Original Article

Comparative study of clinical features and vaccination status in Omicron and non-Omicron infected patients during the third wave in Mumbai, India

Apurva Takke, Mohini Zarekar, Vigneshwaran Muthuraman, Aditee Ashar, Kranti Patil, Anagha Badhavkar, Jayshil Trivedi, Naveen Khargekar, Manisha Madkaikar, Anindita Banerjee

ICMR- National Institute of Immunohaematology (NIIH), KEM Hospital Campus, Mumbai, Maharashtra, India

Abstract

Objectives: The Omicron variant–mediated COVID-19 wave is responsible for a global tsunami of cases. There is scarce data about the clinical and epidemiological characteristic analyses of the third wave. We present the data of COVID-19 patients from Mumbai region during the early third wave by taking S-gene target failure (SGTF) as a proxy for probable Omicron cases. **Methods:** We collected retrospective data of RT-PCR-confirmed (COVID-19) patients, and measured the proportion of possible Omicron cases by SGTF. We segregated and analyzed the clinical and lab data of patients with outcomes such as differing symptoms, vaccination coverage, previous infection, and travel history. We also performed a trend analysis of Mumbai's COVID-19 data before and during the third wave. **Results:** All patients had mild clinical symptoms while few were asymptomatic. Myalgia was more significantly present in SGTF/Omicron cases compared to non-SGTF/Delta patients. Out of the total 101 COVID-positive individuals, 94 individuals (93%) had taken two doses of COVID vaccine. Among these 94 individuals, 9 (8.9%) had been previously infected with COVID 19 in the first or second waves. 77.7% of the previously infected were now infected with Omicron variant and only 22.3% by a non-Omicron variant. **Conclusion:** Rapid rise and fall during the third wave in Mumbai was due to Omicron cases gradually replacing Delta. The overall milder clinical spectrum in both Omicron and Delta cases imply that vaccines might not be effective against re-infection but can attenuate disease severity and mortality, as evident by high coverage of vaccination in the country.

Keywords: 3rd wave, clinical spectrum, COVID-19, immunity, Omicron, vaccination

Introduction

Since the emergence of the COVID-19 in November 2019, several SARS-CoV-2 variants have been identified till date. Currently, the variant responsible for the third and fourth waves worldwide, namely B.1.1.529 also known as Omicron, was first identified in South Africa in November 2021 and declared as variant of concern (VOC) by the World Health Organisation (WHO) on 26 November 2021.[1] The highly transmissible variant contains a plethora of mutations in its spike protein receptor binding domain with three additional deletions and one insertion in the spike apart from other mutations outside the spike protein, making it antigenically unique and escape from neutralizing antibodies, either from vaccination or infection with previous variants.[2,3]

Address for correspondence: Dr. Anindita Banerjee, Scientist E (Medical), Head, Department of Transfusion Transmitted Diseases, ICMR- National Institute of Immunohaematology, 13th Floor, New Multistoreyed Building, KEM Hospital Campus, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: anny.banerjee@gmail.com

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In contrast to its previous variants, the clinical spectrum of Omicron infection is characterized by flu-like symptoms, body ache, intense fatigue and retained smell/taste in a majority of cases.[4] However, one key question is whether previous COVID-19 infection or vaccination could confer some protection from this variant or simply whether it can re-infect all vaccinated populations. Still, overall hospitalization requirements is minimal worldwide, as a majority of Omicron infections are managed at homecare level. Analysis of preliminary data by the UK Health Security Agency (UKHSA) showed that one Omicron patient would less likely be admitted (31%–45%) than someone with the Delta variant (50%–70%).[5]

In India, COVID-19 cases were below 10,000 until the third week of December 2021, and daily cases in Mumbai region were below 400, with the major variant being Delta.[6,7] However, from the third week of December 2021, Mumbai witnessed a sharp rise in COVID-19 cases, with a 16.5% rise in the number of active COVID-19 cases and a doubling time of approximately two days which skyrocketed at 20,000 daily cases by the second week of January 2022.[8] This rapid rise in cases looks similar to that in South Africa in November 2021 and are presumed to be caused by the Omicron variant largely replacing the Delta variant. Moreover, clinical signs and symptoms are also a bit distinct from previous COVID-19 infections, which could be due to vaccination or the strain itself affecting mainly upper respiratory tract. With this backdrop, we wanted to investigate and analyze COVID-19 symptoms and laboratory data during the third wave in Mumbai region to identify difference in clinical picture and laboratory data compared to earlier waves, which could be utilized in public health interest in terms of planning booster dose and COVID-19 management. Since the COVID-19 pandemic affects a majority of the population who usually visit primary health care physicians for their first consultation, adequate knowledge about the clinical and laboratory features of different strains of COVID-19 infection among primary care physicians is extremely useful for patient management and the timely referral of moderate-to-severe patients to a specialized healthcare facility.

