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COVID-19 infection, and reinfection, and vaccine effectiveness against symptomatic infection among health care workers in the setting of omicron variant transmission in New Delhi, India

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Summary

Background Surge of SARS CoV-2 infections ascribed to omicron variant began in December 2021 in New Delhi. We determined the infection and reinfection density in a cohort of health care workers (HCWs) along with vaccine effectiveness (VE) against symptomatic infection within omicron transmission period (considered from December 01, 2021 to February 25, 2022.

Methods This is an observational study from the All India Institute of Medical Sciences, New Delhi. Data were collected telephonically. Person-time at risk was counted from November 30, 2021 till date of infection/ reinfection, or date of interview. Comparison of clinical features and severity was done with previous pandemic periods. VE was estimated using test-negative case-control design [matched pairs (for age and sex)]. Vaccination status was compared and adjusted odds ratios (OR) were computed by conditional logistic regression. VE was estimated as (1-adjusted OR)X100-.

Findings 11474 HCWs participated in this study. The mean age was 36·2 (±10·7) years. Complete vaccination with two doses were reported by 9522 (83%) HCWs [8394 (88%) Covaxin and 1072 Covishield (11%)]. The incidence density of all infections and reinfection during the omicron transmission period was 34·8 [95% Confidence Interval

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(CI): 33·5–36·2] and 45·6 [95% CI: 42·9–48·5] per 10000 person days respectively. The infection was milder as compared to previous periods. VE was 52·5% (95% CI: 3·9–76·5, $p = 0·036$) for those who were tested within 14–60 days of receiving second dose and beyond this period (61–180 days), modest effect was observed.

Interpretation Almost one-fifth of HCWs were infected with SARS CoV-2 during omicron transmission period, with predominant mild spectrum of COVID-19 disease. Waning effects of vaccine protection were noted with increase in time intervals since vaccination.

Funding None.

Keywords: Omicron variant; Symptomatic infection; Reinfection; Covaxin; Vaccine effectiveness; India

Research in context

Evidence before this study

Omicron variant has replaced the delta variant of SARS CoV-2 and is responsible for the majority of COVID-19 cases in early 2022. We searched "PubMed", "medRxiv", websites of leading public health organizations including "World Health Organization", "Centers for Disease and Control, USA" and "UK Health Security Agency" for articles between November 01, 2021 to March 16, 2022, using the search terms "omicron", "SARS CoV-2", "COVID-19", "infections", "reinfections", "breakthrough infections", "clinical severity", "vaccine effectiveness". Omicron has been reported to have high growth rate and transmission potential. Lower disease severity has been found in different settings compared to delta variant. Higher rates of reinfection are noted with this strain. Data for vaccine effectiveness against omicron are largely available for m-RNA vaccines (Moderna and Pfizer BioNtech) and few studies for AstraZeneca vaccine (Vaxzevria) from South Africa, USA, Israel, England, Czech Republic and Denmark. Lower protection in range of 35-50% for infection and symptomatic disease has been reported upto 3 months of completing primary series. There are no real-world data for effectiveness of inactivated vaccines such as BBV152 (Covaxin) against omicron in the published literature.

Added value of this study

We found higher incidence density of infection among those previously infected (45·6 per 10000 person days) compared to overall incidence density (34·8 per 10000 person days) during omicron transmission period (December 01, 2021 to February 25, 2022) in our cohort of health care workers. The hazards were significantly higher in those workers that were likely to handle patients and clinical material in service delivery areas within the hospital setting. We witnessed significantly lower median duration of symptoms and hospitalization, both in infected and reinfected groups during the omicron transmission period, with predominance of milder disease among affected workers. During the omicron transmission period, clinical course encountered had significantly lesser frequency of following symptoms: shortness of breath, chest pain, anosmia, dysgeusia, and higher myalgias reported significantly, compared to infections noted in earlier pandemic periods. The vaccine effectiveness against symptomatic infection [with majority having received BBV152 (Covaxin) vaccine, a whole virion inactivated vaccine and others inoculated with AZD-1222 (Covishield) in our study site] during omicron transmission period was found as 52·5% (95% CI: 3·9-76·5%, p=0·038) for those who were tested within 14-60 days after receipt of second dose of vaccine. Beyond this period (61-180 days), modest effect was observed. To best of our knowledge, this is the first real time report that included assessment of BBV152 effectiveness against symptomatic infection during omicron variant transmission.

Implications of all the available evidence

Health care workers, both previously infected and not infected, had evidence of infection with SARS CoV-2 during the omicron variant transmission and were not prevented against by natural or hybrid immunity. The vaccination (with BBV152 predominant administration) did not offer protection against symptomatic infection to a large number of workers beyond the two months interval post receipt of second dose. It is vital that HCWs continue to adopt to suitable personal protective equipment and distancing as COVID appropriate behavior to prevent risk of infection, owing to continuous occupational exposure and otherwise. Future research should dwell into evaluating impact of booster doses of BBV152 Covaxin and AZD-1222 Covishield, in preventing future COVID-19 infection with further unfolding of the pandemic in the coming times.

Introduction

Completing the second year of the COVID-19 pandemic, there have been over 460 million confirmed cases and 6.1 million deaths reported worldwide.[1]

Currently, the omicron SARS CoV-2 variant (B.1.1.529) is the leading circulating strain across nations, with initial cases being reported in November 2021.[2] The omicron variant is characterized by higher transmissibility, and enhanced magnitude of breakthrough infections, and reinfections owing to increased neutralizing antibody escape mechanisms.[3,4]

By end of February 2022, India reported over 42 million SARS CoV-2 cases, the second largest number reported by a single country after the United States of America.[1] The capital city of New Delhi (with a population of approximately 19 million) has registered a cumulative of 1836581 cases of COVID-19 as of March 17, 2022.[5] Three major waves have been recorded in the city so far with the first in 2020, the second starting in March 2021 with delta variant predominance, and the third starting in December 2021 attributed to the omicron variant.

