What are the reasons that Omicron, the latest SARS-CoV-2 VOC, is so concerning?

Maja Cupic

University of Belgrade - Faculty of Medicine, Institute of Microbiology and Immunology, Dr Subotica starijeg 1, 11000 Belgrade, Serbia
Correspondence: maja.cupic@med.bg.ac.rs

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Abstract: Since it was identified in Wuhan, China, in December 2019, the novel coronavirus has caused devastating severe respiratory infections in the human population worldwide. A new coronavirus named SARS-CoV-2 was isolated from a cluster of pneumonia patients and spread rapidly throughout the planet, establishing the global epidemic COVID-19, making it one of the most serious health disasters in modern public health history. Despite the slow evolutionary rate, SARS-CoV-2 increased transmissibility, virulence and/or immune evasion. Its long-persisting among humans has enabled it to acquire significant genetic diversity. For little, over three years, COVID-19 has driven through five global waves caused by several SARS-CoV-2 variants of concern (VOC). From 2020 until now, we identified Alpha, Beta, Gamma, Delta and the last-fifth SARS-CoV-2 VOC, Omicron. Several reasons make the last VOC so concerning: many mutations, especially in the viral spike protein, and accumulating evidence for increased transmission efficiency and escape from neutralising antibodies. Omicron has outcompeted the previously dominating Delta VOC in an unbelievably short time. It is highly transmissible but seems less pathogenic than pre-existing SARS-CoV-2 variants of concern. Increasing population immunity (whether through vaccination and/or previous infections) raises hopes that severe COVID-19 will become rare and present in risk groups of patients, such as older adults with comorbidities. Hopefully, SARS-CoV-2 will become endemic, similar to seasonal coronaviruses. Because Omicron probably isn't the last SARS-CoV-2, we should learn to live with this coronavirus in the present and future.

Keywords: SARS CoV-2, variants of concern, COVID-19, genetic diversity, evolution

1. Introduction

Although this work is about the emergence of a new pathogen, the appearance of novel causes of human infections in the third millennium was quite certain and expected. These manifested as the consequence of global changes on our planet, disrupting otherwise balanced relationships in nature. However, the world was still surprised by the sudden emergence of a new viral pathogen (Zhu *et al*., 2019). Since emerging from Wuhan, China, in December 2019, the novel coronavirus has caused devastating severe respiratory infections in humans worldwide. A new coronavirus named SARS-CoV-2 was isolated from a cluster of pneumonia patients and spread rapidly worldwide (Xu *et al*., 2022). The World Health Organization (WHO) declared a coronavirus disease 2019 (COVID-19) global pandemic on March 11, 2020 (WHO, 2020). The pandemic resulted in more than 670 million confirmed cases and more than 6.5 million deaths, making it one of the most serious public health disasters in history (https://www.worldometers.info/coronavirus/).

Despite the slow evolutionary rate of SARS-CoV-2 compared with other RNA viruses, its increased transmission fitness and/or immune evasion, as well as a long persistence among humans, enabled it to acquire significant genetic diversity since it first entered the human population (Parczewski & Ciechanowicz, 2020). Today, it has been a little over three years since the COVID-19 outbreak surged with five global waves caused with several SARS-CoV-2 variants of concern (VOC).

The first identified VOC was Alpha in the United Kingdom by December 2020, which suggested that the evolution of SARS-CoV-2 had changed unpredictably. The leading factors of virus evolution include accidental epidemiological effects,

mutations connected with increased transmission and infectivity, severe clinical presentations, immune escape and excellent adaptability to the new host.

Soon after, the second VOC - Beta, the third VOC - Gamma and the fourth – Delta, were identified in South Africa, Brazil and India successively. VOCs were found in areas with high infection rates, which is probably related to the high mutation frequency promoted by the adaptive evolution of the virus. Today, Omicron, the fifth and last SARS-CoV-2 variant of concern, was initially detected in samples obtained in Botswana and South Africa in mid- and late-November 2021, respectively (Jung *et al*., 2022). The last variant caused a new global wave, with faster transmission during the past eight months. It shows different characteristics than previous-ancestral variants: very high infectivity, high spreading rate, minimal pathogenicity, and vaccine and antibody-tolerant (Rana *et al*., 2022). Omicron has evolved into five main lineages, including BA.1, BA.2, BA.3, BA.4, and BA.5. BA.2 sublineage was the dominant strain all over the world for several months with a very high rate of propagation (Le Page, 2022; Callaway, 2021). This subvariant has lower virulence but greater transmissibility than previous variants and predominantly affects the upper respiratory tract, meaning less lung or other organ involvement (WHO, 2021).

