The SARS-CoV-2 Omicron Variant and its Multiple Sub-lineages: Transmissibility, Vaccine Development, Antiviral Drugs, Monoclonal Antibodies, and Strategies for Infection Control – a Review

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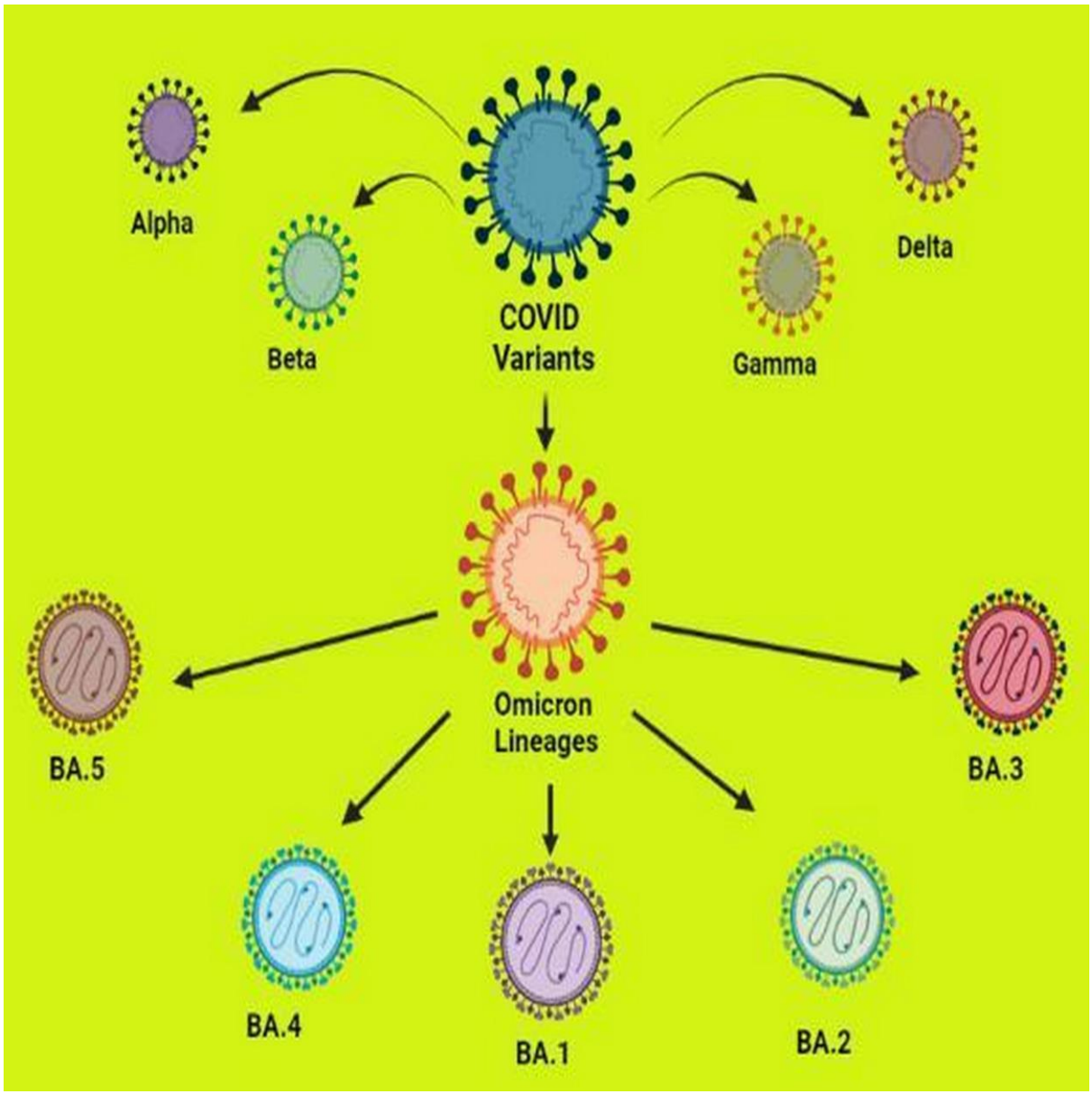
Frontispiece



Abstract

The Omicron (B.1.1.529), fifth variant of concern (VOC) of SARS-CoV-2, initially identified following a steep increase in COVID-19 cases in Southern Africa in November 2021. It is a highly-mutated variant and is more contagious as compared with the Delta variant, however less deadly. Due to its high transmission rate, it spreads dramatically, and causing huge surges worldwide. It causes "mild infection", with hospitalisations less likely to occur. However, this variant is known to show resistance to neutralizing antibodies (nAbs)

generated through vaccination and/or prior infection as well as to monoclonal antibodies (mAbs) used to treat COVID-19 patients. In many countries, booster doses of vaccines have been recommended to increase the protective levels of antibodies in vaccinated individuals. Along with the implementation of appropriate prevention and control strategy measures, current efforts are also focussed on the development of better vaccines and mAbs to counter this variant. This review highlights the global health concerns and challenges posed by the Omicron variant and present an update on its sub-lineages.

