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Review Article

Inter-variant Recombination, Genomic Perspectives and Pathogenicity of Emerging Sub-variants of Omicron: Recent Updates and Challenges

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Abstract

The years 2019–2021 of the twenty-first century are synonymous with the COVID era, as the Coronavirus disease 2019 (COVID-19) wreaked havoc and continues to be aggressively persecuted. Globally, about 300 million COVID-19 cases and nearly 5.3 million fatalities have been recorded so far. Since then, the coronavirus RNA genome has rapidly mutated, giving rise to several mutant and recombinant variants. On March 9, 2022, a new recombinant known as Deltacron/Delmicron emerged due to inter-lineage recombination between Delta and Omicron. Many researchers consider it a "grey rhino" occurrence rather than a "black swan" event. However, some groups of scientists claim it is a "laboratory error". Another COVID-19 variant, XE (a recombination of BA.1 and BA.2), has been discovered, which has a transmission rate ten times higher than the fastest-spreading Omicron subvariant BA.2. Delta and Omicron, two of the most novel strains, co-circulated for many weeks in several parts of the globe, allowing for coinfections and eventual recombination. Consequently, the recombinant strains XD and XF are associated with a very high transmission rate and reduced neutralizing antibody response. Under these circumstances, researchers are rushing to develop a vaccine with high efficacy against the circulating mutants and the variants likely to emerge in the near future. This review article provides recent updates on newly identified sub-variants of Omicron with an in-depth focus on their genomic alterations, infectivity patterns, and pathogenic manifestations.

Introduction

Since late 2019, the world has been experiencing the emergence and rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for the pandemic of acute respiratory disease named "coronavirus disease 2019 (COVID-19)".[1–3] The single-stranded RNA virus SARS-CoV-2 belongs to a highly diverse, mutated family (genus: Coronavirus, family: Coronavirinae, order: Nidovirales).[4] Due to rapid genomic alterations, the strain has become highly mutated, resulting in several variants reported one after another, termed Alpha (α), Beta (β), Gamma (γ), Delta (δ), and Omicron, with enhanced rates of transmission and immune evasion.[5] As per report 10 million people have been infected by COVID-19 worldwide, causing abundant mortality.[6] Nearly three years since it began, the pandemic has been on a downward trend with a decreasing death rate due to rising immunity from vaccinations, which helped combat the illness and allowed most countries to return to pre-COVID conditions.[7] Some emerging variants are categorized as variants of concern (VOCs) such as α variants (B.1.1.7), β variants (B.1.351), γ variants (P.1), and δ variants (B.1.617.2). Others are categorized as variants of interest (VOIs) such as Eta, Iota, Epsilon, Zeta, Kappa, Mu (B.1.621), and Lambda (C.37) by the World Health Organization (WHO).[8,9] Apart from VOCs and VOIs, some variants are designated as "variants under monitoring (VUMs)", such as Pango Lineage AZ.5, B.1.630, C.1.2, B.1.526, B.1.617.1, and B.1.525, which are supposed to possess genetic alterations.[10] The highly contagious Delta variant (B.1.617) with an additional K417K mutation was first discovered in India in October 2020. It later emerged as the Delta Plus variant (B.1.617.2.1), responsible for the second wave of COVID-19.[8,11] The situation took an unusual turn when, on No-

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vember 9, 2021, the first significant Omicron variant (B.1.1.529) was identified from a trial in neighboring Botswana, South Africa.[12] This variant was divided into BA.1, BA.1.1, BA.2, and BA.3 sub-lineages, which will continue evolving over time.[13] The Omicron (BA.1) variant has approximately 50 mutations involving deletions, replacements, and insertions of amino acids. Of these, 32 mutations are in the S-glycoprotein domain (E484K, N440K, F490L, Q493K). A recent study identified several mutations in the viral genome, located in different regions: the Spike (S) protein (D614G, E484K, K417N/T, N501Y, L452R, T478K), the antibody binding region (N501Y, D614G, H655Y, N679K, P681H), near the antibody binding area (S477N, G496S, G446S, T478K, and N440K), the receptor binding domain (RBD) (K444 Q/R/N and V445E), and the N-terminal domain (N148S and K150 T/Q/R/E).[14,15] Although B.1.1.529 shares the 69–70 deletion with about 50% of the available sequences, it is still developing. The spike protein in BA.3 also has a 69–70 deletion.[16] Based on Bayesian phylogenetic methods, it was revealed that two other Omicron sub-lineages, BA.4 and BA.5, were discovered, respectively, between mid-December 2021 and early January 2022. Although BA.4 and BA.5 show similar mutational patterns, they exhibit genetic divergence.[17] On March 9, 2022, researchers from the Institut Pasteur, Paris, provided solid evidence of a hybrid recombinant strain "Deltacron". This newly formed virus uses Delta as its genomic spine, replacing a large section of the original Spike (S) gene with an Omicron ortholog (BA.1).[18] By March 18, 2022, this new lineage was detected across France, the Netherlands, Denmark, Belgium, Germany, the US, and the UK.[19] The UK Health Security Agency (UKHSA) also identified some recombinant strains of Delta and Omicron, such as XD, XE, and XF, in January 2022.[20] The XD variant contains genomic elements (ORF1a and ORF1b) from Delta, and the spike protein from Omicron (BA.1) with the mutation E172D in the genomic region of NSP2. The XE variant was derived from 11,537 bp genomic elements of two Omicron sister variants, BA.1 and BA.2. Similarly, XF contains up to 5,386 bp genomic elements from Delta, followed by genomic elements from the Omicron BA.1 variant.[20]

This review highlights the different mutations in the S-protein of SARS-CoV-2 variants, the causes of these mutations, and discusses recent and upcoming variants. Additionally, it addresses recombination events at the inter-lineage level of different mutant variants, making the emerging variants far more challenging due to their increased transmissibility, resulting in hyper-transmissible recombinant variants.

