PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN

## Why mass vaccination amidst a pandemic creates an irrepressible monster

THE key question is: why does nobody seem to bother about viral immune escape? Let me try to explain this by means of a more easily understood phenomenon: *Antimicrobial resistance*. One can easily extrapolate this scourge to resistance to our self-made 'antiviral antibiotics'. Indeed, antibodies (Abs) produced by our own immune system can be considered *self-made antiviral antibiotics*, regardless of whether they are part of our innate immune system (so-called 'natural' Abs') or elicited in response to specific pathogens (resulting in so-called 'acquired' Abs). Natural Abs are not germ-specific whereas acquired Abs are specifically directed at the invading pathogen. At birth, our innate immune system is 'unexperienced' but well-established. It protects us from a multitude of pathogens, thereby preventing these pathogens from causing disease. As the innate immune system cannot remember the pathogens it encountered (innate immunity has no so-called 'immunological memory'), we can only continue to rely on it provided we keep it 'trained' well enough. Training is achieved by regular exposure to a myriad of environmental agents, including pathogens. However, as we age, we will increasingly face situations where our innate immunity (often called 'the first line of immune defense') is not strong enough to halt the pathogen at the portal of entry (mostly mucosal barriers like respiratory or intestinal epithelia). When this happens, the immune system has to rely on more specialized effectors of our immune system (i.e., antigen-specific Abs and T cells) to fight the pathogen. So, as we grow up, we increasingly mount pathogen-*specific* immunity, including highly specific Abs. As those have stronger affinity for the pathogen (e.g., virus) and can reach high concentrations, they can quite easily outcompete our natural Abs for binding to the pathogen/virus. It is precisely this type of highly specific, high affinity Abs that current Covid-19 vaccines are inducing. Of course, the noble purpose of these Abs is to protect us against Covid-19. *So, why then should there be a major concern using these vaccines to fight Covid-19?*

Well, similar to the rules applying to classical antimicrobial antibiotics, it is paramount that our self-made 'antiviral antibiotics' are made available in sufficient concentration and are tailored at the specific features of our enemy. This is why in case of bacterial disease it is critical to not only chose the right type of antibiotic (based on the results from an antibiogram) but to also take the antibiotic for long enough (according to the prescription). Failure to comply with these requirements is at risk of granting microbes a chance to survive and hence, may cause the disease to flare up. A very similar mechanism may also apply to viruses, especially to viruses that can easily and rapidly mutate (which is, for example, the case with Coronaviruses); when the pressure exerted by the army's (read: population's) immune defense starts to threaten viral replication and transmission, the virus will take on another coat so that it can no longer be easily recognized and, therefore, attacked by the host immune system. The virus is now able to escape immunity (so-called: 'immune escape'). However, the virus can only rely on this strategy provided it still has room enough to replicate. Viruses, in contrast to the majority of bacteria, must rely on living host cells to replicate. This is why the occurrence of 'escape mutants' isn't too worrisome as long as the likelihood for these variants to rapidly find another host is quite remote. However, that's not particularly the case during a viral pandemic! During a pandemic, the virus is spreading all over the globe with many subjects shedding and transmitting the virus (even including asymptomatic 'carriers'). The higher the viral load, the higher the likelihood for the virus to bump into subjects who haven't been infected yet or who were infected but didn't develop symptoms. Unless they are sufficiently protected by their innate immune defense (through natural Abs), they will catch Covid-19 disease as they cannot rely on other, i.e., acquired Abs. It has been extensively reported, indeed, that the increase in S (spike)-specific Abs in

