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Infection, reinfection, and postvaccination incidence of SARS-CoV-2 and associated risks in healthcare workers in Tamil Nadu: A retrospective cohort study

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Abstract:

BACKGROUND: The study was conducted in response to the need to understand the incidence of SARS-CoV2 infection and its determinants in healthcare workers (HCWs) and describe the epidemiology and presentation of reinfection cases. Also, we intended to determine the incidence of post-vaccination infections among health care workers as well as the contributing factors.

MATERIALS AND METHODS: Retrospective cohort design was used to quantify the coronavirus disease (COVID-19) infection among HCWs. The study cohort was all healthcare personnel working during the month of June 2021 in a tertiary care medical college hospital. Individuals diagnosed with laboratory-confirmed positive real-time polymerase chain reaction tests for SARS-CoV-2 infection between March 20, 2020, and May 31, 2021, were included. Univariate and multivariate analysis with Cox regression model elicited potential risk factors for all infections in HCWs.

RESULTS: A total of 2420 HCWs constituted the cohort, in which the majority were primary healthcare providers (67.1%) and others. The mean age of the cohort was 30.27 years \pm 10.53 standard deviation. The cumulative incidence of infection, reinfection, and postvaccination infection was 144.6 cases, 11.4 individuals, and 66.5 per 1000 HCWs respectively. Chronic illness was significantly associated with all infections. However, males and primary-care providers had higher risk of infection, whereas among the postvaccinated participants, partial vaccination status was one of the determinants.

CONCLUSION: Based on the findings, we endorse stringent testing and encourage HCWs to mandatorily follow COVID-appropriate behavior even if they are completely vaccinated and after recovery from previous infection

Keywords:

Cohort, healthcare workers, incidence of COVID-19, postvaccination infection, reinfection

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Introduction

Our world has been in the grip of the coronavirus disease (COVID-19) pandemic since December 2019. Since July 12, 2021, there have been >186 million confirmed

cases and over 4 million confirmed deaths globally.^[1] In India >31 million confirmed cases including 418,480 deaths have been reported.^[2] Healthcare workers (HCWs) are in the forefront of the nation's fight against the pandemic. They risk their lives directly or indirectly for the welfare of the patients, which in developing countries like

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India eventually leads to a shortage of staff. Based on a systematic review, 152,888 HCWs were infected with SARS-CoV-2 globally in 2020.^[3] While HCW represents 2%–3% of our population in many countries, COVID-19 infection has been reported in 14% of HCWs and in some countries as high as 35% according to the World Health Organization.^[4] This affected proportion ranges from 11.1% to 16.43% in various studies conducted in India. Although the true number is unknown, it is steadily increasing.^[5-7] As further COVID variants emerge, it is important to take care of the HCWs who are in the forefront in combating the pandemic.

The possibility of reinfection has been a matter of great anxiety for the epidemiologist and the producers of vaccines. The protection of SARS-CoV-2 reinfection after primary attack is still unresolved and immunity is not yet well understood. However, many cases of virologically confirmed reinfections have been reported globally.^[8-10] Besides, very little is known about the presentation, severity, and outcome of these infections in India. Vaccination against COVID-19 is the chief approach in changing the course of pandemic globally.^[11] Large-scale vaccination of high-risk groups for COVID-19 in India began on January 16, 2021, and was first deployed to HCWs.^[12] Several real-world observational studies have reported vaccination effect on COVID-19 incidence in the general population outside clinical trial settings.^[13,14] However, only a few studies have been done on the most vulnerable HCWs, who are at an increased risk of infection, and are eligible for early vaccination.^[15,16] Conversely, estimation on determinants, severity, and outcome of postvaccination infection was not focused on much in Indian settings.^[15,16]

With this background, it was our aim to conduct a study to understand the incidence of COVID-19 infection and its determinants in HCWs cohort. We intended to describe the reinfection cases in terms of epidemiology and severity. In addition, it was to estimate the incidence of postvaccination infection and its contributing factors in HCWs in a tertiary care medical college hospital.

