Short Communication

Incidence of Early Adverse Events Following Covishield (ChAdOx1 nCoV-19) Vaccination: A Prospective Study

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Abstract

Background: Minor adverse event following immunizations (AEFIs) are often underreported and self-treated. This study aimed to collect information regarding any and every probable adverse event experienced by the recipient of Covishield vaccine up to 10 days following the first and second dose of vaccine. To find the incidence of minor adverse events following Covishield vaccination; draw an association between adverse events and individuals' demographic factors and comorbidities; and report new adverse events, if any. **Materials and Methods:** A descriptive observational study was conducted among 409 participants randomly sampled from the Vaccination Centre at a Tertiary Care Hospital, Mumbai. Participants were followed up post their first and second doses to enquire about adverse events. **Results:** Most commonly reported adverse events included injection site pain, tenderness, chills, fatigue, fever, and myalgia. Females reported more adverse events compared to men ($p < 0.05$). Younger individuals (18–24) experienced adverse events more as compared to individuals above 40 years of age ($p < 0.005$). Reported adverse events were lesser after the second dose in comparison with the first dose. Few participants reported dysgeusia. **Conclusions:** Covishield vaccination has a mild AEFI profile, most commonly: injection site pain, tenderness, chills, and fatigue. It is hoped that the findings of this study will dispel anxiety around the adverse events of vaccination and reduce any persisting vaccine hesitancy. Effective communication with the population on vaccination will enable individuals to make educated and informed decisions.

Keywords: AEFI, COVID-19, COVISHIELD, immunization, incidence, India, vaccination, vaccines

Introduction

As of January 13, 2022, India had 1,117,531 active cases of COVID-19 and completed 1,546,139,465 vaccinations (Covishield, Covaxin, and Sputnik V combined).[1]

India started its COVID-19 Vaccination Program on January 16, 2021. Two vaccines received approval for emergency use in India at the onset of the program: Covishield (Oxford–AstraZeneca) manufactured by the Serum Institute of India and Covaxin, which was developed by Bharat Biotech; Sputnik V received emergency use permission in April 2021. Our center began Covishield vaccination for health care workers (HCWs) and medical students in the first phase of the vaccination drive on January 16.

At the time of initiation of the study and even today, Covishield remains the more widely available and preferred vaccine.[2] Covishield vaccination began with the initially recommended gap between the doses being 28 days, with the interval being increased to 6–8 weeks on March 22, 2021, and subsequently to 12–16 weeks on May 13, 2021. HCWs and individuals older than 60 years with comorbidities are eligible to receive precaution doses from January 10, 2022.[3]

In regards to any vaccination program, severe adverse event following immunization (AEFIs) are much more easily noticed and frequently self-reported by the patient; minor AEFIs such as fever, fatigue, myalgia, or headache might be considered as trivial symptoms and are self-treated, thus underreported. Apart from the initial trials for safety assessment, very few studies had been conducted with a longitudinal design and an extended

Access this article online

Quick Response Code:

Website: www.ijcm.org.in

DOI: 10.4103/ijcm.ijcm_93_22

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How to cite this article: Velhal GD, Kamath YV, Agrawal AS, Vora DS, Dwivedi VR. Incidence of early adverse events following covishield (ChAdOx1 nCoV-19) vaccination: A prospective study. Indian J Community Med 2022;47:613-7.

Received: 28-01-22, **Accepted:** 22-09-22, **Published:** 14-12-22

period of follow-ups. It was felt necessary to conduct a study keeping the Indian population in mind and aiming to collect information regarding any and every minor AEFI experienced by the recipient of Covishield™ Vaccine up to 10 days following the first and second doses of the vaccine.

Materials and Methods

A descriptive observational study was conducted between February 2021 and June 2021, with participants being randomly sampled from the Vaccination Centre at a Tertiary Care Hospital in Mumbai. Institutional Ethics Committee permission was obtained before starting the study procedures. All individuals above 18 years of age who had taken the Covishield vaccine at the time of recruitment were eligible to be participants in the study. Individuals without a mobile handset were not included since our study was based on telephonic follow-up. Individuals were approached during the 30-min observation period after they had taken the vaccine. The study involved participant follow-ups via telephonic interviews on the 1st (first 24 h), 2nd (24–48 h), 3rd (48–72 h), 6th (72–144 h), and 10th (144–240 h) days after receiving first and second doses of Covishield vaccine.

