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Editorial

Evolution and Clinical Trend of SARS-CoV-2 Variants

Evolución y tendencia clínica de las variantes del SARS-CoV-2

As a result of an epidemic outbreak of pneumonia detected in a market in the city of Wuhan (China) in December 2019, a betacoronavirus known as SARS-CoV-2 was identified as the causative agent, which was sequenced on 07th January 2020. The SARS-CoV-2 genome consists of a single-stranded RNA molecule of positive polarity of 29,903 nucleotides.[1–3] Two genes are found in the proximal two thirds (5′) of its genome, ORF1a and ORF1b, which encode two polyproteins, pp1a (ORF1a) and pp1ab (ORF1a and ORF1b), which are then divided into 16 non-structural proteins (including RNA-dependent RNA polymerase) that are later assembled inside the host cell constituting the replication-transcription complex.[1–3] The genes for the structural proteins of SARS-CoV-2 are found in the distal third (3′) of its genome, fundamentally four: S (spike), E (envelope), M (membrane) and N (nucleocapsid).[1–3] Numerous molecules of the N protein bind to RNA, forming a stable helical nucleocapsid. E, M and S proteins are part of the SARS-CoV-2 envelope, a phospholipid bilayer. The S protein is the one that defines the tissue tropism of SARS-CoV-2. SARS-CoV-2 virions, through their S protein, bind to their membrane receptors on host cells, angiotensin-converting enzyme isoenzyme 2 (ACE-2, present especially in the epithelia of the alveoli, lower and upper airways and intestinal tract), to be later endocytosed by them and thus start the infective cycle, in which process the TMPRSS2 cellular protease also participate.[1–3]

Over time, numerous variants of SARS-CoV-2 have been described that show genetic differences with respect to the original Wuhan strain sequenced on 07th January 2020.[4–7] These variants are the result of spontaneous mutations in the viral RNA derived from errors in its replication within the host cell.[1,5] Although coronaviruses, unlike other RNA viruses such as *Influenza* or HIV, have intrinsic mechanisms for correcting these errors that make their mutability less, hence there is greater homology between the genomes of the different variants.[1,5] Several of these mutations have caused SARS-CoV-2 to adapt better to its hosts, which explains why they have persisted afterwards; the objective of SARS-CoV-2 is clear: to replicate and perpetuate itself.[1,5] Thus, the so-called variants of public health concern have appeared: alpha, beta, gamma, delta and omicron (Table 1).[4–8]

These are fundamentally mutations that give SARS-CoV-2 increased transmissibility between different people, as well as greater escape from the host's immune response.[5–8] Most of these mutations are involving S protein, and it is understandable: "a more carefully designed key will fit more specifically into its corresponding lock, which is the cellular receptor ACE-2",[8–10] so that the virions can more easily penetrate into host cells (greater infectivity), which in turn leads to greater transmissibility between different people.[5–8] Omicron has stood out more than previous variants for having undergone a very high number of mutations (>50) with respect to the original strain, especially in its S protein, which shows a perfect affinity for the ACE-2 of the host cell,[8–10] hence its enormous transmissibility rate.[6–8,11,12] It is speculated that the emergence of SARS-CoV-2 in a population with a high incidence of immunosuppression (as is the case with HIV infection in southern Africa), as virions persist longer within the host, may have prompted this high rate of mutations until reaching the omicron variant.

