



Review

Omicron variant (B.1.1.529) and its sublineages: What do we know so far amid the emergence of recombinant variants of SARS-CoV-2?

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ABSTRACT

Since the start of the COVID-19 pandemic, numerous variants of SARS-CoV-2 have been reported worldwide. The advent of variants of concern (VOCs) raises severe concerns amid the serious containment efforts against COVID-19 that include physical measures, pharmacological repurposing, immunization, and genomic/community surveillance. Omicron variant (B.1.1.529) has been identified as a highly modified, contagious, and crucial variant among the five VOCs of SARS-CoV-2. The increased affinity of the spike protein (S-protein), and host receptor, angiotensin converting enzyme-2 (ACE-2), due to a higher number of mutations in the receptor-binding domain (RBD) of the S-protein has been proposed as the primary reason for the decreased efficacy of majorly available vaccines against the Omicron variant and the increased transmissible nature of the Omicron variant. Because of its significant competitive advantage, the Omicron variant and its sublineages swiftly surpassed other variants to become the dominant circulating lineages in a number of nations. The Omicron variant has been identified as a prevalent strain in the United Kingdom and South Africa. Furthermore, the emergence of recombinant variants through the conjunction of the Omicron variant with other variants or by the mixing of the Omicron variant's sublineages/subvariants poses a major threat to humanity. This raises various issues and hazards regarding the Omicron variant and its sublineages, such as an Omicron variant breakout in susceptible populations among fully vaccinated persons. As a result, understanding the features and genetic implications of this variant is crucial. Hence, we explained in depth the evolution and features of the Omicron variant and analyzed the repercussions of spike mutations on infectiousness, dissemination ability, viral entry mechanism, and immune evasion. We also presented a viewpoint on feasible strategies for precluding and counteracting any future catastrophic emergence and spread of the omicron variant and its sublineages that could result in a detrimental wave of COVID-19 cases.

1. Introduction

Since the onset of the COVID-19 pandemic, many SARS-CoV-2 variants have been discovered and documented, and they have been linked to a considerable rise in the mortality rate in numerous countries [1–5].

Recombination, selection pressure, and point mutations all contributed to the acquisition of mutations in the SARS-CoV-2, resulting in the formation of variants [1,2,6,7]. Furthermore, the emergence and circulation of variants have been linked to epidemiological phenomena such as the bottleneck effect, founder effect, and antigenic drift, all of which can

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aid in the acquisition of mutations [8]. A plethora of recent investigations have found that the recurrent occurrence of the mutations in the parental strain of SARS-CoV-2 might affect the neutralizing ability of vaccine-elicited antibodies and monoclonal antibodies (mAbs), resulting in a mild-to-significant reduction in efficacy [2,9,10]. Furthermore, recurrent mutations such as deletions and substitution in the Spike protein (S-protein) of SARS-CoV-2 alter viral transmission, treatment effectiveness, and diagnostic procedures, indicating that the mutations confer a fitness advantage for enhanced virus transmission and increased severity [11].

SARS-CoV-2 variants are classified into four broad classes by the US Department of Health and Human Services, namely variants of interest (VOIs), variants of concern (VOCs), variants of high consequence (VOHCs) and variants under monitoring (VUMs) [12,13]. Till now, World Health Organization (WHO) announced five VOCs, including Alpha, Beta, Gamma, Delta, and Omicron variants. Among the entire VOCs, the Omicron variant has grappled the world swiftly and competed

with other VOCs (Fig. 1). In comparison to other VOCs like Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2), the Omicron variant (B.1.1.529) has more than 30 mutations in the S-protein, as per latest information [2,14]. Substantial alterations in the receptor-binding domain (RBD) and N-terminal domain (NTD) of S-protein are cause for worry, as they have been associated with increased transmissibility and resistance to neutralizing antibodies (nAbs) [15].

As the world is fatigued from the pandemic and still dealing with COVID-19's broad detrimental sociological, psychological, and economic repercussions [16,17], the circulation of the Omicron variant and its sublineages/subvariants possess a serious threat to the humankind [18–20]. Furthermore, recombination events between VOCs like the Delta and Omicron variants raise the likelihood of an improved establishment of a new VOC that integrates favorable mutations from different lineages. Such instances might constitute an evolutionary leap for SARS-CoV-2, boosting the VOC's fitness to the point that this possible variant quickly overcomes current VOCs and causes a new wave over the

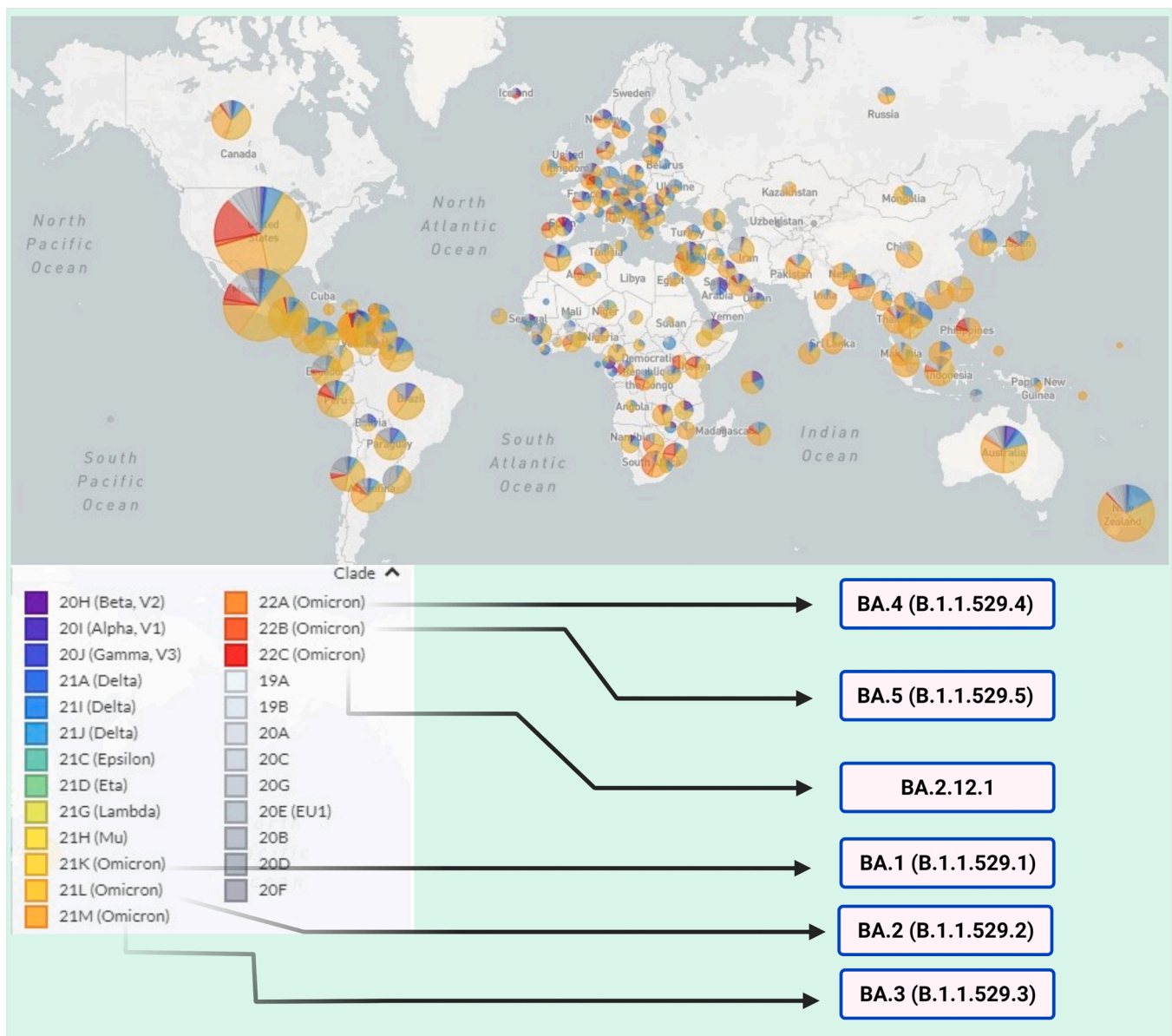


Fig. 1. The figure represents the global dominance and geographical distribution of the Omicron variant and its sublineages as compared to the other VOCs. The prevalence of the Omicron variant and subvariants/sublineages and their circulation among the countries has been linked to the emergence of novel recombinant variants.

Source: <https://nextstrain.org/ncov/gisaid/global?m=div>.

world, which has been observed during the emergence of the Omicron variant [21]. Therefore, this article represents various aspects of the Omicron variant and its sublineages in order to better understand their implications and concerns in the context of multiple countries' considerable efforts to reduce the devastating effects of COVID-19. In addition, several preventive measures have been discussed in order to contain the plausible consequences associated with the Omicron variant and its emerging sublineages.

2. Sublineages of the Omicron variant

Recent computational and sequencing analyses have separated the Omicron variant (B.1.1.529.1 or BA.1) into several sublineages, BA.1.1 (B.1.1.529.1.1), BA.2 (B.1.1.529.2), and BA.3 (B.1.1.529.3), BA.4 (B.1.1.529.4) and BA.5 (B.1.1.529.5) which are the first five branches descending from an original Omicron ancestor [22,23]. The three sub-lineages, BA.1.1, BA.2, and BA.3 of the Omicron variant, are closely related to a common ancestor [24,25]. BA.1 is the first dominating lineage of the Omicron variant. BA.1 has been considered responsible for most of the cases reported amid the emergence of other variants and subvariants [26] (Fig. 1). Genomic sequencing and mutational analysis have shown that BA.1.1, BA.2, and BA.3 vary in the number of mutations from 40 to 34 mutations [24–28]. The BA.1.1 is a sub-lineage with a unique substitution, i.e., R346K in the S-protein [29] (Fig. 2). Moreover, it is important to consider that some scientists have uncovered that the BA.2 sublineage is different from the BA.1.1 sublineage [30]. In several nations, the BA.1 have been superseded by the BA.2 sublineage [31,32]. BA.2 is distinguished from BA.1 by around eight changes in its S-protein [19]. In comparison to BA.1, BA.2 has three new mutations, including T376A, D405N, and R408S, but lacks the G446S and G496S seen in BA.1 [32] (Fig. 2). Furthermore, BA.1 and BA.2 have distinct variances in their susceptibility to therapeutic mAbs [31].

In the evolutionary descent of Omicron lineages, the BA.1.1 sublineage developed first, followed by the BA.2 and BA.3 lineages [28]. The Omicron BA.2 lineage, which produced the winter spike of coronavirus disease 2019 (COVID-19) instances in January 2022, appears to be more infectious than the Omicron BA.1 lineage. When compared to the original Omicron strain, the study discovered that BA.2 is substantially more immunologically resistant and has stronger cell fusion than BA.1 [28,33]. The amino acid sequence of the BA.2 lineage's spike protein differs greatly from that of the BA.1 lineage, signaling that it may give greater antibody immunological resistance. BA.2 was found to be comparable to BA.1 in terms of resistance to the vaccination-induced antibodies, although BA.1 has demonstrated a high level of resistance to antibodies induced by mRNA vaccines as well as the AstraZeneca vaccine [34]. In contrast, the recent findings suggest Omicron sub-lineages such as BA.1.1 and BA.2 can be neutralized by the sera obtained from the patients infected with the Omicron strain. Interestingly, researchers observed that the virological properties of the BA.2 lineage were more infectious than the BA.1 lineage when analyzing the replication process in human nasal epithelial cells [24,35,36].

Recent research in South Africa discovered evidence of the existence of two additional sublineages, named BA.4 and BA.5. It is probable that the formation of these sublineages in South Africa is related to the region's much lower immunization rate when compared to other nations [37]. BA.2.12.1 is an additional developing sublineage. These developing sublineages are spreading faster than other circulating strains, most notably BA.2, which prompted a rise in infections at the start of the year (Fig. 3). However, the most recent Omicron subvariants appear to be causing fewer fatalities and hospitalizations than their older counterparts, indicating that rising population immunity is dampening the immediate repercussions of COVID-19 outbreaks [38]. In contrast to these assumptions, Yao et al. suggested that newly discovered sub-variants of the Omicron lineage, including BA.2.12.1, BA.4, and BA.5,