Material and Methods

This study included nasopharyngeal and oropharyngeal swabs received from various COVID- 19 centers in Mumbai region sent to the Indian Council of Medical Research National Institute of Immunohaemotology (ICMR-NIIH) COVID-19 Laboratory for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR). Data were collected retrospectively from the patient database from November 2021 to January 2022. For COVID-19 data from Mumbai region, the Municipal Corporation of Greater Mumbai (MCGM) daily updates were accessed online.[8] Waiver of consent was granted by the Institutional Ethics Committee due to anonymity and retrospective analysis of routine laboratory data.

COVID-19 diagnosis by RT-PCR

For S-gene target failure (SGTF) analysis, all positive samples were taken between 25 December 2021 and 14 January 2022. All samples were processed by an automated magnetic RNA extractor (Thermo Scientific™ KingFisher™ Flex Purification System) for isolating viral RNA from the viral transport medium (VTM) samples and amplified by COVID-19 multiplex RT-PCR kit (Meril Diagnostics, COVID-19 One- Step RT-PCR Kit) for the presence of nucleocapsid (N), open reading frames (ORF) gene along with internal control for the diagnosis of SARS-CoV-2. The following three gene targets were interpreted as per the manufacturer's instructions: Positive result - Nucleocapsid (N) gene HEX, the *ORF1ab* (1ab) gene FAM plus internal control (R NaseP) ≤35. Negative result - Nucleocapsid (N) gene HEX, the *ORF1ab* (1ab) gene FAM – no Ct or Ct >35 and internal control (R NaseP) ≤35. Inconclusive - presence of either N or ORF along with internal control; these samples were repeated.

For each sample, RT-PCR was conducted once for diagnosis unless inconclusive. Samples with a valid cycle threshold (Ct) value for a positive COVID-19 test were used to determine daily mean Ct values. The positive samples with Ct values <30 were analyzed again by TaqPath kit for the detection of SGTF as an indirect estimate of the proportion of Omicron infections. Results were classified as SGTF when a sample tested positive using the TaqPath COVID19 PCR test with non-detectable S gene target and Ct value ≤37 for either the ORF1ab or nucleocapsid (N) gene targets. Likewise, samples were classified as non-SGTF when they tested positive using TaqPath COVID19 PCR test with Ct ≤37 for either the ORF1ab or nucleocapsid (N) gene targets and had detectable S-gene target.

Statistical analysis

Data were expressed as proportions for categorical data and means with standard deviation or median (with interquartile range) for numerical data. We compared groups using the Chi-squared test for categorical data and the unpaired *t*-test for numerical data with 95% confidence interval (CI) and level of significance $P < 0.05$ * (two-tailed) using GraphPad Prism 9 statistical software.

Results

General characteristics and demographics of the patients

Out of total 101 COVID-positive cases during the first two weeks of January 2022, 46% exhibited SGTF, thereby indicating approximately 46% of COVID-19 cases caused by the Omicron variant, with the rest presumed to be mostly Delta. Mean age of the patients of Omicron and non-Omicron variants were 32.09 ± 9.0 years and 33.7 ± 10.1 years, respectively. Most patients didn't have any comorbidities with only 2.17% of omicron cases and 3.64% of Delta cases with hypertension and diabetes mellitus. 89% of the Omicron patients had been fully vaccinated while 96% of delta cases completed COVID vaccination before infection. Twenty-five (26.8%) of the fully

vaccinated individuals developed COVID-19 infection within four months of the last dose of vaccine. We found that 15% of Omicron patients had previous history of COVID-19, while only 3.64% of Delta patients had the same ($P = 0.042$) [Table 1]. Only four patients among the possible Omicron group had history of travelling while none of the non-Omicron cases had any such history.

