

## REVIEW

# Omicron variant of SARS-CoV-2: Genomics, transmissibility, and responses to current COVID-19 vaccines

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## Abstract

Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide as an Omicron variant. This variant is a heavily mutated virus and designated as a variant of concern by the World Health Organization (WHO). WHO cautioned that the Omicron variant of SARS-CoV-2 held a very high risk of infection, reigniting anxieties about the economy's recovery from the 2-year pandemic. The extensively mutated Omicron variant is likely to spread internationally, posing a high risk of infection surges with serious repercussions in some areas. According to preliminary data, the Omicron variant of SARS-CoV-2 has a higher risk of reinfection. On the other hand, whether the current COVID-19 vaccines could effectively resist the new strain is still under investigation. However, there is very limited information on the current situation of the Omicron variant, such as genomics, transmissibility, efficacy of vaccines, treatment, and management. This review focused on the genomics, transmission, and effectiveness of vaccines against the Omicron variant, which will be helpful for further investigation of a new variant of SARS-CoV-2.

## KEYWORDS

coronavirus, disease control, immune responses, SARS coronavirus, vaccines/vaccine strains, virus classification

## 1 | INTRODUCTION

Different variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been identified since the first coronavirus disease 2019 (COVID-19) infection appeared in December 2019. Until November 2021, the Delta variant was designated as variant of concern (VOC) because of different characteristics.<sup>1</sup> According to the Centers for Disease Control and Prevention (CDC), the variant responsible for increased transmissibility, severe disease course, reduced effectiveness of treatments, and many other alarming factors is designated as the VOC.<sup>2</sup> Omicron variant is a new heavily mutated SARS-CoV-2 variant known as B.1.1.529, and it is now designated as a VOC by the World Health Organization on November 26, 2021.<sup>1-3</sup> Many cases have already been identified after the first confirmed Omicron variant infection from a sample collected on November 9, 2021, in South Africa and reported to WHO on November 24, 2021.<sup>4</sup> However, later it was found out that the Netherlands had the first Omicron variant positive patient diagnosed with the variant a week before the announcement from Africa, and surprisingly, the first Omicron variant positive patients of Africa were international travelers.<sup>5</sup> The Omicron variant is the most heavily mutated variant among all the VOC so far, which paves the way for enhanced transmissibility and partial resistance to immunity induced by COVID-19 vaccines.<sup>4,6</sup> Following the D614G, Beta/Gamma, and Delta VOCs, the SARS-CoV-2 Omicron variant could be the catalyst for the fourth wave of the COVID-19 outbreak to sweep the globe.<sup>7</sup> Unfortunately, this variant has already been spotted in 80 countries worldwide until December 15, 2021. The death of one confirmed patient infected with the Omicron variant of SARS-CoV-2 in the UK was reported on December 13, 2021.<sup>6,8</sup> Therefore, it is important to pay attention and take the required steps to strengthen surveillance and undertake public health measures. As a response, the goal is to raise awareness while avoiding overreaction.<sup>9</sup> New COVID-19 variants, such as Omicron, remind us that the epidemic is far from ended. People must acquire the vaccination as soon as it becomes available and continue to follow existing guidelines for limiting the transmission of the virus, including physical separation, wearing masks, handwashing regularly, and keeping indoor spaces ventilated. Vaccines and other public health measures must be readily available worldwide.<sup>10</sup> This review discussed the genomics of the SARS-CoV-2 Omicron variant with its transmissibility and efficacy of current COVID-19 vaccines. In addition, the treatment and management were discussed along with several recommendations to keep safe from the SARS-CoV-2 Omicron variant.

