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A last word of caution to all those pretending the Covid-19 pandemic is toning down

Synopsis

The current expansion in prevalence of infectious Sars-CoV-2 variants is highly problematic because it erodes natural Ab-based, variant-nonspecific immunity in the non-vaccinated part of the population. The high infectivity rate that results from this expansion not only further enhances the expansion of these variants but may also drive natural selection of viral variants that are featured by an even higher level of infectiousness. Erosion, therefore, of natural Ab-based, variant-nonspecific immunity promotes breeding and transmission of more infectious viral variants in the non-vaccinated part of the population. On the other hand, mass vaccination promotes natural selection of increasingly vaccine immunity (VI)-escaping variants in the vaccinated part of the population. Taken together, mass vaccination conducted on a background of high infectivity rates enables more infectious, increasingly VI-escaping variants to expand in prevalence. This evolution inevitably results in inclining morbidity rates in both, the non-vaccinated and vaccinated population and precipitates the emergence of circulating viral variants that will eventually fully resist vaccine-mediated immunity (VMI). This is why mass vaccination campaigns should not be conducted during a pandemic of a highly mutable virus, let alone during a pandemic of more infectious variants (unless transmission-blocking vaccines are used!). It is critical to understand that a rapid decline in viral infectivity rates that is not achieved by natural infection but merely results from expedited mass vaccination campaigns will only *delay* abrupt propagation of emerging, fully vaccine-resistant viral variants and hence, only delay the occurrence of a high wave of morbidity and mortality. In contrast, mass vaccination campaigns that are progressing more slowly, especially when conducted on a background of relatively low infectious pressure, will result in a steadily growing propagation of increasingly VI-escaping variants and hence, cause a wave of morbidity and mortality that continues to grow bigger and larger as more and more people become vaccinated. It's only when fully vaccine-resistant viral variants will become dominant that this wave will start to peak.

To prevent more detrimental consequences of the ongoing evolution of Sars-CoV-2, we have no choice but to mitigate erosion of natural, Coronavirus (CoV)-nonspecific immunity in non-vaccinated individuals and exertion of strong immune selection pressure on immunodominant vaccinal epitopes in vaccinated individuals. This is to say that we must

will subsequently culminate in a huge case fatality wave when expansion of more infectious, vaccine-resistant variants will explode.

A rapid and substantial decrease in viral infectivity rates could be achieved by a short-term course of large-scale antiviral chemoprophylaxis (suitable candidates have already been identified) and adequate infection prevention measures while early treatment of symptomatically infected subjects and implementation of a healthy eating (including certain dietary supplements) and lifestyle (including exercise!) plan would further contribute to building herd immunity. Although this strategy is unlikely to eradicate the virus, it should allow forcing the pandemic into transitioning to a kind of 'artificial'endemicity. Of course, as asymptomatic reservoirs (asymptomatically infected vaccinated or non-vaccinated humans or even animals) would remain, mass gatherings would still need to be avoided in the future and large-scale chemoprophylaxis campaigns using antiviral drugs would likely need to be repeated at specific time intervals and for as long as no sterilizing immune intervention is available. The action plan proposed above should immediately be implemented: Once the virus will become entirely resistant to the current vaccines, the above-mentioned measures will no longer be able to prevent a dramatic rise in casualties, unless campaigns of antiviral chemoprophylaxis are conducted worldwide and on a permanent basis.

Analysis of current evolution of the pandemic and impact thereon of mass vaccination campaigns

I herewith reiterate that I will continue to distance myself from those who pretend the pandemic is over or at least toning down as a result of growing herd immunity (HI). I take issue with the way the observations of genomic/ molecular epidemiologists are downplayed and with the fact that immunological data are oftentimes ignored, taken out of context, misinterpreted or not understood. I do not concur with experts who pretend that the pandemic has now started transitioning into an endemic phase and that the virus will eventually spontaneously degrade into yet another common cold CoV that is only of minor concern to public health. It seems, indeed, like some experts now tend to attribute diminished severity of disease and declining mortality rates to growing HI and/ or waning viral virulence. As will be explained below, the predictions they make are not taking into account the complex interplay between the growing infectious pressure exerted by more infectious circulating viral variants and the rising immune selection pressure exerted on the virus by the rapidly expanding immunized population. Their predictions are also not in line with recently published data from molecular/ genomic epidemiologists showing how rising population-level immune selection pressure is now driving the genomic evolution of Sars-CoV-2 variants (see my recent contribution: 'Why the ongoing mass vaccination experiment drives a rapid evolutionary response of SARS-CoV-2').

