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Original Research Article

A retrospective cross-sectional study assessing adverse events following immunization (AEFI) of COVID 19 vaccine in a subset of Indian population

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ABSTRACT

Objectives: As the COVID-19 pandemic is an emerging healthcare concern, there has been swift vaccine development with minimal clinical trials questioning its protective efficacy outside of clinical trial conditions. The study aims to analyze the adverse events following immunization (AEFI) with COVID-19 vaccines among the domestic Indian population. It also aimed to evaluate the association between AEFI and demographic characteristics, comorbidities, and type of vaccine.

Materials and Methods: This cross-sectional survey included participants ≥ 18 years of Indian origin for passive reporting of AEFI with COVID-19 vaccination using a questionnaire. The incidence of AEFI was calculated in percentage; the Chi-square test was used to determine associations between AEFI and independent variables.

Results: The incidence of reported AEFI was 76.4%. The most frequently reported AEFI was redness [74.38% (n = 328)], followed by pain [52.83% (n = 233)], swelling [52.83% (n = 233)], and fever [50.34% (n = 222)]. The majority of AEFIs were mild to moderate and resolved spontaneously. Females had significantly more AEFI with longer duration than males. The type of vaccine received had no significant effect on the number or duration of AEFI; 3.63% tested positive for COVID-19 after the first dose and 3.11% after the second dose of the vaccine, with no significant correlation between comorbidities and the presence of AEFI.

Conclusion: More than three-fourths of the vaccines resulted in one or more forms of adverse events, but most events were self-limiting. Females were more prone to develop AEFI. Knowledge about what to expect after vaccination will help educate the public, allay misconceptions and reduce vaccine hesitancy.

1. Introduction

COVID-19 emerged in 2019 in China and devastated numerous lives, affecting nearly 542 million of the world population (according to a WHO International report, June 2022) and continues to do so.[1] Case-fatality usually results from complications, such as respiratory failure. High fatality rates have led to the development of vaccines in haste.[2] Herd immunity via mass vaccination is the most promising method to combat the COVID-19 pandemic, although vaccination distribution has been inequitable.[3]

COVID-19 vaccines developed rapidly, resulting in a lack of long-term follow-ups for evaluating the effectiveness and adverse events (AE). COVID-19 vaccines were not licensed due to the pandemic and therefore, the vaccines need special attention for hasty production and administration in the population. Increased vaccination rates may help evaluate the emergence of new AEFIs in the

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future.[4]

As of February 2022, 65 COVID vaccines were in phase 3 trial, and 33 vaccines received approval.[5] Pre-approved COVID-19 vaccine trials involve a healthy population under controlled settings; they have limited inclusion of diverse ethnicities and are limited by the short follow-up duration with merging of various phases of clinical trials. Therefore, such studies may not detect all safety-related issues emerging after vaccine delivery to the general population.[6]

Initially, two vaccines were approved by the Indian government to boost the largest vaccination drive: the non-replicating viral vector vaccine ChAdOx1 (Covishield ©) by AstraZeneca, Serum Institute of India; the inactivated virus vaccine BBV152 (Covaxin©) by Bharat Biotech.

The efficacy rates of different vaccines against the variants of COVID –19 are variable.[7] Studies have reported AEFIs with all vaccines developed to date, including vaccines for COVID- 19.[3] Studies have documented sex-based differences in immune response and adverse event following immunization (AEFI) across various vaccines.[8] Few studies have also assessed AEFI in comorbid conditions.

Close observation studies and surveys are necessary to evaluate vaccine effectiveness and AEFI on the general population demographics.[6–9] As there is a lack of evidence on the safety profile of these vaccines, reporting AEFI will substantiate the literature.

The objective of this study was to evaluate the associations between AEFI and COVID-19 vaccine within the subgroups relating to patient characteristics of sex, comorbidities, type of vaccine, and positivity to COVID-19 post-vaccination. The study included a survey of vaccinated adult Indians to compare the resultant AEFIs due to COVID-19 vaccine doses. Considering these objectives, we hypothesized that there could be variations in AEFI among different individuals.

2. Materials and Methods

2.1. Study details and criteria

The study was a cross-sectional online epidemiological survey conducted on adult Indians over 20 days from 1 June 2021 to 21 June 2021. Here, we report part of the survey findings.