Variants and the different types of SARS-CoV-2 mutations

Omicron

The SARS-CoV-2 virus contains the S protein, which comprises the S1 subunit, the S2 subunit, and a cleavage site known as Furin protease. The S1 subunit includes the RBD and the N-terminal domain. The angiotensin-converting enzyme II (ACE2) receptor interacts with the receptor-binding motif (RBM) present on the membrane of human cells, which helps the virus evade the immune system and increases its transmissibility.[21] To date, diverse variants of SARS-CoV-2 have been identified, circulating globally with different protein sequences, including Alpha (lineage B.1.1.7), Beta (lineage B.1.351), Gamma (lineage B.1.1.28.1), Delta (lineage B.1.617.2), Omicron (lineage B.1.1.529), Deltacron (AY.4-BA.1), XD (Delta-Omicron), XE (BA.1-BA.2), and XF (Delta-Omicron).[22] Genome sequencing revealed that the Omicron variant corresponded to the Nextstrain clade 21K, the Pango lineage B.1.1.529, and the Global Influenza Surveillance and Response System (GISAID) clade GR/484A.[21] Structural analysis indicates a higher number of non-synonymous mutations in the S-protein, making the virus more transmissible and capable of immune escape. Among those variants, circulating worldwide, four S-proteins (A570D, D1118H, S982A, T71I) are found in the Alpha variant; six S-proteins (A701V, D215G, D80A, Δ241, Δ242, Δ243) in Beta, eight (D138Y, L18F, K417T, P26S, T1027I, R190S, T20N, V1176F), with T19R and (V70F*) in Gamma, ten [T95I, E156-, G142D, F157-, R158G, (W258L*), (A222V*), (K417N*), T478K, L452R, D614G, D950N, P681R] in Delta; and finally, as many as thirty four (A67V, del142-144, T95I, del69-70, del211, Y145D, L212I, S371L, G339D, ins214EPE, S375F, S373P, N440K, K417N, S477N, G446S, T478K, Q493R, E484A, G496S, N501Y, Q498R, H655Y, Y505H, D614G, P681H, T547K, N856K, N679K, Q954H, N764K, D796Y, L981F, N969K) in Omicron.[23] As of now, more than 60 mutations (deletions, alterations, and insertions) have been found in the Omicron genotype, including 30 substitutions (Y145D, A67V, T95I, S371L, L212I, G339D, S373P, K417N, S375F, G446S, N440K, T478K, S477N, G496S, E484A, Q493R, Q498R, N501Y, Y505H, T547K, H655Y, D614G, N679K, D796Y, P681H, N764K, N856K, N969K, Q954H and L981F), three deletions (V70/H69, N211, and G142/V143/Y144), and one insertion (EPE214). Several mutations can also be found in the envelope (E) protein (*T9I*), the membrane (M) protein (D3G, A63T, and Q19E), and the nucleocapsid (N) protein (P13L, G204R, and R203K), which may increase the virus's contagiousness.[24] There are fifteen mutations in the RBD of Omicron. The RBS-A, RBS-B, RBS-C, S309, and CR302 antigenic sites have been characterized in the RBD, and one or more of the 15 Omicron spike RBD mutations can be found in all of them.[24] The S-protein of the Omicron variant carries some common mutations identical to previous VOCs and VOIs, including (Δ69–70, N501Y, P681H, D614G), (K417N), (H655Y, K417N), and (T478K) found in Alpha, Beta, Gamma, and Delta, respectively. Because of this wide range of mutations, Omicron has approximately 10-fold higher transmissibility, infectivity, and virulence than the original virus and 1.4 to 3.1-fold higher compared to Delta.[21] It is worth noting that the Omicron variant also contains three mutations (H655Y, N679K, and P681H) near the furin cleavage site, which makes the virus more transmissible than previous variants.[24] Omicron also reveals three substitutions (T478K, Q493K, and Q498R) that help it bind to ACE2 receptors with much more affinity than its prototype SARS-CoV-2, increasing the binding affinity ($\Delta G^{WT} = 64.65$ kcal/mol < $\Delta G^{Omic} = 83.79$ kcal/mol) of the RBD^{Omic} with ACE2.[25] The Omicron variant accumulated a staggering number of mutations in the open reading frame 1ab (ORF1ab) as well as the S-protein. ORF1a possesses six substitutions (A2710T, K856R, L2084I, P3395H, T3255I, and I3758V), ORF1b has two substitutions (P314L and I1566V), and an additional mutation was identified in ORF9b (P10S). However, only two mutations (nsp4: T492I or ORF1a: T3255I and nsp12: P323L or ORF1b: P314L) with noteworthy prevalence (>40%) were perceived in Delta and Delta Plus variants.[24,26]

Sub-variants of Omicron

The Omicron variant (BA.1/B.1.1.529.1) and its three sub-lineages (B.1.1.529.1.1/BA.1.1, B.1.1.529.2/BA.2, and B.1.1.529.3/BA.3) were initially discovered in the same region. BA.1 [hCoV-19/Botswana/R40B59_BHP_3321001248/2021 (EPI_ISL_6640916) (November 11, 2021, in Botswana, Greater Gaborone, South-East, Gaborone)], BA.2 [hCoV-19/South Africa/CERI-KRISP-

K032307/2021 (November 17, 2021, in South Africa, Gauteng, Tshwane)], and BA.3 [hCoV-19/South Africa/NICD-N22163/2021 (EPI_ISL_7605713) (November 18, 2021, in South Africa, North-West)]. Over time, Omicron has been found to be more contagious. According to the GISAID database, a total of 258,129 complete genome sequences had been recorded by January 11, 2022. Of these, BA.1 accounted for 99.13% (255,898/258,129), BA.2 accounted for 0.85% (2,198/258,129), and BA.3 was accounted for 0.013% (33/258,129).[27] Two novel Omicron lineages, BA.4 and BA.5, were found in South Africa and have identical spike proteins. These lineages caused a resurgence in infections from the first week of April 2022 onwards.[17]

BA.1, BA.1.1, BA.2, and BA.3 lineages

Different sub-lineages of Omicron are referred to as BA.1, BA.1.1, BA.2, and BA.3. Each of these sub-lineages has 39, 40, and 31 mutations, respectively, with 21 shared mutations (G142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, N969K, and Q954H) among all of them (Table 1).[14,17,28–30]

Along with 21 shared mutations, mutations at the RBM (Q493R, N501Y, Q498R, T478K, and Y505H) create a higher positive electrostatic surface potential, which could increase the interaction rate between the viral RBD and the electronegative human angiotensin-converting enzyme-II (hACE2). Other mutations, including N679K, H655Y, and P681H, also facilitate the prefusion state of the spike protein.[13,27,31] BA.1 and BA.1.1 share 8 common mutations (A67V, ins 214EP, R216E, S371L, N856K, G496S, T547K, L981F), while BA.2 and BA.3 share two common mutations (S371F, D405N). Additionally, 10 common mutations (Y145del, N211I, L212V, V213R, G446S, H69del, V70del, T95I, V143del, Y144del) are found among BA.1.1, BA.1, and BA.3.[13] Though BA.1 and BA.2 have 21 spike mutations in common, BA.1 and BA.2 share nine and six common amino acid mutations, respectively, with most VOCs. This suggests the possibility of the genesis of Omicron from these VOCs (Table 2).[10,13,31–33]