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asymptomatically infected people is rather limited and only short-lived. Furthermore, these Abs have not achieved full maturity. The combination of viral infection on a background of suboptimal Ab maturity and concentration enables the virus to select mutations allowing it to escape the immune pressure. The selection of those mutations preferably occurs in the S protein as this is the viral protein that is responsible for viral infectiousness. As the selected mutations endow the virus with increased infectious capacity, it now becomes much easier for the virus to cause severe disease in infected subjects. The more people develop symptomatic disease, the better the virus can secure its propagation and perpetuation (people who get severe disease will shed more virus and for a longer period of time than asymptomatically infected subjects do). Unfortunately enough, the short-lived rise in S-specific Abs does, however, suffice to bypass people's innate/natural Ab. Those are put out of business as their affinity for S is lower than the affinity of S-specific Abs. This is to say that with an increasing rate of infection in the population, the number of subjects who get infected while experiencing a momentary increase in S-specific Abs will steadily increase. Consequently, the number of subjects who get infected while experiencing a momentary decrease in their innate immunity will increase. As a result, a steadily increasing number of subjects will become more susceptible to getting severe disease instead of showing only mild symptoms (i.e., limited to the upper respiratory tract) or no symptoms at all. During a pandemic, especially youngsters will be affected by this evolution as their natural Abs are not yet largely suppressed by a panoply of 'acquired', antigen-specific Abs. Natural Abs, and natural immunity in general, play a critical role in protecting us from pathogens as they constitute our first line of immune defense. In contrast to acquired immunity, innate immune responses protect against a large spectrum of pathogens (so don't compromise or sacrifice your innate immune defense!). Because natural Abs and innate immune cells recognize a diversified spectrum of foreign (i.e., non-self) agents (only some of which have pathogenic potential), it's important, indeed, to keep it sufficiently exposed to environmental challenges. By keeping the innate immune system (which, unfortunately, has no memory!) TRAINED, we can much more easily resist germs which have real pathogenic potential. It has, for example, been reported and scientifically proven that exposure to other, quite harmless Coronaviruses causing a 'common cold ' can provide protection, although short-lived, against Covid-19 and its loyal henchmen (i.e., the more infectious variants).

Suppression of innate immunity, especially in the younger age groups, can, therefore, become very problematic. There can be no doubt that lack of exposure due to stringent containment measures implemented as of the beginning of the pandemic has not been beneficial to keeping people's innate immune system well trained. As if this was not already heavily compromising innate immune defense in this population segment, there comes yet another force into play that will dramatically enhance morbidity and mortality rates in the younger age groups: MASS VACCINATION of the ELDERLY. The more extensively the latter age group will be vaccinated and hence, protected, the more the virus is forced to continue causing disease in younger age groups. This is only going to be possible provided it escapes to the S-specific Abs that are momentarily raised in previously asymptomatically infected subjects. If the virus manages to do so, it can benefit from the (momentarily) suppressed innate immunity, thereby causing disease in an increasing number of these subjects and ensuring its own propagation. Selecting targeted mutations in the S protein is, therefore, the way to go in order for the virus to enhance its infectiousness in candidates that are prone to getting the disease because of a transient weakness of their innate immune defense.

But in the meantime, we're also facing a huge problem in vaccinated people as they're now more and more confronted with infectious variants displaying a type of S protein that is increasingly different from

the S edition comprised within the vaccine (the latter edition originates from the original, much less infectious strain at the beginning of the pandemic). The more variants become infectious (i.e., as a result of blocking access of the virus to the vaccinated segment of the population), the less vaccinal Abs will protect. Already now, lack of protection is leading to viral shedding and transmission in vaccine recipients who are exposed to these more infectious strains (which, by the way, increasingly dominate the field). This is how we are currently turning vaccinees into asymptomatic carriers shedding infectious variants.

