Original Article

Prevalence and determinants of adverse events following ChAdOx1 nCoV-19 vaccination (COVISHIELD) – A retrospective cohort study among healthcare workers in central Karnataka, India

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Abstract

Background: India has launched COVID vaccination program on January 16, 2021 and precautionary dose (third dose) on January 10, 2022. Our study evaluated adverse events following immunization (AEFI) among healthcare workers (HCWs) following first, second, and precautionary dose of ChAdOx1 nCoV-19 (COVISHIELD) vaccine. We also evaluated the association of AEFI with the study participants' characteristics. **Objectives:** (1) To assess the adverse events among HCWs following first, second, and precautionary dose of COVISHIELD vaccine. (2) To determine the factors associated with adverse events of COVISHIELD vaccine. **Materials and Methods:** A retrospective cohort study was conducted among HCWs of a tertiary care teaching hospital in central Karnataka from January 2021 to June 2022. A semi-structured, pretested questionnaire was used to interview the HCW of tertiary care teaching hospital regarding adverse events following first, second, and precautionary dose of COVISHIELD vaccine; data collected was entered in MS Excel 2019 and analyzed using SPSS v24.0. **Results:** Among 454 participants majority of them were females (231, 50.88%) and in the age group 18-27 years (151, 33.25%), and the majority were nursing staff (147, 32.37%). Adverse events were reported among 204 (44.93%) following the first dose, 149 (32.81%) after the second dose, and 230 (50.66%) participants following the precautionary dose. Generalized weakness and fever were the common adverse effects reported by participants. **Conclusion:** Majority of the study population did not report any adverse events following vaccination. Among the study participants who reported adverse events, most events were reported on the same day. Symptoms were mild in severity and short-lived.

Keywords: Adverse events, COVISHIELD, healthcare workers

Introduction

Coronavirus is an infectious disease caused by the SARS-CoV-2 virus, declared a Public Health Emergency of International Concern on January 30, 2020, by the WHO.[1] Since then, it has affected 55.4 million people across the globe, with a death toll of around 6.3 million.[2] Six types of human Coronaviruses (CoVs) have been formally recognized. These comprise HCoVHKU1, HCoV-OC43, Middle East Respiratory Syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) which is the type of the Beta coronavirus, HCoV229E, and HCoV-NL63, which are the member of the Alphacoronavirus. Coronaviruses did not

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draw global concern until the 2003 SARS pandemic, preceded by the 2012 MERS and, most recently, by the COVID-19 outbreaks. COVID-19 is spread by dust particles and fomites while close, unsafe touch between the infector and the infected individual. Airborne distribution has not been recorded for COVID-19 and is not known to be a significant transmission engine based on empirical evidence, although it can be imagined if such aerosol-generating practices are carried out in medical facilities.[3] People with COVID-19 have reported a wide range of symptoms – ranging from mild symptoms to severe illness. Symptoms include fever or chills, cough, shortness of breath, fatigue, body aches, headache, loss of taste or smell, sore throat, nausea, vomiting, diarrhea, etc., Symptoms may appear 2-14 days after exposure to the virus.[4]

Diagnostics have proven to be crucial to the COVID-19 pandemic response. Three types of diagnostics tests are relevant to patient management and pandemic control: molecular or nucleic acid amplification tests (e.g., PCR tests) that detect viral RNA; antigen tests that detect viral proteins (e.g., nucleocapsid or spike proteins); and serology tests that detect host antibodies in response to infection, or vaccination, or both. Molecular tests like PCR are highly sensitive and specific at detecting viral RNA and are recommended for confirming diagnosis in individuals who are symptomatic. Antigen rapid detection tests detect viral proteins and, although they are less sensitive than molecular tests, have the advantages of being easier to do, giving a faster time to result, being lower cost, and being able to detect infection in those who are most likely to be at risk of transmitting the virus to others. They can be used as a public health tool for screening individuals at enhanced risk of infection, protecting clinically vulnerable people, ensuring safe travel and the resumption of schooling and social activities, and enabling economic recovery. Serology tests provide only indirect evidence of infection 1–2 weeks after the onset of symptoms and are best used for surveillance.[5]

