Why do Covid-19 mass vaccination campaigns promote dominance of selective immune escape variants?

- Geert Vanden Bossche

"Mass vaccination campaigns can substantially reduce infection rates and hence, the emergence of new viral variants. *So, enhancement of vaccination campaigns should be able to prevent circulation of additional variants.*" Why is this simplistic postulate fundamentally wrong?

First, in order for emerging more infectious variants to enhance their potency and become well established, they must *adapt* to the suboptimal immune pressure they escaped from. To adapt viruses to grow at high infectious titers under suboptimal conditions[1], it is critical to passage the virus repeatedly under the same 'stress' conditions. Likewise, repeated person-to-person transmission of a highly mutable virus under similarly selective, suboptimal immune pressure would enable 'training' of selected immune escape variants. This will ultimately result in *adaptation* of the viral variant and thereby enable full-fledged replication under conditions which initially restricted its replication. All more infectious Sars-CoV-2 variants are characterized by mutations that are directed at spike (S) protein (herein called: 'S variants'). Selection of S-directed mutations enables enhanced binding of these variants to the ACE-2 cell receptor. By virtue of their enhanced binding to cell receptors on respiratory epithelial cells, S variants are able to overcome limitations in infectiousness imposed by S-specific antibodies (Abs).

In the absence of infection prevention measures or mass vaccination campaigns, spontaneously occurring S variants have no opportunity to compete with circulating wild virus as there is no selective immune pressure mechanism promoting their adaptation to the human host. In case of *de novo* infection of a seronegative population with Sars-CoV-2, there is no selective immune pressure that could promote replication and propagation of immune escape S variants. In case subjects have previously been primed as a result of infection with wild type Sars-CoV-2, their later exposure to variant S antigen (S') will recall a strong response mounted by Abs that effectively recognize both S and S' (https://science.sciencemag.org/content/early/2021/03/24/science.abg9175). Lastly, subjects who are in the process of seroconverting as a result of Coronavirus (CoV) infection will not be susceptible to re-infection by another CoV due to antiviral innate immunity. So, in none of the above-mentioned cases do S variants have an opportunity to repeatedly replicate and propagate under suboptimal selective immune pressure. This is to say that under conditions of *natural* infection, adaptation of S-selective immune escape variants does not usually occur. This seems to be confirmed by the results from virus characterization on archival autopsy samples from subjects who succumbed to Influenza during the pandemic of 1918. Samples isolated during the second, most severe, wave did not indicate any contribution from variant strains (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291398/).

1Suboptimal conditions occur when the virus is, for example, inoculated on host cells that are not usually permissive to the virus or when it is grown on cell culture at suboptimal temperature or in the presence of subneutralizing antibodies

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In case of mass vaccination, however, there is plenty of opportunity for spontaneously occurring S variants to experience selective immune pressure. Mass vaccination campaigns will cause large, not previously primed cohorts of the population to seroconvert against S protein and to even maintain suboptimal Abs for quite some time (e.g., in those waiting for the second dose of a 2-shot vaccine) while being exposed to spontaneously emerging viral variants. Such cohorts include people who have not previously been infected at all as well as subjects who have been asymptomatically infected and only exhibited short-lived Ab titers, presumably due to lack of adequate priming (https://www.medrxiv.org/content/10.1101/2020.12.18.20248447v1; https://www.nature.com/articles/s41392-021-00525-3). Mass vaccination of vulnerable groups does not abrupt viral transmission chains but increasingly redirects transmission events to *asymptomatic* carriers (i.e., vaccinated subjects as well as not yet vaccinated young and healthy people, several of whom experienced asymptomatic infection without mounting long-lived Ab titers[2]). As ongoing mass vaccination campaigns are shifting the 'reservoir' of viral transmission to asymptomatically infected subjects (whether vaccinated or not), the likelihood for unvaccinated, previously asymptomatically infected subjects to experience re-infection with Sars-CoV-2 while being endowed with suboptimal and short-lived anti-S Abs substantially increases. This is to say that within the population that is now most actively involved in viral transmission, new, spontaneously emerging S variants have plenty of opportunity to train under suboptimal immune pressure such as to ultimately adapt to the human host and become part of the dominant circulating Sars-Cov-2 population. This is how - after initial breeding of selected viral variants as a direct result of infection prevention measures - subsequent mass vaccination campaigns will drive enhanced circulation of additional, more infectious viral S variants. 'Training' of such more infectious immune escape variants is thought to be reflected by the plateau that follows the vaccine-mediated decline in cases and the height of which exceeds the one following the previous wave of cases.

As mass vaccination campaigns have started in the vulnerable population, not only vaccinated subjects but also not yet vaccinated younger age groups will become a breeding ground for new infectious variants. There can be no doubt that continued mass vaccination campaigns will enable new, more infectious viral variants to become increasingly dominant and ultimately result in a dramatic incline in new cases despite enhanced vaccine coverage rates. There can be no doubt either that this situation will soon lead to complete resistance of circulating variants to the current vaccines. This is certainly not what would be expected by those who claim that enhanced and accelerated mass vaccination is going to diminish circulation of new dominant variants and will, therefore, further reduce viral infection rates and flatten morbidity and mortality curves.

2It is possible, but not proven, that especially subjects with increased CoV-nonspecific NABs, for example as a result of previous exposure to Sars-CoV-2 during the first wave, will develop S-specific Abs that are short-lived and not fully mature