause common cold are widely prevalent in developing countries. Neutralizing antibodies (nAbs) against human Ad5 have been observed in 100% healthy Indians with medium to high titre nAbs seen in 50% and very high titre in around 30% samples [19]. On the other hand, frequencies, and mean titre of such nAbs are low in the US population [20]. Neutralizing antibodies against chimpanzee adeno viruses are less common but seen in $<$15% Americans, Chinese and Europeans [21]. Though pre-existing humoral immunity against human adenoviruses is unlikely to cross react with chimpanzee adeno virus ChAdOx1, T cells mounted against human adeno viruses are known to cross react with some viruses such as ChAd6 and ChAd7 [21]. Cross-reactivity is a common occurrence with respect to viruses. Multiple models of the effects of varying levels of cross-reactivity on SARS-CoV-2 replication and COVID-19 severity have been analysed by the group of Crotty and others [22]. Cross-reactive immunity is also well-established among flaviviruses and may result in some degree of protection or aggravate immune related damage [23]. Cross-reactivity to endemic coronaviruses has been hypothesized by the authors of the current study as a reason for country specific variations in COVID-19 outcomes [24]. Humans being in a close phylogenetic relationship with chimpanzees, a possibility of cross reactivity between human and chimpanzee adeno viruses exists, which may explain the low reactogenicity rates.