2.2. Data collection

Variables studied: Data on demography, medical history, including a history of SARS-CoV-2 positivity at any time in the past, existing comorbidities, type of vaccine, number of doses received, information on the development of AEFIs, duration of AEFIs, interventions for the management of AEFIs, post-vaccination COVID infection status and lifestyle of individuals, were recorded in a semi-structured Google form questionnaire. Lifestyle and age are discussed in another article.

AEFIs were grouped as mild events, such as fever, chills, headache, and tiredness; severe events, such as allergic reactions, fainting, hyperventilation, and convulsions requiring medical attention. The respondents were asked to report the treatment taken for these AEs. Symptom duration was noted as the longest period for which any of the symptoms was experienced. The provision of free-text reporting allowed the description of any other symptoms.

2.3. Statistical analysis

Results were recorded as frequencies and percentages for data of incidence, type of AEFI, duration and positivity of COVID- 19 infection. The Chi-square test was applied for dichotomous variables, such as sex and type of vaccine, as well as the categorical variable of comorbidity, to determine the association between independent variables and the development of AEFI. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, US).

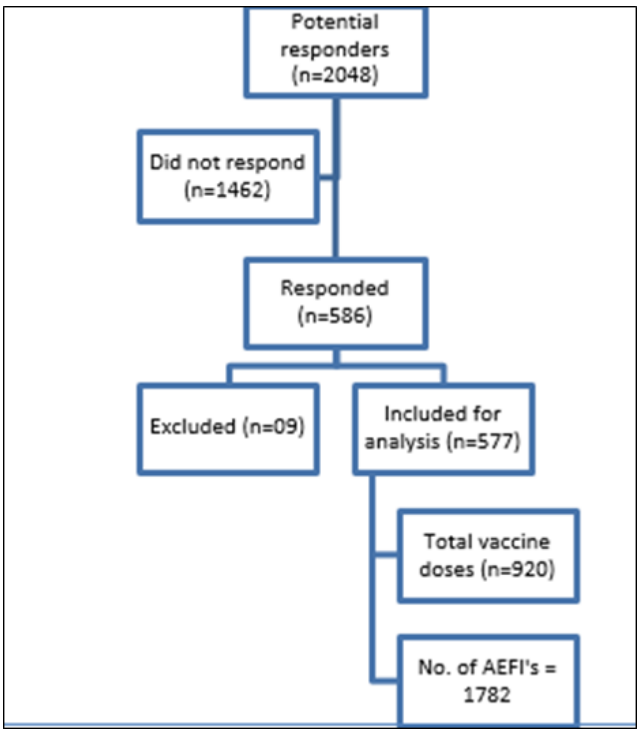


Fig. 1: Flow of study responders.

3. Results

A total of 586 responders of Indian origin completed the AEFI questionnaire; of these, 9 responses were excluded due to incomplete information. Thus, the final cohort

Table 1: Correlation between sex and number of AEFI

		Female	Male	Total	
No. of AEs	No AE	56 (16.8%)	69 (31.1%)	125 (22.5%)	p<0.0001
	1 – 5 AE's	199 (59.8%)	129 (58.1%)	328 (59.1%)	
	6 – 10 AEs	72 (21.6%)	24 (10.8%)	96 (17.3%)	
	>10 AEs	6 (1.8%)	0 (0.0%)	6 (1.1%)	
Total		333	222	555	
		100.0%	100.0%	100.0%	

Table 2: Correlation between sex and duration of AEFI

		Sex		Total	
		Female	Male		
Duration of AE (days)	<3 days	214	133	347	**p<0.0001**
		64.3%	59.9%	62.5%	
	>5 days	17	8	25	
		5.1%	3.6%	4.5%	
	3-5 days	46	12	58	
		13.8%	5.4%	10.5%	
	No AE	56	69	125	
		16.8%	31.1%	22.5%	
Total		333	222	555	
		100.0%	100.0%	100.0%	

