

Covishield India: Demystifying Myths Through an Early Multicenter Safety Study

Sourya Sourabh Mohakuda, MD; Ankur Nigam, MD; K. Rajesh, MBBS; V. K. Sashindran, MD; Himanshu Sharma, MD; Bhupender Singh, MD; Ramanjot Kaur, BSc; and Mamta Thawal, BSc

COVID-19, caused by SARS-CoV-2, was declared a pandemic on March 11, 2020, by the World Health Organization.¹ The pandemic not only inflicted mortality and morbidity across the human race but also crippled the economies of the nations affected by it. Research about the disease worldwide gradually threw light on the effective management of cases with steroids and other investigational therapies. Owing to the virus' high infectivity, social distancing and masks are being advocated to curb its spread. The imperative to rein in this disease has encouraged vaccine research worldwide. Although vaccine development normally takes years due to its stringent administrative requirements, technological checks, and trial protocols, the numerous second and third peaks of COVID-19 across nations have made the world realize the need for a quick and effective vaccine. This has accelerated the process of trials and approvals for the early availability of a vaccine. Currently, more than 250 vaccines against SARS-CoV-2 are in development worldwide, including mRNA vaccines, replicating or nonreplicating viral-vectored vaccines, DNA vaccines, autologous dendritic cell-based vaccines, and inactivated-virus vaccines.²

The first COVID-19 vaccine approved was CoronaVac, developed by SinoVac Biotech Ltd by China's Central Military Commission for use by the Chinese military and the medical staff in late August 2020. The first vaccination drive to be launched across an entire nation began in Russia in December 2020, using the vaccine Gam-COVID-Vac, trade named Sputnik V and developed by Gamaleya Research Institute by the Russian Ministry of Health.³ This was followed by vaccination drives in other countries like the United States and United Kingdom using vaccines developed by Pfizer/BioNTech, Moderna, and Johnson & Johnson.

Owing to the urgent need, 2 COVID-19 vaccines were given restricted emergency use approval by the Drugs Controller General of India on January 3, 2021. The government of India subsequently announced that its countrywide vaccine rollout would go into effect starting January 16, 2021, in a phased manner. Initially, health care workers were vaccinated with either the Covishield or the Covaxin vaccine. Covishield, a viral vector vaccine, was developed by Serum Institute of India in line with the vaccine developed in the United

ABSTRACT

OBJECTIVES: Nationwide COVID-19 vaccination was initiated in India on January 16, 2021, in a phased manner with vaccines including Covishield. This vaccine was indigenously prepared by Serum Institute of India in line with the Oxford-AstraZeneca ChAdOx1 vaccine developed at the University of Oxford. This is the first multicenter study to assess the safety of the indigenously prepared Covishield vaccine in India.

STUDY DESIGN: Multicenter observational descriptive study.

METHODS: This was a multicenter study carried out in northern and eastern India. Individuals who received the first dose of the Covishield vaccine were followed up for 7 days to check for any adverse effects or systemic effects post vaccination. The data were collected by the authors with a participant-administered questionnaire. The primary end point was the incidence of adverse or systemic effects within 7 days post vaccination.

RESULTS: No serious adverse or systemic effects were noted in 7 days of follow-up. Nonserious systemic effects were seen in 42.0% of individuals post vaccination. Myalgia and/or fatigue was the most common effect of vaccination in 25.7%, followed by fever in 22.0% of individuals. In most individuals, the systemic effects started 6 to 12 hours post vaccination. There were no reports of fresh onset of systemic effects of any kind beyond 48 hours of vaccination. Women and older adults tolerated the vaccination better.

CONCLUSIONS: The absence of serious adverse effects in our study will help allay fears around vaccine acceptance and give a boost to the vaccination campaign worldwide.

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TAKEAWAY POINTS

This study, conducted after the rollout of the Covishield COVID-19 vaccine in India, highlights postadministration reactions in the participants during the 7-day follow-up period. The findings of the study can be utilized in the following manner:

- ▶ planning the next phase of vaccination in terms of what reactions to expect in beneficiaries;
- ▶ reducing apprehension surrounding the nationwide vaccine program; and
- ▶ increasing vaccine acceptance during the next rollout.

