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OMICRON VARIANT (B.1.1.529) OF SARS-COV-2, A WORLDWIDE PUBLIC HEALTH EMERGENCY

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Abstract: The whole world facing unpredictable problems with different variants of COVID-19; B.1.1.529 is the newest form of SARS- CoV-2. It was initially reported to the World Health Organization (WHO) on November 24, 2021, by South Africa. WHO recognized it as a variant of concern on November 26, 2021, and named it "Omicron." SARS-COV-19 is a significant lung infection caused by a coronavirus. WHO labelled two variants in that we are experienced with delta (B.1.617.2) variant, now recently the omicron came (B.1.1.529) with highly mutable strikes on it. So WHO predicted it is more dangerous than previous variants because of its mutable capability. In this article, the current state of Omicron variant has been discussed to provide a strong framework for future research. The evolution, mutation, epidemiology, infectivity, vaccine breakthrough, and antibody resistance of the Omicron variant are investigated and discussed.

Keywords: Omicron,COVID-19, SARS-CoV-2, Health Emergency.

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Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has been surging for almost two years. More than 260 million confirmed cases have been reported according to the statistics of the World Health Organization (WHO), including over five million deaths. In November 2021, the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in South Africa.1 Since then, omicron has rapidly spread around the world. On November 26, 2021, the World Health Organization designated omicron as a variant of concern. The omicron variant was found to have at least 33 mutations (29 amino acid substitutions, insertion of three amino acids, and 3 small deletions) in its spike (S) protein, as compared with early SARS-CoV-2 strains identified in Wuhan, China. Notably, 15 of the 29 substitutions were in the receptor binding domain of the S protein, which is the primary target for monoclonal antibody–based therapy[1]. This finding suggests that the monoclonal antibodies that have been approved by the Food and Drug Administration (FDA) may be less effective against the omicron variant. So from that time onwards, scientists worked on COVID and tried vaccines. On the other hand, many of the variants were observed with the different protein sequences of the genome. The omicron genotype has a maximum of 50 mutations, with 32 of them occurring in the spike protein alone. The spike protein helps the SARS-CoV-2 virus adhere to cells and obtain entry by forming projecting knobs on the membrane of the virus. They discovered a D614G change in the spike glycoprotein (S) in the delta form during the evolution of SARS-

CoV-2 in humans; viruses with this mutation have become the prevalent circulating modified type in the SARS-COVID-19 pandemic . Comparatively, delta variant cases were more than Omicron so far, but it may increase in the future.Omicron created chaos around the world and different studies are being conducted to study its presenting symptoms, transmission, risk of reinfection, severity, and its tendency to evade immune responses[2] . There are concerns related to its rampant transmission, which could hinder containment efforts, such as vaccine effectiveness. The surging trend in Omicron cases is worrisome, because this could cause an overwhelming demand on health care systems which have not yet completely recovered from the health and financial damages caused by the initial virus outbreak . Although studies have attempted to understand this new challenge in the COVID-19 strains race, there is still a lot to be demystified. Therefore, the purpose of this review was to summarize the structural or virologic characteristics, burden, epidemiology of the Omicron variant and its potential to evade the immune response.[3]

The protein sequence of the omicron virus and how it is different from other variants?

In the omicron variant, the spikes play a significantly important role in mutations to change its genomic sequence by that I will escape against body-produced antibodies (Immune Cells). The omicron variant compared with other variants is related to the mutations.[2]

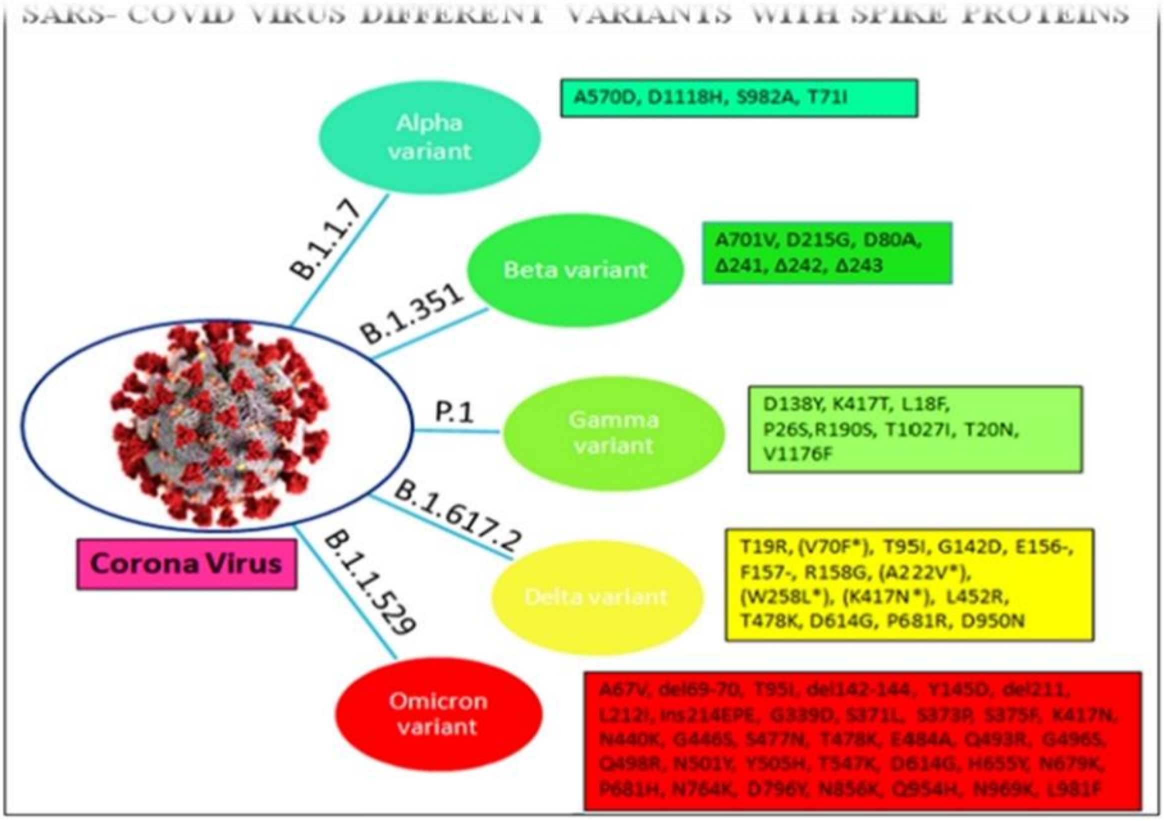


Figure 1. Different variants with their spike proteins

EVOLUTION AND EPIDEMIOLOGY

Omicron variant has been reported to drive rapid epidemic growth since its identification in November 2021. This variant was first detected on November 8, 2021, in South Africa and in the next two weeks more than 70 percent of sequenced samples from Gauteng province in South Africa was Omicron. By November 25, 2021, it has been identified in five different countries and on November 26, 2021, WHO declared Omicron as a variant of concern [3]. United Kingdom reported its first two cases of Omicron on November 27. On December 1, United States identified its first Omicron case along with South Korea, Norway, Saudi Arabia, Ghana, and Nigeria. By December 11, USA reported almost 7% of the COVID cases to be due to Omicron variant. This rate quickly surged to about 23% and 60%, respectively, in the next two weeks [4]. Currently, the variant has been found in all the U.S. states and has become the dominant variant in a mere three weeks' time since its first identification in the USA. According to phylogenetic analysis, the Omicron variant diverged in late September or early October 2021 . Omicron has been observed frequently to infect previously Covid-positive and vaccinated people [5]. The National Institute for Communicable Diseases of South Africa reported that children under the age of 2 accounted for about 10% of total hospital admissions in Tshwane in South Africa . The S gene target failure (SGTF) data of sampled cases in South Africa shows a growth rate of 21% per day compared to Delta, resulting in a 2.4-fold increase in the number of reproductions; Omicron became the majority strain in South Africa around 10 November. UK estimated an exceptionally high logarithmic growth rate of Omicron-associated SGTF cases over S gene target positive (SGTP) cases (to be 0.41) . It was estimated to become the most dominant strain in the UK by December 14. Modeling of both genomic surveillance and SGTF data predicted that Omicron would become the most common variant nationally by December 25, 2021, with some areas surpassing this threshold earlier . According to CDC, the cases due to Omicron variant may peak during early January 2022 [6].