Table 3: Correlation between vaccine type and number of AEFI

		Which vaccine did you receive?		Total	
		Covaxin	Covishield		
No. of AE's	No AE	21	104	125	p= 0.595
		26.9%	21.8%	22.5%	
	1 - 5 AEs	44	284	328	
		56.4%	59.5%	59.1%	
	6 - 10 AEs	13	83	96	
		16.7%	17.4%	17.3%	
	>10 AEs	0	6	6	
		0.0%	1.3%	1.1%	
Total		78	477	555	
		100.0%	100.0%	100.0%	

Table 4: Vaccine type and duration of AEFI

		Covaxin	Covishield	Total	
Duration of AE (days)	<3 days	49 (62.8%)	298 (62.5%)	347 (62.5%)	p = 0.532
	>5 days	2 (2.6%)	23 (4.8%)	25 (4.5%)	
	3-5 days	6 (7.7%)	52 (10.9%)	58 (10.5%)	
	No AE	21 (26.9%)	104 (21.8%)	125 (22.5%)	
Total		78 (100.0%)	477 (100.0%)	555 (100.0%)	

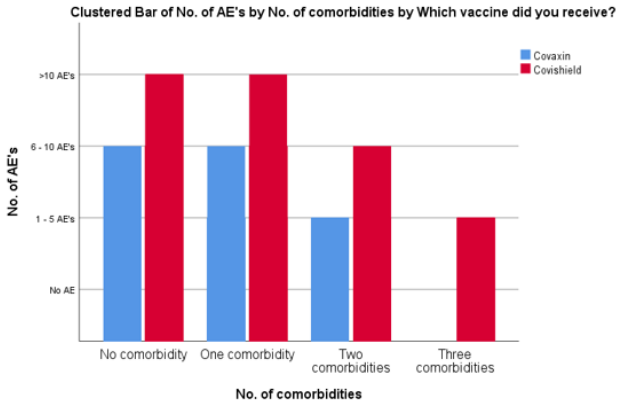
included 577 respondents (231 male and 346 female) between 18 to 84 years. All respondents had received the first dose of the COVID-19 vaccine, whereas only 343 had received the second dose.

AEFIs were analyzed for the number and duration of events. The number of AEFIs reported was divided into 4 groups ((No AE, 1-5, 6-10, and >10 AEs), and so was the duration of AEFI (No AE, <3, 3-5, and >5 days).

The overall incidence of AEFI in our study was 76.4% with 1-5 AEs reported in 337 (77%), 6-10 AEs in 98 (22%), and >10 AEs in 6 (1%) responders. The most frequently reported AEFI was redness [74.38% (n = 328)], followed by pain [52.83% (n = 233)], swelling [52.83% (n = 233)], and fever [50.34% (n = 222)]. The longest duration of any AEFI was represented by the number of days that AEFI was present. Most AEFIs were reported for <3 days [81% (n =358)], followed by 3-5 days [13 % (n =58)], and > 5

Table 5: Correlation between comorbidity and AEFI

	Comorbidity Present			Comorbidity absent			Correlation	
	N	AE present	%	N	AE present	%	r	p
Diabetes Mellitus	58	41	70.7%	519	400	77.1%	0.045	0.258
HypertensionT	75	54	72.0%	502	387	77.1%	0.040	0.333
Cardiac disorder	16	12	75.0%	561	429	76.5%	0.006	0.892
APD	1	1	100.0%	576	440	76.4%	-0.023	0.579
Asthma/COPD	12	12	100.0%	565	429	75.9%	-0.081	0.052
Cancer	1	1	100.0%	576	440	76.4%	-0.023	0.579
Obesity	3	3	100.0%	574	438	76.3%	-0.040	0.336
Dyslipidemia	1	1	100.0%	576	440	76.4%	-0.023	0.579
Thyroid	29	23	79.3%	548	418	76.3%	-0.016	0.708
Hematinics/Vitamins	6	6	100.0%	571	435	76.2%	-0.057	0.172
Bone disorders	1	0	0.0%	576	441	76.6%	0.075	0.072
Polyscystic ovarian disease	3	3	100.0%	574	438	76.3%	-0.040	0.336
Others	3	3	100.0%	574	438	76.3%	-0.040	0.336
Total	149	108	72.5%	428	333	77.8%	0.055	0.188



Graph 1: Graph showing the number of adverse events in comorbid patients with the type of vaccine.

days [6 % (n =25)]; 31.19% (n= 180) took medication, with paracetamol used most often; another 8.3 % (n=48) reported that paracetamol use and sleeping for long hours helped them to manage the adverse event; 20.6 % (n=119) of the respondents reported that they managed without any action. 538 (93.24%) respondents from our cohort had not tested positive, while 21 (3.63%) and 18 (3.11%) tested positive afterthe first and second dose, respectively.

