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ORIGINAL ARTICLE

Revealing COVID-19 breakthrough infection rates among vaccinated individuals at a tertiary care centre in South India

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ABSTRACT

Background and Objectives: The COVID-19 pandemic was mitigated by the rapid development and deployment of vaccines. While vaccines reduce infection severity, breakthrough infections (BTIs) still occur. The CDC defines BTI as a positive SARS-CoV-2 test ≥14 days post-vaccination. This study investigates the occurrence of COVID-19 BTIs at a tertiary care hospital in Puducherry, South India.
Materials and Methods: This retrospective study analysed hospital tested qRT-PCR data of individuals from the ICMR portal (March 2021–March 2022). Demographic and vaccination details were extracted.
Results: Among 8001 tested individuals, 1452 were vaccinated. The BTI rate decreased from 16.6% to 1.2% after the first dose and from 58% to 40% after the second one. Odds ratio indicated a 74% reduction in infection risk for vaccinated individuals compared to unvaccinated. Males had higher infection rates than females, regardless of vaccination status.
Conclusion: Our study demonstrates a higher BTI rate after one vaccine dose compared to two doses. The BTI rate also increased four months post-vaccination, even with two doses, potentially due to waning immunity and the emergence of new variants. Therefore, continued adherence to preventive measures in conjunction with vaccination is crucial for minimizing COVID-19 transmission.

Keywords: Breakthrough infections; SARS-CoV-2 virus; COVID-19; Vaccination; Outbreak

INTRODUCTION

The coronavirus disease 2019 (COVID-19), a disease brought about by the novel coronavirus SARS-CoV-2, a virus from the Coronaviridae family, has had a profound global impact since it first emerged in Wuhan, China, in late 2019 (1, 2). The respiratory illness, which primarily transmitted through respi-

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ratory droplets and aerosols, poses a heightened risk in enclosed spaces, particularly with prolonged close contact or forceful exhalation by infected individuals (3). On August 16, 2023, the World Health Organization (WHO) reported a staggering 769 million cases globally, with India accounting for 4 million of those cases (4). The global death toll attributed to COVID-19 reached 6,495,110 as of September 14, 2022 (5). The WHO has outlined key preventive measures, including isolation, ventilation, social distancing, mask usage, hand hygiene, and vaccination (6).

The rapid development and deployment of vaccines have been crucial in mitigating the pandemic's impact (7). India has spearheaded a monumental vaccination campaign, primarily utilizing Covaxin and Covishield, which have demonstrated around 80% and 90% efficacy, respectively (8). The campaign, launched on January 16, 2021, initially prioritized healthcare workers, frontline personnel, senior citizens, and individuals with comorbidities, subsequently expanding to other age groups. By January 1, 2023, over 2.2 billion vaccine doses had been administered, with more than 90% of the Indian population being fully vaccinated (having received two doses) (9). The vaccines have been instrumental in reducing infection rates, disease severity, and mortality. However, the emergence of breakthrough infections, defined as positive SARS-CoV-2 tests in vaccinated individuals, has raised concerns. The Indian Council of Medical Research (ICMR) has reported breakthrough infection prevalence rates of 0.02% after one Covishield dose, 0.03% after two Covishield doses, and 0.04% after two Covaxin doses (10). The present study aims to evaluate the proportion of breakthrough infections among fully vaccinated individuals at a tertiary care hospital in South India.

MATERIALS AND METHODS

Study design and data gathering. This was a retrospective observational study carried out in the Department of Microbiology at a tertiary care hospital in Puducherry, South India. The study utilized data extracted from the Indian Council of Medical Research (ICMR) COVID-19 data entry portal between March 2021 and March 2022. The study population included both outpatients and inpatients who underwent SARS-CoV-2 qRT-PCR testing for various reasons, including suspected infection, pre-procedural screening, travel requirements, self-testing, and contact tracing. Individuals testing positive for SARS-CoV-2 14 days to 4 months post-complete vaccination were classified as 'breakthrough infections.' The study collected demographic data, symptom profiles, comorbidities, and vaccination details (vaccine type, number of doses) from the patients. The data was then stratified into vaccinated and unvaccinated cohorts for further analysis.

