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REVIEW

Omicron – The new SARS-CoV-2 challenge?

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Abstract

SARS-CoV-2 virus has infected nearly 300 M people worldwide and has been associated with over 6 M deaths by March 2022. Since the virus emergence in December 2019 in Wuhan, several new mutations have been described. The World Health Organization has developed a working name for these emerging variants according to their impact on the worldwide population. In this context a high alert has been paid to variants of concern (VOC) due to their high infectiousness and transmissibility patterns. The most recent VOC, Omicron (B.1.1.529), has become dominant in the shortest time ever and has placed Europe under an overwhelming and unprecedented number of new cases. This variant has numerous mutations in regions that are associated with higher transmissibility, stronger viral binding, affinity and antibody escape. Moreover, the mutations and deletions present in the spike protein suggest that the SARS-CoV-2 specific attachment inhibitors may not be the best option for Omicron therapy. Omicron is the dominant variant circulating worldwide and, at the end of February 2022, it was responsible for nearly all sequences reported to GISAID. Omicron is made up of several sublineages, where the most common are BA.1 and BA.2 (or Nextstrain clade 21K and 21L, respectively). At a global level, it is possible to say that the proportion of BA.2 has been increasing relative to BA.1 and in some countries it has been replacing it at high rates. In order to better assess the Omicron effectiveness on antibody escape, spread and infectious ability it is of the highest relevance to maintain a worldwide tight surveillance. Even though this variant has been associated with a lower death rate, it is important to highlight that the number of people becoming infected is concerning and that further unpredictable mutations may emerge as the number of infected people rises.

KEYWORDS

omicron, SARS-CoV-2, spike mutations, vaccine efficiency, VOCs

Abbreviations: A, Alanine; ACE2, angiotensin-converting enzyme 2; Arg, Arginine; Asp, Aspartic acid; COVID-19, Coronavirus disease 2019; DPP4, Dipeptidylpeptidase 4; FP, Fusion Protein; G, Glysine; Glu, Glutamic acid; HE, Hemagglutinin-esterase dímer; HR, Heptad Repeat; IHU, Instituto Hospitalar Universitário; IT, Intracellular Tail; Lys, Lysine; M, Millions; mRNA, Messenger ribonucleic acid; N, Aspargine; N protein, Nucleocapsid Protein; NTD, N-Terminal Domain; P, Proline; pI, Isoelectric point; Q, Glutamine; R, Arginine; RBD, Receptor-binding domains; RNA, Ribonucleic acid; RTC, Replication and transcription complex; RT-PCR, Real Time-Polymerase chain reaction; S, Serine; SARS-COV-2, severe acute respiratory syndrome coronavirus clade 2; S gene, Spike gene; S protein, Spike protein; T, Theonine; TA, Transmembrane Anchor; V, Valine; VHC, Variants of High Consequence; VOC, Variants of Concern; VOI, Variant of Interest; VUM, Variant under Monitoring; WHO, World Health Organization.

1 | INTRODUCTION

The first sequenced SARS-CoV-2 genome was made public on 5th of January 2020, and since then, more than 3 million genome sequences have been shared on online platforms worldwide, allowing a comparative genomic analysis.[1] This strategy of sequencing a high number of genomes has also enabled the scientific community to follow and keep track of the virus evolution, which was fundamental for the development of more adequate detection methods and treatments, alongside with the detection of emerging new variants. The scientific knowledge acquired so far has allowed the establishment of phylogenetic relationships of SARS-CoV-2 with other known virus. Indeed, the first sequenced genomes revealed a similarity of 96% with a bat coronavirus (RaTG13), which indicates that bats were probably reservoir hosts or even the origin of this virus.[2,3] However, there is not a consensus among the scientific community regarding whether bats were the direct source or if they were an intermediate host.[4]

A fact that is commonly accepted is that the binding receptors are fundamental to better understand the disease evolution upon infection. In MERS-CoV, for example, it was found that preexisting pulmonary disease could increase the dipeptidylpeptidase 4 (DPP4) abundance and, thus, predispose individuals to morbidity and mortality. DPP4 preferential spatial localization in alveolar regions may explain why MERS-CoV is characterised has being a lower respiratory tract disease.[5] On the other hand, SARS-CoV-2 and SARS-CoV use the S protein to bind to angiotensin-converting enzyme 2 (ACE2),[6] a protein that can be found on the surface of many cell types (Figure 1).

Another interesting feature of SARS-CoV-2 is the presence of a nonstructural protein (nsp14) that lowers the known high mutation rate of RNA virus due to its proofreading ability.[7] Despite this proofreading ability, the high recombination rates and, consequently genetic variability of RNA viruses, facilitates the emergence of new mutations and viral variants, thus reinforcing the need for a constant genetic monitoring of SARS-CoV-2.[8]

Analysing the genome-wide patterns on mutations distribution and accumulation, there is a clear lower incidence in genes encoding nsps when compared to genes encoding structural and accessory proteins. This is a really interesting feature of this virus and is probably due to the fact that nsps play a key role in the viral life cycle. Indeed, they are responsible for the formation of the replication and transcription complex (RTC), which enables virus replication, and have a fundamental role in the host's immune response evasion on the initial stage of infection. In contrast, some structural and accessory proteins seem to be more prone to mutations. For example, ORF6 and ORF8 are regions with high mutational rates, most likely due to their involvement in immune response escape upon cell entry and initial infection stage, which may benefit from some of these mutations.[9] Moreover, the S gene seems to be not only a mutational hotspot, but it also has a dN/dS ratio above 1, which is indicative of positive selection.[10] Considering the role of the S protein in the viral life cycle (responsible for the virus binding to the host cell receptor ACE2 and the initiation of the infection process) the existence of a mutation hotspot in this zone may indicate a viral molecular strategy to increase SARS-CoV-2 virulence and transmissibility.[11,12] The follow-up of this and other mutations has led to the identification of new SARS-CoV-2 variants.

2 | VARIANTS OF CONCERN (VOC) EMERGENCE

The high worldwide surveillance on SARS-CoV-2 genetic alterations has allowed the identification of new variants in a timely manner.[13] The majority of the mutations identified are synonymous mutations, that is, nucleotide substitutions that don't alter the encoded amino acid. This type of mutation won't have an effect in viral characteristics, for example, transmission and virulence, but can compromise some COVID-19 diagnosis molecular methods. The majority of the SARS-CoV-2 genome appears to sustain this type of mutations, hence being under purifying or negative selection. On the other side, non-