Materials and Methods

Ethical approval was obtained from the Institutional Review Board vide Letter No. SMC/IEC/2021/07/005 dated 13/07/2021, and informed written consent was taken from all participants. This retrospective longitudinal cohort study was performed at the tertiary care teaching medical hospital in Kanchipuram, Tamil Nadu, a 1250-bed university center that provides broad and specialized medical, surgical, and intensive care services. The study cohort was all the healthcare personnel (2420) working in the hospital during the month of June 2021. This cohort comprised doctors (nonclinical,

paraclinical and clinical), residents and interns, nursing staff, patient care technicians, physiotherapists, patient advocates, human resources team, dieticians, hospital pharmacists, social workers, laboratory assistants, and hospital administrators. The Hospital Infection Control Committee dedicated to COVID-19 infection was approached to identify individuals diagnosed with laboratory-confirmed positive real-time polymerase chain reaction (RT-PCR) tests for SARS-CoV2 between March 20, 2020, and May 31, 2021. HCWs with a clinical diagnosis of COVID-19 without RT-PCR confirmation were excluded.

The laboratory-confirmed diagnosis of COVID-19 was defined as “index event.” All positive RT-PCR tests after entry time were considered as infection or reinfection. Data collection was done retrospectively by telephone either with the HCW or their relatives if they have died. Follow-up for incidence of postvaccination infection was started from January 20, 2021, since vaccination rollout for HCWs began on January 20, 2021, in the study site, 4 days after the national vaccine drive. The follow-up period was calculated in months. End of the follow-up period was defined for those who were not positive for COVID-19 until June 30, 2021. Based on power analysis, we estimated the sample size as 116 with an effect size of 0.15 and a power of 0.90.^[17]

Standardized data were collected on demographic features, comorbidities (prior diagnosis of hypertension, diabetes, immunosuppression therapy, cardiac illness, and respiratory disease [if any]), personal habits (smoking/alcohol including duration and amount), COVID-19 vaccination status (fully/partially vaccinated), epidemiological characteristics of COVID-19, symptoms, imaging data using high-resolution computed tomography (HRCT) – thorax, treatment, and outcome.

Operational definitions were as follows: (1) Reinfection was defined by two positive tests separated by an interval of more than 90 days and after resolution of first infection, confirmed by a negative test in between the two episodes.^[18] (2) A fully vaccinated individual was one who was more than or equal to 2 weeks following the second dose in a 2-dose series or more than or equal to 2 weeks after receiving one dose of a single-dose vaccine.^[18] (3) A partially vaccinated individual was one who had received the first dose of a 2-dose series COVID-19 vaccine or 0 to <14 days after second dose of a 2-dose series vaccine.^[18]

All the positive RT-PCR COVID-19 patients were classified according to the level of severity of the disease: Based on the clinical management of COVID-19, “Mild Disease” has fever or upper respiratory tract infections; “Moderate Disease” with pneumonia and no signs of severe disease,

respiratory rate (RR) >24/min, and SpO₂ <94% on room air; and “Severe Disease” with respiratory distress requiring mechanical ventilation (noninvasive and invasive), RR >30/min, and SpO₂ <90% on room air.^[19] Based on the HRCT changes, COVID-19 infection is further classified as mild, moderate, and severe disease with computed tomography severity score – <8/25, 9–15/25 and ≥16/25, respectively.^[20] The primary outcome of the study was the incidence and severity of SARS-CoV2 infection and reinfection of HCWs during the study period. Secondary outcomes were the incidence and severity of SARS-CoV2 infection in fully and partially vaccinated participants. Outcomes were also analyzed for determinants of infection for predefined subgroups according to age, sex, employment sector, comorbidities, and personal habits.

All analyses were conducted using the SPSS version 25. Baseline characteristics were summarized for categorical data as frequencies and percentages and for continuous variables as mean ± standard deviation (SD) or median and interquartile range (IQR) after checking for normality of distribution. A univariate Cox Regression analysis was performed to compare potential risk factors and “hazards ratios”. Survival analysis using Kaplan–Meier curve was used to deploy the “Hazard function curve” for selected independent variables in re-infection. Confounding factors were controlled using multivariate Cox regression analysis to analyze the factors significant on univariate analysis and adjusted “hazards ratios.” Chi-square test was used to ascertain the association of severity in vaccinated and not vaccinated HCWS. The two-tailed type 1 error of 0.05 was considered statistically significant.

Results

A total of 2420 HCWs comprising the study cohort were screened for eligibility and included in final

analysis. The baseline characteristics of the participants were as follows: the majority were primary healthcare providers (1623 [67.1%]), made up of doctors and nurses and other health workers. Most were females (1474 [60.9%]) followed by males (946 [39.1%]). The mean age of the cohort was 30.27 years ± 10.53 SD.

