

Comments on common questions and criticism

- Geert Vanden Bossche

First, I would like to re-iterate that I cannot respond to the many questions from people who are hesitant about whether or not they should get the vaccine or the second shot thereof. As far as the vaccines themselves are concerned, I will continue to refrain from making any judgement or comparison of those. None of this is part of my 'mission'.

My message and deep concern relates to the risk, both from a public and an individual viewpoint, of using any of the CURRENT VACCINES in MASS VACCINATION campaigns during a PANDEMIC, especially since those campaigns were rolled out after more infectious variants started circulating back in November 2020 as a likely consequence of global infection prevention measures. It is, indeed, my interpretation of the science that ongoing mass vaccination campaigns will only drive the emergence of additional, more infectious variants as a result from selective immune escape and ultimately lead to full anti-vaccine resistance. It is also my conviction that based upon their much stronger binding affinity, S-specific antibodies (Abs) will – at least to a substantial extent - outcompete variant-nonspecific natural antibodies (NABs), even when those may no longer be capable of neutralizing C19. This would primarily affect young and healthy people as they are largely relying on their innate immunity to prevent disease upon infection with any type of C19.

Understandably, I am also receiving many questions and criticism on my scientific interpretation of the current C19 situation and the impact thereon of massive infection prevention measures, more recently combined with mass vaccination campaigns.

I will try to address most commonly asked questions and criticism in regular postings.

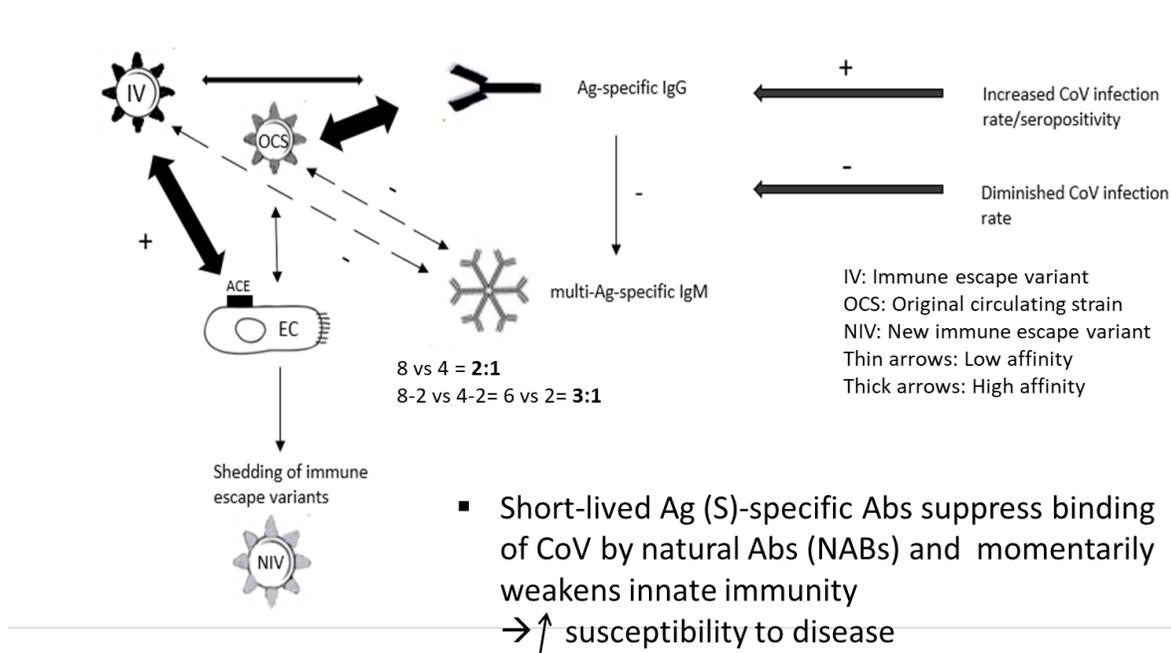
I'll start with the comments and criticism as articulated at <https://healthfeedback.org/claimreview/covid-19-vaccines-are-critical-for-controlling-the-pandemic-vaccines-still-offer-partial-protection-against-new-variants-of-the-virus/>

The article states that C19 variants (e.g. British, South-African, Brazilian) evolved in unvaccinated populations and, therefore, clearly prove that emergence of more infectious variants cannot be due to mass vaccination.