In early 2023, a new rising Omicron subvariant XBB.1.5 (unofficially nicknamed "Kraken" by some scientists online) appears to be the most transmissible strain so far (https://www.yalemedicine.org/news/omicron-xbb-kraken-subvariant). It circulates with two other continuously circulating subvariants recently, such as BQ 1.1 and BA.5. The last identified subvariant shows enhanced transmissibility, which comes from their ability to evade immune responses, especially in people who were previously infected, but not vaccinated (https://www.yalemedicine.org/news/5-things-to-know-omicron).

1.1. The evolution of SARS-CoV-2

Coronaviruses were first isolated in the 1930s as causative agents of respiratory (RT) and gastro-intestinal (GIT) infections in animals. Thirty years later, the first human coronaviruses were discovered and were long associated with mild self-limiting RT and GIT infections in humans until the emergence of two new highly pathogenic coronaviruses during the first two decades of the 21st century (Song *et al*., 2022). It was the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS Co-V), in 2002 and 2012, in the countries where they were registered for the first time (China and Saudi Arabia) caused severe acute infections of the lower parts of the respiratory tract in humans with a high fatality rate of 10% and 35%, respectively (Zhong *et al*., 2003; Zaki *et al*., 2012).

The last three emerging coronaviruses have undergone a long evolution, and their origins are still unknown. It was about animal coronaviruses whose natural reservoirs are certain species of bats. Before jumping over the species barrier and entering the human population, they were highly adapted to another intermediated host (Zhang *et al*., 2020; Lam *et al*., 2020). Although in the recent past, the entry of highly pathogenic emerging coronaviruses into the human population occurred twice according to an identical scenario, these events were still not a sufficient warning for humans that they could be repeated. This is what exactly happened, and the new coronavirus made a third jump, by which it entered the world of humans just like the previous two times, from the animal world, having previously been very well prepared in the intermediate host to continue its survival in human hosts as efficiently as possible (Wong *et al*., 2021).

Analysis of the genomes of the last three identified coronaviruses indicates a high degree of genomic homology between them: ~79% between SARS-CoV-2 and SARS-CoV, slightly less (~50%) between the new SARS-CoV-2 and MERS-CoV. However, despite the high genomic homology of SARS-CoV-2 and SARS-CoV, the difference at the level of the receptor binding domain (RBD) in the spike protein makes the new coronavirus more transmissible, with a stronger binding affinity for target cell receptors and higher replicative fitness (Lu *et al*., 2020). Nevertheless, the highest genome homology of 96% between SARS-CoV-2 and CoV of a specific type, the horseshoe bats RaTG13 Rhinolophus affinis, clearly indicates the origin of SARS-CoV-2 (Zhou *et al*., 2020).

Phylogenetic analyses show that the last SARS-CoV-2 VOC probably did not emerge from other VOCs and suggested that the Omicron VOC evolved independently by convergent evolution. The key question is how Omicron came into existence and why it differs from ancestral variants. Today, researchers are trying to explain the evolution of the origin of Omicron by the existence of three possible scenarios. The first theory is its efficient replication in an immunocompromised person over a long period. The possibility of this scenario which has been reported is that the SARS-CoV-2 last variant replicated in a young HIV/AIDS female from South Africa for more than six months. In that way, the virus accumulated many new and unique mutations (Karim *et al*., 2021). Another theory is that Omicron

has been circulating among humans unnoticed for a while, especially in countries with suboptimal surveillance of COVID-19, with a low frequency of sequencing of emerging variants compared to South Africa. The last possibility is that the Omicron may have evolved in a nonhuman species, from which it went back to humans (Wei *et al*., 2021). Besides that, the fact that Omicron shows an expanded host range and an increased capacity to generate new animal natural reservoirs suggests that SARS-CoV-2 can be detected, e.g., in household pets as well as in farm and wildlife animals, which is of particular importance for the evolution of the virus (Sharun *et al*., 2021).