## 2 | GENOMICS OF OMICRON VARIANT

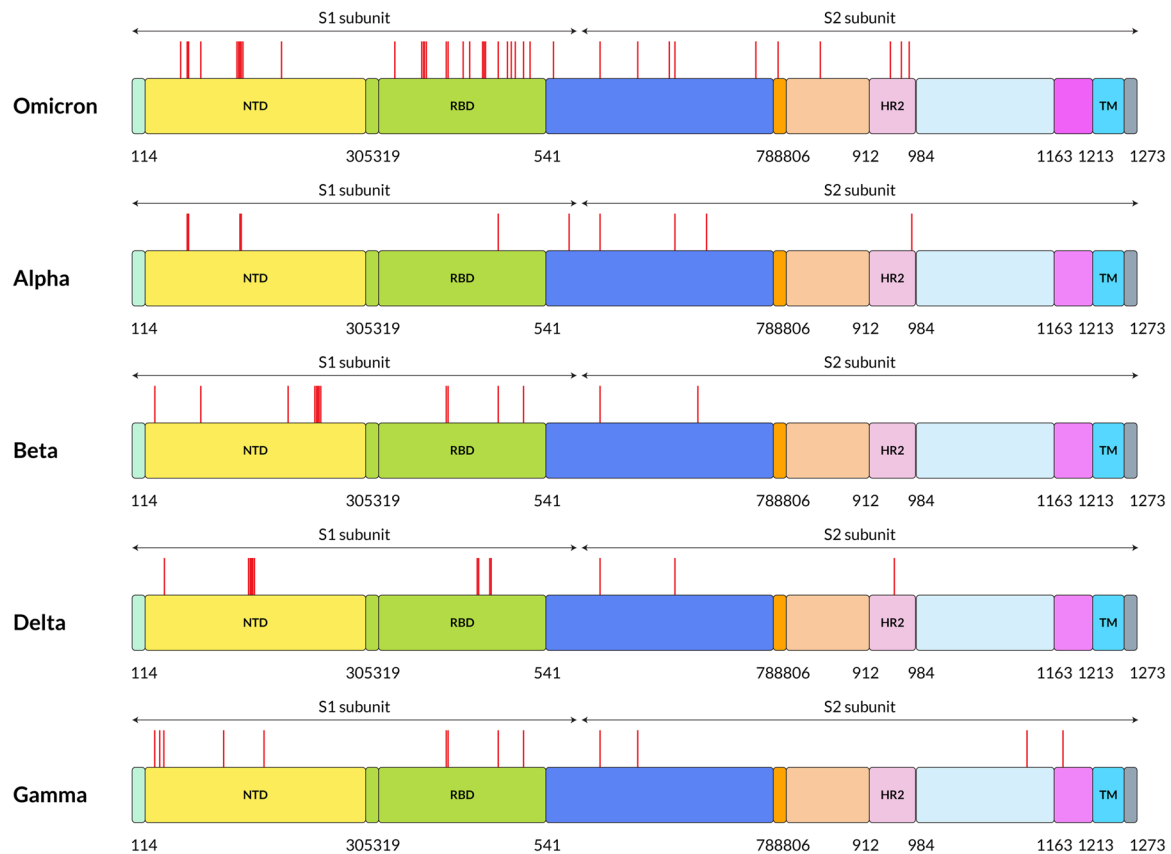
The Omicron variant of the SARS-CoV-2 genome constitutes 18 261 mutations from which more than 97% mutations are present in the coding region, and the remaining 558 are detected in the extragenic

region.<sup>11</sup> Mutations in the coding region are 2965 indels and non-synonymous, and synonymous single-nucleotide polymorphisms (SNPs) mutations are 11 995 and 2743, respectively.<sup>11</sup> Thirty mutations have been found within the spike proteins mostly located at the receptor-binding domain (RBD) of the spike protein of the Omicron variant (Figure 1).<sup>12</sup> For more than 270 million reported SARS-CoV-2 infections worldwide, the virus has evolved into over 1500 distinct Pango lineages.<sup>13</sup> Additionally, three other deletions and one insertion mutation are present outside the spike protein. Preliminary data analyzed from the Global Initiative on Sharing All Influenza 101 Data (GISAID) showed that NTD contains 11 mutations, including six deletions and one insertion, with mutations N211 and ins214EPE being unique.<sup>14</sup>

Interestingly, some of the mutations were already found in the previous VOC that helps in neutralizing antibodies.<sup>15,16</sup> Five different variants of SARS-CoV-2 have been considered VOC at different times.<sup>17</sup> Investigations performed by epidemiologists in South Africa identified the mutational data that manifests some of the concerning mutations (N501Y, D614G, K417N, and T478K) along with new mutations present in the Omicron variant, which increased the overall risk of reinfection, partial resistance to existing vaccines<sup>17</sup> (Figure 1). The Delta variant shares two out of three RBD mutations with Omicron. The first, a lysine to asparagine substitution at position 417, has been linked to S protein structural alterations that may enhance immune evasion. The second mutation, a threonine to lysine substitution at position 478, is likely to boost the residue's electrostatic potential and steric interference, perhaps increasing RBD binding affinity and allowing immunological escape. A leucine to arginine substitution at position 452, which is present in Delta but not in the Omicron variant, is known to boost affinity for ACE2 receptors found on the surface of various human cells, including the lungs.<sup>18</sup> Even though Wuhan-Hu-1 has 1273 amino acids, the Delta variation has 1271, and the Omicron variant has 1270, both contain fewer residues than the wild-type due to sequence loss.<sup>19</sup> Genome analysis by Kandeel et al. reported that the Omicron variant of SARS-CoV-2 forms a new monophyletic clade.<sup>20</sup> On the other hand, Wang et al. showed that the Omicron variant of SARS-CoV-2 evolved from the 20B clade and formed two subclades.<sup>21</sup>