Ethics of study. The study adhered to the ethical principles outlined in the 1975 Declaration of Helsinki and the guidelines for biomedical research involving human participants set forth by the Indian Council of Medical Research (ICMR). The Institute Human Ethics Committee (IHEC) approved the study and granted a waiver of informed consent from individual patients.

Statistical analysis. Data obtained from the ICMR COVID-19 data entry portal was transferred to Microsoft Excel and then analysed using SPSS version 17.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages. The chi-square test was used to compare proportions, while regression analysis was conducted to determine odds ratios (ORs) with 95% confidence intervals. All p-values were two-sided, with a significance threshold set at $p < 0.05$.

RESULTS

Study population and demographics. During the study period from March 2021 to March 2022, a total of 8001 qRT-PCR tests were conducted at our tertiary care hospital. The ages of the study participants varied from 20 to 87 years, with an average age of 46.3 years. Of the total study population, 4710 (58.9%) were male, and 3291 (41.1%) were female. Regarding vaccination status, 18% (n=1452) were vaccinated, 81% (n=6510) were unvaccinated, and 0.5% (n=39) had unknown vaccination status.

Breakthrough infection analysis. Subgroup analysis of the 1452 vaccinated individuals revealed that 7% (n=103) tested positive for SARS-CoV-2. In contrast, 23% (n=1478) of the 6510 unvaccinated individuals tested positive (Figs. 1-3). The majority of vaccinated individuals received Covishield, followed

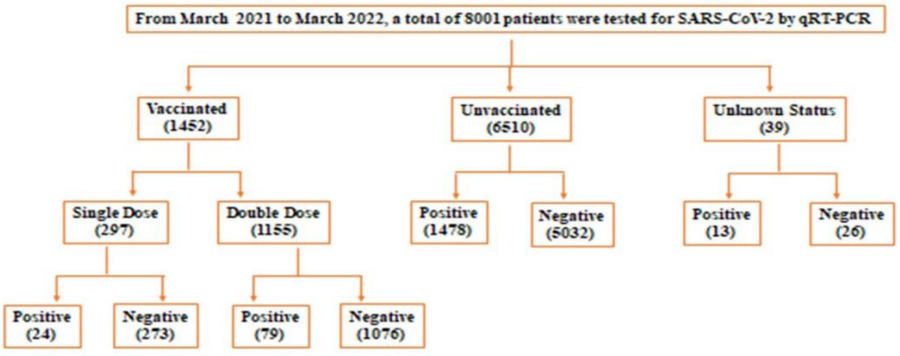

Fig. 1. Frequency of infection among vaccinated and non-vaccinated individuals
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, qRT-PCR: Real-Time Quantitative Reverse Transcription PCR

