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Clinical Insights

Is the competition between variants the end of severe acute respiratory syndrome coronavirus 2 pandemic? A journey from Wuhan to XBB.1.16

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The World Health Organisation (WHO) estimated 780 million severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and approximately 6.9 million deaths related to coronavirus disease 2019 (COVID-19) as of March 2023 (https://covid19.who.int/). These numbers have allowed COVID-19 infection to be ranked as one of the most important pandemics in terms of prevalence and mortality in recent human history, causing widespread fear and concern for global health security.

The biological behavior of SARS-CoV-2 is similar to other respiratory viruses. It spreads in most cases as an airborne pathogen included in exhaled air and droplets. Once in contact with the mucosa of the upper and lower airways, the virus interacts with human cells through its 'spike' protein which binds primarily to the angiotensin converting enzyme 2 (ACE_2) receptors [1].

Different studies have demonstrated the pivotal role of ACE_2 receptors in SARS-CoV-2 infection and subsequent sequela [1,2]. Indeed, once the virus contacts the cell, cleavage of the spike protein between S1 and S2 units is carried out by the transmembrane receptor serine protease 2 (TMPRSS2) which is structurally contiguous to the ACE_2 receptor and facilitates viral entry with resulting down-regulation of the ACE_2 receptors expressed on the cell membrane [1,2].

ACE_2 malfunction is predominantly due to viral occupancy. It dysregulates the protective axis of the renin–angiotensin–aldosterone system (RAAS), with an increased generation and activity of Angiotensin II (Ang II) and reduced formation of $Angiotensin_{1,7}$ ($Ang_{1,7}$) [1,2]. Several observational studies and meta-analyses clearly showed that advanced age, male gender and the presence of comorbidities (including hypertension, chronic obstructive pulmonary disease [COPD], diabetes mellitus and history of cardiovascular events) are risk factors for increased disease severity of COVID-19 [3,4]. Notably, all these conditions are associated with RAAS dysregulation and ACE_2 deficiency [2,5].

Although in these three years of the pandemic the mechanisms underlying infection and viral replication have remained the same, the SARS-CoV-2 has continued to mutate, generating new variants that are more or less dangerous to human health [6–8]. It is known that the SARS-CoV-2 is comprised of a single-stranded positive-sense ribonucleid

Abbreviations: WHO, World Health Organisation; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019; ACE_2, Angiotensin converting enzyme 2; TMPRSS2, Transmembrane receptor serine protease 2; RAAS, Renin–angiotensin–aldosterone system; Ang II, Angiotensin II; $Ang_{1,7}$, $Angiotensin_{1,7}$; COPD, Chronic obstructive pulmonary disease; RNA, Ribonucleid acid; RdRP, RNA-dependant RNA polymerase; ExoN, Exoribonuclease; ORF, Open reading frame; E, Envelope; M, Membrane; N, Nucleocapsid; VOI, Variant of interest; VOC, Variant of concern; RBD, Receptor-binding domain; HIV, Human immunodeficiency virus; SIR, Susceptible-Infected-Recovered.