Symptoms

All the patients had either mild symptoms or asymptomatic contacts and were managed in home isolation with symptomatic medications. 84.7% of Omicron patients were found to be symptomatic as compared to 70.9% of non-Omicron/Delta patients presenting with symptoms [Figure 1]. Fever, cough and sore throat were the predominant symptoms presented by both Omicron/SGTF and non-Omicron/Delta infected individuals. 69.5% of Omicron patients had sore throat compared to non-Omicron (58.1%). While myalgia was reported by many Omicron patients (17.3%), it was only 3.6% in non-Omicron cases ($P < 0.021$) [Table 2]. Loss of taste/smell was reported in 6 of non-Omicron patients (10.9%), while only 2 of Omicron patients (4.3%) complained of the same. Breathlessness was reported in 5.45% of non-Omicron cases while none of the Omicron cases reported complaints of breathlessness. Weakness and fatigue were complained by 4.35% of Omicron patients while it was nil in the other group.

Comparison of viral load

No significant difference in median Ct values between Omicron (28, IQR 25–29) and non-Omicron patients (26, IQR 22–29) were found in our study [Figure 2a]. Trend analysis of daily mean Ct value of total positive cases over the last two months showed no particular trend in change in the mean Ct value (data not shown).

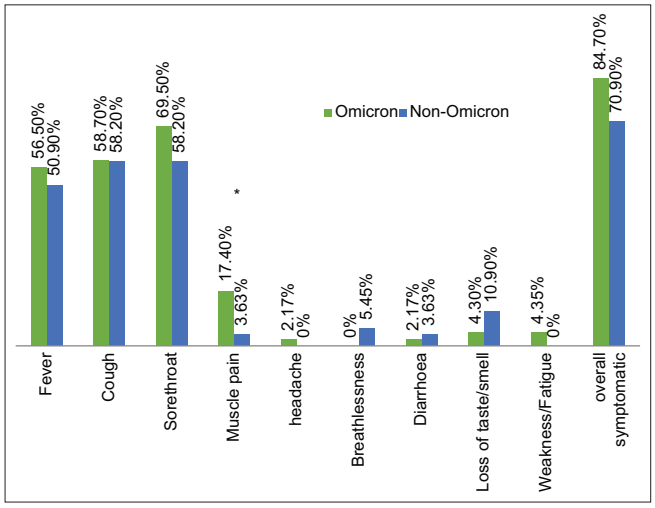

Figure 1: Comparison of symptoms in Omicron vs non-Omicron/Delta infected patients. Bar diagram shows the relative proportion (%) of different symptoms in patients infected with Omicron and non-Omicron variants. *: statistically significant ($P < 0.05$)

Onset of infection and last vaccine dose

We analyzed the window interval between the last dose of COVID vaccine (Covishield or Covaxin) and current RT-PCR positivity, and we found that the mean interval between onset of disease and last vaccine dose was 204 ± 80 (mean ± SD) days in case of possible Omicron cases while the same was found to be 218 ± 81 (mean ± SD) days in case of non-Omicron cases [Figure 2b]. 26.8% (25) of the fully vaccinated individuals developed COVID-19 within four months of the last dose of vaccine, mostly Covishield [Figure 2c].

Trend of Mumbai COVID-19 statistics before and during third wave

A clear-cut rise in percentage positivity since the third week of December 2021 at 2% with peak reaching at 28.3% on 10 January 2022 was found, followed by a noticeable fall till 21 January 2022 [Figure 3a]. A similar pattern was also reflected in our laboratory data. The doubling time of Mumbai cases reduced sharply from 251 to 36 days within a span of 10 days from 31 December 2021, stabilized for 4 days and slowly rose thereafter to 83 days [Figure 3b].

Table 1: General characteristic and demographics of the patients (*n*=101)

Characteristics	Omicron (*n*=46) *n* (%)	Non-omicron (*n*=55) *n* (%)	*P*
Age in years (mean±SD)	32.09±9.0	33.73±10.1	0.39
Sex %	F:M 45:55	F:M 51:49	0.59
Comorbidities	1 (2.17%)	2 (3.64%)	0.67
Smoking	none	none	-
Alcohol	none	none	-
Fully Vaccinated	41 (89%)	53 (96%)	0.15
Previous h/o COVID-19	7 (15%)	2 (3.64%)	0.042*
Travel	4 (8.7%)	0 (0%)	0.025*