In my interviews, I have repeatedly stated that the more infectious variants observed at the end of last year were (of course!) not the consequence of mass vaccination but of infection prevention measures (selected mutations in these variants all converged to domains within S responsible for enhanced viral infectiousness). This being said, I consider it highly likely that mass vaccination (with the current vaccines) will further promote breeding of more infectious variants because of S-selective immune escape. This is scientifically highly plausible as mass vaccinations combined with a pandemic implies that large parts of the population are seroconverting against S protein. Massive seroconversion, whether in

symptomatically or in asymptotically infected people, is almost synonymous for abundance of suboptimal immune response, especially also in terms of antibody affinity. It is reasonable to postulate that highly mutable viruses that are put under suboptimal immune pressure will select mutations in S enabling them to more strongly bind to the ACE2 (angiotensin converting enzyme) receptor. Consequently, ACE2 could outcompete S-directed Abs for binding to the virus. This is to say that the virus becomes more infectious. This, however, does not necessarily imply that the more infectious variant automatically becomes the dominant circulating strain. However, if escape mutants can be passaged from one person to another under similar conditions of high, but insufficient, immune pressure, they may ultimately become dominant. That's why it is difficult to understand how mass vaccination campaigns conducted in the midst of a pandemic would not lead to emergence of dominant, more infectious immune escape variants. Arguing that 'no evidence indicates that C19 vaccines pose a greater risk of immune escape than uncontrolled viral spread' equals ignoring enhanced selective immune pressure and hence, does not take into consideration the abundance of suboptimal immune responses that are simultaneously occurring in large parts of both the vaccinated and unvaccinated population. As a consequence of mass vaccination, unvaccinated subjects are likely to become more readily infected due to the growing amount of immune escape variants and asymptomatic spreading thereof by vaccine recipients.

Mass vaccination of one subpopulation (e.g. the elderly) may drive selective immune escape in another, nonvaccinated segment of the population (e.g. younger age groups). Mass vaccination with vaccines that do not satisfactorily match the antigenic constellation of S in highly infectious variants is prone to generate a substantial amount of asymptomatic spreaders. The latter may enhance viral spread to unvaccinated youngsters and, therefore, increase the likelihood of their re-infection at a point in time when they're still endowed with short-lived, suboptimal Abs as a result of previous infection. The more infectious the circulating variants, the larger the part of the unvaccinated population that will experience re-infection while still having low-affinity Abs from previous infection. It is reasonable to assume that repeated passage of selective escape mutants amongst unvaccinated youngsters will rapidly allow such selected escape mutants to become dominant. Especially in young and healthy people, NABs may be high enough to compete with S-specific Abs and, therefore, bind a certain amount of virus, regardless of the latter's infectiousness. As illustrated in the slide below, this will result in an even higher binding rate of highly infectious as compared to less infectious variants. This is because the relative rate of infectiousness between 2 viral variants increases after interaction with NABs (e.g. $8:4 = 2/1 < [(8-2):(4-2)] = 3/1$). Vaccination of one segment of the population with vaccines comprising spike protein in an antigenic constellation that does not properly match mutated S in the more infectious variants can, therefore, lead to enhancement of immune escape and dominance of new variants in the unvaccinated segment of the population.



The article further states that I have been pretending that current vaccines would not reduce transmission. This is wrong, as depending on the extent of match between vaccinal Abs and S-associated mutations in the more infectious variants, neutralization may still occur although definitely to a lesser degree. So, although viral shedding may still be diminished, current vaccines cannot prevent vaccine recipients from becoming asymptomatic spreaders, nor can they prevent the virus from selecting mutants capable of escaping suboptimal immune pressure.