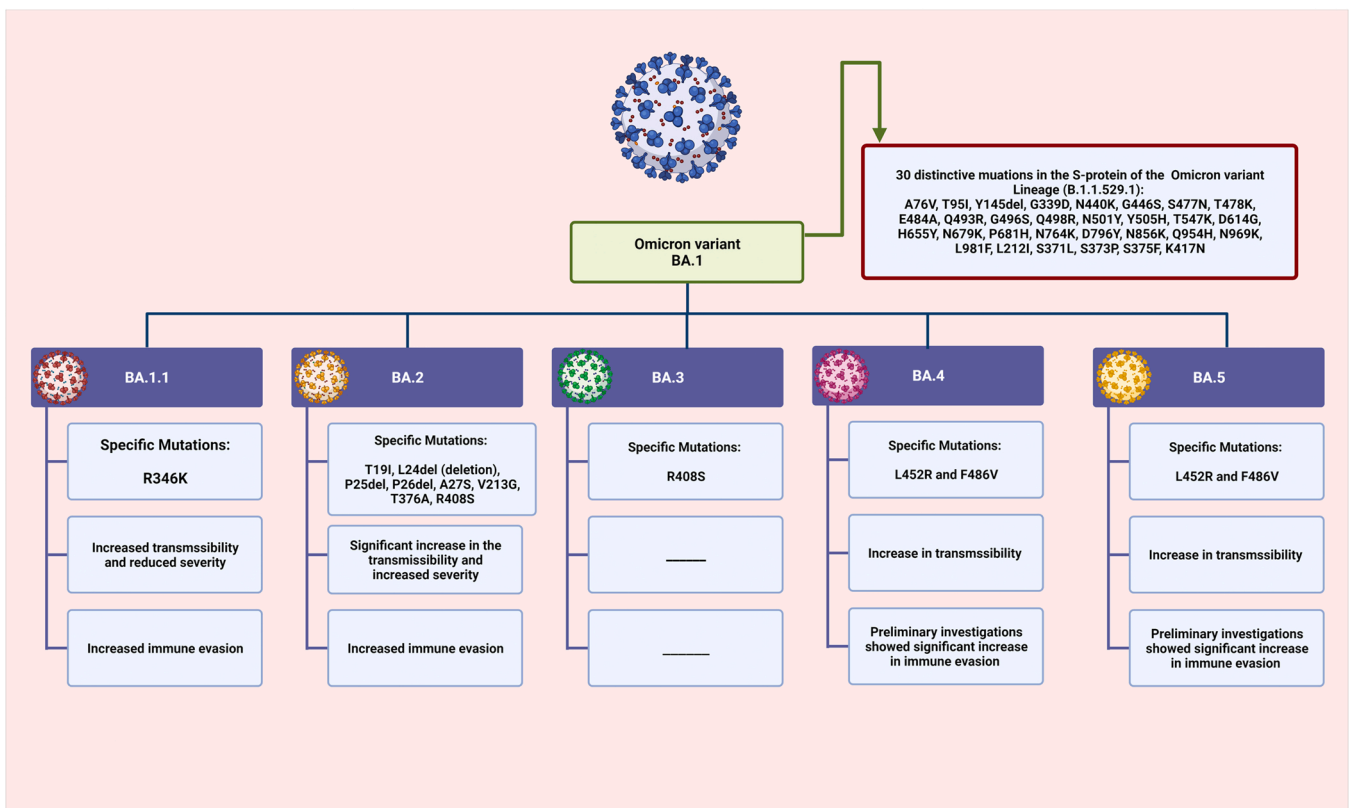


Fig. 2. The figure represents the major differences among the sublineages of the Omicron variant. The unique mutations in the sublineages can be associated with the varying levels of transmissibility and severity of the disease. It is important to notice that the recently emerged BA.4 and BA.5 sublineages can lead to another wave of COVID-19 cases due to increased transmissibility and escape to the immune response.

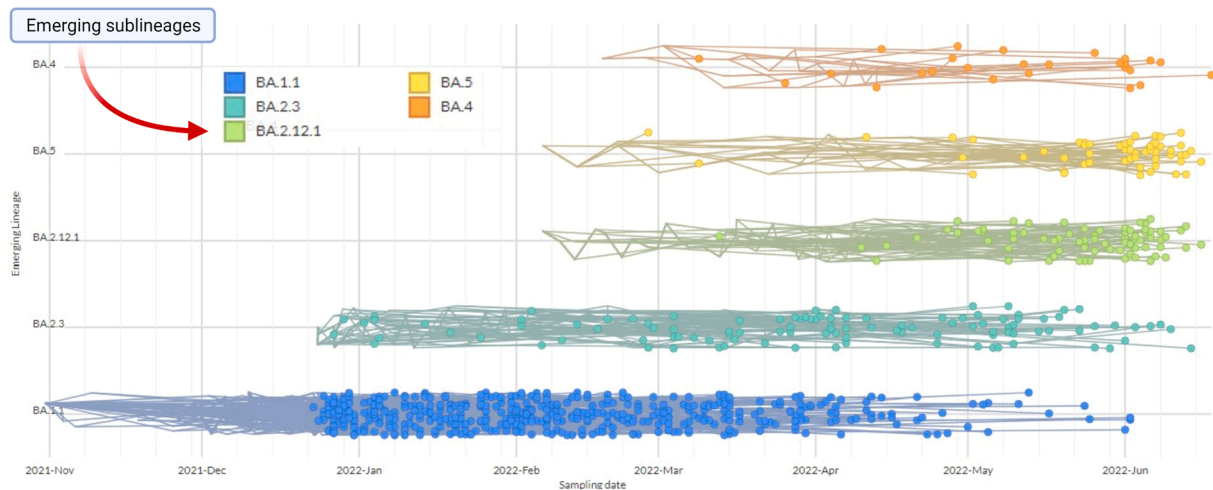


Fig. 3. The figure shows the emerging lineages of the SARS-CoV-2's Omicron variant, which are distinct due to the presence of specific mutations. The emergence of these subvariants or sublineages is based on the genome sampled from November 2021 to June 2022.

Source: https://nextstrain.org/ncov/gisaid/global/6m?c=emerging_lineage&l=scatter.

might resurge the COVID-19 infections [39], which can be associated with increased number of genomic sequences reported lately (Fig. 3).

According to recent research, the newly discovered sublineages have similar RBD sequences to BA.2, but with the addition of L452 and F486 substitutions, notably BA.2.12.1 (L452Q), BA.2.13 (L452M), BA.4, and BA.5 (L452R+F486V), and all have a larger transmission advantage over BA.2. The receptor binding and immune evasion abilities of the novel variations warrant rapid research [32]. Furthermore, new evidence reveals that the Omicron is constantly developing in response to immunological pressure, which explains the occurrence of R346K (BA.1.1), L452 substitutions, and F486V mutations, all of which facilitated better immune evasion. Unlike when Omicron originally developed, Omicron sublineages now have the potential to target humoral immunity caused by Omicron, such as postvaccination Omicron infection. The Omicron breakthrough infections mostly recall wild type (WT)-induced memory B cells [40,41], narrowing the range of antibodies evoked and perhaps facilitating the development of subsequent mutants. These occurrences provide a significant challenge to the herd immunity that has been acquired by WT-based vaccination and BA.1/BA.2 infection. Similarly, it has been indicated that an Omicron BA.1-based vaccination may not be the best antigen for generating broad-spectrum immunity against new Omicron sublineages [32].

Additionally, the upcoming evidences indicate that BA.4 and BA.5 have widely divergent pathogenic features than BA.1 and BA.2, especially when compared to BA.1. Furthermore, the prevalence of BA.5 subvariant has been noticed in Portugal during May 2022, as seen by an increase in COVID-19 instances. Portuguese National Institute of Health determined that BA.5 was responsible for most of the COVID-19 cases during May 2022. BA.5 has a considerably larger expected daily growth benefit over BA.2. If the present pace of expansion persists, BA.5 might become the dominant type in Portugal [42].

The enhanced proliferation and dominance of BA.4 and BA.5 have been linked to their ability to circumvent immunological defense acquired by the previous infection and/or vaccination, particularly if the humoral immune response has diminished over time. In vitro tests of sera from unvaccinated people who have previously been infected with BA.1 show that both BA.4 and BA.5 are capable of evading the protection provided by BA.1 [42,43]. It is critical to remember that unvaccinated persons are considerably more likely to contract the BA.4 or BA.5 sublineage. Alarming, there is a scarcity of information on the severity of illness induced by BA.4 or BA.5 sublineages [42].

3. Possible reasons behind the emergence of the Omicron variant

Several hypotheses have been postulated to explain the evolution of the highly mutated Omicron variant. According to the results of the phylogenetic study, the Omicron variant did not originate from any other VOCs, including the Delta variant (Fig. 4) [44]. Previous research has shown that the Delta and Omicron variants contain a large number of alterations that have been previously observed in other VOCs of SARS-CoV-2. The phylogenetic study, on the other hand, reveals that the VOCs developed independently through convergent evolution. Recently, Bansal and Kumar employed mutational analysis and whole genome-based phylogeny to elucidate how the SARS CoV-2 evolved and how the omicron variant emerged. It has been discovered that the Delta and Omicron do not have a common ancestor and have evolved into separate phylogroups. Omicron, on the other hand, has non-synonymous mutations as its major source of modifications and has a shared origin with lambda variant (VOI) [45].

According to Sonnleitner et al., the genesis of immune escape variants, including Delta and Omicron, is still a subject of debate since numerous ideas have been postulated such as zoonotic origin, selection pressure during antiviral medication therapy, monoclonal antibodies, or convalescent plasma. Few studies have also highlighted the relevance of the unique intra-host environment seen in immunocompromised patients as a possible explanation for the development of resistant mutants [46–48]. In this context, the following discussion highlights how the Omicron variant managed to amass all of the current alterations without being discovered.

Among the various hypotheses, a group of scientists believes that the Omicron variant has evolved within a subset of the population, and then the mutated virus introduces into the larger population. Secondly, long-term retention of SARS-CoV-2 in immunocompromised people has been considered as another theory behind the emergence of the Omicron variant. Thirdly, it has been believed that the Omicron might have evolved in a potential animal (possibly the mouse) and then jumped back to the human population [44,49,50] (Fig. 5). Amid the conflicts among the scientific theories, it is still unclear how the Omicron variant has accumulated a large number of genetic alterations in such a short period of time [15]. It should be noted that all the hypotheses are at a very early stage to justify the accumulation of more than 50 mutations in one variant. Additionally, the emergence and evolution of subvariants/sublineages are yet to be resolved.

The first potential reason behind the emergence of the Omicron

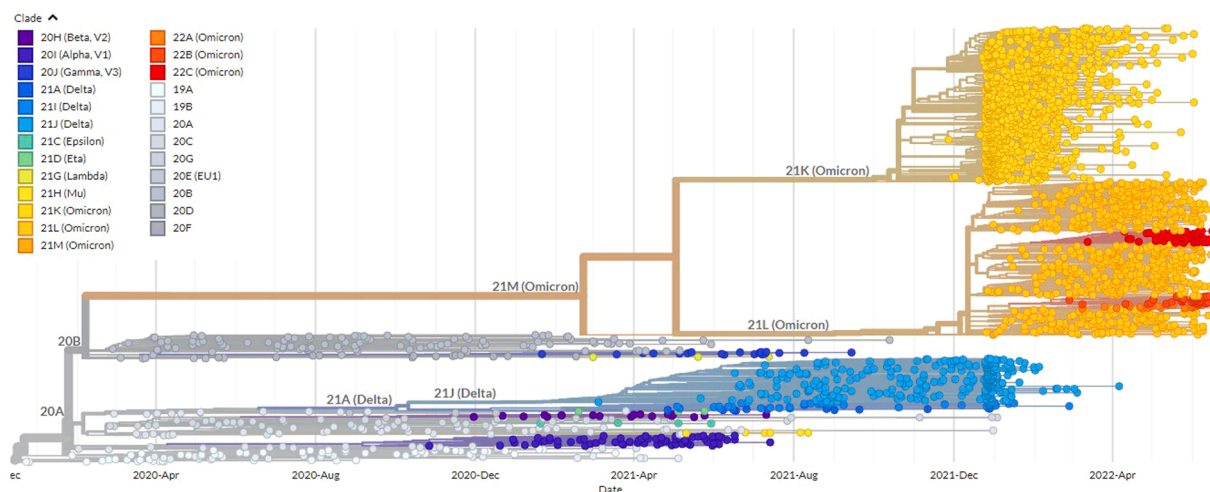


Fig. 4. Phylogenetic analysis of the Omicron variant. It shows the distinct evolution of the BA.1 lineage and other sublineages from other VOCs. Source: <https://nextstrain.org/ncov/gisaid/global?m=div>

variant is that the higher mutation rates have occurred within a subset of the population, and then the mutated virus introduces into the larger population. Moreover, the progenitor of the Omicron variant has been circulating among humans for a long period. However, it is possible that its appearance remained unreported in one or more countries that have reduced provisions of genomic surveillance to monitor the emergence of novel variants of SARS-CoV-2 [14], [15].

Secondly, long-term retention and transformation of the virus in immunocompromised patients can be another hypothesis [15]. The evolution of viral agents in an immunocompromised patient has been considered as an important reason which can justify the accumulation of mutations and explain the evolution of the sub-variants. One probable explanation is a long-term infection, which can result in a lot of diversity in a single viral strain inside a single person. In a single person, this might lead to compartmentalization. As a result, various versions may appear in different places of the body at the same time. The effective multiplication over a considerable length of duration in an immunocompromised host might result in the generation of the Omicron's subvariants. In another interesting finding it has been found that the SARS-CoV-2 reproduced over more than six months in a young South African woman with HIV infection. The long stay of the Omicron variant leads to the accumulation of a large number of mutations which can be the plausible reason for the emergence of the Omicron variant [51].

Thirdly, the Omicron strain might have developed in animals infected with human-adapted SARS-CoV-2, then transmitted back to humans [14]. Epizootic infection in animals from humans, where the virus mutated under different immune pressures and then reintroduced into humans (Fig. 5), can be another potential reason for the accumulation of the mutations [15]. In corroboration to this hypothesis, Wei et al. raised doubts about whether the virus's proximal origin was in humans or another animal host due to a higher number of mutations in the Omicron variant. They discovered 45 genetic mutations in Omicron since it diverged from the B.1.1 lineage. The Omicron S-protein sequence was shown to be subjected to more positive selection than any other SARS-CoV-2 variant known to develop consistently in human hosts, implying the likelihood of host-jumping [49]. The molecular diversity of mutations gained by the progenitor of Omicron was markedly diverse from variants that emerged in the human body, but somehow it approximated that of viral evolution in the mouse. Additionally, Omicron S-protein mutations were shown to coincide considerably with SARS-CoV-2 alterations known to facilitate adaptations to mouse hosts, specifically through increased S-protein binding affinity for the receptors of the mouse cells. Overall, these findings imply that Omicron's progenitor crossed from humans to mice, rapidly gained changes that

made it easier to infect that host and then leaped again into humans, suggesting an inter-species evolutionary pathway for the Omicron breakout [49] (Fig. 5). The Omicron variant acquired variations in a mouse host for more than a year before migrating to humans in late 2021, according to research. The progenitor of the Omicron variant evolved in the mouse cells host by gaining amino acid changes in the S-protein that improved its affinity for mouse ACE2 receptors while developing in mice [49,52]. In addition, mutations linked to immune evasion accumulated, which might play key roles in the virus's fast proliferation in people [49].