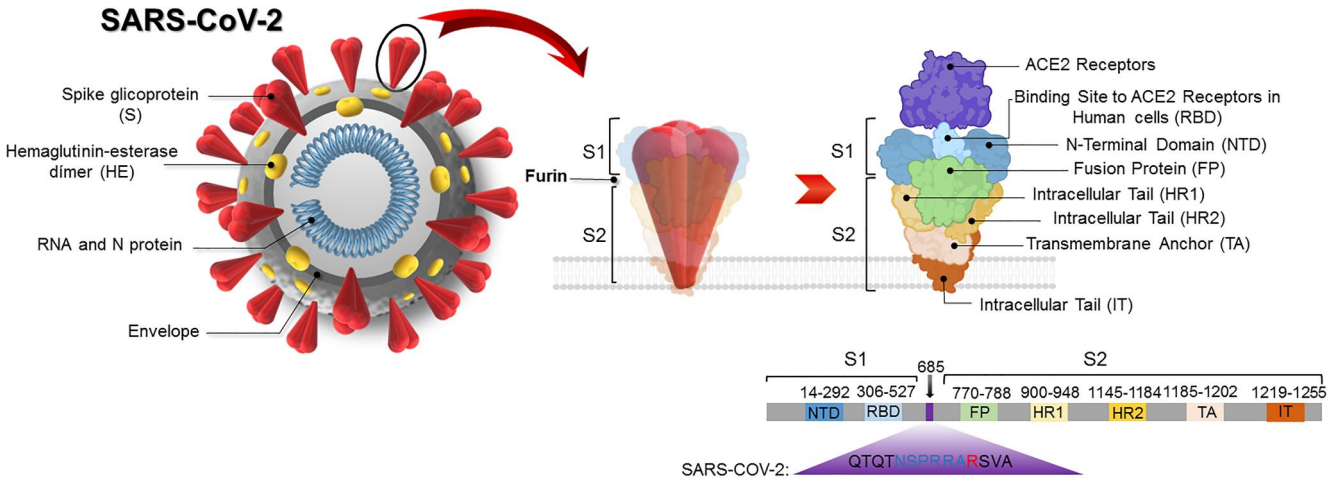

FIGURE 1 Schematic representation of SARS-CoV-2 virus on the right and an amplification of the Spike protein with its representative domains on the left

synonymous mutations will probably change SARS-CoV-2 phenotype. The consequences can vary from imperceptible, on the pathogenic level, to major repercussions on virulence, transmissibility, and general disease prognosis. The first clinically significant non-synonymous mutation detected was an *A* to *G* transition at position 23,403 in the S gene.[14] This amino acid change, also known as the D614 G variant, is suspected to have emerged in January 2020 and 5 months later it was the dominant variant in circulation worldwide, replacing the original variant found in Wuhan.[15] This rapid variant prevalence has been explained by both higher infection and transmission rates.[15,16] Since then, several other variants with clinical consequences have emerged, leading to the need to categorise them into different groups, according to the risk they pose to public health.[17,18]

In this sense the World Health Organization (WHO) has devised a classification with the following working definitions: Variant under Monitoring (VUM), Variant of Interest (VOI), Variant of Concern (VOC) and Variants of High Consequence (VHC), the last is reserved to the most virulent and contagious variants, that make diagnosis, treatment, and vaccination ineffective. Presently, there are no variants in this last category yet.[19,20] When a variant, previously classified as VOI, shows one or more of the following changes at a degree of global public health significance it becomes a VOC: (i) increase in transmissibility or detrimental change in the COVID-19 epidemiology; or (ii) increase in virulence or change in clinical disease presentation; or (iii) decrease in the effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.[19,20] Currently there are 5 VOCs: Alpha, Beta, Gamma, Delta and Omicron of the B.1.1.7, B.1.351, P.1, B.1.617.2 and B.1.1.529, Pango lineage, respectively (Figure 2).

The Alpha variant was first documented on September 2020 in United Kingdom, by 18th of December 2020 it was already designated as a VOC. This variant has two additional amino acids monitored: 484K and 452R when compared to previous variants. On May 2020, South Africa reported a new variant, Beta, that had a particular amino acid monitored, L18 F, but only on 18th of December 2020 it was declared as a VOC. On November of the same year, Brazil reported an additional variant, Gamma, with the following amino acid monitored: 681H. Only 2 months later it was designated a VOC. The Delta variant emerged in India on October 2020. It was declared as a VOI on April 2021 and further classified as VOC a month later. It has

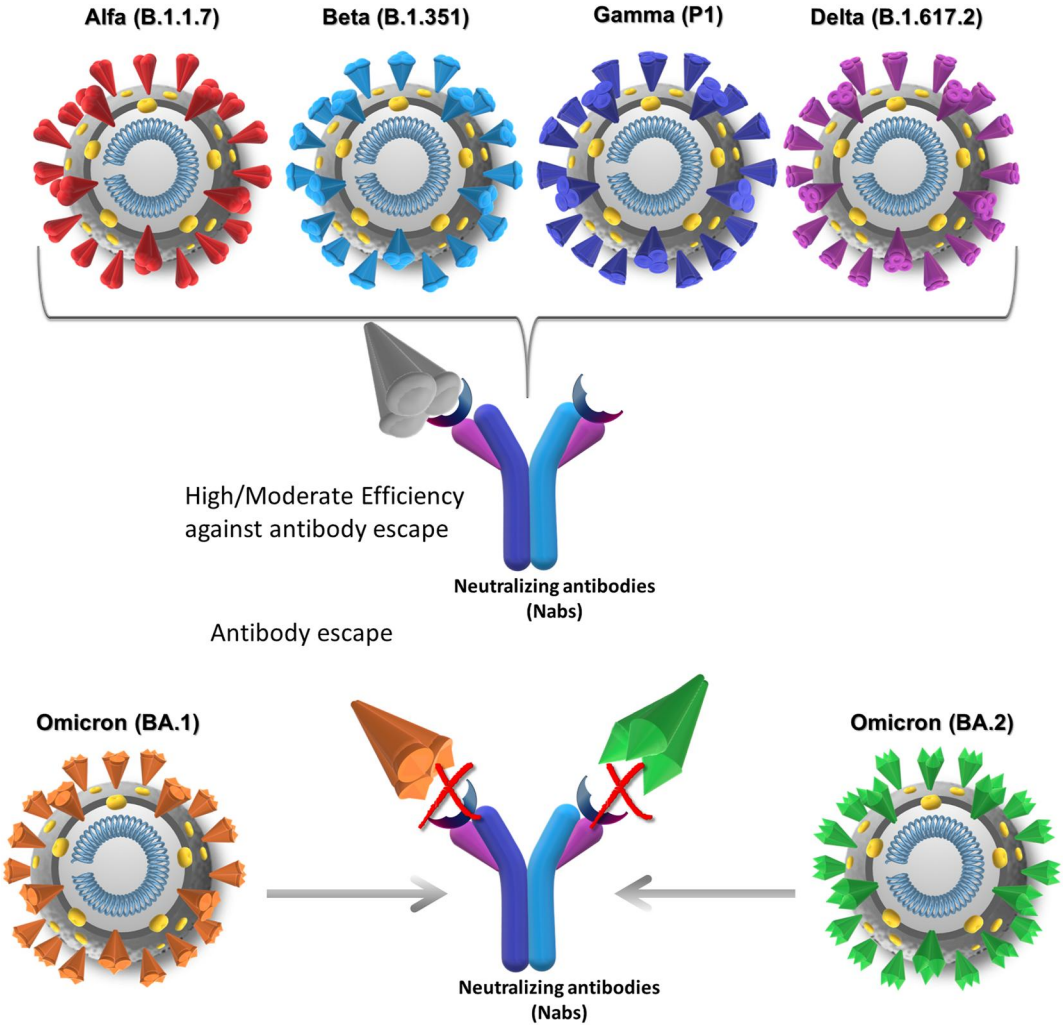

FIGURE 2 Current variants of concern (VOC) and their efficiency in escaping neutralising antibodies

two additional amino acids monitored: 417N and 484K. Lastly, Omicron was reported in many countries in November 2021. Even though most papers report its appearance in South Africa, according to the WHO[20] it has not yet been assigned to a country. This variant was classified as VUM upon its discovery, but within 4 days, the WHO classification was changed to VOC. The additional amino acid change monitored is R346 K.[19,20] It is believed that this variant is a case of inter-species evolutionary trajectory, where a mouse was infected with SARS-CoV-2 and upon mutation jumped back to humans and started the high infection rates that we are currently dealing with.[21]

