Omicron variant from SARS-COV-2 and the obligation to anticipate new scenarios for COVID-19 disease

Letícia Barbosa Teixeira[1], Wilson C. Santos[2,3¶].

[1]Instituto Nacional do Câncer, Programa de Residência Multiprofissional em Oncologia. Rio de Janeiro, RJ, Brasil.
[2]Programa de Pós-Graduação em Ciências Aplicadas a Produtos Para Saúde. Faculdade de Farmácia, Universidade Federal Fluminense, Niterói, RJ, Brasil.
[3]Instituto Teófilo Hernando de I+D del Medicamento, Universidad Autónoma de Madrid, España.

[¶]wsantos@id.uff.br

[¶]leticiabt@id.uff.br

COVID-19 is a great threat to the world health population, and the new strains for the SARS-COV-2 coronavirus has been spoiling all the cumulative efforts to better understand the Pandemic. Omicron variation has cast many doubts on the management of the infection and also in the efficacy of vaccines and approved drugs for the disease.

Since the outbreak of the COVID-19 pandemic in early 2020, the SARS-CoV-2 virus has been circulating worldwide on a large scale and therefore mutating at an accelerated rate.

The Omicron variant (B.1.1.529) of the virus SARS-CoV-2 quickly spreads worldwide, becoming the principal variant circulating in many countries. According to WHO announcement (https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern) the variant showed a large number of mutations, and the evidence suggested an increased risk of reinfection with the variant. Besides, the Omicron expands more easily than the original virus that causes COVID-19 and the Delta variant, contaminating even people who already had the disease previously, or those who had been doubly vaccinated. The main mutations on Omicron rely on the Spike protein, presenting 37 mutations described (Mannar et al, 2022).

The lineage that causes most concern nowadays is called BA.2(UNICEF, 2022). There is still no consensus that clearly shows the origin of the Omicron variant; until now is just known that this variant has no connection with its predecessors Alpha and Delta (Mallapaty S. 2022). The genetic difference of Omicron from previous variants is so great that evolutionary virologists estimated that its closest genetic ancestor dates back more than a year (Martin DP et al., 2022).

The Omicron was first detected in South Africa and Botswana in early November 2021 (Mallapaty S. 2022). Since then, retrospective tests based on data collected by GISAID have found earlier samples from individuals in England, South Africa, Nigeria and the United

FIGURE 1

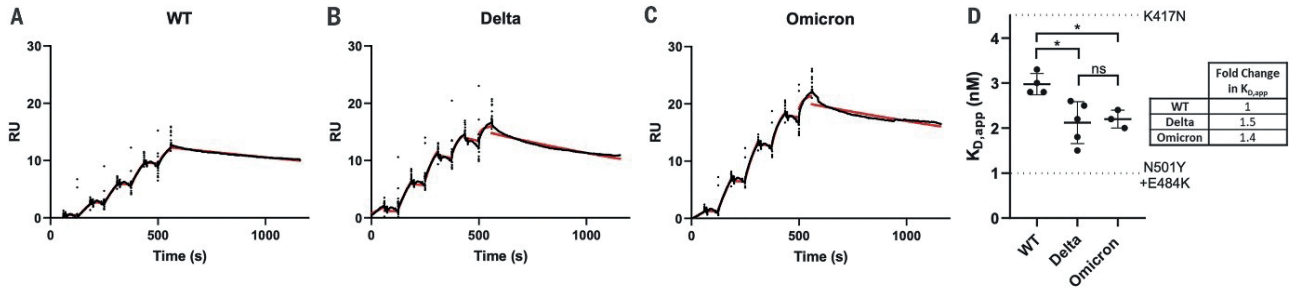

Figure 1. *SPR analysis of the wild-type, Delta, and Omicron spike protein affinities for human ACE2. (A to C) Representative traces of single-cycle kinetic analyses of spike protein–ACE2 binding. The raw data (black) is fit (red) to a model using a 1:1 binding stoichiometry from which apparent dissociation constants were derived. The curves were obtained by injecting 6.25, 31.25, 62.5, 125, and 250 nM of each spike protein in successive cycles. RU, response units; WT, wild type. (D) Quantitation of apparent dissociation constants ($K_{D,app}$) for the wild-type, Delta, and Omicron spike protein–ACE2 interactions. The standard deviation obtained from at least three technical replicates is shown. Horizontal dotted lines are plotted for mutants carrying only K417N (top) or N501Y and E484K (Glu^{484}→Lys; bottom) mutations to demonstrate the range of this assay (see fig. S2 for binding data). A Tukey's multiple comparisons test was performed on the wild-type, Delta, and Omicron binding affinities (*P ≤ 0.05; ns, not significant). A table highlighting the fold changes in $K_{D,app}$ for the Delta and Omicron spike protein–ACE2 interactions relative to wild type is shown.* ***(Extracted from Mannar D. et al. 2022)***.