## 3 | TRANSMISSIBILITY OF OMICRON VARIANT

There is still a scarcity of sufficient essential data regarding the infection rate to analyze the transmissibility of the new heavily mutated Omicron variant. However, analysis from the early data of South Africa manifested that the Omicron variant can spread way more easily from person to person, though experts could not draw any conclusion within this short period.<sup>22</sup> The concern of Omicron variant transmissibility increases as it spreads worldwide within a few days, and cases have been increasing dramatically.<sup>23</sup> According to the report of CDC, a 2.5% increasing capacity of Omicron variant has been observed in the US within 2 weeks. However, in New York/New



**FIGURE 1** Five SARS-CoV-2 variants have different amino acid mutation locations on their S proteins. On this figure, red lines indicate the mutation locations on the S protein of SARS-CoV-2 at the specified positions. FP stands for fusion peptide, and pink color specifies HR2: heptapeptide repeat sequence 2, TM: transmembrane domain, which showed in sky shade, NTD: N-terminal domain shown in yellow and green color denotes RBD: receptor-binding domain

Jersey area, the infection rate is around 13%. On the other hand, in Britain, Omicron variant cases doubled every 2–3 days.<sup>22</sup> The infection rate of the Omicron variant in South Africa is increasing faster than any other country's three previous waves. On November 30, the number of cases was 10.3%, shifting to 16.5% within two days. Surprisingly, on December 2 and 3, cases were 22.4% and 24.3%, respectively.<sup>24</sup> When the linear regressions of each pseudovirus were compared to the wild type over the entire range, it was discovered that while the Gamma variant had similar infection rates to the wild type, the Beta variant had less infection, and Delta was nearly two-fold more efficient at infecting target cells. Infection rates were four times higher in the Omicron variant than in the wild type and twice as high in the Delta variant. These findings indicate that spike sequence influences infectivity, with the Omicron variant displaying more effective ACE2-mediated infection than the wild type or other variant strains.<sup>13</sup>

Numerous factors can influence the high transmissibility of the Omicron variant. Genome sequenced data of the Omicron variant demonstrated more than 30 mutations in the spike protein by which the SARS-CoV-2 protein recognizes host cells.<sup>25</sup> Analysis of these mutations data indicates the chance of increased transmission by evading the immune response.<sup>26</sup> The N501Y mutation increases the

binding affinity with the ACE2 receptor, which is a major influencer of increased transmission, and in combination with Q498R, the binding affinity gets stronger, and the Omicron variant gets easy access into the host.<sup>26</sup> Moreover, the risk of reinfection of previously COVID-19 infected patients with the Omicron variant is very evident, indicating higher transmissibility.<sup>15</sup> Omicron variant mutations H655Y and N679K are present near the furin cleavage site (FCS) and can increase spike cleavage, making the virus more contagious.<sup>27,28</sup> On the other hand, P681H can multiply transmissibility by increasing the spike protein cleavage.<sup>29</sup>

Furthermore, the new variant Omicron gives a false negative result in polymerase chain reaction tests because of the “S gene target failure,” which paves the way of spreading the infection at a higher speed worldwide.<sup>4</sup> A previous study suggested a likely relationship between the positive electrostatic potential and affinity in the Delta VOC.<sup>30</sup> The increased electrostatic potential is revealed in the case of Delta and Delta-plus variants of SARS-CoV-2, including the Omicron variant at the RBD interface with ACE2.<sup>31</sup> The titer of several pseudotyped SARS-CoV-2 S/HIV-1 viruses was determined using HEK293T cells stably expressing the ACE2 receptor. Without ACE2, Omicron variant S/HIV-1 pseudotyped viruses cannot enter the HEK293T. The RBD and