The COVID-19 vaccination program began in India on January 16, 2021 with the first priority group of health care workers (HCWs). The drive utilized two indigenously produced vaccines– Covaxin (BBV152 by Bharat Biotech International Limited), and Covishield (AZD-1222 Oxford, AstraZeneca by Serum Institute of India). Additionally, the Russian vaccine Sputnik-V (distributed in India by Dr. Reddy Laboratory) was also granted emergency use authorization and was available through the private sector through a limited supply. Starting January 10, 2022 homologous precaution (booster) dose was offered for HCWs who had completed two-dose schedule, with priority to those who took the second dose more than 9 months prior.

Health care worker cohorts based at medical institutions offer a unique opportunity of examining SARS CoV-2 infections, and reinfections, over a long period of time, with changing landscape of COVID-19 variant transmission and also examining the protection of vaccines in preventing these infections.[6] This study had three objectives: (1) to determine the incidence of SARS CoV-2 infection, and reinfection in a health worker cohort based at tertiary care institution in New Delhi, in the setting of omicron variant transmission, (2) to describe symptoms and compare its severity with previous periods of SARS CoV-2 transmission, and (3) to estimate vaccine effectiveness of two primary doses against symptomatic infection during omicron variant surge.

Methods

Study design and participants

This is an observational study among a cohort of health care workers from the All India Institute of Medical Sciences (AIIMS), New Delhi. This is a follow-up phase of the cohort (with sub-studies as detailed below), that was assembled in May/June 2021, and SARS CoV-2 infection and reinfection episode details were captured in the first round of study till June 18, 2021.[6] This paper follows the STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting.

Data collection and management

Data was telephonically collected through a team of trained personnel. All the HCWs who participated in the first round of data collection were contacted again to capture details about vaccination history, COVID-19 testing, symptoms, diagnosis for the period of omicron transmission (that is December 01, 2021 onwards). If participants, could not recollect the dates of testing and vaccination, their details were checked and retrieved from testing and vaccination platforms maintained by the Indian Council of Medical Research, and ministry of health and family welfare, Government of India.[7,8] HCWs' personal details were collected in the last round of the study which included age, sex, HCW type (student/administrative/ clerical staff, faculty/scientist/ research staff, nursing staff, junior/senior resident, and paramedical/support staff), weight and height, and presence of any comorbidity- diabetes; hypertension; chronic heart, lung or kidney disease; cancer; hypothyroidism; or other self-reported chronic condition.[6] Data collection for the current round began on February 01, 2022 and was completed by February 25, 2022. The data were entered in a web-based data collection platform with inbuilt range, and consistency checks and were subjected to stringent quality and validation checks; and repeat calls were made if errors were found in the study database. The data analysis were performed using Stata 16·0 (StataCorp LLC, TX, USA). Categorical variables are depicted with frequency and percentages, while for quantitative variables, summary statistics in form of mean/median with standard deviation (SD) /interquartile range (IQR) are reported.

Objectives 1 and 2

Incidence of SARS CoV-2 infection, reinfection, and clinical features. This followed retrospective cohort design. SARS CoV-2 infection/reinfection with omicron was confirmed through any one of the following laboratory tests: RT-PCR (Reverse Transcription Polymerase Chain Reaction)/ CBNAAT (Cartridge Based Nucleic Acid Amplification Test) / RAT (Rapid Antigen Test)/ Self-testing kit at home. Since there was the possibility of asymptomatic infections or mild symptomatic infections, during omicron variant transmission, the Indian Council of Medical Research approved the self-testing kits for maximizing access to testing and self-isolation.[9] "Reinfection" was considered using CDC (Centre for Disease Control, USA) recommended epidemiological definition with two distinct episodes, separated by at least 90 days.[10]

SARS CoV-2 symptomatic infection was considered in a positive individual with the presence of any of the following symptoms- fever, rhinorrhea, sore throat, cough, chest pain, wheezing, difficulty in breathing, shortness of breath, anosmia, dysgeusia, fatigue, myalgia/ body aches, headache, abdominal pain, nausea/ vomiting, and diarrhea. Symptomatic episodes were categorized as mild/ moderate or severe, based on the World Health Organization ordinal scale for clinical improvement.[11] We compared the clinical features, and severity status among the three pandemic periods in our HCWs cohort- period 1 (March 01, 2020 to February 28, 2021), period 2 (March 01, 2021 to November 30, 2021: delta variant predominance) and period 3 (December 01, 2021 to February 25, 2022: omicron variant predominance).

Vaccination categories: HCWs were divided into one of the following categories based on vaccination received as on November 30, 2021: Unvaccinated with no receipt of any COVID-19 vaccine or received one dose with <14 days post receipt; partially vaccinated- receipt of a single dose of any COVID-19 vaccine and ≥14 days elapsed from the date of receipt of the first dose and received two doses but <14 days elapsed post receipt of second dose; completely vaccinated- receipt of two doses of COVID-19 vaccine and ≥14 days elapsed from the date of receipt of the second dose.