1. Introduction

The current COVID-19 pandemic, caused by the emergence of SARS-CoV-2 in December 2019 in China, is the most long-running pandemic ever to happen. This virus, along with its multiple variants, will almost have been around globally for three years. The Omicron variant of SARS-CoV-2 was first documented in November 2021, mostly in South Africa/Botswana but also in Hong-Kong.[1,2] This variant, classified as the fifth variant of concern (VOC) by the WHO and the most mutated variant, induced a rapid increase in COVID-19 cases worldwide, and this fast-moving variant has posed new mysteries in virus transmission, severity and evolutionary dynamics of SARS-CoV-2 that have resulted into global health concerns.[3-7] From a genomic point of view, it shares several mutations with the previously identified Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants (VOC), but it also harbors a large number of specific mutations in the receptor-binding domain (RBD) and NTD region (Fig. 1), which impact on pathogenicity, transmissibility, and immune evasion.[5,8,9] This fast-moving variant is currently the dominant strain around the globe.[6] It is spreading four times faster than the deadlier Delta variant and has mutated into a large number of sub-variants, including BA.1-5.[2,10] The aim of this article is to provide an overview of the global health concerns and challenges posed by the Omicron variant and present an update on its sub-lineages.

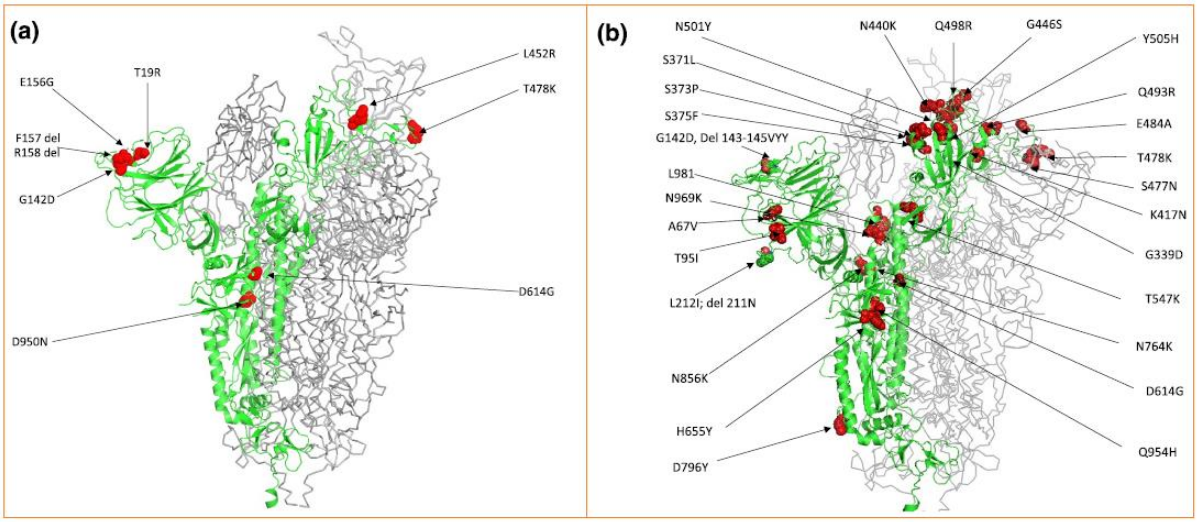


Figure 1. Spike (S-) protein substitution in (a) Delta variant (PDB ID: 7W92), (b) Omicron variant (PDB ID: 7TGW) (reproduced from ref-11) (www.rcsb.com)

2. Evolution of the Omicron variant

The genome of SARS-CoV-2 has evolved significantly since it was first reported in China in December 2019. The Omicron variant that has emerged since November 2021 has been continuously evolving to give several new sub-variants (Fig. 2).