FIGURE 2

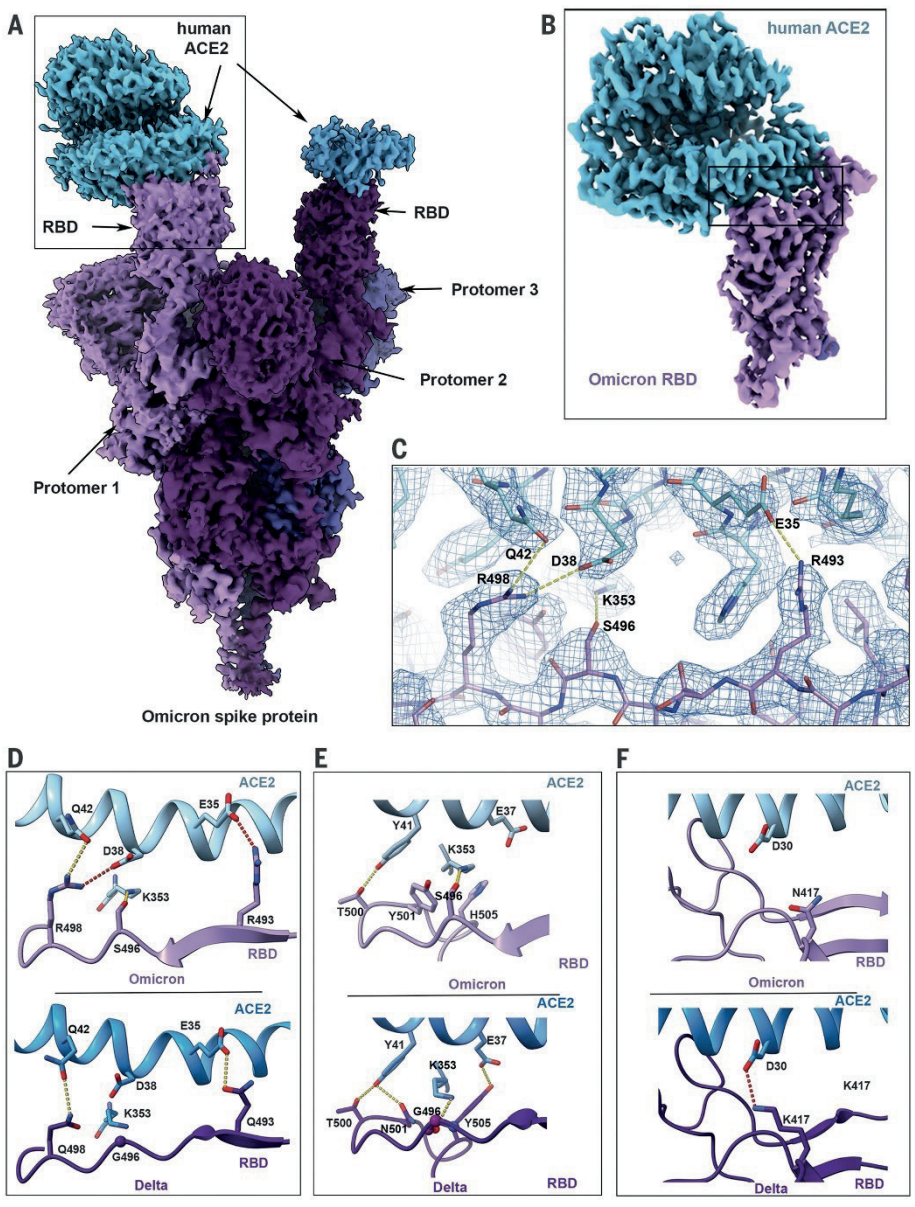

Figure 2. *Cryo-EM structure of the Omicron spike protein–ACE2 complex.(A) Cryo-EM map of the Omicron spike protein in complex with human ACE2 at 2.45-Å resolution after global refinement. The three protomers are coloured in different shades of purple, and the density for bound ACE2 is coloured in blue. (B) Cryo-EM map of the Omicron spike protein RBD in complex with ACE2 at 2.66-Å resolution after focused refinement. The boxed area indicates the region highlighted in (C). (C) Cryo-EM density mesh at the Omicron spike protein RBD–ACE2 interface, with the fitted atomic model. Yellow and red dashed lines represent new hydrogen bonds and ionic interactions, respectively. (D to F) Comparison of the RBD-ACE2 interface between the Omicron (top) and Delta (bottom) variants. Compared with the Delta variant, new interactions are formed as a result of the mutations Q493R, G496S, and Q498R (D) and local structural changes owing to the N501Y and Y505H (Tyr^{505}□His) mutations (E) present in the Omicron variant. The salt bridge between Delta RBD K417 and ACE2 D30 that is present in the Delta variant spike protein but lost in the Omicron variant is highlighted in (F). Yellow and red dashed lines represent hydrogen bonds and ionic interactions, respectively (****Extracted from Mannar D. et al. 2022****).*

States between November 1 and 3, 2021 (Mallapaty S. 2022). Phylogenetic analyzes identified the BA.1/ Omicron sequences as a monophyletic clade rooted in the B.1.1 lineage, without clear basal progenitor; concomitantly, it was observed that the BA.1/ Omicron cluster is highly phylogenetically distinct from any variant of interest and also from any other lineages known to circulate in southern Africa (Viana R. et al., 2022). Following the emergence of BA.1 two other related lineages emerged, BA.2 and BA.3, both sharing common mutations to each other and also with BA.1, in addition to particular mutations to each one within (Martin DP et al., 2022).

Peacock TP et al. (2022) identified some mutations in Omicron that provides a huge affinity (20 times greater than previous variants) for the ACE2 receptor, besides helping to evade the host's immune system (Figures 1, 2). Therefore, the virus is more resistant to blocking neutralizing antibodies produced by the hosts who have been vaccinated or infected by previous variants (Cele S. et al. 2021). Mutations presented in the Spike protein have been identified that make the variant less capable of membrane fusion; on the other hand, instead, it tends to infect the cell by the process of endocytosis (Peacock TP et al. 2022).