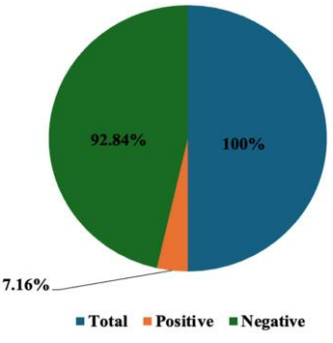

Fig. 2. Frequency of infection among vaccinated individuals

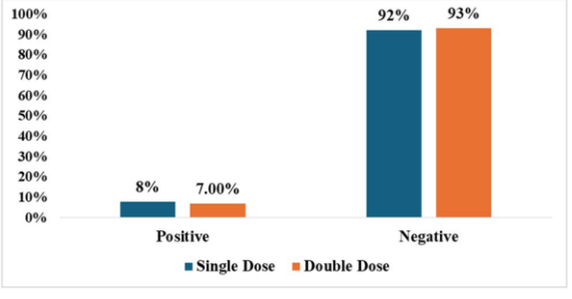

Fig. 4. Breakthrough infection after single and double dose of vaccine

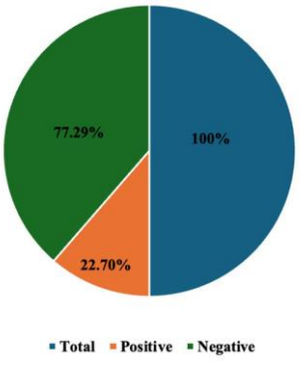

Fig. 3. Frequency of infection among unvaccinated individuals

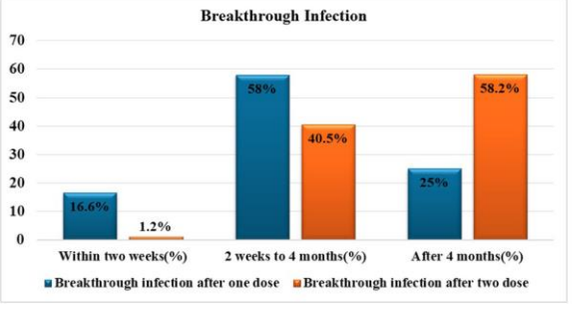

Fig. 5. BTI at different intervals post-vaccination

by Pfizer, administered in two standard doses with a mean interval of 31.7 ± 7.3 days between doses.

No significant difference in breakthrough infection rates was observed between those who received one or two doses of the vaccine ($P > 0.05$) (Fig. 4). The breakthrough infection rate following two doses of the vaccine was lower within the first four months post-vaccination but increased thereafter (Fig. 5).

Post-vaccination infection (PVI) analysis revealed that early PVI (within two weeks) was significantly higher in individuals who received one dose (16.6%) compared to those who received two doses (1.2%). PVI between 2 weeks and 4 months post-vaccination was 58% for single-dose recipients and 40.5% for those who received two doses. However, late PVI (4-10 months post-vaccination) was more frequent among individuals who received two doses (58.2%) compared to those who received one dose (25%). A statistically significant association was found between

the number of vaccine doses received and the timing of post-vaccination infection ($\chi2$=14.33, P=0.0007), suggesting that two doses of the COVID-19 vaccine had a cumulative protective effect and delayed infection (Table 1).

Vaccine type and breakthrough infection. The majority of vaccinated individuals received Covishield (82%), followed by Pfizer (7%). While the infection rate was higher in these two vaccines, no significant association was found between the breakthrough infection rate and vaccine type ($\chi2$=2.9, P=0.407) (Table 2). We performed subgroup analysis to identify the BTI rate between the groups by categorizing the positive patients into two groups based on the types of vaccines used for their first and second doses. We observed that, BTI rates increased after the second dose for Covaxin (3.23%), Covishield (5.69%), and Pfizer (6.86%), which was not statistically significant. Pfizer had the highest BTI rate (6.86%) after the second dose, while Covaxin (3.23%) had the lowest BTI rate. Chi square analysis showed no significant differences between groups for the first dose ($\chi2$=2.31, (P= 0.511) and the second dose ($\chi2$=3.14, p = 0.370) (Table 3). Regression analysis revealed that vaccinated individuals had a 74% reduced risk of COVID-19 infection compared to unvaccinated individuals (OR: 0.26, P=0.01) (Table 4), emphasizing the importance of vaccination in mitigating COVID-19 infection risk.

Gender and COVID-19 infection. Analysis of COVID-19-positive cases among unvaccinated individuals showed that 24% were male and 21% were female. Regression analysis revealed a significant association between sex and COVID-19 infection; males were 1.2 times more likely to test positive compared to females (OR=1.2, P=0.001) (Table 5). Subgroup analysis of positive cases based on vaccination status and gender showed that 7.5% of positive males and 5% of positive females were vaccinated. Even among vaccinated individuals, men were 1.5 times more likely to test positive compared to women (Table 6). Figs. 6 and 7 depict the frequency of infection among vaccinated and unvaccinated individuals, respectively.

