COVID 19 Vaccine Breakthrough Infection among Health Care Workers

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Citation

Tamrakar D, Katuwal N, Adhikari P, Banjara M, Shrestha N, Poudel P, et al. COVID 19 Vaccine Breakthrough Infection among Health Care Workers. *Kathmandu Univ Med J.* 2023;82(2):163-9.

ABSTRACT

Background

Mass vaccination is considered the primary strategy for reducing the impact of COVID-19, and it has been implemented globally.

Objective

To study the extent of SARS-CoV-2 infection and breakthrough infection among the HCWs who were fully vaccinated for at least 14 days and investigated the relation between neutralizing antibody response and breakthrough infection.

Method

This study was a retrospective cohort study among health care workers at Dhulikhel Hospital Kathmandu University Hospital from December 2021 to October 2022. The interviews with semi structured questionnaire were conducted in person or over phone. Out of 1450 participants 137 fully vaccinated HCWs without breakthrough infection were randomly selected for the prospective serological cohort.

Result

Out of 1079 participants' majority (51.8%) were of age 25-34 years. Two thirds (66.7%) were females. More than half of participant (54.7%) had infection with SARS-CoV-2 at least once whereas more than one third people (35%) had reported SARS-CoV-2 infection 14 days after receiving full vaccination. Infection after vaccination had less moderate and sever/critical illness and less need for hospitalization as compared to infection before vaccination. Staffs who were directly involved in patient care had higher chance of breakthrough infection compared to those not involved directly in patient care. Those who had prior infection or booster dose had relatively higher antibody level and participants with low level of antibody had higher chance for breakthrough infection (35.3%) than participants with moderate to high level of antibody (11.9%).

Conclusion

Vaccinations significantly decreased severe diseases and the need for hospitalizations. Breakthrough infection was higher among the health care workers involved in direct patient care and with low level of antibody.

KEY WORDS

Antibody level, Breakthrough infection, COVID 19, COVID 19 vaccination

INTRODUCTION

Mass vaccination is considered the primary strategy for reducing the impact of COVID-19, and it has been implemented globally. In Nepal, the COVID-19 vaccination campaign began on January 27, 2021, with the target of vaccinating healthcare workers and high-risk groups with Covishield.[1,2] Since then, Nepal has conducted several vaccination campaigns targeting the population aged five years and above.[3,4] The country has approved nine vaccines for emergency use, including two-dose series of Covishield, Vero Cell, Astrazeneca, Pfizer-BioNTech, Moderna, Covaxin, Sputnik V, CoronaVac, and a one-dose series of Janssen/ Johnson & Johnson.[5]

Emerging novel strains, waning vaccine effectiveness, and changes in preventive behaviors can contribute to breakthrough infections after COVID-19 vaccination.[6-9] Therefore, the booster dose is required after initial primary vaccination. Nepal started the booster vaccination on December 2021 for age more than 18 years while the cases due to omicron were beginning to peak.[10-12]

As healthcare workers are at a high risk of occupational exposure to the virus, assessing breakthrough infection rates among this cohort is critical to understanding the effectiveness of vaccination and preventing nosocomial disease transmission.[8,13,14]

Neutralizing antibodies are an important measure of immunological protection against COVID-19 and can help predict the extent of protection provided by vaccination or prior infection.[15-18] However, low levels of neutralizing antibodies may not provide adequate protection against infection, which could lead to breakthrough infections.[19-21]

Thus, we aimed to study the extent of SARS-CoV-2 infection and breakthrough infection among the fully vaccinated HCWs and investigate the relation between neutralizing antibody response and breakthrough infection.