The BA.2 sub-lineage lacks a particular genetic structure that distinguishes it from the standard or original variety, to be known as "Stealth Omicron".[34] Among all Omicron sub-lineages, BA.3 and BA.2 have greater transmission potential than BA.1.1 and BA.1. This study predicted that mutations in BA.1.1 (K478), BA.2 (R400, R490, and R495), and BA.3 (R397 and H499) form hydrogen bonds and new salt bridges. Omicron and its sub-variants or lineage mutations at RBM residues such as Q498, Q493R, N501Y, Y505H, and T478K, significantly contribute to the binding affinity with human ACE2. Interactions involving Omicron variant mutations at residues 493, 496, 498, and 501 seem to restore ACE2 binding efficiency lost due to other mutations like *K417N*.[13] BA.2 sub-lineages, including BA.2.12.1 (BA.2+L452Q+S704L) and BA.2.13 (BA.2+L452M), exhibit higher ACE2-binding affinities compared to BA.1 and exhibit higher transmissibility due to the L452 mutation compared to BA.2.[28] Some researchers discovered that BA.2 was significantly more resistant to one class of antibodies that bind to the S-protein portion involved in host cell binding than BA.1, while BA.2 was more sensitive to another type of spike antibody.[35]

BA.4 and BA.5 lineages

The Network for Genomic Surveillance in South Africa identified the BA.4 and BA.5 subvariants of Omicron in January and February of 2022, respectively. By April, these lineages had become the most prevalent, causing the fifth wave of this infection.[36] From April 2022 onwards, these two lineages quickly superseded BA.2, accounting for over 50% of identified cases. By the end of April 2022 in South Africa, BA.4 and BA.5 comprised 35% and 20% of cases, respectively.[37] Mutually the variants share identical amino acid (25 spike mutations) mutations, including F486V, along with the spike trimers T4 fibritin trimerization domain, GSAS, and 6P mutations.[28,34] BA.4 and BA.5 have additional S-mutations such as 69-70del, F486V, L452R, and the wild-type amino acid at Q493, compared to the BA.2 variant (Table 1). Additionally, BA.4 differs from BA.5 by having the N: P151S mutation as well as mutations at N: P151S and ORF7b: L11F as well as a triad amino acid deletion in NSP1: 141-143del outside of the S-protein. BA.5 also has the M: D3N mutation. On the other side, BA.5 has extra reversals at ORF6: D61 and nucleotide positions 27,259 and 26,858, relative to BA.2. Both BA.4 and BA.5 have an identical mutation in NSP8 (nuc: G12160A). Mutations in spike amino acids (L452R, F486V, and R493Q) facilitate the binding between hACE2 and antibodies.[17,38] Although both the BA.4 and BA.5 variants exhibit higher transmissibility due to the L452 mutation compared to BA.2, they have lower receptor-binding capability due to the R493Q and F486V reversals, potentially slowing their dispersion.[28] Compared to BA.2, which spread more than the initial Omicron strain BA.1, BA.4 and BA.5 are more infectious. Omicron variations cannot be detected by several spike gene-targeted PCR tests due to minor losses in this gene.[39] According to studies, BA.5 and BA.4 lineages have arisen with variations like the F486V and L452R mutations in the S-protein receptor binding domain, relative to BA.1 (Omicron). The BA.5 and BA.4 S-proteins are similar to BA.2 (Omicron) except for the L452R and F486V, 69–70 additional deletion. In comparison to BA, both contain the amino acid changes R493Q, L452R, and F486V in the S-protein receptor binding domain. The F486V mutation in the S-proteins of the BA.4 and BA.5 lineages contributes to increased infection. Additionally, the BA.4 and BA.5 lineages can evade immunological reactions.[37]

Delmicron or Deltacron

On January 7, 2022, a group of scientists from Cyprus University in Nicosia, led by virologist Leondios Kostrikis, identified a new "Super Variant" that possesses constituents of both Delta (lineage AY.4) and Omicron (lineage BA.1). They nicknamed it "DELTACRON" and 25 sequences were submitted to the open-source database GISAID.[40] This hybrid variant has the nearly complete spike gene (codons 156 to 179) of an Omicron variant (21K/BA.1) within the spine of the Delta (21J/AY.4) lineage.[41] Genomic analysis of "DELTACRON" revealed that recombination events are rare and only occur in the S gene at the inter-lineage level, as this recombinant variant originated from divergent lineages of the same species, AY.4 and BA.1. The S-protein has 36 amino acid mutations: 27 found in BA.1, 5 in AY.4, and four shared by both BA.1 and AY.4 (Fig. 1).[42,43] On November 11, 2021, the first "Deltacron"-like Omicron strain was isolated in South Africa, followed by Botswana on November 23.[32] In immunocompromised individuals, simultaneous infections with Delta (considered the most deadly) and Omicron (considered the most mutated) may facilitate this recombination, although it is an exceedingly rare event.[22] Shishi Luo, a senior scientist of bioinformatics at the genomics company Helix, explained that if both Delta and Omicron variants infect the same cell simultaneously, there is a possibility of forming this new recombinant variant, Deltacron or Delmicron. When Omicron was detected in America, 29,719 positive samples were collected and sequenced over four months from November 2021 to Febru-

Table 1. The comparison of mutation between different Omicron lineages[14,17,28–30]