Similarly, amino acid changes in the S protein achieve a greater escape from the immune response (both humoral and cellular) induced by vaccines (based on the S protein of the original Wuhan strain) or by infections by previous variants.[5–8,13] In this way, omicron, with regard to the prevention of new infections, has achieved a practically total immune escape, both to vaccines and to infections due to previous variants. Therefore, with the aim of preventing contagion, the need to modify the vaccines to the new variants of SARS-CoV-2 is becoming increasingly evident, trying to achieve greater homology in the S protein between the vaccine and these new variants[13]; or to design new more complete vaccines that include more proteins of the virus apart from S protein so that the immune system recognizes different targets. The latter is really what happens when a person is infected with SARS-CoV-2 and then recovers, their immune system "has seen the virion in its entirety" and keeps a more complete memory, so that this person will be more protected against new infections by this same variant, although a higher rate of reinfections is being observed in the omicron variant than in the previous variants.[6,7]

Likewise, greater variability in S protein can reduce the diagnostic power of antigenic tests based on S protein. In contrast, this problem is not as significant in tests based on genomic amplification (RT-PCR), since they have several target genes, not just the S protein gene.

Another aspect of particular concern is that the mutations may confer greater virulence to the new variants of SARS-CoV-2, causing a greater severity of the disease and greater lethality in the host. Although the alpha and delta variants had greater severity and lethality[6,7] as well as greater transmissibility,[5–7] the omicron variant, on the other hand, has lower severity and lethality[6,7] as

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Table 1
Main characteristics of SARS-CoV-2 and its different variants.

SARS-CoV-2 strain	Declaration as VOC	Majority extension	Epidemic period in Spain[a]	Transmissibility	Severity and lethality	Escape to immune response	Mutations found in the S protein gene
Original	Wuhan (China), 07/01/2020	Worldwide	First and second.	R_0 = 2.5. Incubation period: 2–14 days, median 5.1 days. SAR: 0.7–75%.	81% mild[b]. 14% severe[b]. 5% critical[b]. 2.3% death.	PVE 95% for symptomatic infection.	
Alpha	United Kingdom, 29/12/2020	Europe, Oceania and North America	Dominant in Spain. Third, fourth and fifth.	↑ **Transmissibility** (50% higher). SAR: 25.1%, 1.43–1.82 times higher.	↑ **Severity and lethality.** 1.55–1.73 times more lethality.	↑ **Immune escape.** PVE 89% for symptomatic infection, and 95% for hospitalization or death.	**Del69-70**, **del144, N501Y**, A570D, D614G, **P681H**, T716I, S982A, D1118H.
Beta	South Africa, 29/12/2020	Africa	Minority in Spain. Third, fourth and fifth.	↑ **Transmissibility** (50% higher, 2.5 times higher). SAR higher.	↑ **Severity and lethality.**	↑ **Immune escape.** PVE 84% for symptomatic infection, and 95% for hospitalization or death.	L18F, D80A, D215G, R246I, **K417N**, **E484K**, **N501Y**, D614G, A701V.
Gamma	Brazil, 29/12/2020	Latin America	Minority in Spain. Third, fourth and fifth.	↑ **Transmissibility** (1.7–2.4 times higher). R_0 = 3.4. SAR higher.	↑ **Severity and lethality.**	↑ **Immune escape.** PVE 84% for symptomatic infection, and 95% for hospitalization or death.	L18F, T20N, P26S, D138Y, R190S, K417T, **E484K**, **N501Y**, D614G, **H655Y**, T1027I, V1176F.
Delta	India, 11/05/2021	Worldwide	Fifth and sixth.	↑↑ **Transmissibility** (1.97 times higher). R_0 = 7. Intradomiciliary delta SAR (10.3–21%) 1.70 times higher than intradomiciliary alpha SAR. Shorter incubation period (median 4.5 days). Higher viral load, 2.5 times more in nasopharyngeal exudate and 15 times more in saliva.	↑↑ **Severity and lethality.** 2.20 times more hospitalization. 3.87 times more ICU admission. 2.37 times more lethality.	↑↑ **Immune escape.** PVE 87% for symptomatic infection, and 93% for hospitalization or death.	T19R, **G142D**, del156-157, R158G, K417N (delta plus), **L452R**, **T478K**, D614G, **P681R**.
Omicron	South Africa and Botswana, 26/11/2021	Worldwide	Sixth.	↑↑↑↑ **Transmissibility** (36.5% higher than delta). R_0 = 10. Intradomiciliary omicron SAR 15.8%-31% versus delta SAR 10.3–21%. Extradomiciliary omicron SAR 8.7% versus delta SAR 3.0%. 70-fold higher respiratory viral load at 24 hours in omicron than in original and delta strains. **Shorter incubation period** (median 3 days).	↓ **Severity and lethality.** 0.71 times less (29% less) hospitalization. 10-fold lower viral load in lung tissue at 24 hours in omicron than in original strain.	↑↑↑↑ **Immune escape.** PVE 10% for symptomatic infection, 49% if third dose. PVE 70% for hospitalization. 2.4–5.4 times higher risk of **reinfection**.	**A67V, del69-70,** T95I, **G142D**, **del143-145**, Y145D, del211, L212I, ins214EPE, **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.

