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.

In this paper the authors explore the possible mechanisms of the emergence and evolution of new SARS-CoV-2 variants during the pandemic that has recently occurred. The authors entertain and test two main evolutionary mechanisms: a) mutation-limited (or mutation-driven) and b) selection-limited (or selection-driven) evolution. The fundamental premise of the mutation-limited evolutionary mechanism is that an invasion caused by a new virus variant should fall on the peak of incidence of the prior variant, simply because mutation probability/frequency scales with disease incidence. By contrast, the fundamental proposition of the authors is that a selection-limited evolutionary mechanism may prevail due to the gradual loss of immunity which, if happens to fall below a certain level, gives rise to a time window that allows for the appearance of new infection waves. The predictions of these temporal incidence dynamics were compared with SARS-CoV-2 epidemiological data from several countries. Based on these data the authors conclude that the mutation-limited evolution model should be dropped in favor of the selection-limited one.

The paper is interesting and thought-provoking. However, a few issues need to be addressed and discussed:

1. The readability and understandability of the paper would be much enhanced if the authors took care of defining the most important terms already in the introduction and then stick to these definitions throughout the text. These terms include "incidence", "transmission", "invasion", "wave", "immunity" and "evolution". After all, the appearance of a new virus variant assumes that mutation in the viral genome has taken place. Whether an evolutionary step has occurred is then related to the onset of a wave of infection, but is this the true and real criterion? Could the authors introduce at least a qualitative measure of this evolutionary step?

2. The authors also acknowledge that "immunity" is a complex variable that includes a range of mechanisms and processes. However, considering that their selection-limited evolutionary model relies on it, it would be good to have some kind of qualitative measure presented. Were antibody titer data collected and compared? Do their dynamics follow the time dependence indicated in Figure 1?

3. The SIR model simulations are somewhat confusing, possibly because the equations are not well described and presented. I doubt that the the S to I conversion rate (see page 8) would be proportional to "I" (magnitude of the infected), please correct. It is unclear why Vn(t) is given a small value, and what is its significance. Please, explain.

4. Probably a major shortcoming of the model is the lack of a clear definition and variable-level incorporation of cross-immunity. While the authors do acknowledge the difficulty of introducing such a variable, I wonder whether a simple rate

constant or a weight factor could nevertheless be introduced. Such a variable would reduce the number of infected (or increase the number of removed).

5. Finally, Figure 1 should be corrected. There are several problems with it: a) in the legend there are spelling and typographical errors, b) the time axis does not have a realistic scaling (which would help, considering that a known pandemic is discussed), c) the time axis starts at a non-zero value, yet the immunity titer of the prior variant is 100% (it appears as if immunity was 200% at t0!).