Recently, France has reported 12 new cases of a new variant, IHU, that seem to be associated to a patient that returned from Cameroon.[22] This variant was attributed the scientific name B.1.640.2 according to the Pango lineage. The preliminary analysis of this variant revealed an overall of 46 mutations and 37 deletions. From these, 14 are located in the spike protein, including the mutations recently observed in Omicron: N501Y and E484 K, that are associated with antibodies escape.[22] Moreover, the P681H, which was also found in Omicron, has also raised concern since it is located in the spike cleavage site of S1-S2 subunits.[23]

On 7 January, virologist Leondios Kostrikis announced that his research group at the University of Cyprus in Nicosia had identified several SARS-CoV-2 genomes that featured elements of both the Delta and Omicron variants, "Deltacron".[24] However, it was assumed to be a contamination or otherwise an experimental error, since the scientific community did not confirmed other cases. Recently, WHO has confirmed cases in Denmark, the Netherlands, France and United Kingdom.[25] WHO is still waiting for new data that can further clarify this variant potential threat, hence it has still not been classified as a VOC. Nonetheless if we consider that this variant is the fusion between the deadliest VOC and the most transmissible one, with high vaccine-mediated and previous infection immunity, it seems safe to say that the pandemic is far from being over.

2.1 | Variants of concern (VOC) infectivity and relevant mutations

The different VOCs have distinct characteristics, nonetheless there seems to be an increasing trend in terms of infectiousness rate. The Delta variant managed to invade 163 countries in an approximately 9 months's period upon being discovered. According to the evidence so far[26] the Delta variant is 40%–60% more transmissible than Alpha. Moreover, according to the available data, the Delta variant presented a two-fold increased risk of hospitalisation.[27–29] This led to a high increase, not only on the infected people, but also in hospitalizations and deaths worldwide. On the other hand, Omicron, which was discovered on the 11th of November 2021, was classified as VOC 15 days later, due to its high number of mutations that could have an impact on the transmissibility and the severity of the disease. Omicron did not fail down on the expectations. Indeed, travel-related occurrences were documented in Belgium, Hong Kong and Israel, 15 days after the variant was initially reported. Globally, all countries have reported Omicron-related cases and it has been declared dominant in several European countries in December 2021, only one month upon discovery[19,26] even in communities with strict measures like the ones reported by South Korea.[30]

Kandeel et al.[31] compared the genetic similarities between the VOCs and found that the Omicron had the greatest number of gaps during genome alignment with other SARS-CoV-2 variants. Moreover, according to these authors upon sequence alignment and gaps analysis, they concluded that the Alpha variant was the one that most resembles Omicron. This may be an indication that the Omicron variant was on circulation for some time before it was discovered.[31] Additionally, the authors built a phylogenetic tree with the collected data and concluded that Omicron is phylogenetically distant from other variants, thus producing a monophyletic clade.[31,32] Omicron has more than 50 mutations overall, and of these, 26 are unique, further building upon the 10 concerning and unique mutations previously observed in Delta (Figure 3) and six from Beta.[33] This fact further supports the theory that the environment may play a unique role for viral adaptation.[33]

The overall Omicron incidence by age - especially in children[34] - region and ethnicity differs markedly from Delta.[35] Currently, Omicron is the dominant variant circulating worldwide, accounting for almost all the reported sequences to GISAID.[25] It is composed of several sublineages where the most common are BA.1 and BA.2. More recently, a sublineage identified as BA.3 has also been reported.[25,36] Even though these lineages are monophyletic their sequences are quite distinct. Indeed, BA.1 and BA.2 differ in 50 amino acids, which is almost double of the differences found between Alpha, Beta, Gamma and Delta when compared to Wuhan-Hu-1.[37] Upon its appearance in December 2021 the BA.1 lineage was the most common and reported by every country has the dominant variant; however, recently the number of BA.2 cases are surpassing BA.1. On the 22th of February, the WHO's Technical Advisory Group on SARS-C oV-2 Virus Evolution (TAG-VE) gathered to discuss the evidence on the VOC Omicron and its sublineages BA.1 and BA.2.[25] Taking into consideration the available data on transmissibility patterns, severity, reinfection rates, diagnostics, therapeutics and overall impact of vaccines, the group has reinforced the fact that BA.2 should continue to be classified as Omicron and, as such, to be considered a VOC. Nonetheless the TAG-VE emphasised that a close monitoring should continue and a re-evaluation will be performed if new data arise.[38] According to Professor Adrian Esterman,[39] a former epidemiologist for WHO, the transmissibility of "BA.2 is very close to measles that is the most contagious disease known". This raises a relevant question: Will BA.2 or BA.3 becomes the dominant variant? The knowledge acquired so far indicates that BA.1 has 15 RBD mutations (Table 1) that are associated with its high infectivity and disruption of nAbs (Figure 2) generated by prior viral infection and vaccination. On the other hand, BA.2 and BA.3 share 12 of the BA.1 RBD mutations and have an additional 4 and 3 new ones, respectively[40] (Figure 3).

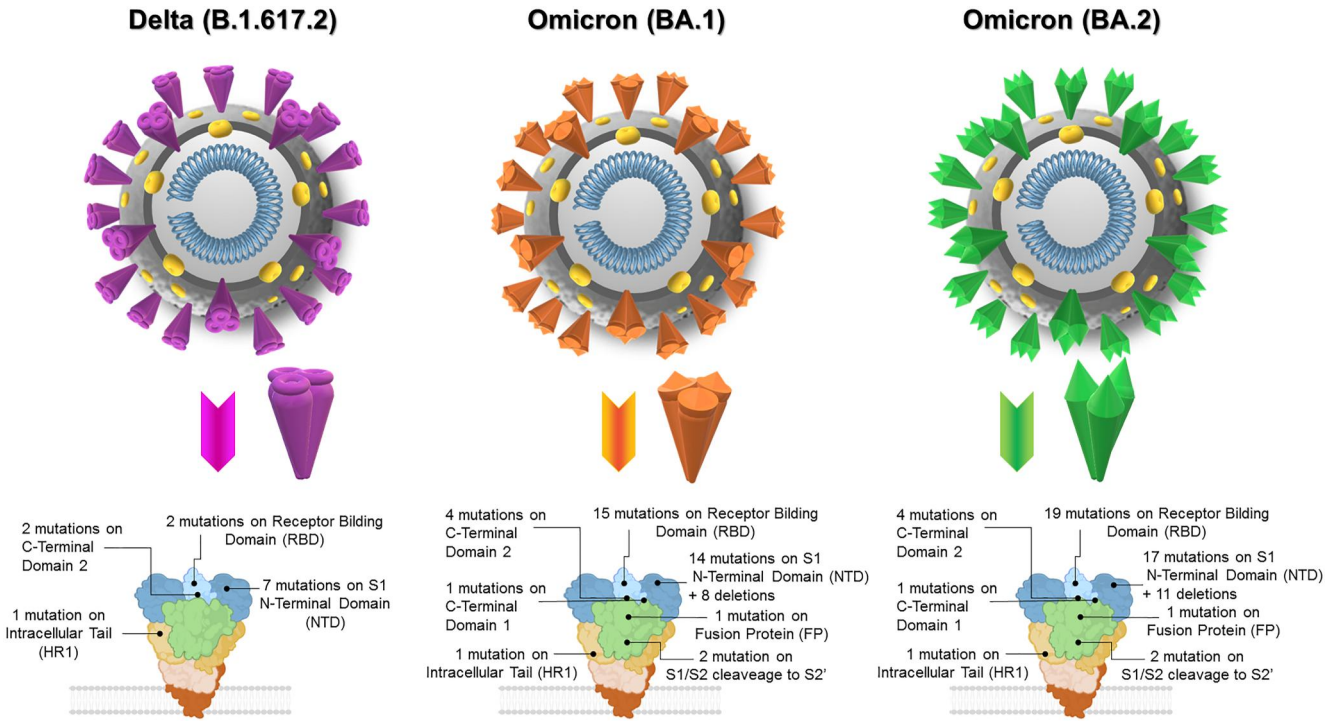

FIGURE 3 Spike mutations on Delta and Omicron variants, BA. 1 and BA. 2, when compared to the original Wuhan variant. Data extracted from[30]