With the follow-up period of 17 months (median – 15 months, IQR: 15), a total of 350 RT-PCR-confirmed cases of SARS COV-2 infection were documented. The cumulative incidence of 144.6 cases per 1000 HCWs was reported. The majority had symptomatic infection (318 [90.6%]), predominantly with fever (75.1%) followed by myalgia (52.2%), cough (37.4%), and loss of smell (32.7%). A larger proportion of HCWs were neither smokers (343 [98%]) nor habitual drinkers of alcohol (347 [99%]). Incidence was more among doctors (49.7%) followed by nurses (26%) and others (24.3%). Among them, only 138 HCWs underwent HRCTs of the thorax, which was classified as mild (100 [72.5%]), moderate (32 [23.2%]), and severe (6 [4.3%]) by definition. Based on the severity, the majority were reported as mild (317 [90.5%]) followed by moderate (29 [8.3%]) and severe (4 [1.2%]). Almost half of the infected HCWs were admitted into hospital (176 [50.3%]), but admission into intensive care unit (ICU) was only three (1.7%). Only two (0.56%) deaths were reported. The various predictors influencing the incidence of COVID-19 infection in HCWs are tabulated in Table 1.

Upon following 350 RT-PCR-confirmed cases of SARS COV-2 infection, four were reported with RT-PCR-confirmed re-infection of SARS-CoV2 infection among the recovered HCW with a median follow-up period of 9 months (IQR 9). Incidence of re-infection was 11.4 cases per 1000 individuals. Among them, two were on treatment for chronic illnesses and another for chronic respiratory illness. One infected individual was

Table 1: Bivariate and multivariate analysis of predictors of COVID-19 infections among healthcare workers in Tamil Nadu (n=2420)

Predictors	Event occurred (n=350) N (%)	Event did not occur (n=2070) N (%)	Unadjusted HR (CI)	Adjusted HR (CI)
Age (years)				
<30	250 (13.9)	1545 (86.1)	1.172 (0.93-1.47)	0.965 (0.76-1.22)
>30	100 (16.0)	525 (84.0)		
Sex				
Female	167 (11.3)	1307 (88.7)	1.799 (1.45-2.22)*	2.261 (1.82-2.8)*
Male	183 (19.3)	763 (80.7)		
Designation				
Primary-care providers	265 (16.3)	1358 (83.7)	1.556 (1.21-1.98)*	1.928 (1.50-2.46)*
Others	85 (10.7)	712 (89.3)		
Chronic illness				
Present	19 (2.7)	290 (97.3)	4.767 (3.89-11.33)*	5.536 (4.99-12.16)*
Absent	331 (19.3)	1780 (80.7)		

Using COX regression and hazard analysis. *P<0.05 significant. HR=Hazard ratio, CI=Confidence interval

a chronic smoker. During both primary and secondary infections, all four re-infected participants were symptomatic. Based on the severity of infection, three were reported to have the moderate disease during their primary infection, while all were classified as mild in subsequent infection.

A total of 1909 HCWs were vaccinated for COVID-19 in June 2021 (vaccination coverage with at least one dose is 78.8%). With a median follow-up period of 4 months (IQR 4) succeeding the vaccination drive, a total of 160 HCWs were documented to have RT-PCR-confirmed SARS COV-2 infection from January 20, 2021. Of these, 127 were vaccinated and 33 were not. The cumulative incidence of postvaccination COVID-19 infection was 66.5 per 1000 vaccinated individuals. The case rate for partially vaccinated individuals was 10.7% (24/225) whereas for fully vaccinated was 6.1% (103/1684). Symptomatic infection was detected in 109 (85.8%). The distribution and comparison of COVID-19 symptoms in infected HCWs with and without vaccination is shown in Figure 1. Based on the severity of infection, the majority were reported as mild (115 [90.6%]) followed by moderate (10 [7.9%]) and severe (2 [1.5%]). The association of disease severity with vaccination status is shown in Table 2. Figure 2 shows the hazard function of various factors influencing reinfection in HCWs. Of the infected HCWs, 41 (32.3%) were admitted into hospital but only two of these required ICU admission (1.5%). One fatality was reported as outcome. Various predictors influencing

the incidence of COVID-19 in postvaccinated HCWs are given in Table 3.