Statistical analysis

Follow-up for this study was considered to begin on November 30, 2021. Person-time at risk for those who got infected/reinfected, ended till date of confirmatory test of diagnosis and for others, it was censored on the date of interview. The incidence density (95% confidence interval) was computed by dividing the number of infections or reinfections with respective total person-time at risk and is presented as the rate per 10000 person-days. Bivariate and multivariable cox proportional model was used to ascertain the risk factors of infection and reinfection during the omicron variant predominance. A two-sided p-value less than 0·05 was considered statistically significant.

Objective 3

Vaccine effectiveness (VE) against symptomatic SARS CoV-2 infection. We used a test-negative, case-control study design for meeting this objective, as this was considered more formal approach removing confounding that might arise from differential COVID testing.[12] Cases were SARS COV-2 confirmed by RT-PCR and CBNAAT laboratory test only, during period 3 (December 01, 2021 to February 25, 2022) and controls had negative SARS CoV-2 test results by same tests. We matched for exact age in completed years and sex and selected case-control (1:1 matching ratio) pairs who reported for complete testing details. Vaccination status (unvaccinated and vaccinated with two primary doses) was compared between cases and controls. To examine the effect of increasing period between second dose of the COVID-19 vaccine and testing, effectiveness was estimated separately for those who were tested 14–60 days, 61–120 days, 121–180 days, and >180 days after receiving the second dose. Assuming 55% vaccine effectiveness, desired precision 20% (±10%), and 80% vaccine coverage among controls, minimum 839 matched pairs (1:1) were needed. Both unadjusted and adjusted odds ratios (OR) were estimated using conditional regression model. Estimated ORs were adjusted for HCW category, BMI category, previous SARS CoV-2 infection, any comorbidity and period of testing. To account for the influence of testing pattern-positivity rates, period of testing was considered with four categories (December 1–31, 2021; January 1–15, 2022; January 16–31, 2022; and February 1–25, 2022) in the multivariable model. VE (%) is calculated as (1-adjusted OR) X100.

Ethics approval

The study was approved by the Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi (Ref. No: IEC-78/14·01·2022). It was conducted as per principles laid out by the Declaration of Helsinki. Informed consent was obtained remotely through all the participants, before enrolling them and the study adhered to national guidelines for ethics committees reviewing biochemical and health research during the COVID-19 pandemic.[13]

Role of the funding source

There was no specific funding received for this study.

Results

Study Profile

The study flow is represented in Figure 1a. A total of 15244 health care workers had participated in the first round of the study during May-June 2021.[6] Out of these, 3379 could not be reached telephonically in the current round due to multiple reasons like phone not being reachable, change of number, and phone calls not picked despite several attempts. Additionally, 227 did not give consent to participate in this round. In our study cohort, 42 deaths were noted starting March 01, 2020 to February 25, 2022 out of which 25 were COVID-related deaths that occurred prior to June 30, 2021. The current round includes the details of 11474 HCWs. The distribution of study participants with respect to different characteristics is shown in appendix p 3. The mean age (SD) of the study participants was 36·2 (±10·6) years. Comparison of baseline