MUTATION PROFILE

The spike (S) protein, the principal antigenic target of antibodies produced by infections or immunization, has 32 mutations in this variant, which is exceptionally high. The deadly Delta variant, on the other hand, contains just 5 S protein mutations, posing a significant worldwide danger and spreading globally . As a result, the panic button has been pressed in a number of cases throughout the world, and several nations have instituted travel restrictions to prevent the Omicron variant from spreading rapidly. Omicron variant mutations are found in a variety of SARS-CoV-2 proteins, including S protein, envelope protein, membrane protein, NSP3, NSP4, NSP5, NSP6, NSP12, NSP14, and nucleocapsid protein [7]. The effect of changes in the S protein receptor-binding domain (RBD) on infectivity and antibody resistance is being investigated. This is because the RBD on the S protein facilitates in the S protein's attachment to the host angiotensin-converting enzyme 2 (ACE2). S-ACE2 binding facilitates SARS-CoV-2 entry into the host cell, which starts the viral infection process. There are at least 30 amino acid substitutions in the spike protein of the Omicron variant . On top of that, there are three small deletions, and one small insertion. The RBD contains 15 of the 30 amino acid substitutions. Moreover, the variant has three mutations at the furin cleavage site which increases SARS-CoV-2 infectivity. A total of 4 pango lineages are currently established to be associated with Omicron variant [15]. The most frequent sublineage is referred to as BA.1 (/B.1.1.529.1) while the two other sublineages are BA.2 (B.1.1.529.2) and BA.3 (B.1.1.529.3). Notably, BA.2 contrasts from the BA.1 by not containing the characteristic SGTF causing deletion (Δ69-70) by which many PCR tests are able to detect a case as an Omicron, or Alpha, variant [8]. Due to this feature, BA.2 is also called the 'Stealth Omicron', however, both BA.2 and BA.3 are very rare until now.

EFFECTS OF OMICRON MUTATIONS ON SPIKE CONFORMATION

We next mapped the Omicron mutations to the spike structure and assessed their potential effects on spike conformation. The majority of the RBD mutations are located in the receptorbinding motif (RBM), inner-side, and outer-side epitope regions. The superimposition of the Omicron and WT RBDs showed an RMSD of 0.75 A˚ . We then calculated Ca distance for each RBD residue between Omicron and WT, and observed that six mutations (S371L, S373P, S375F, G446S, S477N, and T478K) are located at regions with Ca distance larger than 2 A˚ , suggesting that these mutations may account for the conformational change in the Omicron RBD. In particular, we observed that mutations S371L, S373P, and S375F not only alter the conformation of loop 371–376 but also result in the motion of helix 365–370 closer to helix 337–343, which may alter the conformation of the N-linked glycosylation at N343 . The formation of new hydrogen bond networks by mutations G446S, G496S, Q498R, and N501Y stabilize loop 443–451 to a new conformation . The majority of NTD mutations are located at the antigenic supersite targeted by most NTD-directed neutralizing antibodies. Our Omicron structure revealed substantial conformational changes in the NTD supersite . We also determined part of the N3 loop with G142D and D143–145. In addition, in the two RBD-down protomers, we observed Omicron S2 mutations N764K and N856K to form new hydrogen bonds with SD1 and SD2 domains from adjacent protomers respectively . Two conserved residues nearby these mutations also form additional hydrogen bonds in Omicron spike . Because both SD1 and SD2 undergo a substantial rearrangement when the RBD switches to the up conformation, these interactions may help to stabilize the RBD in the down conformation by locking SD1 and SD2, an effect similar to other S2 mutations.[9]

TRANSMISSION, BREAKTHROUGH INFECTION, AND VACCINE EFFICACY OF B.1.1.529

The scientific community currently has little knowledge on infectivity, vaccine breakthrough, or antibody resistance of Omicron variant. Because the S protein, particularly its RBD, is so important in viral infection, vaccines and antibody medicines have focused on it. As a result, studying Omicron's 15 RBD mutations can help researchers learn more about the virus's infectivity, vaccine breakthrough, and antibody resistance. Several studies have revealed that the binding free energy (BFE) between the S RBD and the ACE2 is proportional to infectivity of virus [9], . Consequently, a virus-killing antibody with a high affinity for the RBD could be developed . A substantial number of RBD binding antibodies are produced in the human immunological response to infection or vaccination. To treat viral infections, monoclonal antibodies (mABs) that target the S protein, namely the RBD, are utilized . As a result, any alteration in the RBD of the S protein would raise urgent concerns about the efficacy of existing vaccinations, mAbs, and the danger of reinfection. A comprehensive experimental study of Omicron, on the other hand, may take weeks or even months. Chen et al. reported a quantitative investigation of infectivity, vaccination breakthrough, and antibody resistance of Omicron variant in their article . Omicron might be nearly ten times more contagious than the original virus or roughly twice as infectious as the Delta variant, according to an artificial intelligence (AI) model developed with tens of thousands of experimental data points and extensively confirmed by experimental data on SARS-CoV-2 [10]. It was discovered that Omicron may be twice as likely as Delta to evade existing vaccinations based on 132 3D models of RBDantibody complexes. They concluded that Eli Lilly's monoclonal antibodies (mAbs) that have been authorized by the Food and Drug Administration (FDA) may be gravely compromised and Omicron might potentially reduce the effectiveness of mAbs from Celltrion and Rockefeller University. However, very little effect on the Regeneron mAb combination has been found in their study. In another study, Zhang et al. constructed the pseudotyped Omicron variant of SARS-CoV-2 . The sensitivity of 28 serum samples from COVID-19 convalescent patients infected with the original SARS-CoV-2 strain was tested against pseudotyped Omicron, as well as other VOCs (Alpha, Beta, Gamma, and Delta) and VOIs (Lambda, Mu). The mean neutralization ED50 of these sera against Omicron declined to 66 (almost 8.4 times), as compared to the D614G reference strain (ED50 = 556). The neutralization activity of other VOC and VOI pseudotyped viruses decreased just 1.2-4.5 times. According to the findings of their in vitro experiment, the Omicron version may cause a higher escape from immune protection generated by previous SARS-CoV-2 infection and maybe even current COVID-19 vaccines. Collie et al. analyzed the effectiveness of BNT162b2 vaccine against Omicron Variant in South

Africa . For the comparator period, 133,437 PCR test results were obtained of which 28.6% had been obtained at least 14 days after the patient had received the second dose of vaccine. For the proxy omicron period, they analyzed 78,173 PCR test results, of which 41.4% were obtained at least 14 days after the second dose. During the comparator period, the overall test positivity was 6.4% while it was 24.4% during the proxy omicron period. Admission rate of Covid-19 was 10.8% and 2.2%, respectively, as a percentage of positive PCR test results. During the proxy omicron period positive cases were more prevalent among younger population than during the comparator period. A vaccine efficacy of 70% (95% CI: 62 – 76%) was found during the proxy omicron period, supported by the results of all sensitivity tests. On the other hand, the rate was 93% (95% CI: 90%-94%) against hospitalization for Covid-19 during the comparator period. Thus, the proxy omicron period maintains a reduced effectiveness of the BNT162b2 vaccine against hospital admission, this reduction is presumed to be due to the omicron variant. In a recent study by Ai et al. Omicron variant showed lower neutralizing sensitivity than other SARS-CoV-2 variants to immune sera elicited by vaccines after boost [11]. The immunogenicity of COVID-19 breakthrough patients, the BBIBP-CorV homologous booster group, and the BBIBPCorV/ZF2001 heterologous booster group against SARSCoV-2 pseudotypes corresponding to the prototype, Beta, Delta, and the emerging Omicron variant was investigated. At 14 days following the homologous or heterologous vaccine boosters, 100 percent of samples demonstrated good neutralization activity against Omicron, despite a considerable drop (5.86-14.98 times) of pVNT against Omicron compared to the prototype. Their findings suggest that Omicron may be more prone to evade vaccine-induced immune protection than prototypes and other VOCs. Garcia Beltran et al. investigated neutralization potency of sera from 88 mRNA-1273, 111 BNT162b, and 40 Ad26.COV2.S vaccine recipients against wild type, Delta, and Omicron SARS-CoV-2 pseudo-viruses [12]. They considered three groups: recently vaccinated (<3 months), distantly vaccinated (6-12 months), and recently boosted. Prior SARS-CoV-2 infection of these individuals was also considered. Omicron pseudovirus was more infectious than the other variants tested. Similar to the study of Ai et al., neutralization of Omicron was undetectable in most vaccinated individuals. Individuals boosted with mRNA vaccinations, on the other hand, demonstrated substantial neutralization of Omicron only 4-6-fold lower than wild type. This implies that booster doses increase the cross-reactivity of neutralizing antibody responses. In another investigation, neutralization titers against Omicron in serum samples from mRNA-1273 vaccination recipients were compared to neutralization titers against D614G and Beta in live- and pseudo-virus assays . When blood samples were obtained 4 weeks following two standard inoculations with 100 g mRNA-1273, Omicron was 41-84 times less susceptible to neutralization than D614G and 5.3-7.4 times less responsive than Beta. The authors concluded that a booster dose increased Omicron neutralization titers and may substantially reduce the risk of symptomatic vaccine breakthrough infections, a conclusion consistent with the other studies [13].