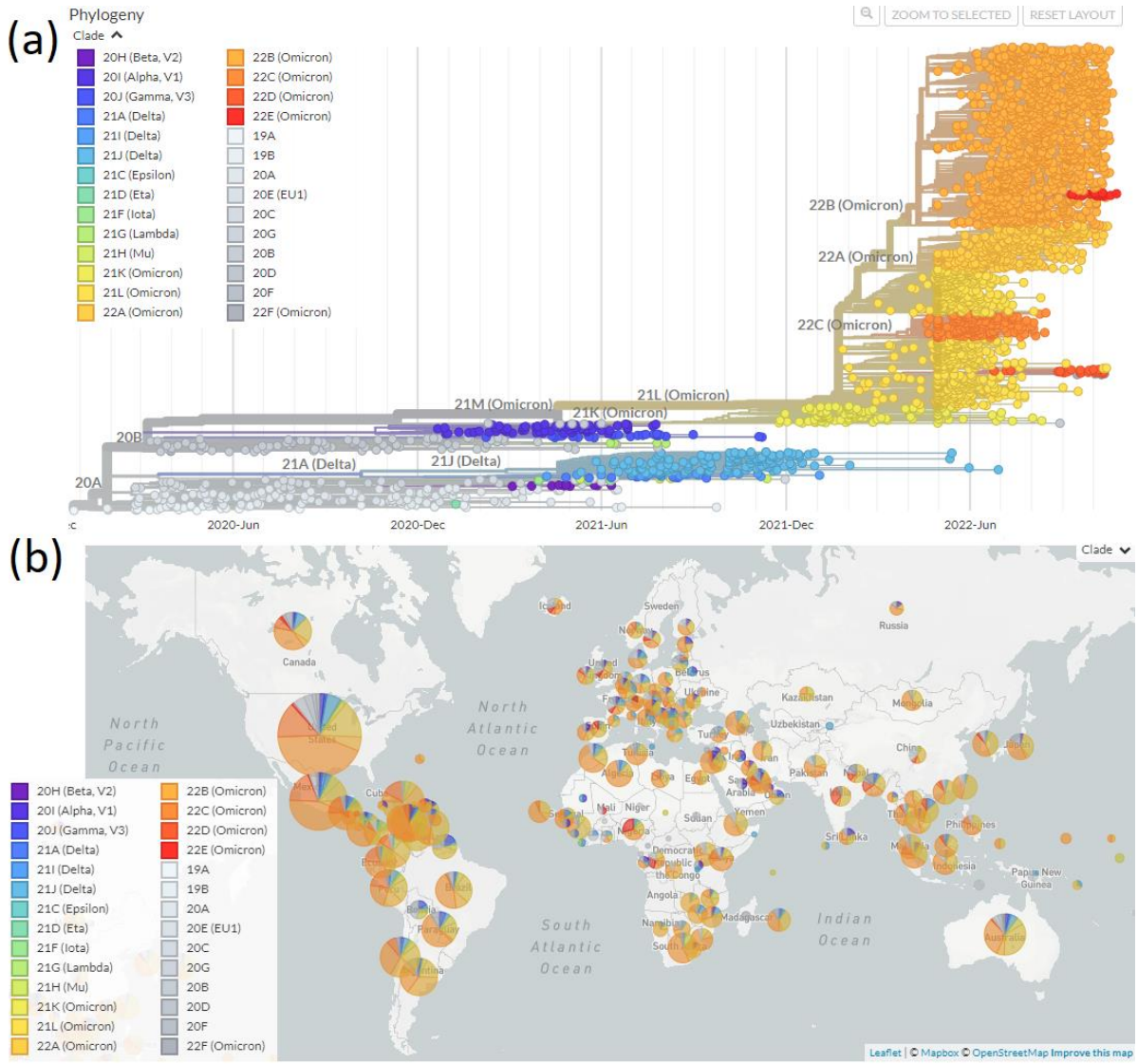


Figure 2. Evolution of SARS-CoV-2 variants (Showing 2942 of 2942 genomes sampled between Dec 2019 and Oct 2022) [reproduced from ref-12] obtained from https://nextstrain.org/ncov/gisaid/global (accessed on 30-10-2022).

The Omicron variant was identified as a new monophyletic clade, different from other variants. Genomic studies revealed that it showed increased similarity with the Alpha variant, in contrast to the Delta variant that was close to the Beta type.[13] Further studies showed that it differed significantly with the previous Delta variant and had no common ancestors. It was also noted that Omicron had emerged from the Lambda variant and that this variant (Omicron) could have emerged due to non-synonymous mutations.[14] *In silico* analysis and evolution predictions indicated that the Omicron variant was distantly related to both the original SARS-CoV-2 virus and the Gamma variant that had evolved in the later stages of the pandemic.[15]

Among nearly 50 mutations discovered in the Omicron variant, 30 mutations were detected on the spike (S-) protein and RBD. Two new and unique mutations (N211 and ins214EPE on the N-terminal domain of the RBD) were not present in previous variants of SARS-CoV-2. Several mutations were common between the Omicron and the Delta variant. However, one mutation (L452A) that was present in the Delta variant was absent in the Omicron variant. This mutation, which favoured the attachment of the virus to the angiotensin-converting enzyme 2 (ACE2) receptors on host cells, made the Delta variant responsible for causing more severe infection.[16] Mutations on N501Y, Q498R, H655Y, N679K, and P681H increase the ability of Omicron to attach to ACE2 receptors and improve cell to cell infections, thereby increasing its transmissibility. Other mutations identified in the Omicron variant (K417N, Q493K, E484A, N501Y, Q498R, and Y505H, G446S, T478K, S477N, G496S, and N440K) contribute to inhibit the antibody-binding ability, and thereby help the virus to escape the host's immune response. Mutations on K417N, T478K, E484A, and N501Y specifically help Omicron to increase its binding ability to ACE2 receptors and reduce its interactions with antibodies.[17] Experimental studies have suggested that the high degree of genetic variation observed in Omicron could be explained because of a jump of this virus from the humans to animals. This sudden change in the host may have been responsible for the increased number of mutations especially at the spike protein region, potentially facilitating viral adaptability and infectivity in the new host.[18] The progenitor of Omicron has been suggested to jump from humans to mice, rapidly gained mutations facilitating to infect this new host, and then again jumped back into humans via an inter-species (human-mice-human) evolutionary trajectory and rapid spread resulting into the Omicron outbreaks.[18] The identification of unique sites (K417, E484, Q493, Q498, and N501) on the genome that are associated with mutations (Q493K, Q498H, Q498Y) favouring adaptability in mouse cells supports the hypothesis that Omicron may have potentially evolved from mice.[19] After adjusting to the animal host, the virus reverted back to humans and may have developed the ability to efficiently adapt and further undergo mutations to develop into several sub-lineages. The WHO's Technical Advisory Group on Virus Evolution (TAG-VE) identified BA.1 and BA.2 as the first sub-lineages of Omicron. Other sub-lineages were subsequently coded as BA.3, and BA.4/5.[2, 10]