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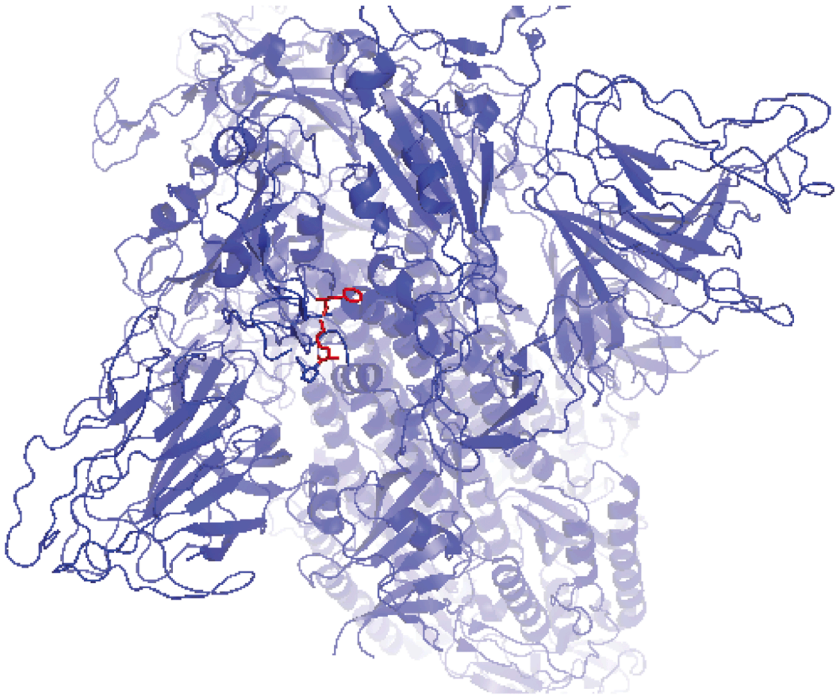

Fig. 1. Three dimensional model of the Spike protein of XBB.1.16 variant; additional mutations (E180V, F486P, and K478R) are highlighted in red in the A chain. See text for details.

acid (RNA) with a genome comprising ~30,000 nucleotides; its replication is mediated by RNA-dependant RNA polymerase (RdRP) and an associated proofreading enzyme exoribonuclease (ExoN). The genetic map of SARS-CoV-2 is composed of 13–15 (12 functional) open reading frames (ORFs) and, structurally, SARS-CoV-2 contains four structural proteins (including spike protein, envelope [E], membrane [M], and nucleocapsid [N] proteins) [9].

To date, new variants are divided into two different classes: variants of interest (VOI) and variants of concern (VOC; https://www.who.int/activities/tracking-SARS-CoV-2-variants). VOI are defined as those variants with genetic modifications that affect some characteristics of the virus including receptor binding and neutralisation by antibodies (an example of this type of variant is Lambda). Conversely, different mutated forms of SARS-CoV-2 which show an enhanced rate of transmission relative to previous variants are termed as 'variants of concern' (VOCs, including Alpha, Beta, Gamma, Delta and Omicron). Thus, VOCs are variants which change the susceptibility to neutralisation by antibodies and drug treatments, finally leading to less protection induced by vaccines, increased diffusion rate and severity of the disease. The increased virus fitness associated with VOCs is the result of a complex mechanism due to the variation of virus biology in the context of changing human immunity due to both prior infection and vaccination [10,11].

All of these variants share one common feature: they have a high number of mutations in the spike protein that promotes entry into viral cells via ACE_2. Of particular relevance are mutations occurring in the receptor-binding domain (RBD) of the spike protein, as this would appear to be the cause of their potential to evade neutralising antibodies triggered by previous infections and vaccines [12]. Moreover, they can affect the spike affinity for ACE_2, increasing the virus transmissibility.

A study published in 2020 estimated the mutation rate of SARS-CoV-2 to be around 10^{-4} nucleotide substitutions per site per year [13], a much lower number than that found for influenza virus [14] or human immunodeficiency virus (HIV) [15]. Nevertheless, a higher-than-expected mutation rate has been observed for SARS-CoV-2. This phenomenon can be explained by the fact that the transmission rates of this virus are high: the greater the number of people infected, the greater the likelihood of mutations appearing.

The first variant of concern that emerged is the Alpha in United Kingdom in early 2021, and gradually replaced G614 strains. The Alpha variant (B.1.1.7) contains several deletions and mutations in its spike protein such as N501Y, A570D, ΔH69/ΔV70, ΔY144, P681H, T716I, S982A, and D1118H. Worthy of note is undoubtedly the N501 mutation, which seems to be associated with greater transmissibility, as it has a greater affinity for ACE_2 slowing the dissociation of the RBD from the ACE_2 receptor.