DIFFERENCE BETWEEN DELTA AND OMICRON VARIANTS

The Omicron variant has more mutable capability than Delta; it doesn't mean it is more dangerous than other variants. So far, no new symptoms were reported due to the omicron variant; in the future, it may spread faster than other variants because of its mutations. The expected spreading with mutations of the two variants, till now one death case reported due to omicron variant in UK, the virus that causes COVID-19, SARSCoV-2, has the greatest mutations of any kind. We still haven't figured out how those genetic changes work. However, they remain for a reason: they aid in the success of a variety.[14]

Omicron has > 30 genetic mutations of the spike protein. The SARS-CoV-2 spike protein acts like a ‘key” and allows the virus to bind to ACE-2 receptor and enter and infect cells in humans.

The spike protein of SARS-CoV-2 is targeted by some currently approved COVID-19 vaccines; therefore, mutations in the spike protein need to be closely monitored

1.1. **Delta Variant**: Nine variations in the spike protein were observed, a protrusion on the virus's surface that aids in the virus's attachment to human tissues. According to Suresh V. Kuchipudi of Penn State University, who researches viral evolution, two are in a molecular hook called the "receptor-binding domain," which helps it attach to cells more tightly.[14]

1.2. **Omicron Variant**: It's a mutation monster, with at least 32 mutations in the spike protein and ten in the receptor-binding domain . On general, two or three people were infected with the first SARS-CoV-2 virus. Delta changed everything by infecting about six people. Delta has a four-day incubation period, which is lower than the six-day incubation period of the original virus, making people contagious sooner. The omicron's transmission rate and incubation period are unknown. Within the next few weeks, we will know better information about the omicron variant growth rates in other geographies .[15]

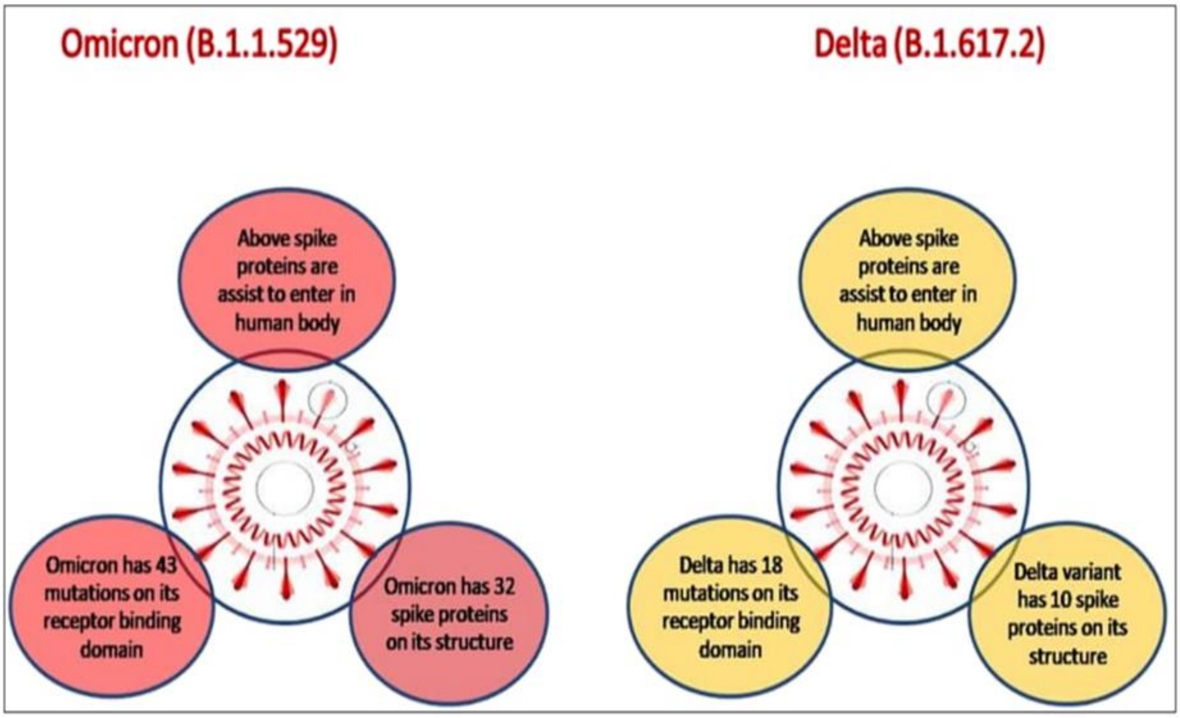
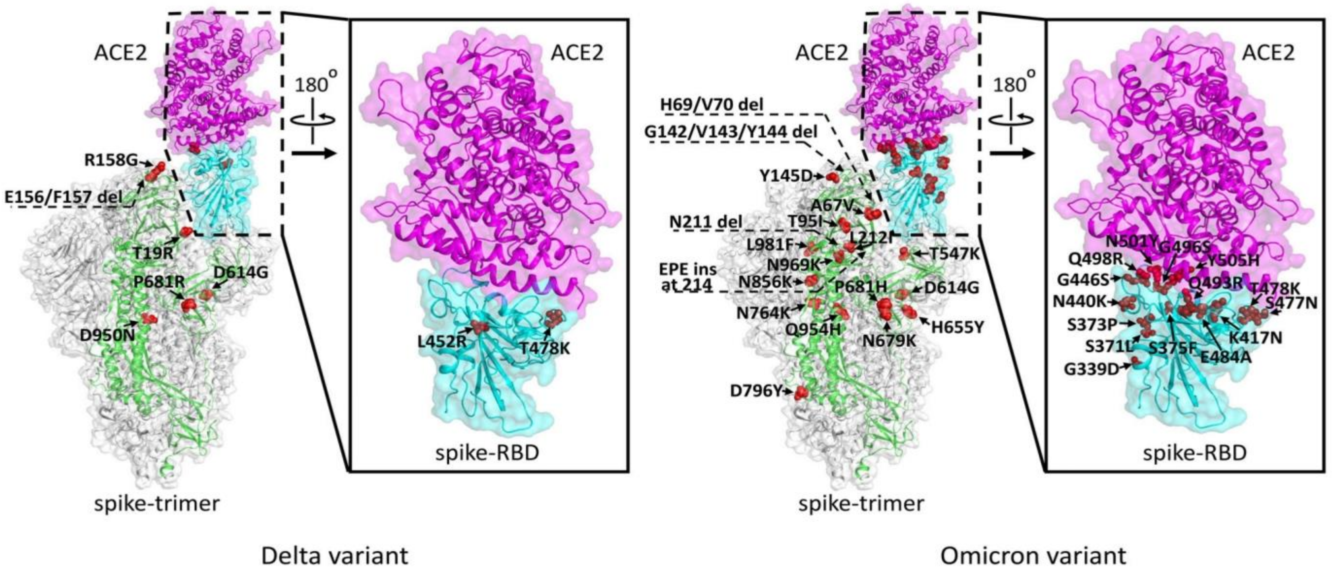


Figure 2. Different spike proteins between delta and omicron variants of SARS-COVID-19-2

CHARACTERISTICS OF DELTA & OMICRON VARIANT[16]:

	DELTA	OMICRON

Transmissibility	Increased transmissibility compared to wild-type SARS-CoV-2, Variants of Interest (VOIs) and Variants of Concern (VOCs) Alpha, Delta and Gamma	Increased growth rate as compared to Delta because of intrinsic characteristics of Omicron and immune escape
Disease severity	Possible Increased risk of hospitalization as compared to early pandemic SARS-CoV-2 and other VOCs	Reduced risk of hospitalization compared to Delta; upper respiratory tract infection compared with lower respiratory tract infection by Delta
Risk of reinfection	Reduction in antibody neutralizing activity reported	Reduced antibody neutralizing activity reported; increased risk of reinfection
Impact on diagnostics	None reported to date	RT PCR and Ag RDTs continue to detect Omicron. Studies on Ag RDT sensitivity are ongoing
Impact on therapeutics	None reported to date	No impact on effectiveness of corticosteroids and Il-6 blockers; Reduced effectiveness of some monoclonal antibodies; limited evidence
Effectiveness of COVID-19 vaccines	Protection retained against severe disease; possible reduced protection against symptomatic disease and infection; limited evidence	Reduced protection against symptomatic disease and infection; booster doses increase vaccine effectiveness; limited and non-peer reviewed evidence



Delta variant

Omicron variant

Figure 3:Landscape of spike mutations in the Delta (left) and Omicron (right) variants. The structures are depicted based on the cryo-electron microscopy spike trimer structure of protein data bank (PDB) code 6VYB and the crystal RBD/ACE2 complex structure of PDB code 6LZG. One protomer of the spike trimer is highlighted in green and its receptor-binding domain (RBD) in cyan. The bound angiotensin-converting enzyme 2 (ACE2) receptor is colored magenta. The mutations defined based on covariants are labelled.