ACE2 maintain a nanomolar level of binding affinity, which is similar in Beta, Delta, and Omicron. Because ACE2 is required for RBD, it appears that all variants have already reached the nanomolar scale, making it difficult for the virus to progress further.<sup>7</sup> Another computational study predicted that the Omicron variant had increased affinity to the ACE2 compared to the other SARS-CoV-2 variant such as Delta. Many mutations in the receptor-binding domain of spike protein of Omicron variants, such as Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K are responsible for this higher affinity to the ACE2.<sup>21,32</sup> Therefore, it suggests that omicron VOC is highly transmissible than other variants.<sup>31</sup>

Moreover, once within the cells, the Omicron variant was less effective than Delta at causing cell fusion, linked to the poor cell-to-cell transmission. Fused cells are frequently found in respiratory tissues collected after a serious illness. Indeed, in a spreading infection experiment utilizing lung cells, a live Omicron variant virus was compared to Delta variant and found that the Omicron variant was considerably worse at replication, corroborating the findings of the decreased entrance.<sup>33</sup>

#### 4 | OMICRON VARIANT AND CURRENT COVID-19 VACCINES

The Omicron variant of SARS-CoV-2 was identified from the COVID-19 vaccinated patients, suggesting the new variant's immune invasion and demanded updated vaccines.<sup>34</sup> Saxena et al. analyzed the mutations reported in the RBD of the spike of Omicron variant of SARS-CoV-2 and hypothesized that currently, available entry inhibitors might not be effective for emerging variants.<sup>35</sup> The heavy mutation in the spike protein of the Omicron variant is related to increased infectivity and antibody evasion.<sup>36</sup> In SARS-CoV-2 convalescent or vaccinated people, the amount of neutralizing epitopes targeted by polyclonal antibodies is a significant predictor of the genetic barrier to viral escape. Single monoclonal antibodies are susceptible to escape mutations, but combinations targeting non-overlapping epitopes are more resistant.<sup>37</sup> Surprisingly, Omicron variant neutralization was undetectable in the majority of vaccines.<sup>14</sup> The computational approach also demonstrated that antigenic properties of the Omicron variant are ominous and correlated with its mutations.<sup>38</sup> Although various investigations have been performed to create effective vaccines, the emergence of new VOCs has raised concern over the efficacy of neutralizing antibodies induced by COVID-19 vaccines as the Omicron variant has already infected vaccinated individuals in South Africa, Hong Kong, and many other countries.<sup>36,39,40</sup> The potential impact of the COVID-19 vaccine is still being analyzed against this new variant. Two BNT vaccinations, which can provide more than 90% protection against serious disease when infected with the Delta variant, maybe significantly less effective against the Omicron type of SARS-CoV-2.<sup>14</sup> However, the effect of COVID-19 vaccines against the previous VOC, such as Delta, manifested the vaccine's potential in reducing severe disease

