

A Pharmacovigilance Study of Covishield in a Tertiary Care Teaching Hospital in Tamil Nadu

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Abstract

Objective: To study the adverse events following immunization (AEFI) with Covishield, a coronavirus disease– 2019 (COVID-19) vaccine. **Materials and Methods:** A prospective observational study was conducted among 422 Covishield vaccinees based on the inclusion and exclusion criteria after the institutional ethics committee approval. They were followed up at the end of 1 and 2 weeks following the first dose of Covishield vaccine, and the details of adverse events were collected. AEFIs were classified using system organ classification, World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment, AEFI causality assessment, and Modified Hartwig Severity Scale. Various classifications of AEFI were analyzed using descriptive statistics. ANOVA and independent *t*-test were used for age group and gender comparison of the duration and number of AEFI, respectively. **Results:** Around 625 AEFIs were reported by 422 vaccinees. Majority of the vaccinees (62.8%) developed adverse events on the day of vaccination. The mean duration of AEFI was 2.52 ± 0.871 days. On WHO-UMC causality assessment, 98.08% were found to be probable, 1.12% possible, and 0.8% unclassifiable. AEFI causality assessment revealed 98.88% vaccine product-related reactions and 1.12% anxiety-related reactions. Regarding the severity, 83.52% of AEFIs were mild and 16.32% were moderate. On comparison of mean duration of AEFI ($P = 0.298$) and mean number of AEFI ($P = 0.569$) between different age groups, no statistical significance was observed. **Conclusion:** The majority of AEFIs reported in this study were mild to moderate in severity for a short duration. The protection offered against the deadly disease and its complication potentially outweighs the mild AEFIs or inconvenience caused by them. Hence, covid-19 vaccination is an important tool to break the pandemic chain.

Keywords: Adverse event following immunization, covid-19 vaccine, pandemic, vaccinees

INTRODUCTION

The worldwide coronavirus disease– 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented freakish health challenges for nations around the world. Some parts of the world are confronting spikes in COVID-19 cases, while other parts are experiencing a lull after the surge. Since humans have little or no immunity against a new virus, this novel disease has knocked around millions of people in the world. Hence, various countries around the world have designed a series of preventive measures, including wearing a face mask, hand washing, maintaining social distance apart from the national and regional curfew to slow down the transmission rate. These lockdowns were designed to buy some time for an effective vaccine or medicine to be developed.^[1]

Several medicines were repurposed for use in prophylaxis and the management of COVID-19, despite which the mortality

and morbidity continued to climb up. Hence, the prevention of the deadly disease is the best way. Several vaccines were developed throughout the world that can help the population to immunize against COVID-19. India has an important role in the COVID-19 vaccination as it is the second-largest populated country with one of the biggest pharmaceutical manufacturing capacities.^[2]

Covishield is a recombinant replication-deficient chimpanzee adenovirus carrying a gene encoding the S protein antigen of

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SARS-CoV-2 manufactured by Serum Institute of India. It is one of the vaccines approved for use in an emergency situation that may prevent COVID-19 disease in individuals 18 years of age and older. The vaccination course consists of two separate doses of 0.5 ml each administered 4–12 weeks apart.^[3] In India, Covishield vaccination was initiated on January 16, 2021, initially for restricted use among health care workers and frontline workers, followed by general public use, including mass vaccine campaigns.^[4]

Adverse effects have been reported with the Covishield vaccine, earlier in clinical trials. These include injection site reactions, generally feeling unwell, fatigue, chills or feeling feverish, fever, headache, nausea, vomiting, joint pain or muscle ache, flu-like symptoms, feeling dizzy, decreased appetite, abdominal pain, lymphadenopathy, excessive sweating, itchy skin, or rash.^[3,5]

Normal vaccine development usually takes 10–15 years.^[6] The unprecedented rapid development of the COVID-19 vaccines followed by its rapid utilization on a mass scale warrants safety monitoring. The limited data available from the preclinical and first three phases of clinical trials make it essential to monitor the adverse effects in the postmarketing phase. Timely detection and reporting of adverse events following COVID-19 vaccination is the first step in ensuring the continued safety of the vaccine, immunization safety surveillance, and response. Hence, this study aimed to determine the incidence, type, duration, seriousness, and outcome of the adverse events in Covishield vaccinees.