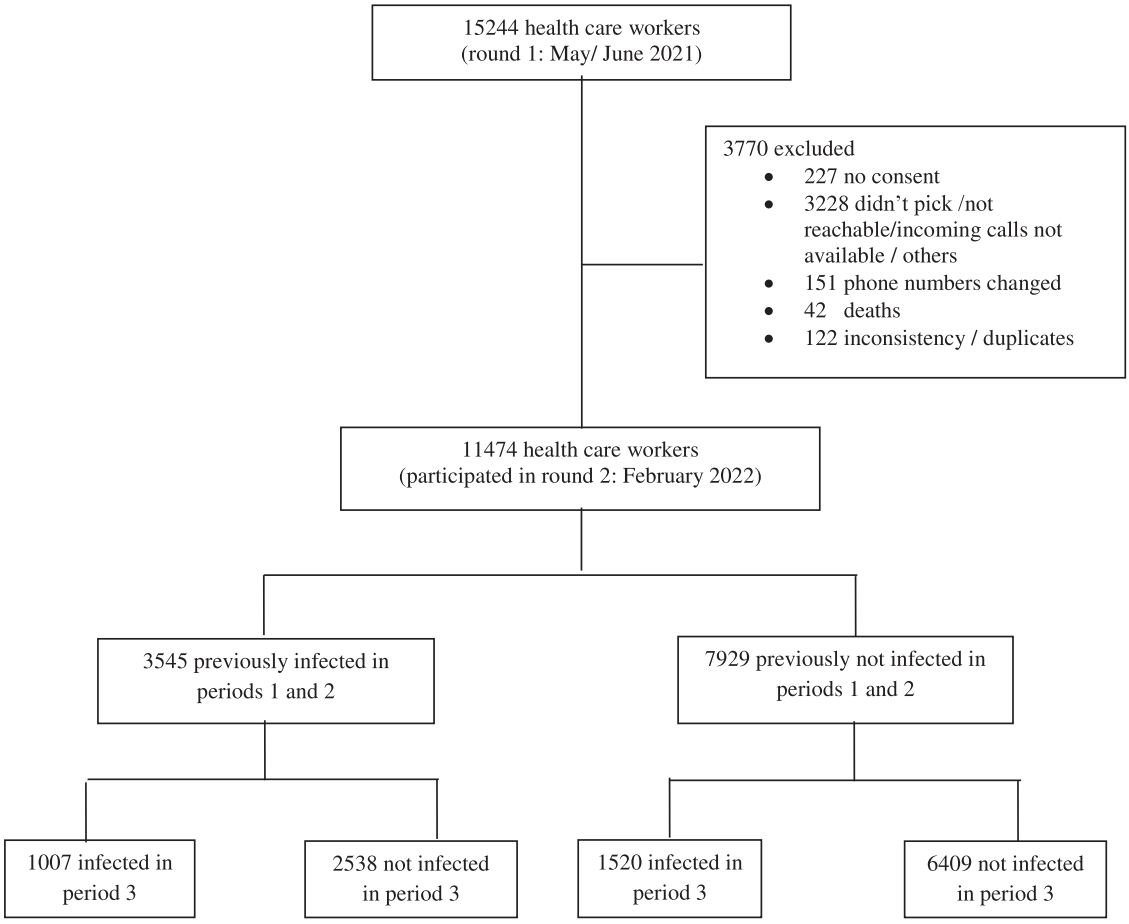

Figure 1a. Study Flow Chart. period 1- March 1, 2020 to February 28, 2021; period 2- March 1, 2021 to November 30, 2021; period 3- December 1, 2021 to February 25, 2021.

characteristics from first round of participants is also shown in appendix p 3 and the distribution was similar in both the rounds. Male: Female ratio was approximately 2:1. Obesity (BMI≥30 Kg/m^2) was observed in 8% HCWs and any comorbid condition in 16% of study participants.

A diagnosis of SARS CoV-2 infection prior to December 01, 2021 was reported by 3545 (31%) HCWs, out of whom 117 (3·3%) had more than one infection episodes. There were 9522 (83%) fully vaccinated, 987 (8·6%) partially vaccinated, and 965 (8·4%) unvaccinated workers in our study cohort, as on 30 November 30, 2021. The type of vaccine received was Covaxin (8840, 84·1%), Covishield (1598, 15·2%), Sputnik-V (16, 0·2%) and rest did not know the type of vaccine (55, 0·5%).

Incidence density of SARS CoV-2 infection, and associated factors

A total of 2527 (22%) HCWs reported diagnosis of SARS CoV-2 infection during this period (December 01,2021- February 25,2022). Predominantly, the diagnosis was done by RT-PCR testing (2073, 82%), and the remaining got it through CBNAAT (257, 10·2%), RAT (170, 6.7%), and self-home test kit (27,1·1%). The majority of the testing was done at AIIMS (2087, 82%). Out of those infected, symptomatic episode was reported by 2424 (96%) HCWs, with 2386 (98·4%) mild type and 38 (1·6%) moderate severity requiring hospitalization. The median (IQR) symptom duration was 5 (3, 7) days. Most HCWs (98%) managed the episode through self-care or teleconsultation/outpatient care.

Total of 726200 person-days were contributed by 11474 health care workers during the study period (omicron transmission period). The SARS CoV-2 infection was observed in 2527 HCWs yielding an incidence density of 34·8 per 10000 person days (95% CI: 33·5-36·2) during the omicron transmission period in the study. The incidence density of SARS CoV-2 among HCWs who were not previously infected was 30.1 per 10,000 person days [95% CI: 28.6, 31.6; 505475 person days; 1520 infections].

The associated factors are shown in Table 1. The infection was seen relatively less in HCWs aged ≥45 years (16·1%) compared to HCWs aged <25 years

Characteristic	Total (n=11474)	SARS CoV-2 infection (%) (n=2527)	Unadjusted Hazard Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)	P value
Age, years						
<25	1404	233 (16·6)	1 [Reference]		1 [Reference]	
25-44	7160	1825(25·4)	1·61 (1·40-1·84)	<0·001	1·02 (0·87-1·19)	0·811
≥45	2910	469 (16·1)	0·97 (0·83-1·13)	0·702	0·82 (0·68-0·97)	0·024
Sex						
Male	7526	1234 (16·4)	1 [Reference]		1 [Reference]	
Female	3948	1293 (32·8)	2·17 (2·00-2·38)	<0·001	1·20 (1·11-1·33)	<0·001
Type of health care worker						
Student, administrative and/or clerical staff	1171	187 (15·9)	1 [Reference]		1 [Reference]	
Faculty, scientist, research staff	830	242 (29·2)	2·00 (1·65-2·42)	<0·001	1·91 (1·55-2·35)	<0·001
Nursing staff	2476	1076 (43·5)	3·11 (2·66-3·64)	<0·001	2·96 (2·47-3·54)	<0·001
Junior or senior resident	934	400 (42·8)	3·24 (2·72-3·85)	<0·001	3·02 (2·49-3·66)	<0·001
Paramedical or support staff	6063	622 (10·3)	0·62 (0·53-0·73)	<0·001	0·68 (0·57-0·82)	<0·001
BMI (Kg/m^2)						
<18·5	440	75 (17·1)	0·78 (0·62-0·99)	0·041	0·98 (0·77-1·24)	0·863
18·5-24·9	6223	1317 (21·2)	1 [Reference]		1 [Reference]	
≥25·0	4811	1135 (23·6)	1·12 (1·04-1·22)	0·004	1·07 (0·98-1·16)	0·120
Comorbidity (Yes)	1845	426 (23·1)	1·07 (0·96-1·18)	0·230	1·05 (0·94-1·17)	0·379
Previous infection (Yes)	3545	1007 (28·4)	1·56 (1·44-1·69)	<0·001	1·01 (0·93-1·09)	0·893
Vaccination Status (as on November 30, 2021)						
Unvaccinated	965	140 (14·5)	1 [Reference]		1 [Reference]	
Partial vaccination	987	169 (17·1)	1·19 (0·95-1·50)	0·123	1·03 (0·82-1·29)	0·785
Complete vaccination	9522	2218 (23·3)	1·68 (1·42-1·99)	<0·001	1·47 (1·24-1·75)	<0·001

***Table 1*: Associated factors of SARS CoV-2 infection among HCWs during omicron transmission period using Cox Proportion Hazards model.**

Comorbidity includes presence of any one of the following- diabetes; hypertension; chronic heart, lung or kidney disease; cancer; hypothyroidism, or other self-reported chronic condition, previous SARS CoV-2 infection includes any previous diagnosis of SARS CoV-2 infection prior to December 01, 2021, completely vaccinated implies receipt of two primary doses with any one of the following- Covaxin/ Covishield/ Sputnik-V.