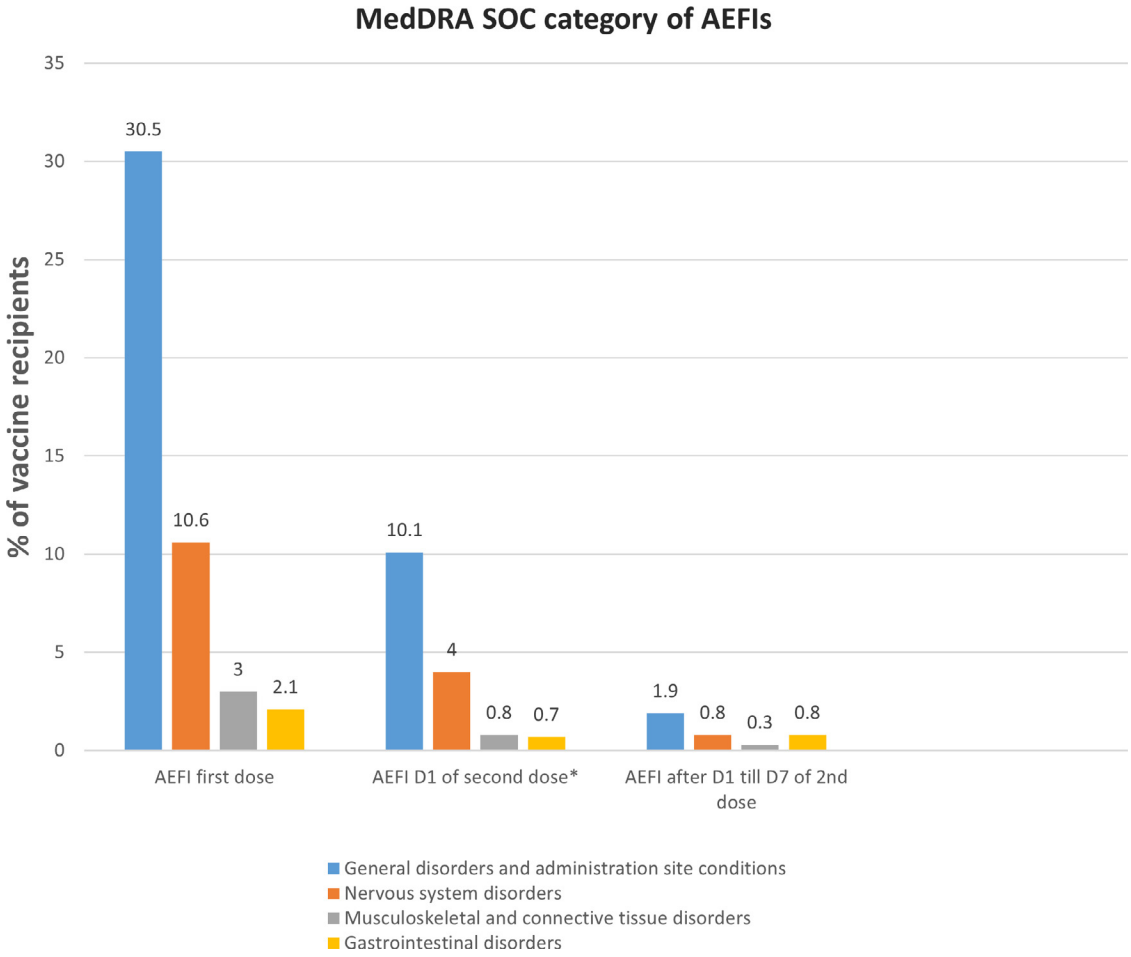

Fig. 2. Continued.

Zhu et al in the phase 2 study on the recombinant Ad5 based vaccine demonstrated that pre-existing neutralising antibodies against human adenovirus 5 might be responsible for low reactogenicity in the elderly compared to the young, which is also a finding of our study [14]. Since this interim analysis is focused on safety outcomes, no inference can be drawn about vaccine effectiveness at present in real world settings.

Information regarding AEFIs throughout 4-6 weeks following the first dose was collected from the subset of vaccine recipients included in this interim analysis, at the time of their second dose of vaccination. A possibility of recall bias and uncertainty regarding some of the parameters such as time to full recovery from AEFIs exists. The authors however do not think that a gap of 4-6 weeks would have significant clinical bearing on the overall analysis. Further attempt was made to verify the AEFIs from caregivers or close family members and to verify all serious AEFIs occurring during this time from any existing medical records of the recipients. Being an unblinded study, the possibility of observer bias, however, cannot be ruled out. Similarly, as blood investigations were not routinely performed, some AEFIs may have been missed. There has been a loss to follow-up of vaccine recipients of nearly 10% due to inability to contact them telephonically. However, the regression analyses performed for all enrolled participants and those with intact follow up yielded similar results, lending strength to our findings. The findings of our study may not be generalized to the larger Indian populace. India is a young country with the < 20-year age group constituting around 35% of the population [25]. This group is not expected in a set of healthcare workers who would mostly be between 18 and 65 years (age of retirement in government service) of age. Similarly, the male:female ratio in our study participants was 2.48 whereas for the general Indian population it is 1.08 [26]. This may reflect a skew in job opportunities and job habits of the Indian society. The prevalence of major comorbidities such as diabetes, hypertension and hypothyroidism are also age and gender-specific and the prevalence in our participant set differs from national prevalence rates. However, in the current and future vaccination campaigns against COVID-19, healthcare workers are certain to be prioritized, making the interim data obtained from the current study relevant. This is also relevant as vaccines are currently approved in India for those above 18 years of age only.

On the basis of interim findings of this safety study, it may be interpreted that the ChAdOx1 nCoV-19 corona virus vaccine (recombinant) (COVISHIELD, Serum Institute of India) carries a good safety profile overall. Younger individuals, females, individuals with hypertension or positive history of allergy or hypothyroidism are at increased risk of AEFIs and vaccines should be administered to such individuals while maintaining adequate watchfulness. In line with the published international evidence on ChAdOx1 nCoV-19 corona virus vaccine, majority of AEFIs observed in our study were mild to moderate AEFIs and mostly self-resolving [10,11]. Larger double blind randomized clinical trials of longer duration will give a more appropriate idea of overall safety and efficacy of COVID-19 vaccines. Future research should also explore the link between AEFIs and hypothyroidism.