METHODS

Dhulikhel Hospital Kathmandu University Hospital (DHKUH) is tertiary care university hospital with more than 1400 employees working in hospital, academics, administration and research. It was the designated referral center for COVID 19 management from the beginning of pandemic. The hospital rapid response team initiated the questionnaire based screening of the exposure to SARS-CoV-2, quarantine of high risk exposure, free testing of infection by means of reverse transcriptase-polymerase chain reaction (RT-PCR), and isolation in case of positive cases. Later the policy was modified to symptoms based screening, testing and isolation. All the HCWs at DHKUH were vaccinated with first and second dose of covishield in January 2021 and April 2021 respectively. Around 99% of staffs are vaccinated with either second dose of covishield (Serum Institute, India) or Vero Cell (Sinopharm, China) till date while 1% were not vaccinated due to ineligibility according to criteria set out for vaccination such as pregnancy or active infection with COVID-19.

We conducted retrospective cohort study among the HCWs of DHKUH who were fully vaccinated for at least 14 days. We chose 14 days' time interval to allow the immune response to develop. Fully-vaccinated was defined as an individual who had received one of the COVID 19 vaccines authorized by the Ministry of Health and Population, Department of Health Services: two doses series of covishield, Vero Cell, AstraZeneca, Pfizer-BioNTech, Moderna, covaxin, Sputnik V, CoronoVac or one dose series of Janssen/ Johnson & Johnson.[5] Partial Vaccination was defined as an individual who had received one dose of two doses series of authorized vaccines. We included all the HCWs who have been working in hospital for at least six months and consented to be part of the study.

Breakthrough Infection was defined as laboratory confirmed (PCR or rapid antigen) SARS-Cov2 infection occurring after being fully vaccinated for at least 14 days. Reinfection was defined as the laboratory confirmed (PCR or rapid antigen) SARS-Cov2 infection among who previously had infection of SAR-CoV-2 irrespective of their vaccine status.

For the serological cohort study, we randomly selected 137 subjects by a computer generated simple random method from fully vaccinated subjects who had not had breakthrough infection at the time of interview. We followed them up after six months to investigate the relationship between breakthrough infection and neutralizing antibody titer.

The contact details of all the vaccinated HCWs was extracted from DHKUH employee database. Between December 2021 - January 2022, a total of 1450 HCWs employed at DHKUH including doctors, nurses, paramedics (health assistants and community medical assistants), administrative staffs (staffs working in administration excluding doctors or nurses), support staffs (staffs working in hygienic department, center sterile supply department, ward boy etc.) and research staffs (staffs working in research department) were contacted through phone calls. The phone calls were conducted by trained research assistants who followed a standardized script to ensure consistency and accuracy of the data. During the calls or in person interview, HCWs were asked series of questions regarding age, sex, time since vaccination, vaccine type, close contact with confirmed COVID 19 cases (defined as within one meter for more than 15 minutes), history of COVID-19 infection confirmed by either antigen test or PCR, symptoms and clinical outcomes of the infection. The collected data were entered in EPIDATA platform which was extracted into SPSS version 23 (IBM Corp., Armonk, NY) for analysis.

Five ml of venous blood was collected from randomly selected serological cohorts. The blood was allowed to clot for 30 minutes then centrifuged at 2500 rpm for 10 minutes. The serum was extracted in aliquot and analyzed for neutralizing antibody by using the cPassTM SARS-CoV-2 neutralization antibody detection kit (GenScript, Cat: L00847). The samples were tested in singlet with blanks and appropriate controls provided by the kit. The kit used was a blocking ELISA detection tool which uses Horse Radish Peroxidase (HRP) conjugated purified Rapid Binding Protein (RBD) protein and host receptor protein ACE2 were used to mimick the virus-host interaction. This interaction was blocked in the presence of neutralizing antibody (NAb) against the RBD.