I often hear that people think I am only focusing on Abs and not aware of other immune responses such as those based on immune effector cells. This is, of course, not true. The reason I am primarily focusing on Abs, and particularly on S-directed Abs (as, for example, elicited by current vaccines), is because anti-S Abs are responsible for binding to C19's spike (S) protein. The latter is known to be responsible for viral infectiousness. Consequently, alterations to S, for example as a result of mutations, may result in changes in viral infectiousness. This is exactly what is currently happening as reflected by the steadily increasing emergence of more infectious variants. Vaccinal anti-S Abs bind with lower affinity/ strength to those variants. It is reasonable to assume that wide-spread occurrence of suboptimal immune responses in asymptotically infected subjects (as a result of growing viral spread of highly infectious variants) combined with and increasing vaccination rates will only drive further selection of viral immune escape variants (see also interviews posted at www.geertvandenbossche.org). This is why all attention is now focused on 'S' protein and on the question as to how long vaccinal anti-S Abs will be able to resist

the growing number of more infectious viral variants and be able to prevent severe disease. There is, of course, no doubt that current vaccines also induce T cell responses as strong and long-lived Abs responses – as induced by these vaccines – cannot be induced without T help. However, there is no evidence whatsoever that any of the current vaccines broadly induces cytolytic CD8+ T cells that are capable of killing C19-infected target cells in vaccine recipients. Unless they are endowed with cytolytic activity towards infected target cells, there is no proven benefit of inducing CD8+ T cells in vaccine recipients. Consequently, T cell responses cannot be used as an argument for stating that ‘reduced efficacy against these variants wouldn’t necessarily render C19 vaccines ineffective’.

Other common questions center around criteria that could possibly support my interpretation of the science involved in this new pandemic (i.e. no longer a pandemic caused by the natural wild type C19, but by a panoply of more infectious C19 variants!). I summarise them as follows:

1. A steadily growing number of highly infectious variants as mass vaccination progresses
2. An increasing number of mutations selected within S1 and especially the RBD of new variants as mass vaccination progresses
3. An increasing number of vaccinees who increasingly spread the virus and ultimately also contract severe disease as mass vaccination progresses
4. A global trend for infection, disease and hospitalization curves to incline as mass vaccination progresses. The latter will, of course, be preceded by a more or less steep decline and more or less extended plateau, depending on the speed of roll-out of mass vaccination campaigns
5. Shortening of lag time for lockdowns to be implemented as a last resort

The article further states that ‘reduced risk of C19 hospitalizations by 50% in vaccinated individuals suggests that C19 vaccines might be effective against new emerging variants’. First, the efficacy of current vaccines against severe disease caused by some of these variants (e.g. South-African, Brazilian,..) has already been reported to be much less than 50%. Furthermore, the problem is not that much about reduced efficacy but more about viral immune escape. Suboptimal immune responses, and especially diminished efficacy against severe disease, are promoting selective immune escape of C19. In the mid or longer term, this is at high risk of rendering the virus completely resistant to the current vaccines (which means 0 % of efficacy).

And then the article proposes to make new vaccines to deal with the more infectious variants. However, as it comes to designing new vaccines (of the same type), the first question coming to one’s mind is: ‘Which variant do we want to target?’ and thereafter: ‘Do we want to inject 10 different vaccines at the same time to cover an as large as possible spectrum of variants?’ We all agree that Abs elicited by vaccines are specific. They can, for sure, be designed to become multi-specific. But even then, it’s unlikely that the increasingly growing and diversified spectrum of new variants that will circulate by the time those new vaccines will be ready for deployment will be adequately matched by those multivalent vaccines. What is certain, though, is that new vaccines will recall previously primed Ab-secreting B memory cells (through phenomenon called ‘antigenic sin’) and thereby recall previous production of S-specific Abs. The latter will now bind with even lower affinity to the new variants. As loss of

neutralization capacity of these Abs would not prevent them from binding to the virus and competing with NABs, mass vaccination with new vaccines would only result in further suppressing the population's innate immunity.