MATERIALS AND METHODS

After obtaining institutional ethics committee approval, this study was done as a prospective observational study among those who received their first dose of Covishield vaccine in Tirunelveli Medical College and Hospital during January and February 2021.

Data collection

The names of vaccinees with their contact numbers were collected from the vaccination site on a daily basis. They were observed in the vaccination site for half an hour before sending them home and then contacted through mobile phones for the occurrence of any adverse event.

Vaccinees of either gender aged 18 years and above who developed an adverse event and were willing for 2 weeks follow-up were included in this study. Those who did not develop the adverse event and were not willing for follow-up were excluded. After enrolment, the vaccinees were followed up at the end of 1st and 2nd weeks after vaccination for monitoring adverse events following immunization (AEFIs). The details of AEFIs pertaining to the onset date, recovery date, outcome, management of the reaction were collected.

The AEFIs were classified based on system organ classification, Modified Hartwig-Siegel Severity Scale, and causality assessment scales by two separate pharmacologists. Causality

assessment was made by World Health Organization-Uppsala Monitoring Centre (WHO-UMC) and AEFI causality assessment scales. The pharmacovigilance coordinator of the institute checked the consistency of the assessment results and sorted out the discrepancy if any.^[7-9]

The system organ classification of AEFIs was based on the Medical Dictionary for Regulatory Activities terms and the summary of the product characteristics released by the manufacturer.^[3] The WHO-UMC system of causality assessment was employed to categorize the causality levels as certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable, taking into account the clinical-pharmacological aspects of the case history and the quality of documentation of observation.^[8] The other scale employed in this study was the AEFI causality assessment scale. It is vital for AEFI risk assessment, decision-making, and the initiation of action. This scale includes vaccine product-related, vaccine quality-defect-related, immunization error-related, immunization anxiety/stress-related, and coincidental reactions.^[9]

The data collected were entered into excel and then analyzed using Statistical Package for Social Sciences (SPSS) software version 23 (IBM Corp., Armonk, NY, USA) for Windows. Age and gender distribution of the vaccinees and various classifications of AEFI were analyzed using descriptive statistics and expressed in percentages. The number and duration of AEFIs were expressed in mean $\pm$ standard deviation. Comparison of the mean of number and duration of AEFIs between different age groups and gender were analyzed using ANOVA and independent *t*-test, respectively.

RESULTS

Out of 1323 vaccinees (676 males and 647 females), 422 (31.9%) had developed adverse events.

Age and gender distribution

Among the 422 vaccinees who had experienced an AEFI, 213 were male with a mean age of 32.24 ± 14.337 , and 209 were female with a mean age of 29.95 ± 11.427 and a $P = 0.070$. The age and gender distribution of the study population is mentioned in [Table 1].

This study observed 625 AEFIs considering the fact that one recipient could have experienced multiple AEFIs. Among the vaccinees, 272 (64.45%) suffered from single AEFIs, 112 (26.54%) suffered from two AEFIs, 26 (6.16%) had suffered from three AEFI, and 12 (2.84%) from four AEFIs.

Time taken for onset and duration of adverse event following immunization

Regarding the onset of AEFI, 265 (62.8%) vaccinees had developed AEFI on the day of vaccination, 136 (32.2%) on the 1st day, 12 (2.8%) on the 2nd day, 3 (0.7%) on the 3rd day, one (0.2%) on the 4th day, 5 (1.2%) on the 5th day following vaccination. All the vaccinees recovered from the

event(s), and the mean duration of AEFI was found to be 2.52 ± 0.871 days.

Classification of adverse events following immunization

The adverse events were classified using system organ classification and the details are outlined in [Table 2]. The severity of the adverse events was assessed using Modified Hartwig Siegel Severity scale as represented in [Table 3]. Only two vaccinees required hospitalization for the AEFI, one being an anxiety attack with palpitation and hyperventilation in intensive medical care unit, and another being fever and vomiting.

The details of the World Health Organization-Uppsala Monitoring Centre causality assessment are illustrated in [Figure 1]. AEFI Causality assessment revealed 619 (98.88%) vaccine product-related reactions and 7 (1.12%) anxiety-related reactions ($n = 625$).