At the time of initiation of the study, due to the lack of other published literature on the subject, we took a convenience sample size of 400. During the process of recruitment, 409 participants agreed to be a part of the study; by the time of the second dose, 23 participants did not complete their follow-up, due to withdrawal of consent and investigators being unable to contact them telephonically, bringing the effective study population to 386.

Study Tools

The questionnaire for the telephonic interview contained the list of symptoms as described in the fact sheet provided by SII.[4] Participants were also asked if they had any complaints other than the ones already mentioned.

Statistical analysis

The data obtained at the end of follow-ups was analyzed using IBM SPSS 26.0 software.[5] The Chi-square test was used to find significant differences in adverse events based on sex, COVID status, and comorbidities.

Results

Descriptive statistics of demographic and comorbidity data is listed in Table 1. Most adverse events lasted the first 3 days [Supplementary Tables 1 and 2], and severity devolved with time [Figures 1 and 2]. Injection site tenderness ($p < 0.001$), pain ($p = 0.002$), malaise ($p = 0.001$), fatigue ($p < 0.001$), chills ($p < 0.001$), headache ($p = 0.003$), muscle pain ($p = 0.003$), fever ($p < 0.001$), dizziness ($p < 0.001$), and decreased appetite ($p = 0.003$) were reported significantly higher in individuals aged 18–24 (Young Adult group), and lower in individuals above 40 years of age.

Table 1: Population descriptive data, comorbidity data, and past COVID-19 infection history ($n = 386$)

Variables	Counts(Percentage)
Age (years)	
Mean±SD	34.3±13.2
Gender	
Female	183 (47.4%)
Male	203 (52.6%)
Comorbidities	
Diabetes	31 (8%)
Hypertension	47 (12.2%)
Asthma	16 (4.1%)
Allergic conditions	19 (4.9%)
Heart diseases	5 (1.3%)
Lung diseases	3 (0.8%)
Kidney diseases	3 (0.8%)
Endocrine disorders	10 (2.6%)
Previous COVID infection	
Present	44 (11.4%)

In total, 175 females (95.6%) and 188 males (92.6%) reported at least one adverse event, with 65 (35.5%) females and 84 (41.4%) males reporting AEFIs only after the first dose, and 2 (1.1%) females and 11 (5.4%) males reporting AEFIs only after the second dose. One hundred eight (59%) females and 93 (45.8%) males reported AEFIs with both doses. Eight females (4.4%) and 15 Males (7.4%) reported no adverse events. In terms of gender distribution of adverse events, more females report injection site pain, redness, swelling, fatigue, chills, headache, nausea, joint pain, flu-like symptoms, dizziness, and decreased appetite (all $P < 0.05$) as compared to males.

Individuals with a past history of COVID-19 reported lower levels of headache ($p = 0.045$, RR = 0.62) compared to people without a COVID-19 history.

After the first dose, individuals with diabetes reported fever lesser ($p = 0.049$, RR = 0.77) and muscle ache more ($p = 0.048$, RR = 1.99) as compared to healthy persons. After the second dose, injection site tenderness ($p = 0.043$, RR = 1.62) and joint pain ($p = 0.043$, RR = 2.86) reports were higher in the same group. Individuals with asthma reported fatigue ($p = 0.03$, RR = 2.27), chills ($p = 0.009$, RR = 2.72), malaise ($p = 0.043$, RR = 2.63), and muscle ache ($p = 0.042$, RR = 2.35) more than healthy individuals. Individuals with hypertension reported injection site swelling ($p = 0.023$, RR = 3.61) and chills ($p = 0.037$, RR = 3.2) more than healthy individuals.

