RESEARCH ARTICLE

Adverse events following immunization of COVID-19 (Covaxin) vaccine at a tertiary care center of India

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Abstract

The study aimed to assess the adverse events following COVID-19 vaccine (Covaxin) immunization at a tertiary care institution and also assess the predictors of the adverse events following immunization (AEFI). The prospective observational study was conducted in a tertiary care institute among the Covaxin beneficiaries between June 28 and September 6, 2021. A total of 1826 participants were assessed for any local or systemic adverse events after seven days of vaccination. A telephonic interview was conducted, and the beneficiaries were assessed according to the adverse event grading. A total of 1826 participants were assessed for AEFI, and 544 (29.8%) reported at least one of the AEFI. No severe adverse events were reported, and about 1.6% had moderate AEFI. Pain at the injection site (14.6%), fever (9.7%), and myalgia (5.9%) were the common adverse events reported by the participants. AEFI incidence was higher in the first dose (38.1%) when compared to the second dose (26.4%), and this finding was significant with a $p < 0.001$. The major factors associated with AEFI were female sex, history of an allergic reaction, presence of comorbidities, acute infection in the past 3 months, and intake of chronic medications. Precaution needs to be taken while vaccinating individuals having allergies, comorbidities, acute infection in the last 3 months, and individuals on chronic medication.

KEYWORDS
disease control, epidemiology, immunity/immunization, SARS coronavirus, vaccines/vaccine strains, virus classification

1 | INTRODUCTION

The COVID-19 disease has spread rapidly, infecting 228 million population and taking the lives of 4.6 million population by September 20, 2021.[1] In India, 33 million population were affected by COVID-19, and 0.4 million died due to COVID-19.[2] As there is no specific treatment available for COVID-19, preventive measures like COVID-appropriate behavior and vaccines remain the mainstay of protection. During the pandemic, vaccines against COVID-19 were developed at an unprecedented speed. These vaccines had a

different level of effectiveness and were approved for emergency use. In India, five vaccines have been approved by the Drugs Controller General of India to date. Vaccines approved in India are Covishield (ChAdOx1), COVID-19 vaccine (Covaxin) (BBV152), SputnikV, Johnson & Johnson, and Zycov-D.[3-5] As of September 15, 2021, a total of 5634 million doses have been administered globally.[1] Nation-wide COVID-19 vaccination in India was started on January 16, 2021, initially for the health care workers (HCWs).[6] Later, the vaccination drive was extended to the citizens of India on March 1st and April 1st, for those aged more than 60 years and 45–59 years,

respectively.[7] After May 1, 2021, it was extended to the 18–44 years age group. The vaccination in India is done through one single portal (https://cowin.gov.in) throughout the country.[8] Since then, more than 800 million doses have been administered by September 20, 2021.[2] Of those, 719 million doses were of Covishield, and 91 million were of Covaxin.[8]

As of September 20, 2021, the adverse events following COVID-19 vaccination was 0.005%. However, these numbers may be grossly underestimated as the mechanism of adverse event following immunization (AEFI) reporting was not known to all. An AEFI is any untoward medical occurrence that follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.[9] As per the Government of India, anyone having any AEFI after receiving any COVID-19 vaccine can contact the helpline number: +91-11-23978046 (Toll free-1075), technical helpline number: 0120-4473222, helpline Email Id: nvoc2019@gov.in, or can contact the vaccination center where they took vaccination.[10]

There have been few studies related to AEFI after COVID-19 vaccination in recent times. The majority of the studies were on Covishield (ChAdOx1) and BNT162b2. In the Phase I trial of Covaxin, 5% of participants reported local adverse events, and 14% reported systemic adverse events.[11] There were no other studies that assessed adverse events following Covaxin vaccination. This study aimed to assess the adverse events following Covaxin and also to assess the factors associated with AEFI among Covaxin beneficiaries.

2 | METHODOLOGY

2.1 | Settings and design

The prospective cohort study was conducted between June 28 and September 6, 2021. The study was conducted at the All-India Institute of Medical Sciences, Bhubaneswar, an institute of national importance in the eastern part of India. Beneficiaries who took either the first dose or second dose of Covaxin (BBV152) during the study period and provided consents were included in the study. The beneficiaries were followed up for 1 week after the vaccine dose. The minimum sample size required for the study was estimated to be 1825, taking 5% prevalence (p) of AEFI from the study by Ramanathan et al.[11] relative precision (ε) as 20%, and confidence interval of 95%. The sample size was calculated using nMaster software using the formula $Z_a^2(1 – p)/\varepsilon^2 p$. The study was commenced after receiving ethical approval from the Institute Ethics Committee of All India Institute of Medical Sciences, Bhubaneswar (reference number: T/IM-NF/CM&FM/21/20).