Comparison of Omicron- and non-Omicron-infected patients in the table show difference in age, gender distribution, comorbidities, smoking or alcohol consumption, travel history, vaccination status and prior history of COVID-19. Data are presented as mean±SD for age distribution and percentage proportion for the rest. Unpaired *t* test was done for age while Chi-squared test was done for all categorical variables. A $P<0.05$ was considered as statistically significant

Table 2: Comparison of symptoms of the study groups

Symptoms	SGTF/Possible Omicron *n* (%)	Non-Omicron *n* (%)	*P*
Fever	26 (56.5%)	28 (50.9%)	0.57
Cough	27 (58.7%)	32 (58.18%)	0.95
Sore throat	32 (69.5%)	32 (58.1%)	0.23
Breathlessness	0 (0%)	3 (5.45%)	0.10
Muscle pain	8 (17.3%)	2 (3.64%)	0.021*
Headache	1 (2.17%)	0 (0%)	0.27
Fatigue	2 (4.35%)	0 (0%)	0.11
Loss of smell or taste	2 (4.35%)	6 (10.9%)	0.22
Diarrhea	1 (2.17%)	2 (3.64)	0.66
Symptomatic	39 (84.7%)	39 (70.9%)	0.097

Comparison of the symptoms of Omicron- and non-Omicron-infected patients in the study. Data are presented as actual numbers (*n*) and percentage proportions (%). Chi-squared test was done for all categorical variables. A $P<0.05$ was considered as statistically significant

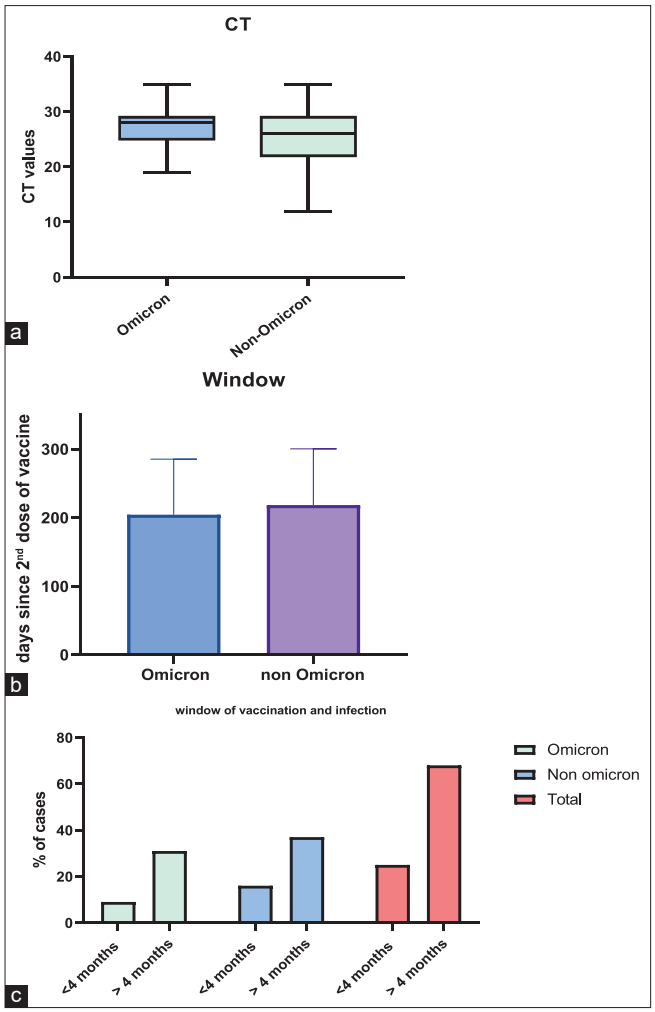

Figure 2: Comparing Ct value, window from infection and last dose of vaccination in study groups. (a) Box and whisker plot represent median and interquartile range (IQR) of cycle threshold (Ct) values in Omicron (28, IQR 25–29) and non-Omicron (26, IQR 22–29) cases. (b) Bar diagram presents the mean gap/window since second dose of vaccine till current RT-PCR positivity in the patients in Omicron and non-Omicron groups. Data shown as mean ± SD of days since day of second dose of vaccination. (c) Proportion of patients developing COVID-19 within four months and more than four months of complete vaccination in total, Omicron and non-Omicron cases. Data shown as percentage