Mutations	Variants						
	BA.1	BA.1.1	BA.2	BA.2.12.1	BA.2.13	BA.3	BA.4/BA.5
T19I			Δ	Δ	Δ		Δ
L24S			Δ	Δ	Δ		Δ
del25-27			Δ	Δ	Δ		Δ
A67V	Δ	Δ				Δ	
del69-70	Δ	Δ				Δ	Δ
T95I	Δ	Δ				Δ	
G142D	Δ	Δ	Δ	Δ	Δ	Δ	Δ
del143-145	Δ	Δ				Δ	
N211I	Δ	Δ				Δ	
del212	Δ	Δ				Δ	
V213G			Δ	Δ	Δ		Δ
G339D	Δ	Δ	Δ	Δ	Δ	Δ	Δ
R346K		Δ					
S371L	Δ	Δ					
S371F			Δ	Δ	Δ	Δ	Δ
S373P	Δ	Δ	Δ	Δ	Δ	Δ	Δ
S375F	Δ	Δ	Δ	Δ	Δ	Δ	Δ
T376A			Δ	Δ	Δ		Δ
D405N			Δ	Δ	Δ	Δ	Δ
R408S			Δ	Δ	Δ		Δ
K417N	Δ	Δ	Δ	Δ	Δ	Δ	Δ
N440K	Δ	Δ	Δ	Δ	Δ	Δ	Δ
G446S	Δ	Δ				Δ	
L452M					Δ		
L452Q				Δ			
L452R							Δ
S477N	Δ	Δ	Δ	Δ	Δ	Δ	Δ
T478K	Δ	Δ	Δ	Δ	Δ	Δ	Δ
E484A	Δ	Δ	Δ	Δ	Δ	Δ	Δ
F486V							Δ
Q493R	Δ	Δ	Δ	Δ	Δ	Δ	
G496S	Δ	Δ					
Q498R	Δ	Δ	Δ	Δ	Δ	Δ	Δ
N501Y	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Y505H	Δ	Δ	Δ	Δ	Δ	Δ	Δ
T547K	Δ	Δ					
D614G	Δ	Δ	Δ	Δ	Δ	Δ	Δ
H655Y	Δ	Δ	Δ	Δ	Δ	Δ	Δ
N679K	Δ	Δ	Δ	Δ	Δ	Δ	Δ
P681H	Δ	Δ	Δ	Δ	Δ	Δ	Δ
S704L				Δ			
N764K	Δ	Δ	Δ	Δ	Δ	Δ	Δ
D796Y	Δ	Δ	Δ	Δ	Δ	Δ	Δ
N856K	Δ	Δ					
Q954H	Δ	Δ	Δ	Δ	Δ	Δ	Δ
N969K	Δ	Δ	Δ	Δ	Δ	Δ	Δ
L981F	Δ	Δ					

Δ shows Mutation present; Blank shows Mutation absent.

Table 2. Comparison of Omicron BA.1 and BA.2 with VOCs[10,13,31–33]

	Common mutations	Mutations
Comparisons with BA.1 variant		
	9 (VOCs)	Δ69–70, ΔY144, K417N, T478K, N505Y, D614G, H655Y, P681H
	6 (Alpha – B.1.1.7)	**Δ69–70, ΔY144**, N501Y, D614G, **P681H**
	3 (Beta – B.1.351)	**K417N**, N501Y, D614G
	3 (Gamma – B.1.1.28.1)	N501Y, D614G, **H655Y**
	2 (Delta – B.1.617.2)	**T678K**, D614G
	7 (Omicron – B.1.1.529)	**Δ69–70, ΔY144, P681H, K417N, H655Y, T678K**
Comparison with BA.2 variant		
	6 (VOCs)	K417N, T478K, N501Y, D614G, H655Y, P681H (NO DELETION in Δ69–70, ΔY144)
	3 (Alpha - B.1.1.7)	N501Y, D614G, P681H
	3 (Beta – B.1.351)	**K417N**, N501Y, D614G
	3 (Gamma – B.1.1.28.1)	N501Y, D614G, **H655Y**
	2 (delta – B.1.617.2)	**T478K**, D614G

Mutations in BOLD show exclusive mutations present in that lineage. VOCs, variants of concern.

ary 2022. Out of these samples, two distinct incidences of infection with a recombinant Delta-Omicron variant, along with 20 co-infections, were discovered. This suggests that if simultaneous infection occurs in a human, the virus may eventually engage in recombination, but it remains very rare.[44] There are ongoing debates as scientific reports examine whether this recombinant strain is a sequencing error or sample contamination. Nevertheless, co-infections of Omicron and Delta variants have been observed in some populations. From December 6, 2021, to January 16, 2022, 14,214 sequences indicated co-circulating Delta and Omicron variants in the United States.[29,32] On January 9, at the Medical University of South Carolina in Charleston, Krutika Kuppalli, a member of the WHO's COVID-19 technical team, stated that no super variant like Deltacron had been formed by Omicron and Delta.[40]

XD, XE, and XF sub-variants

In January 2022, a new SARS-CoV-2 recombinant variant, an amalgamation of Omicron (lineage BA.1) and Delta (lineage AY.4), was detected in France and later named "Deltacron" by the WHO.[22] According to reports published by the UKHSA on March 25, 2022, and by the WHO in its regular epidemiological updates, three new emerging recombinant variants with high transmission rates were identified: XE (BA.1 + BA.2), XF (Delta + Omicron), and XD (Omicron + Delta). The most recent variants, XF and XE, emerged after the XD variant, which was the first to arise.[45,46]