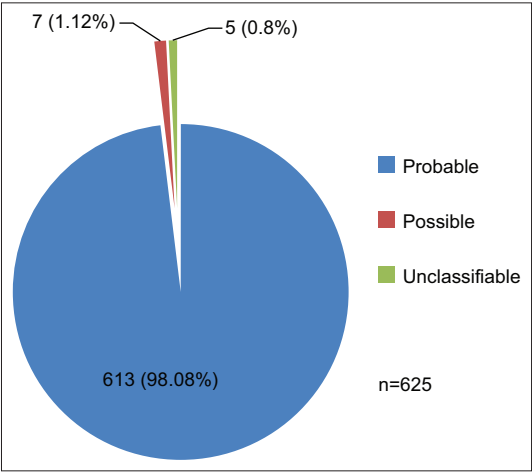


Figure 1: World Health Organization-Uppsala Monitoring Centre causality assessment of the adverse events following immunization

Age and gender comparison of adverse event following immunization

The analysis of variance was carried out to test the homogeneity of the number of AEFIs and three different age groups. The means plot revealed that the number of AEFIs were minimum with >60 years age group. The calculated $F = 0.564$ and $P = 0.569$ [Figure 2a].

The analysis of variance was carried out to test the homogeneity of the mean duration of AEFI and three different age groups. The means plot observed a peak in the duration of AEFI in the 30–59 years age group. The calculated $F = 1.216$ and $P = 0.298$ [Figure 2b].

Gender and adverse event following immunization

The mean number of AEFIs experienced by males was $1.49 (\pm 0.744)$, and for females, it was $1.46 (\pm 0.733)$, with $P = 0.688$. The mean duration of AEFI was $2.53 (\pm 0.899)$ days among females and $2.51 (\pm 0.845)$ days among males, with $P = 0.864$. No statistically significant difference was observed between males and females in this study with regards to the number of AEFIs experienced ($P = 0.688$) and the duration of AEFI ($P = 0.864$) ($n = 422$, data expressed as mean $\pm$ standard deviation).

Table 1: Age and gender distribution of the study population			
Age group (years)	Gender		Total ($n=422$), n (%)
	Male	Female	
<30	121	118	239 (56.6)
30-59	86	83	169 (39.8)
>60	2	12	14 (3.6)
Total	209	213	422

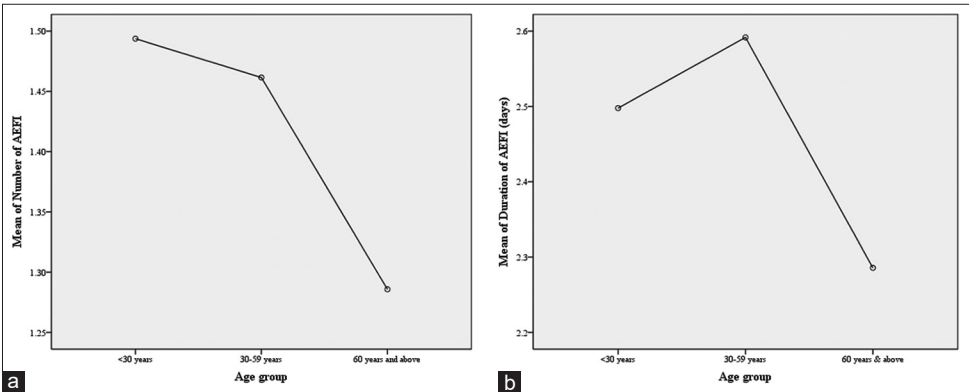


Figure 2: (a) Means plot of comparison of mean number of adverse events following immunization among different age groups. The mean number of adverse events following immunization among the vaccinees aged <30 years was 1.49 ± 0.761 , 30–59 years was 1.46 ± 0.724 and ≥ 60 years was 1.29 ± 0.469 . On comparison of mean number of adverse events following immunization between three different age groups $F = 0.564$ and $P = 0.569$. ($n = 422$, data expressed as mean $\pm$ standard deviation). (b) Means plot of comparison of mean duration of adverse events following immunization among different age groups. The mean duration of adverse event following immunization (in days) among vaccinees aged <30 years was 2.50 ± 0.761 , 30–59 years was 2.59 ± 1.020 , and ≥ 60 years was 2.29 ± 0.726 . On comparison of mean duration of adverse event following immunization between three different age groups $F = 1.216$ and $P = 0.298$. ($n = 422$, data expressed as mean $\pm$ standard deviation)

Discussion

COVID-19 has created the current scenario the public health community had feared for decades, and almost all the countries are fighting hard against this deadly disease with a need of potent weapon. World nations leveraged well-established scientific relationships to facilitate the expeditious development of vaccines and the treatment.