Discussion

Comparative analysis of Omicron and non-Omicron cases

After the WHO declared Omicron as a VOC on 26 November 2021, the first Omicron case in India was detected in Karnataka in a person with history of international travel.[9] Soon after, two cases in Mumbai were detected in the first week of December 2021.[10] Mumbai COVID-19 cases showed a drastic rise from the third week of December 2021. Evaluation of the proportions and clinical spectrum of Omicron (SGTF) and non-Omicron cases in our study revealed that 46 of COVID-19 patients (46%) were possibly Omicron, as reflected by SGTF, while the rest were non-Omicron infections, presumed most likely to be Delta as the pre-existing dominant variant. Compared to 69.5% of Omicron cases complaining of sore throat, 58.1% of Delta cases presented with sore-throat, indicating that Omicron usually involved the upper respiratory tract with less involvement of the lung. Myalgia was more significantly reported by Omicron cases (17.3%) while loss of smell or taste (10.09%) were more frequently reported by non-Omicron patients compared to Omicron cases [Table 2]. Public health management and policies largely depend on the epidemiological data and clinical severity of the Omicron variant compared to previous SARS-CoV-2 variants. In our study, 84.7% of the Omicron cases were symptomatic compared to 70.9% of non-Omicron cases. Clinically, the milder course of Omicron could be attributed to wide vaccination coverage, natural protection from prior infection or due to change in the virus antigenic structure.[3] One recent data linkage study from South Africa has shown that compared to the Delta variant, Omicron-infected patients had significantly lower odds of hospitalization and disease severity.[11] Moreover, the majority of Omicron patients in our study belonged to a relatively young age group which can also be responsible for less numbers of severe illness. Similarly, one recent study comparing characteristics and outcomes in hospitalized COVID-19 patients during earlier waves and the Omicron-led fourth wave in South Africa observed relatively younger patients without comorbidities to be predominantly infected, with fewer hospitalization and mortality.[12] This could be due to enhanced immunity in the older adult population due to prior infection and vaccination. From our laboratory, we observed that the most affected age group during the second wave of COVID-19 (May–August 2021) was the 40–60 years age group. This is in agreement with another study from Uttar Pradesh which found that the mean age group of 46.1 ± 16.8 years had been maximally affected during the second wave.[13]

Role of immune response, viral escape and disease severity

Post natural infection or vaccination, neutralizing antibodies are produced against the receptor binding domain (RBD) of the virus and offer protection against reinfection or severe form of disease in the future. However, the presence of fifteen mutations clustered in the RBD, including nine in the subdomain interacting with host cell ACE2, suggests that Omicron is more likely to dodge the infection- and vaccine-acquired antibodies as well as therapeutic monoclonal Abs.[14–16] In our study, 94 individuals (93%) had taken two doses of COVID vaccine. Among these 94 positive individuals, 9 (8.9%) had been previously infected with COVID-19 in the first or second waves. 77.7% of previously infected were now infected with Omicron variant and only 22.3% by non-Omicron variant. This observation can be explained by the fact that they had enhanced antibodies against non-Omicron due to conjoint effect of natural infection plus vaccination, whereas those antibodies were not protective against the Omicron variant. Epidemiologic data has highlighted greater immune protective response in individuals with previous infection and vaccination, particularly against the Delta variant, compared