This is surprising since it appears that zoonotic pathogens, like SARS-CoV-2, adapt to their new host organism in a streamlined way, acquiring major alterations that promote viral replication and dissemination first and then modifications linked with more subtle benefits afterward. Consequently, some experts speculated that the Omicron variant might have originated in the animals and then spread to humans [49]. Coronaviruses (CoVs) are known for their capacity to traverse species boundaries, and new research suggests that SARS-CoV-2 may be found in a variety of species, including home pets, commercial animals along with wildlife [53], which strongly suggests the animal spillover of the SARS-CoV-2 in a potential host and accumulation of a large number of mutations in the animal host and jump back into the human population (Fig. 5).

Additionally, it has been claimed that SARS-CoV-2 variants have a wider host range and hence have a greater ability to establish new animal hosts [54,55]. The fact that a large fraction of the modifications in the Omicron variant is identical to human-specific alterations discovered in other VOCs, as well as early evidence for high multiplication and dissemination fitness, indicate the emergence of the Omicron variant in humans. However, none of these theories can be ruled out completely at this time, and more study is needed to determine the genesis of the highly mutated Omicron variant [15,44]. Moreover, a different set of circumstances and source of consideration is that different SARS-CoV-2 variants may recombine to integrate. The Delta variant's increased infectiousness and poor response to neutralization [50], with the Alpha variants' higher resistance to immune response induced by interferons (IFNs) [56]. This can lead to the highly evolved variants of SARS-CoV-2 with improved fitness and increased immune escape potentialities.

4. Mutational changes and their impacts

It is interesting that scientists have uncovered the multiple benefits of the large number of mutations acquired by the Omicron variant or the other lineage of SARS-CoV-2. The evolutionary processes that yielded

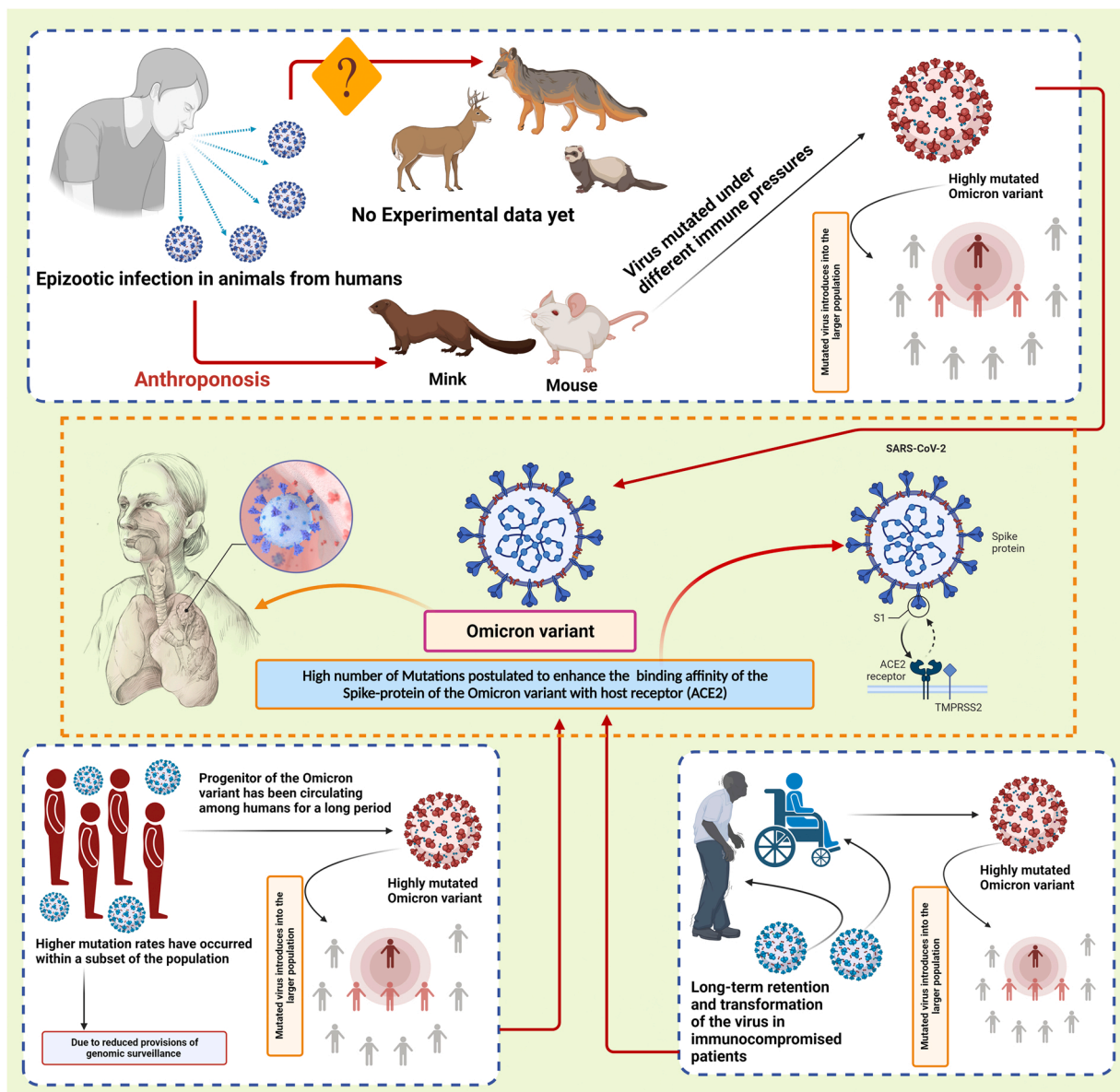


Fig. 5. The figure shows all the possible theories behind the emergence of the Omicron variant.

the Omicron variant and other sublineages can lead to various substantial changes in the virus's characteristics, such as immune escape from the vaccine-generated nAbs [57–61], increased binding potentials of the S-protein to the ACE2 receptor [58,62–65], effective proteolytic priming with TMPRSS2, that significantly improves cell surface entrance [65], greater resistance to endosomal restriction factors including IFITM proteins, which allows for a more effective cellular invasion via the endocytic pathway [66]. Furthermore, the changes can enhance the tendency of Spike protomers to shift to the up configuration for ACE2 interaction and improve the stability of the down configuration to avoid nAbs interaction [62,67,68]. However, despite all the consequences associated with mutational changes, it is interesting to note that this high number of alterations in the Omicron variant did not lead to a significant increase in the severity of the disease [69], which might be due to vaccination given to the mass population worldwide.

More than 22,000 viral amino acid mutations and over 13,000 insertions/deletions have been discovered across the viral genome since the start of the COVID-19 pandemic, with the potential to increase viral transmission, worsen the disease, reduce the efficacy of therapies or vaccines, and/or cause diagnostic detection failures [15,28,70]. The

bulk of changes (73%) was in the ORF1ab, with the Spike and Nucleocapsid contributing 13% and 4%, respectively [28,35,70]. The Omicron variant's genome exhibits several mutations, notably in the spike protein-encoding gene. According to CDC, the S-protein of the Omicron variant has more than 30 amino acid substitutions, including three deletions and one insertion [71]. Despite the ongoing implications of the COVID-19 pandemic, the repeated accumulation of a significant number of mutations in the S-protein of the Omicron variety remains a serious worry. Hence, the following section looks deeper into the mutational profile of the Omicron variant and its impact on the variant's characteristics.

Recently Kannan et al. used high-quality and complete sequences of the Omicron variant from the GISAID repository. To calculate the prevalence of mutations, the sequences obtained from GISAID were processed by using the NextClade CLI and/or an in-house Python script. The Omicron variant (B.1.1.529.1) has 30 distinctive mutations (A76V, T95I, Y145del, G339D, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F, L212I, S371L, S373P, S375F, K417N), defined as mutations with more than fifty percent

prevalence [36,71–73] (Fig. 6). Surprisingly, several Omicron VOC mutations in SARS-CoV-2 are exceedingly rare and have never been identified in other variants [28,36,73–75] (Table 1).

Furthermore, it is important to note that out of these 30 signature mutations, 23 mutations, including A76V, Y145del, G339D, N440K, G446S, E484A, Q493R, G496S, Q498R, Y505H, T547K, H655Y, N679K, N764K, D796Y, N856K, Q954H, N969K, L981F, L212I, S371L, S373P, S375F are unique mutations in the Omicron variant (Fig. 6). These mutations have not been documented in any earlier variants. In addition, nine more mutations were found in genes with above 85% prevalence in Omicron genome sequences [22,72]. According to CDC, the key amino acid substitutions in RBD (receptor binding domain) of the S-protein are G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H [71], these mutations may be associated with the enhanced affinity of S-protein to the ACE2 (Angiotensin Converting Enzyme-2) receptor which might lead to the increased transmissibility of the Omicron variant [76].

The binding of the ACE2 receptor to the S-protein of SARS-CoV-2 is the essential event for gaining entry into the host cell [77]. Following

the interaction of S-protein with ACE2, the S-protein gets cleaved by the human transmembrane protease serine 2 (TMPRSS2). TMPRSS2 cleaves the S-protein into its subunits S1 and S2. This leads to the exposure of the RBD on the S1 subunit of the S-protein [78–80]. On the other hand, the S2 domain facilitates the fusion of viral and cellular membranes by undergoing conformational changes [80,81]. It is interesting to note that the electron microscopic studies have found that the binding affinity of SARS-CoV-2 S-protein to ACE2 is approximately 10–20 times greater than that of S protein of other SARS-CoVs [80,82]. To enter host cells, the S-protein of SARS-CoV-2 must be cleaved at the S1-S2 and S2 sites. This cleavage is carried out by furin²⁴, type II transmembrane serine protease (TMPRSS2), or cathepsin L [83,84]. There are two different SARS-CoV-2 entrance routes that are mediated by TMPRSS2 and cathepsin L breakage at the S2 site. In contrast to cathepsin L in the endosome, which facilitates the endosomal entry route, TMPRSS2 facilitates the plasma membrane pathway of the entrance since it is present on the cell membrane [84,85]. Six distinct changes, including N764K, D796Y, N856K, Q954H, N969K, and L981F in the subunit 2 (S2) [Table 1] of the Omicron variant’s S-protein have been associated with the change in the viral entry into the host cell and the transmissibility

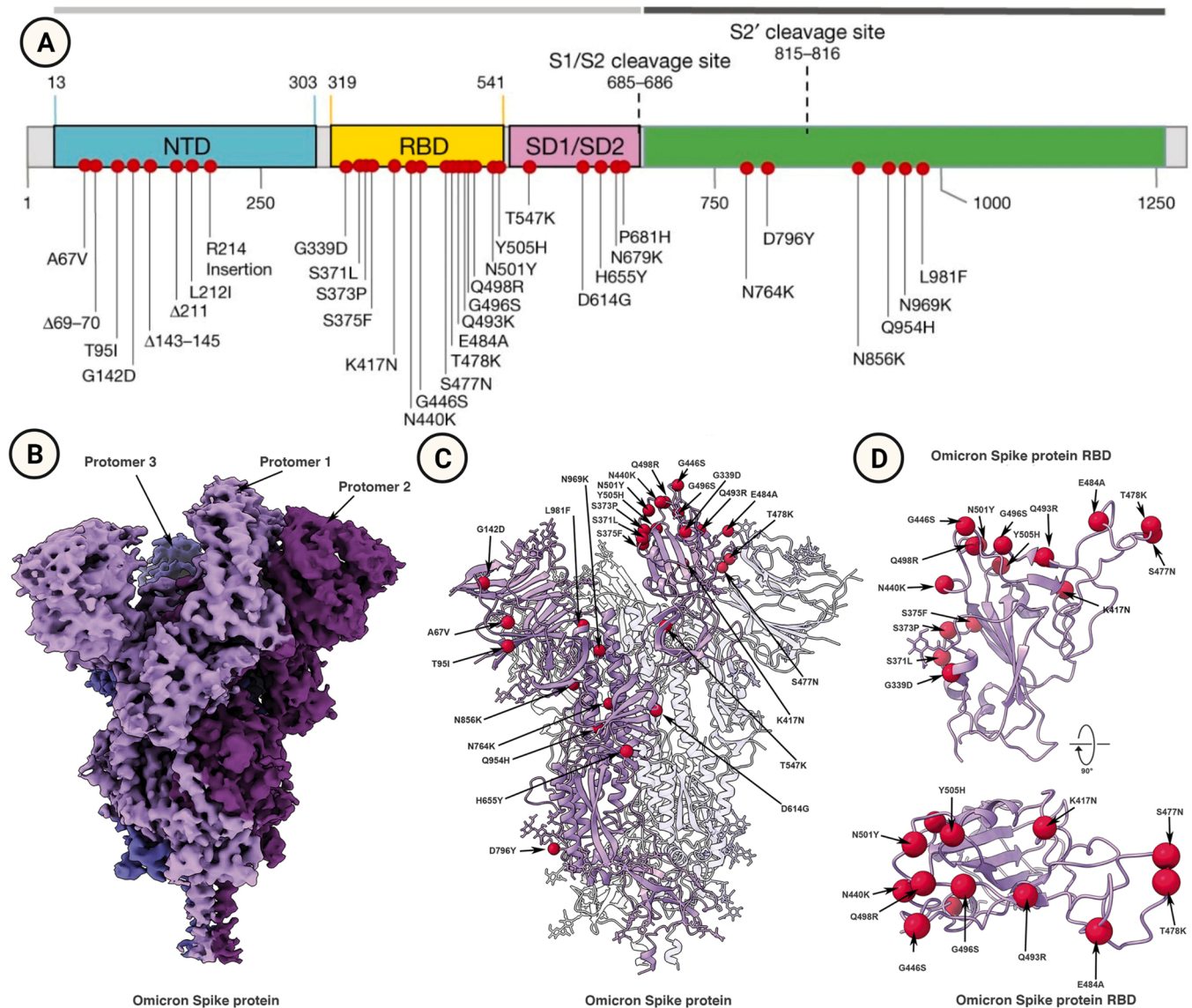


Fig. 6. The representation of mutations in the RBD of Omicron variant’s spike protein (A) showing the mutations in the Spike protein, especially in the RBD of the S-protein [Adapted from Viana et al. [259]]. (B) Cryo-EM map of the Omicron variant’s spike protein (C) Cryo-EM structure of Omicron spike protein indicating the key mutations (D) Two orientations of the highly mutated RBD (receptor binding domain) of the S-protein [Adapted from Mannar et al. [63]].

