Covid-19 Vaccination Policy Risk FAQ

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01: Why is enhanced infectiousness of variants in its own right a reason for concern? How does mass vaccination impact this concern?

Enhanced infectiousness augments viral infectious pressure and hence, the likelihood for previously asymptomatically infected (PAI) subjects to become re-infected at a time where their natural, CoV-nonspecific antibodies (Abs) are suppressed by suboptimal and short-lived S-specific Abs. This makes PAI subjects more susceptible to Covid-19 disease and, therefore, leads to increased morbidity and mortality rates in this group.

Mass vaccination campaigns (first targeting vulnerable people) will reduce infectious pressure and, therefore, reduce morbidity and mortality rates in vulnerable but also in PAI subjects. The more aggressively mass vaccination progresses, the more obvious the number of cases will decline. As previously explained (see contribution: 'Unravelling the complexity of Covid-19 vaccination shaped by mass vaccination'), this beneficial effect will wane quite rapidly and increasingly be countered by enhanced circulation of S-directed viral immune escape variants. As the latter are more infectious, they will rapidly dominate. As a result, viral infectious pressure will increase even more rapidly and at a higher level, thereby rendering younger and younger age groups more susceptible to Covid-19 disease. However, with rising vaccination coverage rates, more younger age groups will become protected against severe disease and hence, further augment immune pressure on viral infectiousness. This will lead to selection of mutations that increasingly converge to regions within the S protein that are capable of resisting vaccinal Abs. A the same time, rising vaccination rates will expand the breeding ground for Sars-CoV-2 variants harboring such mutations and thereby

enhance their adaptation. This evolution will ultimately result in dominant propagation of vaccine-resistant variants. It goes without saying that those pose vaccinees at a high risk of contracting severe Covid-19 disease. Enhanced circulation of more infectious variants diminishes the impact of public health and social measures whereas dominance of vaccine-resistant variants will render these measures again more effective for viral transmission will now primarily be caused by vaccinees who contract Covid-19 illness.

02: In several countries the number of cases are going down. Vaccination rates are going up and vaccinated people are less likely to spread the virus. So, only the spread of the more infectious variants is worrisome, in particular of the Indian variant (B.1.6.1.7.2.). Is it critical that its level of infectiousness be determined asap as control of the pandemic is now going to depend on who is faster, the virus or the vaccine?

The conclusion is desperately wrong. First, a decline in cases is only going to promote breeding of more infectious immune escape variants in asymptomatically infected persons.

It is true that vaccination reduces the level of viral shedding in vulnerable people who get infected and, therefore, diminishes viral infectious pressure. This will result in a decline in the morbidity rate, not only in this group, though, but also in a substantial amount of previously asymptomatically infected subjects. This is to say that the reservoir of asymptomatic transmission is now growing compared to the situation generated by a natural pandemic. In case of the latter, a substantial amount of these subjects would have contracted the disease upon re-exposure as a result of the relatively higher level of infectious pressure. Consequently, mass vaccination makes the virus more frequently encounter suboptimal S-directed immune pressure that it is no longer capable of breaking through. As mass vaccination advances, more and more subjects will enable some level of viral shedding on a background of suboptimal immune pressure but without further diminishing viral infectious pressure (as fewer and fewer of the vaccinees will be naturally vulnerable to Covid-19 disease). Expansion of the reservoir of asymptomatic spreaders exhibiting suboptimal S-directed immune pressure will promote training of more

infectious immune escape variants. The more vaccination, the larger the breeding ground for these variants will grow. As a result, these variants will adapt and propagate more rapidly. This will become even more obvious when large cohorts of younger and younger age groups will soon be enrolled in the mass vaccination program. The earlier-mentioned evolution and dynamics already explain why the debate surrounding the level of infectiousness of the Indian variant isn't really relevant: any 'more infectious' variant that – as a result of inclining vaccine coverage rates – will experience more S-directed immune pressure will rapidly grow its infectiousness, no matter the level thereof at a given point in time. It will not stop growing its infectiousness before it has evolved to resisting vaccinal antibodies (of increasing affinity).