For serological analysis the samples were first diluted with sample dilution buffer and incubated with HRP-RBD to allow the binding of the circulating neutralization antibodies to HRP-RBD. The mixture was then added to the ELISA wells which are coated with hACE2 protein. The unbound HRP-RBD and HRP-RBD bound to non-neutralizing antibodies are captured on the plate while the circulating NAb-HRP-RBD complexes remain in the supernatant and are removed during the washing. After that wash, TMB substrate solution was added followed by the stop solution and the reaction was then quenched which turns the reaction color to yellow. The final absorbance was taken at 450 nm with reference at 655 nm using the BioRad iMark ELISA Plate Reader. The absorbance was recorded and the % neutralization was calculated as provided by the manufacturer. The quality control of the plate was done by evaluating the Optical Density (OD) range of positive and negative control as per the batch of the kit provided by the manufacturer. To calculate the subsequent amount of IU/ml for each sample, International Units (IU) calculator, as per WHO International Units was used by calibrating their neutralization assays against the WHO international standard for SARS-CoV-2 immunoglobulin.[22]

Prior to the study, all the participants were informed about the research objectives and method, and written informed consent was obtained from each participants. For the serological study group, additional consent was obtained for blood draw after explaining the study procedure. The study received ethical approval from Nepal Health Research Council Ethical Review Board and Kathmandu University School of Medical Sciences Institute Review Board.

Following data collection, the research team reviewed the data for completeness and consistency. The review team examined each questionnaire to ensure that all necessary information had been obtained and that there were no discrepancies or errors in the responses. The collected data were analyzed by descriptive and inferential statistics. For serological data, the data was analyzed using the cutoff set in (GenScript, Cat: L00847) kit to investigate the level of antibody present NAbs: < 1500 IU/ml-Low,1500-5000 IU/ml-Medium, > 5000 IU/ml-High. For categorical variables like gender, vaccine type, designation etc. results were expressed in frequencies and percentages and analyzed using Chi-square test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Out of the 1450 Participants, 1082 (74.6%) consented to participate in the study. Three participants were excluded because they were not vaccinated at the time of interview, thus 1079 were recruited in the study (Fig. 1). Majority of participants (n=559; 51.8%) were of age 25-34 years. Two thirds (n=720; 66.7%) were females. Nurses were more (n=313; 29.0%) followed by support staffs (n=296; 27.4%), paramedics (n=166; 15.4%), research (n=139; 12.9%), doctors (n=138; 12.8%) and administrative staffs (n=27; 2.5%). Majority (75.5%) were vaccinated with Covishield (Table 1). Majority of the participants 951 (88.1%) had close contact with COVID-19 positive of which 46.1% had close contact with their worksite colleague, followed by treating patients (31.5%), and family, friends and relatives (20.15%).

Table 1. Distribution of socio-demographic characteristics of HCWs who were fully vaccinated and factors associated with COVID 19 breakthrough Infection after full vaccination (N=1079)

Characteristics	Category	Fully Vaccinated n(%)	Breakthrough Infection n(%)	P value
Age in Years	18-24	223 (20.7)	88(39.5)	<0.001
	25-34	559 (51.8)	203(36.3)	
	35-44	235 (21.8)	76(32.3)	
	45-54	44 (4.1)	8(18.2)	
	55+	18(1.7)	3(16.7)	
Gender	Male	359 (33.3)	106(29.5)	0.007
	Female	720 (66.7)	272(37.8)	
Designation	Doctors	138 (12.8)	51(37.0)	<0.001
	Nurses	313 (29.0)	141(45.0)	
	Paramedics	166 (15.4)	65(39.2)	
	Adminis-tration	27 (2.5)	11(40.7)	
	Supportive Staffs	296 (27.4)	72(24.3)	
	Research and Devel-opment	139 (12.9)	38(27.3)	
Directly Involved in Patient Care	Yes	617(57.2)	257(41.7)	<0.001
	No	462(42.8)	121(26.2)	
Prior Infection Before Full Vaccination	Yes	317(29.4)	105(33.1)	0.39
	No	762(70.4)	273(35.8)	
Type of Vaccine	Covieshield	815 (75.5)	302(37.1)	0.08
	Vero cell	253 (23.5)	74(29.2)	
	Others	11(1.0)	2(18.2)	

SARS-Cov2 Infection among the Health Care Workers

More than half of the participants 590 (54.7%) were infected with COVID-19 at least once of which 25.6% of the participants were infected prior to vaccination, 8.5% after partial vaccination and 46.3% after full vaccination. Reinfection occurred in 17.7% of participants after full vaccination and in 1.9% after partial vaccination. More than one third people (35%) had SARS-CoV-2 infection 14 days after full vaccination meeting the definition of the breakthrough infection (Fig. 1).