Various interventions were implemented to contain the spread of the virus, which included testing, tracing, travel restrictions, quarantine, and lockdown.[6] The development of a vaccine generally takes an average of 10–15 years.[7] However, different public organizations, regulatory agencies, and pharmaceutical companies worked together to develop COVID-19 vaccines rapidly with a scientific approach.[8] India is currently using four vaccines – the Oxford-AstraZeneca jab known as COVISHIELD; Covaxin by Bharat Biotech; Russian-made Sputnik V, and Corbevax.[9] The COVISHIELD vaccine or the ChAdOx1 nCov-19 is a vector vaccine administered in two doses, 4-12 weeks apart.[10] Adverse event following immunization is any untoward medical occurrence that follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, it can undermine confidence in a vaccine and ultimately have consequences for immunization coverage and disease incidence.[11] Minor reactions include local reaction, fever, and systemic symptoms that occur due to the vaccine inducing immunity by causing the recipient's immune system to react to it. An AEFI will be considered serious if it results in death, requires hospitalization, results in persistent or significant disability, or a cluster of AEFIs occur in a geographical area. AEFIs that are not minor but do not result in death, hospitalization, or disability are categorized as severe.[12]

This study evaluated adverse events following immunization (AEFI) among healthcare workers (HCWs) following first, second, and precautionary dose of ChAdOx1 nCov-19 Vaccine. The study also assesses the association of AEFI according to the study participants' characteristics.

Materials and Methods

Study setting

Tertiary care teaching hospital in central Karnataka.

Study design and population

This is a retrospective cohort study conducted for 18 months, from January 2021 to September 2022. The study population comprised all HCWs in a tertiary care teaching hospital. The inclusion criteria were the HCWs who were administered all three doses of the ChAdOx1 nCov-19 vaccine (0.5 ml in the deltoid – first, second, and precautionary dose). The exclusion criteria consisted of those who were not attending calls after three attempts and those who did not consent to be part of the study.

Timeline of vaccination – All the study participants received the vaccination in the tertiary care teaching hospital.

First dose: January to April 2022

Second dose: March to July 2022

Precautionary dose: January to March 2022

Vaccination

The vaccine used in this research is the ChAdOx1 nCoV-19 Coronavirus vaccine which is a recombinant vaccine containing l-histidine, l-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, and disodium edetate dihydrate. It is given as 0.5 ml intramuscularly, with an interval of 12-16 weeks for 18 years and above.

Data collection

A semi-structured, pretested questionnaire was used for telephonic interviews of the participants regarding adverse events following first, second, and precautionary dose of the ChAdOx1 nCov-19 vaccine. Their basic sociodemographic profile and comorbidity history were also collected. The adverse effects were categorized as minor, severe, and serious.

Minor AEFI: local reaction, fever, and systemic symptoms were categorized as minor AEFI. In addition, some of the vaccine's

components (e.g., adjuvant, stabilizers, or preservatives) can lead to reactions.

Severe AEFI: AEFIs that are not minor but do not result in death, hospitalization, or disability were categorized as severe. "Severe" was used to describe the intensity of a specific event (as in mild, moderate, or severe). The event itself, however, may be of relatively minor medical significance.

Serious AEFI: An AEFI was considered serious if it resulted in death or required hospitalization or resulted in persistent or significant disability/incapacity or a cluster of AEFIs occurring in a geographical area.

Data analysis

Data collected were analyzed using IBM SPSS v24.0. Chi-square test and *P* value (<0.05) were used to determine the association of AEFI with sociodemographic factors and comorbidities.

Ethical clearance

The study protocol was approved by the Institutional Ethical Committee. Informed consent was taken from the study participants.

Results

Demographic and comorbidity profile of study participants

A total of 454 HCWs who received all three doses of COVISHIELD participated in this study and were monitored for AEFIs. Out of the 454 HCWs, 223 were males (49.11%), and the remaining 231 (50.88%) were females.

As shown in Table 1, the majority 151 (33.3%) of the HCW belonged to the age group of 18-27 years, with the mean age being 43.0 ± 12.9 years. Among the respondents, the majority were undergraduates (147, 32.3%), followed by professors/consultants (79, 17.4%). Many of them did not have any comorbidities (388, 85.5%).

The prevalence of any AEFI following first, second, and precautionary doses were 44.9%, 32.8%, and 50.7%, respectively. Among those who did not report any adverse events, 116 (25.5%) did not develop any AEFI following all three doses of vaccination.

