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Association of Adverse Effects following COVID-19 Immunization with Previously COVID-19 Infected and Non-Infected Health Care Professionals

Prerna Bansal,[1] Pallavi Koirala,[1] Ayasha Shrestha,[1] Hari Prasad Upadhyay,[2] Kamal Khadka,[1] Ranjeeta Phuyal[1]

[1]Department of Community Medicine, College of Medical Sciences - Teaching Hospital, Bharatpur, Chitwan, Nepal.

[2]Department of Statistics, Birendra Multiple Campus, Bharatpur-10, Chitwan, Nepal.

ABSTRACT

Introduction

The immunogenicity of COVID-19 disease and variability among adverse effects following COVID-19 vaccine in previously infected and non-infected individuals is not clearly understood. So, this study aims to assess the association of adverse effects of COVID-19 vaccine with previously infected and non-infected individuals.

Methods

A case-control study was conducted at College of Medical Sciences, Bharatpur, Chitwan, Nepal from July 2021 to February 2022 among 324 health care professionals who had received two doses of COVID-19 vaccine. Cases included those who developed any adverse effects following COVID-19 immunization and controls included those who did not develop any adverse effects. Exposure was presence and non-exposure was absence of previous COVID-19 infection. The data collected was analyzed in SPSS version 17 software in terms of frequency, percentage, mean, standard deviation, chi-square, exposure rates and odds ratio.

Results

Mild adverse effects like fever, myalgia, headache and pain in injection site were observed following both first dose (46.9%) and second dose (6.17%) of vaccine. The exposure rate was more in cases (23.45%) than in controls (11.11%). Odds ratio was 2.452 (95 % CI, 1.332 to 4.512, $p<0.05$) which is statistically significant.

Conclusions

The risk of developing adverse effects following COVID-19 immunization was 2.452 times more in health care professionals who were previously infected with COVID-19 as compared to those who were not infected. Thus, there is a significant association of adverse effects following COVID-19 immunization with previous COVID-19 infection.

Keywords: adverse effects following immunization; association; case-control studies; COVID-19 vaccines; health care professionals

Correspondence: Dr. Prerna Bansal, Department of Community Medicine, College of Medical Sciences - Teaching Hospital, Bharatpur-10, Chitwan, Nepal. Email: drprernabg@gmail.com. Phone: +977-9841529167.

INTRODUCTION

The COVID-19 pandemic has taken millions of lives globally.[1,2] Vaccines are the most effective protective tools that are being produced at an unprecedented speed and have saved millions of lives.[3] It has been one of the biggest and fastest achievements of health and research.[4] Health care professionals are the first ones to receive the vaccine worldwide including Nepal.[5,6]

The natural history of this disease and how long the protection acquired by the recovered person is still unknown.[7] One of the epidemiological features of this disease which is still unclear is its immunogenicity.[8] The variability among adverse effects in previously infected and non-infected individuals with COVID-19 is also not clearly understood.[9] Adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. Effective vaccines (i.e. vaccines inducing protective immunity) may produce some undesirable side effects which are mostly mild and clear up quickly.[10]

This study aims to assess the association of adverse effects following COVID-19 immunization with previously COVID-19 infected and non-infected individuals. In this research the disease outcome is development of any adverse effects following COVID-19 immunization and the exposure to be investigated is presence or absence of COVID-19 infection before COVID-19 immunization. So, it would help to find out if adverse effects of the vaccine is associated with a previous exposure to the virus.

METHOD

A case-control study was designed and conducted among the health care professionals (HCPs) of College of Medical Sciences-Teaching Hospital, Bharatpur, Chitwan District, Nepal from July 2021 to February 2022. The calculated sample size using case control study design sample size calculation formula was 308 (154 cases and 154 controls) by taking prevalence of adverse effects following immunization in COVID-19 infected group as 33% and prevalence of adverse effects following immunization in COVID-19 non-infected group as 19%[11], 95% CI, r=1, 5% level of significance, 80% power of test and 0.14% margin of error. After matching with variables like age, gender, occupation and type of vaccine, 324 health care professionals were enrolled in the research. Out of these 324, 162 were cases and 162 were controls(r=1) .