VIROLOGIC CHARACTERISTICS EXPLAINED (OMICRON VS. DELTA VARIANT)

Recent studies have reported that Omicron has a different mechanism for entering the host, and is capable of gaining cell entry independent of the transmembrane serine protease 2 (TMPRSS2) . The entry pathway and viral replication of Omicron is through the endocytic pathway rather than TMPRS22 pathway, unlike Delta variant, which may have contributed to the differences in the disease presentation following exposure to Delta and Omicron variants . TMPRS22 is highly expressed in alveolar cells of the lungs; thus, due to the lesser or no dependence of Omicron on the TMPRS22 pathway for its replication, lung involvement following exposure might be absent or limited[17] . In addition, the fusion capabilities to aid syncytia (structure that results following the fusion of multiple cells) formations are reduced in Omicron compared with the Delta variant. The reduced capacity of the syncytia formation translates to the lesser severity of the clinical manifestations and tissue tropism following the Omicron infection.

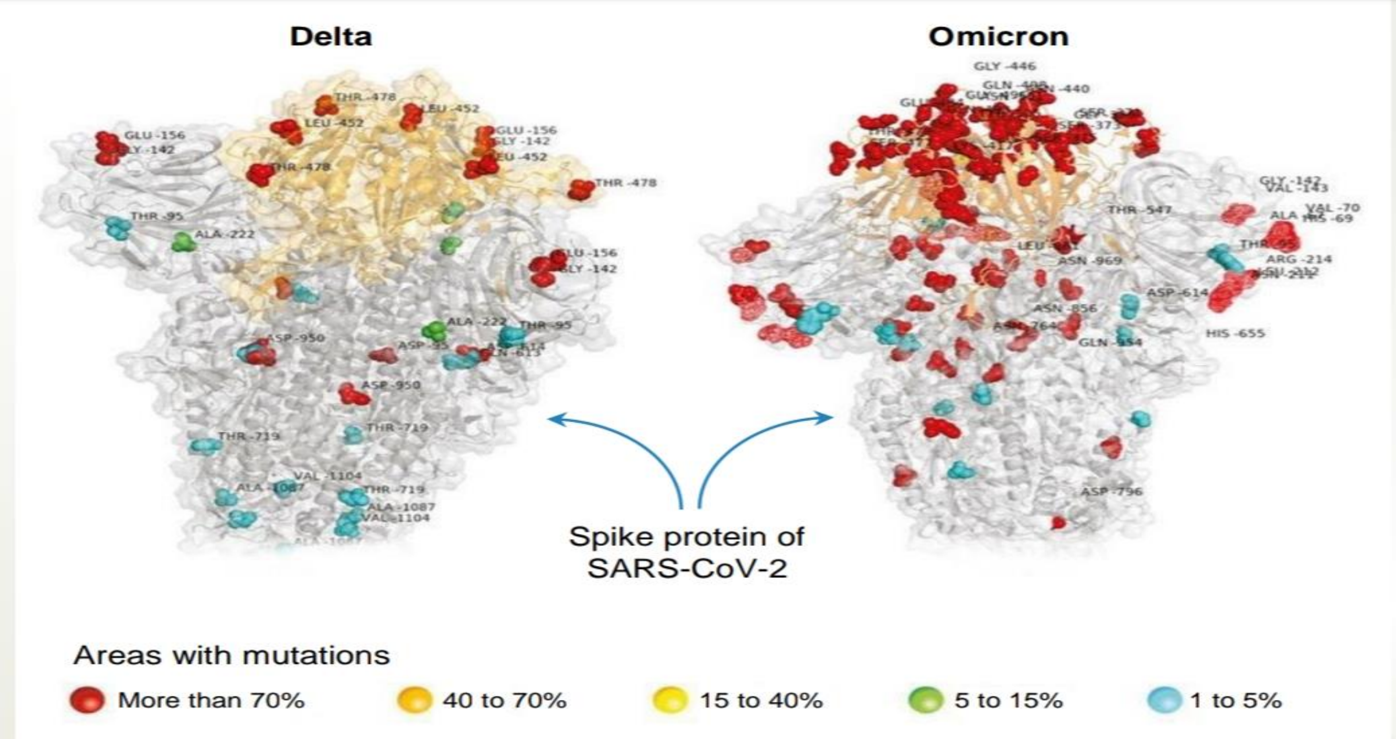


Figure 4:Delta compared to Omicron with mutations in the S1 domain of the spike protein

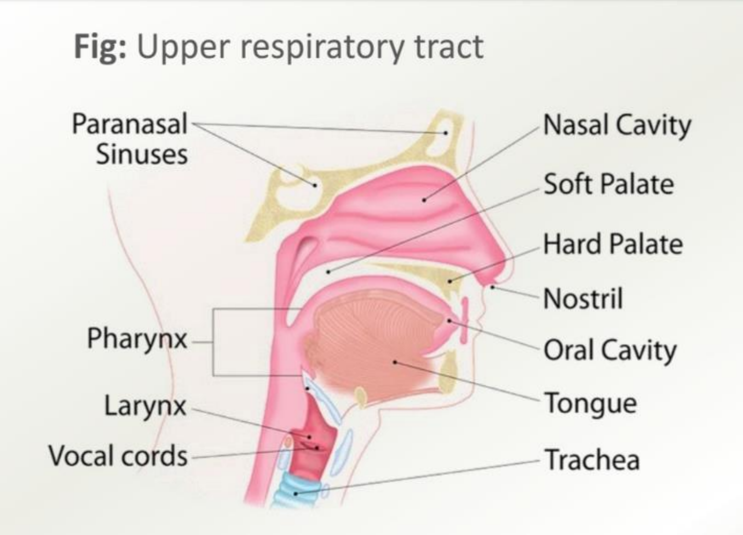
OMICRON SHOWS PREFERENCE FOR UPPER RESPIRATORY TRACT INFECTION

Omicron appears to show preference for infecting and replicating in the upper respiratory tract, compared to Delta and other strains which prefer the lower respiratory tract.

This may confer a transmission advantage independent of immune evasion.

Preliminary studies suggest that Omicron appears to have decreased ability to infect lung tissue, which may be a reason why people infected with Omicron have a less severe disease compared to Delta.

Early studies from animal models show that Omicron-infected animals show fewer clinical signs and have less severe disease. [18]



EMERGENCE OF OMICRON VARIANT

According to the WHO reports, the first known confirmed infection by Omicron could be traced back to a specimen collected on November 9, 2021.3 The first Omicron sequence available, however, was from a specimen collected on November 11, 2021, in Botswana. Ever since the identification of Omicron, the variant appears to rapidly spread. A recent genomic-sequence analysis on 77 virus samples collected in Gauteng province of South Africa from November 12 to 20 showed that all the anallyzed variants were actually B.1.1.529,4 indicating that Omicron was becoming dominant in Gauteng. Furthermore, the identification of Omicron coincides with the recent sharp increase in the number of confirmed COVID-19 cases in South Africa[19]. The mean number of COVID-19 cases per day increased from 280 to 800 after the Omicron variant was verified. This number exceeded 2000 on November 26, 2021, and broke through 10,000 on December 3, 2021.6 In addition, tracing the source of COVID-19 cases revealed that B.1.1.529 had probably spread in western Europe before the first cases were detected in southern Africa. B.1.1.529 variant was first reported to WHO on November 24, 2021. On the day after receiving the report, WHO designated it as VUM and named it as Omicron variant (B.1.1.529). Only 2 days later, WHO categorized the Omicron variant as VOC, which recorded the shortest interval period of reclassifying a variant from VUM to VOC and subsequently brought about great public concerns. A few days after the identification of Omicron in Africa, the variant has emerged in the other continents. At the time of this writing, Omicron has been reported in 34 countries and areas, including Botswana, Hong Kong, South Africa, Israel, Belgium, Italy, and the USA.8 Apparently, the variant has not stopped spreading to other countries and regions. Where and how the Omicron variant evolved remains to be investigated. The analysis of sequences of SARS-CoV2 variants reveals that Omicron is a lot different from the other SARS-CoV-2 variants such that it is difficult to identify its closest relative. The results of phylogenetic studies indicate that the Omicron variant likely has diverged early from other SARS-CoV-2 variants rather than being developed from one of the previous VOCs. It is speculated that the Omicron variant might have been gestated in immunocompromised individuals (e.g., HIV patients co-infected by SARS-CoV-2) for a certain period of time, or it might have evolved in a nonhuman species and is just recently spilled back into human beings[20].