XD sub-variant

The XD recombinant lineage was first identified in December

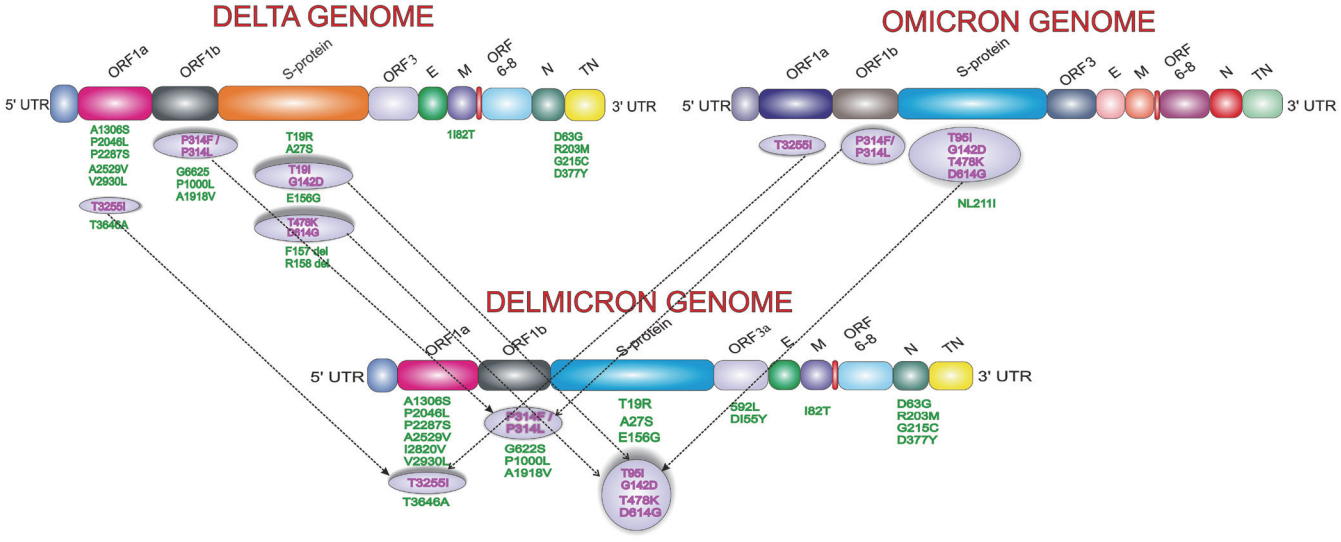

Fig. 1. DELMICRON-a inter-lineage recombinant. Inter-lineage recombination occurs between AY.4 and BA.1, giving rise to Deltacron/Delmicron, where 4 common mutations are found in S-protein (T95I, G142D, T478K, D614G) and 1 common mutation is found in each ORF1a (T3255I) and ORF1b (P314F/P314L). This recombinant variant harbor spike protein from an Omicron BA.1 genome in a Delta AY.4 spine.

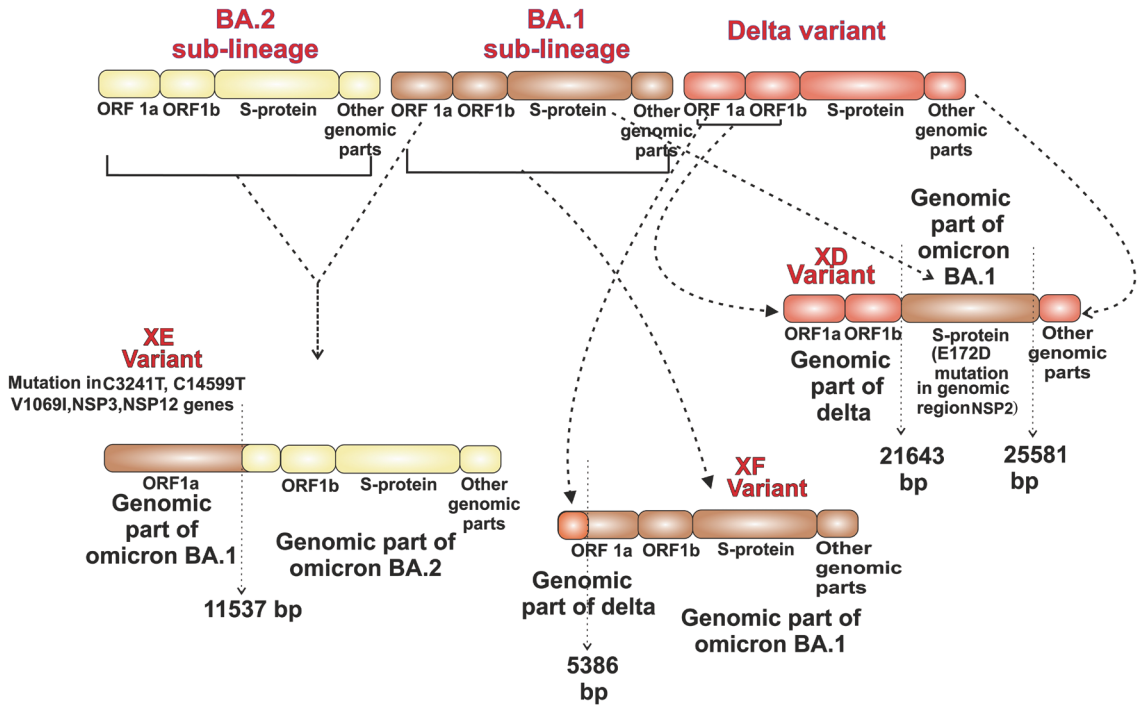

Fig. 2. Formation of XE, XD, and XF variants through recombination (Other Genomic Parts include- E, M, ORF6, ORF7a, ORF7b, ORF8, N, 3UTR). This schematic diagram shows the formation of newly formed recombinants: XD, XE, and XF. XE is formed by the recombination between two omicron lineage- BA.1 and BA.2, where recombination occurs in the ORF1a region at 11,537 bp. Both XD and XF are formed by the recombination between Delta AY.4 and Omicron BA.1. XD harbors the spike protein from the omicron genome whereas the rest of its genomic elements came from the Delta lineage. But in the case of XF, NSP1 to NSP3 came from Delta lineage and the subsequent portion is from Omicron, where recombination occurs at 5,386 bp.

2021 and established in France by the Institut Pasteur.[20,46] Although this variant was initially confined to France, as of March 18, 2022, cluster analysis and random sampling revealed that the XD lineage had spread to several Belgian provinces, as well as the Netherlands, Denmark, and Germany.[19] The XD variant includes genomic parts ORF1a and ORF1b from the Delta AY.4 genome and harbors the spike protein from the Omicron BA.1 genome. XD carries a greater fraction of its genomic parts (nucleotide positions 1 to 21,463 and 25,581 to the endpoint) from Delta AY.4, integrating a lesser portion (nucleotide positions 21,643 to 25,581) from Omicron BA.1 variant (Fig. 2). Additional XD components, such as E, ORF6, M, ORF7b, ORF7a, N, ORF8, and 3UTR, have Delta ancestry.[20] Additionally, the XD recombinant variant carries a novel E172D mutation in the NSP2 genomic region.[46]