(16·6%) and the hazards were 18% less in those aged ≥45 years [adjusted HR 0·82, 95% CI: 0·68-0·97, p<0·024]. In our cohort, women had higher hazards of being infected compared to men [adjusted HR 1·20, (95% CI: 1·11-1·33), p<0·001]. (Table 1)

Based on category of HCWs-resident doctors [adjusted HR 3·02 (95% CI: 2·49-3·66), p<0·001], nursing personnel [adjusted HR 2·96, (95% CI: 2·47-3·54), p<0·001], and faculty/scientists/research staff [adjusted HR 1·91, (95% CI: 1·55-2·35), p< 0·001], had higher hazards of infection, compared to student, administrative, and clerical staff. On the contrary, paramedical and support staff had -32 % lesser hazards for infection [adjusted HR 0·68, (95% CI: 0·57-0·82), p<0·001]. Vaccination status was also significantly associated with infection, with 1·47 times higher hazard ratio among completely vaccinated HCWs compared to unvaccinated HCWs [adjusted HR 1·47, (95% CI: 1·24-1·75), p<0·001]. (Table 1) In our study cohort, 1363 (11.9%) HCWs gave history of receiving booster dose, out of which 96 (7.0%) HCWs had reported infection after receiving booster dose during the study period, with a mean interval between booster dose and diagnosis as 8.5 (±6.9) days.

Incidence density of SARS CoV-2 reinfection, and associated factors

Among 3545 HCWs, who had a previous SARS CoV-2 infection, 220725 person-days at risk were contributed. Reinfection was seen in 1007 HCWs (28·4%) with an incidence density of 45·6 per 10000 person days (95% CI: 42·9-48·5). Symptomatic episode was reported by 963 HCWs (95·6%) - with 956 (99·2%) as mild episodes and 07 (0·8%) as moderate severity episodes. A significantly lesser proportion of HCWs with reinfection had moderate severity omicron episode compared to those who got an infection for the first time (p=0·017). Reinfection hazards was seen relatively 40% lesser in HCWs aged ≥45 years compared to HCWs aged <25 years [adjusted HR 0·60 (95% CI: 0·44-0·81), p<0·001]. Also, reinfection was significantly associated with type of HCW with hazards significantly more in resident doctors [adjusted HR 3·00, (95% CI: 2·14-4·21), p<0·001], nursing personnel [adjusted HR 3·00, (95%

CI: 2·17- 4·14), $p<0·001$], and faculty/scientists/ research staff [adjusted HR 1·80, (95% CI: 1·23-2·64), $p<0·003$], compared to student, administrative and clerical staff (appendix p 4).

Clinical features and severity

As shown in Table 2, among the HCWs, infected for the first time during the omicron transmission period (1520), symptomatic infection was noted in 1461 HCWs (96%), and mild infection was seen in 1430 (98%) and moderate/ severe infection was seen only in 31 (2%) HCWs. Comparing this pattern, with those who got infected for the first time during the period 1 of pandemic and period 2, the proportion of moderate and severe disease was significantly lower in period 3. This was 2% in period 3 compared to 6% in period 2 ($p<0·001$) and 11% in period 1 ($p<0·0001$), as shown in Table 2. The median symptom duration [days (IQR)] in period 3 was 5 (3, 7) days, significantly lesser compared to period 2 [10, (6, 14) days, $p<0·001$] and period 1 [8 (5, 14) days, $p<0·001$]. Those who were hospitalized, experienced significantly lesser median duration of stay [days (IQR)] in period 3 as [6 (5, 7)] days compared to period 2 [7 (5, 10) days, $p=0·019$] and period 1 [10 (7, 14) days, $p<0·001$].

Also, comparing the presence of symptoms in period 3, we found following symptoms to be reported in significantly lesser proportions ($p<0·0001$) compared to previous periods: respiratory (wheezing, shortness of breath, chest pain); loss of taste and smell against both the periods 1 and 2 and gastrointestinal symptoms (vomiting, diarrhea, and abdominal pain) against period 2. On the other hand, myalgia was reported by significantly more HCWs in period 3 compared to periods 1 and 2 ($p<0·001$). Similar findings were seen, when reinfections in omicron variant predominance (period 3) were compared to reinfections seen in period 2 of delta variant predominance (appendix p 5).

Vaccine effectiveness against symptomatic SARS CoV-2 infection

The study flow for the VE component is presented in Figure 1b. There were 943 matched case control pairs (diagnosed by RT-PCR/CBNAAT) considered for this analysis and their characteristics are shown in appendix p 5. As shown in Table 3, compared to unvaccinated HCWs, those who had received COVID-19 vaccines within a period 14-60 days before their testing during the omicron transmission period, the adjusted odds ratio was 0·475 [95% CI: 0·235-0·961, $p=0·038$], yielding a vaccine effectiveness of 52·5% [95% CI: 3·9-76·5]. For whom the time since vaccination was 61-120 days, the adjusted odds ratio was 0·648 [95% CI: 0·348-1·206, $p=0·112$] with VE as 35·2% [95% CI: -20·6-65·2] and thereafter the vaccine proved to be least effective as shown in Table 3.