Ten percent of each day's vaccine beneficiaries were selected using a simple random method with the help of a random number list generated by Microsoft Excel until a sample size of 1826 was achieved. The study age group included 18–44 years and more than 45 years age group, and they were selected proportionately.

2.2 | Data collection

The study participants were observed for 30 min postvaccination to look for any immediate adverse events. A trained interviewer conducted a telephonic interview to assess the adverse events following the Covaxin vaccination. The telephonic follow-up was conducted once between the 7th and 10th day of vaccination. Solicited local adverse events like pain at the injection site, tenderness/soreness, erythema, swelling/induration, pruritus associated with injection, and solicited systemic adverse events like pain, fever, nausea/vomiting, headache, fatigue, myalgia, acute allergic reaction, rash, and joint pain were assessed. All the unsolicited adverse events reported by the study participants were also reported. The adverse events were graded based on the US Food and Drug Administration (FDA) document for the toxicity grading scale for healthy volunteers in preventive vaccine trials.[12] The adverse events were graded as mild, moderate, severe, and potentially life-threatening based on the severity (Table S1).

2.3 | Statistical analysis

Data analysis was done by Statistical Package for Social Sciences Version 22 (SPSS Inc.). The proportion of AEFI reported was calculated. The X^2 test was applied to find out the association between outcome and predictor variables. By logistic regression analysis, the odds ratio with 95% CI was calculated for various risk factors of AEFI. Multivariate logistic regression analysis was performed to calculate the adjusted odds ratio using the variables that were significant in bivariate analysis. A $p < 0.05$ was considered significant.

3 | RESULTS

A total of 2267 participants were interviewed to achieve a sample size of 1826. The nonresponse rate was 19.5%. The mean age of the participants was 40.02 ± 13.34 years. The maximum age of the participants was 88 years, and the minimum age was 18 years. One-fourth of the participants, 469 (25.7%), were from the age group of 40–49 years. Male participants (1000, 54.8%) were more than that of the female participants (826, 45.2%). Among the 1826 participants, 523 (28.6%) beneficiaries took the first dose, and 1303 (71.4%) took the second dose. Government services (497, 27.2%) and homemakers (499, 27.3%) were the major occupations of the participants. More than two-fifths of the participants (794, 43.5%) were graduates (Table 1).

Only 5.8% of the study participants had any of the comorbidities. Fourteen (0.8%) of the participants were taking steroids during the COVID-19 vaccination, and 3 (0.2%) had temporarily stopped steroids though they were taking so previously. Only one participant was taking immunomodulators, and 3 temporarily stopped medication for the vaccination. Only 26 (1.4%) participants had known allergy to any kind

TABLE 1 Demographic profile of the study participants (N = 1826)

Variables	Categories	N (%)
Age group	18–29 years	488 (26.7)
	30–39 years	417 (22.8)
	40–49 years	469 (25.7)
	50–59 years	302 (16.5)
	≥60 years	150 (8.2)
Gender	Female	826 (45.2)
	Male	1000 (54.8)
Occupation	Agricultural worker	55 (3.0)
	Businessman	193 (10.6)
	HCW/FLW	33 (1.8)
	Housewife	499 (27.3)
	IT professional	121 (6.6)
	Manual worker	93 (5.1)
	Not working	104 (5.7)
	Govt services	497 (27.2)
	Student	231 (12.7)
Educational status	Graduate	794 (43.5)
	High school	326 (17.9)
	Intermediate	166 (9.1)
	Middle school	78 (4.3)
	Post-graduate	265 (14.5)
	Primary school	197 (10.8)

Abbreviations: FLW, Frontline Worker; GOI, Government of India; HCW, health care worker.

