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# Assessment of adverse events following first dose of COVISHIELD in healthcare workers of a tertiary care hospital in western Uttar Pradesh: A prospective observational study

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## ABSTRACT

**Background:** COVID-19 pandemic is a great health challenge around the world. Immunization appears best preventive strategy where monitoring the safety of COVID-19 vaccines is immensely important as limited safety data available on them. **Aims and Objectives:** This study was conducted to perform safety surveillance and causality assessment of adverse events following immunization (AEFI) with COVID-19 vaccine. **Materials and Methods:** This prospective observational study was conducted on healthcare workers who received their first dose of COVISHIELD during first phase of COVID-19 vaccination in January–February 2021 at F.H. Medical College and Hospital, Tundla, Firozabad. Approval for the study was taken from institutional ethical committee. The details of AEFIs were collected and duly noted in standard AEFI case reporting form of Ministry Of Health And Family Welfare, Immunization Division, Govt. of India and reported to District Immunization Officer. Causality assessment was done in accordance with protocol of the World Health Organization. **Results:** Out of 419 vaccinees, 210 had developed AEFIs, and 527 AEFIs were reported considering the fact that one recipient could have experienced multiple AEFIs. Majority AEFIs were related to general disorders and administration site conditions (67.35%), where fever (28.46%), chills (16.69%),and pain at injection site (15.75%) were more common, followed by musculoskeletal and connective tissue disorders (19.55%) where myalgia (18.03%) was more commonly reported. Out of 527 AEFIs reported, majority (524, 99.43%) showed consistent causal association to immunization and 3 (0.57%) AEFIs showed inconsistent association. AEFIs classified as consistent causal association (524) mostly were vaccine product related reactions (520, 99.23%) and rest (4, 0.76%) were immunization anxiety related reactions. Severity assessment of AEFIs was done using Modified Hartwig and Siegel Severity Scale, out of total 527 AEFIs reported 60.9% were of mild severity and rest 39.1% were categorized as moderate severity. **Conclusion:** As adverse events post-vaccination with COVISHIELD were mild to moderate in severity and lasted for a short duration, the inconvenience caused by these AEFIs outweigh the protection offered by the vaccination against COVID-19.

**Key words:** Adverse events; Assessment; Causality; COVID-19; Covishield; Immunization; Severity

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## INTRODUCTION

The prevalent illness of global concern, coronavirus disease -2019 (COVID 19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Clinically, the disease ranges from asymptomatic or mild cases with nonspecific symptoms such as sore throat, cough, fever, loss of taste

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and/or smell, headache, nasal congestion to severe cases of pneumonia requiring mechanical ventilation to multiorgan failure and death. Numerous therapeutic strategies such as repurposing of drugs and investigational drug research have been followed to deal with symptomatic cases; however, until now definitive remedy has not emerged yet.[2]

Implementation of transmission-mitigation strategies such as physical-distancing, wearing face mask, hand washing, and lockdown has slowed the transmission of the disease[1] but immunization of the population against COVID-19 is must to induce antibody formation that can neutralize SARS-CoV-2 and hence reduce serious complications and hospitalization.[3] Pharmaceutical companies worldwide have developed various vaccines and India plays an important role in COVID-19 vaccination as it is one of the biggest pharmaceutical manufacturers and second most populated country in the world.[4]

COVISHIELD is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein vaccine manufactured by serum institute of India.[4] In individuals 18 years of age and older use of COVISHIELD was approved for prevention of COVID-19 disease. The vaccination course consists of two separate doses of 0.5 ml each administered 3 months apart. Common adverse reactions related with the vaccine include injection site pain, swelling and redness, fever, chills, shivering, myalgia, arthralgia, lymphadenopathy, nausea, vomiting, diarrhea, headache, dizziness, and flu like symptoms.[4]

Until safe and effective vaccines become available and a global vaccination program is successfully implemented, the world will not return to its prepandemic normalcy. The traditional vaccine development timeline of many years (10–15 years) compressed to shorten development time (1–2 years) of outbreak paradigm has been proposed to meet the urgent need for a vaccine in a pandemic scenario.[3,5] Monitoring the safety of COVID-19 vaccines when administered to large population is important as there is limited safety data available. Therefore, a strong adverse event following immunization (AEFI) surveillance system is needed to monitor and understand the adverse events and safety profile of the vaccines. Determining the likelihood of a causal association between the event and the vaccine received is the critical part of AEFI monitoring which involves systematic review of data about the AEFI cases. Hence, this study was conducted to perform safety surveillance and causality assessment of AEFI in COVISHIELD vaccinees.