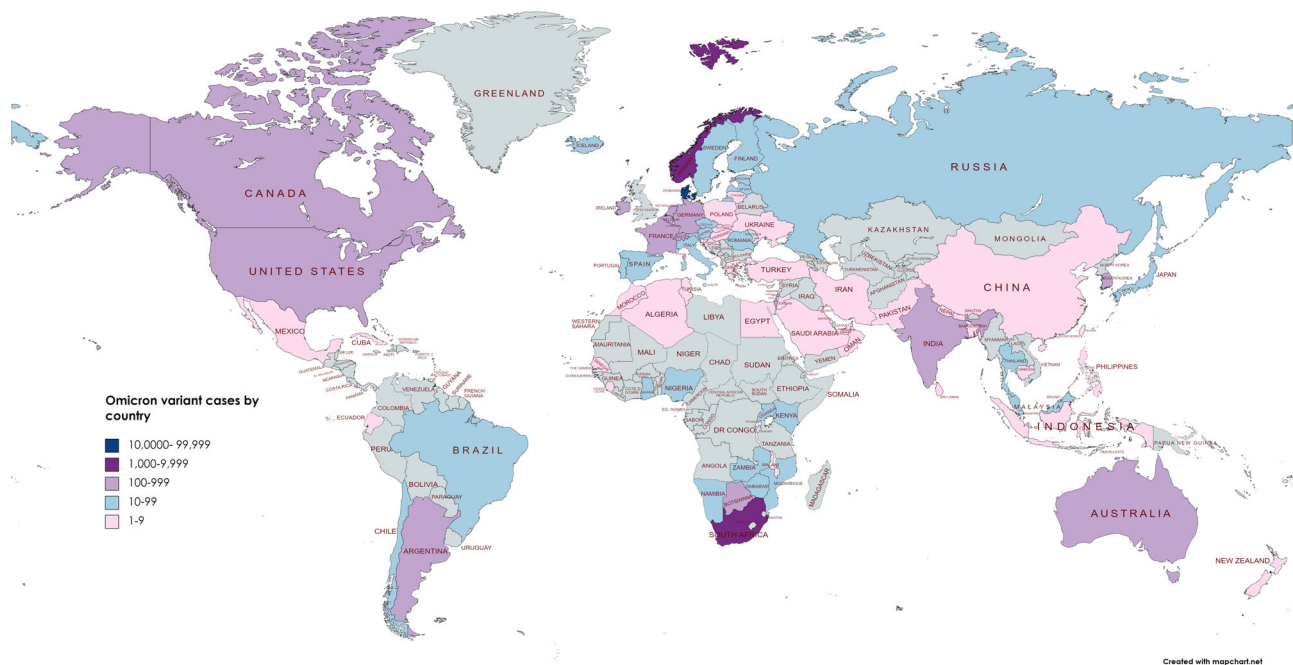
and death.<sup>41</sup> Moreover, multiple Delta transmissions from and between completely vaccinated persons were confirmed using genomic and epidemiological data.<sup>42</sup> As vaccine-induced immunity is targeted through the spike proteins of the virus, heavily mutated Omicron variant spike protein is capable of reducing the neutralization activity of sera of vaccinated individuals that indicated less protection from Omicron variant.<sup>26</sup> Only 20% and 24% of BNT162b2 recipients had detectable neutralizing antibodies against the Omicron variants HKU691 and HKU344-R346K, respectively, but none of the Coronavac recipients did. The geometric mean neutralization antibody titers (GMT) of the Omicron variant isolates were 35.7–39.9-fold lower than the ancestral virus for BNT162b2 recipients, and the GMT of both Omicron isolates were significantly lower than the Beta and Delta variants. Between HKU691 and HKU344-R346K, there was no discernible difference in GMT.<sup>43</sup> Pfizer/BioNTech and Moderna's mRNA vaccines have been essential in launching mass vaccination campaigns in the United States and worldwide. Both vaccines produce high-titer anti-SARS-CoV-2 Spike (S) protein-specific antibodies that can neutralize the original circulating SARS-CoV-2 strains and subsequent variations developed after the vaccine design phase. In animal models and humans, neutralizing antibodies generated by mRNA vaccinations appear to be the primary correlate of COVID-19 protection.<sup>44</sup> Laboratory investigations on Pfizer-BioNTech vaccines show a high level of protection from the Omicron variant with three doses.<sup>45</sup> Only the booster dose can increase the neutralizing antibody titers by 25-fold compared with the other two doses. Anti-spike antibody levels can predict the neutralization of SARS-CoV-2 variants. CD4 + T cell responses are strong in SARS-CoV-2 mRNA vaccines. TFH cell responses are critical in the formation of long-term immunity by this successful human vaccination, according to recent findings.<sup>44</sup> Individuals given mRNA vaccinations had robust neutralization of the Omicron variant that was only 4–6 times lower than the wild type, implying increased cross-reactivity of neutralizing antibody responses.<sup>14</sup> Therefore, it is hypothesized that current COVID-19 vaccines will protect in reducing disease severity to the vaccinated individuals as a majority of the epitopes targeted by vaccine-induced T cells are not mutated in the Omicron variant. However, the various institutions have already started the development of Omicron variant-specific COVID-19 vaccines and are confident enough to supply the vaccine within March 2022 in the market.<sup>45</sup> Because of worries about diminishing immunity and the likelihood of a new wave of illnesses throughout the winter, booster doses of the COVID-19 vaccine have been rolled out in many nations since summer.<sup>46</sup> On the other hand, 75% of Omicron variant-positive patients in a South African hospital (NetCare's Hospital) are unvaccinated and have critical outcomes compared to the vaccinated individuals, which indicates the possible protection of the existing vaccines from the variant Omicron.<sup>47</sup> Omicron variant, a novel and potentially more transmissible strain of the SARS-CoV-2, is suspected of having emerged in a location where vaccination rates are low, with only 7.5% of people in South Africa vaccinated. Scientists have discovered that the virus is more likely to mutate in low vaccination rates and high transmission rates.<sup>48</sup>