1.2. The main properties of the coronaviruses: SARS-CoV-2 genom organisation and composition of the spike protein

SARS-CoV-2 belongs to the family of coronaviruses, to the order Nidovirales, subfamily Orthocoronavirinae and genus ß-coronavirus. Coronaviruses are spherical particles 80-120 nm in diameter. Due to vertical projections in the form of spikes from the outer surface, the viral particles appear like the solar corona or crown, which determines their name (Lazarevic *et al*., 2021). The genome of the coronavirus is in the form of single-stranded positive RNA ("+"ssRNA) and represents one of the longest genomes among RNA viruses, consisting of ~30,000 nucleotides. The first two-thirds of the genome, starting from the 5¢non-transcriptional UTR end, comprises the ORF1a and ORF1ab genes known as replicase complexes, which encode polyproteins pp1a and pp1ab. These are cleaved by autocatalytic degradation into 16 non-structural proteins (nsp 1-16) that have multiple roles in the transactivation of other viral genes, transcription and replication of the genome. Also, nonstructural gene products are involved in immune modulation and evasion of innate immunity mechanisms (Kim *et al*., 2020). The last third of the viral genome consists of genes encoding four structural proteins of the virus: S (glycoprotein outgrowths of the virus envelope in the form of spikes named spike protein), E (envelope proteins), M (transmembrane glycoprotein) and N (nucleocapsid protein), as well as a set of accessory genes (Wu *et al*., 2020; Tortorici & Veesler, 2019). The S gene encodes the S protein, the most prominent part of the viral particle that ensures the virus attaches to and enters the target cell. M and E proteins, products of the M and E genes, are responsible for forming the viral envelope during the final stages of the virus life cycle, assembly and release of the virions. The E protein, which is the most conserved, has an essential role in the pathogenesis of COVID-19 because it binds the human PALS1 protein, which is crucial in the biogenesis of adherence and the establishment of polarity in epithelial cells. Finally, the N protein product of the N structural gene participates forming of helical ribonucleocapsid (Teoh *et al*., 2010). A set of accessory genes encodes proteins, disrupting signalling ways in the cell and avoiding the effect of interferon, as one of the first lines of defence of the activated innate immunity during early virus-induced infection. (Michel *et al*., 2020)

The spike is a transmembrane glycoprotein on the virus's surface of a homotrimer comprising three identical units. There is a high degree of similarity in the amino acid composition of the S protein of human-infecting CoV and coronaviruses of other animal species (civet cat ~77%, bat 75-98% and pangolin ~92%) (Zhang *et al*., 2020; Zhou *et al*., 2020). It consists of S1 and S2 subunits. The S1 subunit is composed of the N terminal domain (NTD) and the RBD, which plays a crucial role in binding to a specific cell receptor-angiotensin-converting enzyme 2 (ACE2) (Huang *et al*., 2020; Song *et al*., 2018). Also, RBD targets the immune system (humoral and T-cell response) and antiviral drugs. Within the RBD is a region designated as the receptor binding motif (RBM), representing a highly variable structure within the splice, which is particularly important for binding with ACE2 (Walls *et al*., 2020). The second S2 subunit consists of several parts: fusion protein (FP), heptapeptide domains-1 and -2, and transmembrane and cytoplasmic domains (Hoffmann *et al*., 2020). S protein exists in open and closed forms. When the RBM is closed, it is hidden. At the same time, in the open conformation, the RBM, as part of the RBD, protrudes above the homotrimeric units of the spike, which enables the virus to bind to ACE2 as an initial step in the initiation of infection. The next step is entering the virus by fusing the envelope with the cell membrane, utilising the S2 subunit (Xu *et al*., 2022). Spike, in its native form, exists as an inactive precursor of S1 and S2 subunits, which are joined by non-covalent bonds in the pre-fusion phase. Upon binding to the receptor on the target cell, the S protein is cleaved by the activity of cellular protease enzymes: furin and transmembrane serine protease (TMPRSS2). This cleavage results in irreversible conformational changes in the junction crucial for virus entry into the cell (Hoffmann *et al*., 2020). The uniqueness of the genomic organisation of SARS-CoV-2 is the existence of a short RRAR sequence, which precisely at the site of very precise polybase cleavage of the S protein conditions, the insertion of four amino acids that make up the motif recognised by the furin protease. This cleavage is thought to destabilise SARS-CoV-2, leading to conformational changes necessary for the RBD to bind to the receptor (Lan *et al*., 2020).

Comparative analyses of the genome of SARS-CoV-2 and other related animal coronaviruses point to the uniqueness of this event only in the case of human SARS-CoV-2, except the coronavirus of one species of bats, Rhinolophus malazanus (RmYN02), where also at the site of polybase cleavage three amino acids are inserted (Wrobel *et al*., 2020). It is this similarity that clearly shows that the S protein is not only a key player in the pathogenesis of infection but also in the evolution of the coronaviruses, ensuring that it infects different species, evolves to adapt to a new host and is relatively easy to pass from species to species (Dhama *et al*., 2020).

