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 paper makes several appealing arguments. In its present form, it should be treated as a good opening shot but there is still a lot of ground to cover before it is perfect.

Major concerns and comments:

1.

The authors present the ability to evade host immunity as a most important source of selective advantage between variants. Besides this, they acknowledge that the variants may gain certain “selective advantage within a host's body” (intracellular competition, competition for entering a new host cell). There are however many more aspects in which the variants can differ and hence gain selective advantage. For instance:

I. Variants causing symptoms that facilitate better spread of viral particles may gain a selective advantage.

II. Less virulent variants that spare their host may gain a selective advantage because they are spread for longer and at places with higher abundance of susceptible hosts (such as workplaces). The opposite may be true for “hospital infections” at places and contexts where superinfection and fierce competition of unrelated pathogen variants within a single host is more likely.

III. Variants that elicit familiar sets of symptoms gain a selective advantage because they are not recognized as novel and dangerous. (This explains why more than 200 unrelated pathogens all cause common cold. Although the authors claim that “Currently, there are limited efforts to comprehend the selection acting on new variants during the pandemic, and our understanding of the nature of this selection remains inadequate,” we argue for this kind of symptomic mimicry in Tureček, P., & Kleisner, K. (2022). Symptomic Mimicry Between SARS-CoV-2 and the Common Cold Complex. *Biosemiotics*, *15*(1), 61-66. I am sure other papers make comparable points for different sources of selection pressure. There is also a vast literature on virulence evolution in general, see e.g. Chao, L., Hanley, K. A., Burch, C. L., Dahlberg, C., & Turner, P. E. (2000). Kin selection and parasite evolution: higher and lower virulence with hard and soft selection. *The Quarterly review of biology*, *75*(3), 261-275. or Buckling, A., & Brockhurst, M. A. (2008). Kin selection and the evolution of virulence. *Heredity*, *100*(5), 484-488.)

The article would benefit from extended literature review and discussion on these and other selection pressures. Some of them may even invite new hypotheses. For example, variants that go undetected or that are not recognized as SARS-CoV-2 may be favored more during the periods of overall low incidence when restrictive measures are lifted (which is in

accord with the pattern presented in Figure 6.)

2.

The waves could be observed even in the absence of a new variant but they rarely are, since the decline in herd immunity poses a better opportunity for several less usual variants that compete for the infectable substrate. The selection-limited evolution, as authors present it, however, seems to allow only for the prediction of WHEN new waves occur. It presents no expectations about the traits (symptomatic manifestations) of new variants. Even if the statement “while the new variant may not be the cause of the wave, it will coincide with it,” is true – which I believe it is – it is still possible to predict in what aspects will the new variants differ from the old.

Are all selective advantages (see above) subsumed under the Hypothesis 2 of Mutation-limited side as the formulation “probability of a new variant arising within a given time interval will be proportional to the area under the incidence curve or remain constant over time, depending on whether selection unrelated to epidemiological parameters or drift is the predominant factor” suggests? If so, it is a bit confusing, since if the host population (or mutation rate within a host) is large enough, evolution along all dimensions of hypothetical virus trait space is selection-limited. This part of the manuscript needs clarification.

3.

To some extent evolution (if not modelled in the abstract realm of infinite populations and infinite genes contributing to every single trait) is always both selection-(when there are opportunities for takeover) and mutation-(what variants enter the competition) limited. The authors hardly discuss this at all. Perhaps it is due to focus on unidimensional (immunity-related) selection?

4.

The authors report that “72 waves exhibited a pattern consistent with a prior variant wave” or that “In 92 waves, there was evidence of prior invasion by a new variant well before the onset of the wave” but the variants were global – not local as authors treat them. The assumption that probability of new variant emergence is highest around the peak of previous wave holds only for autochthonous variants! If new variants invade from a neighboring geographical units (as they must if we speak about the sample of 125 local and not 3 global waves), the invasion rate is constant over time – or rather depending on the global proportion of infected population.

5.