Table 1

Depicting the total number of the mutations in the S-protein has been considered an important factor in increasing transmissibility and infectiousness. It is important to consider some of these features have been documented on the basis of docking and preliminary studies. The exact concrete information is yet to be produced.

Site of the Mutations	Name of the Mutations	Mutations shared with other variants	Impact of the mutation on transmissibility and infection rate	Additional characteristics	Ref.	
Subunit 1 (S1) of the Spike protein	RBD (Receptor Binding Domain)	G339D	-	Increased transmission and severity	Increase in the binding affinity of S-protein with ACE2 receptor	[20,185]
		S371L	-	Increase in transmissibility	Increased resistance to the antibodies	[147,186]
		S373P	-	Increase in the infection rate	Increased RBD binding with ACE2	[20]
		S375F	-	Increase in transmissibility and infection rate	Has been associated with immune escape	[21,185,186]
		N440K	-	Increase in the infection	Increased RBD binding with ACE2	[186]
		G446	-	Increase in the infection	-	[41]
		S477N	-	Increase the binding affinity of S-protein with ACE2 receptor	S477N mutation found to increase the resistance to the neutralization by human convalescent plasma (CP), but susceptible to vaccine-induced sera.	[41,46]
		T478K	Delta	Increase in the infectiousness capacity	Increase in resistance to the convalescent sera.	[20,46]
		E484A	-	Enhanced transmissibility	-	[20]
		Q493R	-	Increase in infection rate	Contribute to immune escape	[20,41]
	G496S	-	Increase in infection rate	Reduces the protein stability	[20]	
	Q498R	-	Increase in infection rate	Reduces the protein stability	[20]	
	N501Y	Alpha, Beta and Gamma	Increased infectiousness	Enhanced binding affinity to ACE2 and increased immune invasion	[185]	
	Y505H	-	Increase in the infectiousness	-	[187]	
	NTD (N-Terminal Domain)	A67V	-	-	-	-
		Δ 69–70	Alpha	-	Leads to S gene target failure (SGTF); Decreases neutralization reactions mediated by the anticipated antibody.	[188,189]
		T95I	Delta	Increased transmissibility and viral binding affinity	Associated with immune escape	[188]
		G142D	Delta	-	-	-
		Δ 143–145	-	Increased transmissibility and viral binding affinity	Associated with immune escape	[188]
		Δ 211	-	-	-	-
Ins214EPE		-	-	-	-	
T547K		-	Not confirmed	Stabilize the RBD of the S-protein	[190]	
D614G		Alpha, Beta, Gamma, and Delta	Increase in infectiousness and transmissibility	Lower Ct values were observed in G614 infections indicating higher viral load	[93,185,189–191]	
H655Y		Gamma	Enhanced transmissibility and infectivity	Conferring resistance to monoclonal antibodies.	[189,192]	
Subunit 2 (S2) of the S- protein	N679K	-	Enhanced transmissibility and infectivity	-	[185,189]	
	P681H	Alpha	Enhanced transmissibility and infectivity	-	[185,189]	
	N764K	-	The immunogenic relevance of such locations yet to be resolved. The precise functionality of these alterations is still to be established.	These changes have been linked to a considerable shift in the electrostatic potential of the S-protein, which might be critical in improving the transmissibility of the Omicron variant.	[189]	
	D796Y	-	-	-	-	
	N856	-	-	-	-	
	Q954H	-	-	-	-	
N969K	-	-	-	-		
L981F	-	-	-	-		

[65,86,87] [Table 1]. Interestingly, the Omicron variant prefers the endosomal entry route over the plasma membrane entry route, according to recent studies [66,88]. Scientists have also discovered that Omicron spike pseudotyped virus infection was limited in TMPRSS2 expressing cells but enhanced in cells that facilitate an endosomal pathway for the entrance [66,88].

These results imply that genetic changes on the Omicron S protein non-RBD could change the pathway by which the virus enters host cells, which is linked to a change in the cellular tropism away from TMPRSS2 expressing cells. These observations also illustrate why Omicron replicates more quickly in the upper respiratory system than in the lungs compared to other VOCs like the Delta variant [65,88–90]. Apparently, the furin cleavage area of the Omicron variant also contains three important alterations such as P681H, H655Y, and N679K (Table 1). It has been established that alteration like P681H in the polybasic cleavage site (PBCS), which is also found in other VOCs like Alpha and Gamma, facilitates furin-mediated cleavage of the S protein and may thus increase pathogenicity [91]. Interestingly, among the SARS-CoV-2

variants, Omicron's cleavage level by furin is the lowest, suggesting that further alterations close to the furin cleavage site may seriously impair its cleavage [92]. Furthermore, similar to SARS-CoV [92,93], the fusion ability of the Omicron strain is the weakest of all the known SARS-CoV-2 variants so far [65,90,93,94].

In addition, several scientists tried to evaluate the impact of specific mutations on the transmissibility and severity of the Omicron variant. Several mutations, such as Q498R, and N501Y in the Omicron variant, are associated with increased transmissibility and infectiousness. In previous strains, the presence of three critical mutations, including S477N, Q498R, and N501Y, have been linked to the increment in the binding capability of S-protein with ACE2 receptor [95–97]. In this context, the occurrence of similar mutations in the omicron variant can be associated with the enhanced infectiousness and transmissibility of this strain [22]. In addition, the presence of mutations like H69/V70 deletions along with T478K and E484A in previously reported VOCs have been associated with the increased immune escape capabilities of the strains [95]. However, the presence of T478K and E484A in the

omicron variant can be postulated as a crucial factor leading to increased neutralizing antibody resistance and associated with higher immune escapes [22,95,97].

It is also worth noting that researchers have identified that the sublineages of the Omicron also differ in the number of mutations and their levels of infectiousness from one another [74,98]. Recently, Desingu et al. analyzed almost all BA.1 (289,761 sequences), BA.2 (3562 sequences), and BA.3 (39 sequences) sequences available in GISAID. They have found 37 mutations in the spike protein of BA.1, 31 mutations in BA.2, and 33 mutations in BA.3. It is interesting to note that 21 mutations, including G142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y Q954H, and N969K were the most common mutations in all three lineages [19,28,75]. Two of the 21 mutations, N501Y and Q498R, were designated as necessary and significant modifications since they are predicted to improve S-protein binding to the host receptor (ACE2). Other alterations, including H655Y, N679K, and P681H, were also deemed necessary because they are thought to promote spike cleavage and viral propagation [19,22,99] [Table 1].

Over the previous few months, the Omicron variant has emerged into multiple sublineages. A distinct collection of nucleotide polymorphisms (SNPs) distinguishes each lineage. Some SNPs result in amino acid modifications and may result in functional adaptations that benefit the virus in its interaction with the host, such as increasing the affinity of the S protein's RBD to the ACE2 receptor, resulting in higher infection rates and a higher chance of successful transmission [100] and increased rate of immune evasion [24]. However, a number of polymorphisms are silent and have no effect on the amino acid sequence (so-called synonymous mutations). Synonymous mutations, on the other hand, may affect viral transmission [101,102]. There are several theories on how synonymous mutations impact phenotypes and can influence viral transmissibility and severity [103,104]. The structure of the mRNA might be affected by synonymous changes. Low 5' stability is considered to increase translation rates, but stem-loop topologies across the open reading frame might have variable impacts on translation. The inclusion of infrequently used codons with low tRNA abundance, or Shine-Dalgarno-like sequences [105], might affect translation rates locally. Any process that changes translation rates has the potential to alter the amount of protein generated, translation accuracy, and co-translational protein folding. Finally, differing translation error rates and spectra for distinct synonymous codons may alter the phenotypic characteristics, leading to negative or potentially even favorable consequences [106]. Hence, the synonymous mutations can influence the variants' characteristics.

The Omicron variant's S-protein contains an abnormally significant number of amino acid alterations and deletions, particularly in the RBD. Immune evasion, enhanced transmission characteristics, and diagnostic concealment are all possible outcomes of these alterations [101]. The exact effects on immune evasion and advantageous transmission are currently being investigated [107]. Extensive characterization of Omicron's mutational portfolio is an important first step in deciphering its common and distinct clinical symptoms, sensitivity, or resistance to current vaccinations, and if future Omicron-like variations may have greater virulence [102]. Indeed, the Omicron variant has evolved into several sub-lineages as a result of a mix of missense, deletion, insertion, and other changes. Missense mutations in the Spike (S) protein, which engages the ACE2 receptor on human cells to promote viral entry, have led to significant differences in Spike-ACE2 binding affinity, whereas deletions (e.g., Y144) have altered the efficiency of neutralizing anti-Spike antibodies [101,102]. Insertion mutations in the generation of Omicrons subvariants have become less prominent. The S-protein from Omicron carries an insertion mutation (214EPE) that is not present in any other SARS-CoV-2 progenitor. Given the significance of viral genetic recombination and the likelihood of SARS-CoV-2 host genome integration, there are a variety of host-viral and inter-viral genomic

matter exchange scenarios that might have contributed to the adoption of this insertion mutation in the Omicron progenitor [70].

4.1. Impact on the transmissibility

The efficiency with which the Omicron variant can transmit from person to person is yet to be resolved clearly. The Omicron variant and its sublineages became the dominant variant not only in Africa but all around the world. The rapid emergence of the Omicron variant over the Delta variant in South Africa has raised serious concerns that the Omicron variant is more transmissible and infectious than the Delta variant and other VOCs. Initially, due to the small number of cases in South Africa when Omicron first appeared, it was unclear whether the Omicron variant is significantly transmissible as compared to other VOCs such as Delta variant. Structural changes in the S-protein due to the mutations suggest that the Omicron variant is more transmissible than the parental strain of SARS-CoV-2 [71]. However, several recent studies have suggested that the Omicron variant is significantly higher transmissible in nature, but the severity of the disease caused by the Omicron variant is at par with the Delta variant. The Omicron variant has been considered a challenge worldwide since its discovery due to its highly transmissible nature. Furthermore, several experts hypothesized that the Omicron variant's increased transmissibility is not caused by the discharge of a large number of viral particles from sick individuals. Instead, its capacity to dodge immunity induced by a previous infection or immunization is the best explanation for its incredibly rapid proliferation [108]. In this context, Puhach et al. not only measured the viral RNA but also measured the number of infectious virus particles among the samples collected from various vaccinated individuals. They did not discover a statistically significant difference between the viral loads of vaccinated people with Omicron infection and those with Delta infection [109]. This suggests that the infectiousness can be independent from the Omicron's highly transmissible nature [109].

Although there is currently a lack of knowledge on the transmission properties of Omicron's subvariants such as BA.4 and BA.5, research has demonstrated that the Omicron variant spreads about four times faster than the SARS-CoV-2 Beta variant and has an average doubling time of three days [28]. Previous research has found that BA.1 and BA.2 patients do not differ significantly in terms of hospitalization, or fatality (Fonager et al., 2022). However, there are disparities in transmissibility of various sublineages of the Omicron variant. In an investigation of Danish families, BA.2 was related to a greater secondary attack rate than BA.1 [110]. Household members were more vulnerable to BA.2 infection than to BA.1 infection, and this impact was more evident in vaccinated persons than in unvaccinated people. Furthermore, the transmission of BA.2 was greater in unvaccinated persons than in vaccinated participants; however, the difference was not observed in vaccinated individuals [110]. Apart from immune evasion, BA.2 appears to have more intrinsic transmissibility than BA.1 [30].

In another recent study, infection rates were found to be four times higher in the Omicron variant than in the wild-type SARS-CoV-2. In addition, a significant increase in infectiousness has been reported in the Omicron variant as compared to the Delta variant [10]. Pseudovirus forms of various variants such as Delta, Gamma, and Omicron variants were compared with the wild-type SARS-CoV-2 by linear regressions of neutralization assays. Gamma variant recorded a similar infection rate to wild-type SARS-CoV-2. The Beta variant recorded less infection rate. Moreover, the Delta recorded a two-fold increase in the efficiency of infecting target cells. Such findings highlight the importance of mutations in the S-protein of SARS-CoV-2, which significantly influences infectivity. In addition, effective binding of ACE2 receptors with S-Protein of the Omicron variant has been associated with increased infectiousness as compared to the other VOCs [10].