The evolution of the dynamics described above should rather be monitored by measuring viral shedding and performing viral characterization (e.g., via sequencing) in healthy people, regardless of whether they have been vaccinated or not. The more vaccination rates grow, the more important it becomes to monitor viral transmission and evolution in vaccinees. Unfortunately, it is exactly this type of data that are now increasingly missing.

03: As Sars-CoV-2 variants exhibit a high level of sequence homology with the original Wuhan strain, is there indeed no reason to believe that mass vaccination (using S protein from the wild strain) could enable selection and adaptation of immune escape variants? (according to M. Yeadon's theory)

This is wrong as only very few mutations in the spike (S) protein suffice to enable Sars-CoV-2 to escape suboptimal S-directed immune pressure. S-directed immune pressure is exerted by vaccinees who have not yet mounted a full-fledged immune response or in previously asymptomatically infected persons whose infection did not result in memory B cell priming. As mass vaccination campaigns are first targeting vulnerable subjects (e.g., elderly, subjects with underlying or immunocompromising conditions or at high risk of viral exposure), viral transmission will increasingly occur among vaccinees and non-vaccinated, asymptomatically infected persons. Suboptimal S-directed immune pressure provides a competitive advantage to spontaneously emerging variants of which the S protein carries one or more mutations that

enable stronger binding to the receptor-binding domain (RBD) of susceptible epithelial cells. Stronger binding of S to the receptor-binding domain (RBD) translates into higher viral infectiousness. Consequently, when there is an opportunity for the virus to regularly encounter suboptimal S-directed immune pressure, as is typically the case when people are mass-vaccinated in the heat of a pandemic, immune escape variants with enhanced infectiousness will be selected and reproduce more effectively. Even though many epitopes, especially also T cell epitopes, are conserved and shared amongst Sars-CoV-2 wild type and its variants, immune responses against these epitopes do not intervene in preventing early viral infection and replication. They intervene at a later stage of infection as they require these epitopes to first recall cytolytic memory T cells that have previously been primed as a result of vaccination. In addition, there is no evidence that any of the current vaccines induces a cytolytic T cell response across a genetically diversified MHC class I background. Even if M. Yeadon's theory were to relate to natural infection, MHC class I-restricted cytolytic T cells would only be capable to control viral infection (i.e., by killing virus-infected target cells) at a later stage of infection (as it takes time to prime these T cells). In none of these cases, therefore, will cytolytic T cells be capable of preventing S-directed immune escape variants from being selected and enjoying a competitive advantage under the conditions described above. These cells play, however, an important role in controlling the infection in people who got the disease and thereby contribute to their recovery. Because adaptive cell-mediated immune responses do not appear before the infected person has been able to eventually transmit the virus, selective pressure on T cell-based immunity also has much less impact on the evolution of the virus.

04: Why does the mantra that 'higher vaccination rates more dramatically reduce viral replication and thus the incidence of disease and occurrence of emergent variants' not apply to this pandemic?

A pandemic is featured by the introduction of a new virus into a naïve (i.e., previously nonexposed) human population. Mass vaccination usually starts in the elderly or otherwise vulnerable people. This will reduce the infection rate in the population due to the induction of anti-S antibodies which protect these

people from disease. In the meantime, non-vulnerable people (e.g., children, youngsters in good health) will be protected by virtue of innate immune mechanisms (i.e., natural antibodies and natural killer cells) and only develop short-lived anti-S antibodies of low affinity (there is, indeed, no evidence of generation of memory B cells in asymptomatically infected individuals).