### Aims and objectives

The aim of the study was to perform safety surveillance and causality assessment of AEFI with COVID-19 vaccine.

## MATERIALS AND METHODS

This prospective observational study was conducted on healthcare workers who received their first dose of COVISHIELD vaccine during first phase of COVID-19 vaccination in January–February 2021 at F.H. Medical College and Hospital, Tundla, Firozabad. Study commenced after taking approval from institutional ethical committee (IEC/IRB No.2/2021).

All the healthcare workers of both the genders aged 18 years and above volunteering for COVID-19 vaccination and willing for follow up to 2 weeks were included in the study. While those who were not willing to participate in the study and those who did not develop any adverse event were excluded from the study. The names of vaccinees, their demographic details and contact numbers were collected and they were observed for a period of 30 min after vaccination for any AEFI that develops at session site. Thereafter for occurrence of any adverse event they were contacted through mobile phones and were followed regularly up to 2 weeks.

The details of AEFIs pertaining to the type of reactions, time and date of onset of reactions, recovery, outcome, and management of the reactions were collected and duly noted in standard AEFI case reporting form (CRF) of Ministry of health and family welfare, Immunization division, Govt. of India. All the AEFIs recorded in AEFI standard CRF were reported to District Immunization Officer.

Causality assessment was done in accordance with globally accepted causality assessment protocol of World Health Organization (WHO). For causality assessment a checklist is designed to assemble information on the patient-immunization-AEFI relationship in the following key areas - evidence for other causes, association of the event and the vaccine/vaccination with the vaccine product(s), immunization error or immunization anxiety, evidence against a causal association and other qualifying factors for classification such as previous history of a similar event, the background rate of the event, pre-existing, present and past health conditions, potential risk factors, other medications, and exposure to triggering factors.[6]

After completion of the checklist, records associated with the investigation were applied to the algorithm. The stepwise approach of the algorithm helps to classify the AEFI as consistent or inconsistent with an association to immunization, an indeterminate outcome or unclassifiable. The cause-specific definitions provide clarity on consistent causal association to immunization, inconsistent causal association to immunization (coincidental) and the association is considered indeterminate when adequate

information on the AEFI is available but it is not possible to assign it to either of the above categories.[6]

The data collected were entered into Excel sheets and then analyzed using Statistical Package for the Social Sciences software version 23. Age and gender distribution of the vaccinees, classifications of AEFIs, causality association, and severity assessment of AEFIs were expressed in percentages.

## RESULTS

Out of 419 healthcare workers who received first dose of COVISHIELD, 210 had developed AEFIs. Out of 210 vaccinees who developed and reported AEFIs number of males were 148 (70.5%) while females were 62 (29.5%). The age group ranged from 18 years to above 60 years. Mean age of the vaccinees was 33.90±10.64 years (Table 1).

527 AEFIs had been reported by 210vaccinees where it was considered that one recipient could have experienced multiple AEFIs. These AEFIs were classified using system organ classification. Most of the AEFIs were related to general disorders and administration site conditions (67.35 %), where fever (28.46%), chills (16.69%), and pain at injection site (15.75%) were most common followed by musculoskeletal and connective tissue disorders (19.55%) where myalgia (18.03%) was most commonly reported (Table 2).

The revised WHO classification (second edition) was used for assessment of causality of AEFI. Out of 527 AEFIs reported, majority (524, 99.43%) showed consistent causal association to immunization and 3 (0.57%) AEFIs showed inconsistent association (Table 3). Out of 524 AEFIs classified as consistent causal association, mostly were vaccine product related reactions (520, 99.24%) and rest (4, 0.76%) were immunization anxiety related reaction (Table 4).

In most of the vaccinees (72.86%), first adverse event was reported up to 12 h of vaccination whereas 5.71% of the vaccinees showed onset of first symptom within half an hour of observation period after vaccination (Table 5).

Severity assessment of AEFIs was done using Modified Hartwig and Siegel Severity Scale. Out of total 527 AEFIs reported, 60.9% were of mild severity and rest 39.1% were categorized as moderate severity (Table 6).