TABLE 1 Nonsynonymous and synonymous mutations of BA.1 and BA.2

		BA.1	BA.2
Nonsynonymous	**S**	A67V; H69-; V70-; T95I; G142-; V143-; Y144-; Y145D; N211-; L212I; **G339D**; S371L; **S373P**; **S375F**; **K417N**; **N440K**; G446S; **S477N**; **T478K**; **E484A**; **Q493R**; G496S; **Q498R**; **N501Y**; **Y505H**; T547K; **D614G**; **H655Y**; **N679K**; **P681H**; **N764K**; **D796Y**; N856K; **Q954H**; **N969K**; L981F	T19I; L24-; P25-; P26-; A27S; G142D; V213G; **G339D**; S371F; **S373P**; **S375F**; T376A; D405N; R408S; **K417N**; **N440K**; **S477N**; **T478K**; **E484A**; **Q493R**; **Q498R**; **N501Y**; **Y505H**; **D614G**; **H655Y**; **N679K**; **P681H**; **N764K**; **D796Y**; **Q954H**; **N969K**
	N	**P13L**; **E31-**; **R32-**; **S33-**; **R203K**; **G204R**	**P13L**; **E31-**; **R32-**; **S33-**; **R203K**; **G204R**; S413R
	ORF1a	K856R; S2083-; L2084I; A2710T; **T3255I**; **P3395H**; L3674-; **S3675-**; **G3676-**; I3758V	S135R; T842I; G1307S; L3027F; T3090I; L3201F; **T3255I**; **P3395H**; **S3675-**; **G3676-**; F3677-
	ORF1b	**P314L**; **I1566V**	**P314L**; R1315C; **I1566V**; T2163I
	ORF3a	-	T223I
	ORF6	-	D61L
	ORF9b	**P10S**; **E27-**; **N28-**; **A29-**	**P10S**; **E27-**; **N28-**; **A29-**
	E	**T9I**	**T9I**
	M	D3G; **Q19E**; **A63T**	**Q19E**; **A63T**
Synonymous		C241T; **C3037T**; T5386G; T13195C; C15240T; **C25000T**; **C25584T**; **A27259C**; **C27807T**; **A28271T**	**C3037T**; C4321T; A9424G; C10198T; G10447A; C12880T; C15714T; A20055G; **C25000T**; **C25584T**; C26858T; **A27259C**; **C27807T**; **A28271T**

2.2 | Spike mutations and their relationship with antibody escape

Spike glycoprotein is responsible for the virus interaction with ACE2 and, consequently, by the viral internalisation on host cells[41] (Figure 2). As such, to avoid virus attachment, most of the therapeutics and vaccines approved for emergency use have been developed to specifically act and inhibit the ACE2-spike interactions.[42] Thus, understanding the mutations, their possible role and location, is crucial for the design of effective target-specific therapeutics and preventive strategies.[43] Omicron has at least 30 amino acid substitutions in the spike protein, three deletions and an

insertion (Figure 3). It is noteworthy to highlight that 15 of these mutations are on the receptor-binding domains (RBD) that are responsible for the spike-ACE2 binding.[44]

In order to better assess the effect that these mutations have on the spike binding affinity, Kumar co-workers,[41] conducted a study to determine the highest theoretical docking score between the spike protein and ACE2. In this study a comparison between Omicron, the original Wuhan and Delta variants was established. They concluded that Omicron has the highest affinity towards ACE2 when compared to the other reported variants.[41]

Indeed, the Omicron variant is the most divergent so far, which can be seen, for example, in terms of transmissibility. This raises concerns on the vaccine efficiency and risk of reinfection. This apprehension is mainly due to the high mutation rate on the S gene, particularly since many of these mutations are in the receptor binding and the N-terminal domains, that play fundamental roles in ACE2 binding and antibody recognition[45,46] (Figure 2). Omicron also has a particular cluster of mutations at the S1-S2 furin cleavage site (H655Y, N679 K, P681H; Figure 3) that can be responsible for immune-escape and high transmissibility.[47,48] It is believed that its transmissibility surpasses the Delta variant, considered the most transmissible up until now. Additionally, there are also 3 amino acid deletions in the ORF1a gene that seem to be related with higher immune evasion.[49,50]

Among the many Omicron mutations, it is also important to highlight the relevance of the mutation E484 in the spike protein. It has been previously demonstrated that this mutation may be critical in avoiding vaccination immunity.[41] This mutation is also present in the Beta and Gamma VOCs, as well as, in the Mu VOI and was found to have a key role in resistance to neutralising antibodies generated by prior infection[51] (Figure 2).

It is important to highlight that the effect of Omicron mutations must be seen as a whole.[43] N501Y mutation is responsible for improving the ACE2 receptor binding, which is associated with high transmission rate; however, additional Omicron spike protein modifications may also alter the affinity towards ACE2 receptor.[52] The H655Y mutation is adjacent to the furin cleavage point (Figure 3), thus it could speed up spike cleavage and assist transmission. Furthermore, it can also be responsible for the virus resistance towards monoclonal antibody therapy.[53] Moreover, N679 K mutation is also close to the furin cleavage site and contributes to its polybasic character, which may enhance spike cleavage and help transmission.[43] Overall, there are 15 mutations in the Omicron RBD (Figure 2). From these, only N501Y mutation is associated with increased protein stability. On the other hand, the mutations G339D, S371 L, S373P, S375 F, K417 N, N440 K, G446S, S477 N, T478 K, E484 A, Q493 R, G496S, and Q498 R, are related to decreased protein stability. Nonetheless, all these mutations share a common trade: they are an indicator of increased disease vulnerability.[26]

Considering the knowledge acquired for BA.1 and the unveiling of the particularities of BA.2 spike protein, it seems reasonable to assume that virological properties, such as, immune resistance and pathogenicity, are most likely different too.[36] Indeed, as the number of people infected by Omicron sub variants rise, so did the number of reinfections. This raised a pertinent question: can BA.2 escape from the natural immunity acquired shortly after the BA.1 infection? There is not a consensus on this subject. Indeed, even though there are studies pointing out that previous infection with an Omicron sublineage induced strong but not full protection against reinfection for several weeks after the initial infection.[53] There are also studies proving exactly the opposite, that is, from a total of 187 reinfection cases, 47 (25%) where associated with BA.2 reinfection shortly after BA.1 infection.[40] These cases where mostly, but not all, in young unvaccinated individuals with mild disease, not resulting in hospitalisation or death. These differences may be due to the particularities of the studies. Indeed Chemaitelly et al.,[53] concluded that there was strong protection against reinfection using data collected in Qatar during a large Omicron (BA.1 and BA.2) wave. But in Qatar the BA.1 was dominant for a very short period of time (days), and the sample was constituted by only 23.8% BA.1 confirmed cases and 76.2% BA.2. Despite the fact that this sample is intrinsically biased, it is important to analyse these data keeping in mind that the reinfection cases reported are associated with BA.2 infection after BA.1. This reinforces the idea that data need to be carefully integrated into the exiting information in order to provide an overall idea on the subject instead of creating doubts and non-consensus information, particularly when the topic is so new and relevant and important measures are being implemented all around the world through the outputs science is providing.