The article then goes on stating 'the humoral immune response enables the body to respond swiftly and effectively upon encountering natural infection by that pathogen in future'. This statement seems to ignore the importance of the innate immune response which is activated even faster, without need for priming and is directed against all C19 variants (or coronaviruses at large). The problem of the antigen-(e.g. S-)specific Abs is that – in future - they will not only be recalled by 'that (same) pathogen' but also by new C19 variants (see above: 'antigenic sin') and thereby generate high titers of Abs with little or no neutralizing capacity towards the ever growing spectrum of new, more infectious variants.

The author of the article further complains about me not providing evidence of NABs protecting against C19. Already some time ago, we provided on our website a list of references that support our interpretation of the current dynamics of the pandemic. This list also comprises at least one publication that is specifically dealing with NABs against C19 ('Therapeutic Potential of B-1a Cells in COVID-19'). The authors of this publication conclude that there is compelling evidence for a role of B-1a cells (which produce NABs) in protecting against C19 and recommend that studies be conducted to further explore the therapeutic potential of B-1a cells to treat COVID-19!

In addition, I don't think it is fair to conclude that 'experts unanimously warn that natural infection poses great health risks, even for healthy people'. I do not agree that experts considered natural infection with the original wild type strain being of great health risk to healthy people. However, as mentioned on several occasions, I do agree that the situation may have dramatically changed since the first wave as the likelihood of healthy people becoming re-infected while seroconverting is now increasing as a result of growing infectivity rates (not at least due to the increasing number of asymptomatic carriers as a result of mass vaccination campaigns). Hence, the risk for healthy people to contract severe disease is no longer negligible.

Another common question relates to the competition between Ag (antigen)-specific (e.g. S-specific) Abs and NABs. As one will appreciate from the literature I posted on my website (<https://www.frontiersin.org/articles/10.3389/fimmu.2020.02139/full>), the affinity of NABs, primarily sIgMs, towards a specific Ag is about 100-1000 times lower than that of Ag-specific Abs. The latter are the type of Abs generated in subjects recovering from C19 disease or being immunized with C19 vaccines. It is, therefore, reasonable to assume that - as far as binding to S is concerned (and that is what currently matters in view of the highly infectious variants featured by enhanced binding strength of S to ACE2) - S-specific Abs bind with much higher affinity to S than multimeric natural sIgMs do. Although characterized by high avidity to the overall viral surface (due to multivalent binding interactions), NABs would bind to S protein on C19 (variants) with much lower affinity than S-spec Abs. Even if the latter are no longer able to neutralize the virus, they may still be able to bind to S. This is to say that anti-S Abs can outcompete NABs, even though they may no longer be able to neutralize the virus. Of course, this will

never lead to an 'ALL' or 'NOTHING' effect. So, despite their (partial) suppression by S-specific Abs, high levels of variant-nonspecific NABs may still be able to prevent infected people from contracting the disease, even if the former are no longer able to neutralize the virus. I tend to conclude, therefore, that short-lived S-specific Abs after asymptomatic infection (AI) are capable of momentary suppression of NABs (that are of course still present!) and hence, could make asymptotically infected subjects susceptible to disease upon re-infection with C19. This might also explain why people (especially healthy and younger people) who resisted disease during the first wave are now becoming increasingly susceptible to (severe) disease (similar to the age group primarily affected by the second wave in the 1918 Flu pandemic). I don't think that the short-lived surge in S-specific Abs after AI (no longer detectable after 8w) is the result of a true 'priming' event. If this were the case, we would expect that asymptotically infected people would ultimately develop high, long-lived Ab titers (in the absence of any symptoms), which, so far, has only been documented to be the case in people who recovered from disease as a result of natural infection or, of course, in vaccinees. It's also clear that this short-lived Abs are not responsible for eliminating the virus in asymptotically infected subjects.