Vaccination plays a major role in the prevention of many dangerous infectious diseases in a simple and effective way. Despite the rush to develop vaccines to combat COVID-19 in this turbulent time, the safety and efficacy of the vaccines are important as they are to be deployed to millions of people. Any sort of safety issue of the vaccine will shake the confidence and tumble the overall prospect of successful immunization apart from precipitating anxiety. Hence, it is pivotal to evaluate the vaccine at every stage of development, especially at the postmarketing stage.^[10]

Like any vaccine, COVID-19 vaccines can cause adverse effects, most of which are mild to moderate and have lasted no longer than a few days on their own. As shown in the results of clinical trials, more serious or long-lasting side effects are also possible, and hence, the vaccines are continuously monitored to detect adverse events.

This study showed that 31.9% vaccinees who received their first shot of Covishield had experienced AEFI. Vaccines are designed to mimic a natural infection, and hence, experiencing adverse effects after vaccination means the vaccine is working and the immune system is responding as it should.

Among the 422 vaccinees who experienced AEFI, 213 (50.5%) were male, and 209 (49.5%) were female. Around 56.6% of them were adults below 30 years, 39.8% belonged to the age group of 30–59 years, and a meager 3.6% were 60 years and above [Table 1].

The most frequently reported adverse reactions were fever (32.64%), myalgia (31.36%), injection site pain (13.6%), and headache (6.56%). One or two AEFIs of blepharospasm, menstrual disturbances, hypoglycemia, oral ulcer, pruritis, rash, ecchymosis, hair fall, supraclavicular lymphadenopathy and increased appetite were also reported in this study. Among them, evidence of Covishield-related hair fall, menstrual disturbances, hypoglycemia, increased appetite, dysphagia, and oral ulcer was lacking. These may or may not be related to vaccination [Table 2].

Based on system organ classification, the majority of AEFIs belonged to the general disorders and administration site conditions (53.92%) and musculoskeletal and connective tissue disorders (31.84%). This study also had adverse events reported in the cardiac, eye, reproductive and metabolic systems with no evidence in the literature released by the manufacturer [Table 2].

Administering a COVID-19 vaccine, could cause effects similar to the disease but in a milder form. Many theories have

Table 2: System organ classification (n=625)

System organ classification	Type of AEFI	Number of AEFIs, n (%)	Total, n (%)
General disorders and administration site conditions	Fever	204 (32.64)	337 (53.92)
	Chills	18 (2.88)	
	Fatigue	20 (3.2)	
	Malaise	8 (1.28)	
	Injection site pain	85 (13.6)	
	Injection site swelling	2 (0.32)	
Musculoskeletal and connective tissue	Myalgia	196 (31.36)	199 (31.84)
	Cramps	2 (0.32)	
	Small joint arthralgia	1 (0.16)	
Nervous system	Headache	41 (6.56)	43 (6.88)
	Fainting	1 (0.16)	
	Giddiness	1 (0.16)	
Gastrointestinal	Nausea	4 (0.64)	16 (2.56)
	Vomiting	4 (0.64)	
	Diarrhea	5 (0.8)	
	Dysphagia	1 (0.16)	
	Oral ulcer	1 (0.16)	
Skin and subcutaneous tissue	Pruritis	1 (0.16)	4 (0.64)
	Rash	1 (0.16)	
	Ecchymosis	1 (0.16)	
	Hair fall	1 (0.16)	
Respiratory, thoracic and mediastinal	Cough	2 (0.32)	17 (2.72)
	URI	7 (1.12)	
	Sore throat	7 (1.12)	
	Nasal congestion	1 (0.16)	
Metabolism and nutrition	Hypoglycemia	1 (0.16)	3 (0.48)
	Increased appetite	2 (0.32)	
Cardiac	Palpitation	2 (0.32)	2 (0.32)
Blood and lymphatic system	Supraclavicular lymphadenopathy	1 (0.16)	1 (0.16)
Eye	Blepharospasm	1 (0.16)	1 (0.16)
Reproductive system and breast	Menstrual disturbances	1 (0.16)	1 (0.16)
Psychiatry	Anxiety attack	1 (0.16)	1 (0.16)