Overall trends and disease outcomes. Fig. 8 illustrates the total number of samples tested and positive cases from August 2020 to December 2022. Table 7 summarizes breakthrough infections and their disease outcomes in India among vaccinated individuals.

DISCUSSION

The frequency of viral outbreaks has notably increased in recent decades, with several coronavirus outbreaks, including SARS-CoV-1 in 2003, MERS-CoV in 2012, and the ongoing SARS-CoV-2 pandemic that began in 2019. The critical factors in mitigating such outbreaks lie in robust surveillance programs and effective laboratory preparedness for the identification of novel pathogens. The SARS-CoV-2 outbreak in India, which began in January 2020, has witnessed three successive waves. In the Union Ter-

Table 1. Association between numbers of vaccination doses received and post-vaccination infection

No. of vaccination doses	Within two weeks	2 weeks to 4 months	After 4 months to 10 months	χ^2	P-value
Post-vaccination infection after one dose	4	14	6	14.33	0.0007
Post-vaccination infection after two doses	1	32	46		

Table 2. Breakthrough infection after different types of vaccine

Types of vaccine	Total N (%)	Positive N (%)	Negative N (%)	χ^2	P-value
Covaxin	93 (6%)	4 (4%)	89 (96%)		
Covishield	1196 (82%)	91 (8%)	1105 (92%)		
Pfizer	102 (7%)	7 (7%)	95 (93%)	2.90	0.407
Others	61 (4.2%)	2 (3.3%)	59 (96.7%)		
Total	1452	104	1348		

Table 3. Breakthrough infection after first and second doses of vaccine types

Types of vaccine	Total N (%)	Positive N (%)		χ^2	P-value
		After 1st dose	After 2nd dose		
Covaxin	93 (6%)	1 (1%)	3 (3.2%)	2.31	0.511
Covishield	1196 (82%)	23 (1.9%)	68 (5.6%)		
Pfizer	102 (7%)	0 (0%)	7 (6.8%)		
Others	61 (4.2%)	1 (1.6%)	1 (1.6%)		
Total	1452	24	79	3.14	0.370

Table 4. Odds ratio among vaccinated and unvaccinated individuals

	Positive	Negative	Odds ratio (OR)	95% CI	P-value
Vaccinated	104	1348	0.26	0.21-0.32	0.01
Unvaccinated	1478	5032			

OR: Odds Ratio

Table 5. Gender wise analysis among unvaccinated individuals

	Unvaccinated Positive	Unvaccinated Negative	Odds ratio (OR)	P-value
Male	887 (24%)	2780 (76%)	1.2	0.001
Female	591 (21%)	2252 (79%)		

Table 6. Infection among vaccinated and unvaccinated individuals

	Positive		χ^2	Odds ratio (OR)	P-value
	Vaccinated	Unvaccinated			
Male	72 (7.5%)	887 (92.5%)	3.946	1.5	0.046
Female	31 (5%)	591 (95%)			

OR: Odds Ratio

ritory of Puducherry, a surge in cases from March 2020 prompted the government to implement emergency training for healthcare workers and bolster outbreak management preparedness. The initial reliance on government colleges with Biosafety Level-2 (BSL-2) laboratories for testing and surveillance was augmented by the establishment of NABL-accredited BSL-2 laboratories in private institutions due to the increasing caseload. Our institution, having obtained NABL approval, commenced SARS-CoV-2 testing in August 2020, encompassing surveillance, outpatient, and inpatient samples. As of January 2023, we had tested approximately 13,954 samples, with 2688 testing positive.