TABLE 2 Medical conditions of the study participants (N = 1826)

Variables	Categories	N (%)
Comorbidities	No	1721 (94.2)
	Yes	105 (5.8)
History of steroid intake	No, never taken	1808 (99.0)
	Temporarily stopped	3 (0.2)
	Yes, currently taking	14 (0.8)
History of intake of immunomodulators	No, never taken	1821 (99.7)
	Temporarily stopped	3 (0.2)
	Yes, currently taking	1 (0.1)
History of allergy (food, drug, pollen, dust, others)	No	1631 (89.3)
	Yes	26 (1.4)
	Don't know	169 (9.3)
History of medication in last 6 months (chronic disease)	No	1741 (95.3)
	Yes	85 (4.7)
COVID-19 infection in last 3 months	No	1822 (99.8)
	Yes	4 (0.2)
Hospital admission in last 3 months	No	1822 (99.8)
	Yes	4 (0.2)
History of acute infection in last 3 months	No	1789 (98.0)
	Yes	37 (2.0)

of food, drug, pollen, dust or other allergens, and 169 (9.3%) were not aware of their status. Only 85 (4.7%) of the participants were taking medication for chronic diseases in the last 6 months. Only 4 (0.2%) had COVID-19 infection in the last 3 months, and 4 (0.2%) were admitted to the hospital in the last 3 months. A history of acute infection was observed in 37 (2.0%) of the participants (Table 2).

A total of 544 cases of AEFI are reported during the study. Among them, 29 (5.3%) reported moderate symptoms, and the rest 515 (94.7%) were mild in nature. No severe cases were reported. More than one AEFI was reported in 219 (12.0%) of the study participants, and 325 (17.7%) of the participants had reported only one AEFI. Pain at the injection site (267, 14.6%) was the most common AEFI, followed by fever (178, 9.7%) and myalgia (107, 5.9%). The proportion of cases reporting AEFI was more after the first dose (199, 38.1%) than that of the second dose (345, 26.4%), and the difference was also found to be statistically significant. However, no statistically significant difference was reported for individual AEFI for the first and second dose except that for the pain at the injection site ($p < 0.001$) and joint pain ($p = 0.026$). We did not find any immediate adverse event (Table 3).

The younger population had more AEFI than the older ones. Individuals aged 60 years or more were 0.66 times less likely to have AEFI than those aged 18–29 years. Females were 1.30 times more likely to have AEFI when compared to males, and the difference was found to be statistically significant ($p = 0.010$). Individuals with any comorbidities were 2.08 times more likely to have AEFI than those having no comorbidity ($p < 0.001$). AEFI was 2.39 times more reported among individuals with a history of allergic reaction than those with no previous history ($p = 0.028$). Individuals who took medication for chronic disease reported 2.07 times higher AEFI than those who were not taking medication ($p = 0.001$). Individuals who had an acute infection in the last 3 months reported 3.99 times more AEFI than those who did not have an acute infection in the last 3 months ($p < 0.001$). Individuals having COVID-19 infection in the last 3 months and history of hospital admission in the last 3 months had 7.10 times more AEFI, but the difference was not significant statistically. On multivariate logistic regression, gender, and past history of acute infection in the last 3 months were found to be significantly associated with AEFI (Table 4).

Only 27 (5%) of the study participants consulted any physician for the adverse events, and 54 (9.9%) took self-medication. None of the participants got admitted for any of the adverse events. The majority of the participants took tablet Paracetamol for their symptoms.

TABLE 3 Types of AEFI reported among the study participants (N = 1826)

Type of AEFI	Total (N = 1826), N (%)	First dose (N = 23), N (%)	Second dose (N = 1303), N (%)	p value
Pain at the injection site	267 (14.6)	134 (25.6)	133 (10.2)	<0.001
Tenderness/soreness	78 (4.3)	23 (4.4)	55 (4.2)	0.898
Redness/erythema	4 (0.2)	1 (0.2)	3 (0.2)	1.000
Swelling/induration	11 (0.6)	6 (1.1)	5 (0.4)	0.057
Itching/pruritus associated with injection	1 (0.1)	1 (0.2)	0 (0.0)	0.286
Pain	10 (0.5)	5 (1.0)	5 (0.4)	0.134
Fever	178 (9.7)	55 (10.5)	123 (9.4)	0.483
Nausea/vomiting	8 (0.4)	4 (0.8)	4 (0.3)	0.181
Headache	104 (5.7)	37 (7.1)	67 (5.1)	0.107
Fatigue	88 (4.8)	19 (3.6)	69 (5.3)	0.134
Muscle pain/myalgia	107 (5.9)	27 (5.2)	80 (6.1)	0.422
Rash	13 (0.7)	1 (0.2)	12 (0.9)	0.094
Joint pain	2 (0.1)	2 (0.4)	0 (0.0)	0.026
Others	3 (0.1)	1 (0.2)	2 (0.2)	0.857
Individuals having any AEFI	544 (29.8)	199 (38.1)	345 (26.4)	<0.001

Abbreviation: AEFI, adverse events following immunization.