It is simply mind-blowing that some experts still continue to ignore the negative impact of mass vaccination on the evolution of this pandemic. On the contrary, some of them even pretend that *the weak link between the number of infectious cases and morbidity/ hospitalization rates, as now observed in several countries in Europe and in the US, proves that variants do not escape the immune system.* They attribute this to *a kind of* broadly

19 vaccination. Some experts even continue to emphasize the role of cross-reactive T cells elicited by one or more of the above-described immunization events as a key contributor to HI. That cross-reactive memory T cells would prevent spike(S)-directed immune escape and, therefore, prevent S-directed immune escape variants from propagating and adapting to the host population is not based on any scientific evidence. There is, indeed, no scientific proof whatsoever that cross-reactive memory T cells in previously exposed or vaccinated individuals effectively contribute to eliminating/ killing CoV-infected cells. There is not even proof that *any kind of T cell* could possibly eliminate CoV-infected host cells in the absence of S-specific memory B cells. There is, therefore, no scientific evidence that cross-reactive, variant-nonspecific T cells contribute to curtailing or diminishing viral transmission and thus, contribute to HI. If the opposite would apply, one would not understand why, at a later stage of the pandemic, some previously asymptomatically infected subjects all of a sudden contract Covid-19 disease!

But even anti-S Abs generated upon previous exposure to common cold CoV or upon previous asymptomatic infection with Sars-CoV-2 or after immunization with Covid-19 vaccines fail to control viral transmission. This is because

1. Anti-S Abs elicited by previous exposure to common cold CoV do not neutralize Sars-CoV-19
2. Anti-S Abs elicited by asymptomatic infection are short-lived and not fully functional (there is no evidence that asymptomatic infection with Sars-CoV-2 induces memory B cells). It has been reported that these short-lived Abs are not responsible for virus elimination (the latter occurs even before anti-S-Abs start to peak)
3. Anti-S Abs elicited by vaccination lose their neutralizing capacity towards more infectious and increasingly S Ab-resistant variants (hence, explaining the steadily increasing occurrence of 'breakthrough' cases).

But, even more importantly: How do these experts reconcile an allegedly growing HI with rising infectivity rates that are currently observed in many countries due to increased circulation of the delta variant? Wouldn't this argue for a *growing erosion* rather than for a consolidation of HI? This observation is certainly far from indicating that the pandemic is currently transitioning into endemicity.

So, if HI cannot account for reduced severity of the disease, then maybe spontaneous attenuation of the virus could? But how on earth would a treacherous virus all of a sudden breed descendant variants that are no more harmful than a common cold CoV? Viruses can only replicate, mutate or hide. Selection and adaptation of the mutations they produce is driven by selection pressure placed on specific phenotypic features of the virus. But what kind of selection pressure would force the virus into *attenuation*? And how could that happen, given that the current selection pressure on Sars-CoV-2 is reportedly known to be exerted by the population's overall immune status and is directed at the S protein, which is known to enable viral *infectiousness*? When and how does natural immune selection pressure on the *infectiousness* of a pathogen cause *diminished* virulence? If these mass vaccination campaigns were really driving the propagation of 'attenuated' viral variants that are no longer of public health concern, I would rather welcome them as a blessing rather

currently evolving mutations that would mediate a more benign course of the disease or enable the virus to become intrinsically more infectious for younger age groups.

The scientifically more plausible explanation for the observed decline in disease severity in the non-vaccinated is that the delta variant, or any other more infectious variant, increasingly affects younger age groups (e.g., young adults). Younger age groups have higher levels of natural, polyreactive B1b Abs and can, therefore, better cope with antigenic variants than the elderly or individuals with underlying disease (see references from the literature on my website under topic 1). This already explains why the delta variant is seemingly 'less virulent'. But why does the delta variant (or other more infectious variants) increasingly target young to middle-aged adults? This, most likely, has to do with its higher level of infectiousness rather than with its intrinsic virulence. Higher viral infectiousness implies enhanced affinity of the variant spike protein for the Ace-2 (angiotensin-converting enzyme 2) entry receptor. Enhanced affinity results in diminished capture of the virus by natural, variant-nonspecific Abs. There is abundant and compelling scientific evidence on the protective effect of polyreactive, natural Abs, including their protective effect against a number of viral infections (see references from the literature on my website under topic 1). Elevated levels of these Abs are to be considered a hallmark of *natural protection* from symptomatic infection upon Sars-CoV-2 exposure. It is, therefore, reasonable to assume that individuals with low functional levels of natural Abs will be more prone to contracting severe Covid-19 disease.

But how or why do more infectious variants arise?