3. Omicron sub-lineages

3.1. BA.1 sub-variant

The BA.1, BA.1.1, BA.2, BA.2.2 and BA.3 sub-variants of Omicron possess substantial genomic differences. The BA.1 (member of the B.1.1.529 family) sub-lineage of Omicron was the first to have been discovered. It is now the most dominant sub-lineage of Omicron causing infections worldwide. Around 99% of all the current COVID-19 cases in the United States are caused by this sub-variant. Its high spread across the globe matched that of the Delta variant. This sub-variant has the ability to escape the neutralizing effect of the antibodies elicited by existing COVID-19 vaccines. However, infections caused by BA.1 are being quickly replaced by a new sub lineage called BA.2. Both lineages share some common mutations and possess unique ones. This may be attributed to the protection imparted by the cross-reacting immunity among people infected with these lineages.[20] Increased genome sequencing has also identified a newer BA.1 variant (known as BA1.1) with an additional mutation (BA.1+R346K mutation).[21] This may have additionally contributed to the immune escape by the virus as evidenced by breakthrough infections after vaccination, and re-infections. Almost all the currently available neutralizing monoclonal antibodies (mAbs) are inefficient against the sub-lineage BA.1.[21]

3.2. BA.2 sub-variant

The BA.2 sub-variant (also known as Nextstrain clade 21L) is a new contagious strain of Omicron that has an initial spreading rate of about 30%. This sub-variant appears to be more contagious than the original Omicron variant.[2,10] The rapid spread of BA.2 quickly overtook the original Omicron variant first identified in Southern Africa. It is currently displacing and competing with BA.1.[22] BA.2 is the current dominant variant in countries like the UK, Denmark, India, Norway and South Africa. Although it has been reported that some infections caused by BA.2 may occur shortly after BA.1 infections, these are rare. However, it is still important to understand whether BA.2 can specifically escape immunity acquired after BA.1 infection.[23] Although its origin is still a mystery, BA.2 was first reported in November 2021 in the Philippines. Studies have further confirmed that BA.2 had 8 additional mutations that were not seen in the BA.1 sub-lineage and lacked around 13 unique mutations present in BA.1. Also noted was the fact that the antigenic variations showed by these sub-lineages were distinct from each other and from the parent SARS-CoV-2 virus. Almost all the currently available mAbs are inefficient against BA.2.[21]

In silico studies and the use of mathematical models have revealed that among the SARS-CoV-2 variants and the Omicron sub-lineages (BA.1, BA.2, and BA.3), BA.2 appears to be

the most dominant in terms of transmissibility, potential to evade the immune system, and resist vaccines.[24] Evidence suggests that BA.2 spreads in clusters and is the most dominant sub-lineage globally.[25,26] BA.1 and BA.2 differ by up to 40 non-synonymous mutations and deletions, including the key mutations in NTD and RBD of the s-gene, both regions that influence the immune response.[27] Immunity induced by Omicron original version (BA.1) has been found to protect against the emerging BA.2 subvariant alike vaccination, hence BA.2 might not pose a major pandemic wave in people earlier infected during BA.1 wave of infection.[28]

3.3. BA.3 sub-variant

The BA.3 sub-variant is currently the least prevalent among the Omicron sub-lineages. Studies thus far have identified 33 mutations in BA.3 wherein it was found to share 10 mutations (A67V, T95I, N211I, G446S, H69del, V70del, V143del, Y144del, Y145del, and L212del) with BA.1 and two (D405N and S371F) with BA.2. It was also noted that BA.3 had lost six mutations (ins214EPE, S371L, T547K, G496S, L981F and N856K) from BA.1 and acquired two mutations from BA.2 (D405N and S371F). These mutations could be the reason as to why BA.3 infectivity and spread is slower compared to the BA.1 and BA.2 sub-lineages.[29] Almost all the currently available neutralizing mAbs are inefficient against the sub-lineage BA.3.[21]

Among the circulating Omicron sub-lineages, 21 common mutations were identified in BA.1 (39), BA1.1 (40), BA.2 (31), and BA.3 (34). A recent study revealed that all the Omicron sub-lineages had higher positive electrostatic surface charge on the RBD that may increase the affinity to bind to the negatively-charged human ACE2 receptors. Mutations such as Q493R, T478K, Q498, N501Y, and Y505H on the RBD may have contributed to such increased affinity.[29] This may explain why Omicron and its sub-lineages are more transmissible compared to the parent SARS-CoV-2 virus. BA.2 and BA.3 revealed higher transmissibility compared to BA.1 and BA1.1.[30]

3.4. BA.2.2 sub-variant

Very recently, a new BA.2.2 sub-variant of Omicron was detected in Thailand. Reports identified the strain as one first reported in Hong-Kong.[31] Two COVID-19 patients with the BA.2.2 strain were later identified in Israel with mild symptoms (fever, headaches and muscle aches). Moreover, the BA.2.2 strain also expected in China, India and other countries.[32] There is still, however, insufficient information on BA.2.2 to be able to

accurately predict the severity or transmissibility of this new strain. However, the Global Initiative on Sharing Avian Influenza Data (GISAID) has not yet confirmed officially BA.2.2 as a new variant. BA.2.2 is very contagious and its main symptoms include dizziness and fatigue. A very similar sub-variant, named BA.2.3, was recently reported in the Philippines.[31,33] Recent evidences have suggested the emergence of the recombinant strains of the Omicron sub lineages, and a few emerging recombinants of the Delta variant and Omicron sub variants.[34, 35] The XE is a recombinant of BA.1 and BA.2, and XF and XD are recombinants that emerged from Delta and Omicron BA.1.