4 | DISCUSSION

In this study, we have investigated AEFI among Covaxin beneficiaries. AEFI was reported among 29.8% of the Covaxin beneficiaries. Higher AEFI was reported among the beneficiaries who took the first dose (38.1%) when compared to the second dose (26.4%). The majority of the AEFI was mild in nature. Pain at the injection site was the most common AEFI, followed by fever and myalgia. Young adults reported AEFIs more frequently than the elderlies.

Females reported higher AEFI than males in our study. This finding was similar to a study done by Menni et al.[13] in the United Kingdom. In contrast to this, no gender difference was reported in a study done by Kamal et al.[14] from South India. In our study, 29.8% of the study participants had reported at least one of the AEFI. The reported AEFI in our study was higher than that of the Phase 2 trial of Covaxin. Ella et al.[15] reported 21% AEFI for BBV152 (Covaxin) with 6 μg Algel IMDG and 17% with 3 μg Algel IMDG. However, Kamal et al.[14] reported a 57% rate of AEFI among the study participants. The difference may be due to the difference in vaccines. Kamal et al. studied the AEFI for Covishield, whereas our study was among Covaxin recipients. A higher percentage of reactogenicity was also observed in Phase 2 clinical trial of ChAdOx1 (Covishield) in India.[16] The difference may also be due to the difference in age of the participants in the study. The frequency of AEFI decreased with an increase in age in our study. The result is in accordance with other published trials of viral vector vaccines.[17,18] In our study, 18–29 years (younger) age group patients were

34.6%, whereas it was 48.4% in South India, and a majority of the AEFI were reported among the younger age groups. Kaur et al.[19] also reported higher AEFI among the younger participants.

The proportion of AEFI was 38.1% after the first dose and 26.4% after the second dose. This finding was similar to a study conducted by Kaur et al.[19] in North India; they have reported 40% and 16.6% of the AEFI among first and second-dose beneficiaries, respectively.

We did not find any serious adverse events in our study. Kim et al. in South Korea reported only one serious AEFI. The severe AEFI rate reported by Kaur et al.[19] among the first dose and second dose beneficiaries was 0.3% and 0.1%, respectively. In all the studies majority of the AEFI are mild-moderate in nature. These results depict the higher safety profile of the COVID-19 vaccines. Females reported higher AEFI than the male participants. A similar result was reported in studies by Kamal et al.[14] and Kaur et al.[19] A descriptive study based on the WHO database also supported our result.[20]

The common adverse events reported in our study were injection site pain, tenderness, fever, headache, fatigue, and myalgia. These are also the common adverse events reported in the Phase 2 trial of the BBV152 vaccine.[15] However, the incidence of reactogenicity was higher in our study than in the clinical trial results. We did not find any serious adverse events in the first 7 days, and this was in accordance with the trial results.[15] However, few serious adverse events were reported in the studies from ChAdOx1 in India, Korea, and Nepal.[14,19,21–23]

Other than gender, other significant predictors for AEFI in our study were comorbidities, history of steroid intake, history of allergy, history of medication in last 6 months, and history of acute infection in the

TABLE 4 Factors associated with AEFI among the study participants (N = 1826)