CHARACTERISTICS OF OMICRON VARIANT

Since early 2020, three big waves of COVID-19 outbreaks have been recorded in South Africa. Among them, two are caused by the Beta and Delta variants respectively . The epidemiological data showed that the percentage of infections associated with the Beta variant increased to ∼50% of the total daily infections within approximately 100 days since its outbreak . The infection percentage of the Delta variant, however, raised to ∼80% during the same period of time, echoing higher transmissibility among people for Delta than for the Beta variant. In contrast, the percentage of Omicron infection reached ∼90% within approximately 25 days in South Africa. The early doubling time of the Beta, Delta, and Omicron variants was calculated to be about 1.7, 1.5, and 1.2 days, respectively. These data indicate that the Omicron variant is probably more infectious than the Delta and Beta variants. It is also noteworthy that a recent retrospective study based on the population-wide epidemiological data in South Africa indicates an increased risk of SARS-CoV-2 reinfection associated with Omicron[21].The possibility of a new wave of COVID-19 epidemic in South Africa and even around the world therefore should not be ignored. Analysis of the genomic sequences of the Omicron variant has revealed a high number of non-synonymous mutations, including several ones in spike that have been proved to be involved in transmissibility, disease severity, and immune escape. Overall, more than 60 substitutions/deletions/insertions have been identified in the Omicron variant, making Omicron a variant possessing the largest number of mutation sites of all SARSCoV-2 variants characterized so far. Within ORF1a, the Omicron variant harbors six substitutions (K856R, L2084I, A2710T, T3255I, P3395H, and I3758V) and two deletions of in total four amino acids (amino acid 2083 and amino acids 3674–3676). Within ORF1b, the variant contains two substitutions (P314L and I1566V). In addition, a P10S substitution and a three-residue deletion at positions 27– 29 are observed in ORF9b. For the structural proteins, there are one substitution (T9I) in the envelope (E), three substitutions (D3G, Q19E, and A63T) in the membrane (M), and three substitutions and a three-residue deletion in the nucleocapsid (N) proteins, respectively[22]. While the aforementioned mutations emerge along the whole viral genome, the remaining mutations, which account for more than half of the total Omicron mutations identified, are accumulated in the spike. These include 30 substitutions of A67V, T95I, Y145D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, three deletions of H69/V70, G142/V143/Y144 and N211, and one insertion of three amino acids (EPE) at position 214 (in some reports, the changes are described as the V143/Y144/Y145 deletion in combination with G142D and the L212 deletion in combination with N211I).

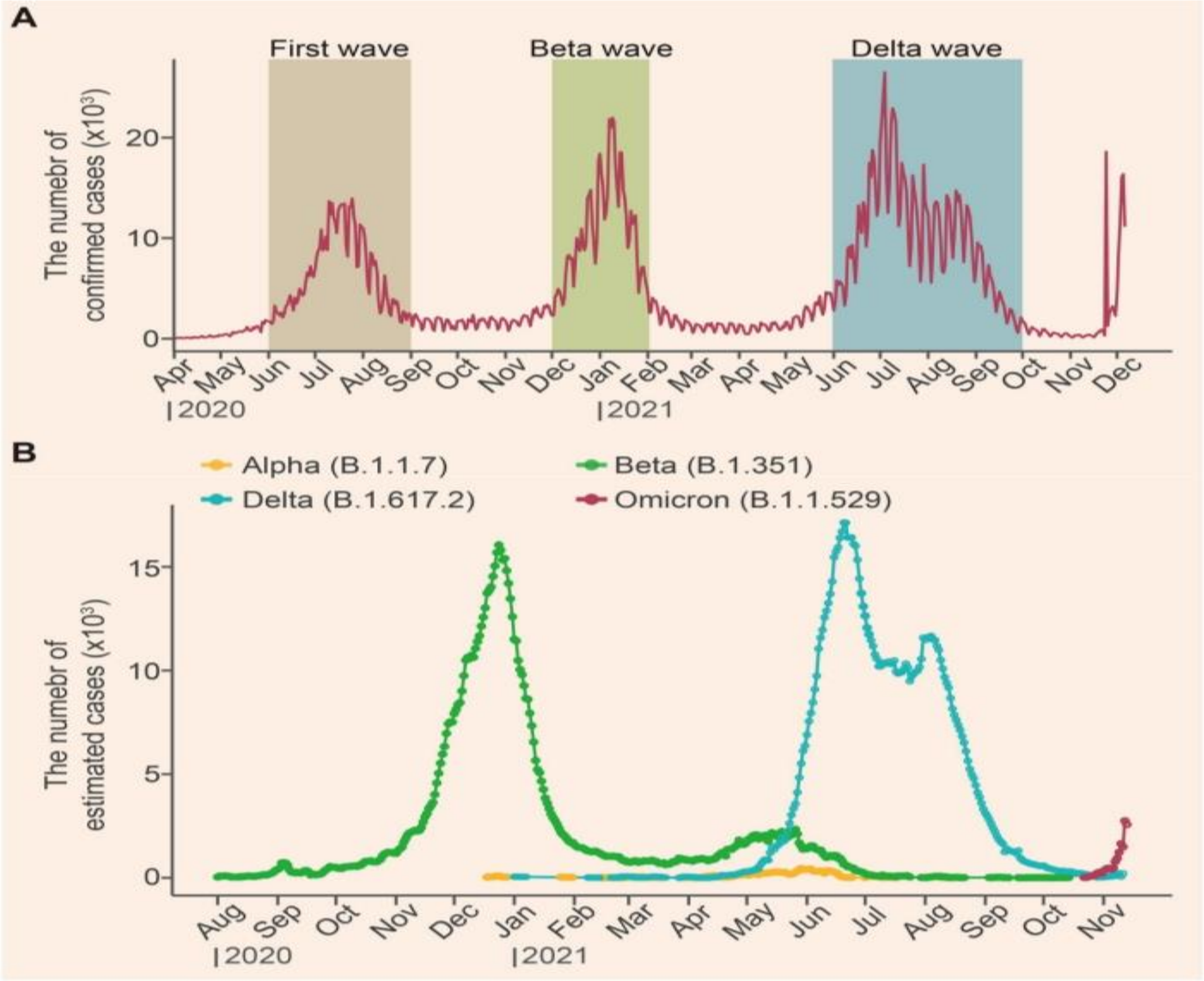


Figure:5-Waves of Coronavirus disease 2019 (COVID-19) epidemics recorded thus far in South Africa. (A) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused three waves of epidemics in South Africa. The number of daily confirmed infection cases is plotted. Data were downloaded from the World Health Organization (WHO). (B) The number of estimated cases infected by the indicated variants of concern (VOCs) in South Africa. The original data were downloaded from global initiative on sharing all influenza data (GISAID)

In comparison to those observed in the other four VOC variants, the spike mutations identified in Omicron out-number by about 3–4 times . It is notable that all the five VOCs contain the amino acid change D614G in spike. Previous studies have clarified that D614G is associated with higher upper respiratory tract viral loads and the younger age of patients. The Omicron variant also shares N501Y with the Alpha, Beta, and Gamma variants. This mutation is believed to enhance the binding between spike and angiotensin-converting enzyme 2 (ACE2) and to induce higher transmissibility. When combined with the H69/V70 deletion, the transmissibility might be further increased. Besides, Omicron also has N679K and P681H mutations near the furin cleavage site. The incorporation of basic amino acids around the furin cleavage site could facilitate the cleavage of the spike into S1 and S2, thereby enhancing fusion and virus infection. As a matter of fact, the P681H mutation was also identified in the Alpha variant. This mutation has been suggested to enhance SARS-CoV-2 infectivity.It should also be noted that the spike receptor-binding domain (RBD) is the authentic virus entity that recognizes the ACE2 receptor to mediate virus entry.19,20 While the currently predominant Delta variant only possesses the L452R and T478K mutations in the RBD, 15 mutations have been accumulated in the RBD of the Omicron variant. Among these substitutions, a bunch of residues is observed to locate nearby the bound ACE2 receptor. How these mutations would affect the receptor binding, however, remains to be investigated in the future. Whether or not and to what extent the Omicron variant can escape from immune recognition is another concern. It is notable that the spike RBD is the major target for neutralizing antibodies and that Omicron has accumulated 15 substitutions in the RBD region. We noted that multiple antigenic sites have been characterized in RBD, featured with the RBS-A, RBS-B, RBS-C, the CR302, and the S309 sites. All the 15 mutations identified in Omicron spike RBD can be located to one or more of these antigenic sites, indicating potential resistance of Omicron to one or more of the monoclonal antibodies targeting these sites. As for the antibody treatment in clinical use, the cocktail consisting of LY-CoV555 (also known as Bamlanivimab) and LY-CoV016 (also known as Etesevimab) has been authorized for emergency use. Previous studies have revealed that the mutations at 484 and 417 positions of the spike are associated with immune evasion22 and that both Beta and Gamma variants could escape the neutralization of LY-CoV555 (due to E484K) and LY-CoV016 (due to K417N/T).23 Since the Omicron variant also contains E484A and K417N mutations, it is likely that Omicron would also resist these two antibodies. Taken together, some spike mutations of Omicron have also been identified in the other VOC variants, such as D614G, N501Y, K417N, P681H, and the residue-substitution of E484. These mutations have been indicated in higher binding affinity with ACE2, enhanced transmissibility and pathogenicity, and reduced ability of neutralization by monoclonal antibodies and immune evasion. The functions of other mutations and whether combined effects of these mutations exist, however, are not clear, resulting in great uncertainty about how the viral behaviour and susceptibility will develop[23].