3.5. BA.2.75 sub-variant

BA.2.75 shows some unique mutations in the RBD regions (D339H, N460K, G446S and R493Q) and NTD regions (K147E, F157L, W152R, I210V, and G257S) of its spike protein.[36, 37] It also contains additional mutations outside the spike protein (P1640S, S1221L, and N4060S at ORF1a, G662S and E:T11A at ORF1b). Such mutations provide BA.2.75 with immuno-evasive capabilities that help facilitate re-infections, including in vaccinated individuals. In particular, the R494Q mutation can increase the ability of BA.2.75 to attach to ACE2 receptors thereby favouring virus entry and replication within the host's cells. Having said that, there is still potential for the current vaccines to provide antibodies against BA.2.75.

3.6. BA.4/5 variant

BA.4 and BA.5 have a high ability to evade immune responses following infection and vaccination.[38] This is due to the presence of additional mutations (L452R, F486V, and wild type Q493) in the RBD region of their S-protein (unlike the BA.2 variant). Post-vaccination neutralizing antibody titer studies have noted that there is decrease in the concentration of nAbs against BA.4/5 compared to what is observed for BA.1 and BA.2 variants.[39, 40] One study confirmed that people vaccinated with the BNT162b2 (Pfizer) or Ad26.CoV (Johnson and Johnson) vaccines had more than a 7-fold reduction in their neutralizing antibodies against the BA.4/5 variants.

3.7. XBB variant

XBB is a new hybrid variant that emerged from the combination of BA.2.10.1 and BA.2.75.[41] This sub-variant has a breakpoint in the S1 region and possesses additional mutations including V83A, Y144, Q183E, H146Q, V213E, G252V, R346T, G339H, L368I,

G446S, V445P, N460K, F486S, and F490S. XBB and other currently circulating variants (e.g. BA.2.3.20, BA.2.75.2, BM.1.1.1, BR.2, CA.1, BN.1, BQ.1.1, BF.7 and BU.1) have additional specific mutations in the RBD region that favor transmission and provide immuno-evasive properties, in turn increasing transmission. The XBB and BQ.1.1 sub-variants show resistance against mAbs that target RBD and demonstrate increased binding affinities to ACE2 receptors.[36, 42] A comparison of mutations in the spike proteins of the different Omicron sub-lineages is provided in Fig. 3 and Table 1.[36,43-45]

Table 1. Comparison of spike protein mutations of Omicron sub-lineages

WHO Classification	Name	Lineage	Spike mutations of interest	Country of origin (month/year)
VOC	Omicron	BA.1	Δ69-70, T95I, A67V, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, K417N, S373P, S371L, S375F, S477N, T478K, N440K, E484A, G446S, Q493R, Q498R, G496S, N501Y, D614G, Y505H, H655Y, T547K, N764K, N679K, D796Y, P681H, N969K, N856K, L981F, Q954H	Botswana, South Africa, (November, 2021)
		BA.2	G142D, N211I, Δ212, S371F, V213G, S373P, S375F, G339D, T376A, K417N, N440K, D405N, S477N, R408S, T478K, Q498R, N501Y, E484A, Y505H, Q493R, H655Y, N679K, D614G, D796Y, Q954H, P681H, N969K, N764K	South Africa, (November, 2021)
		BA.3	A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S375F, S371F, D405N, S373P, G446S, K417N, S477N, N440K, Q493R, T478K, Q498R, E484A, D614G, N501Y, H655Y, Y505H, D796Y, N679K, P681H, N969K, Q954H	South Africa, (November, 2021)
		BA.4	L452R, F486V, wild type Q493	South Africa, (January, 2022)
		BA.5	L452R, F486V, wild type Q493	South Africa, (February, 2022)

		BA.2.75	R493Q, G446S, D339H, N460K, K147E, W152R, F157L, I210V, G257S	India, (July, 2022)