XE sub-variant

The XE sub-variant, a recombinant of the Omicron sister variants BA.1 and BA.2, was first discovered in the UK on January 19, 2022, by genome sequencing.[22,45] Later, it has also been found in Thailand.[47] As daily COVID-19 cases rise and many countries face the possibility of a fourth pandemic wave, this virus has caused serious concern among scientists and attracted global attention.[48] The XE variant has BA.1 mutations for NSP1-6 and BA.2 mutations for the remainder of the genome, with the recombination site located within the non-structural protein (NSP6) of the SARS-CoV-2 genome (nucleotide location 11,537) (Fig. 2). Therefore, compared to BA.2, this recombinant variant has fewer genetic elements from BA.1.[20,45] However, the XE variant has three unique mutations not found in all BA.1 or BA.2 sequences: synonymous mutations C3241T and C14599T, and the amino acid mutation-V1069I in NSP3, NSP12, and NSP3, respectively, which cleaves the viral polyproteins during replication.[45,49] According to Maria Van Kerkhove of the WHO, XE appears to be 10% more transmissible than its parent variant BA.2, which was previously the most contagious strain of SARS-CoV-2. Additionally, the UK has recently recorded growth rates for XE that are up to 20% higher than those for BA.2.[50]

XF sub-variant

According to a report by the European Centre for Disease Prevention and Control, the XF variant was first identified in the UK in January 2022.[38] The XF variant comprises genomic components (NSP1 to NSP3) from the Delta variant and the subsequent portion (spike and structural proteins) from the Omicron BA.1 variant. Nucleotide positions 1 to 5,386 belong to Delta, while the remainder of nucleotides belong to Omicron BA.1 (Fig. 2). Unlike the XD variant, the XF variant contains more genetic elements from Omicron BA.1.[20]

Infection rate and pathogenicity

Omicron

Omicron contains a lot of mutations in the S-protein, such as one insertion and three short deletions, as well as the substitution of 30 amino acids, differentiating it from the ancestral SARS-CoV-2. These potent mutations allow Omicron to skillfully evade neutralizing antibodies in vaccine serum and modify its pathogenic capacity.[51] The Omicron variant spreads much faster than previous variants, boasting a 13-fold upsurge in contagion, nearly 2.8

times more contagious than the Delta variant. Two studies, one from Denmark and the other from South Africa, have revealed that the effective reproduction number of Omicron is 3.19 times (95% confidence interval: 2.82~3.61) and 4.2 times (95% confidence interval: 2.1~9.1) higher than that of the Delta variant.[52] Researchers at Hong Kong University also stated that Omicron spread faster than its previous variants.[53] By December 24, 2021, Omicron had been detected in 108 countries, affecting nearly 151,368 individuals with 26 deaths, while in India, the number stood at 358. An analysis by the ICMR (Indian Council of Medical Research) of 183 cases revealed that almost 50% of those infected were fully vaccinated.[54] Early in November 2021, reports of the Omicron (B.1.1.529) strain originated in South Africa and quickly expanded across the globe. In the UK, the same situation exists, a recent report states that between November 1 and December 11, 2021, 5,153 individuals received an Omicron infection diagnosis, 305 of which were linked to previously identified infections. The faster transmission was noticed in South Africa, where Delta is less prevalent. However, in the UK in December, where Delta was the dominant strain, Omicron rapidly replaced it, leading to a new surge in the pandemic. GISAID reported that not only in the UK but also in other countries like India, France, Brazil, and the United States, a similar situation occurred where Omicron rapidly replaced the previously existing variants. As of February 2022, Omicron had been detected and identified in more than 98.11% of global sequences, as concluded by GISAID. The dominant prevalence of Omicron continues worldwide; as of now, it has spread to 157 countries, resulting in a sharp rise in COVID-19 cases.[52,54–57] This extremely high transmission rate of Omicron (BA.1) is attributed to triple mutations such as P681H, N679K, and H655Y.[13] Omicron is not as efficient for spike cleavage, leading to inefficient transmembrane protease serine 2 (TMPRSS2) usage. SARS-CoV-2 internalizes into lung tissue via the TMPRSS2-mediated plasma membrane entry pathway. The inefficient spike cleavage and TMPRSS2 usage result in significantly attenuated virus replication in the lungs and a notable reduction in virus pathogenicity.[51,58,59] Additionally, a recent *in vivo* research study found that mice K18-hACE2 was diseased with Wild-type (WT) SARS-CoV-2, Alpha, Beta, Omicron, and Delta using the same virus inoculum showed that Omicron is less harmful compared to other strains.[51,60] Omicron contagion resulted in the highest survival rate and the lowest degree of body weight loss, replication rates, and lung damage induced by the virus in the infected mice compared with all evaluated virus strains. Omicron is not that efficient for spike cleavage, which leads to incompetent TMPRSS2 usage. SARS-CoV-2 internalizes into lung cells via the TMPRSS2-mediated plasma membrane entrance pathway. The use of TMPRSS2 and inefficient spike cleavage causes virus pathogenicity to be greatly reduced and virus multiplication to be meaningfully suppressed in the lungs.[51,58,61] Omicron (R346*K*) variation's illness characteristics, such as the Delta variant's pathogenesis or disease in hamsters, include viral replication in interstitial pneumonia and the respiratory tract. In a research study, Omicron (R346K) infection in hamsters showed low weight reduction of body and low viral RNA load present in wash samples of nasal and throat swabs, compared with Delta variant infection.[62] The remarkable resistance of Omicron to the immunological responses induced by previous infections and vaccines is noteworthy. Omicron replicates less quickly in cell cultures than the Delta and early pandemic SARS-CoV-2 variants. Experimental hamster models suggest that one reason for Omicron's reduced pathogenicity is its lower viral propagation in lung tissues. It is assumed that Omicron has developed with decreased pathogenicity because it is classified phylogenetically as an offspring of the B.1.1 lineage (B.1.1.529 and BA lineages).[60,63]