2. Genetic variability and major variants of SARS-CoV-2 VOC

The emergence of new virus variants results from mutations in the viral genome. It is known that the mutation rate of RNA viruses is significantly higher than viruses with DNA genomes, mainly due to uncorrectable errors made by RNA-dependent RNA polymerase during RNA replication (Parczewski *et al*., 2020).

Although with about 30,000 base pairs, SARS-CoV-2 has the largest genome of all known RNA viruses, the integrity of its genome is retained by the proofreading function of the viral polymerase (Jung *et al*., 2022; Gorbalenya *et al*., 2006). Specifically, the nonstructural protein 14 (Nsp14) and its cofactor Nsp10 perform exonuclease activity, substantially reducing the accumulation of mutations in the viral genome (Saramago *et al*., 2021). This event is crucial in limiting SARS-CoV-2 mutation rates, registered with a frequency of 1:1000 substitutions per place/year (Buchan & Yao, 2021). However, the appearance of a large number of SARS-CoV-2 variants is a consequence of the accumulation of mutations that affect many properties such as virus transmissibility, its cellular tropism and pathogenicity, virulence, infectivity, which poses a serious challenge to the effectiveness of current vaccines, antiviral therapy and diagnostic tests (Lazarevic *et al*., 2021). Initially, the evolution of SARS-CoV-2 was relatively slow until the emergence of the D614G variant, whose increased transmissibility resulted in it becoming the globally dominant variant (Korber *et al*., 2021). Since then, the speed at which new variants of SARS-CoV-2 have continued to emerge has steadily increased.

2.1. Alpha VOC - B.1.1.7 (20I/501Y.V1, VOC 202012/01)

Alpha subtype or B.1.1.7 (20I/501Y.V1, VOC-202012/01) represents the first identified VOC in the United Kingdom (UK) during September 2020. Compared with pre-existing variants, the Alpha variant is associated with increased transferability and risk of death in hospitalised patients. So many studies reported that the mortality rate was 61% (42–82%), much higher than other variants (Davies *et al*., 2021a; Davies *et al*., 2021b).

Alpha subtype has nine mutations (169–70 deletion, 1144 deletion, N501Y, A570D, P681H, T716I, S982A, D1118H, and D614G) in the S protein and some with significant biological impact. Mutation N501Y is associated with enhanced RBD affinity to human ACE2. The second one, also in the spike, represents a deletion at position 69/70, related to avoiding the immune response. The third P681H is connected with the conformational changes nearby of the furin polybase cleavage site in S protein into S1/S2 subunits (Graha *et al*., 2021).

2.2. Beta VOC - B.1.351 (20H/501Y.V2)

The next SARS-CoV-2 VOC, the Beta variant, was first detected in South Africa in October 2020 and resulted in the second wave of COVID-19 infections (Cascella *et al*., 2022). Beta, as the previous Alpha variant, contains nine mutations in the S protein (L18F, D80A, R246I, K417N, D215G, N501Y, E484K, D614G, and A701V). Three mutations (N501Y, E484K, and K417N) on the RBD of S protein raise its binding affinity for ACE receptors (Mwenda *et al*., 2021) and increase the risk of transmission but decrease its susceptibility to neutralisation by postvaccination sera, monoclonal antibody therapy, and convalescent sera (Cascella *et al*., 2022).

2.3. Gamma VOC -P1 (B.1.1.28 ; GR/501Y.V3)

Gamma VOC was identified for the first time in four travellers from Brazil, who were tested at an airport in Japan (Fujino *et al*., 2021), also termed the Brazilian variant. This subtype possesses 17 unique mutations, including three K417T, E484K, and N501Y, located in the RBD of the S protein (Wang *et al*., 2021). Some of this variant's mutations affect the virus's transmissibility and antigenic profile. They also significantly impact the reduction of neutralising roles of antibodies.