Several factors and reasons have been postulated that can significantly alter the transmissibility of the Omicron variant. Among these factors, mutations are the most critical aspect of increasing

transmissibility. In the corroboration of these speculations, data obtained from genome sequencing of the Omicron variant demonstrated that certain mutations in S-protein significantly alter the recognizing capability of S-protein for the ACE-2 receptors. Hence, the Omicron variant can recognize host cells efficiently as compared to the parental strain of SARS-CoV-2 [18,111].

Furthermore, an examination of these mutations' data reveals the possibility of greater transmission by escaping the immune response [112,113]. N501Y mutation has been associated with the increased binding affinity of S-protein with the ACE2 receptor. Furthermore, the presence of the Q498R mutation with N501Y dramatically boosted the ability of S-protein to bind to the host cell receptor. Such alterations allow the Omicron variant to enter the host cell with ease [71,112].

Additionally, the Omicron variant poses a greater risk of reinfection in previously COVID-19-infected individuals, demonstrating stronger transmissibility [114]. The presence of H655Y and N679K mutations around the furin cleavage site (FCS) in the Omicron variant has been shown to promote S-protein cleavage, making the virus more infectious [115,116]. N679K is close to the furin cleavage site and contributes to its polybasic character, which may enhance spike cleavage and help transmission. P681H mutation can increase the risk of transmission by boosting the cleavage of the S-protein [71,117].

Escalera et al. characterized emerging SARS-CoV-2 spike polymorphisms in vitro and in vivo to understand their impact on transmissibility and virus pathogenicity and fitness. We demonstrate that the substitution S:655Y, represented in the gamma and omicron VOCs, enhances viral replication and spike protein cleavage. The S:655Y substitution was transmitted more efficiently than its ancestor S:655 H in the hamster infection model and was able to outcompete S:655 H in the hamster model and in a human primary airway system.

In addition, recent computational studies revealed that the Omicron variant possesses a higher affinity for ACE2 as compared to other variants of SARS-CoV-2, such as Alpha, Beta, and Delta variants. Contradictorily to the computer modeling, real binding experiments reported the weaker binding affinity of the Omicron variant's S-protein towards the ACE2 compared to Beta and Delta variants. This suggests that the enhanced binding affinity of the S-protein with the ACE2 receptors may not be the driving force behind the enhanced transmissibility of the Omicron variant [118].

The presence of mutations, including Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K, all together in the RBD of the S-protein of the Omicron variant has been associated with the greater affinity for the ACE2 receptor [22,25]. Moreover, many recent studies also speculated that the Omicron variant appears to be more communicable than other VOCs due to the presence of the combination of Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K [18,119].

Moreover, the alterations in the electrostatic potential of the RBD of S-protein have been associated with the binding capabilities of S-protein with the ACE2 receptor. A significant increase in the positive electrostatic potential at the RBD interface with ACE2 can be postulated as an important factor that can increase the affinity of RBD with ACE2 [119,120]. From the initial viral strain through the Delta and Delta plus variants to the most recent Omicron variant, there appears to be a tendency toward an increase in positive electrostatic potential [119,121,122]. Because ACE2 has negative electrostatic surface potential patches, it is logical to assume that increase in the positive charge on the RBD of S-protein will boost viral contact affinity of S-protein with ACE2. Pascarella et al. previously discussed the possible link between increasing positive electrostatic potential and increasing affinity in the Delta variant [121]. If there is a direct link between electrostatic potential and receptor affinity, then infectivity exists, and the Omicron VOC should be more transmissible, as some preliminary research suggests. Furthermore, a significant change in the surface electrostatic potential of Omicron RBD might have an impact on interactions with some other biomolecules, including antibodies [119,122]. Additionally, Pawowski et al. stated that if the virus uses electrogenic alterations to modify the

electrostatic force between the RBD of spike protein and ACE2, the resultant Coulomb attraction is greater in Omicron compared to the original SARS-CoV-2 virus [120,123]. Hence, collectively it can be stated that the higher number of mutations leads to significant alterations in the electrostatic potential of the S-protein, which can be a plausible reason for its higher transmissible nature.

Furthermore, it is worth noting that Omicron and its recently emerged sublineages, such as BA.4/BA.5, transmit better than the previously reported lineages since it can avoid the initial line of resistance offered by immunizations. By attaching to the viral surface, the antibodies inhibit infection. However, because of the second line of protection offered by vaccinations, where T and B cells act after the infection begins, Omicron may not lead to severe illness in the vaccinated individuals [124]. The ability of antibodies to protect upper respiratory tract infections may wane over time or owing to spike protein mutations. The vaccinations, on the other hand, give the second line of defense against the infection caused by the Omicron variant [125]. Considering how swiftly the T and B cells operate, one can possibly stay asymptomatic [31,124]. Omicron contains various novel mutations in the RBD of the S-protein that dramatically increase binding affinity in the RBDhACE2 complex while also evolving and rapidly spreading in humans all over the world [126]. It may have provided an advantage to the ancient SARS-CoV-2 and previous VOCs in lung cells and primary human airway epithelial cells by permitting spike activation by the plasma membrane protease TMPRSS2, allowing for fast cell surface fusion [124,127]. Recently, Saxena et al. reported that the dynamic transmission of Omicron appears to be stronger than that of previous SARS-CoV-2's strains. His655Tyr is close to the furin cleavage point (speed up spike cleavage) which may help in the transfer of monoclonal antibody therapy resistance [128]. Hence, any further evolution in the Omicron variant can be a serious concern amid serious containment efforts.

4.2. Impact on disease severity

Emerging sublineages have aroused several concerns in the scientific community, such as greater transmissibility, lower vaccine efficacy, and a higher likelihood of reinfection. Particularly compared to other varieties, the Omicron sublineages such as BA.2 have expanded swiftly over the world and within communities, indicating a greater level of transmission and possible development advantage [28]. Despite the fact that much regarding clinical presentation and epidemiology remains unclear, the majority of cases reported to authorities are asymptomatic or have minor symptoms, signifying that illness severity is low [36,107]. There is no doubt that during the resurgence of the COVID-19 infection due to the emergence of the Omicron variant, there were several discrepancies regarding the severity of the infection caused by the Omicron variant [20]. Based on preliminary clinical studies from various parts of the world, it has been found that the disease caused by the Omicron variant is less severe, rather mild, or even asymptomatic [8,22,129,130], which is consistent with in vitro studies [22,91,129]. Previous immunization is likely to blame for some of the lessened severity [130]. Furthermore, many countries have provided booster doses of the vaccine, which has been linked to increased humoral and cellular immune responses against the virus, including the Omicron variant [131]. This can be associated with the reduced severity of the infection among the fully vaccinated population. However, the durability of the immune response and protection provided by mRNA vaccines against the emerging sublineages such as BA.4 and BA.5 is yet to be uncovered. In association with this, recent resurgence of COVID-19 cases and hospitalization even in mass vaccinated population of countries like England has been associated with the newly emerged BA.4 and BA.5 [42].

Reports have suggested that the Omicron variant reproduces higher in nasal epithelial cells, which suggests more contagiousness of the omicron variant. In addition, reduced viral loads in human lung cells or the lower respiratory tract correspond to decreased severity of the

disease [91,122]. From a molecular approach, the Omicron variant appears to have achieved certain essential requirements for a host-adapted virus version with high dissemination capability and less severe symptoms [132]. The Omicron variant might challenge human's post-immunized waning humoral and cell-mediated immune response to induce a more general and possibly long-lasting immunity by widening humoral and cellular immune response while simultaneously increasing T-cell mediated immune response, as reported for Delta [133,134] and very recently for Omicron [135]. These studies can be associated with the lesser or mild severity of the disease caused by the Omicron variant. However, the severity of the disease is yet to be resolved in the unvaccinated population [123].

A recent systematic review of regular epidemiological monitoring figures indicates that the Omicron variant may be linked to an increased potential of reinfection after a first infection, according to the first epidemiological research available [114]. This finding, based on data from 35,670 probable reinfections among 2,796,982 people with laboratory-confirmed SARS-CoV-2 infection, demonstrates that the Omicron variant can overcome past infection immunity. Because vaccination coverage in South Africa was extremely low throughout the trial, the findings are not relevant to immunization. With each new variant, the issue of whether COVID-19 severity is increasing or decreasing emerges. Well before documented information, some believe that the new version would result in much less severe cases, whereas others claim that it may result in a poor prognosis of the disease, particularly in youngsters [136].

The Omicron variant has been observed to cause less severe disease as compared to the Delta variant, according to early research, with a risk of hospitalization varying between 15% and 80%, which is relatively low than the Delta variant [130,137]. Omicron may not cause serious disease, especially in those who have been vaccinated and who have received a booster dose [10,138–140]. The majority of these cases fall into the category of clinically asymptomatic or moderate instances. A runny nose, headache, tiredness (moderate or severe), sneezing, and sore throat are among the characteristics of the Omicron variant [141, 142]. The children, on the other hand, were participating in the Omicron-led fourth wave in South Africa, where early data revealed that the risk of hospital admission for children was 20% greater than in the D614G-led first wave [143]. In ex vivo culture investigations, it has been discovered the Omicron variant multiplies ten times slower in lung tissue, which might explain why Omicron-infected individuals had a milder illness [144].

In addition, the Omicron variant has been found to replicate at significantly lower rates in Calu3 and Caco2 cell lines. It is interesting to notice that the Omicron variant is comparatively less efficient in utilizing the TMPRSS2, which is essential in the plasma membrane-mediated entry pathway into the host cell. Omicron's preference for the endosomal mediated pathway to enter the host cell has been associated with reduced severity as it leads to increased viral reproduction in the upper respiratory tract only. Shuai et al. reported that the replication of the Omicron strain is reduced in the lower respiratory tracts of Omicron-infected K18-hACE2 mice [131]. The lower viral load resulted in an improved lung pathology as compared to other VOCs [90]. Furthermore, other research groups recently stated that compared to the Delta strain, the Omicron strain seemed to reproduce at a lower rate in lung cells (expressing TMPRSS2) and lung organoids [101,145], which led to reduced viral load. Relative to Beta and Delta strains, experimental infection with Omicron live virus in C57BL/6 mice, BALB/c mice, K18-hACE2 transgenic mice (producing hACE2 under an epithelial cytokeratin promoter), and Syrian hamsters displayed significantly less severe illness [146]. Similarly, hamsters inoculated with WT viral strain of SARS-CoV-2 and other VOCs such as (Alpha, Beta, or Delta) lost up to 10–17% of their body weight by day 6; however, hamsters inoculated with Omicron strain did not record any weight loss [147].

There are currently too many complicating variables to compare individuals infected with the Omicron variant to patients infected with

other strains. COVID-19 morbidity and fatality differ tremendously according to the country, vaccination coverage, and population variables such as age, socioeconomic status, comorbidities, and medical care standards. To critically scrutinize clinical symptoms, large-scale case-control studies with as many of these factors as possible are required [136].

4.3. Impact on vaccine effectiveness

With the advent of VOCs and the mutation of SARS-CoV-2, the antibodies created by existing vaccinations may lose their capacity to neutralize different variants [148,149]. As a result, it's critical to assess the current vaccines' potential to protect against various variants of SARS-CoV-2 [150,151], especially the Omicron variant [152]. To examine the influence of the Omicron variant on vaccination efficacy and outbreak infections, laboratory and epidemiological investigations are needed, especially in those who have received booster doses. Additionally, alternative inoculation routes (e.g., intranasal) and mixing schemes of vaccinations could be urgently needed [153]. Vaccination, on the other hand, is expected to remain a protective capability against hospitalization and mortality due to the COVID-19 pandemic. Omicron adapts to hosts differently than Delta and other variants [154], explaining the reason why preliminary data suggested that the vaccines against prior SARS-CoV-2 variants appeared to be less effective against the Omicron variant [155]. In the following section, we will establish the effectiveness of present vaccines against the Omicron variant.

In clinical trials and observational research, vaccines have proven sustainable efficacy and effectiveness in avoiding severe disease and mortality caused by SARS-CoV-2, with only a minor reduced efficacy against new VOCs [156]. Concerns are increasing with evidence of waning of vaccine immunity [157]. It was recently proven that the risk of SARS-CoV-2 breakthrough infections is mostly linked to reduced levels of the virus-specific humoral immune response [158] with a rapid reported breakthrough infection incidence during the Omicron wave. A significant surge in cases of the SARS-CoV-2 Omicron variant in highly vaccinated populations has raised questions about the effectiveness of current vaccines [159].

It was noted that unvaccinated persons with documented previous SARS-CoV-2 infection received some protection against hospitalization and significant protection against death. Whereas in the case of vaccinated individuals, previous SARS-CoV-2 infection offered additional protection for the death endpoint. In breakthrough confirmed Omicron infections, booster vaccination with mRNA vaccines provides over 70% protection against hospitalization and mortality [160].

A study published in January 2022 by two Hong Kong institutions showed that three doses of the Sinovac COVID-19 vaccine (CoronaVac) failed to provide adequate antibodies to fend off Omicron. Participants who had received two previous doses of BNT162b2 or CoronaVac did, however, develop protective antibodies against Omicron after receiving the third dose of BNT. That had motivated study researchers to recommend Sinovac recipients take BNT162b2 booster about six months after their previous shot to protect against Omicron [152]. CoronaVac's ineffectiveness against the Omicron variant could have ramifications for China's internal control efforts and, more worryingly, for other developing countries utilizing it.