Discussion

Our study aimed to collect the incidence of minor AEFIs following Covishield vaccine administration. No acute (anaphylactic) reactions were seen in any participant during the 30-min postimmunization observation period, and no delayed allergic or severe reaction was reported during follow-up calls. Most patients reported experiencing only mild

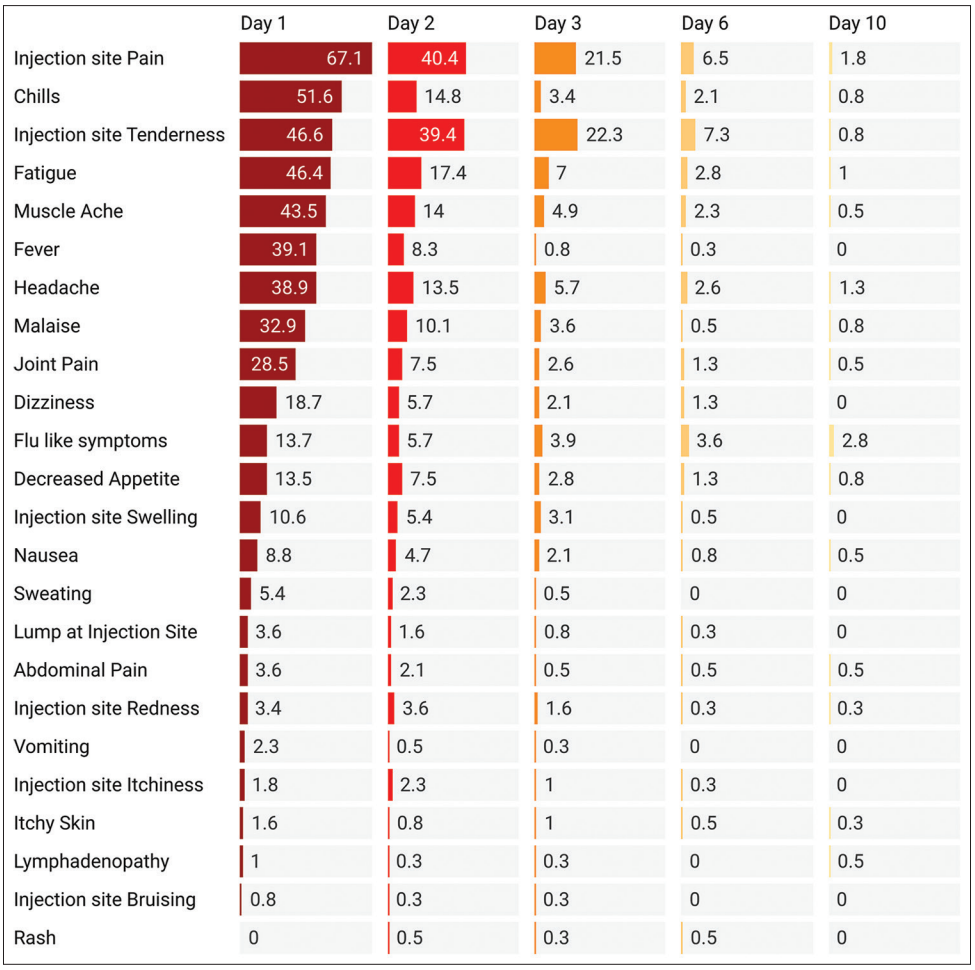

Figure 1: Incidence of adverse events after the first dose of covishield (in %)

symptoms that lasted up to Day 6 for the first dose and Day 3 for the second dose.

From the results, 94.04% of participants experienced adverse events at least once after either dose. Other studies have found similar incidences of adverse events.[6,7] The presence of adverse events has been found to indicate a functional immune system and the development of an immune response.[8]

All vaccine recipients had been instructed by the vaccination staff to take paracetamol in case of fever. During the process of the telephonic interview, participants reported the onset of fever in the evening of Day 0, following which most participants reported taking paracetamol. However, the usage of PCM and its effect on the AEFI profile was not within the objectives of the study, although it can be hypothesized that they reduced the severity and duration of AEFIs – however, no study has stated this effect for Covishield immunization. The fever reduced during the night and recurred the next morning. The product insert provided by SII quotes the Indian study findings as "Injection Site Pain – very common, along with Fever, Nausea, Myalgia, Malaise, Fatigue, Arthralgia, which are common".[9] This is in line with our findings in Table 2.