Kingdom by the Jenner Institute at the University of Oxford. Covaxin, an inactivated virus vaccine, was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research.²

Covishield had undergone phase 1/2 blinded randomized controlled trials in April to May 2020 in the United Kingdom, Brazil, and South Africa, with randomization to the Covishield vaccine and the MenACWY (standard meningococcal) vaccine as the test and the control arms, respectively. It showed that the spike-specific T-cell responses peaked on day 14 and immunoglobulin G (IgG) response peaked by day 28, and these responses were boosted following the second dose. Neutralizing antibodies were found in 91% after a single dose and 100% after the second vaccine dose. Phase 2/3 trials for this vaccine were carried out in the United Kingdom from May to August 2020, with participants being enrolled in an age-escalation manner into cohorts aged 18 to 55 years, 56 to 69 years, and 70 years and older. The results showed that the median antispikes IgG response after 28 days was similar across all age groups. The analysis of data showed an acceptable safety profile among trial participants and also showed it to be better tolerated in older individuals.^{4,5}

The rapid approval of the vaccine and the myths being propagated have made the general public in India doubt the safety of the vaccine.^{6,7} In this study, we have highlighted the adverse and systemic effects on individuals post vaccination. This study looks solely at the safety and not the efficacy of the vaccine. To the best of our knowledge, this is the first paper on the safety of Covishield in India.

MATERIALS AND METHODS

This multicenter study was conducted in 4 tertiary care centers in northern and eastern India to document the adverse and systemic effects following exposure to the Covishield vaccine and to study the factors thereof. All the participants who consented to the study were included. The participants, who were either health care workers or frontline workers, were administered the first dose of the Covishield vaccine. All the vaccinees were detained at immunization centers for 30 minutes post administration of the vaccine. They were followed up for adverse and systemic effects over 7 days via self-reporting format. Individuals who did not self-report were followed up telephonically daily. The vaccine was administered by a trained vaccinator through an autodisposable syringe into the deltoid muscle, and the onset of adverse and systemic effects was monitored by a supervisor through a participant-administered

questionnaire. Individuals complaining of any symptoms post vaccination were cross-checked by the supervisor for coherence in reporting of symptoms. Data of all the vaccine recipients from various centers were compiled and collated in an Excel sheet (Microsoft) and were analyzed after data cleaning using SPSS version 23 (IBM). Vaccine recipients who did not fill out the questionnaire were contacted on the telephone by the supervisor and were asked

for their wellness and reactions, thus minimizing loss to follow-up.

For the study, serious effects were defined as any event post vaccination that required hospital admission. Local reactions were defined by complications at or around the injection site. Systemic effects were defined by the new onset of self-limiting systemic symptoms such as fever, headaches, myalgia and fatigue, diarrhea, vomiting, and flu-like symptoms post vaccination that could not be explained by any other etiology.

Assuming adverse and systemic effects to be present in 80% of the population and a margin of error of 5% (95% CI, 75%-85%), we calculated the minimum sample size to be 246. However, we had enrolled and followed up with 268 individuals in this study.⁸

Statistical Analysis

Descriptive statistics (frequency and percentages) were calculated for sample demographic characteristics. Chi-square analysis was done to find out the association of various demographic features with the onset of adverse or systemic effects among the study participants. Binary logistic regression was done for variables that were found to have a statistically significant association with the outcome of interest.

RESULTS

In the study were 268 participants; their mean (SD) age was 33.75 (8.86) years. No hospital admissions or serious adverse effects were observed over 7 days. Systemic effects post vaccination were seen in 118 (44.0%) study participants. The study population was composed of 200 (74.6%) men and 68 (25.4%) women. The study population was divided into 4 subgroups based on their age profile. Comorbid conditions were present in 8 (3%) of the study population. The demographic features of the study population are given in [Table 1](#).