All health care professionals of College of Medical Sciences - Teaching Hospital, Bharatpur who were immunized with two doses of COVID 19 vaccine either with ChAdOx1 nCoV-19 Vaccine -Covishield or with Inactivated Sinopharm- Vero Cell were included in the study and those health care professionals who had not been immunized with two doses of any of the COVID-19 vaccine during the study period were excluded from the study. For collection of data a self-structured questionnaire was used. Health care professionals of the study place were interviewed over phone calls and during immunization campaigns by the data collection unit and all the informations were recorded in the self-structured questionnaire. Health care professionals who developed any adverse effects following COVID-19 immunization were recorded as case and health care professionals who did not develop any adverse effects following COVID-19 immunization were recorded as control. Exposed group involved all health care professionals who had been diagnosed of

having COVID-19 infection by a positive RT-PCR test prior immunization with COVID-19 vaccine. Non-exposed group involved all health care professionals who had not been tested positive on a RT-PCR test for COVID-19 prior immunization with COVID-19 vaccine. Any adverse effect following immunization with at least one dose of COVID-19 vaccine was included as adverse effects following immunization (AEFI). The data set was matched with four variable i.e age, gender, occupation (doctor, nurse, paramedics, supporting health staff) and type of vaccine received (ChAdOx1 nCoV-19 Vaccine -Covishield and Inactivated Sinopharm- Vero Cell) by the health care professionals. Matching was done to minimize selection bias. To minimize recall bias collected data and informations were also verified with available hospital records.

Ethical approval was taken from Institutional Review Committee of College of Medical Sciences Teaching Hospital (Ref no. COMSTH-IRC/2021-135). Informed verbal consent was taken from all the health care professionals prior enrollment into the study. Confidentiality of all data and information were maintained throughout the research.

The data collected was entered, cleaned, checked for completeness and accuracy before subsequent analysis in SPSS version 17 software. For continuous variables mean and standard deviation was calculated while categorical variables were analyzed in terms of frequency and percentage. To find the association between dependent and independent variables chi-square test was used. P-value <0.05 were considered as statistically significant. To find the odds of exposure and strength of association between exposure and outcome odds ratio was calculated by Mantel-Haenszel method.

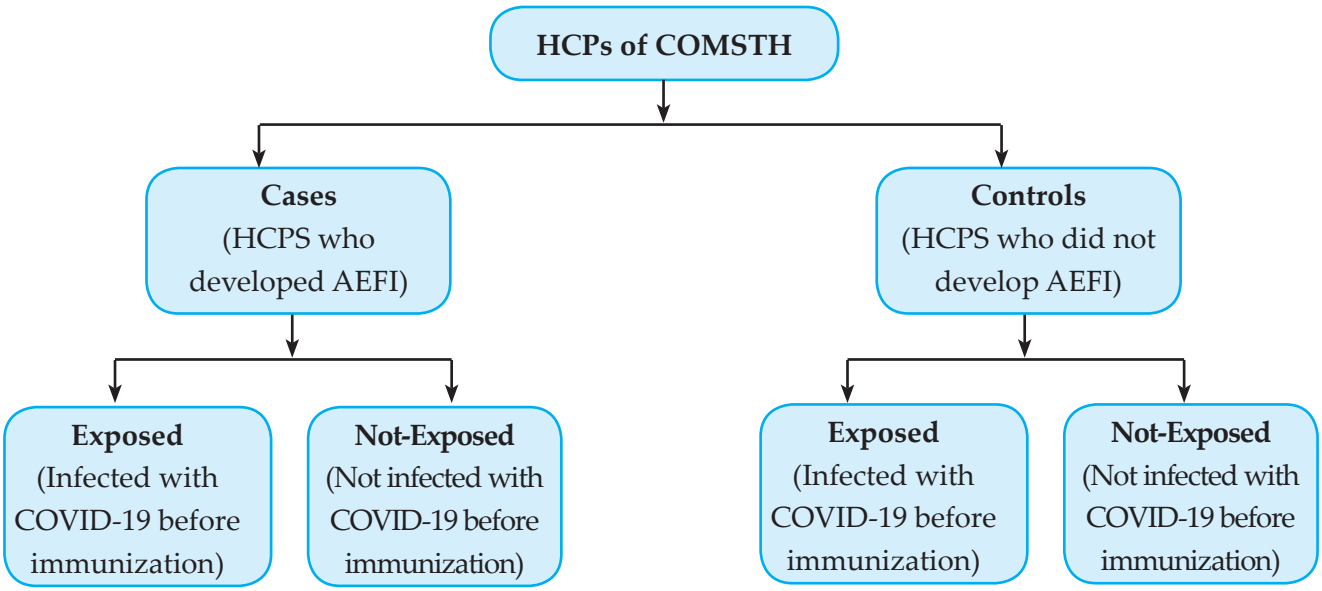

Figure 1. Conceptual Framework of Case-Control Study Design.