2.4. Delta VOC - B.1.617

Variant B.1.617, known as Delta, was identified for the first time at the end of 2020 in India and rapidly spread worldwide from April 2021. There are three sublineages: B.1.617.2, B.1.617.1 and B.1.617.3, with different mutation profiles (Mlcochova *et al*., 2021). The Delta variant contains ten mutations (T19R, G142D*,156del, 157del, R158G, L452R, T478K,

D614G, P681R, and D950N) in the S protein – only two in the RBD, while the rest are located in N terminal domain (NTD). All sublineages possess the P681R mutation in the spike protein, which is crucial for increased transmissibility. Also, the P681R mutation stimulates the polybase cleavage of S protein by the cellular furin protease by extension in RRAR motive, which results in significantly higher replicative fitness and "viral load" (Singh *et al*., 2021). Sublineage B.1.617.2, soon after identification, was recognised as a variant with a high transmission capacity, even more than 60% compared to the Alpha variant. It has four mutations within RBD associated with a significantly increased virus ability for efficient and rapid transmission and immune evasion. Still, it is believed that they also impact the severity of clinical outcomes. The Delta variant causes more severe disease than the previous four VOCs. Mutation T478K in RBD of the B.1.617.2 variant shows reduced neutralisation by monoclonal antibodies and antibodies from convalescents' sera.

3. What makes Omicron, the latest SARS-CoV-2 VOC, so concerning?

Omicron VOC, the fifth SARS-CoV-2 variant, was reported for the first time in mid-November 2021 in Botswana and South Africa and immediately raised global concern because of its high transmissibility (Le Page, 2022). A short while later, it became known that the Omicron comprises multiple sublineages: BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.4 (B.1.1.529.4), and BA.5 (B.1.1.529.5) (Rana *et al*., 2022). Compared with the Wuhan viral genomes of ancestral COVID-19, Omicron has approximately 60 mutations predominantly located in the S gene. Twelve of the 31 changes in the S1 region of the Omicron spike are located in the N-terminal domain (NTD); 15 in the ACE2 receptor-binding domain (RBD), (DH69/V70, T95I, DY144, K417N, T478K, N501Y, D614G, H655Y, and P681H) where 10 of 15 alterations are located in the receptor-binding motif (RBM) and finally five at the C terminus (Kannan *et al*., 2021; Ingraham & Ingbar, 2021)

Significant mutations in the S1 subunit affect spike affinity for ACE2 (Q498R and N501Y), phenotypic effects such as increased transmission and immune evasion (E484A), increased viral infectivity and spike processing DH69/V70 (Meng *et al*., 2021), but also may be associated with negative results of PCR based S-assays. Another six mutations are found in the S2 subunit of the S protein. Three of the six are in the heptapeptide repeat 1 (HR1) region required for fusion as the virus entry mechanism into the cell.

The critical question is: what role do these mutations play in the phenotypic characteristics of Omicron?

According to the CDC, the Omicron variant spreads faster than the original SARS-CoV-2 and the Delta variant. In the first months of 2022, the Omicron subvariant named BA.2 began to spread even quicker than other subvariants, followed by BA.4 and BA.5, only to be outdone by the BQ and recently reported XBB.1.5 subvariants. Omicron VOC favours infection of the upper respiratory tract and reduces the risk of invasion of the lung (Willet *et al*., 2022). Consequently, Omicron replicates less efficiently in the lower part of the respiratory tract. Additionally, Omicron is often mild but will still cause severe COVID-19 and death in certain patient risk groups, including the elderly with comorbidities or unvaccinated individuals (Cele *et al*., 2022). Also, numerous recent studies show that the Omicron VOC evades many, but not all, neutralising antibodies induced by vaccination or previous SARS-CoV-2 infection. The mutations known as D405N, F486V and 69-70 del in BA.2, BA.4 and BA. 5, the last three Omicron subvariants, are associated with immune escape, and it is possible that these mutations were selected during the prolonged virus survival in the human population (Willett *et al*., 2022). Moreover, Omicron VOC causes significantly more vaccine breakthrough infections than pre-existing Alpha and Delta variants (Cele *et al*., 2022). Still, Omicron is showing sensitivity to antiviral therapy, such as remdesivir, molnupiravir, nirmatrelvir, hydroxycytidine, Paxlovid, and Acriflavine (Vangeel *et al*., 2022).

4. Perspective - Should we learn to live with SARS-CoV-2 in future?

The answer to this question is yes, we should learn to live with SARS-CoV-2 in the coming times. The appearance of Omicron or future new emerging variants of SARS-CoV-2 is not surprising. On the contrary, this is the expected natural process of virus evolution. Just as all ancestral SARS-CoV-2 variants were never the last ones, likely, Omicron will not be the ultimate variant either.

The hope and expectation are that severe forms of the disease with fatal outcomes will become rare, that COVID-19 will become an endemic disease, that the virus will have a seasonal character, and that the global level of immunity against COVID-19 is sufficiently protective. Should it come to pass, all of this is highly encouraging for future times.

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