Based on Qatar's National Database, Altarawneh et al. (2022) developed a study that showed the effectiveness of previous infection by variants before Omicron in preventing reinfection by variants Alpha, Beta and Delta in approximately 90%. They have found that such protection against the Omicron variant, corresponded to 60%, (Altarawneh et al. 2022). Furthermore, protection of the previous infection against hospitalization or death from reinfection was shown to be robust, regardless of variant (Altarawneh et al. 2022) founded. Stegger M. et al. (2022) have investigated the occurrence of reinfection cases by Omicron from a set of samples of more than 1.8 million cases, and it was founded a total of 187 cases of reinfection. They have described that about 25.13% represented BA.2 reinfections followed by BA.1 infection. According to Stegger M. et al. (2022), cases of BA.2 reinfection followed by BA.1 are rare, as previously proposed by Ledford H. (2022), who has pointed out that T cells continue to respond to infection by new strains from the virus.

The increase in antibody evasion and preservation of strong interactions at the ACE2 receptor represent important molecular features that likely contribute to the rapid spread of the Omicron variant (Mannar D. et al. 2022).

Mannar D. et al., (2022) have experimented six monoclonal antibodies directed to the Spike protein (four RBD-directed antibodies [ab1, ab8, S309, and S2M11] and two NTD-directed antibodies [4-8 and 4A8]) to test the susceptibility of Omicron to neutralization. Five of the tested monoclonal antibodies (Figure 3) did not counteract the Omicron variant, even at maximum concentration . The loss of neutralizing activity for both NTD-directed antibodies (4-8 and 4A8) against Omicron is likely due to the Δ144-145 deletion, which lies in the footprint of both antibodies (Mannar D. et al. 2022). The leakage of antibodies directed to RBD (receptor binding domain) is likely due to the several (16 in total) RBD-Omicron mutations that lie within their respective footprints (Tian F et al., 2021).