## 5 | CURRENT SITUATIONS AND REACTION TO OMICRON VARIANT WORLDWIDE

The Omicron variant of SARS-CoV-2 did not stop after being detected in South Africa and Botswana and now has been detected in more than 80 different regions of the world till December 15, 2021. Along with South Africa, Botswana spreads rapidly in Britain, Denmark, and Norway. Thirty-six (36) states of the United States have already been affected by the Omicron variant, and cases are increasing at a higher rate.<sup>8</sup> Among all the countries, the Omicron variant has been locally transmitted in Canada, USA, Britain, France, Spain, Zambia, Botswana, Namibia, South Africa, Iceland, Norway, Ireland, India, South Korea, Singapore, Hong Kong, Australia, and Mozambique till December 15, 2021. Though the other countries such as Brazil, Argentina, Thailand, Russia, China, Mexico, and many more countries have Omicron variant patients, it was detected in visitors who had traveled from the infected countries (Figure 2). It is hypothesized that the new heavily mutated variant will not be transmitted locally.<sup>8</sup> The patients infected with the Omicron variant are still not showing any severe disease outcome. Thus, it is considered that the variant is a mild one compared with the other VOCs. However, more data are needed to conclude the disease severity due to the Omicron variant of SARS-CoV-2.<sup>49</sup> Due to the scarcity of data, the infectivity and pathogenicity of the Omicron variant cannot be determined. Reports of a newly identified coronavirus variety in

South Africa sent many of those doors crashing shut again, just as several countries around the world were beginning to relax their border restrictions.

On November 26, the World Health Organization (WHO) identified the novel B.1.1.529 variant of SARS-CoV-2 named Omicron. Therefore, various tactics have been taken throughout the world to restrict the spread of this new variant.<sup>50</sup> WHO has taken several approaches in South Africa to help with monitoring, contact tracing, infection prevention, and treatment. Oxygen production and delivery have increased in Botswana, vital for treating critically ill patients.<sup>51</sup> To protect the United States from Omicron, the American government announced multiple plans on December 2, 2021. It includes reaching individuals eligible for booster dose, making at home COVID-19 tests free, travel restrictions, paid time off for getting booster dose, and to help other countries beat Omicron variant, USA is planning to send 200 million more doses of vaccine.<sup>52</sup> Exemptions apply to all sorts of hospitality establishments. They also take the initiative to keep places adequately ventilated and emphasize wearing masks. The vaccine program and the test, as well as tracing and isolating the system remain the most effective ways of reducing transmission.<sup>53</sup> All private-sector workers in New York City will be required to be vaccinated.<sup>54</sup> Similarly, the UK government has announced different measures, such as mandatory masking in all public places, isolation for ten days if contact with an Omicron variant infected individual, and compulsory self-isolation for travelers.<sup>4</sup>



**FIGURE 2** The total number of confirmed Omicron variant cases per country and the probability of identifying a case. The figure shows that South Africa sequences many more samples than any other African country, but slower than most Western countries. Additionally, returning a viral sequence might take up to 2 weeks in countries with technical competence. Thus reliable statistics on verified instances lag behind the actual situation. Cases detected using their variant qPCR test, which is rather fast and tests numerous genes, are considered sufficient for counting as an Omicron variant by Norway and Denmark, even before full sequencing. So, it can be said that the sequencing rate influences the probability of discovering a case



One of the most densely populated countries, India, has taken five steps to combat the new COVID-19 spread. The mandatory risk profile of each individual, institution-wide quarantine, genome sequencing of samples, intensive contact tracing of suspects, and strict adherence to COVID-19 appropriate behavior are among them.<sup>55</sup> Bangladesh, a low-income country, has announced a plan to tackle the Omicron strain, though it is yet to be discovered in Bangladesh. The plan includes travelers from South Africa, Namibia, Zimbabwe, Botswana, Eswatini, Lesotho, and other new variant-infected countries listed by the WHO that should be exposed to increased medical testing and screening. Whether social, political, religious, or otherwise, any type of public gathering must be avoided. Facemasks must be worn when leaving the house, and all other basic health needs.<sup>56</sup> The introduction of the Omicron variant is causing concern in countries worldwide, emphasizing the significance of pandemic preparedness.<sup>51</sup> However, there is growing hope that the Omicron variety of SARS-CoV-2, becoming more prevalent, will cause less severe disease than prior strains. Researchers in England, Scotland, and South Africa discovered that the Omicron variation has a 15%–80% reduced risk of hospitalization than the delta variant. Despite far greater case counts, surveillance data shows that the latest omicron-driven wave of illnesses has significantly fewer hospital admissions and deaths than past waves.<sup>57</sup>