During the first ten months of the pandemic, high waves of infectious cases that occurred in overcrowded areas (e.g., slums, favelas, highly populated cities,..) affected by the pandemic may have caused immune pressure on viral infectiousness, especially upon re-exposure of previously asymptomatically infected individuals. It is possible that such events have been driving natural selection and enhanced circulation of more infectious, S-directed immune escape variants. The higher and more widespread the viral infectious pressure, the higher the likelihood that previously asymptomatically infected subjects become re-exposed to the virus at a point in time where their titers of low affinity, S-directed Abs are still high enough to compete with their natural, polyreactive Abs for binding to the circulating Sars-CoV-2 lineage (see Fig. 1; in previous contributions, I have explicitly explained why S-specific Abs have higher affinity for S protein than natural IgMs, which bind to virus surface-expressed motifs through multivalent interactions). Consequently, enhanced infectivity rates could lead to a transient increase of the susceptibility of younger age groups (< 60-65 years) to Covid-19 disease and may, therefore, raise morbidity and hospitalization rates in these age groups (as is currently observed in many European countries as well as in the US). So, the higher and more widespread the viral infectious pressure, the more productive the breeding ground for more infectious variants and the higher the likelihood for natural selection of certain S-directed immune escape variants (i.e., such that evolved mutations capable of resisting suboptimal immune pressure on viral infectiousness). Immune escape variants that are selected because of their capacity to overcome such immune pressure exhibit a higher level of infectiousness. This is how high infectivity rates facilitate breeding of increasingly infectious viral variants. During the first year of the pandemic, several of such 'more infectious' immune escape variants have emerged (e.g., alpha (2), beta, gamma, delta).

age groups, and children in particular, may not even show any symptoms at all, even though dominant circulation of more infectious variants (e.g., delta variant) is now substantially increasing the risk of repeated exposure. This already explains why Covid-19 disease in the non-vaccinated is primarily observed in young, middle-aged adults. Since younger age groups are generally better protected by natural, poly-reactive Abs, cases of severe disease in these groups are rather rare. The severity of the disease in these subjects is thought to depend on the time point of re-exposure after their previous infection (i.e., the shorter thereafter, the higher the concentration of blocking S-specific Abs, the higher the likelihood for contracting more severe disease).

Because both, binding of natural CoV-nonspecific Abs to Sars-CoV-2 and binding of Sars-CoV-2 to the Ace-2 entry receptor is mediated by multivalent interactions, it is reasonable to assume that the blocking effect of natural, CoV-nonspecific Abs on the interaction between the Ace-2 receptor and a given Sars-CoV-2 lineage primarily depends on the functional concentration of these natural Abs. This would already explain why, under normal circumstances (i.e., if not suppressed by S-specific Abs), young and/ or healthy individuals can effectively deal with all Sars-CoV-2 viral variants. The higher the affinity of S for Ace-2 (i.e., the higher the level of intrinsic viral infectiousness) and the older the age group, the lower the residual (i.e., non-suppressed) functional capacity of natural Abs.

In contrast, vaccinal Abs are directed at a limited set of S-derived Sars-CoV-2 motifs (i.e., epitopes primarily comprised within the receptor-binding domain [RBD] of the S protein). Hence, very few mutations within this limited set of epitopes will already substantially diminish the affinity of vaccinal Abs for binding to Sars-CoV-2. This, however, does not apply to S-specific Abs acquired upon recovery from natural Covid-19 disease as those are directed at a much broader and diversified spectrum of B cell epitopes. This would already explain why more infectious Sars-CoV-2 variants more readily escape from vaccinal S-specific Abs than from naturally acquired S-specific Abs and also why we are now seeing more and more breakthrough disease cases with the more infectious delta variant in vaccinees whereas young and/ or healthy individuals or previously symptomatically infected people (provided seronegative for S protein (3)) remain largely protected from Covid-19 disease.

Molecular epidemiologists conclude that, because of the steadily increasing S-directed immune pressure exerted by the human population, circulating variants are now increasingly evolving mutations that drive resistance to S-specific Abs, especially to those recognizing immunodominant epitopes that are situated within the RBD and N-terminal domain (NTD) of the S protein. It is highly unlikely that naturally acquired S-specific Abs are responsible for this immune pressure as people who recover from Covid-19 disease only constitute a relatively small subset of the population and mount Abs against a much broader and more diversified panel of S-derived epitopes. Given the nature of the vaccinal Abs and the large vaccine coverage rates in most countries, there can be no doubt that the steadily increasing population-level immune pressure found to be exerted on RBD, for example, is caused by vaccination of large masses of people (in a previous contribution, I have expressed my astonishment about the fact that these brilliant scientists didn't even mention 'mass vaccination' at all as a potential cause of the massive increase in S-directed immune pressure; (see my recent contribution: 'Why the ongoing mass vaccination experiment drives

functional, S-specific Abs elicited by the vaccine may not necessarily further increase the affinity of the virus for the Ace-2 receptor (and hence, not commonly cause more disease in young and healthy individuals), it is reasonable to assume that such evolution will rapidly raise the number and severity of disease cases in the vaccinated part of the population. This is because growing VI escape will cause vaccinees to lose their vaccine-mediated immune protection while having their natural, CoV-nonspecific natural Abs suppressed by high titers of long-lived, S-specific vaccinal Abs (4). It is reasonable to assume that, as a general rule, the level of suppression of natural, CoV-nonspecific Abs will increase with increasing strength (adjuvantation!), frequency and coverage rate of booster immunizations (including 2nd generation vaccines!).