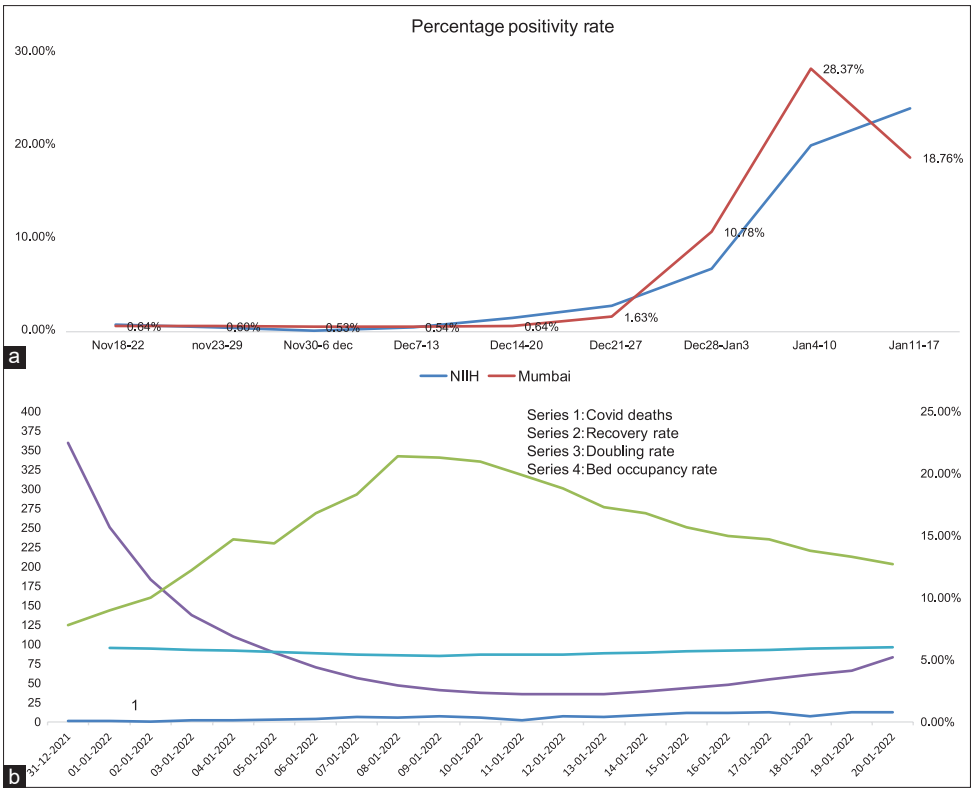

Figure 3: Trend analysis of COVID-19 daily statistics in Mumbai during the third wave. (a) Percentage positivity data of Mumbai and our lab (NIIH) from 18 November 2021 to 20 January 2022. (b) Statistics of COVID death (1), recovery rate (2), doubling rate (3) and bed occupancy rate (4) in Mumbai region. 1–3 are represented by the primary axis on the left, and data 4 is represented by secondary axis (in %) on the right side of the graph

to individuals neither previously infected or vaccinated.[17] The cause of 8.9% of reinfection among fully vaccinated 94 individuals in our study was most probably due to the immune-evasion properties of Omicron, decline in immunity, or both. However, these observations are limited by small sample size and require large-scale studies in the future to unfold the epidemiology of the Omicron variant. A recent Danish household study found that Omicron was 2.7–3.7 times more infectious than the Delta variant among vaccinated people.[18] Interestingly, scientists found that that only 6/44 neutralizing mAbs could effectively neutralize Omicron.[19,20] In line with, a study by Callaway E *et al.* found that people who had already been infected before vaccination tended to have higher levels of neutralizing antibodies against Omicron than vaccinated people with no known history of infection.[19] However, it will be important to determine the extent to which immune mechanisms other than neutralizing antibodies, such as T cells, ameliorate severe disease caused by infection.

While influenza antigenic shift is mediated by genetic reassortment between the viral RNA segments, the exact mechanism frequent number and type of mutations in SARS-CoV-2 Omicron variant remains to be elucidated. Although studies on coronaviruses suggest the role of recombination events for frequent genetic changes,[21] accumulating evidence indicate that the novel mutations might result from prolonged viral replication in immunodeficient hosts[22,23] or from inter-species jump between humans and rodents.[24,25] Furthermore, the virus could be present months before due to being limited to and evolved in certain population left out of sequencing and surveillance or due to lower vaccination in resource-poor countries favoring viral evolution.

Mean intervals between the second dose of COVID vaccine and current infection were about 204 ± 80 and 210 ± 81 days in Omicron and non-Omicron cases, respectively [Figure 2b]. This indicates that vaccine-mediated protection against reinfection might not be lasting beyond six months. Furthermore, 25 (26.8%) of the fully vaccinated individuals developed COVID-19 within four months of the last dose of vaccine [Figure 2c]. This highlights the variable immune response to vaccination as well as efficacy of the vaccine. However, it can attenuate severe disease and prevent complications in breakthrough infections as evident from our data. Recent evidences show that Ct values inversely correlate with disease severity and mortality in hospitalized patients due to COVID-19.[26–28] However, its utility for treatment or prognosis is limited by variability in biological sample collected in nasal/oropharyngeal swab, RT-PCR assay, target gene amplification, and RT-PCR's inability to differentiate between presence of live virus or viral debris. Ct value trend could also be an early indicator of an upcoming surge in cases.[29] However, longitudinal analysis of daily median CT values from our laboratory failed to show any specific trend nor did we find any significant difference in Ct values between Omicron and Delta cases [Figure 2a].