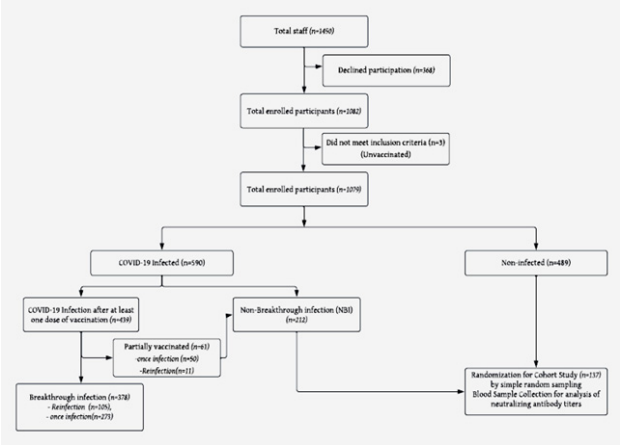

Figure 1. Flow Diagram Depicting Enrollment and COVID 19 infection; Breakthrough infection; laboratory confirmed SARS-Cov2 infection in HCWs after 14 days of full vaccination, Non breakthrough infection: laboratory confirmed SARS-Cov2 infection in un-vaccinated or partially vaccinated or during 14 days full vaccinated HCWs

Majority of the participants with SARS-CoV-2 infection after at least one dose of vaccination had asymptomatic/ mild illness (91.9%) and few had moderate illness (9.5%.) whereas most of the participants with SARS-CoV-2 infection before vaccination had asymptomatic or mild illness (86.8%).

Moderate illness (11.3%) and severe or critical illness (2.0%) among those who had SARS-CoV-2 infection before vaccination was higher than infection after at least one dose of vaccination which was statistically significant. Need for hospitalization was significantly higher in SARS-CoV-2 infection before vaccination (13.6%) than infection after vaccination (3.0%) (Table 2).

Breakthrough Infection

Breakthrough infection was significantly higher in younger age group 18-24 (39.5%), then 25-34 (36.3%), and decreased as age group increased. Similarly, female employees (37.8%) had greater rate of breakthrough infection as compared to male employees (29.5%). Staff who were directly involved in patient care (41.7%) had greater chance of breakthrough infection compared to those not involved directly in patient care (26.2%). The staff like nurses and paramedics had greater rate of breakthrough infection.

Table 2. Comparison of Clinical Outcome between SARS-Cov2 infection in unvaccinated individuals and at least one dose vaccinated individuals (N=590)

Characteristics	Category	Infection after Vaccination n (%)	Infection before Vaccination n (%)	P value
Severity Status	Mild/ Asymptomatic Illness	400(91.1)	131(86.8)	0.008
	Moderate Illness	39(8.9)	17(11.3)	
	Severe/ Critical Illness	0(0.00)	3(2.0)	
Needed Hospitalization	Yes	13(3)	13(8.6)	0.004
	No	426(97.0)	138(91.4)	

More than one third (37.1%) of participants vaccinated with Covishield, 29.2% Vero Cell and 18.2% vaccinated with other vaccines (Johnson and Johnson and Moderna) had breakthrough infection. There was no statistical significance in association between breakthrough infection and type of vaccine. Around 1/3rd of the participants (29.4%) had infection before the 2nd dose of the vaccination and there is no significant difference in the incidence of the breakthrough infection based on prior history of the infection (p value: 0.39) (Table 1).