Among the participants, 250 (55.07%) after the first dose, 304 (67.18%) after the second dose, and 224 (49.34%) after the precautionary dose did not report any AEFI. Fever was reported among 138 (30.4%) of the participants after the first dose, 60 (13.22%) after the second dose, and 105 (23.13%) after the precautionary dose. Flu-like symptoms were seen in 46 (10.13%) participants after the first dose, 23 (5.07%) after the second dose, and 73 (16.08%) after the precautionary dose. Twenty-five (5.51%) of the HCWs complained of sore throat after the first dose, 27 (5.95%) after the second dose, and 92 (20.4%) after the precautionary dose. A majority, 156 (34.46%) of the HCWs, reported generalized weakness after the first dose, 93 (20.48%) after the second dose, and 183 (40.31%) after the precautionary dose. Changes at the injection site were reported among 80 (17.62%) after the first dose, 60 (13.22%) after the second dose, and 98 (21.59%) after the precautionary dose [Figure 1].

Table 1: Sociodemographic profile of study participants

Age	Number	Percentage (%)
18-27	151	33.3
28-37	116	25.6
38-47	82	18.06
48-57	66	14.5
58-67	33	7.3
≥68	6	1.3
Occupation	**Number**	**Percentage (%)**
Professor/consultant	79	17.4
PG	76	16.7
Intern	64	14.0
Undergraduate	23	5.0
Nursing staff	147	32.3
Ministerial staff	65	13.6
Comorbidities	**Number**	**Percentage (%)**
No comorbidities	388	85.5
Diabetes	21	4.6
HTN	16	3.5
Diabetes and HTN	26	5.7
Other	3	0.7

The majority of the respondents reported any AEFI on the same day of vaccination, 327 (72.06%) HCWs after the first dose, 356 (78.52%) after the second dose, and 294 (64.78%) after the precautionary dose. None of them reported any AEFI after 3 days of vaccination following first and second doses, and only 14 (3.04%) HCWs complained of persisting symptoms more than three days after vaccination [Figure 2].

Among the study participants, 375 (82.6%) after the first dose, 421 (92.73%) after second dose, and 382 (84.14%) after the precautionary dose carried out daily activities without any difficulty postvaccination [Figure 3].

Determinants of AEFI following first, second, and precautionary doses

As seen in Table 2, 116 females (25.6%) reported AEFI after the first dose. 86 (18.9%) HCWs in the 18-27 years age range reported symptoms after the first dose along with 51 (11.2%) members of the nursing staff. 170 (37.4) HCWs with no comorbidities had AEFI after the first dose. In association of AEFI with sociodemographic factors and comorbidity after the first dose, gender, age, and occupation are statistically significant.

In Table 3, it is seen that 80 (17.6%) females reported AEFI after the second dose. Fifty-six (12.3%) HCWs in the age group of

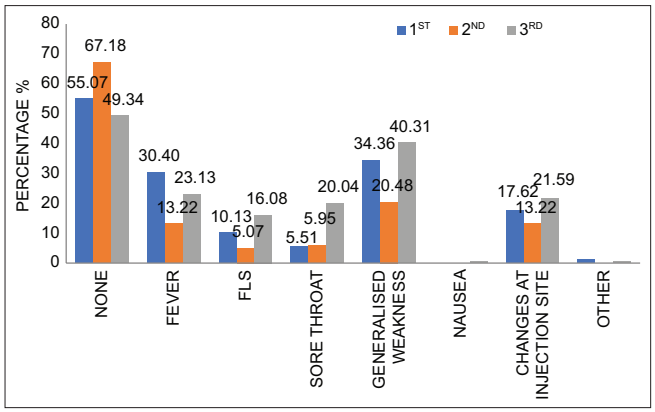

Figure 1: AEFI following first, second, and precautionary dose

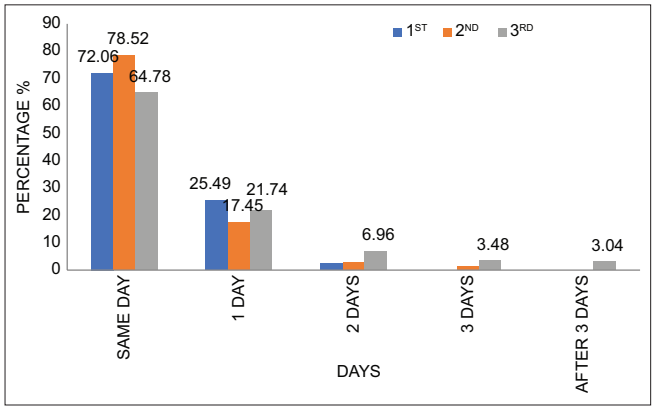

Figure 2: Timeline of AEFI following first, second, and third dose of vaccination