BA.1, BA.1.1, BA.2, and BA.3 lineages

A study using the Expasy protparam analyzed the amino acid number, molecular weight, amino acid composition, theoretical pI, and charged remnants, comparing BA.1, BA.1.1, BA.2, and BA.3 with the wild type (WT) (Wuhan-Hu-1). The WT comprises 1,273 amino acids, while Omicron BA.1, BA.1.1, and BA.2 have 1,270 amino acids, and BA.3 includes 1,267 amino acids, showing a deficit of three and six amino acids compared to WT. The molecular weights of WT, BA.1, BA.1.1, BA.2, and BA.3 are 141,178.47, 141,328.11, 141,300.09, 141,185.78, and 140,900.61, respectively. BA.3 has a lower molecular weight than WT due to the lack of six amino acid residues. Despite having three fewer amino acid residues, BA.1.1, BA.1, and BA.2 have a slightly higher molecular weight than WT. The theoretical pI value of the wild type is 6.24, whereas the theoretical pI values of BA.1, BA.1.1, BA.2, and BA.3 stand at 7.14, 7.14, 7.16, and 7.35, respectively. Therefore, Omicron BA.1, BA.1.1, BA.2, and BA.3 manifest as more alkaline than WT. Proteins with a solidity score under 40 have a stable structure, as per the instability index. The instability index of BA.1, BA.1.1, BA.2, and BA.3 ranges between 34.21 and 34.69, whereas the value stands at 33.01 for WT. Thus, the prior variants have slightly improved stability compared to WT. Hawkdock and ClusPro docking programs were used to establish that BA.1, BA1.1, BA.2, and BA.3 have a greater affinity for binding with *hACE2* than the WT. WT has a docking energy of −799.6 with *hACE2*, whereas BA.1 has a docking energy of −943.4, BA.1.1 has a docking energy of −946.8, BA.2 has a docking energy of −974.0, and BA.3 has a docking energy of −999.3 with *hACE2*. It was concluded that BA.1, BA1.1, BA.2, and BA.3 have a higher transmission rate than WT, and among Omicron sub-lineages, BA.3 and BA.2 have a higher affinity and communication rate. As of February 10, 2022, based on the outbreak information webpage, the overall prevalence of BA.1 (found in at least 135 countries), BA.1.1 (found in at least 69 countries), BA.2 (found in at least 69 countries), and BA.3 (found in at least 16 countries) are 8%, 5%, 1%, and 0.5%, respectively. In the United States, BA.2.12.1 represents approximately 30% of the aggregated new diseases, and in Belgium, BA.2.13 accounts for just under 5% of novel sequences.[28] Regarding spike function, distribution, and vulnerability to neutralization, the impacts of BA.2 and BA.1, spike mutations of omicron in the inherited S protein were examined. Specific mutations in the ACE2-RBD, such as S371F/L, S375F, and T376A, as well as Q954H and N969K in the hinge region 1, reduced contagion, whereas D614G, G339D, N764K, and L981F somewhat increased it. The majority of mutations in the RBD and N-terminal area decreased the S-protein's sensitivity to neutralization by therapeutic antibodies.[64] While D614G caused a weight loss of over 10%, BA.1 and BA.2 had no noticeable clinical symptoms. Higher viral loads were discovered in nasal turbinate, nasal washes, and the lungs of BA.1-inoculated hamsters than in BA.2-infected hamsters. When D614G was able to communicate effectively during the experiment, no BA.1 or BA.2 aerosol transfer was observed. The spread of both BA.1 and BA.2 was enabled through direct contact between hamsters and showed no recombination. However, with respect to the competitive transmission model, BA.1 was more effective than BA.2. Omicron BA.1 and BA.2 exhibited reduced pathogenicity and decreased spreading ability in hamsters compared to early SARS-CoV-2 strains.[65] Compared to Delta, Omicron BA.1.1-induced pulmonary damage in hamsters is not

significantly attenuated because the spike protein in BA.1.1 has been changed from BA.1 to *R346K*. While having a similar capability for antibody avoidance, the BA.2 transmits more effectively than the BA.1.[66]

BA.4 and BA.5 lineages

The United Nations Organization stated that the rise in people testing positive for COVID-19 is due to infections associated with different Omicron variants named BA.5 and BA.4. Updated data from the COVID-19 (UK Consortium Genomics) finds that nowadays BA.5 and BA.4 account for 50% of sequenced cases in England.[67] Samples collected between January 1, 2022, and April 20, 2022, have confirmed BA.4 and/or BA.5 in 7 regions in South Africa: Eastern Cape, Northwest, Western Cape, Gauteng, KwaZulu-Natal, Mpumalanga, and Limpopo.[17] By the first week of April, BA.4 and/or BA.5 accounted for 50% of nearly 500 new genome sequences. However, by April 18, 2022, BA.4 and BA.5 had quickly replaced BA.2 in the two most populous regions in South Africa (Gauteng and KwaZulu-Natal), accounting for 16% approximately, 60–75% of sequenced cases from then on.[17,28,68] Compared with BA.2, Omicron BA.5 and BA.4 sub-lineages had a day-to-day growth gain of 0.08 and 0.12, respectively, in South Africa in April 2022. Recently, BA.4 has also been detected in a few trials globally like in , including adjacent Botswana, Europe, the USA, and Hong Kong, China.[17,69] WHO reports that BA.4 and BA.5 are present at very low levels in several countries, and as of now, there is no significant epidemiological alteration detected between BA.4 and/or BA.5.[45] India reported as of May 21, 2022, one instance of each of the BA.5 and BA.4 subvariants; however, the BA.4 patient had no prior history of travel, while the second BA.5 case had.[38] In terms of human population growth effectiveness, endurance to humoral immunity against viruses, and toxicity in an investigational *in vivo* model, BA.4 and BA.5 present the greatest potential concern. The L452R/Q boosts viral contagiousness independently, and the HV69-70del was discovered in the Alpha variant as well as the S proteins of BA.5 and BA.4, making the BA.2 S protein backbone more infective than before. Multiple changes in the S protein of BA.4/5 result in increased lung development potential in experimental animal models and human lung cell cultures. Compared to the Omicron BA.2 variant, the BA.4/5 variant has a higher fusogenic S and is more pathogenic.[70] A study showed that the medically isolated BA.5 had less infectivity than the original Delta in hamster models,[71] and according to Tamura *et al*.,[72] compared to the prior Omicron subvariant named BA.2, the S protein of BA.5 contributes to increased infectivity. BA.5 has evolved to increase the inflammatory response, giving it pathogenicity, which could be a major contributing factor to the decreased mobility caused by BA.5 infection in the human population. The significant haemorrhage and alveolar damage caused by BA.5 infection in hamsters supported the virus' increased phenotype for invading respiratory tissues. The BA.5 isolate effectively invades the alveolar space, infects the bronchial and bronchiolar epithelium, and causes viral replication in the lung. The fact that BA.5 has a higher morbidity than BA.2 indicates that inflammation affects subsequent clinical presentations. The inflammatory region of the infected lungs with BA.5 on the fifth day after infection (d.p.i.) was bigger compared to that with BA.2 and nearly equal to B.1.1, demonstrating that BA.5 is more immunopathogenic than BA.2.[72]