Table 3
Details of vaccine recipients developing AEFIs of FDA severity grade ≥ 3

Age	Medical history	BMI (kg/m^2), Blood group	Drug history	Symptoms at first or second dose of vaccine	Onset of symptoms	Description of symptoms	SOC involved	Whether hospitalization required	Outcome	TTR	Causality till interim analysis
37, F	Hypothyroidism,	34.44, B+	Thyroxine 100μg	First	Hours	Tingling, dizziness, palpitations, heaviness in chest, tachycardia, and fluctuating blood pressure. On admission, BP 150/80 mm Hg, HR 130/min, remaining vitals stable and routine blood investigations including cardiac enzymes were normal.	Cardiac disorders, Nervous system disorders, Vascular disorders, ISRR suspected	Yes	Improved	4 days	Possible
43, F	Hypothyroidism and scalp psoriasis, history of severe allergic reaction in the past to IV ondansetron	27, B+	Thyroxine 150 μg	First	2-3 minutes	Dizziness, BP 170/110 mm Hg, HR 110/min, heaviness in chest, shivering and cold extremities. Vitals fluctuated over next few days and then became stable. She also developed mild itching that persisted for 6-7 days.	Cardiac disorders, Vascular disorders, General disorder and administration site conditions, Skin and subcutaneous tissue disorders, ISRR unlikely but suspected	No, but kept under supervision at vaccination site for 2 hours, received injectable tramadol, dexamethasone, chlorpheniramine, and oral levocetirizine	Improved	6-7 days	Probable
45, F	No	25.1, NK	No	First	24 hours	Palpitations, BP 180/110 mm Hg, HR 90/min	Vascular disorders, Cardiac disorders	No, was prescribed amlodipine for three days	Improved	3 days	Probable
57, F	T2DM, HTN, hypothyroidism	28, B+	Glimepiride, metformin, losartan, thyroxine	Second	48 hours	Abdominal discomfort, vomiting, diarrhoea	Gastrointestinal disorder	No, received injectable metronidazole, ondansetron, IVF and pantoprazole at home	Improved	2 days	Probable
35,M	Polycythemia, HTN	23.1, A+	Takes tramadol on-off	Second	24 hours	Feverishness, headache, recurrence of haematuria and haemoptysis. History of similar symptoms present in the past. Advised detailed work up.	Vascular disorders, General disorder and administration site conditions	Received tramadol and tranexamic acid	Intensity reduced but symptoms still present on day 7 of follow up	NA	Unclassifiable

[AEFI: Adverse event following immunization, BMI: Body Mass Index, T2DM: Type 2 diabetes mellitus, HR: Heart rate, HTN: Hypertension, ISRR: Immunization stress related response, NA: Not applicable, NK: Not known, SOC: System organ class, TTR: Time to recovery]

Table 4a
Logistic regression analysis to determine risk factors of AEFIs in total enrolled vaccine recipients (n=804)

Tentative risk factors for AEFI	OR (CI)	P value
Age (as continuous variable)	**0.97 (0.96-0.99)**	**0.001**
Gender		
Female	**2.1 (1.5-2.8)**	< **0.001**
Male (reference)		
Diabetes mellitus		
Yes	0.8 (0.4-1.4)	0.4
No (reference)		
Hypertension		
Yes	**2 (1.2-3.6)**	**0.01**
No (reference)		
Past history of COVID		
Yes	1.5 (0.84-2.6)	0.17
No (reference)		
History of allergy		
Yes	**2 (1.1-3.6)**	**0.02**
No (reference)		
Hypothyroidism		
Yes	**3.1 (1.2-7.6)**	**0.01**
No (reference)		

[AEFIs: Adverse events following immunization, CI: Confidence interval, OR: Odds ratio]

Table 4b
Logistic regression analysis to determine risk factors of AEFIs in 730 vaccine recipients with follow-up till 7 days post-second dose

Tentative risk factors for AEFI	OR (CI)	P value
Age (as continuous variable)	**0.97 (0.96-0.99)**	<**0.001**
Gender		
Female	**1.8 (1.3-2.5)**	**0.001**
Male (reference)		
Diabetes mellitus		
Yes	0.8 (0.43-1.47)	0.48
No (reference)		
Hypertension		
Yes	**1.96 (1.09-3.52)**	**0.02**
No (reference)		
Past history of COVID		
Yes	1.5 (0.83-2.64)	0.19
No (reference)		
History of allergy		
Yes	1.73 (0.91-3.3)	0.09
No (reference)		
Hypothyroidism		
Yes	**2.76 (1.04-7.35)**	**0.04**
No (reference)		

[AEFIs: Adverse events following immunization, CI: Confidence interval, OR: Odds ratio]

Data sharing statement

Since this is an interim analysis of a currently ongoing longitudinal study, associated data may be made available by corresponding author on request.

Funding

No funding support.