Serological Cohort Study

Serological assay was done in 137(12%) participants in serological cohort study of which majority (62%) were female and majorly of age group 25-34 years (49.2%) followed by age group 35-44 years (27.7%). Most of the participants were nurses 29.9% and support staffs 26.3%. When the neutralizing antibody (NAbs) were quantified in IU/ml, 13.1% subjects had low NAbs (< 1500IU/ml) ,81.0% had medium NAbs (1500-5000IU/ml) and 5.8% subjects had high NAbs (> 5000 IU/ml). Out of 137 participants 19.7% had prior infection before vaccination and 70.8% of the participants had been vaccinated with booster vaccination at the time of blood draw. Those who had prior infection or booster dose had relatively higher antibody level high however, this interpretation was not statistically significant.

Out of the cohort of 137 participants, only 126 could be followed up after 6 months. The remaining (n=11) either could not be contacted or had left the institution. Among them, 15.1% of participants had breakthrough infection. All of the participants with breakthrough infection had mild infection except one who had moderate infection. Those who had low level of antibody had higher chance of the breakthrough infection than those who have moderate to high antibody level which was statistically significant. Similarly, those who received second booster dose had less chance of the breakthrough infection which was marginally statistically significant.

Table 3. Distribution of Antibody Level among Serological Cohort with Prior and Booster Infection

Variable	Category	Mild n(%)	Moderate-High n (%)	P value
Prior infection	Yes	1(3.7)	26(96.3)	0.10
	No	17(15.5)	93(84.5)	
Booster Vaccine	Yes	11(11.3)	86(88.7)	0.33
	No	7(17.5)	33(82.5)	
Either Booster or Infection	Yes	11(10.6)	93(89.4)	0.11
	No	7(21.2)	26(78.8)	

Table 4. Breakthrough Infection among the Cohort with Different Antibody Level

Variable	Category	Breakthrough Infection n(%)	No Breakthrough Infection n (%)	P value
Antibody Level	Low	6 (35.3)	11(64.7)	0.01
	Moderate-high	13 (11.9)	96(88.1)	
Booster	Yes	19(16)	100(84)	0.25
	No	0	7(100)	
Second Booster	Yes	5(8.5)	54(91.5)	0.052
	No	14(20.9)	53(79.1)	

DISCUSSION

In this study, more than half of HCWs had been infected with SARS-CoV2 at least once, while more than one third of HCWs (35%) reported breakthrough infection 14 days after receiving full vaccination. Infections after at least one dose of vaccination were associated with less severe illness and lower rate of hospitalization compared to infections prior to vaccination. Breakthrough infections were more common among the younger age female HCWs, as well as HCWs directly involved in patient care such as nurses, paramedics, and doctors.

The breakthrough infection was observed in more than one third of enrolled participants in current study. Other studies have reported various percentages of breakthrough infection from 0.7% to 13.3% in vaccinated healthcare workers.[23-27] Our study reported relatively high breakthrough infection as the majority of the cases were reported during third wave of COVID 19 infection caused by omicron variant, which was reported to cause higher breakthrough infection.[28] Other reason behind higher breakthrough post full vaccination could be attributable to waning of vaccine effectiveness and seasonal periods of SARS-CoV-2 infection.[29]

In our study, the young females had higher frequency of breakthrough infection. According to a study carried out by CDC, breakthrough infection was reported majorly in females, with median patient age 58 years.[30] Likewise, a study done in Qatar and India reported COVID 19 infection among young median age with majority being females.[25,31] The reason for the higher breakthrough infection among young females could be because most of the employees at DHKUH are young of which majority are nurses who are directly involved in the patient care.

