Adverse events following ChAdOx1 nCoV-19 Vaccine (COVISHIELD) amongst health care workers: A prospective observational study

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ABSTRACT

Background: During ongoing COVID-19 pandemic, researchers worked enormously to develop effective vaccines against COVID-19 infection. Two Indian-made vaccines [COVishield (ChAdOx1 nCoV-19) and Covaxin] were granted Emergency Use Authorization. India launched its COVID-19 vaccination drive starting with healthcare workers (HCW). Aim of the study was to evaluate adverse events following immunization (AEFI) amongst the HCW with two doses of Covishield vaccine. We also evaluated association of AEFI according to sex, profession and age groups.

Methods: A prospective observational study was conducted in a tertiary care COVID dedicated hospital of Southern India from 16 Jan - 15 Apr 2021. Nine hundred and eighty one HCW who received 2 doses (4 weeks apart) were enrolled. Active and passive surveillance was conducted after 48 hours, and at days 8,15, 22 and 28 for both doses. The rate of AEFI for each dose was determined. Incidence and association of AEFI with various demographic variables was determined.

Results: 1020 non-serious and two serious AEFI (altered sensorium) were reported within 48 hours of first dose. Two hundred and twenty non-serious AEFI were reported within 48 hours of second dose. No AEFI was reported after 15 days for both the doses. We found no association of AEFI with sex and profession (p >0.5). Significant association of AEFI was found with age (p <0.01) Conclusion: Short-term AEFI were predominantly observed in first 48 hours. Incidence decreased in subsequent weeks with no occurrence after 15 days in both doses. Symptoms were mild in severity and short-lived. No serious AEFI attributable to vaccines were reported.

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Introduction

SARS-Cov 2, the deadly virus that causes Coronavirus disease 19 (COVID-19) has rampantly spread over the globe. The pandemic has diseased millions of people with more than 3 million deaths over a period of the year to date. Researchers worked enormously to develop effective and safer vaccines against COVID-19 infection. Two Indian-made vaccines were granted Emergency Use Authorization. These were ChAdOx1 CoV-19 VACCINE - Covishield (developed by Oxford-AstraZeneca and manufactured by Serum Institute of India- SII) and Covaxin (manufactured by Bharat Biotech Limited).

India launched COVID-19 vaccination drive on 16 January 2021 with Covishield and Covaxin vaccines in phases. The aim was to vaccinate health care workers (HCW) followed by frontline workers in phase I. In phase II, People over 60 was to vaccinate health care workers (HCW) followed by frontline workers in phase I. In phase II, People over 60 and between 45 and 59 but who have other illnesses were targeted.

Covaxin includes inactivated Corona Virus. Covishield is prepared using the viral vector platform in which a chimpanzee adenovirus - ChAdOx1-is modified to enable it to carry the COVID-19 spike protein into the cells of humans. This inactivated virus is incapable of infecting the receiver but prepares the immune system to act against such viruses. Serum Institute of India released fact sheets mentioning “adverse events” of Covid-19 vaccines.

The aim of the study is to evaluate the occurrence of adverse events following immunization (AEFI) amongst HCW with two doses of Covishield. We also evaluated the association of AEFI according to various demographic variables (sex, profession and age groups).

Material and methods

Settings and design

Our study is a prospective observational study done from 16 Jan 2021 to 15 Apr 2021. The study was conducted in a tertiary care COVID dedicated hospital of Southern India. The minimal sample size required for the study was estimated to be 384, anticipating that 50% of study subjects will have AEFI with 5% level of significance and 5% absolute error margin at a 95% confidence interval. Ethical approval was obtained from the ethics and research committee of the hospital. Total 1007 HCW (doctors, nurses and paramedics) were vaccinated during the vaccination drive. The first dose was given from 16 Jan 2021 to 15 Feb 2021. The second dose was administered after four weeks of the first dose. Surveillance was conducted for AEFI of the two doses for four weeks.

Vaccination and eligibility

All health care workers received 02 doses, each containing 0.5 ml of Covishield vaccine intramuscularly 04 weeks apart. The recipients were provided written informed consent and a leaflet containing information about the vaccine, possible AEFI and medical care. The adverse events were cited from the WHO guidelines and information brochure, published by the manufacturer.

Inclusion criteria

Age >18 years, received two doses of vaccine.