Vaccinal S-specific Abs cannot outcompete S-specific Abs from previously symptomatically infected individuals for binding to viral variants due to multivalent B-cell epitope recognition by the naturally primed immune system. On the other hand, immunity acquired upon recovery from natural Covid-19 disease is very robust and has repeatedly been reported to be capable of dealing very effectively with a diversified range of antigenic variants upon re-exposure (including variants of concerns; VoCs). Non-antigen (Ag)-specific innate immune adjuvantation enables epitope spreading and is, therefore, likely to contribute to broad immune recognition. Naturally acquired immunity is, therefore, an almost 'invariant' component to herd immunity. It is, however, uncertain whether binding of S-specific Abs from previously symptomatically infected individuals to circulating VI-escaping viral variants could render these individuals more susceptible to Ab-dependent enhancement of disease (ADE).

Based on all of the above, it becomes already apparent that mass vaccination campaigns conducted in the midst of a pandemic of more infectious variants will rapidly and dramatically weaken instead of strengthen the population's overall immune protection status and, therefore, not contribute to generating herd immunity. This is because mutual viral transmission between the non-vaccinated and vaccinated population enables a self-amplifying, synergistic effect between high viral infectivity rates (due to more infectious circulating variants) and high vaccine coverage rates (due to mass vaccination). This results in enhanced expansion of more infectious, increasingly VI-escaping variants as depicted in Fig. 2:

- High infectivity rates turn the non-vaccinated population into a breeding ground for increasingly infectious variants and a factory for the production and transmission of such infectious variants. Due to their increasing infectiousness and expansion in prevalence, viral infection and transmission rates rapidly increase and further erode natural immunity in a number of previously asymptomatically infected individuals (i.e., starting with healthy, middle-aged adults and progressively involving younger and younger individuals). This, in turn, increases S-directed immune selection pressure and drives natural selection and possibly adaptation of even more infectious variants.
- High vaccine coverage rates turn the exposed vaccinated population into a brewery for more VI-escaping viral variants.

> Abs will be selected as those gain a competitive advantage in vaccinees and will, therefore, reproduce more effectively. Subsequent transmission of the VI-escaping variants to non-vaccinated subjects will enable them to rapidly expand in prevalence and, therefore, replace or at least dominate previously circulating variants.

The interactions described above allow to understand how mass vaccination on a background of enhanced viral infectiousness (pandemic!) engages both, the vaccinated and unvaccinated population to expedite natural selection and adaptation of immune escape variants harboring additional, RBD-associated mutations which increasingly inhibit VMI. This is to say that mass vaccination campaigns conducted during a pandemic of more infectious variants will precipitate resistance of more infectious Sars-Cov-2 variants to S-based Covid-19 vaccines.

The more 'more infectious' variants expand and dominate and the more these variants are subject to vaccine-mediated immune selection pressure, the more rapidly the beneficial effect from mass vaccination (i.e., reduction of viral transmission and prevention of disease) will be replaced by a growing failure of the vaccines to protect the vaccinees and of the vaccinees to protect the unvaccinated. This evolution is currently expedited by relaxation of infection-prevention measures, including more frequent contacts among healthy individuals. More frequent contacts between asymptomatically infected vaccinated and non-vaccinated subjects (5) will only promote breeding of new variants that are both, more infectious and more readily escape from vaccine immunity (e.g., lambda variant).