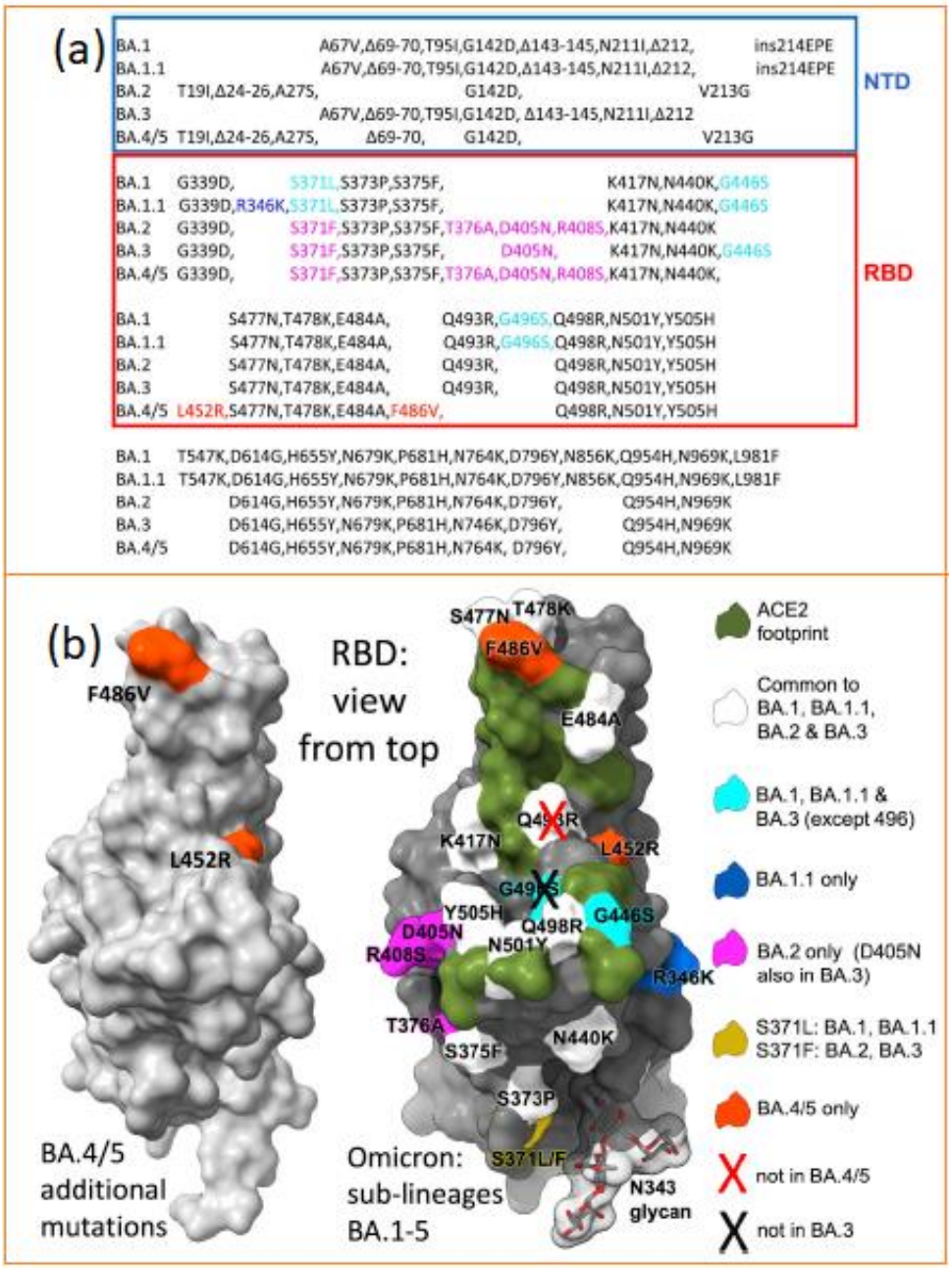


Figure 3. (a) Comparison of spike protein mutations of Omicron sub-lineages, (b) Position of RBD mutations of Omicron sub-lineages (grey surface with the ACE2 footprint in dark green) (reproduced from ref-45).

4. Transmissibility and mortality

The Omicron variant (initially discovered in Southern Africa in November 2021) has a high transmissibility and ability to escape immunity. It quickly became a dominant strain worldwide resulting in a high surge in COVID-19 cases. Interestingly, it caused less severe infections than the parent SARS-CoV-2 virus.[6,7] Omicron and its BA.1 sub-lineage have mutations on the spike protein and RBD region which interfere with their ability to attach to ACE2 receptors.[46] If infected with Omicron, vaccinated individuals will show only mild symptoms whilst unvaccinated people risk developing serious infections and will show a higher mortality rate.[47] The high transmissibility of the BA.2 sub-lineage has been linked to the presence of a unique mutation (C12525T).[48] Despite their increased transmissibility and immuno-evasive ability, the BA.1 and BA.2 sub-lineages, lead to milder infections and lower mortality rates than the parent SARS-CoV-2 virus.[10] However, further emergences of future variants may still remain a continuing threat especially when the virus replicates in the people with immunodeficiency disorders. Also, variants may emerge when the virus spills over to an animal host and re-infects humans. Such evolutionary changes may still contribute to the development of more virulent strains or otherwise in the future.

5. Diagnostics tests

The Omicron (B.1.1.529) lineage has been linked to an increased risk of re-infection in convalescent and vaccinated people compared to other VOCs. At the time of its discovery, Omicron escaped detection in many of the PCR diagnostic tests available. Screening using the non-amplification of S-gene (S-gene drop) was later used to identify Omicron cases.[49] Omicron sub-variants can now be detected using lateral flow (rapid) tests and PCR. A new RT-qPCR test (using the Δ31-33 amino acid deletion in the N-gene) has recently been developed to specifically detect Omicron and its sub-variants (BA.1, BA.2, and BA.3) with the opportunity to differentiate BA.1 from BA.2/BA.3.[50,51]

The Omicron variant presents high mutations in its spike/RBD regions compared to previous SARS-CoV-2 variants. This could lead to false negative results in the PCR assays that are equipped only to detect the S-gene. Fortunately, many current PCR tests detect other genes, including the N-gene, e-gene, and RdRp gene, along with the S-gene. This helps with the detection of Omicron, which otherwise would not have been possible.[52] The Omicron variant also present mutations in regions coding for nucleocapsid proteins. Lateral flow tests

rely on the detection of such proteins and it is not completely evident how this may affect the diagnosis of Omicron cases.[53]