Myalgia and/or fatigue was the most common effect of vaccination, observed in 69 participants (25.7%), followed by fever in 59 (22.0%), headache in 46 (17.1%), flu-like symptoms in 8 (2.9%), diarrhea in 3 (1.1%) individuals and vomiting in 1 (0.3%) individual, as shown in [Table 2](#). Injection site pain was observed in 56 (20.9%) of the study participants, which in the majority lasted for 24 to 48 hours without affecting routine daily activities.

In most individuals, the systemic symptoms started at 6 to 12 hours post vaccination. There were no reports of fresh onset of systemic symptoms of any kind beyond 48 hours post vaccination. The duration of the above symptoms in the majority was less than 2

hours for fever ($n=22$), 6 to 12 hours for headache ($n=12$), and 12 to 24 hours for myalgia and fatigue ($n=26$). None of the systemic symptoms lasted for more than 48 hours in any individual. The distribution of the symptoms as per their onset and duration are shown in [Table 3](#).

A χ^2 test was used to find out the association of various demographic features with the outcome of interest. It was found that in the study population, gender and age group both had significant associations with systemic effects post vaccination ([Table 4](#)).

Binary logistic regression was further applied to the variables that had a significant association with the outcome of interest. The odds of men developing systemic effects following exposure to the Covishield vaccine were 2.08 times that of women ($P=.01$). The odds of participants in the groups aged 29 to 39 years and 39 to 49 years developing minor reactions following exposure to the Covishield vaccine were 1.90 ($P=.029$) and 2.37 ($P=.034$), respectively, vs those of participants in the group aged 19 to 29 years ([Table 5](#)).

DISCUSSION

The Covishield vaccine has been studied for safety in various published phase 1/2/3 trials. Serum Institute of India had developed this vaccine with 5×10^{10} viral particles per dose. The total population ($N=268$) in the study consisted of health care workers. No reports emerged of serious adverse effects requiring hospitalization or causing them to miss their hospital routine activities over 7 days of follow-up post vaccination. In a study carried out by Zhu et al in Wuhan, China, using a recombinant adenovirus type 5 vectored COVID-19 vaccine with a similar dosage of viral particles, the rate of reported serious effects was 1% in a study population of 129.⁸ This study population did not have participants from India. Our study population size was larger than that of the previous study; therefore, the absence of serious adverse effects is significant in this population.

In phase 2/3 trial data published on the same vaccine with fewer viral particles (2.2×10^{10} particles per mL) by Ramasamy et al, the observed systemic effects were much higher, ranging from 65% to 86% across various age groups.⁵ The size of the population in this study was 560, and they were studied over 28 days post vaccination. This result may be interpreted as indicating better tolerance of the vaccine in our study population.

In comparison with the study published by Zhu et al, the number of systemic effects in our study was higher in cases of fever (22.0% vs 16%, respectively) and lower in cases of fatigue and myalgia (25.7% vs 52%, respectively), headache (17.1% vs 28%), diarrhea (3.5% vs 8%), and vomiting (0.8% vs 1%). There were no individuals with symptoms of hypersensitivity, dyspnea, or pruritus as observed in the study by Zhu et al.⁸

Men had a higher probability of having systemic effects than women post vaccination (odds ratio, 2.08; $P=.01$). Because this study is the first of its kind in India to the best of our knowledge, the significance of this finding will get clearer as data from the various geographical locations of the country are published. Presently there is no reason that we could attribute to explain this difference across genders.