## 6 | TREATMENT AND MANAGEMENT STRATEGIES

Omicron variant-positive patients in South Africa showed very mild symptoms, and no oxygen support was required until now.<sup>58</sup> However, the UK is facing a different scenario in the case of Omicron variant-positive patients. In an interview with Global Health Crisis Coordination Center, vaccine expert Shabir Madhi said that “In the South African much of the immunity that currently exists is large because of the prior infection that has taken place during the first three waves.” Thus, being ready with all the existing treatment and management procedures for any unfortunate situation is a must.<sup>59</sup> A recovered Omicron variant positive patient from India shared his recovery journey and informed that he did not experience any concerning symptoms and tiredness while in hospital in contrast to the period he had been in hospital with Delta. Based on the severity of the infection, he had been given vitamin C and antibiotics.<sup>60</sup> Dr. Angelique Coetzee, one of the first doctors in South Africa treating Omicron variant positive patients, informed that the symptoms of the disease are just a sore throat, fatigue that stays for a day; thus, meeting with a health professional and getting tested is compulsory to have efficient treatment as per need.<sup>61</sup> According to health experts Kumar and Wu, antiviral pills from Pfizer and Merck can efficiently treat mild to moderate COVID-related illnesses.<sup>62</sup> Different laboratory findings have manifested the usefulness of so-trovimab, a monoclonal antibody found in the blood of recovered SARS patients, as it has the potential of blocking SARS and

SARS-CoV-2.<sup>63</sup> According to recent data, corticosteroids and IL6 receptor blockers are still effective in treating people with severe COVID-19 cases.<sup>41</sup>

To manage the upcoming surge, WHO recommends that countries improve surveillance and sequencing of cases, share genome sequences on publicly available databases like GISAID, report initial cases or clusters to WHO, and conduct field investigations and laboratory assessments to understand better if Omicron variant has different transmission or disease characteristics, or has an impact on vaccine effectiveness.<sup>41</sup> WHO issues travel advisory due to the Omicron variant. People aged 60 and above and those with particular health concerns are advised to limit the trip plans for the time being. Experts recommended vaccines and maintained up to date on all injections until further information is available since they may still protect people from all variants of the SARS-CoV-2.<sup>64</sup> Individuals infected with the new variant must be isolated.<sup>65</sup>

## 7 | CONCLUSIONS AND RECOMMENDATIONS

Mutation in the SARS-CoV-2 is a continuous process leading to multiple variant introductions. The VOC is the reason behind the waves of heavy infection, which might continue with the new variant Omicron. Though the latest variant's infectivity, prevalence, and severity are still unknown, investigations are ongoing to get every detail about the SARS-CoV-2 Omicron variant to recommend efficient ways to prevent the upcoming surge. Meanwhile, the previous recommendations to tackle the COVID-19 pandemic need to be maintained worldwide along with the newly improvised directions, such as genome sequencing of all the samples, maintaining social distance, continuing vaccination for everyone, and isolating the Omicron variant positive patients in a different place. WHO recommended countries strengthen surveillance and adopt necessary actions since the Omicron variant has been classified as a VOC.

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### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### AUTHOR CONTRIBUTIONS

Yusha Araf and Md. Golzar Hossain designed the manuscript. Md. Golzar Hossain and Chenfu Zheng supervised the study. Yan-dong Tang, Fariya Akter, Yusha Araf, and Rabeya Fatemi wrote the preliminary draft manuscript. Yusha Araf illustrated the figures. Md. Golzar Hossain and Chenfu Zheng reviewed the preliminary draft manuscript. Yusha Araf, Md. Sorwer Alam Parvez, Md. Golzar Hossain, and Chenfu Zheng edited, revised, and finalized the manuscript. All the authors read and approved the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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