Review of: "Evolution of new variants of SARS-CoV-2 during the pandemic: mutation-limited or selection-limited?"

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Potential competing interests: No potential competing interests to declare.

The manuscript tests three possible hypotheses regarding the spread of novel SARS-CoV-2 virus variants in the general population. The first hypothesis is based on the ability of a novel mutation to evade the immune system. The second hypothesis is related to the first one assuming the random appearance of a mutation through which the virus gains an advantage other than immune evasion. The third hypothesis is a combination of the previous two favouring a context-dependent selection model where immune evasion, viral replication gains and other factors like the vaccination status in a population define viral spread. In the result section, different theoretical models are applied and the time lines between the first appearance of a variant and the peak of infections are studied.

Overall the paper does not add much novelty to the already extensive discussion on the evolution of SARS-CoV-2 variants. It is difficult to read as it lacks a clear narrative drifting through the three hypothesis without reaching a clear conclusion. For inspiration regarding story telling please see sosi-3-13-toolkit-pdf (3m.com); https://www.nature.com/articles/nmeth.2726

Scientifically, I miss the crucial importance of the animal reservoirs and the zoonosis events which did and will play important roles in the evolution of the SARS-CoV-2 virus and other viruses (https://jamanetwork.com/journals/jama/fullarticle/2795140); https://www.who.int/news/item/07-03-2022-joint-statement-on-the-prioritization-of-monitoring-sars-cov-2-infection-in-wildlife-and-preventing-the-formation-of-animal-reservoirs); https://pubmed.ncbi.nlm.nih.gov/33892621/

The article would also benefit from the discussion of a few example mutations like D614G in the spike receptor (related to hypothesis 2) or N501Y in the spike receptor (related to hypothesis 1). Other mutations in the RNA-dependent RNA Polymerase as well as the inracellular RNA editing mechanisms and viral recombination that create quasi species in a patient should be considert. Further more, the role of the small bottle neck (i.e. the low number of infecting viral particle (probable less than 20) that escape from an infected person after intra-patient selection) needs to be taken into account.