Discussion

Our study with retrospective cohort design is one of the few studies which highlights the availability of systematically collected RT-PCR data and other information on a well-characterized cohort of HCWs, allowing relatively robust assessment of the incidence of disease, reinfection, and postvaccination infection of HCWs.

The current study illustrates the cumulative incidence of COVID-19 infection as 144 per 1000 population (case rate 14.4%), which is consistent with other studies conducted throughout India with a range of 11% to 16.3%.^{15,71} The systematic review on the prevalence of COVID-19 infection of HCWs reported 51.7% (confidence interval [CI] 34.7–68.2), which is in contrast to the current findings, as it included 30 articles most of which included positive HCWs primarily from China.¹²¹ There was a younger working age population of infected HCWs in the current study (residents, interns, and trainees) with a mean age of 30.2 years and fewer comorbidities (2.7%); however, in spite of acquiring infections, a majority developed a mild disease (90.5%) and rarely required hospitalization (1.7%). Even though the larger proportion of the current cohort was female (60.9%), as the majority of HCWs like registered nurses, doctors, and medical and physical assistants were female, males were predominantly affected (19.3%). This preponderance of

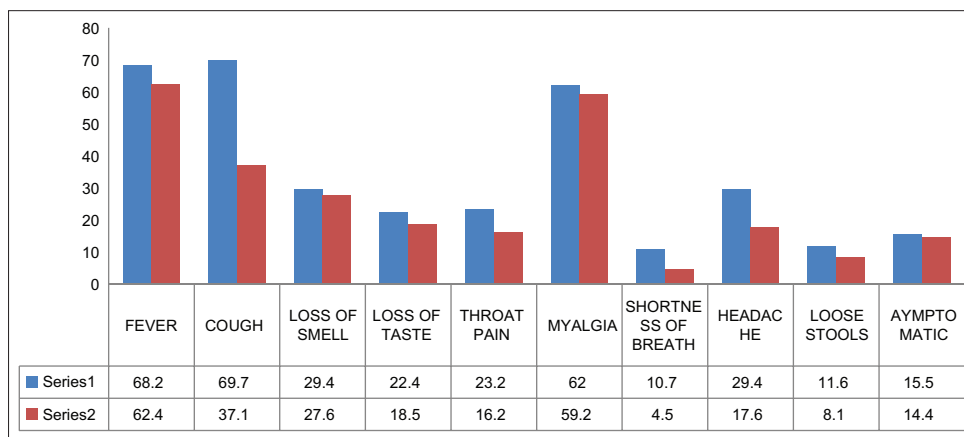


Figure 1: Distribution of COVID-19 symptoms among healthcare workers infected before and after vaccination for COVID

Table 2: Association of disease severity with vaccination status of COVID-19 among healthcare in Tamil Nadu (n=2420)

Severity (n=350)	Partially vaccinated (n=24) N (%)	Fully vaccinated (n=103) N (%)	Without vaccination (n=223) N (%)	χ^2 (P-value)
Mild (317)	20 (83.3)	95 (92.2)	202 (90.5)	3.0402 (0.551)
Moderate (29)	3 (12.5)	7 (6.7)	19 (8.5)	
Severe (4)	1 (4.1)	1 (0.9)	2 (0.9)	