## DISCUSSION

Vaccination is an important measure for prevention of many infectious diseases including COVID-19 by

**Table 1: Age and gender distribution of study population**

| Age Group (Years) | Total (N=210) | Female (n=62, 29.5%) | | Male (n=148, 70.5%) | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| 18–44 years | 183 | 53 | 85.5 | 130 | 87.8 |
| 45–60 years | 19 | 7 | 11.3 | 12 | 8.1 |
| >60 years | 8 | 2 | 3.2 | 6 | 4.1 |

**Table 2: SOC for classifying AEFIs (n=527)**

| SOC | AEFI symptoms and/or signs | Number of AEFIs n(%) | Total n(%) |
|---|---|---|---|
| General disorders and administration site conditions | Fever | 150 (28.46) | 355 (67.35) |
| | Chills | 88 (16.69) | |
| | Pain at injection site | 83 (15.75) | |
| | Malaise | 20 (3.79) | |
| | Swelling at injection site | 07 (1.33) | |
| | Itching at injection site | 04 (0.76) | |
| | Fatigue | 02 (0.38) | |
| | Redness at injection site | 01 (0.19) | |
| Connective tissue and musculoskeletal disorders | Myalgia | 95 (18.03) | 103 (19.55) |
| | Arthralgia | 06 (1.14) | |
| | Backache | 02 (0.38) | |
| Nervous system disorders | Headache | 44 (8.35) | 47 (8.92) |
| | Dizziness | 03 (0.57) | |
| Gastrointestinal disorders | Nausea | 05 (0.95) | 12 (2.28) |
| | Vomiting | 04 (0.76) | |
| | Loss of appetite | 01 (0.19) | |
| | Loss of taste | 01 (0.19) | |
| | Diarrhea | 01 (0.19) | |
| Respiratory, thoracic, and mediastinal disorders | Cough | 02 (0.38) | 05 (0.95) |
| | Throat pain | 01 (0.19) | |
| | Breathlessness | 01 (0.19) | |
| | Flu like symptoms | 01 (0.19) | |
| Psychiatric disorders | Anxiety | 04 (0.76) | 05 (0.95) |
| | Insomnia | 01 (0.19) | |

SOC: System organ classification, AEFI: Adverse events following immunization

**Table 3: Causality assessment of adverse event following immunization**

| S.No. | Causality Classification | Number of AEFIs (n=527) | Percentage |
|---|---|---|---|
| 1. | Consistent causal association to immunization | 524 | 99.43 |
| 2. | Inconsistent causal association to immunization | 3 | 0.57 |
| 3. | Indeterminate | Nil | Nil |
| 4. | Unclassifiable | Nil | Nil |

AEFI: Adverse events following immunization

**Table 4: Consistent causal association of adverse event following immunization**

| S.No. | Consistent causal association to immunization | Number of AEFIs (n=524) | Percentage |
|---|---|---|---|
| 1. | Vaccine product related reaction | 520 | 99.24 |
| 2. | Vaccine quality defect reaction | Nil | Nil |
| 3. | Immunization error related reaction | Nil | Nil |
| 4. | Immunization anxiety related reaction | 4 | 0.76 |

AEFI: Adverse events following immunization

**Table 5: Time taken for onset of first adverse event following immunization**

| S. No. | Time taken | Number of Vaccinees (n=210) | Percentage |
|---|---|---|---|
| 1. | Within half an hour | 12 | 5.71 |
| 2. | Half an hour–12 h | 153 | 72.86 |
| 3. | 12–24 h | 43 | 20.48 |
| 4. | >24 h | 2 | 0.95 |

**Table 6: Severity assessment of AEFIs**

| S.No. | Severity (Modified Hartwig and Siegel Severity Scale) | Number of AEFIs (n=527) | Percentage (%) |
|---|---|---|---|
| 1. | Mild (Levels 1 and 2) | 321 | 60.9 |
| 2. | Moderate (Levels 3 and 4) | 206 | 39.1 |
| 3. | Severe (Levels 5,6, and 7) | Nil | Nil |

AEFI: Adverse events following immunization

strengthening immune system of the vaccinated person. Safety and efficacy of vaccines are important factors as they are administered to millions of people, any sort of safety issue with the vaccine can prove to be a hindrance in the path of successful vaccination. Hence, it is important to evaluate every stage of vaccine development especially the post marketing phase.[4]