Exclusion criteria

Age <18 years, not completed both doses of vaccine, recently hospitalized in last 14 days, past COVID-19 infections, pregnant and lactating women.

Out of total 1007 vaccine recipients, 26 participants either did not give consent/respond to phone calls. Finally, total of 981 recipients were enrolled in the study.

Surveillance system

A surveillance system was established, as per WHO guidelines. The AEFI is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease. Reported adverse events can either be ‘True’ (resulting from the vaccine or immunization process) or ‘Coincidental’ (not due to the vaccine or immunization process but are temporally associated with immunization). ‘Serious’ adverse events, as per WHO guidelines, were defined as events involving hospitalization, prolongation of existing hospitalization, life-threatening illness, or permanent disability or death. ‘Non-serious’ adverse events were defined as any event that is not serious and does not pose a potential risk to the health of the recipient. Staff interview topic guide was prepared and panel of 02 medical officers and 04 paramedics were trained for surveillance of AEFI. The team was well conversant with Non-serious and Serious adverse events.

Reporting of adverse effects

Active and passive surveillance of the adverse events were done. The recipients were observed for 04 weeks after each dose of vaccine for the development of any adverse events.

Active surveillance

All the recipients were enquired telephonically. The first inquiry for the AEFI was done after 48 h of vaccination. Subsequently, the weekly enquiry was made regarding the development of AEFI on days 8, 15, 22 and 28. If the physical examination was required, the recipient was called and evaluated for the adverse events. All the recipients who needed admission due to AEFI were mentioned separately.

Passive surveillance

At the time of vaccination, recipients were instructed to inform adverse events, if any, to the surveillance team. The leaflet included the emergency telephone numbers, in case, if required.
Statistical analysis

The outcome measures in this study included the rate of reported adverse events. Adverse events according to various demographic variables (sex, profession and age) were determined. Chi-square test and p-value was used to determine the association of non-serious AEFI with the demographic variables. Serious AEFI were negligible hence no association was determined for the same. All the results are calculated by using SPSS software version 25.

Results

The demographic profile of vaccine recipients is described in Graph 1.

AEFI after the first dose

A total of 1020 non-serious adverse events were reported within 48 h of the first dose of vaccination. Common adverse events included feeling unwell (N-186, 19%), headache (N-171, 17.4%), fever (N-123, 12.5%), fatigue (N-121, 12.3%) and muscle ache (N-110,11.2%). 123 non-serious AEFI were reported between 3 and 7 days (day 8). 66 non-serious AEFI were reported between 8 and 14 days (day15). No adverse events were reported in the last two weeks. Two serious adverse events (altered sensorium) were noted in the first 48 h of vaccination which can be considered negligible. No serious adverse events were reported after 48 h (Table 1).

Adverse events following immunization after the second dose

A total of 220 non-serious adverse events were reported within 48 h of the second dose of vaccination. Common adverse events included feeling unwell (N-50, 5.1%), headache (N-48, 4.9%), muscle ache (N-22, 2.2%), decreased appetite (N-22, 2.2%), and fever (N-19,1.9%). 68 non-serious AEFI were reported between 3 and 7 days (day 8). 61 non-serious AEFI were reported between 8 and 14 days (day15). No AEFI (non-serious/serious) were reported in last two weeks after the second dose (Table 2).

Adverse events and its association with various demographic variables

Adverse events (Non-serious and serious) according to sex, profession, and age groups is elaborated in Table 3. We found no association of AEFI with sex and profession (p > 0.5). Significant association of AEFI was found with age (p < 0.01), with the incidence of adverse events being higher in the older age group (>50 years).

Discussion

The majority of adverse events reported after the ChAdOx1 nCoV -19 vaccine (Covishield) were non-serious. Overall 57% recipients developed non-serious AEFI rate after the first dose of vaccination; the overall rate of serious adverse events reported was approximately 0.2%. The overall rate of non-
serious adverse events was approximately 14.1% after the second dose of vaccination. No serious adverse events were reported after the second dose of vaccination. This supports the findings of phase 1 and phase 2/3 trial of ChAdOx1 nCoV-19 vaccines wherein the majority of recipients reported non-serious AEFI.6,7,10

**Non-serious AEFI**

The majority of adverse events were noted within the first 48 h of vaccination after first and second doses. As seen in Graph 2 the rate of adverse events showed a declining trend after 48 h of vaccination. No AEFI were noted after two weeks (post day 15) of vaccination.