6. Vaccine development

The emergence of Omicron variant and its sub-lineages have led to increased global efforts to develop new (variant-specific) vaccines and urgently deploy such vaccines worldwide.[54-56] The available COVID-19 vaccines show low effectiveness against the Omicron sub-lineages, but, they still remain effective in preventing disease severity, hospitalization, and death.[57-61] The Omicron variant has a substantial ability to evade immunity from prior infection or vaccination. This is associated with an increased risk of breakthrough infection in vaccinated individuals and re-infection in recovered patients.[6,62,63] Studies have shown that the present COVID-19 vaccines provide less immunity to Omicron than to other variants[64] and that the sera from vaccinated individuals have lower neutralizing ability (~40%) against Omicron than the wild-type SARS-CoV-2.[65] However, more data about the effectiveness of the current COVID-19 vaccines are needed to ultimately conclude the levels of protection and whether they can effectively protect against the Omicron variant or not. In such scenario, the recommendation of booster shots of vaccines needs to be promoted so as to increase and improve the protective levels of immunity to counter Omicron and other variants of SARS-CoV-2.[66]

A third (booster) dose of the Pfizer-BioNTech and Moderna vaccines has been reported to potentially increase protective antibody levels and provide protection against Omicron. The Omicron variant RBD binds to the human ACE2 receptors with enhanced affinity[67] and it replicates better (over 70 times more) in the bronchi than in the lung tissue compared with the Delta variant.[68] Its lower replication ability in the lungs leads to less disease severity compared to the Delta variant. The immunity induced from the COVID-19 vaccines, booster doses, and previous SARS-CoV-2 infections may be responsible for the lower hospitalization and lesser mortality observed with Omicron infected cases. Several research efforts are currently underway to develop a pancoronavirus vaccine that may be useful against the multiple variants occurring worldwide.[63] The U.S. National Institute of Allergy and Infectious Diseases (NIAID) and researchers in academia are working on a vaccine to cover all human coronaviruses that come under the Sarbecovirus family.[69,70] A multitope subunit vaccine (UB-612) developed against SARS-CoV-2 have been found to provide long-lasting B cell (viral-neutralizing antibodies) and T cell immunity against Delta and Omicron variants

along with a potent booster effect on memory immunity with increased cross-reactive neutralizing titers.[71]

Despite the concerns of immune escape and breakthrough infections with Omicron VOC and its sublineages, it was noted that the booster doses of vaccines prepared from the original Wuhan SARS-CoV-2 spike protein may still be able to produce adequate quantities of neutralization antibodies against the BA.1, and BA.2.[72] Moreover, neutralizing antibody concentrations were recently analyzed after the booster dose vaccination with BNT162b2 vaccine. The results of this study suggested that similar quantities of both the BA.1, and BA.2 neutralizing antibodies were noticed.[73] Lower concentrations of neutralizing antibodies against the RBD of Omicron variant were demonstrated among people who received 2-doses of BNT162b2-vaccine. Also noted were the reduced binding abilities of the Omicron RBD with the ACE2 receptors in contrast to the previous Delta, Beta, and other previous VOCs.[74] Booster dose vaccination with BNT162b2 COVID-19 vaccine was able to produce significant concentrations of neutralizing antibodies irrespective of the age of the vaccine recipients. Therefore, a booster vaccination dose is recommended for some protection against the Omicron VOC.[75]

7. Anti-viral drugs & Oral drugs, and mAbs

The BA.2 sub-lineage has increased rapidly worldwide since January 2022. In Hong Kong, the exceptionally high transmissibility of the BA.2 sublineage may be due to the unique mutation C12525T.[76] Continual genomic surveillance is highly recomended in monitoring the emergence of epidemiologically important Omicron sub-variants. BA.2 has increased vaccine evasion properties as compared to the other Omicron lineages.[73] The current COVID-19 vaccine boosting regimens may provide sufficient protection against Omicron-induced disease.[72] More recently, antiviral oral drugs such as Molnupiravir and Nirmatrelvir-Ritonavir have shown promising results in treating COVID-19 patients and a high hope against Omicron and other SARS-CoV-2 variants.[77-79] Analysis of the studies with regards to the antibody evasion characteristics of Omicron sublineages have more recently revealed that any of the authorized mAbs therapy could provide adequate protection against all sublineages, except for recently authorized LY-CoV1404 (bebtelovimab).[21]

Variable susceptibility to mAbs was observed with the Omicron sub-lineages (BA.2 and BA.2). Bamlanivimab, Etesevimab, Casirivimab, Cilgavimab, Imdevimab, Tixagevimab and Sotrovimab, Adintrevimab (ADG20), and Regdanvimab were tested for their usefulness in

the treatment of infections against Delta variant, and sub-lineages of SARS-CoV-2, and the Omicron, respectively. The quantities of the neutralizing antibody titers among the patients who received the monoclonal antibody dose showed significant reduction in response to BA.2 (9-fold), and BA.1 (344-fold). However, mAbs were able to significantly inhibit the Delta VOC. The BA.2 was found sensitive to cilgavimab, moderately responsive to Imdevimab and resistant to Adintrevimab and Sotrovimab.[80] Considering that most of the available mAbs target the RBD and because the BA.2 developed 16 mutations in the same region with 12 shared mutations with the BA.1 sub lineage, the efficacy of the mAbs remain highly questionable against both the sub lineages. The activities of remdesivir, molnupiravir, and nirmatrelvir against the Omicron and BA.2 sub lineage were like the Wuhan strain. However, monoclonal antibodies including imdevimab, casirivimab, tixagevimab, cilgavimab, and sotrovimab precursor showed lower neutralizing capacity against the BA.2 sub lineage.[81] Sotrovimab and CR3022 are a amongst the selected group of mAbs that target conserved sites of the SARS-CoV-2 and therefore could still be effective in the management of patients infected with the Omicron VOC.[82]