We also, performed an additional analysis in our sample, retaining only those HCWs that received covaxin in the matched case control study. A sample of 1376 HCWs (688 matched pairs) was available for analysis, lower than the desired sample. The adjusted odds ratio was found to be 0.589 [95% CI: 0.237-1.468, $p=0.257$], 0.735 [95% CI: 0.361-1.496, $p=0.397$], 1.281 [95% CI: 0.684-2.398, $p=0.438$], and 1.289 [95% CI: 0.692-2.401, $p=0.423$] for the periods 14-60, 61-120, 121 -180, and beyond 180 days as time since vaccination.

Discussion

Our study reports SARS CoV-2 infection and reinfection density among health care workers during the omicron dominant transmission period. Among 11,474 HCWs, infection was reported by 22%. The incidence density was more for previously infected HCWs compared to those who were not infected earlier, though on adjustment with other variables, association was not significant. We also estimated a vaccine effectiveness of 52·5% for those who had received COVID-19 vaccines within a period 14−60 days before their testing during the omicron transmission period.

We found younger age groups to experience more infection and reinfection compared to relatively older age groups (≥45 years) in omicron transmission period. This is consistent with our previous report in the earlier periods, where less reinfection was seen in older age groups, as the previous infections were more severe in older age groups for the first time.[6] Also, in another setting, it has been reported that omicron significantly infected a larger proportion of HCWs in the age group 18-30 years compared to 55 plus years.[14] In our group of HCWs, women had higher hazards of being infected. All previous SARS CoV-2 seroprevalence surveys in Delhi have reported females in all age groups to have higher odds of seropositivity.[15,16] In our study, nurses, resident doctors, faculty/scientists and research staff were most important staff categories that exhibited infection and reinfection during omicron period. This possibly is due to higher risk and gradient of infection exposure while handling patients in service areas by different categories of HCWs.[17,18]

We witnessed predominantly mild infection episodes in HCWs affected during the omicron period, compared to the previous periods (including delta transmission period). This is consistent with the global evidence that omicron is being linked to milder spectrum of COVID disease with fewer hospitalizations, Intensive Care Unit (ICU) admissions and reduced hospital stay compared to delta and previous waves.[19,20] Milder infections could be a result of multitude of factors apart from omicron variant, including effects of previous infection and vaccination protection that could be difficult to delineate in the current study.

Characteristics	Period 1	Period 2	Period 3	p-value	
				Period 1 vs Period 3	Period 2 vs Period 3
Mean Age (SD)	37·3±10·5	35·8±9·8	34·9±9·9	<0·001	<0·001
Sex				<0·001	0·019
Male	862 (58·8)	1120 (53·9)	759 (49·9)		
Female	604 (41·2)	959 (46·1)	761 (50·1)		
Testing place				<0·001	<0·001
n	1466	2079	1520		
At AIIMS	1308 (89·2)	1775 (85·4)	1230 (80·9)		
Outside AIIMS	158 (10·7)	304 (14·6)	290 (19·1)		
Testing type				<0·001	0·280
n	1466	2079	1520		
RT-PCR	1269 (86·6)	1708 (82·2)	1263 (83·1)		
CBNAAT	68 (4·6)	177 (8·5)	136 (8·9)		
RAT (Rapid antigen test)	77 (5·3)	176 (8·5)	104 (6·8)		
Don't know/ Self-home test kit*	52 (3·6)	18 (0·9)	17 (1·1)		
Symptom severity				<0·001	<0·001
n	1466	2079	1520		
Asymptomatic	200 (13·6)	172 (8·3)	59 (3·9)		
Mild	1102 (75·2)	1780 (85·6)	1430 (94·1)		
Moderate/Severe	164 (11·2)	127 (6·1)	31 (2·0)		
n	1266	1907	1461	<0·001	<0·001
Symptom duration (Days)	8 (5-14)	10 (6-14)	5 (3-7)		
n	451	200	31	<0·001	0·011
Hospital duration (Days)	10 (7-13)	7 (5-10)	6 (5-7)		

Symptom type	Period 1 n=1266	Period 2 n=1907	Period 3 n=1461		
Fever	993 (78·4)	1602 (84·0)	1206 (82·6)	0·007	0·259
Runny Nose	261 (20·6)	518 (27·2)	336 (23·0)	0·134	0·006
Sore throat	565 (44·6)	1084 (56·8)	795 (54·4)	<0·001	0·160
Cough	527 (41·6)	1080 (56·6)	808 (55·3)	<0·001	0·441
Wheezing	56 (4·4)	128 (6·7)	40 (2·7)	0·017	<0·001
Shortness of breath	108 (8·5)	233 (12·2)	36 (2·5)	<0·001	<0·001
Chest pain	71 (5·6)	213 (11·2)	33 (2·3)	<0·001	<0·001
Loss of taste	584 (46·1)	943 (49·5)	120 (8·2)	<0·001	<0·001
Loss of smell	589 (46·5)	983 (51·6)	78 (5·3)	<0·001	<0·001
Nausea/ Vomiting	87 (6·9)	233 (12·2)	103 (7·1)	0·864	<0·001
Abdominal pain	56 (4·4)	153 (8·0)	43 (2·9)	0·039	<0·001
Diarrhea	150 (11·9)	346 (18·1)	97 (6·6)	<0·001	<0·001
Headache	429 (33·9)	847 (44·4)	681 (46·6)	<0·001	0·204
Myalgia	560 (44·2)	979 (51·3)	972 (66·5)	<0·001	<0·001

***Table 2*: SARS CoV-2 diagnosis parameters and symptom severity status across three periods of pandemic.**
Period1-March 1, 2020 to February 28, 2021; Period 2- March 1, 2021 to November 30, 2021; Period 3- December 1, 2021 to February 25, 2022 and * Testing type- Self-home test kit introduced in period 3; AIIMS- All India Institute of Medical Sciences, RT-PCR- Reverse Transcription Polymerase Chain reaction, CBNAAT- Cartridge Based Nucleic Acid Amplification Test.