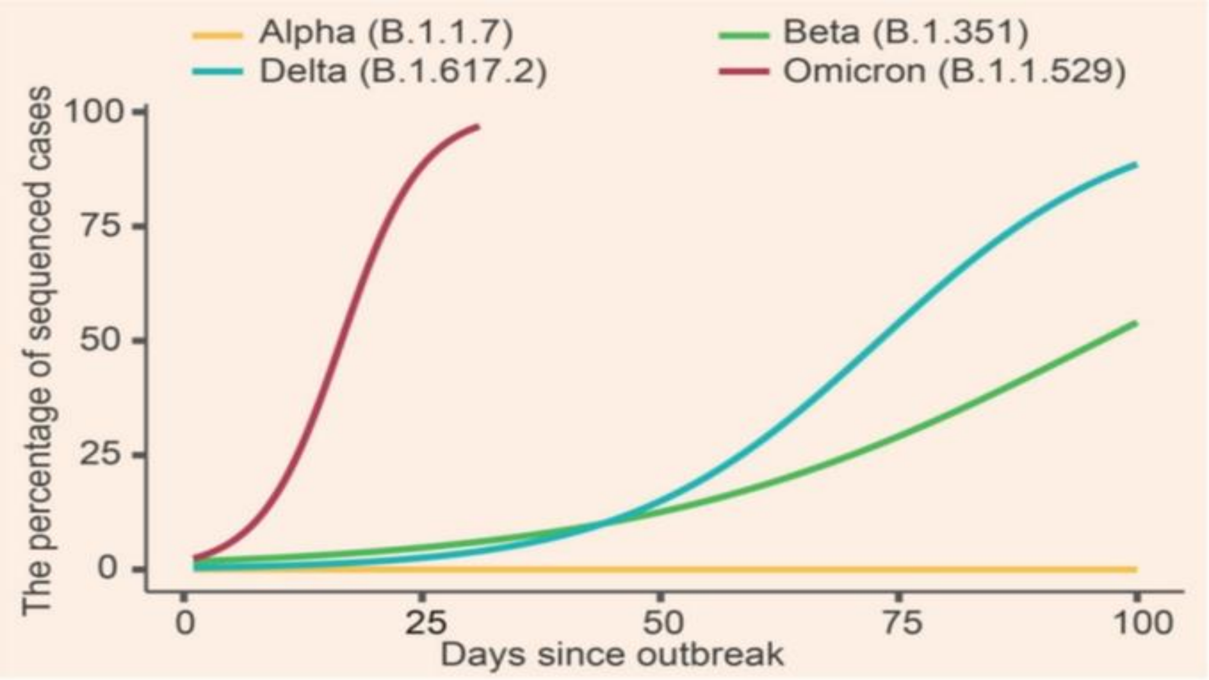


Figure6:Omicron is spreading faster than other variants of concern (VOCs) in South Africa. The full genomic sequences were downloaded from global initiative on sharing all influenza data (GISAID), and the original data were processed with a logistic function

EPIDEMIOLOGY OF OMICRON AND A TROPISM SHIFT

Omicron spreads faster than the original virus; however, data related to its reproductive number remain limited. According to the European Center for Disease Prevention and Control, this variant could be more transmissible than the Delta variant . Early reports from South Africa in November suggested the effective reproductive number (Re) of the variant to be in the range of 1.5–3; however, a recent estimate of Re as low as 0.75 was also reported . These latest estimates should be interpreted with caution, because several factors, including changes in the testing measures or efforts and lag in case reporting, might have contributed to the change in the reproductive number . The collective evidence suggests that Omicron has greater infectivity and potential to cause reinfection as compared with its predecessors ; however, data are insufficient to quantify its overall impact[24]. The symptoms of Omicron include a dry cough, scratchy throat, body aches, fatigue, runny nose, fever, and night symptoms . According to recent evidence from South Africa, no peculiar symptoms associated with the variant have been reported, and some patients remained asymptomatic or only presented mild symptoms . The patients infected with Omicron had fewer or no symptoms related to neurotropism (i.e., loss of taste and smell), which were peculiar with the earlier strains of the virus . This tropism shift is attributed to the reduced dependence of Omicron on TMPRS22-expressing cells, such as the lower respiratory tract, brain, heart, kidney, and other extrapulmonary organs . Among the initial Omicron VOC cases reported by the end of 2021 by EU/EEA countries to TESSy, 7 of every 10 cases were symptomatic . Furthermore, the average age range for these reported cases was between 20 and 49 years . The incidence of Omicron cases was higher among females compared with males . The patients with pre-existing conditions and those with the acute respiratory attacks were among the Omicron-associated hospitalizations . Furthermore, it was reported that the risk of hospital and ICU admissions was lower compared with the preceding waves in South Africa . In addition, a lower proportion of patients required oxygen therapy and mechanical ventilation . The median length of stay was reduced by half in this current wave as compared with what was observed in the previous waves (3–4 days vs. 7–8 days) . Preliminary data from South Africa suggested that Omicron causes less severe symptoms than the original SARS-CoV-2 virus, although rapidly increasing case loads and overall transmissibility remain the serious concerns. Omicron seems to weaken the association between cases and mortality, which is supported by the U.K.-based evidence, according to which the Omicron case rate in the United Kingdom was 35% per day; however, the death rate continuously declined, unlike the patterns which were observed in the first wave of the COVID-19 pandemic [30,35]. Data also suggested that every 3 in 10 cases which emerged in the existing cases were fully vaccinated, which points to the ability of Omicron to evade immune response[25] .

LABORATORY TESTING

Although reverse transcription—polymerase chain reaction (RT-PCR) tests remain the gold standard in COVID-19 testing, many rapid antigen detection tests (RADTs) and self-RADTs have been introduced and widely adopted. With the emergence of new variants, reductions in the RADT sensitivity have not yet been reported . Studies have reported the effectiveness of antigen tests in detecting the Omicron variant at the lowest dilutions [26]. It is important to note that studies which will provide more insight to the analytical sensitivity of RADTs to detect the Omicron variant in settings with high transmission are ongoing. RT-PCR-based S-gene target failure (SGTF) assays that do not detect the S-gene with Δ69–70 deletion may serve to screen for the Omicron VOC . Screening for VOC-specific amino acid substitutions can also be performed using specific RT-PCR assays targeting single-nucleotide polymorphisms (SNPs) . Some commercially available SNP test kits for the identification of T478K, N501Y and P681H fail to reliably identify these mutations for Omicron, even with S-gene mutations . The U.S. FDA has identified and listed molecular tests that may be impacted by new Omicron variant mutations [27]. The currently widely used real-time RT-PCR tests can detect the new variant, but rapid antigen detection tests may need more confirmatory studies in this regard[28].

THERAPEUTICS

The WHO established its Joint Advisory Group on COVID-19 with the aim of collecting and synthesizing evidence related to the potential impact of the emergence of Omicron on the effectiveness of drugs currently being used or under investigation . At present, limited evidence is available regarding the effectiveness of bioequivalents of monoclonal antibody therapies, including Sotrovimab, Casirivimab, Imdevimab, Bamlanivimab, etc. against Omicron[29]. Some early reports have indicated that the cocktail mixture of Casirivimab and Imdevimab does not neutralize Omicron in vitro , whereas the neutralization capability of Sotrovimab was retained against Omicron . There is presumptive thought based on the genetic analysis regarding the efficacy of Remedisivir that it may continue to be active against Omicron; however, laboratory confirmative study data are needed . Clinical and laboratory data on the effectiveness of newer oral antivirals against Omicron are not yet available. Owing to genomic changes, the variant might be responsive to some available treatments and may not respond to other modalities effective against the original virus. To assess the effect on the three currently available monoclonal antibody treatments (Sotrovimab, Bamlanivimab and Etesevimab, and REGEN-COV) more data need to be evaluated[30].

Diagnosis

SARS-COVID-2infection was diagnosed reverse transcriptase-polymerase assay (RT-PCR), high-throughput genome sequencing, and serological evaluation of anti-viral immunoglobulin M (IgM), G (IgG) antibodies, and lung X-ray [10] (CT scan value). The food and drug administration (FDA) has approved two tests to diagnose SARS-COV2 infection[31].

Those include:

- **PCR Test (also known as a molecular test):**This COVID-19 test uses a lab technique called polymerase chain reaction to detect the virus's genetic material (PCR). A fluid specimen from infected can be collected with a nasal swab or swab from throat, or a saliva can be obtained by spitting into a tube[32]. Results could be generated in less time if processed on-site or in a few days. The test processing delays, if evaluated off-site if transferred to an independent lab. The test give maximum percent precise results when done by a skilled professional; nonetheless, the fast results may be failure to identify few cases[33].

- **Antigen Test :**The COVID-19 test looks for the virus's specific proteins. The nasal swab used to capture a fluid sample, the results generation time was less. Others may be referred to a laboratory for examination. A positive antigen test result is considered accurate when procedures are followed correctly. Even yet, there's a larger chance of false-negative results, which means you could be infected but get a negative test. A PCR test may be recommended by the doctor to confirm either the person is positive for antigen test or negative, depending on the circumstances[34].