Summary

In summary, it is reasonable to postulate that the expansion of a series of more infectious variants and the concomitant explosion of infection rates is due to self-amplifying natural selection and adaptation of more infectious circulating variants, some of which likely emerged and propagated as a result from overcrowding. As the more infectious alpha, beta, gamma or delta variants emerged prior to the deployment of mass vaccination campaigns, the latter can, indeed, not be at the origin of these variants. However, as the human population have recently been reported to exert more and more immune pressure on immunodominant epitopes comprised within the RBD, it is reasonable to assume that this additional immune pressure results from mass vaccination because vaccine coverage rates are steadily growing. More infectious variants that have evolved to harbor naturally selected, S-directed immune escape mutations will readily gain a competitive advantage as continued mass vaccination campaigns with current S-based Covid-19 vaccines cause vaccinees to augment and broaden immune selection pressure on critically important, immunodominant epitopes comprised within those vaccines. Due to widespread immune selection pressure combined with a high viral infection rate and more frequent contacts between healthy vaccinated and non-vaccinated people, more infectious immune escape variants will now rapidly further evolve to fully escape VMI while expanding in prevalence. This is to say that new immune escape variants that can no longer be eliminated by any kind of VMI will soon become the dominant circulating strains.

population while high vaccine coverage rates drives natural selection of increasingly VI-escaping Sars-CoV-2 variants. This evolution is now driving enhanced rates of disease in both populations. Consequently, mass vaccination during a pandemic of more infectious variants self-amplifies natural selection and expansion of more infectious, increasingly VI-escaping Sars-CoV-variants. Both, the vaccinated and non-vaccinated part of the population fully contribute to this evolution.

Because of all of the above, I can certainly not endorse the opinion of those who think that the decrease in disease severity and hospitalizations that is now observed in several countries where mass vaccination is well advanced would be due to some kind of 'attenuation' of viral variants or to some kind of growing HI. One rather concludes that this pandemic is far from over or from transitioning into endemicity. There can be no doubt that, at this stage, the pandemic is gearing up for breeding vaccine-resistant 'supervariants', a phenomenon that is at risk of fueling an even larger wave of morbidity, hospitalization and, unfortunately, also death, not at least in the vaccinated part of the population.

The ongoing mass vaccination campaigns must immediately be abrogated because the vaccines fail to block viral transmission and their large-scale use during a pandemic of more infectious variants will inevitably lead to vaccine resistance of circulating Sars-CoV-2 variants. Instead, mass chemoprophylaxis campaigns should be conducted at regular intervals to reduce viral infectious pressure and transmission and prevent more infectious viral variants from fueling the breeding and dominant propagation of more infectious, vaccine-resistant variants. Furthermore, people should boost their health status whereas early treatment of patients who come down with Covid-19 disease (for more information, please consult, for example, prof. Dr. P. McCullough's presentations and publications) would not only prevent severe disease and hospitalization but also enable these patients to more rapidly acquire broadly protective Abs facilitating killing/ elimination of virus-infected host cells and, therefore, diminish viral transmission and contribute to herd immunity. The above-mentioned interventions have been summarized in Fig. 3.

As we are now dealing with a pandemic of highly infectious variants (e.g., delta variant), we cannot afford any longer to target herd immunity without relying on large scale antiviral chemoprophylaxis combined with early treatment of Covid-19 diseased patients. This, together with an immediate halt of all Covid-19 mass vaccination campaigns, should now constitute the main pillars of our battle against this otherwise totally uncontrollable pandemic.

As much as I follow reports on vaccine safety issues with a great deal of concern, worry and anxiousness, I tend to believe that the potential epidemiological impact of these vaccination campaigns on human lives could be orders of magnitude larger than that of their potential short- or long-term sequelae. I am, therefore, begging the WHO and all stakeholders of these campaigns to immediately intervene as proposed above. After the first experiment failed (instead of generating herd immunity, mass vaccination is now turning vaccinees into potential spreaders of VI-escaping variants!), our human race cannot afford a second large scale experiment that aims at continuing mass vaccination while promoting exposure of the

Overall Conclusion

Both, long-lived Sars-CoV-specific immunity acquired upon recovery from disease and innate, CoV-nonspecific Ab-mediated immunity *normally* contribute to establishing broadly protective herd immunity and thereby enable a natural CoV pandemic (or, for that matter, any pandemic of an acute, self-limiting viral disease) to eventually transition into an endemic phase. However, circulation of *more* infectious variants comes with a high price to pay for herd immunity to establish as high infectivity rates are *more* likely to erode natural, polyreactive (i.e., CoV-nonspecific) immunity in young and/ or healthy individuals. As a result, morbidity and hospitalization rates, and ultimately also the number of deaths, will increase. This self-amplifying cycle of enhanced viral infectiousness (resulting in enhanced viral infectivity rates) would only come to an end when the population density is diluted down to a level low enough for viral transmission (of a highly transmissible/ infectious variant!) to substantially diminish.