We found modest effect of COVID-19 vaccines after 2 months of completion of second dose (61-180 days), and worthwhile benefit of vaccines beyond 6 months could be excluded. The finding is corroborated with neutralization studies that have shown significant reduction in neutralizing ability of immunity induced by vaccination (BBV152 Covaxin/ Covishield used in Indian settings) and natural infection against the omicron variant.[21] Multiple studies worldwide have pointed out reduced or no effect of different COVID-19 vaccines

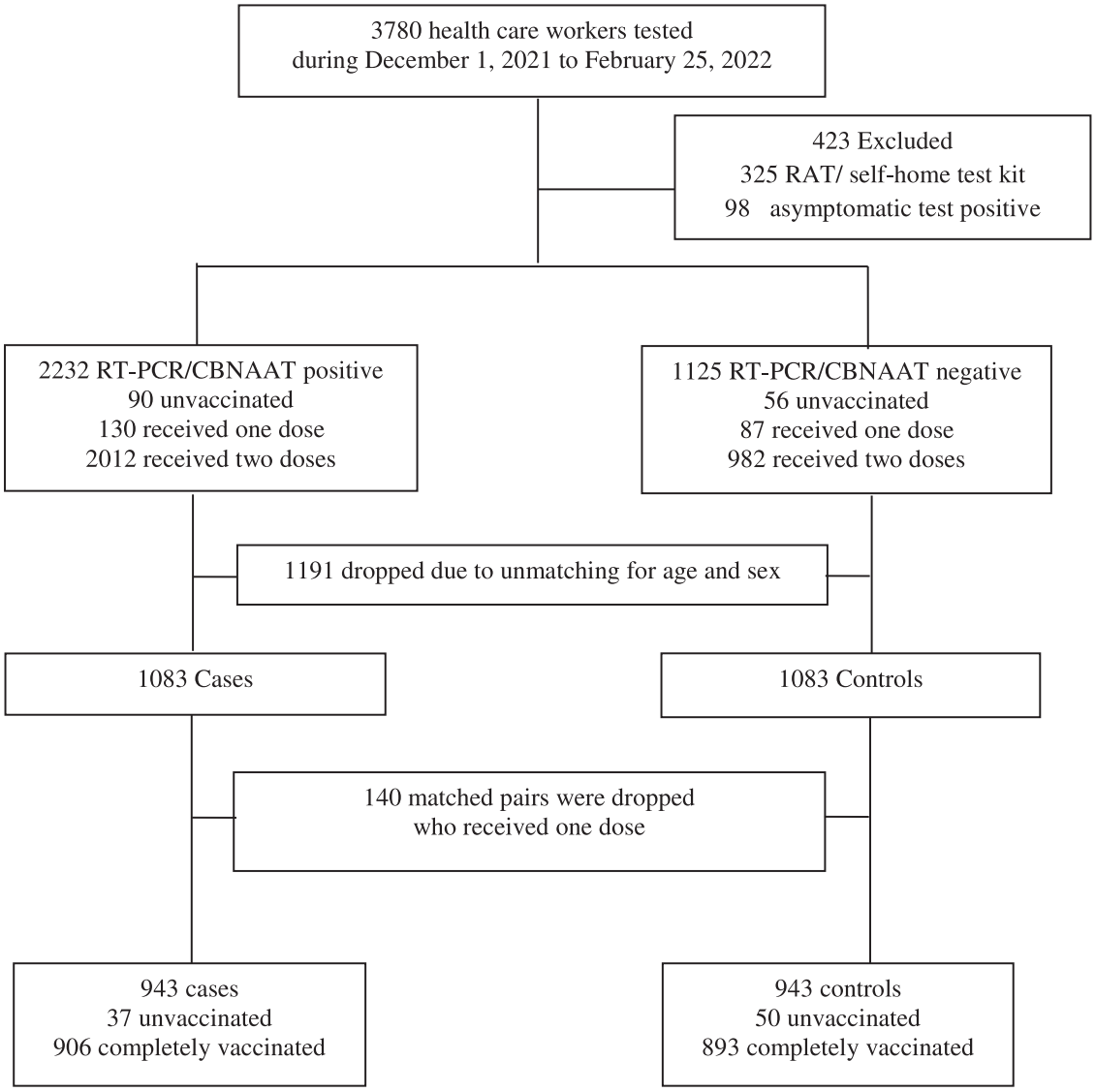

Figure 1b. Test-negative case-control study flow. RAT- Rapid Antigen Test, RT-PCR- Reverse Transcription Polymerase Chain Reaction, CBNAAT- Cartridge Based Nucleic Acid Amplification Test.

against the omicron variant.[22,23,24] Studies have also reported waning effect of vaccines with passage of time.[25] The booster dose helped in increasing the effect against the variant, though that also reduced with increasing time.[26] In a study from England, no effect was seen against omicron after 5 months of two doses of AZD-1222 vaccine (AstraZeneca) and other vaccines also.[27] In view of absence of variant specific vaccine, COVID-appropriate behavior will be imperative for halting further infection transmission.