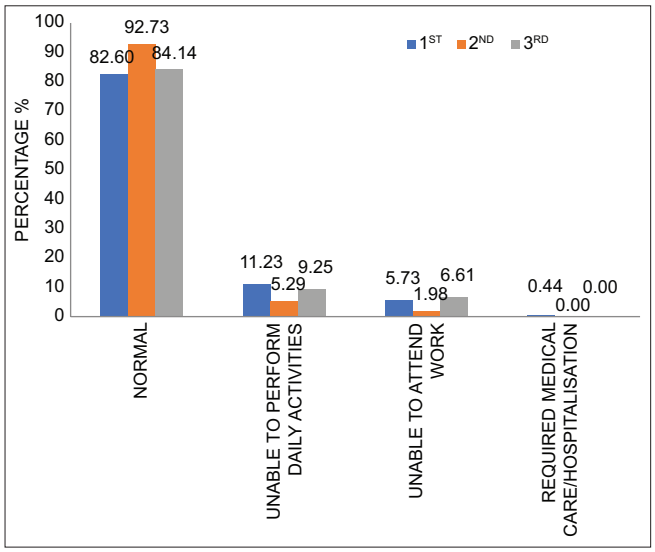

Figure 3: Health impact following first, second, and precautionary doses

18-27 years, 35 (7.7%) professors/consultants, and 122 (26.9%) HCWs with no comorbidities reported AEFI after the second dose. In association of AEFI with sociodemographic workers and comorbidity after the second dose, only occupation is statistically significant.

Table 2: Association of AEFI with sociodemographic factors and comorbidity

		After dose					
Characteristics		**Yes**	**%**	**No**	**%**	**x^2**	***P***
Gender	Male	88	19.4	143	31.5	8.89	0.002
	Female	116	25.6	107	23.6		
Age	18-27	86	18.9	65	14.3	18.04	0.002
	28-37	45	9.9	71	15.6		
	38-47	27	5.9	55	12.1		
	48-57	32	7.04	34	7.5		
	58-67	13	2.9	20	4.4		
	≥68	1	0.2	5	1.1		
Occupation	Professor/consultant	31	6.8	48	10.6	16.67	0.005
	PG	38	8.3	38	8.4		
	Intern	38	8.3	26	5.7		
	Undergraduate	14	3.08	9	2.0		
	Nursing staff	51	11.2	96	21.1		
	Ministerial staff	33	7.2	32	7.0		
Comorbidities	No comorbidities	170	37.4	218	48.02	2.31	0.67
	Diabetes	12	2.6	9	2.0		
	HTN	7	1.54	9	2.0		
	Diabetes and HTN	13	2.9	13	2.9		
	Other	2	0.4	1	0.22		

As mentioned in Table 4, 116 (25.6%), females reported symptoms after the third dose. It is also seen that 84 (18.5%) HCWs in the age range of 18-27 years, along with 55 (12.1%) nursing staff and 203 (44.7%) HCWs with no comorbidities reported AEFI after their precautionary dose—association of AEFI with sociodemographic factors and comorbidity after the third dose only occupation was statistically significant.

Discussion

In the present study, vaccine used was the ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 5 × 10 virus particles (vp) which contain l-histidine, l-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate (EDTA), and water for injection. The vaccination was given intramuscularly on the right forearm, first and second doses were given 12-16 weeks apart, and after a 1-year precautionary dose. Most of the HCWs following the first dose (250, 55.07%), second dose (304, 67.18%) and precautionary dose (224, 49.34%) did not report any AEFI. The most common AEFI reported was generalized weakness and fever following any of the doses.

In a similar study conducted by Joshi RK *et al.* among Armed Forces Medical Services HCWs deployed in Northern India, who took the first dose of ChAdOx1 nCoV-19 Coronavirus vaccine (Recombinant) voluntarily in January-February 2021, 105 vaccine recipients reported at least one AEFI symptoms. All AEFIs reported were of minor grade, with no severe or serious AEFI being reported among the vaccine recipients.[13] In another study by Menni C *et al.* from United Kingdom, systemic side-effects were reported among 33.7% of the