The apparent advantage of BA.2 over BA.1 is currently the topic of several research studies.[25,35,36] Chen and Wei (2022)[35] performed a comparative analysis on all the main variants, namely, Alpha, Beta, Gamma, Delta, Lambda, Mu, BA.1, BA.2 and BA.3 and determined that BA.2 is about 1.5 times more infectious than BA.1 and 4.2 times more infectious than Delta. Moreover, it is also 30% and 17% more capable than BA.1 and Delta, respectively, to escape current vaccines.[35] In Japan, Yamasoba et al.,[36] analysed the effects of BA.2 and BA.1 on animal models. According to their results, the effective BA.2 viral reproduction is 1.4- fold higher than BA.1. Their cell culture experiments also reinforced the knowledge that BA.2 is more replicative in human nasal epithelial cells and more fusogenic than BA.1. When using animal models, namely hamsters, BA.2 superior infection ability was also confirmed. Moreover, this study neutralisation experiments showed that the vaccine-induced immunity fails on both Omicron sublineages despite the fact that their individual antigenicity is different.[36] These data along with the high number of cases being reported of BA.2 it seems to indicate that this variant is more infectious than BA.1, thus suggesting that it can potentially pose serious threats to human health. Nonetheless there are little experimental results reported for BA.2 and BA.3. According the phylodynamics analysis performed by Yamasoba et al.,[36] BA.1 emerged first closely followed by BA.2 and BA.3. Moreover, the data also suggest that all these lineages have emerged in Gauteng Province, South Africa, where the first cases where reported. Overall these studies are suggesting that the risk for global health is higher for BA.2 lineage.

3 | PHYSICOCHEMICAL PARAMETERS: EVOLUTION FROM THE ORIGINAL TO DELTA AND OMICRON VARIANT

The emergence of new variants, particularly Delta and Omicron, was followed by a sequence loss, deletions, and consequent amino acid decrease. But following these sequence changes, an interesting feature has emerged. A protein's isoelectric point (pI) is an indication of the protein acid-base behaviour. From the original Wuhan variant to Omicron, an increase in the theoretical pI was observed, changing from acidic to alkaline (from 6.24 to 7.14, for the Wuhan to Omicron variants, respectively).[26] It is also interesting to notice that despite the fact that Omicron has less 3 amino acids than the Wuhan variant, its molecular weight is higher than Wuhan and Delta variants, as well as its pI. Moreover, when compared to the Delta variant, Omicron has an increase in the following amino acids: arginine (Arg), lysine (Lys), aspartic acid (Asp), and glutamic acid (Glu). These amino acids are responsible for salt bridge formation, thus increasing the stability of the protein, particularly because these amino acids are charged residues that are in an exposed section of the protein. Additionally, Omicron spike core is composed by a high content of non-polar amino acids, which is an advantage feature, since the core is inaccessible to the solvent hence it won't pose as a solubility problem and at the same time it allows rising the protein pI.[54]

4 | EFFECTIVENESS OF DIAGNOSTIC TESTS

Considering the mutation rate and all the mutations that have arisen in the SARS-CoV-2 genome, it is important to evaluate the effectiveness of the diagnostic tools available. Indeed, depending on the mutations and differences in infection levels, these may compromise some diagnostic tools if they are not constantly being monitored and updated. Currently there are numerous diagnostic tools available. In Europe alone, there are more than 364 tests approved and available for commercialisation.[55,56]

The difference in test performance regarding specificity and sensitivity, the equipment required, the cost and the information that each result provides are all variables that need to be taken into consideration when choosing the best option. Each test has a more or less specific window of time in which its results have higher accuracy, and sometimes, the test choice simply isn't the most adequate for a given situation, leading to false results. Symptom's presentation, time of infection, type and quality of the sample, are some of the variables that can greatly influence test results and their efficacy. The most accurate test so far is the RT-PCR; however, as in all tests, the targeted genomic region needs to be carefully chosen, more when the virus undergoes such a high number of mutations, which can compromise detection efficiency. It is necessary to highlight that the identification of Omicron in South Africa was possible due to the S-gene target failure approach.[43] Thus, and based on the known changes in the virus genome, the rapid antigen detection tests need urgent re-evaluation for their validity in the detection of Omicron cases.

5 | VACCINE EFFICACY TOWARDS OMICRON VARIANT

The vaccine-induced immunity mostly targets the spike protein in an attempt to neutralise the interaction between the protein and ACE2. In each variant, the spike protein has suffered several mutations; however the 15 RBD mutations pose a great concern.[26,43,55]

The neutralising capacity of our current interventions, namely vaccines and convalescent plasma, need to be addressed through in vitro assays and in vivo studies[57]; however this will take some time to accomplish.[58] As previously explained, some of the spike mutations are on immune-dominant regions that are thought to be extremely relevant in the antibody-mediated host defence.[33,59] Some of the other known mutations are located in domains that are targeted by T cell-mediated host defence. This is an additional problem. Indeed when virus evolution results in the neutralisation of the existing antibodies it is possible that memory T cell responses offer a path for long term protection.[43] This can be assessed by the major effectiveness to assist activated naive B cells by CD4 + T cells responding to the altered spike protein, or by direct lysing of SARS-CoV-2 infected cells mediated by CD8 + T cells. According to the number of mutations on the RBD, it is likely that the Omicron variant is more susceptible to monoclonal antibody therapy, when compared to other variants with fewer mutations on this domain.[43,59] Moreover, the data collected by Cao and co-workers,[60] indicated that even though Omicron can cause significant humoral immune evasion, the use of neutralising antibodies targeting the Sarbecovirus conserved region seems to be more effective. These authors suggest that efforts should be employed in developing neutralising antibodies and vaccines targeting this region as an effective measure to neutralise Omicron and future variants.[60]

According to the knowledge acquired so far, scientists from South Africa believe that previous SARS-CoV-2 infection provides relatively low-to-none immune protection against subsequent infection with the Omicron variant. These facts have led the vaccine manufacturers to launch major efforts to create mRNA-based vaccines adjusted to the Omicron variant.[61] The known facts regarding vaccine effectiveness obtained through the use of isolated Omicron viruses have showed incomplete immune escape from antibodies in individuals without prior SARS-CoV-2 infection that had taken two doses of the Pfizer vaccine. However, individuals with two doses of the Pfizer vaccine who have had previous SARS-CoV-2 infection showed antibody levels expected to be protective.[62] On another study, testing sera from individuals with full vaccination (Pfizer/BioNTech or Moderna, or heterologous AstraZeneca/BioNTech), the neutralisation levels were highly reduced. However, the administration of a booster shot seemed to increase the antibody levels to a significant level.[63] Nonetheless, it is still early to have a detailed vision of this variant impact in the immune response, and several more studies and data are needed to confirm these initial results[58]

Recent studies have proved that BA.1 and BA.2 are highly resistant to the vaccine-induced antisera.[36,64] Moreover, BA.2 was also almost completely resistant to two monoclonal antibodies,