Achieving herd immunity, estimated at 60-70% of the population, is crucial for pandemic management, and vaccination remains a potent tool in this endeavour. The Indian government launched a massive COVID-19 vaccination campaign in January 2021, primarily utilizing Covishield and Covaxin, which demonstrated good efficacy against infections and mortality. However, the emergence of the Omicron variant a year later presented a challenge, with breakthrough infections reported within two weeks to three months post-vaccination. These breakthrough infections as a global concern can exhibit high virulence and transmissibility, potentially leading to increased morbidity and mortality. Previous studies

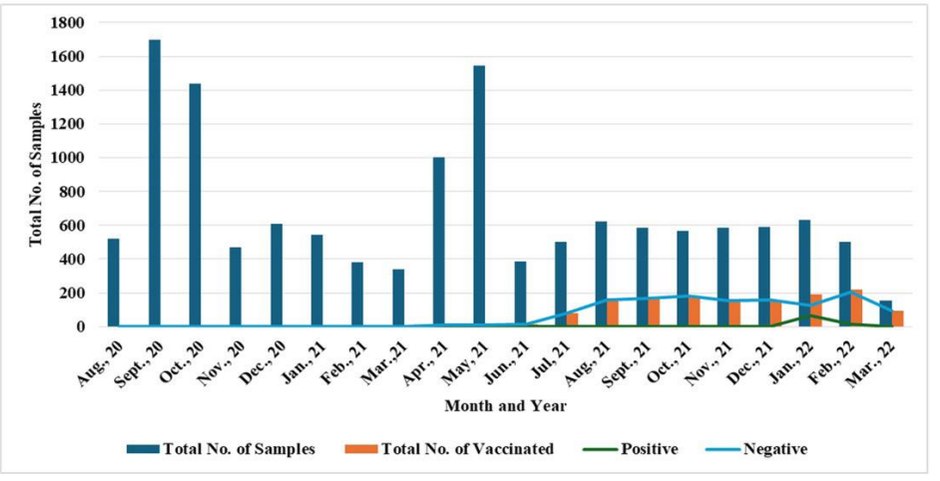

Fig. 6. Frequency of infection among vaccinated individuals

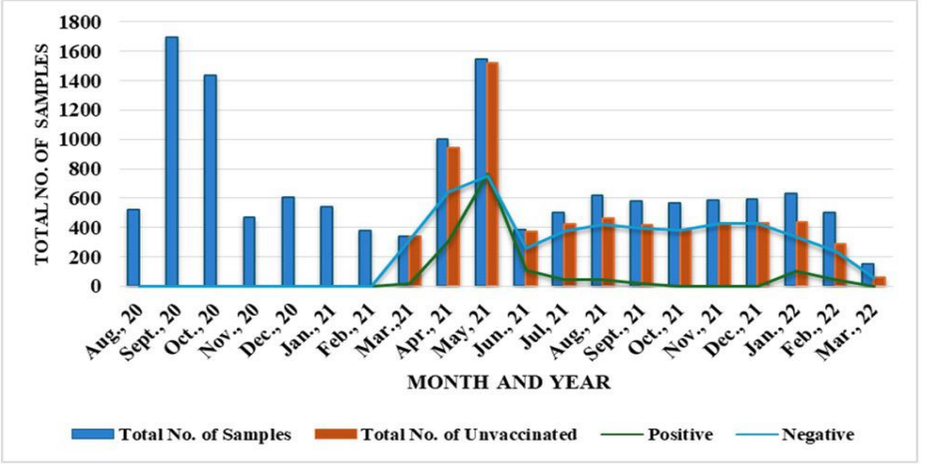

Fig. 7. Frequency of infection among unvaccinated individuals

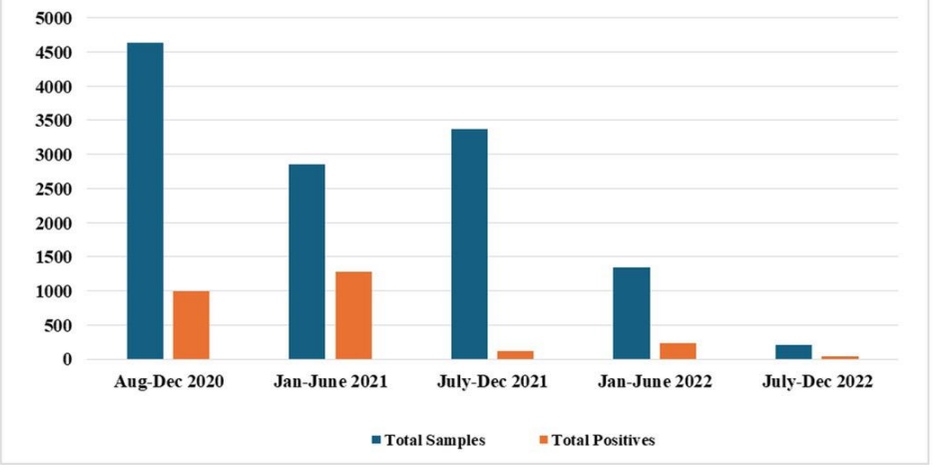

Fig. 8. Total number of samples and total positivity from August 2020 to December 2022

Table 7. Breakthrough COVID-19 infection and disease outcome in India

Study done by	Study type	Study group	BTI	Vaccine effectiveness	Disease Outcome	Ref.
Priyamadhaba Behera et al. (2022)	Hospital-based test-negative case-control study, AIIMS, Bhubaneswar Retrospective test-	HCWs		COVAXIN-29%, overall vaccine effectiveness-22%	-	(11)
Raju Vaishya et al. (2021)	negative case-control study, Apollo groups Data collection, New Delhi, India	HCWs	Covishield-5.11%, Covaxin-4.58%	-	predominantly mild and did not result in hospitalization ($p < 0.0001$), or death	(9)
Kanika Tyagi et al. (2021)		HCWs	13.30%	-	1 hospitalization, others had mild infection	(10)