Table 3: Association of AEFI with sociodemographic factors and comorbidity

After second dose							
Characteristics		**Yes**	**%**	**No**	**%**	**x^2**	***P***
Gender	Male	70	15.4	161	35.5	1.59	0.2
	Female	80	17.6	143	31.5		
Age	18-27	56	12.3	95	20.9	3.42	0.49
	28-37	36	7.9	80	17.6		
	38-47	23	5.07	59	13.0		
	48-57	25	5.51	41	9.03		
	58-67	9	2.0	24	5.3		
	≥68	0	0	6	1.3		
Occupation	Professor/consultant	35	7.7	44	9.7	19.53	0.001
	Postgraduate	33	7.3	43	9.5		
	Intern	25	5.5	39	8.6		
	Undergraduate	5	1.1	18	4.0		
	Nursing staff	32	7.1	115	25.3		
	Ministerial staff	18	4.1	46	10.1		
Comorbidities	No comorbidities	122	26.9	266	58.6	4.37	0.35
	Diabetes	11	2.4	10	2.2		
	HTN	5	1.10	11	2.4		
	Diabetes and HTN	10	2.2	16	3.5		
	Other	1	0.2	2	0.4		

Table 4: Association of AEFI with sociodemographic factors and comorbidity

After Precautionary dose							
Characteristics		**Yes**	**%**	**No**	**%**	**x^2**	***P***
Gender	Male	114	25.1	117	25.77	0.32	0.57
	Female	116	25.6	107	23.56		
Age	18-27	84	18.5	67	14.8	8.86	0.11
	28-37	58	12.8	58	12.8		
	38-47	34	7.5	48	10.6		
	48-57	39	8.6	27	6.0		
	58-67	12	2.6	21	4.6		
	≥68	3	0.7	3	0.7		
Occupation	Professor/consultant	51	11.2	28	6.2	22.4	0.0004
	Postgraduate	45	9.9	31	6.8		
	Intern	37	8.1	27	5.9		
	Undergraduate	14	3.1	9	2.0		
	Nursing staff	55	12.1	92	20.3		
	Ministerial Staff	28	6.1	37	8.1		
Comorbidities	No comorbidities	203	44.7	185	40.7	8.34	0.07
	Diabetes	9	2.0	12	2.6		
	HTN	4	0.9	12	2.6		
	Diabetes and HTN	14	3.1	12	2.6		
	Others	0	0	3	0.7		

participants, and local side-effects were reported by 58.7% of the participants after the first dose of ChAdOx1 nCoV-19 vaccination. Both figures are much higher than that observed in our study.[14]

In our study, fever was the commonest adverse event following first, second, and precautionary dose of vaccination, and it was similar to another study conducted by Jeon M *et al.* from the Republic of Korea (27.6%).[15]

In our study, the second commonest adverse event reported by the majority of the HCWs was generalized weakness following first, second, and precautionary dose whereas in a study by Jeon M *et al.*, from Republic of Korea the most reported systemic AEFIs were fatigue (92.9%) and malaise (83.8%).[15]

In our study, the incidence of AEFI was reported more among males, younger populace (18-27 yr old), nursing staff, and those with no morbidities following the first dose, but significant association was found with gender, age, and faculty. And following the second dose, the incidence of AEFI was higher among females, 18-27 years old, consultants, and those with no morbidities, but significant association was found only with occupation/designation of the study participants. Following third/precautionary dose, AEFI incidence was more among 18-27 years old nursing staff and those with no morbidities, whereas a significant association was found only with occupation. This was different compared to a similar study conducted by Jeon M *et al.*,[13] who found a higher incidence of AEFI among older respondents (>50 years) and a significant association with increased age of the study populace. Differences in the incidence of adverse events with gender, designation, morbidities, and age groups might be due to the type of study population (HCWs) and relatively smaller sample size.

Conclusion

The majority of the study population did not report any adverse events following vaccination. Among the study participants who reported adverse events, most events were reported on the same day. Symptoms were mild in severity and short-lived. The incidence of adverse events was more following a precautionary dose of vaccination, and the overall incidence of AEFI was found to be a statistically significant association with younger age groups and type of work.

Strength of the study

The present study has looked at the incidence of adverse events following three doses of the ChAdOx1 nCoV-19 Coronavirus vaccine and compared the determinants for each dose. In this study, we have conducted active surveillance for the AEFI among HCWs following the precautionary dose of vaccine for up to 1 month. All the study participants had received three doses of vaccine, and the completeness of reporting was ensured as dedicated team members were responsible for surveillance of accurate and complete reporting of the adverse events. The authenticity and accuracy of adverse events reporting were better as the study participants were HCWs who would understand and precisely report the adverse events.

Limitations

As the study participants were asked to recollect events following first and second dose of vaccination over the past 1-year, there is a high chance of recall bias. This study was performed on a specific occupational group, thus leading to selection bias and not representing the population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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