The number and duration of AEFI varied significantly with sex. Females [277 (83.2%)] reported an overall higher occurrence of AEFIs than men [153 (68.9%)], with significantly more number and longer duration of AEFI (p<0.0001, 2-tailed Chi-square test) [Tables 1 and 2].

AEFI were reported [n=57(73.1%)] by Covaxin recipients and [n=373(78.2%)] Covishield recipients. The type of vaccine received had no significant effect on the number of AEFI (p=0.595, 2-tailed Chi-square test) or the duration of AEFI (p=0.532, 2-tailed Chi-square test)[Tables 3 and 4]. 22 respondents had taken vaccines other than Covaxin or Covishield ; since they were very few in number, they were not included in the statistical analysis. One hundred and forty nine had a pre-existing medical history; hypertension (13.2%) was the most common condition, followed by diabetes (10.2%) and cardiac disease (2.8%). No significant correlation was found between the presence of any form of comorbidity and the presence of AEFI (Table 5). A higher number of AEFI was seen in people with comorbidities who received Covishield than those who received Covaxin [Figure 1].

4. Discussion

Vaccination is a major preventive factor in infectious diseases. Vaccines were introduced over a century ago. However, the COVID vaccine has undergone only short-term surveillance before its introduction to the population. To date, 15 companies have developed and licensed vaccines.[9] Covishield and Covaxin are the most widely administered in India. Around 1,963 million doses of the COVID vaccine have been administered in India till June 2022.[10]

The mode of action for vaccines is through the triggering of immune responses. Vaccines act through altered immunity and can cause adverse effects through these immune reactions. The WHO has defined adverse effects following immunization (AEFI) as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine, but may be related to other factors.

AEFI may be a local reaction (redness, swelling, rash, and pain) or a systemic effect (fever, allergic reactions, and convulsions).[11]

Along with the efficacy of vaccines, immunization safety is equally important in the national vaccine-preventable disease (VPD) programs. Higher expectations of efficacy and lower acceptance of adverse effects after vaccination in society make immunization a challenging task.[12]

In our study, the overall incidence of AEFIs experienced with Covishield and Covaxin was 76.4%. Most cases showed 1-5 AEs in 337 (77%) cases. Most AEFIs were reported for <3 days [81% (n =358)], followed by 3-5 days [13 % (n =58)] and > 5 days [6 % (n =25)]. The most frequently reported AEFI was redness [74.38% (n = 328)], followed by pain [52.83% (n = 233)], swelling [52.83% (n = 233)], and fever [50.34% (n = 222)]. A study conducted using the COVID Symptom Study app in the UK showed the incidence of local and systemic reactions as 58.7% and 33.7%, respectively, following the first dose of the ChAdOx1 nCoV-19 vaccine.[13] Kaur et al. reported an incidence of 40%, with fever, headache, and dizziness being the most commonly reported AEFIs in a subset of HCW in India. Regarding severity, 70% AEFIs were mild, 28.7% were moderate, and 0.3% were severe, leading to hospitalization. The median time of complete recovery was 1 day. The AEFIs were managed with paracetamol, antihistamines, and proton pump inhibitors.[6]

The biological basis of sex differences in vaccine response could be multifactorial. Studies have consistently demonstrated higher immunogenicity and reactogenicity of vaccines in females, including evidence of more frequent and severe adverse reactions, such as fever, injection site pain, and inflammation, across several vaccines and age groups.[8] Womenhave 2 times higher odds ratio than men for developing AEFIs.[6] Basal levels of Ig, frequency of circulating CD4+ T cells, CD4 to CD8 T cell ratios, and helper T cell type1 (Th1) responses to viruses and vaccines are higher in women than men.[14] Differences in the immune systems of males and females are also related to the expression of Y and X-linked genes. A disproportionately higher number of messenger RNAs are present on the X chromosome than on the autosomal chromosome. Moreover, several immune-related genes are encoded on the X chromosome, and there is some evidence of greater activation of X-linked genes in immune cells from females than in males.[15] Estrogen enhances IgG and IgM production, while testosterone inhibits the production in males and females.[16] The results of the study showed that females had significantly more number and duration of AEFI than males ($p<0.0001$), which is consistent with previous studies where females were 73% more likely to develop AEFI than males,[3] and the onset of symptoms was slightly earlier and longer-lasting in females across all age groups.[17,18]