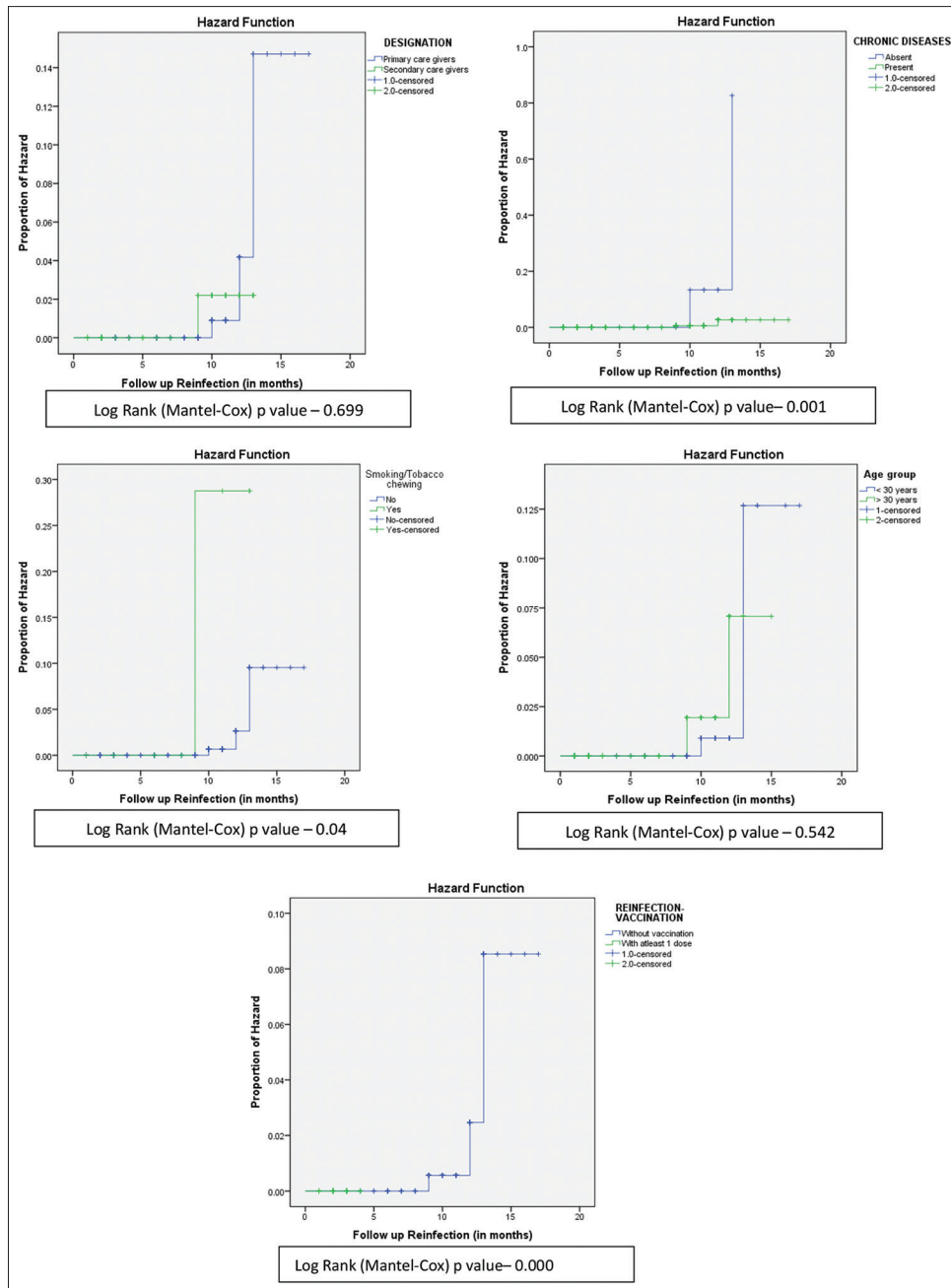


Figure 2: "Hazard Function Curve" of factors influencing re-infection of COVID 19 (n = 4)

male sex (58%) and younger age (mean 34.7 years) was also observed in the study conducted on countrywide data on HCWs obtained from the Indian Council of Medical Research portal in India.^[22] However, there was no significant association of infections with age of the participants in the current study, as shown in Table 1.

With regard to the severity and outcome, the present study reported two (0.56%) deaths, while a similar study conducted in North America showed a higher proportion of ICU admission (26%) and deaths, 7 (5.5%) in 127 HCWs.^[21] A systematic analysis on HCWs had a

mortality rate of only 1.5%.^[23] This risk is highly variable and depends on the peaks of the pandemic, intensity, duration of exposure, country-specific variation in density, deprivation in socioeconomic status, and overall healthcare settings, all of which require further investigation. To our knowledge, no other study has demonstrated an association of independent variables to obtain determinants on large cohort of HCWs in the Indian subcontinent.

We presented four cases of HCWs who had symptoms suggestive of reinfection of COVID-19. Cumulative

Table 3: Bivariate and multivariate analysis of predicting factors in postvaccination COVID-19 infection among healthcare workers in Tamil Nadu (n=1909)

