Comments on common questions and criticism II
- Geert Vanden Bossche

There are a number of misinterpretations or misunderstandings of my message that I would like to address:

1. Emergence of additional infectious variants as a result of mass vaccination would NOT necessarily lead to more severe disease. More infectious variants merely enhance viral entry into susceptible cells due to increased affinity of S for ACE2; however, it is possible that strong innate immune suppression (e.g., by S-specific Abs) in healthy children might be responsible for enhancement of severe disease.

2. Ag-specific, adaptive immunity does not destroy but bypass innate immunity in that existing NABs can be fully or partially outcompeted by S-specific Abs for binding to virus surface-expressed spike protein, thereby preventing killing of C19-infected cells by NK cells (as is thought to naturally occur in NACs as shown below)

3. NK-cell mediated killing of C19-infected cells is likely due to adjuvant-mediated upregulation of a C19-derived, self-mimicking peptide motif that is juxtaposed to a universal MHC cl I-restricted T

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cell epitope (see references from the literature under Topic 3). The resulting highly repetitive pattern of pathogen-associated self-mimicking motifs can be recognized by NK cells. Activation of the latter would enable recognition of similar patterns expressed on the surface of C19-infected cells at an early stage of infection.

The following summarizes my feedback to further comments and criticism at

https://noorchashm.medium.com/dr-geert-vanden-bossches-call-for-a-full

https://noorchashm.medium.com/vanden-bossches-dangerous-fallacy-en-mas

In order for a selective immune escape variant to become dominant, it needs to be able to adapt to the stress conditions it is trying to escape from (e.g., immune pressure). As virus replication can only occur in living cells, in vitro adaptation of an immune escape variant would require repeated passage of this variant on the same cell line under the same stress conditions (e.g., suboptimal neutralizing Abs). In vivo, this would translate into ‘passaging’ the immune escape variant from one individual to another under the same conditions of suboptimal immune pressure. As already mentioned above, mass vaccinations in the heat of a pandemic featured by multiple circulating viral variants generate plenty of opportunity for C19 to infect people on a background of suboptimal neutralizing Abs. Transient post-infection neutralizing Abs in asymptptomatically infected subjects and vaccine recipients who are mounting Abs against nonhomologous S from the wild type strain substantially contribute to this background. So far, there are only very few countries who manage to conduct their mass vaccination campaigns on a background of low infectious pressure (UK, Israel,...) as the number of more infectious variants steadily increases. Consequently, the chances that an escape mutant repeatedly encounters similar suboptimal immune pressure upon spreading across the population only increase. This is how immune escape variants ultimately become dominant. As already explained above (see also fig.), it is reasonable to assume that the infectiousness of a more infectious as compared to a less infectious variant (e.g., wild type or a variant more infectious than wild type) experiences a relative increase when infecting young and healthy populations. This is because NABs bind with similar strength to both more and less infectious variants (cfr. fig 2). As a result, the more infectious a new variant, the more dominant it will become, especially when capable of causing (severe) disease in the young and healthy population.

From the above, it becomes obvious that the mechanism of selection of immune escape variants is very different from what is proposed by Noorchashm. He proposes that spontaneously occurring mutants/variants will escape immune pressure and get established in people who happen to mount the type of suboptimal immune response that would match the spontaneously occurring mutations. As a result, he states, variants would selectively ‘prey’ on subjects exhibiting suboptimal immune pressure, for example as a result of vaccination. This is wrong as the mechanism of immune selection works the other way around. Again, it’s not like spontaneously occurring mutations become dominant because some of them happen to bypass vaccinal immune responses in a certain cohort of vaccinees. According to the scenario

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he’s proposing, emerging variants that are, for example, completely resistant to the vaccine would have the same chance to become dominant as those which are more infectious but far from fully resistant to the vaccine. That is definitely not how evolutionary pressure and selective immune escape work as pressure (including immune pressure) and escape therefrom are interdependently co-evolving. This particularly applies to C19 which has been experiencing a steadily growing pressure on its S(1) protein (responsible for its infectiousness), first through global infection prevention measures and second, through mass vaccination campaigns using vaccines that are targeted at S1, and particularly at the RBD, to prevent binding to ACE2 and hence, to prevent infection. That’s also why selected mutations in more infectious variants have been found to increasingly converge to S1, even including RBD.

In conclusion, I do all but concur with Noorchashm’s conclusion that C19-infected subjects are the source of more infectious variants. I am under the impression that he confuses ‘mutations’ with ‘selection of immune escape variants’ or ‘emergence/selection of viral variants’.

Re: Natural infection. As already pointed out on several occasions, it’s important to discriminate between subjects who get naturally infected and don’t develop (severe) disease, thanks to a strong innate immune response, and those who get symptomatically infected. The first are protected anyhow against C19 disease (regardless of previous infection) whereas the latter are primarily protected thanks to S-specific Abs acquired upon their recovery from disease. To be clear, it is my understanding that in asymptotically infected subjects, infection might even lead to enhanced susceptibility upon reinfection for as long as transient S-specific Abs bind strongly enough to C19 to suppress NABs.

Re: Herd immunity. It’s not clear to me how ‘insufficient herd immunity could cause immune escape’...? It’s not because extensive viral replication and mutation is taking place that more infectious variants will be selected! Rather the opposite applies. Furthermore, it is difficult to understand how vaccinated people could protect those who’re not immunized given the fact that there is now abundant evidence from the literature that current vaccines do not protect against infection and that especially more infectious variants can rapidly be transmitted from vaccinated to nonimmunized people. There is now an increasing consensus that mass vaccination campaigns with vaccines will not manage to provide herd immunity for vaccine recipients will increasingly be turned into asymptomatic spreaders as new, more infectious variants arise. I’ve already explained above why new vaccines designed along the same lines will all but help to enable herd immunity.

Comparing the current evolution of C19 and the ongoing emergence of more infectious variants with Influenza is not correct. Regularly observed variations in HA and NA are not the result of progressive/evolutionary selective immune escape but merely result from antigenic drift. The same level of invalidity applies to the comparison of the ongoing pandemic with the Flu pandemic in 1918. As far as I am aware, previous Flu pandemics have not be featured by a concomitant emergence of a panoply of more infectious viral variants.

Taken together all of the above, I don’t grasp the rationale behind Noorchashm’s statement that natural infection, but not vaccination, drives the emergence of new variants. In Oct-Nov of 2020, infectivity rates

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in most countries were still relatively low. Nevertheless, several more infectious variants emerged just within a few weeks. Not sure how this correlates with the infectivity rates observed back then. As can be seen from more recent references from the literature posted on my website (Topic 5), a growing number of scientists consider mass vaccination being at least at risk of immune escape and driving the emergence of more infectious variants.

There is certainly also no evidence that the original, wild type C19 strain (as responsible for the first wave of this pandemic) would have caused more severe disease and death than will be the case with all of the currently circulating highly infectious strains. The latter are out of control and nobody knows how we’ll ever get rid of those. Again, as much as I was in favor of letting the original pandemic (wild type!) run its natural course (in the absence of vaccines inducing sterilizing immunity!) while protecting the vulnerable and focusing on early treatment, I am now convinced that the only way to get rid of this pandemic is to use vaccines capable to eradicate C19 and all its variants. There can be no doubt that such vaccines ought to operate according to a completely different principle.