Literature shows that COVID-19 vaccines are safe for older adults with chronic health conditions. However, the question remains regarding AEFIs in the future. Therefore, observational studies and surveys are necessary to determine exact outcomes.[10] This study analyzed the side effects in known cases of various chronic health issues, such as hypertension, diabetes mellitus, cardiac disease, cancer, and asthma, to monitor the AEFIs. Comorbidities may play an important role in the variation of efficacy and AEFIs.[11] Our study results indicate that comorbidities, such as diabetes mellitus, hypertension, asthma, or congestive obstructive pulmonary disease, showed no statistically significant association with AEFIs. However, a study involving health care workers in Kerala reported an increased risk of AEFI among individuals with bronchial asthma but no significant association with other comorbidities.[3] Kaur et al. found that recipients with hypertension compared to those with normal blood pressure and recipients with a history of allergy compared to those without allergy had 2 times higher odds ratio of developing AEFIs, and hypothyroidism had three times higher odds ratio.[6] Won Suk Choi and Heen Jin Cheong reported similar efficiency and safety margins of COVID-19 vaccines in both populations with and without comorbidities.[19] Individuals with chronic health conditions show impaired immunity, which can affect the reaction to immunization. Comorbidities, such as hypertension, can downregulate levels of ACE receptors; diabetes mellitus with a poor glycemic index, cardiovascular diseases with myocarditis alter inflammatory markers, and cancers can also modify immune reactions.[20,21] Thus, vaccine efficacy and side effects need monitoring and evaluation for long-term results.

In the present study, AEFIs were reported by 73.1% Covaxin recipients and 78.2% Covishield recipients. However, the type of vaccine received had no statistically significant effect on the number or duration of AEFI. In a retrospective observational study on 75 vaccinated volunteers, the authors reported that AEFI experienced with Covishield vs. Covaxin during 1st dose was 92.45 % vs. 77.27 % and with 2nd dose 86.79 % vs. 72.72 %, respectively; 66 % of volunteers got an infection with COVID-19 post-vaccination.[22] Vijayakumar et al. reported a high percentage of no adverse events in 93.95% of individuals who received Covaxin and 88.825% who received Covishield. They indicated that Covishield had more number of adverse events than Covaxin/.[23]

Low reactogenicity rates with BBV152 Covaxin AZD 1222 (ChAdOx1) Covishield (Serum Institute of India) than with Oxford-AstraZeneca's Covishield ChAdOx1 vaccine and other adenovirus-based vaccines, to some extent, could be due to pre-existing immunity against human and chimpanzee adenoviruses in the Indian population via exposure to such viruses in the past, which are widely prevalent in developing countries compared to

the Americans, Chinese and Europeans.[12,18,24] Pre-existing neutralizing antibodies against human adenovirus 5 might be responsible for low reactogenicity in older adults than younger individuals. Cross-reactivity to other viruses can be a reason for country-specific variations in COVID-19 outcomes.[6]

5. Conclusion

In conclusion, the available data indicates that COVID-19 vaccines have satisfactory short-term acceptance. Large-scale and long-term population-level surveillance with diverse ethnicities is highly recommended to assess the safety profile of COVID-19 vaccines. All data reports on vaccine safety and efficacy in the literature should be investigated and evaluated regularly to minimize the risk factors and rationalize their application.

6. Limitation

The study population from whom we have collected the findings is small. So, this could be expanded in terms of population to obtain more accurate result of the reported adverse events.

7. Ethical Approval

This study was conducted after obtaining approval from the Institutional Review Board of D.Y. Patil University, Navi Mumbai (Approval No**:** IREB / 2021 / OMDR / 01). Informed consent from the responders was obtained via Google forms circulated for the study.

8. Source of Funding

None.

9. Conflict of Interest

None.

10. Acknowledgement

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