AEFI=Adverse event following immunization, URI=Upper respiratory infection

Table 3: Classification of Adverse events following immunization based on Modified Hartwig-Siegel Severity Scale (n=625)

Modified Hartwig-Siegel Severity Scale	Number of AEFIs, n (%)
Mild (level 1 and 2)	522 (83.52)
Moderate (level 3 and 4)	102 (16.32)
Severe (level 5, 6 and 7)	1 (0.16)

AEFI=Adverse events following immunization

been suggested in the pathogenesis of these effects. The general disorders, musculoskeletal and connective tissue disorders

could be directly linked to the mass production of immune signaling molecules/cytokines triggered by the vaccine.^[11] The intramuscular injection and local reaction might attribute to the administration site conditions.

Dysphagia had been reported only in patients with severe COVID-19 disease. Hence, the nonserious event dysphagia reported in this study could be an anxiety reaction.^[12] Aphthous ulcers are believed to be a neutrophil attack to the oral mucosa triggered by the cytokine storm, especially tumor necrosis factor alfa.^[13]

The pauci-inflammatory thrombogenic vasculopathy with the deposition of complement components C5b-9 and C4d within the cutaneous microvasculature plays a role in the pathogenesis for petechial/purpuric skin lesions.^[14]

Enlargement of ipsilateral axillary or supraclavicular lymph nodes following vaccination often results from the normal reaction that typically goes away with time.^[15]

Blepharospasm and menstrual disturbances could be linked with anxiety or stress associated with a novel vaccine rather than the vaccine product as such.^[16,17] Recently, menstrual disturbances have been reported increasingly with covid-19 vaccines, even though a causal relationship is not established.^[17,18] Evidence of decreased appetite has been documented in the literature, in contrast with increased appetite reported in this study.

The majority of adverse events were mild to moderate in severity according to Modified Hartwig-Siegel Scale and usually [Table 3] resolved within a few days of vaccination with a mean duration of 2.52 ± 0.871 days. By day 7, after the vaccination, only three vaccinees were suffering from mild to moderate AEFI. These findings were in accordance with the summary of product characteristics released by the manufacturer.^[3]

Causality assessment refers to the systematic review of data about an AEFI case, which determines the likelihood of a causal association between the event and the vaccine. WHO-UMC scale and AEFI causality assessment scale are the two generally used for this purpose. According to the WHO-UMC causality assessment scale, 98.08% AEFIs were classified as probable/likely, 1.12% as possible, and 0.8% as unclassifiable [Figure 1]. In this study, around 98.88% AEFIs were classified as a vaccine product-related reaction that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product and 1.12% as immunization anxiety-related reaction/stress-related response. The anxiety/stress-related responses include palpitation, anxiety attack, hair fall, dysphagia, blepharospasm, and menstrual disturbances.

While comparing the number of AEFIs and the duration of the event between different age groups, those who were 60 years and above experienced less number of AEFIs for a shorter duration, as shown in the means plot [Figure 2a and b]. Even though it was not statistically significant, the manufacturer too claimed that elderly individuals experienced milder and less

frequent adverse events.^[3] No statistically significant difference was observed between male and female vaccinees in this study, whereas a study in United Kingdom reported more side effects in the women and younger individuals.^[19]

The strength of this study is the prospective design of the study and the active surveillance method used for the data collection. The AEFI monitoring limited to the first dose of Covishield is the limitation of this study.

CONCLUSION

This study observed that there was a preponderance of mild to moderate AEFIs for a brief duration among the 422 vaccinees who had experienced AEFIs. Only one severe AEFI was reported. Even though misinformation and misconception about COVID-19 vaccines had spread like wildfire, this study concludes that the Covishield vaccine is safe based on the results, and getting vaccinated will help to break the COVID-9 chain.

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Conflicts of interest

There are no conflicts of interest.

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