- **Lateral Flow Tests:** Rapid or lateral flow tests (LFTs) are currently performed, although they cannot tell you which variant you have; nonetheless, they are supposed to be able to tell you whether you are negative or positive, suppose you get a positive LFT result, self-isolate immediately, and get a PCR test to confirm the result[34].

General Symptoms by SARS- COVID-19 including Omicron Variant and Spreadability: Fever, cough, running nose, body ache, loss of sensation (smell and taste) and difficulty in breathing in severe cases. On the other hand, they observed severe body ache, chills, dizziness, and mild fever , According to them, Omicron-positive people didn't have any breathing issues to date, and saturation levels remained normal[35].

How fast is Omicron Spreading?

Omicron is rapidly spreading in South Africa, particularly in Gauteng province, including Johannesburg and Pretoria. Testing has revealed that it is responsible for more than 90% of all infections. In the week ending November 30, the seven-day average of daily cases in South Africa increased fourfold to 2,756. According to the WHO, the COVID omicron variant has been detected in 57 countries (December 15), and based on preliminary data graph was drawn, this graph indicated reported cases were observed in top 5 countries and also in India , and the data was reported Table 1. In table we reported about reported omicron cases by daily news hunt South Africa , United Kingdom, South Korea , Europe , United States and India . According to South Africa's government reports more children got hospitalized with medium to high symptoms of omicron variant.[36]

THE REPORTED DATA OF OMICRON CASES IN THE TOP 5 COUNTRIES AND INDIA (TILL DEC 15, 2021)

South Africa	37875
United Kingdom	>10000
India	653
South Korea	7000
United States	1500

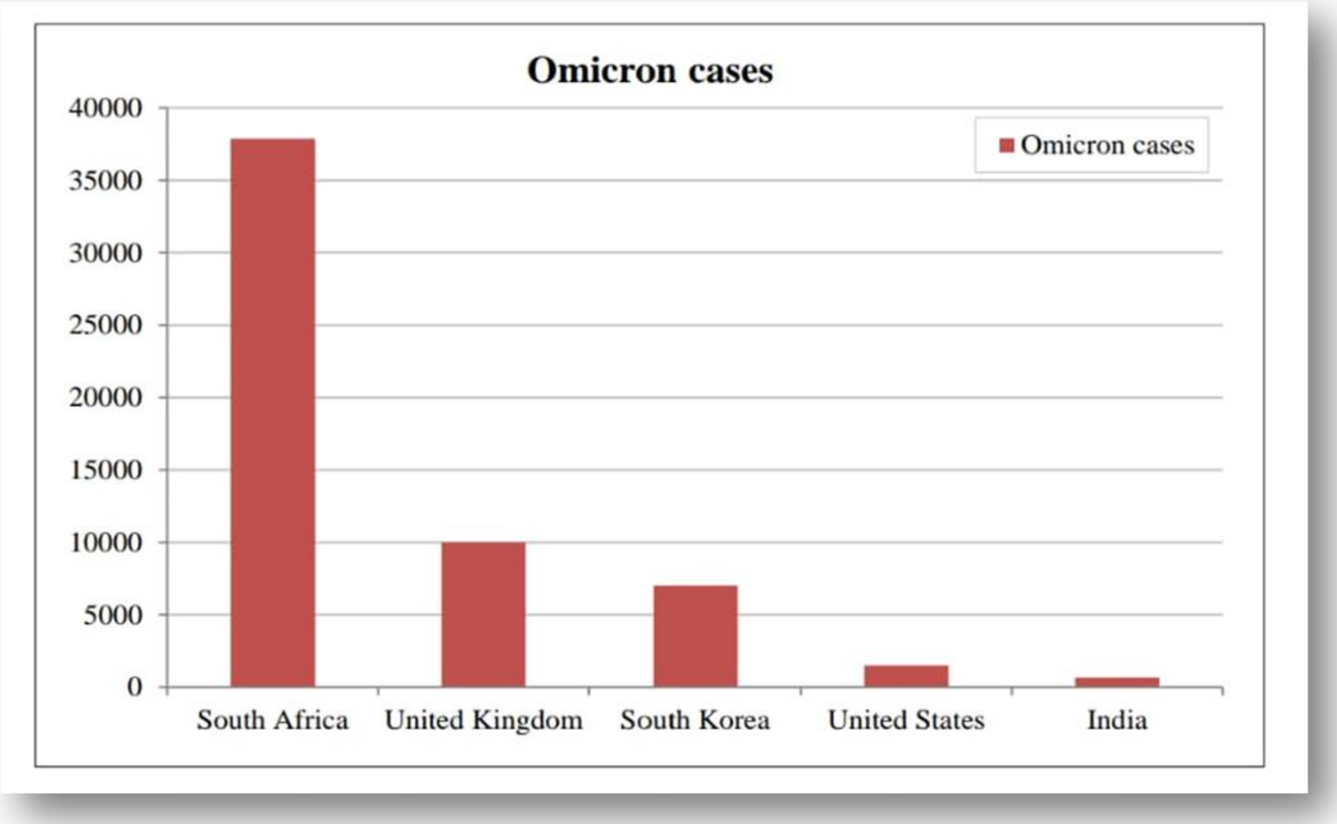


Figure 7: Reported cases of Omicron variant in top 5 countries and India

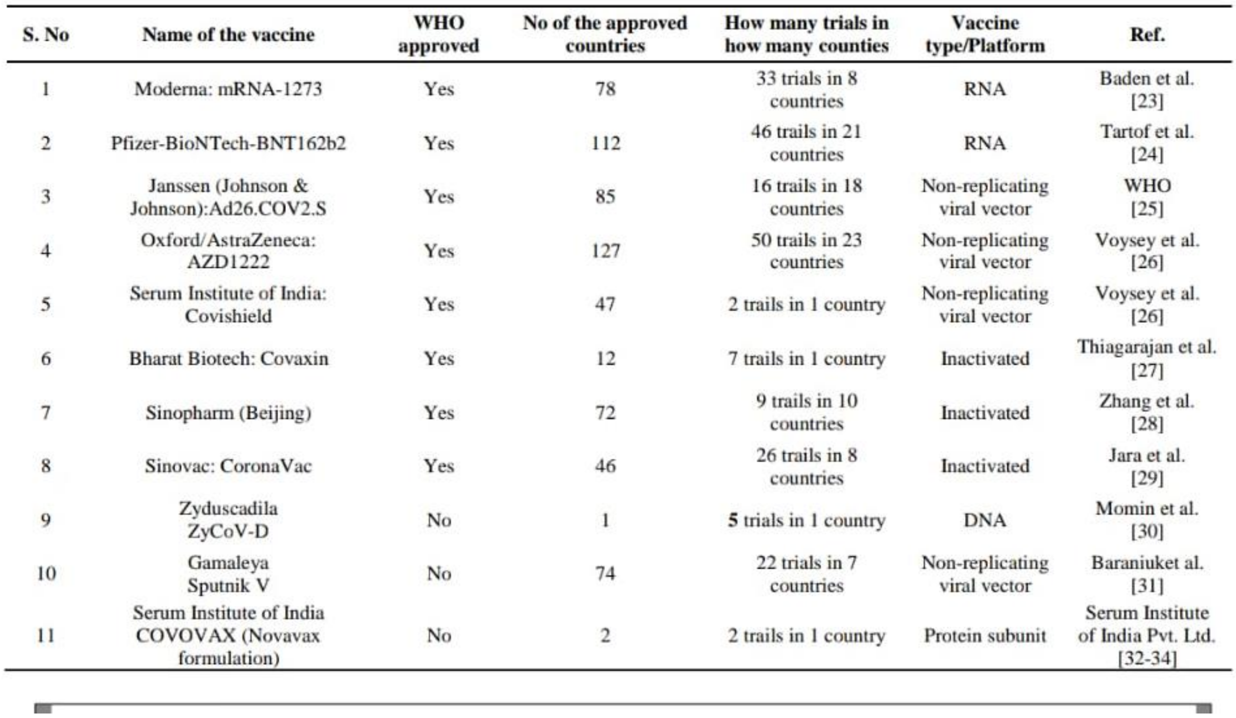
Treatment of SARS-COVID-2 by Drugs

SARS-COVID-2 in the primary stage, there is no need of takes any anti-viral treatment; in the initial stages, the virus load in the body is less usually so symptomatic relief and boosting of the immune system recommended by most of the physicians. If the patient's condition is worst, difficulty in breathing such situations, they advised anti-viral drugs. The list of anti-viral drugs used in the treatment of covid-19 is mentioned below[37]. Anti-viral medications like ribavirin and lopinavir-ritonavir have been attempted with HIV, SARS, and MERS infection therapy based on anecdotal evidence. In case of the new variant the UK government-approved Xevudy or Sotrovimab as a medicine active against it. Xevudy or sotrovimab for those with mild to moderate COVID-19 and who are at high risk of developing severe disease, according to the Medicines and Healthcare Products Regulatory Agency (MHRA). Sotrovimab is an intravenous infusion that requires 30 minutes to complete and is recommended for people aged 12 and up who weigh more than 40 kg. The MHRA stated that it is very early to confirm whether the Omicron variant affects the effectiveness of sotrovimab, but they intend to collaborate with the producers to find out . Pfizer company confirmed nirmatrelvir pill was found to be effective against omicron patients (severe cases)[38].