Predictors	Event occurred (n=127) N (%)	Event not occurred (n=1782) N (%)	Unadjusted HR (CI)	Adjusted HR (CI)
Age (years)				
<29	80 (5.9)	1269 (94.1)	0.739 (0.51-1.06)	0.834 (0.56-1.22)
>29	47 (8.4)	513 (91.6)		
Sex				
Male	60 (8.2)	668 (91.8)	1.526 (1.07-2.16)*	1.422 (0.98-2.05)
Female	67 (5.7)	1114 (94.3)		
Designation				
Primary-care providers	110 (7.5)	1350 (92.5)	1.931 (1.15-3.22)*	1.926 (1.14-3.23)*
Others	17 (3.8)	432 (96.2)		
Chronic illness				
Present	13 (6.7)	181 (93.3)	0.980 (0.55-1.74)	0.729 (0.40-1.31)
Absent	114 (6.6)	1601 (93.4)		
Vaccination status				
Partially vaccinated	24 (10.7)	201 (89.3)	1.827 (1.17-2.85)*	1.900 (1.21-2.97)*
Fully vaccinated	103 (6.1)	1581 (93.9)		

Using Cox regression and hazard analysis. *P<0.05 significant. HR=Hazard ratio, CI=Confidence interval

incidence of reinfection was 11.4 cases per 1000 participants. This frequency is less than the SIREN-large cohort multicentric study in England (18.7 cases per 1000).^[8] However, the median interval between the two episodes in the current study was 270 days (range 92–330) which is nearly parallel to the SIREN study (241 days [range: 90–345]). However, the clinical presentation between episodes in the HCWs varied. During primary attack, three out of four had moderately severe infection and one mild disease, but all four HCWs had marginally mild infection in the course of second episode. In contrast, a few studies reported severe second episode compared to the first,^[9,10] raising the question of the longevity of immunological response and antibody titers, which requires further studies.

Combatting the pandemic depends on the development of an efficacious vaccine. In line with this, “Covishield” which is the version of AstraZeneca vaccine was rolled out in India during initial phase of vaccination.^[24] The current study had vaccination coverage of at least one dose of vaccine at 78.8% and cumulative incidence of postvaccination infection at 66.5 per 1000 individuals with a median follow-up period of 4 months, which is much lower than a similar study conducted in Mumbai, India, which was 101 per 1000 HCWs.^[15] But in contrast, the SIREN study in England reported only 7.3 per 10000 HCWs.^[16] This can be explained by the fact that unlike the SIREN study, in which a large cohort of 108,256 individuals with a vaccination rate of almost 90% of at least one dose of the messenger RNA vaccine (Pfizer vaccine)^[15,16] were followed up for two calendar months, in the Indian study, there were only a few (393) participants. The current study had a

case rate of 6.1% with fully vaccinated HCWs, which is higher than the study in Indonesia of 1.25% of 1040 fully vaccinated HCWs.^[25] and in Israel of 0.54% of 4081 vaccinated HCWs.^[26] This high incidence can also be attributed to multiple parameters such as the period of study coinciding with the second peak of pandemic; the study site had 620 dedicated COVID beds increasing the exposure. More importantly, there was a lack of COVID-appropriate behavior, there was improper use of personal protective equipment, and the accommodation for younger workers, especially in boarding houses, was rather crowded.

The majority of infected vaccinated HCWs were symptomatic (85.8%) and the rest (14.2%) were asymptomatic. This finding is consistent with the study in Mumbai, India, in which symptomatic infection of HCWs was 92.5%,^[15] but English study revealed 19% asymptomatic, 51% symptomatic, and other 30% uncertain in 23,324 participants.^[17] This can be attributed to the fact that many hospitals including the study site in developing countries do not have a policy of routinely checking its employees for infection. Besides, RT-PCR is done only for symptomatic HCWs and their immediate contacts. The current study, similar to another study conducted in India,^[15] showed that primary-care providers have a high risk of contracting the infection (HR 1.926) since they are in close contact with patients and their relatives.

This study has several limitations. First, the generalizability of the findings due to the inherent characteristics of a single tertiary care health-center is limited. Second, there may be other confounding factors that were unaccounted for in the regression analyses.

For example, body mass index, antibody titers, strain of the virus, and other laboratory investigations cannot be excluded and require further study.

Conclusion

We reported 14.4% of SARS-CoV-2 infection rate with 1.14% of re-infection rate and 6.65% of postvaccination infection, of whom 10.7% partially vaccinated and fully vaccinated HCWs had 6.1% infection rate. Based on findings, we endorse stringent testing and encourage HCWs to strictly adhere to COVID-appropriate behavior even if they are completely vaccinated or fully recovered from previous infection. This needs to be brought to the attention of healthcare authorities and policymakers to help them design strategies for HCWs in the COVID-19 epidemic.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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