Variables	Categories	AEFI yes, N (%)	AEFI no, N (%)	p value	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age group	18–29 years	169 (34.6)	319 (65.4)	0.021	1			
	30–39 years	132 (31.7)	285 (68.3)		0.87 (0.66–1.15)	0.344		
	40–49 years	121 (25.8)	348 (74.2)		0.65 (0.49–0.86)	0.003		
	50–59 years	83 (27.5)	219 (72.5)		0.71 (0.52–0.97)	0.037		
	≥60 years	39 (26.0)	111 (74.0)		0.66 (0.44–0.99)	0.049		
Gender	Male	273 (27.3)	727 (72.7)	0.010	1		1	0.010
	Female	271 (32.8)	555 (67.2)		1.30 (1.06–1.59)	0.010	1.31 (1.07–1.61)	
Comorbidity status	No	496 (28.8)	1225 (71.2)	<0.001	1		1	0.200
	Yes	48 (45.7)	57 (54.3)		2.08 (1.39–3.09)	<0.001	1.75 (0.74–4.11)	
History of steroid intake	No	534 (29.5)	1275 (70.5)	0.009	1		1	0.535
	Yes	10 (58.8)	7 (41.2)		3.41 (1.29–9.00)	0.013	1.41 (0.47–4.20)	
History of taking immunomodulators	No	542 (29.7)	1280 (70.3)	0.587	1			
	Yes	2 (50.0)	2 (50.0)		2.36 (0.33–16.80)	0.391		
History of allergy	No	531 (29.5)	1269 (70.5)	0.023	1		1	0.373
	Yes	13 (50.0)	13 (50.0)		2.39 (1.10–5.18)	0.028	1.47 (0.62–3.46)	
Medication history in last six months for chronic disease	No	505 (29.0)	1236 (71.0)	0.001	1		1	0.869
	Yes	39 (45.9)	46 (54.1)		2.07 (1.33–3.21)	0.001	1.08 (0.43–2.70)	
COVID-19 infection in last 3 months	No	541 (29.7)	1281 (70.3)	0.048	1			
	Yes	3 (75.0)	1 (25.0)		7.10 (0.73–68.44)	0.090		
Hospital admission in last 3 months	No	541 (29.7)	1281 (70.3)	0.048	1			
	Yes	3 (75.0)	1 (25.0)		7.10 (0.73-68.44)	0.090		
Acute infection in last 3 months	No	521 (29.1)	1268 (70.9)	<0.001	1		1	0.001
	Yes	23 (62.2)	14 (37.8)		3.99 (2.04–7.83)	<0.001	3.26 (1.59–6.65)	

Abbreviation: AEFI, adverse events following immunization.

last 3 months. The results are in accordance with the results reported by Kaur et al.[19] Comorbidity was significantly associated with AEFI in a study by Khalil et al.[21] in Bangladesh. As per Government of India guidelines, individuals having Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are deferred for vaccination by 3 months. Therefore, we had only four participants having infections in the last 3 months, and the variable could not be analyzed further. A higher incidence of reactogenicity was reported in participants with previous SARS-CoV-2 infection.[24,25]

In our study, 9.9% of the participants had taken self-medication. Most of the participants took tablets of Paracetamol for adverse events. In our Institute, we provide four tablets of Paracetamol tablets to all the beneficiaries after vaccination. This finding was similar to a study by Shrestha et al.[22] in Nepal, where 55% of the participant with AEFI took self-medication. Covaxin (BBV152), for which reactogenicity was assessed in our study, was an inactivated vaccine. The majority of the compared studied are mRNA-based vaccines, which are likely to have

higher reactogenicity than the inactivated vaccine.[26] This may explain the lower reactogenicity in our study than other studies.

5 | STRENGTH AND LIMITATIONS

To our knowledge, it is the first prospective observational study of Covaxin (Bharat Biotech vaccine) after its emergency approval. Only one follow-up was conducted. The exact day when the symptom first appeared was not recorded. The large number of non-responders could underestimate the results. However, the age and gender characteristics of the non-responders were similar to the responders. Many of the registered phone numbers belonged to the relatives who were not staying together or of the agents who booked slots for vaccination; this may lead to selection bias. We only assessed the past SARS-CoV-2 infection in the last 3 months. So, the reactogenicity in past SARS-Cov-2 infections could not be assessed.

6 | CONCLUSION

The study exemplifies that Covaxin (BBV152) carries a good safety profile overall and is well tolerated by the adult population. Younger individuals, females, individuals with comorbidities, past history of allergy, and history of acute infection in the last 3 months are at higher risk of AEFI. The vaccines should be administered to these individuals with an adequate observation period after vaccination as Covaxin is an inactivated vaccine and safer than mRNA vaccines which can be considered for widespread use. Long-term adverse events should be assessed at AEFI surveillance sites.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Swayam Pragyan Parida, Dinesh Prasad Sahu, Arvind Kumar Singh, Biswa Mohan Padhy, Binod Kumar Patro, and Sonu Hangma Subba conceived and designed the study. Data were collected by Dinesh Prasad Sahu, G. Alekhya, Arvind Kumar Singh, and Abhisek Mishra. Dinesh Prasad Sahu, G. Alekhya and Arvind Kumar Singh drafted the manuscript. All author reviewed the manuscript before submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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