The mutations in BA.2.75 may facilitate resistance of the viral variant to neutralizing monoclonal antibodies (mAbs).[83] Experimental studies that assessed the activities of neutralizing monoclonal antibodies against different Omicron sub lineages like B.1 (D614G), BA.2, BA.4/5, BA.2.12.1, and BA.2.75 have demonstrated that bebtelovimab and others showed high neutralizing potential against BA.2.75 on par with other sub lineages. However, BA.2.75 showed decreased susceptibility to vaccine induced neutralizing antibodies unlike the BA.2, BA.4, and BA.5 Omicron sub lineages.[84-86] This could possibly suggest the fact that BA.2.75 could be equipped with other characteristics in addition to vaccine escape abilities that potentially favour infection.[87]

It was noted that BA.2.75 showed more than 10-fold reduced susceptibility to Cilgavimab (mAb) when compared with its predecessor BA.1 (D614G) and other sublineages like BA.5. However, the activities of Cilgavimab on BA.2.75 was better when compared to BA.2. The study also observed that Casivirimab, imdevimab, bamlanivimab, and etesevimab showed reduced neutralizing activity against BA.2.75.[88] Neutralizing antibodies demonstrated after BA.1 and BA.2 infections revealed that these antibodies showed cross reactivity against other Omicron sub lineages. This was evident by the occurrence of high concentrations of neutralizing antibodies against BA.2.75 in patients infected with BA.1 and BA.2.

8. Strategies for infection control

As per the preliminary data, the RBD mutations impact the neutralizing activity of mAbs and vaccine immune sera.[89,90] Further, multiple mutations in RBD region (especially E484K mutation) also lead to breakthrough infection.[91] Although COVID-19 vaccines are rapidly developed and in the beginning it was thought that the end of the pandemic however due to the emergence of several virus variants and their lineages, decline of vaccine efficacy and massive breakthrough infections among vaccinated populations emphasized the need for the development of next-generation and mutation-proof vaccines.[92-96]

As the efficacy of current COVID-19 vaccines on the Omicron variant and vaccination strategies are debatable, other preventive measures including adequate social distancing, wearing of well-fitting face masks, regular hand washing, use of recommended sanitary and hygienic practices and other public health measures still remain the mainstay to counter the spread of COVID-19.[60,61,97] Only 64% of the world population is fully vaccinated as on 05 July 2022, apart from Africa.[98] Proportionately, a lesser population in African continent is fully vaccinated, which may explain why the variants have emerged from Africa. Vaccine inequity and vaccine hesitancy may be possible reasons for the emergence of multiple variants of SARS-CoV-2.[1] So, the vaccination programs must be strictly implemented and be enhanced towards obtaining herd immunity at earliest feasible time. Any failure to timely tackle infections caused by the current Omicron variant and sub-variants will facilitate the continued emergence of newer variants of SARS-CoV-2 and would pose situations of a never ending COVID-19 pandemic. The implementation of adequate prevention and control measures and designing newer vaccine strategies are the priority requirements to counter SARS-CoV-2 infections caused by Omicron, other variants and variants of future. The continuous vigilance, reporting and comparative analyses of the genomic sequences of the various Omicron sub-lineages are also crucial in understanding how this pathogen evolves, which would help in designing effective prevention and control strategies to limit the spread of the ongoing COVID-19 pandemic.[99,100]

9. Conclusion

A huge surge in infections caused by the Omicron variant has been noted worldwide since late 2021. Cases have increased substantially again recently due to the emergence of several Omicron sub-lineages presenting extensive mutations in their genomes that provide the virus with immuno-evasive capabilities. Despite their high transmissibility and immune evasion capabilities, these sub-lineages are not causing severe infections. However, there is still an

opportunity for severe variants/sub-lineages to further emerge quickly. Therefore, every effort should be focussed on speeding up testing, improving genome sequencing capacity and continuously monitoring evolving variants/ sub-lineages to assess how specific mutations may influence disease severity and clinical outcomes. This genomic surveillance can also assist in the development of improved vaccines and mAbs that may protect against current and future emergent variants/sub-lineages. The existing COVID-19 vaccines are likely to require modifications to be able to fully protect against future variants. The next generation of vaccines should ideally include a pancoronavirus vaccine, variant-specific vaccines, multivariant (multiple antigen-based) and mutation-proof vaccines. Further studies should also focus on discovering effective mAbs and antiviral drugs against any future emerging SARS-CoV-2 variants.

Keywords: Anti-viral drugs; Omicron sub-lineages; Strategies for infection control; Transmissibility; Vaccine development.

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TOC

The course of SARS-CoV-2 pandemic has been extremely complex and highly intriguing. Given the persistence of the virus and its continued influence on people's health throughout the world despite the availability of vaccines augment further understanding of the evolution of virus. The viral variants have been continuously emerging and the currently circulation Omicron variant has been re-emerging into sublineages. The BA.1, BA.2, BA.3, BA.4, BA.5, BA.2.75, and the XBB lineages have been replacing the preceeding ones and it is not clear when the virus slows down mutating and adapts to settle in the environment like the Influenza virus. Moreover, restricting viral spread has become difficult due to mutations in the spike protein that are favoring vaccine and monoclonal antibody resistance and causing breakthrough infections. Therefore, strategies to control the viral spread could still be essential in prevention of infections and the emergence of newer variants.