TABLE 1. Demographic Features of the Study Population ($N=268$)

	n (%)
Gender	
Male	200 (74.6)
Female	68 (25.4)
Age group in years	
19-29	84 (31.3)
29-39	122 (45.5)
39-49	40 (14.9)
49-59	22 (8.2)
Comorbidity	
Present	8 (3)
Absent	260 (97)
COVID-19 positive in past	
Yes	15 (5.6)
No	253 (94.4)
Place of work	
Active patient care	164 (61.2)
Administrative job	104 (38.8)

TABLE 2. Distribution of Symptoms Among the Study Participants ($N=268$)

Symptom present	n (%)
Myalgia and/or fatigue	69 (25.7)
Fever	59 (22.0)
Headache	46 (17.1)
Flu-like symptoms	8 (2.9)
Diarrhea	3 (1.1)
Vomiting	1 (0.3)

TABLE 3. Distribution of Symptoms by Their Onset and Duration

	Fever	Headache	Myalgia and/or fatigue
Time until onset of symptom, n			
< 2 hours	1	6	3
2-6 hours	16	16	24
6-12 hours	28	14	29
12-24 hours	14	9	12
24-48 hours	0	1	1
> 48 hours	0	0	0
Duration of symptom, n			
< 2 hours	22	12	3
2-6 hours	21	10	10
6-12 hours	10	12	20
12-24 hours	5	7	26
24-48 hours	1	5	10
> 48 hours	0	0	0

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TABLE 4. Association of Various Demographic Characteristics With Onset of Systemic Effects

Demographic characteristics	Minor reactions, n		P
	Present	Absent	
Gender			
Female	39	29	.004
Male	75	125	
Age group in years			
19-29	47	37	.02
29-39	46	76	
39-49	13	27	
49-59	8	14	
Place of work			
Active patient care	76	88	.114
Administrative job	38	66	
Previous COVID-19 status			
COVID-19 positive	8	7	.384
COVID-19 negative	106	147	
Comorbidity status			
Yes	5	3	.246
No	109	151	

TABLE 5. Binary Logistic Regression for Minor Reactions to COVID-19 Vaccine, by Demographic Characteristics

	OR	SE	95% CI	P
Gender				
Female	Ref	Ref	Ref	
Male	2.08	0.295	1.170-3.710	.013
Age in years				
19-29	Ref	Ref	Ref	
29-39	1.90	0.294	1.069-3.385	.029
39-49	2.37	0.409	1.067-5.296	.034
49-59	2.39	0.504	0.891-6.421	.084

OR, odds ratio; ref, reference; SE, standard error.

There is a significant difference ($P = .02$) in the incidence of systemic effects across various age groups. The group aged 29 to 49 years had a significantly higher odds ratio for developing systemic effects post vaccination. Although the group aged 49 to 59 years had a higher odds ratio compared with the group aged 19 to 29 years, the P value was not significant. This might translate into better toleration in this age group, which is commensurate with findings of a study published by Ramasamy et al in which they had noticed lesser systemic effects in the older adult population. The higher incidence of systemic effects in the younger population can be attributed to their robust immune function, leading to a greater immune response to the vaccine.⁵

Previous COVID-19–positive status and workplace were analyzed for their association with systemic effects post vaccination, but they were not found to be statistically significant.

Limitations

This study was done as a short-term safety study after the first dose of vaccination. The authors plan to look at the long-term safety effects and the effects post the second dose of vaccination.

CONCLUSIONS

Our study has tried to address the concerns around the safety of the Covishield vaccine in light of the doubts in the general public after emergency approval of the vaccine. The absence of serious adverse effects and the fact that none of the systemic effects affected daily activities are the highlights of the study, which might indicate better tolerability in this geographic area. The lower systemic effects in older adults and women were also noteworthy in this study. Presently, no postvaccination safety data are available in India. In the current health scenario, the feasibility of waiting for long-term safety data of the vaccine before vaccination is debatable.

In this context, our study becomes more relevant in disseminating short-term safety data post vaccination. This will help individuals in their decision to accept vaccination. ■

Author Affiliations: Department of Internal Medicine, 7 Air Force Hospital (SSM, KR, VKS, BS, RK, MT), Kanpur, India; Public Health Specialist, Med Branch, 17 Mountain Div (AN, HS), Gangtok, India.

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Address Correspondence to: Sourya Sourabh Mohakuda, MD, Department of Internal Medicine, 7 Air Force Hospital, Kanpur, India. Email: souryasourabh@gmail.com.

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