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

Lilia Melnik[1]

1 Tulane University

Potential competing interests: No potential competing interests to declare.

This manuscript looks at the evolution of SARS-CoV-2 by examining the invasion of new viral variants as being limited by mutation or selection. The authors formulated alternative hypotheses regarding the origin and spread of new viral variants and evaluated these hypotheses based on epidemiological data. The results of the analysis of large-scale epidemiological data indicate that the invasion of novel variants is primarily limited by selection rather than mutation.

The article is well written. The methods are described in detail, and the limitations of simulations are indicated. The authors raise interesting questions about the evolution of SARS-CoV-2. I would like to provide several helpful suggestions.

Page 4. "Variants are unlikely to possess a selective advantage when hosts are fully immune." Does this statement refer to SARS-CoV-2? Immunity to coronaviruses in general is relatively short.

Page 5. Figure 1. What data did you use to make this figure? Time on X-axis are in months or weeks? Does immunity titer in percent or other units? Does the figure specifically illustrate immunity to SARS-CoV-2 and the selection of new SARS-CoV-2 variants, or does it simply illustrate a concept that can be generally applied to a wide variety of viruses? Immunity to viral infections differs greatly depending on the virus. Maybe some clarification would be helpful.

In the description of the blue line, it says "prior varinat Prior variant." Please remove "prior varinat."

Page 7. Figure 2. Please provide the title of the figure. Please indicate that Figures 2b, 2c, and 2d describe Hypothesis 3 as described in the text on page 6.

Page 10. Figure 3. What are the units on the x and y axes? Days for time and arbitrary units for the incidence?

Page14. Figure 6. In this figure, the origins of different variants are plotted alongside the incidence curves in different countries. The lowest incidence of variants from 7-1-2020 until the end of 2021 was observed in Norway, followed by a large wave in 2022. Like Denmark, Norway was able to deal with the pandemic better than other European countries. What factors and public health policies might have contributed to this result? This could be addressed in the discussion in the second-to-last paragraph.

Page 16. "Mutation rates are unlikely to differ significantly across viruses." This is not the case. Please clarify this statement.

When you are mentioning the immunity to poxvirus and poliovirus, it might be appropriate to discuss the immune response

to DNA and RNA viruses. Both DNA and RNA viruses have evolved multiple mechanisms to subvert different arms of the immune system.

Also, DNA and RNA viruses adopted two general pathways to evolve. In one pathway, viruses coevolve with their hosts and share their faith. It is generally true for DNA viruses. In another pathway, viruses infect multiple species to avoid extinction in the compromised species. This strategy is common for RNA viruses (Flint, J., Racaniello, Rall, G.F., Haziioannou, T., and Skalka, A.M. 2020. Principles of Virology, Fifth Edition).