Geetika Arora et al. (2022)	questionnaire based survey, Delhi School of Public Health, & Dr. B.R. Ambedkar Center for Biomedical Research, New Delhi, India	Indian Population	7.91%		Post vaccinated symptomatic BTI 31.25% mild, 43.75% moderate, 25% severe	(12)
Apurve Parameswaran et al. (2022)	online voluntary survey, Medicover (Formerly Maxcure) Hospital, Telangana	HCWs	31%	-	Hospitalised Covishield After one dose -11%, After 2 doses-8%; COVAXIN After one dose-21%, After two doses-5%	(13)
Upinder Kaur et al. (2022)	Observational study (Telephonic interview), Banaras Hindu University, Varanasi, Uttar Pradesh	HCWs	After single dose-41.5% After double dose-18.9%		Severe infection seen in 6.7% after single dose and 1.5% after double dose of vaccination	(14)
Vishal Malhotra et al. (2022)	semi-structured validated Proforma and telephonic interview, Government Medical College, Patiala, Punjab	HCWs	4.6%		Mild infection	(15)
Bhavya Krishna et al. (2022)	cross-sectional study -questionnairre, AIIMS, New Delhi	HCWs	23.36%	78.5% covishield, covaxin 72.4%	mild 21.25%, moderate 1.91% (postvaccination)	(16)
Malathi Murugesan (2022)	non-concurrent cohort study, CMC Vellore	HCWs	-	prior infection-86%, vaccination+prior infection-91%, vaccination alone-32%	First wave M-98%, md-0.7%,s-1.3%; Second Wave M99.44%, MD-0.2%, S-0.4%	(17)
Aashish Contractor et al. (2022)	cohort study, HN Reliance Foundation Hospital and Research Centre, Mumbai	HCWs		70% after full vaccination, prior infection-88%	Hospitalization very low and no death	(18)

have reported on breakthrough infections and their outcomes in India (11-18).