Casiriviman and Imdevimad.[36] Additionally, this Omicron lineage was also found 35% more resistant to Sotrovimab,[36] another therapeutic antibody that has been proven useful, in the last VOCs, for decreasing the disease progression risk in high-risk patients with mild-to-moderate COVID-19.[65,66]

Before Omicron appearance a SIREN UK cohort study of health care workers estimated 85% protection provided by previous infection against a new one, over 6 months.[67] This study dictated a reference that countries like Portugal used for RT-PCR testing. Currently, another UK study, Report 49 of the Imperial College COVID-19 response,[33] obtained similar results to Pulliam et. al. in South Africa, that suggests strong evidence for immune evasion of Omicron sublineages when compared to Delta.[61] Indeed using the same time spam established before Omicron (6 months upon initial infection), the remaining protection is only 19%. This evasion is similar from both previous infection and vaccine-induced protection, where a risk of reinfection is 5.41-fold higher for Omicron than for Delta. Thus, it is of the outmost relevance to update the testing guidelines according to these findings. Report 49 results also support the findings of Andrews et al.,[68] that suggests very limited remaining protection against symptomatic infection afforded by two doses of AZ, low protection afforded by two doses of Pfizer, but moderate to high (55%–80%) protection in people boosted with an mRNA vaccine.[34,69] Indeed, SARS-CoV-2 mRNA vaccines have demonstrated efficiency prior to Delta and Omicron VOCs appearance in the prevention of asymptomatic infection or mild symptomatic disease[70–72] but taking into consideration the current knowledge it is still not clear if additional vaccines boosts or the development of a more specific vaccine will be an emerging need.[69,73] This vaccine-immune and prior infection antibodies evasion by Omicron is particularly interesting. It is important to highlight that mRNA vaccines were designed to create antibodies that target the spike protein and Omicron has 23 specific spike mutations and most of these are on the RBD[44] (Figure 3). Kannan et al.,[44] analysed the spike protein mutations and their possible relation with Omicron immune escape and found evidence that these spike mutations can effectively affect the antibodies attachment to it (Figure 2), thus reducing the efficacy of vaccination and prior infection immunity. Lytras et al.,[74] went a bit further and concluded that the large mutations number present in Omicron are only beneficial when present together and that the immune evasion characteristic of this VOC would not be so effective if they were not present simultaneously. It is also interesting to highlight that these mutations are also associated with a higher binding capacity to ACE2 for a broader range of species,[75,76] making the reverse zoonosis identified in SARS-CoV-2[77] particularly troubling.

Even though this new VOC has been associated with a lower mortality and severity rates, this fact is not synonymous of benign. On the contrary, there is still much uncover on the effects of long COVID and the long-term effects of severe and mild symptomatic infections. Indeed, a recent study with 785 participants it has been demonstrated that even in mild case infection it is possible to develop brain-related abnormalities due to COVID-19 infection.[78] This study proved that this viral infection can effectively lead to: (i) reduction in the grey matter thickness and tissue-contrast in both orbitofrontal cortex and parahippocampal gyrus; (ii) alteration in tissues markers in regions functionally connected to the primary olfactory cortex, and (iii) reduction in global brain size. Additionally the study participants also revealed an average larger cognitive decline when comparing the scan results obtained upon diagnostic and 141 days later. Moreover no differences were observed between patients that had been hospitalised and those who had mild symptoms that did not require hospitalisation.[78] This reinforces the fact that these brain abnormalities can occur even in mild COVID-19 symptoms cases. This study is possibly a hallmark for proving in vivo degenerative spread of diseases via olfactory pathways, neuroinflammatory events or even the loss of sensory input due to anosmia. It remains unknown whether these effects are reversible or not.[78]

6 | CONCLUSIONS

Ever since the emergence of SARS-CoV-2 at the end of 2019, several new variants have been reported worldwide, as the numbers of the pandemic keep rising and reaching new peaks from time to time. The uprise of Omicron has brought a new challenge to the already fragile world economy. In November 2021 it was first reported by the South African entities the appearance of a new variant and less than a month later it was considered the dominant variant in every country it reached. Indeed, the high transmissibility rate is now being compared to the measles virus. This variant has raised red flags all over, mainly due to the elevated number and the location of these mutations. Omicron has over 50 mutations, 15 of which in the RBD, that are responsible for binding to host cells. Moreover, some mutations are also associated with antibody escape and host immune evasion. This has raised concerns to the possibility of dealing with a variant that is more transmissible, that poses a higher risk of reinfection and ultimately for which the vaccine efficiency is lower. According to the data collected so far it is safe to say that it is much more transmissible than the previous Delta variant, the deadliest VOC so far. Regarding the other two main problems flagged, data acquired so far, proved that Omicron, particularly the sublineage BA.2 is more transmissible, has a high risk of reinfection and a high capacity to evade host-immunity provided by vaccines and previous infections. Even though this variant seems to have more mild symptoms, mostly associated with an upper respiratory tract infection, it is necessary to keep in mind that the number of infected people is strongly related to the emergence of new variants. Moreover, it has been proven that patients with mild COVID-19 had several brain alterations. Up to this moment it is still not clear if these changes, including the reduction of brain size, are reversible. Additionally, the high infection rates associated with Omicron (BA.1, BA.2 and BA.3) are associated with the cases of double infection (where a patient is contaminated by both variants) and the appearance of the new variant “Deltacron”, which is a fusion between VOCs, Delta and

Omicron. The emergence of these new potentially harmful variants needs to be taken into consideration when revising the restrictions relieves worldwide.

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CONFLICT OF INTEREST

All authors declare that there is no conflicts of interest.