Whereas fast and dominant propagation of naturally selected, more infectious variants continues to erode the natural first line of variant-nonspecific immune defense in the non-vaccinated part of the population, vaccination of large parts of the population and contacts among vaccinated and non-vaccinated subjects are driving natural selection and adaptation of increasingly VI-escaping variants and are, therefore, increasingly compromising VMI. Neither previous CoV infection (including Sars-CoV-2 infection), nor higher vaccine coverage rates can compensate for the lost immunological capacity. Indeed, memory T cells elicited upon previous CoV infection or vaccination are not reportedly known to be endowed with cytotoxic activity towards CoV-infected cells, nor can S-specific Abs elicited upon previous CoV infection or vaccination prevent spreading of more infectious Sars-CoV-2 variants. Molecular epidemiologists have suggested that immune failure to block viral transmission (e.g., in immunosuppressed patients) causes variants to convergently evolve specifically selected mutations, thereby enabling escape from VMI. VI escape together with suppression of natural, CoV-nonspecific Abs by vaccinal Abs will make vaccinees highly susceptible to contracting Covid-19 disease.

Dominant propagation of more infectious viral variants could be mitigated by mass chemoprophylaxis using a potent antiviral. At the same time, immune pressure on vaccinal S-specific epitopes must be mitigated by calling an immediate halt to mass vaccination campaigns. Furthermore, early treatment of symptomatic subjects can prevent severe disease and provide them with durable protection against a diversified spectrum of more infectious variants and, thereby, also reduce viral transmission. However, this is the last opportunity to limit the disastrous consequences of mass vaccination

Indeed, it is yet uncertain and unexplored to what extent naturally selected immune escape variants can recombine upon co-infection and generate even more complex variants, the phenotypic characteristics of which are totally unpredictable. It is also unclear whether early treatment could prevent vaccinees who have become highly susceptible to Covid-19 disease (i.e., due to viral resistance to VMI) from succumbing to severe disease. In addition, it is completely unknown whether vaccinees and even individuals who previously contracted

treatment of patients with ADE may be much more difficult and the outcome less predictable.

The more Sars-CoV-2 evolves to acquiring VI-escaping properties, the less likely vaccinees will benefit from the above-proposed strategy. This is because even low infectivity rates of circulating variants could suffice to boost their vaccinal Abs and hence, suppress their innate immune defense. Such re-stimulation could only be prevented by eradicating all of the currently circulating Sars-CoV-2 variants. Eradication of those could be achieved by using universal vaccines (6) that induce sterilizing immunity. The development of such vaccines may require a fundamentally different approach to immune intervention in that induced immune effector cells ought to be capable of *CoV-nonspecific* killing of CoV-infected cells and provide durable protective immunity *in all subjects of the population* (regardless of their immunization history and immunogenetic background). It goes without saying that such characteristics would render a vaccine highly and durably effective, even when used in mass vaccination campaigns in the midst of a pandemic of a highly mutable virus, and even if more infectious viral variants would already be circulating. Vaccine safety remains of course paramount and cannot be subject to any compromise, especially not when a smart combination of antiviral chemoprophylaxis, infection prevention, early treatment and adherence to health-strengthening eating and life-style habits could still be safe and effective in preventing cases of severe disease and prevent VI-escaping variants from becoming dominant.

Unless continued mass vaccination with S-based vaccines in populations exposed to a CoV pandemic would be proven to not cause immune selection pressure on the functionality of the vaccinal Abs and unless S-specific Abs would be proven to not compete with natural, CoV-nonspecific Abs for binding to Sars-CoV-2, mass vaccination campaigns during a pandemic, especially during a pandemic of more infectious variants, will neither enable herd immunity nor mitigate future waves of disease (unless transmission-blocking vaccines are used!). In fact, they have exactly the opposite effect in that they promote the spread of increasingly VI-escaping variants and suppress natural immunity in vaccinees. This will only result in higher morbidity and mortality rates in the part of the population that is normally naturally protected from Covid-19 (i.e., the vast majority of the population). A decline of severe morbidity and mortality rates is only observed in the elderly and in people with some underlying diseases. The outcome, therefore, of the mass vaccination campaigns is very different from the original objective, which was to protect the vast majority of people, including those who are immunologically Sars-CoV-2 naïve (via herd immunity!). Scientifically speaking, it is hard to understand how the circulating, more infectious Sars-CoV-2 variants would not rapidly evolve to overcome the RBD-directed immune pressure that is currently exerted by large parts of the human population and merge into a supervariant that evades the immune response induced by all of the S-based Covid-19 vaccines. It is simply unthinkable that the ongoing mass vaccination campaigns could mitigate, let alone terminate, this pandemic of more infectious Sars-CoV-2 variants and force the virus into adopting milder instead of even more problematic features.

I, therefore, reiterate that the currently observed convergence of naturally selected mutations towards S-derived antigenic sites that facilitate or are directly responsible for

heavily backfire if we continue mass vaccination on a background of high viral infection rates while largely relaxing infection prevention measures.