A study published in The Lancet Global Health [161] showed that individuals/participants completed a primary immunization schedule (two doses) with CoronaVac and received a homologous booster with CoronaVac and a heterologous booster with AZD1222, BNT162b2. The study showed that vaccine effectiveness was 78.8%, 93.2%, and 96.5% for a three-dose schedule with CoronaVac, an AZD1222, and BNT162b2 booster. Additionally, the study reported that the vaccine effectiveness against COVID-19-related hospitalization, ICU admission, and death was 86.3%, 92.2%, and 86.7% for a homologous CoronaVac booster, 96.1%, 96.2%, and 96.8% for a BNT162b2 booster, and 97.7%, 98.9%, and 98.1% for an AZD1222 booster. This study provided extra evidence for

the outperformance of heterologous boosters over homologous boosters [161].

Khong et al. [162] found that the immunogenicity of the booster dose against the Omicron variant is significantly reduced. The geometric mean titers (GMTs) levels in the BNT162b2 (B-B-B) group that received three doses of BNT162b2 (27.6) and the BNT162b2/CoronaVac (C-C-B) group that received two doses of CoronaVac with a booster dose of BNT162b2 (23.8) were greater after the booster dose than in the CoronaVac (C-C-C) group that received three doses of CoronaVac (5.83) and the B-C-B group (10) [162]. Notably, on April 14, 2022, Sinovac reported that its inactivated COVID-19 vaccine (Omicron strain) had been approved for clinical testing in Hong Kong, China.

Cele et al. found that plasma neutralization in infected and BNT162b2 vaccinated individuals to the ancestral virus was much higher than in Omicron compared with vaccinated-only participants [59]. Andrews et al. found that primary immunization with two BNT162b2 or ChAdOx1 doses provided no or limited protection against symptomatic disease with the Omicron variant. Boosting with BNT162b2 following either primary course significantly increased protection [159].

Gruell et al. [163] evaluated the serum neutralizing capacity of vaccinated and convalescent individuals in longitudinal cohorts. They reported a near-complete absence of neutralizing activity against Omicron in polyclonal sera from convalescent individuals and individuals vaccinated with two doses of the BNT162b2 vaccine [163]. Liu et al. [164] found that serum neutralizing antibody levels in previously infected participants getting the BNT162b2 booster dose were higher against the Omicron variant than in naive, uninfected participants [164]. Cameroni et al. reported that the neutralization activity of serum specimens from BNT162b2 booster-dose recipients significantly increased. More importantly and worryingly, its neutralization capability against the Omicron variant still decreased by at least 4-fold compared with the Wuhan-Hu-1 strain [58].

Dejnirattisai et al. found that the neutralizing capacity against Omicron was lowered by around 14.2-fold on the 28th day after the booster dose of BNT162b2 compared to the ancestral strain and 3.6-fold with Delta (B.1.617.2). Following the third dose of BNT162b2, the neutralization titers for Omicron were increased by 34.2-fold compared to 28 days after the second dose [165]. Powell et al. have recommended the need for regular boosters of BNT162b2 in adolescents age (12–15 and 16–17 year-olds) following reporting the rapid waning of immunity after the first and second BNT162b2 dose against symptomatic disease with the Omicron variant compared with the Delta variant [166]. Pérez-Then et al. [167] found that the heterologous BNT162b2 vaccine booster on the humoral immunity of participants who had received a two-dose regimen of CoronaVac resulted in a 1.4-fold increase in neutralization activity against the Omicron variant compared with the two-dose BNT162b2 vaccine [167]. However, Omicron's neutralizing antibody titers were lowered by 7.1 and 3.6 times, respectively, when compared to the ancestral strain and the Delta variant. Nemet et al. reported a high neutralization efficacy of the 3rd dose of the BNT162b2 vaccine against the Omicron variant than after the second dose [168].

Many studies reported that the three doses of BNT162b2 mRNA are likely required to protect against Omicron-driven COVID-19 [168–173]. Strikingly, Gao et al. suggested that established SARS-CoV-2 spike-specific CD4 + and CD8 + T cell responses, particularly following BNT162b2 vaccination, are mostly intact against Omicron (Gao et al., 2022).

It was noted that more than half of mRNA-1273 recipients' serum failed to neutralize the Omicron variant, resulting in the GMTs being lowered by 43 times [174]. After the primary two doses of the mRNA-1273 vaccine, Pajon et al. found that neutralization titers against the Omicron variant were 35 times lower than those against the D614G variant. However, neutralization titers against the Omicron variant were 20 times greater after the booster dose of the mRNA-1273 vaccine than after the second dose, suggesting that the risk of breakthrough infection

may be reduced significantly. Six months after the booster injection, neutralization titers against the Omicron variant dropped [175]. Edara et al. used a live-virus assay to measure the neutralization activity of the serum of mRNA-vaccinated individuals (mRNA-1273 and BNT162b2) against the Omicron variant. They found a 30-fold reduction in neutralizing activity against the Omicron at 2–4 weeks after a primary series of vaccinations. No neutralizing activity against the Omicron was reported after six months from the initial two-vaccine doses. Additionally, they found a 14-fold decline in neutralizing activity against the Omicron in naive patients after a booster shot (third dose) [176].

Carreño et al. found that sera from individuals double vaccinated with either BNT162b2 or mRNA-1273 showed a reduction in the neutralization of Omicron compared with wild-type of more than 23-fold or 42-fold, respectively. BNT162b2-boosted individuals had a 7.5-fold reduction in Omicron neutralization compared to wild type, while mRNA-1273-boosted individuals had a 16.7-fold reduction [172]. Convalescent individuals who received 2 BNT162b2, 2 mRNA-1272, or 3 BNT162b2 vaccine doses showed reductions in Omicron neutralization compared with wild-type of 14-fold, 11-fold, and 13-fold, respectively [172]. In a Qatari study, researchers found that booster doses of BNT162b2 or mRNA-1273 vaccine are less effective against symptomatic infection due to Omicron infections than that due to Delta infections. At the same time, both vaccines are highly protective against hospitalization and death due to Omicron and Delta infections [177]. Ai et al. found that serum neutralization activity from the BBIBP-CorV homologous booster group and the BBIBP CorV/ZF2001 heterologous booster group increased; however, 80% of samples still failed to neutralize the Omicron variant [178]. Wang et al. reported that the 4th BBIBP-CorV could recall waned immune responses six months after the 3rd dose. Disappointingly, the induction of nAbs targeting the RBD of the S-protein was largely suppressed in participants against the Omicron variant [179].

Yu et al. studied the efficacy of a homologous booster dose of BBIBP-CorV vaccine in health care workers (HCWs) using a pseudovirus-based neutralization assay. HCWs had received the booster dose 8–9 months after completing the priming two-dose vaccination schedule. They reported that the serum neutralization capacity induced by the boost against the Omicron variant was reduced, and they weren't able to produce effective neutralizing antibodies against the Omicron [180]. The collected sera from individuals who received two doses of inactivated SARS-CoV-2 vaccines (CoronaVac and BBIBP-CorV) showed 13.9 times decrease compared with D614G [154].

Van Doremalen et al. have studied the efficacy of AZD2816, encoding the spike (S) protein of the Beta VoC, and AZD1222 (ChAdOx1 nCoV-19), encoding the S protein of the wild-type strain of SARS-CoV-2 (Wuhan-1), against the Omicron variant using the Syrian hamster model. They found that AZD2816 and AZD1222 vaccines are protective against the Beta, Delta, and Omicron VOCs in the hamster model [181]. Dejnirattisai et al. found that the neutralizing capacity against Omicron was lowered by around 12.7-fold on the 28th day after the booster dose of AZD1222 compared to the ancestral strain Victoria and 3.6-fold with Delta (B.1.617.2). Following the third dose of ADZ1222, the neutralization titers for Omicron were increased by 2.7-fold, compared to 28 days after the second dose [165].

It was found that the neutralizing activity of serum samples from Ad26. COV-2 vaccinees against the Omicron variant were reduced by 17 times [174]. In late 2021, Gray et al. evaluated the efficacy of a homologous boost of the Ad26. COV.2 vaccine is given 6–9 months after the initial vaccination in HCWs in South Africa in preventing hospital admissions. They found that vaccine effectiveness for hospital admissions increased over time since booster dose, from 63%; to 84% and then 85%, 0–13 days, 14–27 days, and 1–2 months post-boost [182]. Liu et al. evaluated the cross-reactivity of vaccine-elicited cellular immune responses against the SARS-CoV-2 Omicron variant in individuals vaccinated with the Ad26. COV.2. S or BNT162b2 vaccine. They found durable spike-specific CD8 + and CD4 + T cell responses, with

extensive cross-reactivity against both the Delta and the Omicron variants [183]. It is noted mentioning that a booster dose of NVX-CoV2373 was given following the primary vaccination series by six months, resulting in an incremental rise in reactivity as well as improved immune responses [184].

The first two doses play a greater role in reducing the worst clinical outcomes and hospital admission. A third or booster dose significantly provides additional protection to overcome the reduced neutralization associated with the Omicron variant. However, the modest cross-neutralization against Omicron from previous non-Omicron infections encourages vaccination of previously infected people against the Omicron infection [185]. Serum antibody titers from COVID-19 patients or mRNA vaccines were considerably lower against Omicron RBD compared to the original Wuhan strain. The Omicron variant elicits an immune escape against neutralizing antibodies induced by the current vaccination protocols, such as mRNA-based vaccinations. However, boosted vaccination elicited strong variant cross-neutralization and increased the level of anti-RBD antibodies against Omicron [174,186]. Worryingly, the 4th dose of the BNT162b2 or mRNA1273 vaccine was reported that it isn't able to prevent Omicron infection (<https://www.shbaonline.org/>).

Both homologous and heterologous enhancers were able to boost the neutralization activity of individuals' serum against the Omicron variant; furthermore, the neutralization efficacy of a booster dose from the heterologous vaccine was higher, implying that heterologous vaccines should be given sequentially [153]. Polyvalent vaccines are able to induce antibodies to diverse epitopes, reducing the immune pressure on certain epitopes while maintaining efficacy across multiple VOCs [153].

Zhao et al. reported that Omicron does have a severe immune escape in convalescents. they hypothesized that a multi-boost strategy with a longer delay between the second and third jabs (4–6 months) to allow for immune maturation would be effective for NAb against deadly variants like Omicron [187].

In those who were vaccinated, protection against Omicron symptomatic infections was consistently lower and faded faster than protection against Delta [188]. At the same time, hybrid immunity (prior infection and at least one vaccine dose) gave the most effective protection against the symptomatic Omicron infection. Vaccination with the previous infection produces a neutralizing capacity against Omicron, equivalent to what vaccination alone does against the ancestral SARS-CoV-2 virus [189]. That could be the explanation for the scene in South Africa, wherein the Pfizer BNT162b2 vaccine has been proven to reduce the risk of Omicron infection-related hospitalization [190]. The previously infected individuals who were vaccinated are likely to have a deeper antibody response as well as a larger and deeper poly-epitopic T-cell response [191,192], which should help overcome some expected omicron antibody evasion. Zhang et al. used intramuscular Ad5-nCoV (adenovirus-vectored vaccine), aerosolized Ad5-nCoV, ZF2001 (recombinant protein subunit vaccine), or CoronaVac to assess the immune responses to their boosters in those who had received two doses of CoronaVac 6 months prior. They found that aerosolized Ad5-nCoV generated the greatest neutralizing antibody responses against the Omicron variant on day 28 after booster vaccination. Additionally, the aerosolized Ad5-nCoV booster produced the greatest IFN γ T-cell response on day 14 after booster vaccination and also produced the greatest spike-specific B cell response compared to IM Ad5-nCoV, ZF2001, or CoronaVac [193].

Kurhade et al. recently reported the neutralization of BNT162b2-vaccinated serum, which was collected after one month of the third dose of vaccine against the three sublineages of the Omicron variant. They have designed the whole BA.1, BA.2, or BA.3 spike into a mNeonGreen USA-WA1/2020 SRAS-CoV-2 to simplify the neutralization testing. USA-WA1/2020, BA.1-, BA.2-, and BA.3-spike SARS-CoV-2 s are all neutralized by all BNT162b2-vaccinated serum with titers of greater than 20; the neutralization GMTs against the four strains were 1211, 336, 300, and 190, respectively. As a result, the USA-WA1/2020 is

3.6, 4.0, and 6.4 times more effective in neutralizing the BA.1-, BA.2-, and BA.3-spike SARS-CoV-2 s [194].

4.4. Impact on presently available therapeutic regimens

Therapeutic approaches, such as the use of mAbs like Sotrovimab and Bebtelovimab appear to be successful against the Omicron variant as per the preliminary investigations [20,136,195]. However, greater study on the Omicron strain, specifically mAbs, is recommended in order to gather more accurate and valid data on therapeutic approaches. To block viral entrance into human cells, nearly all mAbs designed to treat COVID-19 target the spike protein. As a result, it's not unexpected that the majority of these antibodies fail to work against the Omicron form [196].

Presently, Bamlanivimab, Regdanvimab Etesevimab, Cilgavimab, Tixagevimab, Casirivimab, and Imdevimab are among the effective and reliable mAbs to treat the SARS-CoV-2 infection [196]. The majority of these mAbs inhibit viral S protein, which is essential to bind with ACE2 host receptors. In this context, it seems that the Omicron variant may resist these mAbs due to a higher number of mutations acquired in the S-protein (Fig. 7). Recently, it has been revealed that viral changes in the Omicron variant altered the antibody binding of approved therapeutic antibodies, such as Casirivimab + Imdevimab and Bamlanivimab + Etesevimab [197].

