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 present study convincingly demonstrates the existence of a selection-limited scenario for the evolution of new SARS-CoV-2 variants, based on the consequences of a SIR model of the epidemic. However, this demonstration is based on a series of extremely simplifying assumptions that have not been taken into account or discussed, so that the conclusions of the article, particularly in terms of the policy to be favored for managing the epidemic or future epidemics of the same family, seem questionable. In general, "selection" is a very general concept which should be examined in terms of its concrete implementation. Furthermore, mutation rates are considered here to be homogeneous in both space and time, whereas this is certainly not the case. Indeed, mutation rates in SARS-CoV-2 are not constant throughout the evolution of the virus (see doi: 10.5802/crbiol.16 exploring the first stages of the epidemic).

Here are a few specific points that might have been raised and suggest that many specific factors should be taken into account in further studies. Before going in to some details I would like to suggest that a few specific points be considered and modified, particularly with regard to the authors' perception of virus mutation rates.

“Mutation rates are unlikely to differ significantly across viruses” : this is certainly not right, as viruses may be able to, and in fact often do manipulate their host’s metabolism, in particular in terms of nucleotide metabolism. This is especially true of the coronaviruses with their large genomes.

In this respect there should be a considerable difference between DNA and RNA viruses. A key question is availability of CDP for DNA synthesis (see doi: 10.1093/dnares/4.1.9) and CTP for RNA synthesis, as well as for many other cell processes, (see our study doi: 10.1093/gbe/evaa229). The importance of CTP is witnessed in the emergence of the specific innate immunity enzyme viperin which synthesizes a toxic analog of CTP, ddhCTP, that may interfere with all metabolic steps involving the triphosphate (noting that knowledge in the domain is essentially missing). This is summarized in Figure 3 in doi: 10.1111/1462-2920.16140

In parallel, viruses, especially those with large genomes, may have a proofreading system that corrects errors (this is particularly true of coronaviruses). Our analysis of the evolution of SARS-CoV-2 during the first year of its evolution suggests that there has been a specific change in the mutation type witnessed in different branches of its evolution tree (doi: 10.5802/crbiol.16). It would be most interesting to develop now a similar approach to study the present situation, noting that understanding cell metabolism is a critical point to generate proper models of evolution. We should also

remember that bats are hosting a large number of viruses without much deleterious consequences in general. This would make interesting to understand the details of their metabolism that differ from that of other mammals where the corresponding infection is often virulent. Bats make viperin and it is somewhat difficult to see why this does not seem to have a considerable consequence in terms of the C content of the genome of the viruses infecting them, for example.

The question of the duration of adaptive immunity is considerably more complex, and there, the very nature of the antigens displayed by viruses is certainly critical and possibly highly variable, with sudden emergence of antigens with considerable potency variation in terms of generating an immune response. The quest for universal vaccines against whole families of viruses (for example influenza A and their variants) is a case in point. There must be a link between mutation rates and emergence of important antigens, with consequences in the selective role of the immune response, so that there should be some sort of “convolution” between the two lines explored in this article.

Finally, the author’s discussion in terms of cost of infection vs cost in terms of immune response is certainly interesting, but it must be made explicit and carefully documented, especially considering the huge genetic polymorphism of the human species, for example. Before constructing any model, involving a “cost” it would be important to provide details about what is an “immune response”, especially in terms of the organs involved (metabolism is different in different organs), time course and environmental factors for example. Because the immune response is essentially a process discriminating between self- and non-self entities (or discriminating between an alarm and a standard situation) one should consider the cost of discriminating classes of events in terms of energy dissipation. For example Horton Johnson has discussed the remarkably energy-costly role of the kidney, as the organ discriminates classes of ions and metabolites (doi: 10.1038/206930a0, 10.1126/science.168.3939.1545 and for discussion see doi: 10.1111/1462-2920.16140). In short “cost” is not a straightforward concept despite its apparent simplicity.

In conclusion, this article, for me, is an interesting trigger to explore further the details of mutagenesis in viruses, as well as the tenets of selection processes involved in immunity against them.