Last but not least, it must be emphasized that those calling themselves 'experts' while pretending that this pandemic is 'a pandemic among the non-vaccinated' are devoid of any scientific insight in the evolutionary dynamics of Sars-CoV-2 as currently shaped by a combination of high viral infectivity and vaccine coverage rates. Neither the vaccinated (who merely believed the vaccine would protect them from Covid-19 disease) nor the non-vaccinated (who simply believe there is no need for them to take the vaccine in order to stay protected) are to be blamed for the escalation of this pandemic. Mass vaccination is the one and only culprit.

Note: A copy of this letter has been sent to WHO, NIH, CDC, the Bill & Melinda Gates Foundation, GAVI, CEPI, FDA, EMEA and to R&D leaders from Pfizer, Moderna, Astra-Zeneca, J&J, Novavax and GSK

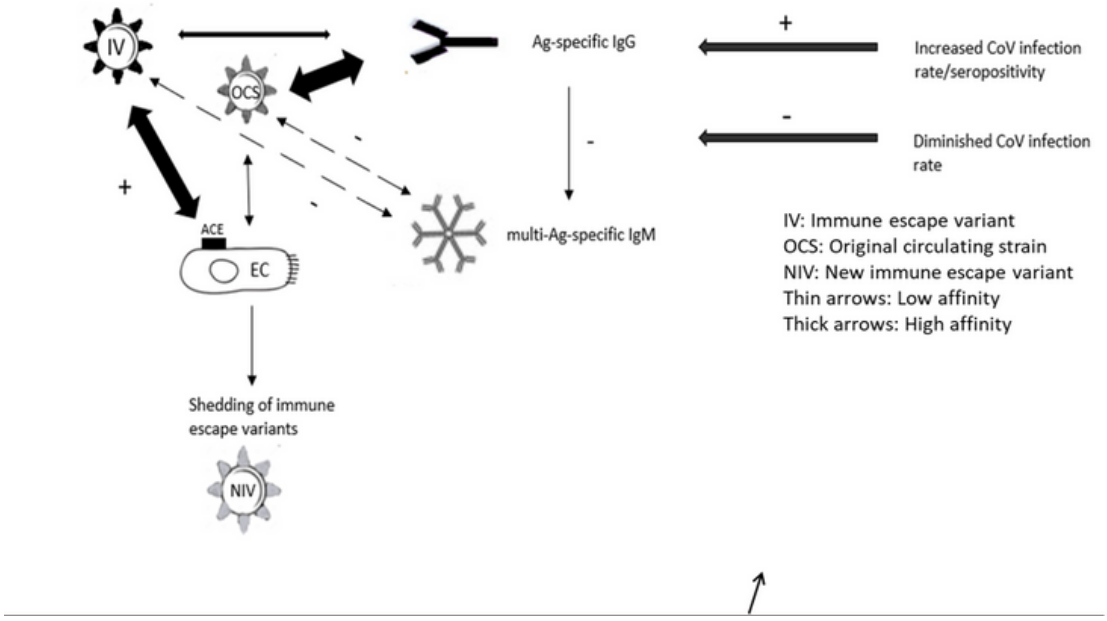


Fig 1: More infectious immune escape variants outcompete the original virus lineage (Wuhan strain) for binding to Ace-2 entry receptor. Antigen (Ag)-specific IgG antibodies (Abs) outcompete natural, poly-reactive (multi Ag-specific) IgM Abs for binding to Sars-CoV-2. Ace-2 outcompetes Ag-specific but not natural, polyreactive Abs for binding to more infectious variants.