Early outcomes indicated that the REGN-COV2 (Casirivimab and Imdevimab) antibodies could be effective against the Omicron variant [198,199]. The preventative and therapeutic antibodies NA8 and NE12 were produced utilizing combinatorial antibody phage-display library technology, and they were also effective against the Omicron variant at picomolar doses [200]. To counter the Omicron variant in the future, high-potency medications are needed that can inhibit viral replication and spread while still being effective against all circulating strains, as well as any subsequent variants that may appear [142,201]. Sotrovimab (S309) or Tixagevimab + Cilgavimab combinations binding was unaffected by Omicron mutations [202].

Hoffmann et al. observed similar results, with the Omicron spike being resistant to numerous marketed monoclonal antibodies but susceptible to suppression by Sotrovimab [113]. In vitro studies have shown that Sotrovimab is effective against the Omicron variant [140]. Sarbecovirus mAbs that neutralize the virus broadly identify the region outside of the RBD. Three mAbs, sotrovimab, S2X259, and S2H97, fit into this category, finding conserved epitopes and neutralizing Omicron [52]. Additionally, more than 40 mAbs were tested against the Omicron variant while evaluating the neutralizing capabilities of RBD binding sites (I, I, IV, and V), and only a few of the mAbs targeting conserved epitopes were found to be broadly neutralizing. These results can be utilized in specifically targeting Omicron, which is resistant to antigenic shift due to virus evolution [52], and may effectively manage the recurring disease outbreak.

4.5. Impact on the neutralization capabilities of the convalescent plasma (CP)

Convalescent plasma (CP) isolated from people infected with a parental strain of SARS-CoV-2 was tested in vitro and shown to have much-reduced neutralization against VOCs, such as the Beta strain [203]. As a result, it is critical to compare the efficacy of CP to that of the Omicron variant. As vast unvaccinated populations continue to increase the risk of variant generation, it is vital to rediscover the potential of CP-based treatment against novel variants of SARS-CoV-2, notably VOCs such as Delta and Omicron variants [98]. Antibodies (Abs) or the CP induced by vaccines or through natural infection mostly target the S-protein. A significant number of mutations in the S-protein, including fifteen mutations in the RBD of the Omicron variant, have been linked to immune escape. Significant decreases in neutralizing activity of sera from vaccinated or previously infected people, which may suggest lower

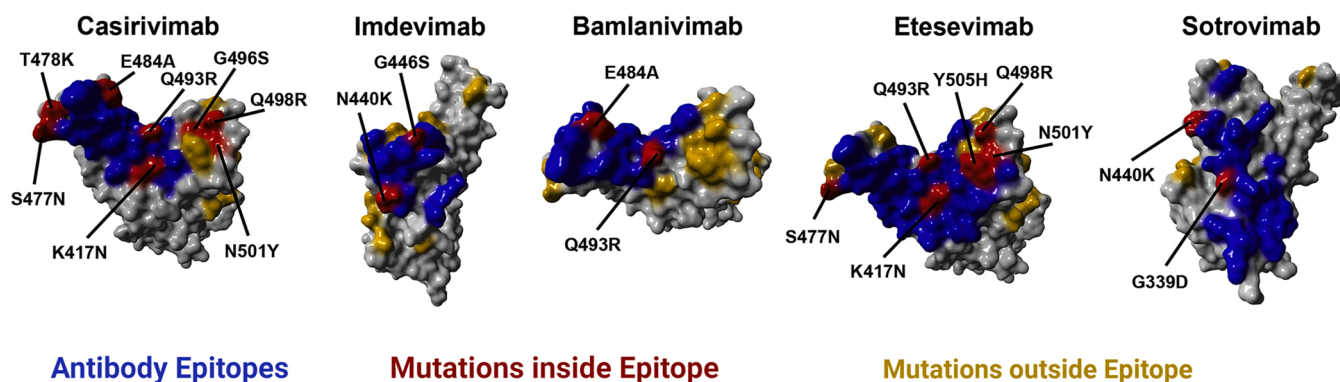


Fig. 7. The figure represents the locations of the mutations in the S-protein of the Omicron variant used by various mAbs such as casirivimab, imdevimab, bamlanivimab, etesevimab, and sotrovimab to target the SARS-CoV-2. (RBD, gray; epitope targeted by the antibody, blue; Omicron-specific mutations within the epitope, red; Omicron-specific mutations outside the epitope, orange) [Adapted from Hoffmann et al. [173]]. However, the changes among these regions are associated with the resistance toward the mAbs [173,260].

protection from infection, are expected based on the number of substitutions, their position, and evidence from other variations with similar spike protein mutations [204].

According to recent studies, the Omicron strain can escape antibodies generated by both the parental strain and the inactivated vaccines [204,205]. With just two mutations in the RBD, the Delta variant shows a small reduction in the RBD's binding capacity to both vaccinated and convalescent sera, which is consistent with recent research [206,207]. Omicron, on the other hand, successfully evades antibodies induced by ancestral variants and inactivated vaccines, despite a significant reduction in the binding potential of its RBD [204]. Individuals who had been immunized had a considerably decreased risk of serious Omicron infection, as per records on past VOCs. Vaccine sera and monoclonal antibodies, on the other hand, have shown a lower degree of Omicron neutralization. In order to better understand Omicron's capacity to evade immunity gained via vaccination and infection, *in vitro* studies evaluating the ability of both vaccine and convalescent sera to kill live Omicron pseudo or viral isolates is critical [208]. Importantly, an active Omicron surveillance program will aid us in better understanding the transmission patterns and identifying current outbreaks [128].

Several recent investigations have found that the novel Omicron type has an unrivaled level of neutralizing antibody escape. It has been proposed that enhancing and promoting antibody affinity maturation in people who have already been infected or vaccinated with existing vaccinations can provide greater immunity from infection with the omicron strain [128,205].

4.6. Impact on diagnostic procedures

Due to the high number of mutations in this novel variety, concerns have been raised regarding the effectiveness of commercial and in-house designed PCR-based diagnostic methods [209]. Furthermore, partial failure in the detection of the Alpha variant has been recorded previously. The possible partial detection failure of some tests where a multiple target assay provides a positive result for only a few targets, and a low or negative result for others can be employed to diagnose the individuals infected with the Omicron variant [209].

SARS-CoV-2 infection is still detectable using commonly used reverse transcription-polymerase chain reaction (RT-PCR) techniques [1]. However, the actual detection can be dependent on genome sequencing and further analysis. It is worth noting that in South Africa, the diagnosis of the Omicron-related incidence is founded on the S-genome target failure. Nevertheless, so far, the confirmation of the Omicron variant is dependent on whole-genome sequencing [29].

Many developing nations do not have provisions for performing

whole-genome sequencing on a regular basis. Hence, the occurrence of an actual number of Omicron cases can vary from the available data. In this context, rapid antigen detection methods must be evaluated urgently for their accuracy in detecting Omicron infections [210]. Molecular screening tools should really aim for conserved areas, in particular, with the perception that genomic sequences acquire mutations over time. An unusual number of genomes are accessible at this time in the COVID-19 pandemic, and putative conserved regions appropriate for diagnostics can be quickly discovered. Manufacturers and laboratories should assess the chosen diagnostic targets on a frequent basis to guarantee continuing effective primer binding in presently existing variants [210].

5. Future concerns and emergence of recombinant variants

Humans are the biggest and most important carriers of SARS-CoV-2, and they regularly come into contact with other animals, such as cattle, dogs, and other wild animals. Given SARS-CoV-2's capacity to crossover between species, it is indeed likely that worldwide communities will be exposed to more animal-derived strains until the pandemic is well under control.

Furthermore, while it has recently been postulated that a single viral strain may only produce SARS-CoV-2 infection, it is important to keep in mind that multiple SARS-CoV-2 lineages may invade the host simultaneously, which is a very rare event [211]. A newly found Delmicron double variation has also been proposed based on current information and media attention. However, further research is needed before any conclusions can be reached. If both forms of SARS-CoV-2, including the Delta and Omicron versions, infect patients at the same time, and persons with weaker immune systems can harbor both variants of SARS-CoV-2, a so-called new super-variant might emerge. The Delmicron variation, which is currently being attributed to a new epidemic of COVID-19 infections in North America, Europe, and maybe India and several countries [211], is thought to have been generated by mixing the fatal Delta and most evolved Omicron strains of SARS-CoV-2. Nevertheless, if such assertions are proven, additional study and WHO approval will be required. Because the mutations are validated using genome sequencing, which is done on only a small percentage of COVID-19 cases, the real number of Omicron and Delta cases is predicted to be significantly higher than the number of verified instances disclosed thus far [211–213].

Recently, a number of recent recombination events between the Omicron major subvariants, such as BA.1 and BA.2, have been reported. Additionally, the recombination was observed in VOCs and VOIs [214]. Evidence shows that co-infection and subsequent genome recombination are crucial to SARS-CoV-2's continual evolution. Eighteen core

mutations of BA.1 (frequency >99%) and 27 core mutations of BA.2 (nine more than BA.1), of which 15 are unique to Omicron, were found by examining high-quality finished Omicron spike gene sequences. The majority of VOCs and BA.1 subvariants had nine common amino acid alterations (three more than BA.2) in the spike protein, which raises the possibility that Omicron descended from these VOCs through recombination. In comparison to BA.2, BA.1 has three additional mutations that are connected to Alpha, and BA.1 is phylogenetically closer to Alpha than other variations. Some dominant mutations in the BA.1 have revertant mutations (frequency > 95%). Most significantly, many distinctive amino acid alterations in the "Deltacron"-like Omicron Variants isolated after November 11, 2021, in South Africa have also been found, indicating recombination events between the Omicron and Delta variants [214]. All these observations suggest that the recombination among various variants and sublineages/subvariants is a major threat to public health.

Furthermore, Das et al. stated in their recent review that the emergence of the Omicron variant is not the end of the COVID-19 pandemic because a super strain or recombinant strain known as Delmicron, which combines earlier Delta and Omicron types, has been discovered in some regions of the world. If it has virulence like Delta and a transmissibility frequency like Omicron, it will become more severe due to a combination of both VOCs. The recombinant strain might represent a major challenge to the world [215]. Furthermore, during the co-infection of two VOCs, AY.33 (Delta) and P.1 (Gamma), intra-host SARS-CoV-2 recombination was observed in a recent investigation. The intersecting areas that overlap lineage-defining mutations from Gamma and Delta were discovered using next-generation sequencing. Within a single sample, six recombinant areas have been discovered, four of which are mapped in the S-protein gene and two in the nucleocapsid gene. Mosaic reads containing a mix of VOC lineage-defining mutations have been discovered. It was the first study of intra-host RNA-RNA recombination between two SARS-CoV-2 lineages, which might pose a danger to public health management during the COVID-19 pandemic if viruses with

recombinant phenotypes develop [21]. In this context, it is important to remember that Omicron sublineage recombination with other VOCs might have disastrous consequences during the continuing pandemic.

Recently, WHO reported the emergence of three recombinant variants of SARS-CoV-2, namely XE (BA.1 & BA.2), XF (Delta & Omicron), and XD (Pango lineage & Delta/Omicron), with potentially high rates of transmission that require further investigation through threat assessment analysis [216]. While many strains infect a similar individual simultaneously, recombinant strains can evolve. This enables variants to combine during replication by mixing their genetic elements in the human body, resulting in unique combinations. Such occurrences are more likely to occur when viral infections are on the rise, as COVID-19 cases are on the rise again after a period of decline [211]. As a result, there is a significant need to restrict the spread of variants among the general population in order to prevent the establishment of any possible recombinant strain of SARS-CoV-2. Tracking the SARS-CoV-2 genotypes as they develop, especially for recombination, is crucial for identifying any sudden alterations to viral properties, such as its epitopes, that might require vaccine adjustments [214].

6. Prevention and control measures

Recent findings highlight the need for viral surveillance and sequencing in animals, particularly those that come into close contact with humans. Additionally, computational assessment of the RBD of S-protein and identification of their propensity to interact with human ACE2 would most likely aid in the prevention of future SARS-CoV-2 variant epidemics [49]. In light of the future concerns, in the following sections, we will provide all the possible preventive measures to combat deleterious consequences associated with the omicron variant or the emergence of any future variants as well (Fig. 8).

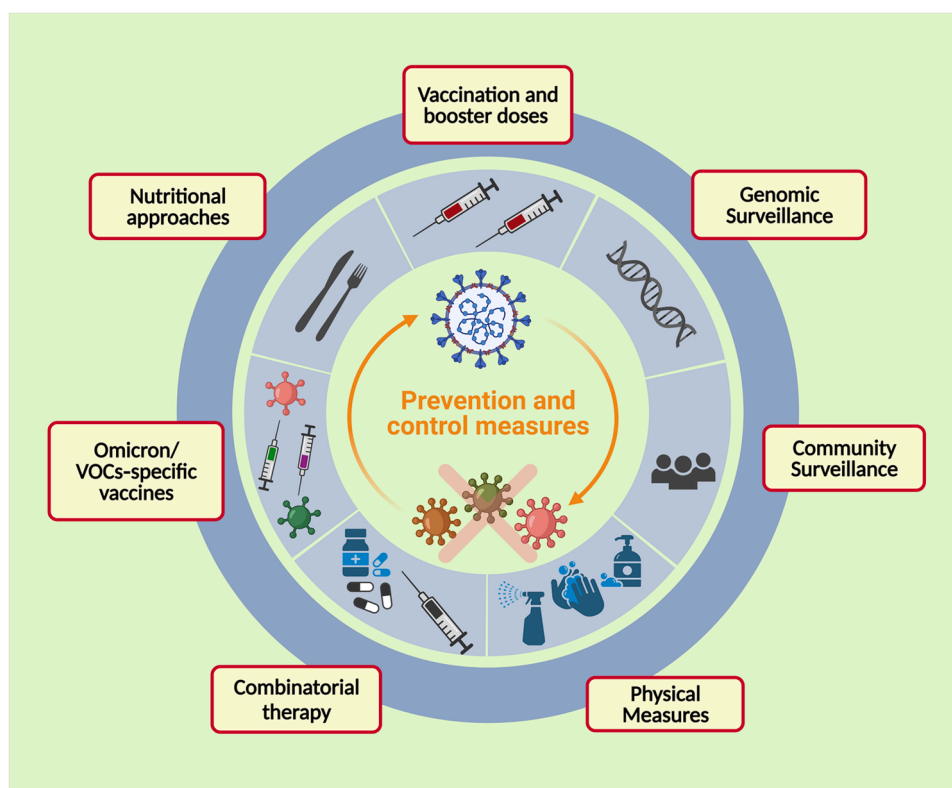


Fig. 8. The representation of preventive measures to contain the possible deleterious consequences associated with the Omicron variant.