The strength of our study lies in reporting comprehensively the infection and reinfection occurrence during omicron transmission period with estimated VE of Indian vaccines to combat the same using test-negative, case-control study design. This allowed us to control for biases influenced by differential health seeking behavior, access to testing and its type, and case finding. However, our study has a few limitations also. This was a single center study in urban Delhi, though it included a large number of HCWs. We focused on analysis for the period when omicron transmission was predominant in New Delhi.[28] There might be misclassification, due to imperfect diagnostic abilities of different tests utilized by HCWs. Also, there might be a fraction of our workers, who would be asymptomatic and did not get their testing done. Also, some of the HCWs might not have tested despite being symptomatic. However, we feel that this would be a small miss, as HCWs in our setting have access to all testing facilities and regulations within workplace setting mandate testing and isolation, if found

Characteristics	Tested[#] positive by RT-PCR/ CBNAAT SARS-CoV-2	Tested negative by RT-PCR/ CBNAAT SARS-CoV-2	Unadjusted Odds Ratio (95% CI)	p-value	Adjusted[*] Odds Ratio (95% CI)	p-value	Vaccine[$] effectiveness (95% CI)
	n	n					
Unvaccinated	37	50	1		1		
Vaccinated with two doses							
Tested within 14-60 days after second dose	32	64	0·755 (0·443-1·284)	0·300	0·475 (0·235-0·961)	0·038	0·525 (0·039-0·765)
Tested within 61-120 days after second dose	65	90	0·979 (0·606-1·582)	0·931	0·648 (0·348-1·206)	0·171	0·352 (-0·206- 0·652)
Tested within 121-180 days after second dose	80	109	1·413 (0·908-2·202)	0·126	0·706 (0·385-1·295)	0·261	0·294 (-0·295-0·615)
Tested >180 days after second dose	729	630	1·679 (1·074-2·626)	0·023	1·237 (0·743-2·059)	0·413	-0·237 (-1·059-0·257)

***Table 3*: Estimated vaccine effectiveness against diagnosed symptomatic SARS-CoV-2 infection during omicron transmission period.**
* Adjusted for health care worker category, BMI category, previous SARS-CoV-2 infection, any comorbidity and calendar time.
[#] includes RT-PCR/CBNAAT.
[$] includes Covaxin/Covishield/Sputnik V/Don't know, RT-PCR- Reverse Transcription Polymerase Chain reaction, CBNAAT- Cartridge Based Nucleic Acid Amplification Test.

positive. The information gathered was based on self-reports and possibility of recall bias could not be ruled out.

VE was not limited to particular vaccine type due to small numbers in matched pairs. Our participants included less unvaccinated HCWs, as this was expected at this stage of pandemic, and majority of them had time since complete vaccination more than 180 days. We did not evaluate the effect of severe disease due to omicron, as the number of events with severe disease was nil in our cohort of HCWs and even, moderate disease requiring hospitalization was low, not sufficient to compute vaccine effectiveness against hospitalization. We did not exclude HCWs who received boosters also (in VE analysis 124 HCWs that received boosters were also included), owing to a limited sample available for matching and achieving desired sample size. We also did not evaluate the effect of boosters specifically, as they were introduced late during the study period, and their effect was not expected in such a small span. We also did not exclude HCWs who obtained their second dose within 14 days of testing (17 such HCWs) and this could result in some misclassification.[29] Though the results were only considered for protection where interval between testing and complete schedule dose was at least 2 weeks and beyond, in the case control analysis. m-RNA vaccines were not introduced in Indian context and thus studying its effect in the study was not possible. We did not perform genomic sequencing of cases in our study, owing to resource constraints, though the predominant variant in community transmission in Delhi during the study period was omicron, as evident through sequenced samples otherwise.[28] This was an observational study and some of the residual confounding due to variables not measured, could not be eliminated from the study. Further serological, and immunological correlations will be needed to strengthen the evidence generated from this study. The generalizability to other age groups including children, adolescents and elderly will be limited, owing to inclusion of HCWs only in this study.

In sum, approximately one-fifth of HCWs in our cohort had infections during omicron transmission period. A greater risk of reinfections was observed in omicron surge compared to previous pandemic periods. Clinical severity was largely mild, with vaccines used in Indian setting (Covaxin/ Covishield /Sputnik-V) offering modest protection to symptomatic SARS CoV-2 infections during omicron surge. Role of COVID-19 booster dose will need further evaluation for offering protection against future surges.

Contributors

RG, SM, KM, RL, PG, MJS, PK, PG, VA, VD, HSC, and SS conceptualized the study. VPM, AD and SA led the literature review. SM, KM, SB, VPM and PG were involved in designing the study. SM, KM, RL, PK, VA, AD, KA, ADU and HCS contributed towards the methodology. KM did the analysis with the support from SM, RL and SB. ADU, SS, Sw, Mamta, DK, VV, PD, and HCS assisted in the data analysis. SM, KM, SB, VPM, PG, VA and SS wrote the original draft of the manuscript. All the authors contributed to data collection, curation, validation, data interpretation, reviewing and editing of the manuscript. RG, SM, RL, SB, SK, MJS,

VH, VA and SS critically reviewed the manuscript. All authors read and approved the final version of the manuscript.
RG, SM, KM had full access of all of the data in the study and SM and KM take responsibility for the integrity of the data and accuracy of the data analysis.
SM and KM contributed equally and they are joint first authors.

Data sharing statement

All relevant data is available in the paper. Additional requirements, if any will be welcome and de-identified dataset and related codes for analysis will be made available to researchers on request after publication. Requests for data should be addressed to the corresponding author (director.aiims@gmail.com).

Declaration of interests

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lansea.2022.100023.

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