The breakthrough infection was higher in health care workers directly engaged in patient care viz nurses and paramedics. These findings are similar to a study done in Qatar that reported HCWs in the nursing and midwifery constituting the largest group with breakthrough infection (41.5%), followed by allied health professionals (20.7%).[25] Similarly, another study done in Israel reported higher breakthrough infection among nursing staff (46%).[23] These cohorts of staff could also be at risk of multiple exposure with patients, infected colleagues, and high-risk areas like ICU or emergency room. In the study, high risk close contact with SARS-CoV-2 positive individuals was from worksites colleagues followed by infected patients. This could be because of tendency to ignore safety measures during social interaction as compared to while taking care of the patients.

Studies have shown that there has been lower incidence of breakthrough infection among individuals who had a prior SARS-CoV-2 infection before vaccination, compared to individuals who had vaccination without SARS-CoV-2 infection.[32-34] However, this study did not find any difference in breakthrough infection between individuals who had SARS-CoV-2 infection before vaccination and those vaccinated without SARS-CoV-2 infection. This could be because most of the breakthrough infection occurred during the peak of Omicron variant infection. Omicron variant SARS-CoV-2 infections variants have been known to overcome antibodies in fully vaccinated individuals or natural infection.[35]

The clinical outcome of infection among vaccinated participants were favorable with few moderate illness and none severe illness and less need of hospitalization. This finding is supported by a study done in Israel where most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (> 6 weeks).[23] Whereas study from India, among symptomatic breakthrough infections, 31.25% had mild, 43.75% moderate and severe illness respectively.36 This highlights vaccination can prevent severe or critical infection including need of hospitalization.

In our study, most of the individuals had medium titer of antibody followed by low titer. The median titer was higher than some recent studies done in India.[20,37] Our study also showed low level of antibodies, had higher chance of the breakthrough infection. This has been observed by several studies around the world, which reported low level of antibodies corresponds to possible breakthrough infection.[19-21,23] Also, antibodies have weaker neutralization against newer variants such as Omicron, even during one month after booster vaccination.[21] Our study also showed higher antibodies level for individuals receiving booster

dose. However, due to small sample size and overlapping between the time of booster and sample collection, this observation was not significant enough. Studies have shown that third vaccine dose significantly improved antibody concentration and neutralizing capacity.[38-40]

The strength of the study is that it was done is a tertiary health care setting where most of the HCWs were engaged in pandemic management and patient care and hospital had free testing of COVID 19 for staff after screening. DHKUH was well equipped with the laboratory set up for the assay of antibody level in the serological cohort which made the analysis efficient. However, the study has several limitations: First, we studied the healthy young population, hence majority of the illness were mild/asymptomatic with no severe illness following SARS-CoV-2 infection after vaccination. Thus what we could determine does not represent the population with co-morbidities who might have severe infection following vaccination. Second, we may have overlooked asymptomatic patients since initially, every high risk exposure with SARS-CoV-2 positive patient were tested irrespective of symptoms, but later the policy was amended to screen only employees with symptoms indicative of SARS-CoV-2 infection. Third, serological cohort was planned before the start of the booster dose however because of start of omicron wave pandemic, the booster dose vaccination and data collection was done at the same time. Thus, obscuring the true representation of antibody level before or after the booster. We could not recruit enough participants in cohort due to financial constraint which limited the power of the study for sub categorical analysis of antibody level.

CONCLUSION

Breakthrough infection was present in more than one-third of HCWs, which was high among those directly involved in patient care. The subjects with lower antibodies were at higher risk of breakthrough infection. Nevertheless, it was found that vaccinations significantly decreased severe diseases and the need for hospitalizations.

ACKNOWLEDGEMENTS

We would like to thank Nepal Health Research Council for the financial support of the study. The study was part of Provincial Health Research Grant 2078/2079. We would also like to extend thank you to Anil Khanal, Shishir Ranjitkar, Aastha Shrestha, Sudichhya Tamrakar, Sony Shrestha and Urusha Ranjitkar who have helped in data collection and serological analysis. We would like to specifically acknowledge Dr. Shristi Jonche contribution in development and writing the proposal.

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