Trend of infection across the third wave in Mumbai

We analyzed the percentage positivity data in the whole of Mumbai region [Figure 3a] and found a distinct rise in percentage positivity since the third week of December 2021 at 2%, with peak reaching at 28.3% on 10 January 2022 followed by a noticeable fall till 21 January 2022. A similar pattern was also reflected in our laboratory data, thereby indicating the representativeness of our samples for the Mumbai region. This rapid rise and fall are quite similar to that of South Africa during the fourth wave and are due to high transmissibility of the Omicron variant. Higher transmission of Omicron could be due to its ability to remain suspended in air, its binding capacity to target cells or evasion of the body's immune system.[30–33] One study from UK found the secondary household infection rate to be 19% in Omicron, compared to 8.3% of Delta index cases.[30] However, hospitalization and bed occupancy has not greatly increased in contrast to what was observed during the second wave of COVID-19. Trend of Mumbai COVID-19 data since the third week of December 2021 has shown a sharp fall in case doubling time from 251 to 36 days within a span of 10 days, stabilization for 4 days and slow rise thereafter to 83 days [Figure 3]. This indicates very high transmissibility and possible community transmission occurring early in Mumbai region, most likely caused by Omicron surge. However, bed occupancy rate marginally increased from 12.7% to 21% during the peak near 10 January 2022 followed by a similar fall in contrast to very high occupancy of COVID beds during the second wave. The data indicates that the milder spectrum of COVID-19 cases in general reflected the protection against complications via massive vaccination coverage in India.

Study limitations

The study has a number of limitations. Firstly, SGTF identified by RT-PCR, used as a proxy for Omicron variant detection, can sometimes detect Alpha variant as SGTF. However, it can be mentioned that before the third wave in India, most of the COVID-19 cases were caused by Delta. Unlike BA.1 and BA.3 sub-lineages of the Omicron variant with a deletion at amino acid 69–70, which is targeted for S-gene amplification during RT-PCR, BA.2 doesn't contain this deletion and can therefore escape detection by SGTF.[34] However, it needs to be mentioned that BA.1 is the dominant sub-variant responsible for 99% of COVID-19 infections worldwide, and thus, SGTF could be able to identify Omicron vs non-Omicron in a majority of cases.[35] Furthermore, the data collected for this study are limited by the relatively smaller study population, lack of other medical details and follow up. In spite of such limitations, the data is well informative of the disease spectrum in Omicron and non-Omicron cases and provides scrutiny of the trend of infection in the region.

Conclusion

Results from our study showed that about 46% of cases were mediated by possible Omicron variant and the high transmissibility indicated by sharp fall of doubling time and rapid rise in percentage positivity suggest that Omicron largely replaced Delta over time by causing community transmission. Still, 54.4% (55) were Delta infections, but with milder clinical features as compared to the second wave. It could be attributed to high vaccination coverage which prevented severe manifestations and complications. However, the question still remains whether the differing symptoms are a result of existing immunity or antigenically distinct Omicron infection. This could be explained by further detailed immunological studies in the future. Our data will aid in planning the target population and timing of vaccine booster dose in order to prevent infection in vulnerable people. As primary care plays a significant role in COVID-19 management through early diagnosis, identifying warning signs of severity, timely referral, reducing hospitalization demand, and educating people about vaccination, our data can guide them towards delivering efficient primary health care to cope with the upcoming COVID-19 infections in the coming days.

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Take home message

1. What is the current understanding of this subject?
Omicron infection is causing a global surge in COVID-19 cases but few studies have been conducted to compare its clinical spectrum vs previous variants.

2. What does this report add to the literature?
Our study shows that all patients were vaccinated and had mild symptoms. A proportion of reinfection cases was higher in Omicron compared to people infected with non-Omicron variant.

3. What are the implications for public health practice?
Our results indicate that high vaccination coverage in our study population could prevent severity and complications but not breakthrough or reinfection, and thus, adds important information in formulating future vaccination strategies. This will be helpful for primary care physicians coping with an upcoming surge in COVID cases, if any in future.

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Conflicts of interest

There are no conflicts of interest.

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