Author contributions

UK designed the study methodology, supervised data collection, wrote the article and performed statistical analysis
BO and BKP collected data and performed literature review
AS (Anup Singh) assisted in data analysis
KRG and AS (Amit Singh) assisted in literature review
AD and AM assisted in data collection and compilation
AKY assisted in statistical analysis
SK designed the study methodology, supervised data collection, and edited the final version of manuscript
SSC designed the study methodology, supervised data collection, performed statistical analysis and edited the final version of manuscript

Declaration of Competing Interest

The authors have nothing to declare.

Acknowledgement

The authors would like to acknowledge Dr VB Singh and Dr DN Gupta for their guidance.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101038.

References

[1] Kang SJ, Jung SI. Age-related morbidity and mortality among patients with COVID-19. Infect Chemother 2020;52:154–64.
[2] McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020;2:e437–45.
[3] Rodriguez-Guerra M, Jadhav P, Vittorio TJ. Current treatment in COVID-19 disease: a rapid review. Drugs Context 2021;10:1–8.
[4] Dondorp AM, Hayat M, Aryal D, Beane A, Schultz MJ. Respiratory Support in COVID-19 Patients, with a Focus on Resource-Limited Settings. Am J Trop Med Hyg 2020;102:1191–7.
[5] U.S. Food and Drug Administration. COVID-19 vaccines. 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines (accessed July 5, 2021).
[6] European Medicines Agency. COVID-19 vaccines. 2021.
[7] Kumar VM, Pandi-Perumal SR, Trakht I, Thyagarajan SP. Strategy for COVID-19 vaccination in India: the country with the second highest population and number of cases. npj Vaccines 2021;6:60.
[8] Ministry of Health and Family Welfare Government of India. Information regarding COVID-19 vaccine. 2021. https://www.mohfw.gov.in/covid_vaccination/vaccination/index.html (accessed July 5, 2021).
[9] Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Med 2021;27:205–11.
[10] Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020;396:467–78.
[11] Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020;396:1979–93.
[12] Zhu F-C, Li Y-H, Guan X-H, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020;395:1845–54.
[13] Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021:NEJMoa2034201.
[14] Zhu F-C, Guan X-H, Li Y-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2020;396:479–88.
[15] Rubingh J, van der Spek A, Fliers E, Boelen A. The role of thyroid hormone in the innate and adaptive immune response during infection. Compr Physiol 2020;10:1277–87.
[16] Brix TH, Hegedüs L, Hallas J, Lund LC. Risk and course of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism. Lancet Diabetes Endocrinol 2021;9:197–9.
[17] Gornik HL, Creager MA. Medical treatment of peripheral artery disease. Vascular medicine: a companion to Braunwald's heart disease. Elsevier; 2013. p. 242–58.
[18] Cohen S, Weissler AM, Schoenfeld CD. Antagonism of the contractile effect of digitalis by EDTA in the normal human ventricle. Am Heart J 1965;69:502–14.
[19] Pilankatta R, Chawla T, Khanna N, Swaminathan S. The prevalence of antibodies to adenovirus serotype 5 in an adult Indian population and implications for adenovirus vector vaccines. J Med Virol 2010;82:407–14.
[20] Barouch DH, Kik SV, Weverling GJ, et al. International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. Vaccine 2011;29:5203–9.

[21] Fausther-Bovendo H, Kobinger GP. Pre-existing immunity against Ad vectors. Hum Vaccin Immunother 2014;10:2875–84.
[22] Lipsitch M, Grad YH, Sette A, Crotty S. Cross-reactive memory T cells and herd immunity to SARS-CoV-2. Nat Rev Immunol 2020;20:709–13.
[23] Rathore APS, St. John AL. Cross-reactive immunity among flaviviruses. Front Immunol 2020;11. doi: 10.3389/fimmu.2020.00334.
[24] Chakrabarti SS, Kaur U, Singh A, et al. Of Cross-immunity, herd immunity and country-specific plans: experiences from COVID-19 in India. Aging Dis 2020;11:1339.
[25] Population Pyramids. Population of India 2020. https://www.populationpyramid.net/india/2020/ (accessed July 5, 2021).
[26] Alesina A, Giuliano P, Nunn N. Traditional agricultural practices and the sex ratio today. PLoS One 2018;13:e0190510.