Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

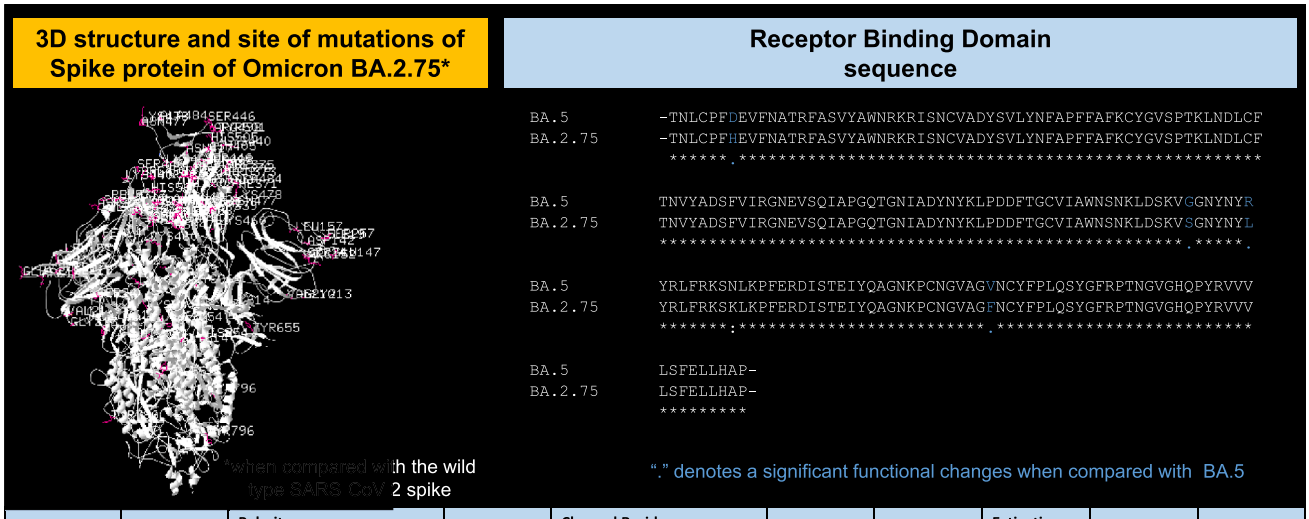
Knowing the new Omicron BA.2.75 variant ('Centaurus'): A simulation study

Dear Editor,

Omicron BA.5 is the most dominant strain of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), with an estimated 85% of cases in United States (https://covid.cdc.gov/). A new subvariant known as BA.2.75 (unofficially Centaurus) was detected in India in May 2022, and several cases have been recently reported. It is not clear how mutations of this subvariant in the gene encoding for receptor binding domain (RBD) of the spike (S) protein of the virus can affect rate of infectivity. Of note, the RBD of SARS-CoV-2 docks to angiotensin converting enzyme 2 (ACE_2) receptors [1], gains entry into cells and dysregulates the renin-angiotensin system leading to an Angiotensin II storm [2–7].

We studied the effect of mutations of BA.2.75 subvariant on RBD, the conformational dynamics of the S protein and its adhesivity to ACE_2 receptors. After download of the proteins sequence and structure for SARS-CoV-2 and ACE_2 receptor from the Protein Data Bank (https://www.wwpdb.org/), we used the Pymol mutagenesis wizard (https://pymol.org) to introduce the specific mutations at the appropriate residues in wild type SARS-CoV-2 spike in order to create Omicron BA.5 and BA.2.75 variants. In addition and to evaluate the positions of new mutations, we did a pairwise alignment of the RBD's sequence of Omicron variants with Clustal omega (https://www.ebi.ac.uk/Tools/msa/clustalo/). The online server EMBOSS Pepstats (https://www.ebi.ac.uk/Tools/seqstats/emboss_pepstats/) was used to calculate the biochemical proprieties of the two variants. To evaluate binding affinity (ΔG) and Kd prediction we used the PRODIGY webserver (https://wenmr.science.uu.nl/prodigy/). After preparing the protein, Cluspro (https://www.ebi.ac.uk/Tools/msa/clustalo/) was used to dock the reference Omicron variants to the ACE_2 receptor.

Fig. 1 (upper panel) shows the position of mutations in the S protein of BA.2.75 (left side), and the aminoacidic sequences in the RBD (right side) of Omicron BA.2.75 when compared with Omicron BA.5. For effect of these mutations, Omicron BA.2.75 showed a 57-fold higher binding



Variant	Molecular weight	Polarity		GRAVY	Charged Residues		Net Charge	Isoelectric Point	Extinction coefficient (1mg/ml)	Instability index	Aliphatic index
		Polar	Non-polar		Acidic	Basic					
BA.5	118079.04	45.386	54.614	-0.107	7.910	9.510	10	7,60	0,978	33.95	82.50
BA 2.75	118290.31	45.677	54.323	-0.105	7.895	9.680	11	7.62	0.932	33,31	82.99

Fig. 1. Mutations observed in Omicron BA.2.75 variant with 3D structure of S protein (left panel), comparison alignment of the receptor binding domain's sequence of BA.5 and BA.2.75 subvariants (right panel), and conformational dynamics of S protein of both BA.5 and BA.2.75 variants (lower panel).

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RBD, receptor binding domain; ACE_2, angiotensin converting enzyme 2; S, spike.

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affinity with ACE_2 when compared with the BA.5 variant (ΔG BA.5/BA.2.75=1.3E-45/2.3E-47=56.52).

In conclusion, the evolution of SARS-CoV-2 S protein [8], and the mutated S protein of Omicron BA.2.75 is characterized by a markedly higher adhesivity to ACE_2 (estimated increased affinity >3,000-fold when compared with Alpha B.1.1.7 variant)[8]. This new variant is therefore expected to spread quicker and possibly enhance the Angiotensin II "intoxication"[9] and $Angiotensin_{1-7}$ deficiency [3]. Future vaccines will have to be built on the aminoacidic sequence of newer Omicron sub-variants in order to elicit a more robust antibody response [10] and to avoid immune evasion [11–13]. Indeed, a national surveillance consortium for SARS-CoV-2 sequencing established in Israel evaluated neutralizing antibody titres against wild type SARS-CoV-2 and four Omicron variants (BA.1, BA.2, BA.4 and BA.5) in healthcare workers who had breakthrough BA.1 infection [14].

Briefly, Kliker and co-workers demonstrated that Omicron breakthrough infection in individuals vaccinated three or four times before infection resulted in increased neutralising antibodies against the wild type virus [14]. Notably, the fourth dose of vaccine did not further improve the neutralising efficiency over the third dose against all Omicron variants [14].

Declaration of Competing Interest

None of the authors of this study has financial or other reasons that could lead to a conflict of interest.

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