FIGURE 3

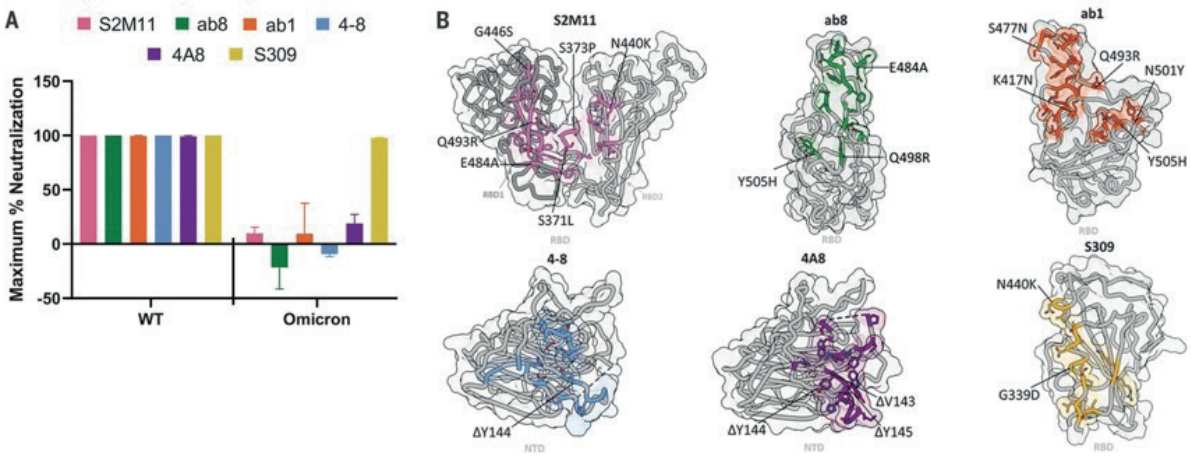

Figure 3. *Monoclonal antibodies show decreased potency to neutralize Omicron. (A) Maximum neutralization was achieved by the indicated monoclonal antibodies against wild-type and Omicron pseudoviruses (n = 3 technical replicates). Error bars denote the standard deviation of the mean. (B) Antibody binding footprints for the monoclonal antibodies tested in this study. Omicron spike protein mutations that fall within each antibody footprint are labelled. (**Extracted from Mannar D. et al. 2022).***

Takashita E. et al. (2022) examined the neutralizing capacity of approved monoclonal antibodies for the treatment of COVID-19 to the variant Omicron/BA.1 and Omicron/BA.2. The results demonstrated that Etesevimab and Bamlanivimab (in single and/or combined use) lost their neutralizing capacity for BA.1 and also for BA.2. However, Imdevimab (individually and in combination with Casirivimab) hasn't displayed neutralizing capacity to BA.1, although being able to neutralize BA.2 (Takashita E. et al 2022). The susceptibilities of Omicron/BA.2 to Remdesivir, Molnupiravir and Nirmatrelvir remained similar to those of the ancestral strain and other worrying variants: about 50% maximum inhibitory was described (Takashita E. et al. 2022).

A negative test case-control was developed by Andrews N. et al. (2022) to estimate vaccine efficacy against symptomatic disease caused by Omicron and Delta variants in England. Results have pointed out limited protection against symptomatic disease caused by the Omicron variant. However, the primary course of ChAdOx1 nCoV-19 or BNT162b2 followed by BNT162b2 or mRNA-1273 boosters showed a substantial increase in protection that, nevertheless, still declined over time (Andrews N. et al. 2022). Regarding the BA.1/Omicron and BA.2/Omicron strains, Yu et al. (2022) have compared neutralizing antibody titers against both variants after immunization. Overall, data showed lower median titers against BA.2 than BA.1, and both strains required a third dose of the BNT162b2 vaccine to induce consistent neutralizing antibody titers (Yu et al. 2022). Authors also showed that vaccinated people infected with BA.1 were able to develop robust neutralizing antibody titers against BA.2, which suggests a substantial degree of natural cross-reactive immunity.

Taken together, all findings have important public health implications and suggested that the increased frequency of BA.2 over BA.1 is probably related to increased transmissibility and not to increased immune escape. However, the decrease in the effectiveness of vaccines and pharmacotherapy in the context of the emergence of new variants leads to the need to constantly update our technologies to face the COVID-19 pandemic.

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