Our study found a breakthrough infection rate of 7% among vaccinated individuals and 22% among unvaccinated individuals, highlighting the continued risk of infection even after vaccination. Notably, breakthrough infections were observed even after two vaccine doses. These findings align with other studies reporting breakthrough infection rates ranging from 4% to 31% (Table 6). The reasons for these infections are multifaceted, including reduced immunogenicity in immunocompromised individuals and the emergence of mutant strains capable of evading vaccine-induced immunity. Other factors, such as viral characteristics, host factors (age, comorbidities, immune status), and vaccination parameters (dose, interval, route), also play a role.

We observed a low rate of breakthrough infections within the first four months after the second vaccination, followed by a gradual increase. This observation is consistent with previous reports highlighting concerns about waning immunity and the potential impact of emerging variants on vaccine efficacy (10, 19-20). A study by Mishra et al. linked the increase in breakthrough infections after four months to waning protective immunity, evidenced by a 50% reduction in IgG antibodies four months post-infection (21).

Contrastingly, a population-based study from Italy by Vitale et al. demonstrated that BTI risk is very rare in patients who recovered from COVID-19 infection (22). However, these post-vaccination BTI rarely need hospitalization and intensive care unit (ICU) admission compared to infections in unvaccinated people (23). The reported varied factors attributed to post-vaccination infections are lifestyle factors, obesity, improper compliance to COVID-19 preventive measures and other comorbidities like hypertension, diabetes, cardiac disease, intake of immunosuppressant and inappropriate operation and storage of vaccines.

While breakthrough infections can raise concerns and vaccine hesitancy, they can contribute to achieving herd immunity if they remain mild. Importantly, our study demonstrated a 74% reduction in infection risk for vaccinated individuals compared to unvaccinated individuals, underscoring the real-world effectiveness of vaccination. This finding is supported by other studies reporting reduced severity, hospitalization rates, and mortality among vaccinated individuals (24-26).

Interestingly, our study revealed a sex-specific difference in COVID-19 susceptibility, with males exhibiting a higher likelihood of infection compared to females. This observation aligns with previous reports of male overrepresentation in COVID-19 cases (27). However, some studies have noted a higher prevalence of post-COVID-19 symptoms, such as sleep disturbances and anxiety, in females (28). These gender disparities may be attributed to various factors, including behavioural, hormonal, genetic, and immunological differences. Further research is needed to elucidate the complex interplay between gender and COVID-19 outcomes.

CONCLUSION

Our study revealed a substantial prevalence of breakthrough COVID-19 infections among healthcare workers, even after two vaccine doses. This highlights the critical need for increased awareness about the potential for breakthrough infections in managing the pandemic.

We observed distinct patterns between vaccinated and unvaccinated individuals. While nearly all unvaccinated individuals experienced symptomatic and severe COVID-19, most vaccinated individuals had mild or asymptomatic infections. Despite this, breakthrough infections were significantly higher among individuals who received only one vaccine dose compared to those who were fully vaccinated. Also, no significant difference in breakthrough infection rates between one and two doses of the vaccines might be due to the low proportion of individuals who received Pfizer (7%) and Covaxin (6%) compared to those who received Covishield (82%). Furthermore, the emergence of SARS-CoV-2 variants, particularly Omicron, Beta, Delta, and Alpha, substantially impacted vaccine efficacy due to their unique mutations, primarily in the spike protein. Nonetheless, vaccination remained effective in preventing severe disease.

Our analysis also indicated a sex-specific variance in COVID-19 virulence, suggesting the importance of considering gender in future COVID-19 research. To fully understand the implications of these findings, prospective studies examining gender differences in COVID-19 infectivity are warranted.

Based on our results, we conclude that breakthrough infections may be difficult to entirely prevent. Conse-

quently, consistent adherence to COVID-19 prevention measures, even after full vaccination, is strongly recommended.

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