The author correctly observe that “New variant does not increase the slope in new infections” but they conclude that “This analysis challenges the popular belief that new variants are inherently more infectious than prior ones” which was, however, firmly established on a biochemical level (see Popovic, M. (2022). Strain wars 2: Binding constants, enthalpies, entropies, Gibbs energies and rates of binding of SARS-CoV-2 variants. *Virology*, *570*, 35-44.) How do the authors explain this dissonance? Is it possible that the slope of new infections is directed predominantly by events at the level of host population, while the prevalence of specific variants results from competition between them as I suggest above? The variants that fail in this competition go under the radar. It should be discussed how do the new dominant variants differ from the previous hegemons. Do they differ by one mutation of large effect, or does it take several minor-effect mutations in the right direction to succeed? This is a parallel line of thought that should be pursued by the authors if they wish to strengthen their conclusions – if new successful variants differ by a few non-synonymous regions, the evolution of the pathogen is more mutation limited, if they differ by a lot, the availability of beneficial mutations is not the bottleneck. The statement “mutations continue to accumulate within these variants and sub-variants, and not all of them have been identified and named” is a good start.

6.

The authors claim that “Mutation rates are unlikely to differ significantly across viruses.” while the opposite seems to be the consensus in both foundational (Smith, D. B., & Inglis, S. C. (1987). The mutation rate and variability of eukaryotic viruses: an analytical review. *Journal of General Virology*, *68*(11), 2729-2740.) and recent (Pauly, M. D., Procario, M. C., & Lauring, A. S. (2017). A novel twelve class fluctuation test reveals higher than expected mutation rates for influenza A viruses. *Elife*, *6*, e26437.) literature. I am not contesting the conclusion that the evolution of coronaviruses is selection-limited, but it might be the case precisely because of their relatively high mutation rate (not only because of lower immune response to less virulent groups of viruses). If authors make controversial statements that are not explicitly tested in the article, they should support them with citations.

7.

In several assertions, such as "Secondly, since the rise of new variants is not limited by mutations alone, restricting the viral population to realistic limits may not prevent the emergence of new variants," the authors imply that the emergence of new variants is undesirable, while the opposite is true (despite a popular misconception). It has been shown that later variants of interest have higher basic reproduction numbers but lower virulence (for instance, see Nyberg, T., Ferguson, N. M., Nash, S. G., Webster, H. H., Flaxman, S., Andrews, N., ... & Thelwall, S. (2022). Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B. 1.1. 529) and delta (B. 1.617. 2) variants in England: a cohort study. *The Lancet*, 399(10332), 1303-1312). This is no coincidence. In an environment of heightened vigilance, variants that cause less harm to their hosts can often go undetected or ignored, allowing them to spread more readily

(again, see above). This is why lockdowns can be particularly effective and desirable during the initial waves of a pandemic – it's critical to minimize the number of people infected by the early variants, which tend to have higher mortality rates as they are optimized for organisms other than humans. The authors can also mention this in the context of their correct observation that a frequent occurrence of mutants is expected even within a single host.

Questions:

What was the formal criteria for inclusion of a wave into one of the categories? (e.g. “as illustrated in Figure 2c”) Did the authors just gaze at the plots and then filed the waves based on their impressions? This needs a detailed elaboration in the paper. Sharing the analysis code alongside the data would also be very helpful (osf.io is a nice platform for that but even github is fine).

Minor comments:

Some sentences contain pleonastic constructions: “…predictions for each hypothesis, along with**potential** evidence that could **potentially** disprove them.”

First panel in **Figure 1** bears a label that probably resulted from incomplete deletion of older version: “Immunity to prior variant Prior variant”. I guess it should read “Immunity to prior variant” only.

It would help to have the axes and panels labeled in**Figure 5**.

By clicking the link

https://ourworldindata.org/explorers/coronavirus-data-explorer

we get to

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(becuase of an attempt to open a new tab) which registers as a non-existent webpage. The same goes for a few more links I have tried. This might be a problem of the interaction between the webpage and my browser (Firefox) and not the article, but it definitely needs fixing.