# Review of: "The Changing Trajectory of Covid-19 and How Immunity is Evolving with It"

Antoine Danchin[1]

1 University of Hong Kong

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Viral evolution comes under the heading of game theory in that there is always a back-and-forth between the virus and its host. It is well known that the number of solutions to such games (host/parasite interactions) is unlimited. This type of observation should probably have been introduced in the background justifying the present otherwise quite interesting work. Indeed the number of context-dependent processes that will affect the propagation of the virus, and possibly its establishment as an endemic pathogen is huge. A large number of these processes have been discussed far from the situation exposed in human viral infections, when investigators explored the bacteriophage / bacteria interactions, and in particular the justification of the existence of lytic phages as compared to their lysogenic counterparts (a lysogen might be taken as a kind of “endemic” viral form). We have extensively discussed a related matter in several articles so that we provide here a short summary of some of the features we might see as missing in this otherwise interesting article.

In this article, the authors do not explicitly distinguish between innate and adaptive immunity. Yet it is clear that innate immunity represents a considerable challenge for viral evolution and restricts the pathways that can be used. In particular, there is pressure on the very sequence of the viral genome in terms of nucleotides, as well as on the synthesis of its envelope and translation resulting from the action of viperine, which synthesises 3'-deoxy-3',4'-didehydro-CTP (ddhCTP) as an extremely effective antiviral nucleotide. The consequence is that the evolutionary landscape of the virus will change accordingly, with selection pressure on variants that are able to escape the action of ddhCTP. We have discussed this original metabolic pressure (doi:10.1093/gbe/evaa229) so that the authors can consider whether it may have consequences for their viewpoint. This is not a far-fetched view as it appears that this family of antiviral molecules has emerged through evolution multiple times and is even present in prokaryotes (doi:10.1038/s41586-020-2762-2.).

Let us now consider adaptive immunity. The authors provide a convincing exploration of the coevolution of host immunity and SARS-CoV-2. However, many caveats should probably be taken into account, in particular the considerable human polymorphism. For example, the distribution of HLA markers differs from one population to another, implying that the overall selection pressure on the virus may be different (this may explain the variety of new forms that appear in different parts of the world). Another characteristic is the common evolution of many viruses towards attenuated forms (which, again, comes under the heading of game theory).

Another typical form of evolution, which is difficult to predict, is the change in the way the virus enters cells. This question has been widely debated in the context of studies into the role of the furin site in the spike protein. The change in tropism of comparable viruses in pigs is evidence that this can happen, perhaps quite frequently. There is an alternation between intestinal and respiratory tropism of coronaviruses in these familiar mammals, and this should be taken into account, particularly in view of the sudden emergence of highly pathogenic SADS in pigs (doi: 10.3389/fvets.2022.1083605). This is not a betacoronavirus but an alphacoronavirus, but the barrier between these viral species is quite tenuous and very sensitive to co-infection by different viruses (doi: 10.1093/gbe/evac161). We might suggest that the authors discuss at least some of the implications of this possibility, as it would significantly affect their proposed scenario. Again, the origin and evolution of the furin site is a case in point.

Finally, taking the point of view of the virus might be rewarding. However the authors take a strongly anthropocentric view. The key idea there is that modulation of the functions encoded in the virus genome can result in considerable changes in its evolutionary landscape. We certainly understand that the literature about SARS-CoV-2 is so large that the authors could just scrape the surface of what has been published but rather than develop this here, it might be useful that the authors read the extended discussion we proposed some time ago (doi:10.1111/1462-2920.15487).