At some point, in a likely very near future, it's going to become more profitable (in term of 'return on selection investment') for the virus to just add another few mutations (maybe just one or two) to the S protein of viral variants (already endowed with multiple mutations enhancing infectiousness) in an attempt to further strengthen its binding to the receptor (ACE-2) expressed on the surface of permissive epithelial cells. This will now allow the new variant to outcompete vaccinal Abs for binding to the ACE receptor. This is to say that at this stage, it would only take very few additional targeted mutations within the viral receptor-binding domain to fully resist S-specific anti-Covid-19 Abs, regardless whether the latter are elicited by the vaccine or by natural infection. At that stage, the virus will, indeed, have managed to gain access to a huge reservoir of subjects who have now become highly susceptible to disease as their S-specific Abs have now become useless in terms of protection but still manage to provide for long-lived suppression of their innate immunity (i.e., natural infection, and especially vaccination, elicit relatively long-lived specific Ab titers). The susceptible reservoir comprises both, vaccinated people and those who're left with sufficient S-specific Abs due to previous Covid-19 disease). So, MISSION ACCOMPLISHED for Covid-19 but a DISASTROUS SITUATION for all vaccinated subjects and Covid-19 seropositive people as they've now lost both, their acquired and innate immune defense against Covid-19 (while highly infectious strains are circulating!). That's '*one small step for the virus, one giant catastrophe for mankind*', which is to say that we'll have whipped up the virus in the younger population up to a level that it now takes little effort for Covid-19 to transform into a highly infectious virus that completely ignores both the innate arm of our immune system as well as the adaptive/acquired one (regardless of whether the acquired Abs resulted from vaccination or natural infection). The effort for the virus is now becoming even more negligible given that many vaccine recipients are now exposed to highly infectious viral variants while having received only a single shot of the vaccine. Hence, they are endowed with Abs that have not yet acquired optimal functionality. There is no need to explain that this is just going to further enhance immune escape. Basically, we'll very soon be confronted with a super-infectious virus that completely resists our most precious defense mechanism: The human immune system.

From all of the above, it's becoming increasingly difficult to imagine how the consequences of the extensive and erroneous human intervention in this pandemic are not going to wipe out large parts of our human population. One could only think of very few other strategies to achieve the same level of efficiency in turning a relatively harmless virus into a bioweapon of mass destruction.

It's certainly also worth mentioning that mutations in the S protein (i.e., exactly the same protein that is subject to selection of escape mutations) are known to enable Coronaviruses to cross species barriers. This is to say that the risk that vaccine-mediated immune escape could allow the virus to jump to other animal species, especially industrial livestock (e.g., pig and poultry farms), is not negligible. These species are already known to host several different Coronaviruses and are usually housed in farms with high stocking density. Similar to the situation with influenza virus, these species could than serve as an

additional reservoir for SARS-COVID-2 virus.

As pathogens have co-evolved with the host immune system, natural pandemics of acute self-limiting viral infections have been shaped such as to take a toll on human lives that is not higher than strictly required. Due to human intervention, the course of this pandemic has been thoroughly disturbed as of the very beginning. Widespread and stringent infection prevention measures combined with mass vaccination campaigns using inadequate vaccines will undoubtedly lead to a situation where the pandemic is getting increasingly 'out of control'.

Paradoxically, the only intervention that could offer a perspective to end this pandemic (other than to let it run its disastrous course) is …VACCINATION. Of course, the type of vaccines to be used would be completely different from conventional vaccines in that they're not inducing the usual suspects, i.e., B and T cells, but NK cells. There is, indeed, compelling scientific evidence that these cells play a key role in facilitating complete elimination of Covid-19 at an early stage of infection in asymptomatically infected subjects. NK cells are part of the cellular arm of our innate immune system and, alike natural Abs, they are capable of recognizing and attacking a broad and diversified spectrum of pathogenic agents. There is a sound scientific rationale to assume that it is possible to 'prime' NK cells in ways for them to recognize and kill Coronaviruses at large (include all their variants) at an early stage of infection. NK cells have increasingly been described to be endowed with the capacity to acquire immunological memory. By educating these cells in ways that enable them to durably recognize and target Coronavirus-infected cells, our immune system could be perfectly armed for a targeted attack to the universe of Coronaviruses prior to exposure. As NK cell-based immune defense provides sterilizing immunity and allows for broad-spectrum and fast protection, it is reasonable to assume that harnessing our innate immune cells is going to be the only type of human intervention left to halt the dangerous spread of highly infectious Covid-19 variants.

If we, human beings, are committed to perpetuating our species, we have no choice left but to eradicate these highly infectious viral variants. This will, indeed, require large vaccination campaigns. However, NK cell-based vaccines will primarily enable our *natural immunity* to be better prepared (memory!) and to induce herd immunity (which is exactly the opposite of what current Covid-19 vaccines do as those increasingly turn vaccine recipients into asymptomatic carriers who are shedding virus). So, there is not one second left for gears to be switched and to replace the current killer vaccines by life-saving vaccines.

I am appealing to the WHO and all stakeholders involved, no matter their conviction, to immediately declare such action as THE SINGLE MOST IMPORTANT PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN.

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