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.

1. Discussion, first paragraph. The sentence “Mutation rates are unlikely to differ significantly across viruses“. I would disagree at this point”. Evolutionary analyses estimate a mutation rate of SARS-CoV-2 to range from 1.12 × 10^{-3} to 6.25 × 10^{-3} substitutions/site/year (e.g. *BMC Evol Biol.* (2004) 4:21. doi: 10.1186/1471-2148-4-21; *Bull World Health Organ.* (2020) 98:495–504. doi: 10.2471/BLT.20.253591). In contrast, while seasonal influenza virus has a lower evolutionary rate (0.60-2.00 × 10^{-6}) (*J Virol.* (2006) 80:3675–8. doi: 10.1128/JVI.80.7.3675-3678.2006). Thus, significant differences exist even among RNA viruses. One of the reasons could be that SARS-CoV-2, like all other Coronaviruses, possesses a replication proof-reading mechanism conferred by the nsp14 exonuclease, that significantly reduces the mutation rate to a level close to that of DNA viruses. Suggestion: Modify or delete the sentence.

2. Figure 1. Please explain what the time units on x-axis represent.

3. My other comment is rather conceptual one. Much of the emphasis is devoted to the idea that selection of variants is driven by immunity-related processes. It is stated that “Our analysis indicates that the invasion of novel variants is primarily limited by selection rather than mutation“. I unsure whether selection can be decoupled from selection. In my opinion, one must recall that evolution by natural selection is a two-step process. The first step involves the generation of new variation by mutation and recombination, whereas the second step determines which randomly generated variants will persist into the next generation. Most new mutations are neutral with respect to survival and reproduction and therefore are irrelevant in terms of natural selection (but not, it must be pointed out, to evolution more broadly). The majority of mutations that have an impact on survival and reproductive output will do so negatively and, as such, will be less likely than existing alternatives to be passed on to subsequent generations. However, a small percentage of new mutations will turn out to have beneficial effects in a particular environment /e.g., immunity system/ and will contribute to an elevated rate of reproduction by organisms possessing them.

In short, I would like authors to pay attention to this more Darwinian view of SARS-CoV-2 evolution.

4. Discussion, sentence towards the end “In summary, based on multiple tested predictions, it can be concluded that new variants are not necessary and sufficient causes of new waves as proposed by Hypothesis 1.“. While I agree partially with this conclusion, I feel that the statement cannot be generalized. For example, a notoriously known D614G mutation present in the alpha variant undoubtedly increased virus infectivity and contributed to virus spread world-wide. Similarly, some omicron mutations /N460K, S486P, F490S/ are suspected to increase transmissibility according to WHO reports.