The Beta variant was first identified in South Africa; overall, it has 21 mutations, with 9 mutations in the spike protein (three of which are common to other variants: the K417N, E484K and N501Y substitutions). Of note, this variant appeared to be highly transmissible than the previous strains [16].

The Delta variant, was first identified in India and it showed to have the highest transmissibility rate, when compared to the previous variants. It contains the mutation D614G in the spike protein which is also detected in the Alpha and Beta variants. As N501 mutation, it increases the affinity of the Spike protein for the host ACE_2 receptors. Interestingly, additional substitutions were found in the spike protein at the RBD (L452R and T478K), in the NTD (R158G, T19R, G142D, Δ156–157), in the S2 region (D950N) and a mutation at the furin cleavage site. These mutations appeared to contribute in the efficiency of replication and regulation of spike protein as well as escape from antibodies [17].

The Gamma variant was detected in Japan in travellers arriving from Brazil in January 2021. When compared with the original Wuhan strain, it presented twelve mutations in the Spike protein. Nonetheless, it showed a similar transmission rate [18].

The Omicron variant was first detected in Botswana in late 2021. Omicron is characterized by more than 30 mutations in the Spike protein (of which 15 different mutations involved RDB), resulting in increased transmissibility, as they increase the affinity of the spike protein for ACE_2. These mutations are also associated with immune escape from the host and reduced neutralisation of vaccine-induced antibodies [19].

Since January 2022 a new phase of the pandemic emerged and different sub-variants of Omicron were identified with varying genetic

characteristics such as BA.1, BA.1.1, BA.2, BA.3, BA.4, BA.5, BA.2.12.2, BA 2.75, XBB.1.5, and the last emerged XBB.1.16 [6].

XBB.1.16 was detected for the first time in India and it shows three additional mutations in the SARS-CoV-2 spike protein (E180V, F486P and K478R) compared with its parent lineage, XBB (Fig. 1).

The co-transmission of different variants is triggering a competitive behavior which may influence the pandemic transmission dynamics. Competition between strains is common in the real world. Pathogen like influenza A is an example of infections with multiple strains that behave competitively in a population or within a single host. In the context of SARS-CoV-2 pandemic, a similar scenario may be hypothesized; in other words, variants with a competitive advantage dominate (increased ability to transmission and immune escape) and influence the course of the pandemic.

Different studies proposed mathematic models to understand this phenomenon. The first model was built considering took cross-immunity and immune escape [20]. The report analyzed the competitive relationship between Omicron and non-Omicron strains [20]. The Authors hypothesised that competition between strains may influence not only the final size and replacement time of variants, but also the possibility of emergence of new variants [20]. However, this model has some limitations since it does not take into adequate account population heterogeneity and the effects of non-pharmaceutical measures [20].

Others researchers have proposed a modified Susceptible-Infected-Recovered (SIR) model which focuses on the competition between different strains of the virus under the effects of vaccination [21]. This model suggests that strain competition inevitably implies the extinction of one of the strains, with the winner remaining endemic in the long term [21].

It is worthy to be mentioned that in the context of SARS-CoV-2 pandemic a specific protein evolution has been recorded [10]. At the beginning of the pandemic there were several mutations which significantly enhanced the affinity of SARS-CoV-2 to ACE_2 [10]. However, a reduction over time may occur in the probability of mutations tied to enhanced diffusivity of the virus.

Taken together, these data suggest that we are probably approaching a post-epidemic era. The SARS-CoV-2 variants are continuing to evolve and survive, but the virulence of infection associated with novel strains may stabilize at lower levels, as result of the evolutionary changes, when compared to previous strains. In any case, tracking SARS-CoV-2 variants remains mandatory and the effects of COVID-19 restrictions and vaccination on the evolution of the virus remain to be fully elucidated.

Declaration of Competing Interest

None.

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