Similarly, declining trend was observed in one study where researchers found that 89% of recipients who have logged at least one systemic adverse event after vaccination did not report any systemic adverse event after 3 days and 98.3% did not report any after one week.11

In our study, overall, 57% of recipients reported at least one or more adverse events after the first dose. The adverse events were reported at much lower frequencies in comparison to the Phase 2/3 trial of the ChAdOx1 nCoV19 vaccine wherein 88% of participants (18–55 years) reported adverse events.19 However in another study 33.7% of recipients reported adverse events after the first dose of vaccine.15 Variation in the rate might be because we did active surveillance by enquiring repeatedly for AEFI. Hence, we could trace for adverse events for more period. However, in their study passive surveillance through the app was done for one week only.11

| Table 1 – Adverse events after first dose of vaccination. | Table 2 – Adverse events after second dose of vaccination. |
|----------------------------------------------------------|----------------------------------------------------------|
| **Non serious adverse effects (N = 981)** | | **Non serious adverse effects (N = 981)** |
| First 48 h (Day-3) | 3–7 days (Day-8) | 8–14 days (Day-15) | First 48 h (Day 3) | 3–7 days (Day 8) | 8–14 days (Day 15) |
| No. of cases | % | No. of cases | % | No. of cases | % | No. of cases | % | No. of cases | % |
| Feeling unwell | 186 | 19.0 | 9 | 0.9 | 7 | 0.7 | 186 | 19.0 | 9 | 0.9 | 7 | 0.7 |
| Headache | 171 | 17.4 | 4 | 0.4 | 6 | 0.6 | 171 | 17.4 | 4 | 0.4 | 6 | 0.6 |
| Fever | 123 | 12.5 | 3 | 0.3 | 2 | 0.2 | 123 | 12.5 | 3 | 0.3 | 2 | 0.2 |
| Fatigue | 121 | 12.3 | 12 | 1.2 | 7 | 0.7 | 121 | 12.3 | 12 | 1.2 | 7 | 0.7 |
| Muscle ache | 110 | 11.2 | 8 | 0.8 | 6 | 0.6 | 110 | 11.2 | 8 | 0.8 | 6 | 0.6 |
| Decreased appetite | 80 | 8.2 | 26 | 2.6 | 5 | 0.5 | 80 | 8.2 | 26 | 2.6 | 5 | 0.5 |
| Joint pain | 45 | 4.6 | 7 | 0.7 | 4 | 0.4 | 45 | 4.6 | 7 | 0.7 | 4 | 0.4 |
| Dizziness | 40 | 4.1 | 6 | 0.6 | 1 | 0.1 | 40 | 4.1 | 6 | 0.6 | 1 | 0.1 |
| Nausea | 27 | 2.8 | 3 | 0.3 | 3 | 0.3 | 27 | 2.8 | 3 | 0.3 | 3 | 0.3 |
| Lump/pain/redness over site | 27 | 2.8 | 9 | 0.9 | 3 | 0.3 | 27 | 2.8 | 9 | 0.9 | 3 | 0.3 |
| Enlarged lymph nodes | 18 | 1.8 | 0 | 0 | 0 | 0 | 18 | 1.8 | 0 | 0 | 0 | 0 |
| Chills | 14 | 1.4 | 5 | 0.5 | 4 | 0.4 | 14 | 1.4 | 5 | 0.5 | 4 | 0.4 |
| Itching | 11 | 1.1 | 9 | 0.9 | 5 | 0.5 | 11 | 1.1 | 9 | 0.9 | 5 | 0.5 |
| Abdominal pain | 11 | 1.1 | 0 | 0 | 0 | 0 | 11 | 1.1 | 0 | 0 | 0 | 0 |
| Vomiting | 6 | 0.6 | 4 | 0.4 | 9 | 0.9 | 6 | 0.6 | 4 | 0.4 | 9 | 0.9 |
| Sore throat | 5 | 0.5 | 3 | 0.3 | 1 | 0.1 | 5 | 0.5 | 3 | 0.3 | 1 | 0.1 |
| Running nose | 3 | 0.3 | 1 | 0.1 | 1 | 0.1 | 3 | 0.3 | 1 | 0.1 | 1 | 0.1 |
| Cough | 3 | 0.3 | 13 | 1.3 | 2 | 0.2 | 3 | 0.3 | 13 | 1.3 | 2 | 0.2 |
| Others | 19 | 1.9 | 1 | 0.1 | 0 | 0 | 19 | 1.9 | 1 | 0.1 | 0 | 0 |
| **Serious symptoms** | | | | | | | | | | | | |
| Altered sensorium | 2 | 0.2 | 0 | 0 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 |
| Weakness in limbs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Altered colored urine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |

We reported fewer adverse events after the second dose. Overall 14.1% recipients reported adverse events after the second dose. Findings are in line with the observations of phase 1 and phase 2/3 trials where the incidence of adverse events were fewer after booster doses.7,10

In our study, overall common adverse events included feeling unwell (20.6%), headache (18.4%), fever (13.04%), and fatigue (14.27%) after the first dose. The incidence of local adverse effects in our study was 3.9%. In one study, <30% of users complained of injection site pain and <25% of fatigue and headache after the first dose.15 According to SII tenderness, pain, warmth, redness, itching, swelling, or bruises where the injection is given, feeling unwell, fatigue, chills, or feeling feverish, headache, nausea, and joint pain or muscle ache are included in “very common” side effects affecting more than 1 in 10 people.3 However, lower incidence of local adverse events were observed in our study.

**Serious AEFI**

They were noted in the first 48 h after the first dose of vaccination. No adverse events were noted after the second dose of vaccination. We admitted and thoroughly evaluated both the cases of serious AEFI who reported with altered sensorium. One patient was a known case of primary hypertension with poor drug compliance and was diagnosed as hypertensive encephalopathy after complete evaluation. The second patient was a known case of diabetes mellitus on insulin.
evaluation hypoglycaemia was found to be the cause of altered sensorium. Hence, direct correlation of adverse events with vaccination could not be established and was ‘coincidental’ in both the patients.

**Association of adverse events with demographic variables**

One study mentions that side effects were significantly more prevalent in women than in men. We found no association of AEFI with sex. In the same study, it was reported that the vaccine was safe and well-tolerated with a lower reactogenicity profile in older adults than younger adults. In our study we found significant association of AEFI with age, however the incidence was higher in the age group of >50 years.

Differences in the incidence of adverse events with sex and age groups might be due to the type of study population (health care workers) and relatively smaller sample size.

**Strengths and limitations**

To the best of our knowledge, this study is the first of its kind to date where active surveillance was conducted and all the vaccine recipients were enquired about the adverse events on weekly basis. We could not find any similar published study in the public domain till the date of submission of data. We studied adverse events for four weeks from each dose. Hence, we could report all the possible adverse events with more precision. We conducted both active and passive surveillance that might have reduced the probability of dropout from the surveillance amongst the recipients. All the recipients received two doses of vaccines and we did surveillance for the occurrence of adverse events for both doses. The completeness of reporting was ensured as dedicated teams for surveillance were kept to ensure accurate and complete reporting of the adverse events. The authenticity and accuracy of reporting the adverse events were better as the study was conducted exclusively in health care workers who could assess or understand and precisely report the adverse events to the surveillance teams. Surveillance was done several times after each vaccination. This might have mitigated the probable underreporting of adverse events.

**Graph 2** — Adverse events following first and second dose of vaccination.
The limitation of the study is the relatively small sample size to assess serious/rare AEFI. The study was conducted only on health care workers. So reporting bias is the possibility as reporting of adverse events might be different from the general population. Also, some recipients might have reported symptoms more than others would have, as they were keenly assessing for adverse events. Results of the study might not be a true representation of the incidence of adverse events and bigger metacentric studies are required to generalize the results to the general population. Moreover, our results might have been affected by collider bias (i.e. when a risk factor and an outcome both affect the likelihood of being sampled). We did not include the data according to existing common medical conditions of recipients, hence could have altered the incidence of adverse events. Few adverse events could have been coincidental and not attributable to the vaccination directly as the period of surveillance was more. Also, we evaluated only short-term adverse effects, and long-term surveillance in the general population will be required to investigate possible future effects.

Conclusion

The short-term adverse events of both the doses were observed in the first 48 h predominantly. Incidence decreased in subsequent weeks with no occurrence after two weeks of both the doses. Symptoms were mild in severity and short-lived. No serious adverse events attributable to vaccines were reported. Our study showed that the vaccine was safe and well-tolerated with a lower reactogenicity profile.

Disclosure of competing interest

The authors have none to declare.

Acknowledgements

Niyakshi Shah.

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