AUTHOR CONTRIBUTIONS

A. Lino, M. A Cardoso, P. Martins-Lopes e H.M.R. Gonçalves conceived the project and contributed to writing the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. GISAID. GISAID initiative. *Adv Virus Res*. 2020;2008:1-7. Accessed September 3, 2021. https://www.gisaid.org/
2. Ge XY, Wang N, Zhang W, et al. Coexistence of multiple coronaviruses in several bat colonies in an abandoned mineshaft. *Virol Sin*. 2016;31(1):31-40. https://doi.org/10.1007/s12250-016-3713-9
3. Zhou P, Yang X, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273. https://doi.org/10.1038/s41586-020-2012-7
4. Singh D, Yi SV. On the origin and evolution of SARS-CoV-2. *Exp Mol Med*. 2021;53(4):537-547. https://doi.org/10.1038/s12276-021-00604-z
5. Meyerholz DK, Lambertz AM, McCray PB. Dipeptidyl peptidase 4 distribution in the human respiratory tract implications for the Middle East respiratory syndrome. *Am J Pathol*. 2016;186(1):78-86. https://doi.org/10.1016/j.ajpath.2015.09.014
6. El-Arif G, Farhat A, Khazaal S, et al. The renin-angiotensin system: a key role in SARS-CoV-2-induced COVID-19. *Molecules*. 2021;26:6945-6976. https://doi.org/10.3390/molecules26226945
7. Ogando NS, Zevenhoven-Dobbe JC, van der Meer Y, Bredenbeek PJ, Posthuma CC, Snijder EJ. The enzymatic activity of the nsp14 exoribonuclease is critical for replication of MERS-CoV and SARS-CoV-2. *J Virol*. 2020;94(23). https://doi.org/10.1128/jvi.01246-20
8. van Dorp L, Acman M, Richard D, et al. Emergence of genomic diversity and recurrent mutations in SARS-CoV-2. *Infect Genet Evol*. 2020;83:104351. https://doi.org/10.1016/j.meegid.2020.104351
9. Jaroszewski L, Iyer M, Alisoltani A, Sedova M, Godzik A. The interplay of SARS-CoV-2 evolution and constraints imposed by the structure and functionality of its proteins. *bioRxiv*. 2020:1-22. Published online. https://doi.org/10.1101/2020.08.10.244756
10. Cagliani R, Forni D, Clerici M, Sironi M. Computational inference of selection underlying the evolution of the novel coronavirus, severe acute respiratory syndrome coronavirus 2. *J Virol*. 2020;94(12). https://doi.org/10.1128/jvi.00411-20
11. Boehm E, Kronig I, Neher RA, Eckerle I, Vetter P, Kaiser L. Novel SARS-CoV-2 variants: the pandemics within the pandemic. *Clin Microbiol Infect*. 2021;27(8):1109-1117. https://doi.org/10.1016/j.cmi.2021.05.022
12. Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature*. 2020;584(7819):115-119. https://doi.org/10.1038/s41586-020-2380-z
13. Cedro-Tanda A, Gómez-Romero L, de Anda-Jauregui G, et al. Early genomic, epidemiological, and clinical description of the SARS-CoV-2 omicron variant in Mexico city. *Viruses*. 2022;14:545-567. https://doi.org/10.3390/v1403054
14. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*. 2020;182(4):812-827:e19. https://doi.org/10.1016/j.cell.2020.06.043
15. Zella D, Giovanetti M, Benedetti F, et al. The variants question: what is the problem?*J Med Virol*. 2021;28(12):1-7. Published online. https://doi.org/10.1002/JMV.27196
16. Volz E, Hill V, McCrone JT, et al. Evaluating the effects of SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity. *Cell*. 2021;184(1):64-75:e11. https://doi.org/10.1016/j.cell.2020.11.020
17. Hou YJ, Chiba S, Halfmann P, et al. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. *Science*. 2021;370(6523):1464-1468. https://doi.org/10.1126/science.abe8499
18. Cantón R, De Lucas Ramos P, García-Botella A, et al. New variants of SARS-CoV-2. *Rev Española Quimioter*. 2021;34(5):1-10. Published online 2021. https://doi.org/10.37201/req/071.2021
19. WHO. Tracking SARS-CoV-2 variants. WHO; 2021. Accessed December 30, 2021. Published https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
20. CDC. SARS-CoV-2 variant classifications and definitions. Cdc. Published online 2021:1-12. Accessed December 30, 2021. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html
21. Wei C, Shan K-J, Wang W, Zhang S, Huan Q, Qian W. Evidence for a mouse origin of the SARS-CoV-2 Omicron variant. *J Genet Genomics*. 2021;24(12):1111-1121. Published online. https://doi.org/10.1016/j.jgg.2021.12.003
22. Colson P, Delerce J, Burel E, et al. Emergence in Southern France of a new SARS-CoV-2 variant of probably Cameroonian origin harbouring both substitutions N501Y and E484K in the spike protein. *medRxiv*. 2021. Published online December 29, 2021. https://doi.org/10.1101/2021.12.24.21268174
23. Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. *Lancet*. 2021;398(10317):2126-2128. https://doi.org/10.1016/s0140-6736(21)02758-6
24. Kreier F, Deltacron: the story of the variant that wasn't. *Nature*. 2022;602(7895):19. https://doi.org/10.1038/d41586-022-00149-9
25. WHO. Tracking SARS-CoV-2 variants. Published online 2021. Accessed March 18, 2022. https://www.who.int/en/activities/tracking-SARS-CoV-2https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

26. Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G. Omicron and delta variant of SARS-CoV-2: a comparative computational study of spike protein. *J Med Virol*. 2021;27(4):1641-1649. Published online. https://doi.org/10.1002/jmv.27526
27. Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22(1):35-42. https://doi.org/10.1016/S1473-3099(21)00475-8
28. Bager P, Wohlfahrt J, Rasmussen M, Albertsen M, Krause TG. Hospitalisation associated with SARS-CoV-2 delta variant in Denmark. *Lancet Infect Dis*. 2021;21(10):1351. https://doi.org/10.1016/S1473-3099(21)00580-6
29. Shah SA, Moore E, Robertson C, et al. Predicted COVID-19 positive cases, hospitalisations, and deaths associated with the Delta variant of concern, June-July, 2021. *Lancet Digit Heal*. 2021;3(9):e539-e541. https://doi.org/10.1016/S2589-7500(21)00175-8
30. Kim D, Ali ST, Kim S, et al. Estimation of serial interval and reproduction number to quantify the transmissibility of SARS-CoV-2 omicron variant in South Korea. *Viruses*. 2022;14:533-541. https://doi.org/10.3390/v14030533
31. Kandeel M, Mohamed MEM, Abd El-Lateef HM, Venugopala KN, El-Beltagi HS. Omicron variant genome evolution and phylogenetics. *J Med Virol*. 2021;10(4):1627-1632. Published online. https://doi.org/10.1002/jmv.27515
32. Posada D, Crandall KA. Selecting models of nucleotide substitution: an application to human immunodeficiency virus 1 (HIV-1). *Mol Biol Evol*. 2001;18(6):897-906. https://doi.org/10.1093/oxfordjournals.molbev.a003890
33. Ingraham NE, Ingbar DH. The omicron variant of SARS-CoV-2: understanding the known and living with unknowns. *Clin Transl Med*. 2021;11(12):e685. https://doi.org/10.1002/ctm2.685
34. Tagarro A, Coya ON, Villena AP, et al. Features of COVID-19 in children during the omicron wave compared with previous waves in madrid, Spain. *Pediatr Infect Dis J*. 2022;41(5):e249-e251. https://doi.org/10.1097/inf.0000000000003482
35. Ferguson N, Ghani A, Cori A, Hogan A, Hinsley A, Volz E. Report 49: growth, population distribution and immune escape of Omicron in England. *Imperial College London*. 2022. https://doi.org/10.25561/93038
36. Chen J, Wei G-W. Omicron BA.2 (B.1.1.529.2): high potential to becoming the next dominating variant. *ArXiv*. 2022. Published online. https://doi.org/10.21203/rs.3.rs-1362445/v1
37. Yamasoba D, Kimura I, Nasser H, et al. Virological characteristics of SARS-CoV-2 BA.2 variant. *bioRxiv*. 2022. Published online. https://doi.org/10.1101/2022.02.14.480335
38. Parums D. Editorial: revised world health organization (WHO) terminology for variants of concern and variants of interest of SARS-CoV-2. *Med Sci Monit Int Med J Exp Clin Res*. 2021;27:e933622. https://doi.org/10.12659/MSM.933622
39. ABC News. Two years of COVID: three things we got wrong, and three things to look out for - ABC News. 2022. Published. Accessed March 18, 2022. https://www.abc.net.au/news/2022-03-11/covid-second-anniversary-what-we-got-wrong/100899780
40. Stegger M, Edslev SM, Sieber RN, et al. Occurrence and significance of Omicron BA.1 infection followed by BA.2 reinfection. *medRxiv*. 2022. Published online. https://doi.org/10.1101/2022.02.19.22271112
41. Kumar S, Saxena SK. Structural and molecular perspectives of SARS-CoV-2. *Methods*. 2021;195:23-28. https://doi.org/10.1016/j.ymeth.2021.03.007
42. Gupta A, Pradhan A, Maurya VK, et al. Therapeutic approaches for SARS-CoV-2 infection. *Methods*. 2021;195:29-43. https://doi.org/10.1016/j.ymeth.2021.04.026
43. Saxena SK, Kumar S, Ansari S, et al. Characterization of the novel SARS-CoV-2 omicron (B.1.1.529) variant of concern and its global perspective. *J Med Virol*. 2021;14(4):1738-1744. Published online. https://doi.org/10.1002/jmv.27524
44. Bhattacharya M, Sharma AR, Dhama K, et al. Omicron variant (B.1.1.529) of SARS-CoV-2: understanding mutations in the genome, S-glycoprotein, and antibody-binding regions. *GeroScience*. 2022. https://doi.org/10.1007/s11357-022-00532-4
45. Kannan SR, Spratt AN, Sharma K, Chand HS, Byrareddy SN, Singh K. Omicron SARS-CoV-2 variant: unique features and their impact on pre-existing antibodies. *J Autoimmun*. 2021;126:102779. https://doi.org/10.1016/j.jaut.2021.102779
46. Zahradník J, Marciano S, Shemesh M, et al. SARS-CoV-2 variant prediction and antiviral drug design are enabled by RBD in vitro evolution. *Nat Microbiol*. 2021;6(9):1188-1198. https://doi.org/10.1038/s41564-021-00954-4
47. Gong SY, Chatterjee D, Richard J, et al. Contribution of single mutations to selected SARS-CoV-2 emerging variants spike antigenicity. *Virology*. 2021;563:134-145. https://doi.org/10.1016/j.virol.2021.09.001
48. Wise J. Covid-19: the E484K mutation and the risks it poses. *BMJ*. 2021;372:n359. https://doi.org/10.1136/bmj.n359
49. Benvenuto D, Angeletti S, Giovanetti M, et al. Evolutionary analysis of SARS-CoV-2: how mutation of Non-Structural Protein 6 (NSP6) could affect viral autophagy. *J Infect*. 2020;81(1):e24-e27. https://doi.org/10.1016/j.jinf.2020.03.058
50. Chakraborty C, Sharma AR, Bhattacharya M, Lee SS. A detailed overview of immune escape, antibody escape, partial vaccine escape of SARS-CoV-2 and their emerging variants with escape mutations. *Front Immunol*. 2022;13(801522):1-26. https://doi.org/10.3389/fimmu.2022.801522
51. Zhang Y, Wei Y, Yang S, et al. Rapid and accurate identification of SARS-CoV-2 variants containing E484 mutation. *Innov*. 2022;3(1):100183. https://doi.org/10.1016/j.xinn.2021.100183
52. Ali F, Kasry A, Amin M. The new SARS-CoV-2 strain shows a stronger binding affinity to ACE2 due to N501Y mutant. *Med Drug Discov*. 2021;10:100086. https://doi.org/10.1016/j.medidd.2021.100086
53. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nat Med*. 2021;27(4):717-726. https://doi.org/10.1038/s41591-021-01294-w
54. Chemaitelly H, Ayoub HH, Coyle P, et al. Protection of Omicron sub-lineage infection against reinfection with another Omicron sub-lineage. *Medrxiv*. 2022;25. Published online. https://doi.org/10.1101/2022.02.24.22271440
55. Ortega JT, Serrano ML, Pujol FH, Rangel HR. Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 whow: an in silico analysis. 2020;19:410-417. https://doi.org/10.17179/excli2020-1167
56. Falzone L, Gattuso G, Tsatsakis A, Spandidos DA, Libra M. Current and innovative methods for the diagnosis of COVID-19 infection (Review). *Int J Mol Med*. 2021;47(6):1-23. https://doi.org/10.3892/ijmm.2021.4933
57. European Centre for Disease Prevention and Control. Implications of the emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron) for the EU/EEA Event background. 2021; 1-7.
58. Callaway E. Omicron likely to weaken COVID vaccine protection. *Nature*. 2021;600(7889):367-368. https://doi.org/10.1038/d41586-021-03672-3
59. Mohapatra RK, Tiwari R, Sarangi AK, Islam MR, Chakraborty C, Dhama K. Omicron (B.1.1.529) variant of SARS-CoV-2: concerns, challenges, and recent updates. *J Med Virol*. 2022:1-7. https://doi.org/10.1002/jmv.27633

60. Buonaguro FM, Ascierto PA, Morse GD, et al. Covid-19: time for a paradigm change. *Rev Med Virol*. 2020;30(5). https://doi.org/10.1002/rmv.2134
61. Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature*. 2021. https://doi.org/10.1038/d41586-021-03796-6
62. Pulliam JRC, Schalkwyk C van, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. *medRxiv*. 2021;2. Published online. https://doi.org/10.1101/2021.11.11.21266068
63. Omicron incompletely escapes immunity induced by the pfizer vaccine - Africa health research institute. Accessed December 17, 2021. https://www.ahri.org/omicron-incompletely-escapes-immunity-induced-by-the-pfizer-vaccine/
64. Wilhelm A, Widera M, Grikscheit K, et al. Reduced neutralization of SARS-CoV-2 omicron variant by vaccine sera and monoclonal antibodies. *medRxiv*. 2021. Published online. December 8. https://doi.org/10.1101/2021.12.07.21267432
65. Suzuki R, Yamasoba D, Kimura I, et al. Attenuated fusogenicity and pathogenicity of SARSCoV-2 Omicron variant. *Nature*. 2022;603(7902):700-705. https://doi.org/10.1038/s41586-022-04462-1
66. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for covid-19 with SARS-CoV-2 neutralizing antibody Sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. https://doi.org/10.1056/nejmoa2107934
67. Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet*. 2021;397(10283):1459-1469. https://doi.org/10.1016/S0140-6736(21)00675-9
68. Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. *medRxiv*: 2021. Published online. December 14. https://doi.org/10.1101/2021.12.14.21267615
69. Rössler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 omicron variant neutralization in serum from vaccinated and convalescent persons. *N Engl J Med*. 2022;386(7):698-700. https://doi.org/10.1056/nejmc2119236
70. Thompson M, Natarajan K, Irving S, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19 associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):139-145. https://doi.org/10.15585/mmwr.mm7104e3
71. Johnson A, Amin A, Ali A, et al. COVID-19 incidence and death rates among unvaccinated and fully vaccinated adults with and without booster doses during periods of delta and omicron variant emergence. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):132-138. https://doi.org/10.15585/mmwr.mm7104e2
72. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. *Nat Med*. 2022;21. Published online. https://doi.org/10.1038/s41591-022-01753-y
73. Chu L, Vrbicky K, Montefiori D, et al. Immune response to SARS-CoV-2 after a booster of mRNA-1273: an open-label phase 2 trial. *Nat Med*. 2022;3:1-8. Published online. https://doi.org/10.1038/s41591-022-01739-w
74. Lytras S, Hughes J, Martin D, et al. Exploring the natural origins of SARS-CoV-2 in the light of recombination. *Genome Biol Evol*. 2022;14(2). https://doi.org/10.1093/gbe/evac018
75. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. *Cell*. 2022;185(3):447-456:e11. https://doi.org/10.1016/j.cell.2021.12.032
76. Flemming A. Omicron, the great escape artist. *Nat Rev Immunol*. 2022;22(2):75. https://doi.org/10.1038/s41577-022-00676-6
77. Munir K, Ashraf S, Munir I, et al. Zoonotic and reverse zoonotic events of SARS-CoV-2 and their impact on global health. *Emerg Microb Infect*. 2020;9(1):2222-2235. https://doi.org/10.1080/22221751.2020.1827984
78. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*. 2022:1-17. Published online. https://doi.org/10.1038/s41586-022-04569-5

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