RESULTS

The mean age of health care professionals was 27.29 ± 7.282 with majority of them i.e. 71.6% participants of 21-30 years age group. Majority of the HCPs were females (72.2%)

as compared to males (27.8%). The study population comprised of 43.2 % nurses, 31.5 % doctors and remaining were paramedics and supporting health staff. Out of total 324 health care professionals, 90.7 % had received two doses of ChAdOx1 nCoV-19 Vaccine (Covishield) and 9.3 % had received two doses of Inactivated Sinopharm (Vero Cell) Vaccine. There was no significant association found between development of adverse effects following COVID-19 vaccines with variables like age, gender, occupation of health care professionals and type of vaccine received by health care professionals. The p value was > 0.05 (Table 1).

About 46.9 % of health care professionals developed at least one type of adverse effect following first dose whereas, 6.17 % health care professionals developed adverse effects following the second dose of COVID-19 vaccine. Mild adverse effects like fever (34.56 %), myalgia (8.02 %), headache (3.08 %), pain in injection site (2.77 %), chills (0.61%) and dizziness (0.61%) were seen following first dose of vaccine.

Similarly, following second dose of vaccine also mild adverse effects like fever (2.46%), myalgia (2.46%) and headache (0.92%) were

Table 1. Descriptive characteristics of cases and controls and their association. (n=324)

Descriptive characteristics		Cases Frequency (50%)	Controls Frequency (50%)	Total Frequency (%)	Chi-square (p-value)
Age (years)	≤ 20	10	10	20 (6.2)	0.000 (1.000)
	21-30	116	116	232 (71.6)	
	31-40	22	22	44 (13.6)	
	41-50	13	13	26 (8.0)	
	>50	1	1	2 (0.6)	
	Mean ± SD	27.29 ± 7.282			
Gender	Male	45	45	90 (27.8)	0.000 (1.000)
	Female	117	117	234 (72.2)	
Occupation	Doctor	51	51	102 (31.5)	0.000 (1.000)
	Nurse	70	70	140 (43.2)	
	Paramedics	7	7	14 (4.3)	
	Supporting health staff	34	34	68 (21.0)	
Type of vaccine received	ChAdOx1 nCoV-19 Vaccine (Covishield)	147	147	294 (90.7)	0.000 (1.000)
	Inactivated Sino-pharm (Vero Cell)	15	15	30 (9.3)	

observed (Table 2).

Table 2. Adverse effects following immunization (AEFI) with COVID-19 vaccine. n = 324

	After First Dose (Frequency, %)	After Second Dose (Frequency, %)
AEFI	152 (46.9)	20 (6.17)
Fever	112 (34.56)	8 (2.46)
Myalgia	26 (8.02)	8 (2.46)
Headache	10 (3.08)	3 (0.92)
Pain in injection site (PIS)	9 (2.77)	1 (0.30)
Chills	2 (0.61)	0
Dizziness	2 (0.61)	0
Common cold	1 (0.30)	0
Rigor	1 (0.30)	0
Joint pain	1 (0.30)	0
Nausea	1 (0.30)	0
Diarrhoea	0	1 (0.30)

The exposure rate among cases was 23.45% whereas among controls was 11.11%. Odds ratio was calculated using Mantel-Haenszel test which was found to be 2.452 (95 % CI, 1.332 to 4.512) where p value was <0.05, which is statistically significant (Table 3).

Table 3. Exposure Rates and Odds Ratio. (n = 324)

	Cases (AEFI observed following immunisation)	**Controls** (No AEFI observed following immunisation)	**Total**
Exposed (Infected with COVID prior immunisation)	38	18	56
Non-exposed (Not infected with COVID prior immunisation)	124	144	268
Total	162	162	324
Exposure Rates among cases	23.45%		
Exposure Rates among controls	11.11%		
Odds Ratio (OR)	2.452, 95 % CI, 1.332 to 4.512, p = 0.005		