Females experienced certain adverse events more than males, namely, injection site pain, redness, swelling, fatigue, chills, headache, nausea, joint pain, flu-like symptoms, and dizziness. Younger individuals (ages 18–24) experienced more adverse events as compared to older individuals (age >40) [Supplementary Table 3]. This is consistent with the findings of Kim (2021)[6] and Bae (2021).[7] However, one study found no link between sex and AEFIs;[10] AEFIs had varying incidence rates across different studies and the factsheet provided by the SII. For example, in our sample, AEFIs such as dizziness and decreased appetite were reported in more than 10% of the participants (the SII information sheet shows it to be <1%).[6,9,10]

Headache was the only adverse event significantly lower in individuals with a history of COVID-19 infection prior to vaccination. Few prior investigations demonstrated no statistically significant link between previous COVID-19 infection and the occurrence of any AEFI.[11] Two studies, on the other hand, have linked previous COVID-19 infections to an increase in systemic and local AEFIs.[12,13] More testing with larger populations will be required to confirm these conclusions.

Our study showed a significant association between minor adverse events and comorbidities, with participants who

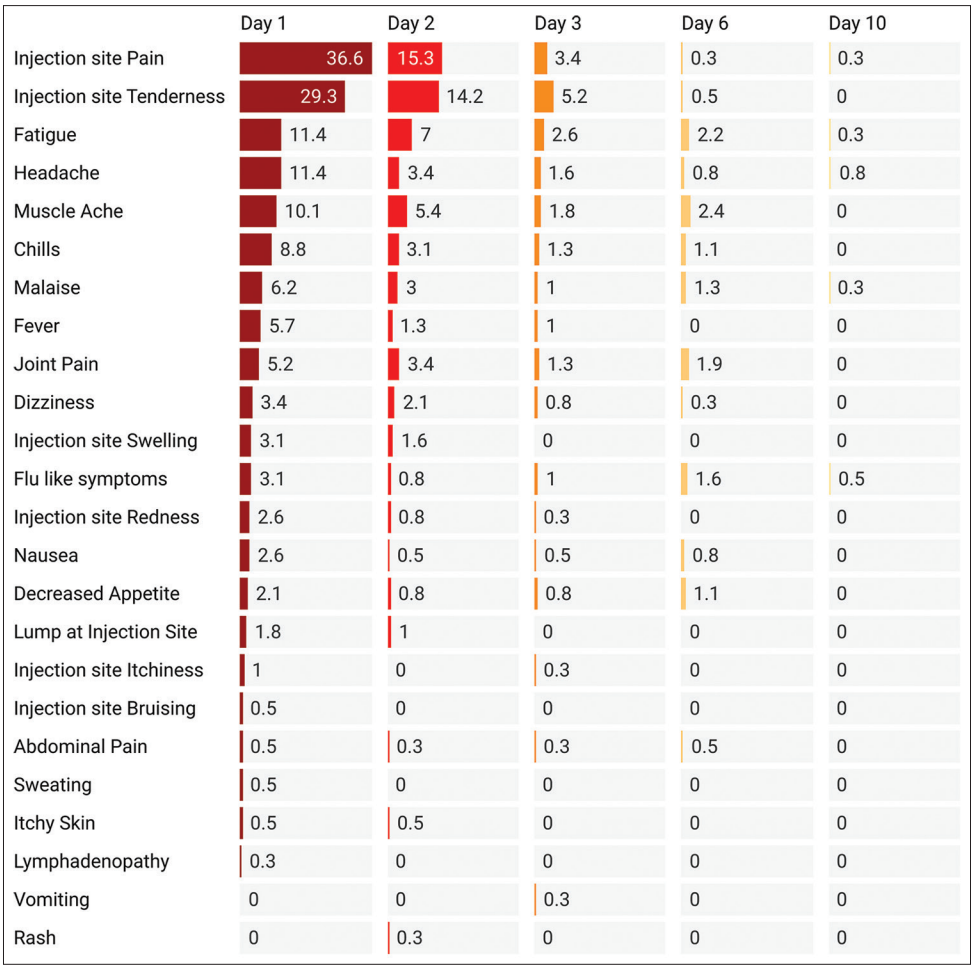

Figure 2: Incidence of adverse events after the second dose of covishield (in %)