6.1. Physical measures

The exact characteristics of the Omicron variant have been described by various recent studies. In this context, given the mutations in the S-protein, especially concerning that Omicron may have developed with the potential to spread more easily among individuals and to withstand currently effective antibody therapies. This situation emphasizes the significance of retaining current public health preventative measures, such as mask use, regular ventilation, physical distance, and hand hygiene. These procedures have been shown to be successful in preventing the spread of viral strains, and they should be useful in stopping the spread of the Omicron variant and its sublineages as well. Additionally, early diagnosis and quarantine are also important elements in limiting viral spread during a pandemic. Epidemiological research suggests that the failure of PCR tests targeting the spike gene is growing in tandem with the number of people diagnosed with Omicron and its sublineages. To stop the Omicron strain from spreading, it's also vital to improve diagnosis accuracy so that detected patients can be isolated and treated quickly [217].

6.2. Combinatorial therapy

Currently, a drug concoction has been recommended as the first line of protection against coronaviruses [218]. In COVID-19 patients, it has been believed the combination of molnupiravir and nirmatrelvir is critical for improving antiviral efficacy, limiting toxicity, and avoiding drug resistance. Potential antiviral therapy, particularly fast viral load reduction, is predicted to enhance patient outcomes while also limiting virus transmission. When oral antiviral medications become widely available and inexpensive, their use in the real world would be a huge breakthrough in countering the Omicron variant's spread [196].

Molnupiravir and nirmatrelvir have been shown to effectively prevent or protect against the infection caused by the Omicron variant. The uses of molnupiravir and nirmatrelvir together have a significant antiviral effect. Despite this, their findings suggest that molnupiravir and nirmatrelvir should be used to treat Omicron-infected individuals. They also urge the start of clinical trials to assess the efficacy of molnupiravir and nirmatrelvir in treating COVID-19 [196]. Additionally, recent studies have revealed the potential of another oral antiviral drug called Paxlovid against COVID-19. Paxlovid interferes with the SARS-CoV-2's processing proteins, preventing it from spreading. In COVID-19 patients, up until this point, the prescription of oral antiviral drugs has been well received [219–221]. Nevertheless, further research is required to fully understand any potential negative effects [221]. The use of a concoction of different drugs is a novel approach that can be significantly better than the use of traditional therapeutics. The use of mAbs, along with antiviral drugs such as remdesivir, can be exploited.

6.3. Vaccination and booster doses

Even though some forecasts suggest that the explosive growth of Omicron in South Africa might indicate the start of a new pandemic wave throughout the world, the impact of this strain and what it signifies for the present pandemic has been unresolved by several recent studies. In reality, the situation with Omicron expansion in South Africa might be very different from that in other nations. In South Africa, for example, only approximately 20% of the population is properly vaccinated. This figure is significantly lower than the worldwide average immunization rate [27]. A significantly lower percentage of vaccination has been associated with the accelerated spread of the Omicron variant and its sublineages in South Africa, underlining Africa's urgent need for increased vaccine coverage [217]. Despite the fact that the authorized COVID-19 vaccines have shown decreased effectiveness against variants [222–224], the vaccines have been shown to be successful in avoiding severe diseases, hospitalization, and fatality [222,225–227]. Hence, it is essential to vaccinate the maximum number of people while providing

booster doses to the immunocompromised and elderly population. It is possible to reduce virus transmission, hospitalization rates, and death by the fair allocation of vaccinations among the developing and developed nations and the use of oral antiviral medications at the outset of illness [221].

Decreased concentrations of the antibodies in those infected with SARS-CoV-2 or those who have been vaccinated against it may potentially aid in the development and survival of novel strains. In light of many studies, showings that serum neutralizing antibodies drop drastically six months after immunization and that booster vaccination might restore and even increase vaccine efficacy [228,229]. As a result, it has been postulated that providing an extra booster dosage of COVID-19 vaccine to the immunization programs of the countries will surely aid in the management of Omicron infection and dissemination of its [217], which in turn halt any plausible repercussions associated with the emergence of sublineages of the Omicron variant.

In addition, it was stated in a recent study that vaccine-induced immune protection would be more likely to be evaded by Omicron compared to prototypes and other VOCs. Hence, it has been suggested that following the administration of two doses of inactivated whole-virion vaccinations as the "priming" shot, a third heterologous protein subunit vaccine and a homologous inactivated vaccine booster have the potential to increase the neutralization potentials against the Omicron variant [207].

Primary vaccination, along with booster doses, significantly increases the antibody-mediated immune response, which results in serum neutralizing activities against VOCs that are comparable to or greater than the neutralizing activity against the parental strain achieved by vaccination [213,230,231]. Antibody somatic mutation, memory B cell clonal turnover, and development of monoclonal antibodies have been seen as possible mechanisms which provide an immune response that is not susceptible to the mutation found in the RBD of S-protein of the VOCs [205].

Furthermore, B cell clones that produce broad and effective antibodies are kept in the repertoire throughout time and grow significantly following immunization. The findings show that convalescent immunity will be highly long-lasting and that those who get accessible mRNA vaccines will generate antibodies and memory B cells that should protect them from circulating strains of SARS-CoV-2 [232]. Hence, pushing for booster shots as quickly as possible, especially among susceptible groups, should be considered as the utmost need [233].

6.4. Omicron/VOCs-specific vaccines

The appearance of the Omicron variant in South Africa has been linked to an increased risk of SARSCoV2 reinfection, suggesting that the Omicron variant may be connected with a significant ability to circumvent protection provided by past infection [15,18]. Furthermore, there is a lot of interest in seeing if the existing COVID-19 vaccinations can protect against the Omicron strain and its sublineages along with recombinant variants. According to the most recent studies, COVID19 vaccinations give less protection to the omicron form than other VOCs [217]. Nevertheless, compared to the parental strain, vaccinated persons' plasma demonstrated a decreased neutralizing capability against the Omicron variant [51]. However, it will be proved in the future that the available vaccines provide may or may not provide protection for newly emerged sublineages of the Omicron variant. Such findings exhibited that COVID-19 vaccines may not be as effective against the Omicron variant as they are against other VOCs and VOIs. Hence, further details on the efficacy of existing COVID-19 vaccines will be needed. Mutations in the S-protein of the Omicron variant may affect the efficiency of presently available vaccinations [224]. In a recent study, it has been shown that the vaccines developed against spike mutations have a higher level of neutralizing antibodies (nAbs) against emerging variants but recorded reduced neutralization potential against the parental strain of SARS-CoV-2 [217].

These findings emphasized the significance of establishing variant-specific vaccines focused on the S-protein mutations, particularly for the Omicron variant. As a result, based on the altered S-protein of the Omicron variant, targeted vaccinations against the Omicron variant have been developed. In addition, vaccines developed on other strains but having one or more mutations of the Omicron variant might be utilized to combat Omicron infection and dissemination. Unofficial data implies that Moderna has designed two multivalent vaccine candidates: candidate mRNA1273.211 is thought to contain several mutations found in both the Omicron and Beta variants, while mRNA1273.213 is thought to contain a certain number of mutations found in the Omicron, Beta, and Delta variants [234,235]. Additional research on the efficacy of such potential vaccines against the Omicron variant is required [235].

6.5. Genomic surveillance

Genomic surveillance and evolutionary dynamics investigations should be conducted significantly more frequently, as well as contact tracing of variants. This would greatly aid the current understanding of VOCs, especially the VOCs like the Omicron variant, allowing researchers to amend COVID-19 vaccines and develop second-generation vaccines [236]. Genomic surveillance employs next-generation sequencing techniques, tends to create whole-genome data available, and enhances phylogenetic methods. Technological innovations created additional avenues for detecting phenotypically or antigenically different variants [237,238]. In the battle against viral outbreaks like SARS-CoV-2 and its variants, genomic surveillance is crucial, and it must be implemented globally in a systematic and integrated manner. Despite waiting for herd immunity to be obtained by vaccination, it can provide the crucial data needed to construct a more personalized public health plan that addresses local priorities through stakeholder engagement and mitigation actions. Additionally, enhanced global coordination offers unique opportunities for attaining rapid genomic monitoring and using high-income countries' experience, notably the United Kingdom's, and spreading it to low- and middle-income countries throughout the world. The discovery of efficient techniques to mitigate and control epidemics will be aided by genomic surveillance, which will allow for improved early identification of SARS-CoV-2 modifications and the emergence of novel variants of SARS-CoV-2 [237].

In the fight against COVID-19, genome-based surveillance has proven to be effective. The extraordinary volume of genomic information, with six million full SARS-CoV-2 genome sequences now in repositories, poses a challenge to existing information storage, processing, and bioinformatics analysis methods [239–242]. These systems were still in the early phases of construction when SARS-CoV-2 appeared in December 2019 due to a variety of technological challenges. COVID-19 has resulted in the rapid deployment of financial, scientific, and developmental resources, with several worldwide monitoring systems supplying resources for epidemic response employing SARS-CoV-2 genome analysis. The prompt deployment of GISAID and Nextstrain in response to COVID-19 is one prominent example. SARS-CoV-2 genetic data collection and analysis have been consolidated thanks to this technique [242].

6.6. Community surveillance

Infection prevention and clinical management, along with case detection, contact tracing, and community surveillance, are effective strategies that can be employed to contain COVID-19 [243]. Early detection and reporting can be beneficial, and contact tracing is a common monitoring strategy widely used to combat the ongoing pandemic [243]. Contact tracing and surveillance in the community can be exploited as an efficient and reliable strategy to comprehend the dissemination and epidemiology of any sudden outbreak of COVID-19 cases due to the emergence of novel variants and their sublineages [243]. Many countries have faced two or three waves of COVID-19 cases

due to the emergence of VOCs such as Delta and Omicron variants. In this context, scientists have claimed that the dissemination of the variants and associated mortality rate can be contained with community surveillance and contact tracing. In the United Kingdom, app-based contact tracing has been proven as an efficient strategy to reduce the death rate, which can be a reliable method to contain any future outbreaks in other countries [244]. Proximity tracking, a digital technological system, has been used as an effective surveillance system to contain the negative repercussions of the pandemic [243,245].

6.7. Nutritional approaches

Some dietary supplements, in addition to drug repurposing, may be beneficial in the management of SARS-CoV-2 patients with mild symptoms [246]. Undernourishment has a negative impact on the immune system, dampening immune responses and promoting susceptibility to viral infections such as SARS-CoV-2. As a result, boosting immunity against infections and diseases by improving gut health with a nutrient-dense diet [246,247] can be an efficient strategy to reduce the mortality rate [248]. Higher-than-recommended daily dosages of minerals, such as vitamins, zinc, and selenium, may have a beneficial effect on individuals with SARS-CoV-2, reducing viral load and length of hospitalization. Certain micronutrients, especially vitamin D and B, along with zinc, have been found to have immunoregulatory capabilities, reducing the harmful consequences of a variety of viral infections [249–260]. As a consequence, merging dietary methods with other pharmaceutical regimens might be a safe and effective strategy for treating Omicron-infected persons [247].

7. Conclusion and future directions

Many nations have documented the Omicron variant and its sublineages, which have since been viewed as a serious danger to containment strategies against COVID-19. Because of the significant proportion of mutations in the RBD (receptor binding domain) of the spike-protein (S-protein), the Omicron variant is believed to have exacerbated transmissible potentialities. However, it is yet unknown if it will cause a serious ailment or if it will be immune to vaccines. Furthermore, many experts believe that the Omicron variety may readily escape an individual's humoral immune response, increasing the chances of reinfection dramatically. There seem to be no definitive answers to these questions, but also several studies have found that VOCs (Variants of Concern) successfully undermine the neutralizing capabilities of antibodies acquired from COVID-19 vaccines and earlier infections, implying that the Omicron variant and its emerging sublineages can conveniently circumvent the immune protection acquired from vaccines. Nevertheless, recombinant strains such as Delta-micron, which combine previous Delta and Omicron forms, have been detected in some regions of the world, suggesting that the advent of the Omicron variant is not really the culmination of the pandemic. If it has virulence like Delta and a transmissibility potential like Omicron, it will become more terrible due to a combination of both of these VOCs. The novel recombinant variant might represent a significant threat to mankind. Likewise, the recent discovery of recombinant variants, XE, XF, and XD might lead to an increase in COVID-19 cases, worsening the situation. Several containment methods, such as using genomic and community surveillance, as well as expanding vaccination and offering booster doses to the susceptible group, have been developed in order to limit the harmful consequences associated with the Omicron variant.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets supporting the conclusions of this study are included within the article.

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