In the present study, out of 419 vaccinees who received first dose of COVISHIELD, total 527 AEFIs were reported by 210 (50.11%) vaccinees. Most of the AEFIs were related to general disorders and administration site conditions (67.35 %), where fever (28.46%), chills (16.69%),and pain at injection site (15.75 %) were more common followed by musculoskeletal and connective tissue disorders (19.55%) where myalgia (18.03%) was most commonly reported. Out of 527 AEFIs reported, majority (524, 99.43%) showed consistent causal association to immunization and 3 (0.57%) AEFIs showed inconsistent association. AEFIs classified as consistent causal association (524) mostly were vaccine product related reactions (520, 99.23%) and rest (4, 0.76%) were immunization anxiety related reactions. Severity assessment of AEFIs concluded that 60.9% were of mild severity and rest 39.1% were categorized as moderate severity.

Similar findings were reported by Goldlin et al.,[4] where 31.9% vaccinees who received their first dose of COVISHIELD developed AEFI. The most frequently reported adverse reactions were fever (32.64%), myalgia (31.36%), injection site pain (13.6%), and headache (6.56%). The majority of AEFIs belonged to the general disorders and administration site conditions (53.92%) and musculoskeletal and connective tissue disorders (31.84%). Around 98.88% AEFIs were classified as a vaccine product - related reaction and 1.12% as immunization anxiety - related reaction/stress - related response. Regarding the severity, 83.52% of AEFIs were mild and 16.32% were moderate. Jha et al.,[7] in their pharmacovigilance study on COVISHIELD concluded that fever, chills, headache, myalgia, diarrhea, vomiting, flu such as symptoms and malaise were the most commonly reported AEFI, which had probable causal association with vaccination.

Kumar et al.,[8] in their AEFI monitoring study on COVISHIELD in primary healthcare workers observed that there were 97.3% of solicited reactions and 2.7% of unsolicited reactions. Pain and swelling at injection site, mild fever, chills, rigors, headache, myalgia, arthralgia, nausea, vomiting, and influenza such as illness were solicited reactions with duration of symptoms generally 2–3 days. In the unsolicited reactions moderate to high grade fever, decreased appetite and dizziness were observed. Deb et al.,[9] in their study on ADR profile of the COVISHIELD vaccine among healthcare workers observed that out of 1261 beneficiaries vaccinated, 69 ADRs were reported in 24 healthcare workers. The most common ADR reported was fever (25%) followed by myalgia (19%), 84% ADR were classified as probable as per WHO-UMC scale. John et al.,[10] conducted a study to observe adverse drug reactions following vaccination with COVISHIELD in healthcare workers, the most commonly reported local adverse effects were injection site pain, local redness, rashes, and swelling over injection site while common systemic adverse effects reported were fever, headache, fatigue, arthralgia, myalgia, and chills. Similar findings were observed in the present study and AEFIs reported had consistent causal association with vaccination.

The COVID-19 pandemic is a global crisis with enormous loss to human race and vaccines are the most important long-term tool to stem the pandemic. Alongside making available vaccine for all and promoting mass vaccination drive globally preparations must be made within countries

for COVID-19 vaccine safety surveillance to investigate AEFI to evaluate risk benefit ratio of vaccination and overcome fear and anxiety related to COVID-19 vaccines.[11]

### Limitations of the study

Limitation of the present study is small sample size and restriction of the study to healthcare workers only, widespread study on larger diverse population will draw better conclusion.

## CONCLUSION

In the present study, majority of AEFI reported post-vaccination with COVISHIELD were mild to moderate in severity and none of the AEFIs were severe. These results prove that COVISHIELD is safe and the protection offered by vaccination against the deadly disease outweighs the AEFIs caused by the vaccine. Hence, COVID-19 vaccination is an important tool to break the pandemic chain.

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**Author's Contributions:**
**SS**- Concept and design of the study, manuscript preparation and revision, data collection, statistical analysis; **SJ**- Data collection, data analysis and statistical analysis, manuscript revision; **BHK** - Data collection, data analysis and statistical analysis; **VG**- Manuscript preparation, manuscript revision, and data collection; **MB**- Data collection

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