Table 2: Symptom overlap in participants after the first and second doses (*n*=386)

Adverse events at the injection site	First dose no (%)	Second dose no (%)
Pain and chills	157 (40.7)	22 (5.7)
Pain and fatigue	140 (36.3)	29 (7.5)
Pain and fever	117 (30.3)	15 (3.9)
Pain and headache	118 (30.6)	26 (6.7)
Pain and joint ache	90 (23.3)	13 (3.4)
Pain and malaise	101 (26.2)	19 (4.9)
Pain and muscle ache	131 (33.9)	28 (7.3)
Pain and tenderness	139 (36)	76 (19.7)

had hypertension, asthma, and diabetes showing a different distribution of adverse events compared to participants with no comorbidities. After the first dose, diabetic individuals reported lesser fever and muscle ache more as compared to healthy persons. After the second dose, injection site tenderness and joint pain reports were higher in the same group. Asthmatic individuals reported fatigue, chills, malaise, and muscle ache more than healthy individuals. One study found that only individuals with asthma[14] to have an increased risk of the development of adverse events after the first dose as compared to a healthy individual, with other comorbidities having no significant association with an incidence of adverse events. Individuals with hypertension reported injection site swelling and chills more than healthy individuals. A study from the UK showed no significant association with comorbidities and the incidence of adverse events.[13] Due to the number of participants with these comorbidities being relatively low, to properly establish the trends across doses and comorbidities, further studies would be required.

Adverse events were reported to be fewer after the second dose as compared to the first dose [Figures 1 and 2]. For example, the incidence of injection site pain, which was the most commonly reported AE, decreased from 67.1 to 36.6% from the first to second dose, a marked decrease. Other adverse events followed a similar pattern, a trend reflected in Kim *et al.* (2021)[6] and Falsey *et al.* (2021).[15]

An interesting finding was dysgeusia and ageusia reported by 4.9% of participants. There is potential to investigate further into mechanisms of production of dysgeusia in some individuals. There were some reports of "heaviness" (2.8%) and tingling sensation in hands (2.3%). "Excessive sleepiness" (1.6%) was described as closer to "being drowsy," distinct from bodily

fatigue, and some patients had evanescent red boils on their bodies (1.3%). In total, 1.6% of participants reported a burning sensation in their eyes. "Acidity," burning sensation during micturition, and oral ulcers were reported by less than 1.5% of the participants. To the best of our knowledge, these AEFIs have not been mentioned in any other study.

Limitations

To begin with, the symptoms and adverse events reported were based on the participant's subjective perceptions; no objective scales were used, so extrapolating the severity of the symptoms is not possible – however, most participants described their discomfort as being highest on day 1 and almost nonexistent by day 3. Second, there is a risk of recollection bias for events happening between the 6th and 10th day. Furthermore, we did not account for the participants' use of antipyretic-analgesics, and its effects on the occurrence and severity of AEs cannot be determined. Since this study has been conducted at a single center, its results may not be generalizable to the population.