Vaccination Data

The complete information about vaccines approved by countries was mentioned in Table 2 More than 4.32 billion people, or around 56.2 percent of the world's population, have received a dose of the Covid-19 vaccination. The vast disparity in immunization regimens in different countries is depicted in this map. In all over India, 33.7 population got fully vaccinated[39] .

Table 2. List of the approved Covid-19 vaccines



S. No	Name of the vaccine	WHO approved	No of the approved countries	How many trials in how many counties	Vaccine type/Platform	Ref.
1	Moderna: mRNA-1273	Yes	78	33 trials in 8 countries	RNA	Baden et al. [23]
2	Pfizer-BioNTech-BNT162b2	Yes	112	46 trails in 21 countries	RNA	Tartof et al. [24]
3	Janssen (Johnson & Johnson):Ad26.COV2.S	Yes	85	16 trails in 18 countries	Non-replicating viral vector	WHO [25]
4	Oxford/AstraZeneca: AZD1222	Yes	127	50 trails in 23 countries	Non-replicating viral vector	Voysey et al. [26]
5	Serum Institute of India: Covishield	Yes	47	2 trails in 1 country	Non-replicating viral vector	Voysey et al. [26]
6	Bharat Biotech: Covaxin	Yes	12	7 trails in 1 country	Inactivated	Thiagarajan et al. [27]
7	Sinopharm (Beijing)	Yes	72	9 trails in 10 countries	Inactivated	Zhang et al. [28]
8	Sinovac: CoronaVac	Yes	46	26 trails in 8 countries	Inactivated	Jara et al. [29]
9	Zyduscadila ZyCoV-D	No	1	5 trials in 1 country	DNA	Momin et al. [30]
10	Gamaleya Sputnik V	No	74	22 trials in 7 countries	Non-replicating viral vector	Baraniuket al. [31]
11	Serum Institute of India COVOVAX (Novavax formulation)	No	2	2 trails in 1 country	Protein subunit	Serum Institute of India Pvt. Ltd. [32-34]

Various Vaccine Effects on Different Variants:

The vaccines had a high level of neutralization against the original SARS-CoV-2 mutation, as expected. According to Pfizer, antibodies from patients who had previously been vaccinated with the two-dose Pfizer vaccine showed a significant loss in neutralizing power against Omicron, with a 40-fold decrease in neutralizing ability19.Infection with the Omicron form is predicted to cause severe sickness, hospitalization, and death. Current immunizations are intended to protect against this[40]. Breakthrough infections are more likely to arise in patients who have been fully immunized. Vaccines against other variations, such as Delta, have proven to help reduce severe disease, hospitalizations, and death. The new appearance of Omicron highlights the significance of immunization and boosters even more. Scientists were working on it; still, they have not revealed which vaccine is effective for the omicron variant. Some medications are likely to remain helpful despite Omicron's changing genetic make-up, and some may be less successful. The expected risk frequency order of omicron variant mentioned below; high to low $Notvaccinatedpeople > partiallyvaccinated > fullyvaccinated > boosterdosevaccinated$[41]

STRATEGIES FOR PREVENTION OF OMICRON VARIANT

Interruption of SARS-CoV-2 variant spread: At present, the detailed feature of the Omicron variant is unclear. In view of those spike mutations that are also observed in other VOCs, it is of particular concern that Omicron might have evolved with the capacity of easier spread among people and the ability to resist currently available antibody treatments. Such circumstance highlights the importance of maintaining present public health prevention measures, including wearing masks, frequent ventilation, keeping physical distance, and washing hands[42]. These measures have been proved to be effective in interrupting the transmission of other variants and should also be effective in dealing with the Omicron variant. In addition, early diagnosis and timely quarantine are key factors that can minimize virus transmission during a pandemic. There have been epidemiological evidence showing that the failure of PCR tests by targeting the spike gene is rising along with the increasing cases infected by Omicron. Thus, improving diagnostic accuracy to enable timely isolation and treatment of diagnosed cases is also important to cut off the transmission of the Omicron variant[43].

Improving COVID-19 vaccine coverage

Although some speculations show that the rapid spread of Omicron in South Africa might be a signal of a new wave of pandemic worldwide, the influence of this variant and what it means for the current pandemic are still far from clear. As a matter of fact, the situation of Omicron spread in South Africa could be dramatically different from those in other countries. For example, the proportion of the fully vaccinated population in South Africa is only about 24%.24 This value is far lower than the average vaccination percentage of 42% globally[44].24 This may accelerate the spread of Omicron in South Africa, highlighting the urgent need of increasing the vaccination coverage in the country. Although the authorized COVID-19 vaccines showed decreased effectiveness against the variant viruses,25–31 it has been shown that the vaccines remain effective in preventing severe diseases, hospitalization, and death.32–34 It is also noteworthy that the low antibody level in the infected or the vaccinated against SARS-CoV-2 might promote the evolution and selection of new variants. In light of several studies reporting that the serum neutralizing antibodies dramatically decline 6 months post-vaccination and that further vaccination with an extra booster dose can restore and even improve the vaccine effectiveness,35–39 we, therefore, believe that adding an extra boosting dose of the COVID-19 vaccine to the vaccination program could undoubtedly help control the Omicron spread and infection[45].

Developing variant-specific vaccines

It has been reported that the increased risk of SARS-CoV-2 reinfection is associated with the emergence of the Omicron variant in South Africa, indicating that the Omicron variant may be associated with substantial ability to evade immunity from prior infection.Moreover, whether the current COVID-19 vaccines can protect against the Omicron variant attracts much attention. The most recent evidence showed that the current COVID-19 vaccines provided less immunity to the omicron variant than other VOCs.40 Meanwhile, the sera from vaccinated individuals also had about 40 lower neutralizing ability against the Omicron variant compared to the wild-type SARS-CoV2. These results suggested that the present COVID-19 vaccines might not be effective against the Omicron variant as other SARS-CoV-2 variants. More data about the effectiveness of current COVID-19 vaccines need to be further investigated in the future. Although the impact of the Omicron spike mutations on the effectiveness of currently available vaccines remains to be investigated, it is well documented that vaccines developed based on wild-type SARS-CoV-2 are less effective in preventing variant infections. Our previous study has shown that the vaccine based on the mutant spike would have a higher level of neutralizing antibodies against mutant viruses, but lower neutralizing antibodies against wild-type SARS-CoV-2.These observations highlight the importance of developing variant-specific vaccines based on the mutated spike, especially towards the Omicron variant[32]. Therefore, we are developing the specific vaccines against the SARS-CoV-2 Omicron variant based on the mutated spike of the Omicron variant. Alternatively, the vaccine candidates developed based on the other variants but containing one or more Omicron mutations might also be used to prevent the Omicron infection and transmission. For example, some unofficial information indicates that Moderna has developed two multivalent vaccine candidates: candidate mRNA-1273.211 is believed to harbor several mutations observed in both the Omicron and Beta variants, and mRNA-1273.213 is believed to have included a certain number of mutations present in the Omicron, Beta and Delta variants. The effectiveness of these candidate vaccines against the Omicron variant needs to be further studied[33].

PUBLIC HEALTH RESPONSE TO MINIMIZE OMICRON TRANSMISSION

Similarly to other infectious and highly transmissible diseases, efforts at macro (country level) and micro level (individual level) are vital. First and foremost, surveillance plays an integral role in the public health response in curbing the transmission of Omicron. Recently, the CDC established a genomic surveillance system to improve the understanding of predominant strains circulating in the community. The CDC has partnered with commercial laboratories and universities to supplement public health sequencing efforts and conduct genomic surveillance research [33]. According to the WHO recommendations, countries should extend their research infrastructure to develop a science-based approach to curb the spread of COVID-19. Ensuring equitable access to healthcare will be critical to overcoming the disparate effects of the pandemic and new challenges induced by the mutated strains. At individual level, physical distancing, the use of masks, avoiding public gatherings and getting vaccinated will remain useful in curbing the spread[34,46].

CONCLUSION

This paper concludes with little idea about the omicron variant in different aspects than previous variants. The Omicron variant has a higher mutation capacity than earlier variants, leading to a high rate of spread-ability and complete effects and severity of the variant yet to unknown. It will take a few more weeks to complete about it; so far one death was reported due to the omicron variant in UK, and we concluded that re-infection rate was also high in case of omicron than other variants, the conclusion of the study to be completely for public awareness about new variant. Above information also gave idea about what symptoms observed with Omicron, the effects of available vaccines, and treatment.

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CONFLICT OF INTEREST

Conflict of interest declared of none.

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