VOC: variant of public health concern.
R_0: basic reproductive number: average number of new cases generated (by contagion) from a single case.
SAR: secondary attack rate: number of new cases of a disease among the total number of exposed susceptible people within a specific group (i.e., household or close contacts), that is, the proportion of contacts of a primary case who become ill.
PVE: preventive vaccine effectiveness, in all cases after two doses with Comirnaty vaccine (based on messenger RNA technology).
[a] Epidemic periods ("waves") in Spain: first (11/03/2020–21/06/2020), second (22/06/2020–06/12/2020), third (07/12/2020–14/03/2021), fourth (15/03/2021–19/06/2021), fifth (20/06/2021–13/10/2021) and sixth (14/10/2021–present).
[b] Mild: all cases of COVID-19 without pneumonia, and cases of SARS-CoV-2 pneumonia with normoxemia and adequate respiratory mechanics; they do not require any oxygen therapy. Severe: SARS-CoV-2 pneumonia with hypoxemia ($SpO_2 \leq 93\%$ and/or PaO_2/FiO_2 ratio < 300), tachypnea ≥ 30 breaths/min, use of respiratory accessory muscles, dyspnea and/or extension of pulmonary infiltrates > 50% in the first 24–48 h; solvable with standard oxygen therapy in a conventional hospitalization area. Critical: acute respiratory failure refractory to standard oxygen therapy, septic shock, multi-organ dysfunction syndrome; they require high performance respiratory support, non-invasive (HFNC, CPAP, BPAP) in an IRCU, or invasive (IMV, ECMO) in an ICU, or vasoactive support in an ICU.

well as extraordinarily high transmissibility,[6–8,11,12] which would be understandable from an evolutionary point of view. If SARS-CoV-2 were to cause very high fatalities in hosts, its transmissibility would be severely limited and it would be destined to disappear, as happened with SARS-CoV-1. In an experiment carried out on *ex vivo* tissue samples, it was observed that the omicron variant replicated about seventy times faster in bronchial tissue at 24 h after infection than the delta variant and the original strain, as

well as about ten times less fast in lung tissue than the original strain, which may be an indicator of less virulence and greater transmissibility.[14] Although we should not forget that the severity of the disease is not determined only by the degree of viral replication in the lungs, but also by the degree of the host's immune response against SARS-CoV-2, we should remember that severe cases are characterized by immune dysregulation and inflammatory hyperresponse ("cytokine storm"). Factors such as advanced age, pregnancy, immunosuppression or significant comorbidities make the subject more prone to developing a serious disease.

And although the omicron variant seems intrinsically less pathogenic, it can cause severe disease and mortality even more frequently than previous variants since it can infect a much larger proportion of the population given its extremely high transmissibility.[14]

Apart from the lower intrinsic virulence of omicron, previously acquired memory immunity from previous variant infections or from the vaccine plays a very important role in protection against severe disease or death. Clearly, the vaccinated population has a much lower frequency of hospitalizations, ICU admissions, and deaths than the unvaccinated population.[6–8,15]

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