Acknowledgements

We would like to acknowledge the contributions of Ms. Nandini Naldiga, Ms. Riya Nandu, and Mr. Tanmay Gholap in data collection. We also appreciate the guidance of Dr. Deepika Sadawarte from the Department of Community Medicine and the cooperation by the Vaccination Centre staff.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Incidence of First Dose adverse events Day-wise Distribution (*n*=386) (figures in %)

Adverse Events after 1st Dose	Day 1	Day 2	Day 3	Day 6	Day 10
Injection site Pain	67.1	40.4	21.5	6.5	1.8
Chills	51.6	14.8	3.4	2.1	0.8
Injection site Tenderness	46.6	39.4	22.3	7.3	0.8
Fatigue	46.4	17.4	7	2.8	1
Muscle Ache	43.5	14	4.9	2.3	0.5
Fever	39.1	8.3	0.8	0.3	0
Headache	38.9	13.5	5.7	2.6	1.3
Malaise	32.9	10.1	3.6	0.5	0.8
Joint Pain	28.5	7.5	2.6	1.3	0.5
Dizziness	18.7	5.7	2.1	1.3	0
Flu like symptoms	13.7	5.7	3.9	3.6	2.8
Decreased Appetite	13.5	7.5	2.8	1.3	0.8
Injection site Swelling	10.6	5.4	3.1	0.5	0
Nausea	8.8	4.7	2.1	0.8	0.5
Sweating	5.4	2.3	0.5	0	0
Lump at Injection Site	3.6	1.6	0.8	0.3	0
Abdominal Pain	3.6	2.1	0.5	0.5	0.5
Injection site Redness	3.4	3.6	1.6	0.3	0.3
Vomiting	2.3	0.5	0.3	0	0
Injection site Itchiness	1.8	2.3	1	0.3	0
Itchy Skin	1.6	0.8	1	0.5	0.3
Lymphadenopathy	1	0.3	0.3	0	0.5
Injection site Bruising	0.8	0.3	0.3	0	0
Rash	0	0.5	0.3	0.5	0

Supplementary Table 2: Incidence of Second Dose adverse events Day-wise Distribution (*n*=386) (figures in %)

Adverse Events after 2nd Dose	Day 1	Day 2	Day 3	Day 6	Day 10
Injection site Pain	36.6	15.3	3.4	0.3	0.3
Injection site Tenderness	29.3	14.2	5.2	0.5	0
Fatigue	11.4	7	2.6	2.2	0.3
Headache	11.4	3.4	1.6	0.8	0.8
Muscle Ache	10.1	5.4	1.8	2.4	0
Chills	8.8	3.1	1.3	1.1	0
Malaise	6.2	3	1	1.3	0.3
Fever	5.7	1.3	1	0	0
Joint Pain	5.2	3.4	1.3	1.9	0
Dizziness	3.4	2.1	0.8	0.3	0
Injection site Swelling	3.1	1.6	0	0	0
Flu like symptoms	3.1	0.8	1	1.6	0.5
Injection site Redness	2.6	0.8	0.3	0	0
Nausea	2.6	0.5	0.5	0.8	0
Decreased Appetite	2.1	0.8	0.8	1.1	0
Lump at Injection Site	1.8	1	0	0	0
Injection site Itchiness	1	0	0.3	0	0
Injection site Bruising	0.5	0	0	0	0
Abdominal Pain	0.5	0.3	0.3	0.5	0
Sweating	0.5	0	0	0	0
Itchy Skin	0.5	0.5	0	0	0
Lymphadenopathy	0.3	0	0	0	0
Vomiting	0	0	0.3	0	0
Rash	0	0.3	0	0	0

Supplementary Table 3: Age division of symptoms

	Age Group				Total
	Young Adult (18-24)	Adult (25-40)	Middle Age (41-59)	Old Age (>60)	
AEFIs after First Dose					
Absent					
Count	8	15	8	5	36
% within Age Group	6.60%	10.00%	8.00%	33.30%	9.30%
Present					
Count	113	135	92	10	350
% within Age Group	93.40%	90.00%	92.00%	66.70%	90.70%
Total					
Count	121	150	100	15	386
% of Total	31.30%	38.90%	25.90%	3.90%	100.00%
AEFIs after Second Dose					
Absent					
Count	46	73	44	9	172
% within Age Group	38.00%	48.70%	44.00%	60.00%	44.60%
Present					
Count	75	77	56	6	214
% within Age Group	62.00%	51.30%	56.00%	40.00%	55.40%
Total					
Count	121	150	100	15	386
% of Total	31.30%	38.90%	25.90%	3.90%	100.00%