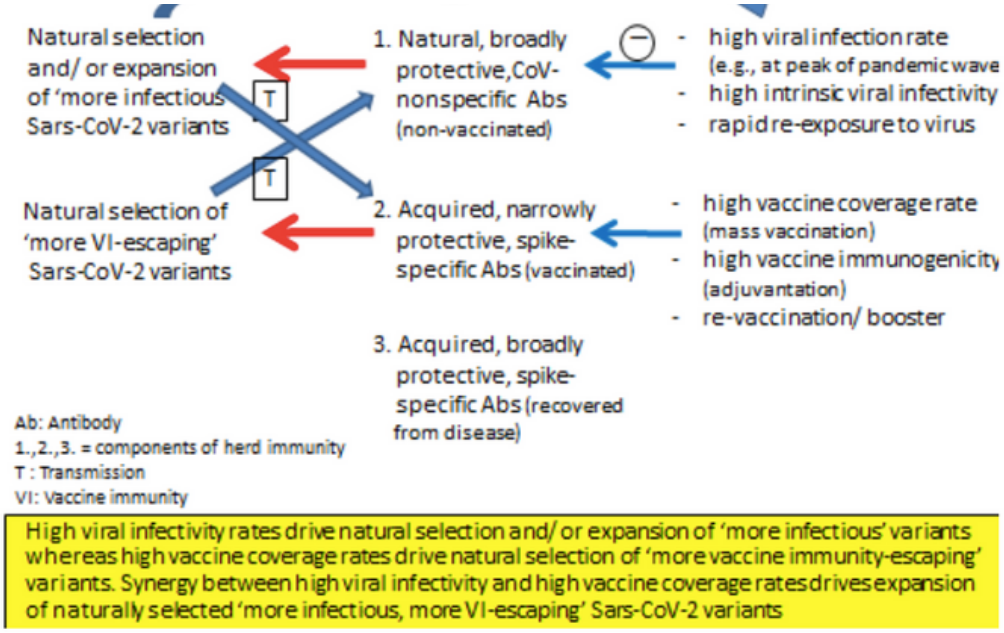
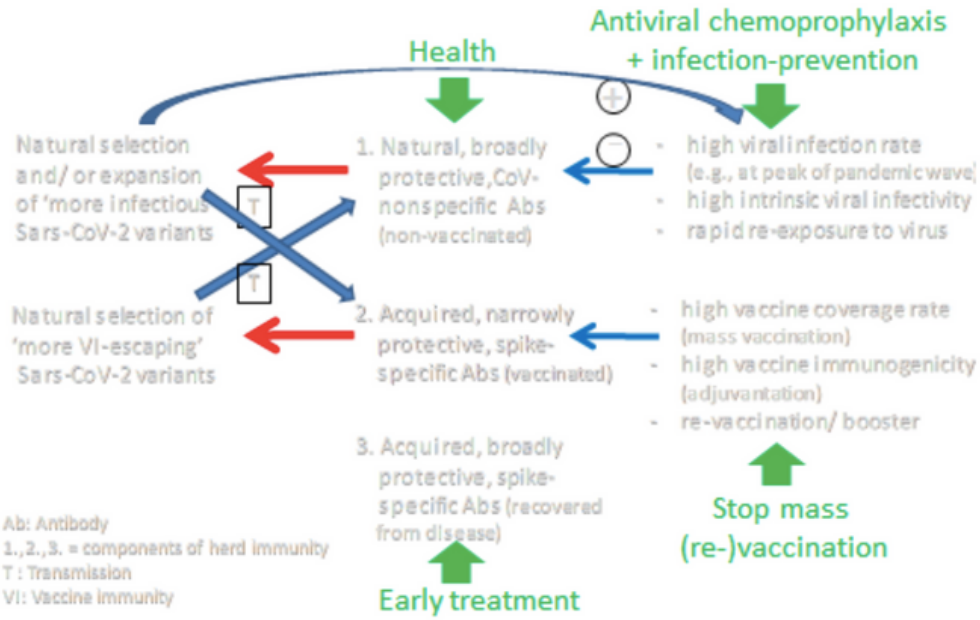


Fig 2: Effect of S(pike)-based Covid-19 vaccines on viral evolution when used for mass vaccination during a Sars-CoV-2 pandemic.



contributes to strengthening broadly protective immunity mediated through acquired, S specific Abs.

(1) Several experts who have stated that currently circulating variants are evolving more 'benign' features have also stated that mass vaccination must stop because vaccine efficiency is diminishing due to immune escape and, therefore, does not justify the administration of vaccines that have a number of safety concerns.

(2) One cannot rule out that large-scale lockdowns and widespread usage of masks could also be responsible for natural selection and propagation of enhanced viral infectiousness. It is, indeed, plausible that lack of exercise coupled with low exposure to environmental stimuli, including microbes and other foreign antigens, could result in poor training of innate immunity and, therefore, diminished availability of mucosal natural B1 Abs at the level of the respiratory mucosae. This might explain the origin of the British (i.e., alpha) variant.

(3) As already mentioned, the increasing number of (mild to moderate) disease cases in young adults is thought to be due to re-infection shortly after their first exposure to the same viral lineage/ varian.

(4) Although S-specific vaccinal Abs may no longer be functional (i.e., unable to neutralize the circulating immune escape variant), they may still be able to outcompete natural Abs when present in high concentration, which typically occurs and perdures after full-fledged vaccine-mediated priming.

(5) It is a myth that asymptomatically infected subjects do not spread the virus. Asymptomatic transmission has even been highlighted as a particular feature of Sars-CoV-2 that fundamentally distinguishes it from Sars-CoV-1 (see references from the literature on my website under topic 2).

(6) Universal means M(ajor)H(istocompatibility)C(omplex)-unrestricted or: not immunogenetically restricted.

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