This fifth VOC variant Omicron (B.1.1.529) with changes in biological function and antigenicity has acquired a significant ability to avoid antiviral immunity from vaccination, hybrid immunity, or monoclonal antibodies.[51,73–75] Being an important part of viruses to interact with human Angiotensin-Converting Enzyme 2 (ACE2) receptors, the mutation of RBD should alter the ability of antibodies to neutralize pathogens.[76] The immune evasion is primarily conferred by some unique alterations in spike proteins such as the deletion of H69/V70 in Omicron (BA.1), alteration of R3467 in BA.1.1, and mutation of T376A, L452, F486, and R408S in BA.2, the changes of L452R, F486V in BA.4 and BA.5. These changes in the S protein make those variants more infective with the ability to evade human immunity.[77] Most vaccines and monoclonal antibodies were developed to target the spike protein, and alteration in this significant lesion the effectiveness of pre-existing immunity that has been brought about by either current vaccinations or a previous natural infection.[78] Due to several mutations in this variant, the infectious capacity and transmissibility are enhanced, which make it immune evasive. These mutations also lead to reduced vaccine effectiveness and heightened reinfection, with moderate clinical symptoms and deaths.[55] Vaccines against Omicron have demonstrated a decreased humoral immune response, but the T-cell immune response plays a crucial role in reducing the chances of evading immunity of Omicron even with future variants.[77,79]

Delmicron variant

A study was conducted using 537,360 genomes from the GISAID database, among which 1,175 (0.2%) putative recombinants were observed, suggesting that up to 5% of SARS-CoV-2 could be recombinants circulating in the USA and UK.[80] However, only in the UK, between November 2021 and February 2022, 29,719 positive samples were sequenced, and among those samples, 18 cases of co-infections with Delta-Omicron recombinants were found.[29] On March 10, an international database of viral sequences reported several cases of Delmicron, including 33 from France, 1 from Germany and the Netherlands each, and 8 from Denmark. In the UK, 30 new cases were recorded according to the UKHSA.[41] On March 9, the WHO classified certain strains in the Netherlands and Denmark, but Deltacron/Delmicron could not be classified as VOCs due to its low number of confirmed cases.[81]

XD, XE, and XF sub-variants

XD sub-variant

XD (recombination's of the BA.1 and Delta variants) was responsible for numerous clusters in Europe.[19] As XD is a recombinant of Delta-Omicron and Delta is associated with severe disease outcomes, this variant is causing more concern. Reports suggest that the XD variant exhibits immune escape characteristics and neutralizes antibody responses. There is no evidence suggesting that delta is associated with a higher transmission rate.[19,46] The S protein of the Delta-Omicron XD variant exhibits more mutations than the Delta variant, potentially increasing its infectiousness and ability to evade immune defenses mediated by antibodies and vaccines. It is unclear whether XD is as communicable and successful in evading the immune system as the Omicron variant while causing illnesses with a severity comparable to the Delta variant.[69]

XE sub-variant

As of March 22, 2022, UKHSA has recorded almost 637 XE cases across the UK, indicating possible community transmission.[38] The XE variant was predominantly found and widely dispersed in London. Its lineage BA.2 exhibits a 75 percent booming increase rate compared to its other BA.1 lineage. However, the recombinant XE shows around a 10% higher growth rate compared to the BA.2

Omicron sub-lineage. Further explorative investigations are needed to determine the true extent of the infection, as it is currently the most prevalent strain of the virus circulating.[46] Additional mutations have been found in the XE variant, which was not found in either BA.1 or BA.2. In England, as of April 5, 1,125 confirmed cases of XE have been reported.[34] Despite the limited number of cases, it is concerning because two fully vaccinated individuals showed the BNT162b2 vaccination to be ineffective against XE.[38]

XF Sub-variant

In the UK, at the time of mid-February 2022, a total of 38 reported cases were recognized and confirmed as XF recombinant lineage.[38] However, one case of XF was reported from the South-East country.[46]

Future perspective and challenges

Effective vaccine manufacturing is gaining emergence against the virus's mutating nature, primarily through insertions and deletions. Due to spontaneous mutations, the virus has found a unique path to immune evasion. Therefore, under these alarming circumstances, researchers must find a way to develop new therapeutic drugs that can combat the growing mutation variants of the viruses and advance the modification of vaccines to hinder pathogen-host interactions. Micro-surveillance systems should be geographically inclusive and encompass all individuals and communities at risk. To halt the spread of COVID-19 and ensure the ongoing application of control measures, it is crucial to implement comprehensive surveillance. In this context, the available database needs regular updates with detailed information on emerging or decreasing new cases of COVID-19 to raise awareness among the public. The variant's mutational nature poses a significant threat to the existing population, so precautions should be taken to control or prevent reinfection, including wearing masks, using sanitizers, practicing social distancing, isolating after infection, and more.

Conclusions

The attenuated infectivity of the Omicron variant is due to mutations in the S-protein of the RBD domain, aiding in immune evasion and increasing transmissibility compared to the prototype SARS-CoV-2. This rapid surge caused the healthcare system to collapse as hospitalization rates exponentially increased. The recently discovered Omicron sub-lineages BA.1, BA.2, BA.3, BA.4, and BA.5 exhibit multiple RBD mutations, potentially leading to significant neutralizing antibody evasion. The co-circulation and co-infection events during this global pandemic have created opportunities for the virus to form new recombinants, resulting in variants such as Deltacron/Delmicron, XE, XD, and XF Notably, there is a great risk of transmission as a fugitive encounter with infected individuals can amplify the virus's infectivity rate. If this pattern persists, SARS-CoV-2 may continue its progressive or evolutionary path to become more infectious, potentially reducing the effectiveness of therapeutic antibodies and vaccines and resembling influenza. Despite these challenges, there is hope with Paxlovid, the first orally available drug against COVID-19, which targets the main protease to disrupt the virus's replication cycle. However, it's too early to draw conclusions, as many new recombinant variants may emerge due to inter-lineage recombination. Nevertheless, increased immunity from booster doses has helped control the mortality rate, although there is ongoing debate on whether a global emergency still exists.

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Conflict of interest

None of the authors disclose any conflict of interest.

Author contributions

Information gathering, article writing, and figure design (GD, RA, JB, SS), critical revision for essential intellectual content, and figures finalizing (SD, SP, BD, BG), and supervision for the whole work, conceptualization, and critically revision (SKD). All authors have made a significant contribution to this study and have approved the final manuscript.

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