DISCUSSION

In this study, the mean age of health care professionals was 27.29 ± 7.282 whereas in the study conducted by Rajneesh K. Joshi showed the mean age was 32.04 (7.84) years.[12] Majority of the health care professionals were females (72.2%) as compared to males (27.8%) in this study which was similar finding like an another study done among health care workers in India.[13] The present study population comprised

of 43.2 % nurses, 31.5 % doctors and remaining paramedics and supporting health staff.A study done in Turkey by Abanaib Raid et al., showed that among 780 participants, 32% were physician, 37.8% dentist, 19.2% pharmacist, 5.5% nurses and 1.3% midwives which was similar to our findings.[14]

In this study adverse effects following immunization was seen in 152 (46.9%) health care professionals following the first dose of vaccine, whereas after second dose of COVID-19 vaccine adverse effects following immunization was seen in 20 (6.17 %) health care professionals. Similarly, another study done among medical workers in Kerala, India showed that 63.3% developed adverse effects after the first dose and 24.3% after the second dose of Covishield vaccine.[15] But in study done by Chaudhary et.al, 57% and 33.7% of recipients reported adverse events after the first dose of vaccine and much higher frequencies of adverse events (88%) were found after second dose of the vaccination.[13]

The five most common AEFI's reported in the present study were: Fever in 112 (34.56%), Myalgia in 26(8.02%), Headache in 10 (3.08%), Pain in injection site (PIS) in 9(2.77%) and Chills in 2(0.61%) health care professionals. No severe adverse effects of the vaccine were seen in this study. The common AEFIs observed in our study and the frequency of occurrence were comparable to the data from the interim analysis of pooled data on COVID-19 vaccine from four clinical trials conducted in the United Kingdom, Brazil and South Africa.[16]Another study also found that most common mild systemic adverse effects experienced were fatigue (9%), headache (8%) and chills or shivers (4%), most of them appeared in the first two days after the vaccination and only 3% of people have any adverse effects beyond three days.[11]

In a study done in India about adverse effects following immunization among health care workers there was no association of adverse effects following immunization with sex and profession and significant association was found with age. No serious adverse effects following immunization was reported.[17] Study done in Bangladesh showed that the adverse events were 54.1% and 41.3 % after the first and second dose respectively and the difference was statistically significant ($p<0.001$). Age and co-morbidities were significantly associated with the adverse events in another study.[18]Similarly, in the present study adverse effects following immunization among the health care professionals found no association with their age, gender, occupation and type of vaccine received by them.

A study done in Nepal by Shrestha et al., showed out of 807 vaccine receipts with previous history of COVID-19, 709 (87.%) had AEFI while of the 3184 with no past history of COVID-19, 2685 (84.3%) had AEFI.[19] A study done among medical workers in Kerala, India showed that 8.5% had a history of previous COVID infection and it had no association with adverse events.[15] One another study also evaluated the prevalence of adverse effects after the first dose of either the Pfizer or Moderna vaccines in 231 patients who had previously tested positive for SARS-CoV-2 or had never been exposed to it. It showed that symptoms such as pain or swelling at the injection site were comparable in both groups of patients, whole-body reactions like headache, chills, fever, and muscle or joint problems were more frequently reported by those who had recovered from COVID-19.[20]

In the present study 23.45% of health care professionals who had previous history of COVID-19 developed adverse effects and 11.11% of health care professionals with no past history of COVID-19 did not develop any adverse effects. The Odds ratio was found to be 2.452 (95% CI, 1.332 to 4.512), $p<0.05$ which

is statistically significant and showed that there is 2.452 times risk of developing adverse effects following COVID-19 immunization in previously COVID-19 infected health care professionals than previously non-infected health care professionals. These findings correlated well with the findings of ZOE COVID Symptom Study which states that, people who have had a previous COVID-19 infection are almost twice as likely to experience one or more systemic adverse effects compared to people who didn't have COVID-19 (33% vs 19%) from a Pfizer/BioNTech vaccine dose.[11] The findings of this study are similar like the above mentioned studies.

Thus, the present study shows that there is association of adverse effects following COVID-19 immunization with previously COVID-19 infected and non-infected individuals. So, the sign of effectiveness of vaccines, i.e. producing some undesirable side effects which are mostly mild and clear up quickly is dependent on a previous exposure to the virus. Hence, the findings of this research would help researchers to understand the immunogenicity of the the disease further.

CONCLUSIONS

The risk of developing adverse effects following COVID-19 immunization was found to be 2.452 times more in health care professionals who were previously infected with COVID-19 as compared to those who were not infected with COVID-19. Thus, there is a significant association between presence or absence of COVID-19 infection and development of adverse effect following immunization with COVID-19 vaccine.

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