

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

Guido Vanham¹

¹ Institute of Tropical Medicine

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The review by Azizul Haque and Anadeep B pant on "Changing trajectories of COVID-19..." is well-written and reads easily. The figures are very illustrative and didactic.

It provides a good overview on several aspects that could influence the evolution of the COVID pandemic towards endemicity and addresses a well-educated, but not not necessarily hyper-specialized audience of biomedical scientists.

A few remarks to be considered

p. 3 Fig 1 panel A lists viral mutations and characteristics that will promote a pandemic. It is doubtful, however, whether mutations that "cause less severe disease" are an important factor to promote the pandemic. After all, SARS-CoV-2 has only killed a small minority of infected subjects, unlike for instance EBOLA. Another characteristic of SARS-CoV-2 might be more important: the fact that infected but fully asymptomatic subjects can spread the infection. See <https://pubmed.ncbi.nlm.nih.gov/34105202/>

Panel D states that "Specificity and sensitivity of testing is uncertain", without much explanation. In fact, standardized and quality-controlled PCR testing is quite reliable, but the performance of the many "rapid tests" on the market for ever-changing new variants is indeed uncertain.

p. 4 Arcturus variant is XBB.1.16 (not XBB.1.6) see <https://www.who.int/activities/tracking-SARS-CoV-2-variants> and <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>

p. 7 the concept "consistent levels of a key T cell", induced by several vaccines (from ref 45) should be clarified. The paper shows in fact the induction of both "follicular helper" CD4 T cells, important for affinity maturation of antibodies, and of "cytolytic CD4 T cell", able to support and complement the weaker CD8 T cell response.

p. 8 What is not clearly mentioned in the discussion on vaccines is the concept of "imprinting": the observation that repeated stimulation with the "ancestral" SARS-CoV-2 strain (which is still part of the current bivalent vaccines) may skew the antibody response towards "old and obsolete" epitopes that the present variants have escaped from and therefore weaken the induction of responses to the "new and more relevant" epitopes. Obviously, if imprinting is an important factor in the lower efficiency of current booster vaccines, future boosters should avoid to include ancestral and escaped epitopes as much as possible. See <https://pubmed.ncbi.nlm.nih.gov/37112787/> and <https://pubmed.ncbi.nlm.nih.gov/37105169/>

p. 9 The authors rightfully defend the concept on intranasal vaccines to complement or even replace intramuscular injections by stimulating mucosal immunity. The cited ref 66, however dates back to 2020 and uses an Adenovirus based vaccine. Other experimental intranasal vaccines have been developed with varying levels of success in animal models. A intranasal vaccine against Influenza is used already for a long time, but it is not more effective than the intramuscular format. Several human trials with intranasal SARS-CoV-2 vaccines are underway, but, as a recent review states: *Overall 100 mucosal SARS-CoV-2 vaccines are in development and 20 are in clinical trials. First human trials demonstrate that this will not be an easy task.* See <https://pubmed.ncbi.nlm.nih.gov/36464938/>