During a natural pandemic, the infectious pressure generated by the vulnerable part of the population mounts to a level high enough to ensure re-exposure of a substantial amount of asymptomatically infected subjects. These subjects now become susceptible to Covid-19 disease because of suppression of their natural antibodies by suboptimal anti-S antibodies (the latter are no longer detectable after ca 8 weeks). However, any measure capable of diminishing the infectious pressure in the population, be it by means of mass vaccination of the elderly and/ or implementation of stringent infection prevention measures, will prevent Sars-CoV-2 from breaking through the innate immune defense of previously asymptomatically infected people (as their re-exposure is increasingly unlikely to occur shortly after their primary infection); instead, a substantial number of these subjects will now become re-exposed to Sars-CoV-2 on a background of suboptimal anti-S antibodies without developing the disease. This is to say that mass vaccination will ultimately enable the virus to adapt to suboptimal S-directed immune pressure exerted by previously asymptomatically infected people. This broadly exerted selective immune pressure on viral transmissibility will enable more infectious Sars-CoV-2 variants to become dominant. The more people get vaccinated, the more young and healthy or otherwise non-susceptible people will be turned into (potential) asymptomatic carriers, thereby enabling more infectious variants to reproduce more effectively. When mass vaccination campaigns are extended to younger age groups, more and more subjects who - upon natural infection - would normally shed virus for only a short period of time will now contribute to expanding this breeding ground. This is likely due to the time needed for vaccinees to mount a full-fledged immune response and the potential mismatch between the S protein of the vaccine and that of the circulating variant. As mass vaccination increasingly includes younger people, the impact thereof on reducing the infectious pressure in the population will diminish. This is because the impact of their vaccination on the number of prevented cases of disease is much less pronounced. Instead, enhanced

vaccination rates will raise the S-directed immune pressure in that it will gradually shift to targeting the receptor-binding domain (RBD) of the virus, thereby resulting in more efficient reproduction and propagation of vaccine-resistant immune escape variants.

Conclusion: As increasing vaccination rates will result in a gradually expanding reservoir of asymptomatic viral spreaders, the benefit of reduced disease and hence, reduced viral shedding in vaccinated elderly (or otherwise vulnerable subjects) will be countered by enhanced spread and breeding of more infectious variants in the less vulnerable part of the population. The higher the vaccination rate, the more the latter effect will outweigh the benefit of vaccine-mediated reduction of immune pressure exerted by the vulnerable part of the population. Concomitant implementation of stringent infection prevention measures will merely delay but not prevent the vaccine-mediated impact of diminished Covid-19 morbidity rates in the elderly (or otherwise vulnerable subjects) on the evolution of the virus in younger and healthy subjects. The more younger and healthy age groups will be enrolled in these mass vaccination campaigns, the faster the predominantly circulating Sars-CoV-2 will evolve to more infectious, and ultimately vaccine-resistant variants.

05: How do you explain that mass vaccination combined with stringent public health measures will not be effective in mitigating the course of the ongoing Covid-19 pandemic?

I know, this sounds, indeed, very counterintuitive as both infection prevention measures and mass vaccination diminish viral load!

Let’s first consider the situation in countries which are currently witnessing fairly low infection rates (e.g., Israel, UK, Portugal,…). After a fulminant wave of infection and disease, the viral infection pressure in these countries is now too low in order for the virus to break through the innate immune defense of previously asymptomatically infected people (currently, the main reservoir of viral transmission). As explained before, this is because of the low likelihood for these subjects to become re-exposed to the virus shortly after their previous natural infection, i.e., during a period of strong suppression of their

natural antibodies (Abs) by S-specific Abs acquired as a result from said natural infection. However, post-infection S(pike)-specific Abs in previously asymptomatically infected individuals will exert suboptimal immune pressure on viral infectiousness (as the latter is S-dependent). Provided sufficient viral infection pressure and a sufficient number of subjects experiencing suboptimal, S-directed immune pressure, viral variants capable of escaping this suboptimal immune response will be selected and trained to reproduce more effectively. This will drive propagation of S Ab-resistant viral variants. One could legitimately argue that stringent infection prevention measures on a background of low infectious pressure could further reduce viral infectivity rates down to a level that renders re-exposure frequency in previously asymptomatically infected subjects low enough to only cause sporadic cases of disease and considerably diminish the likelihood for S-directed immune escape variants to become dominant. Of course, this would assume adherence to stringent infection prevention measures across all of the population.

However, combination with mass vaccination is going to revert the impact of stringent infection prevention measures in countries that are conducting mass vaccination campaigns on a background of low infectious pressure. This is because mass vaccination will lead to a substantial increase of subjects endowed with suboptimal S-specific Abs (e.g., due to a not yet fully completed vaccination schedule, incomplete maturation of nascent Abs and/ or exposure to dominant more infectious variants that were responsible for the previous surge in cases and the antigenic features of which are different from the vaccinal S protein). Consequently, the further decrease in infectious pressure mediated by stringent infection prevention measures will be counterbalanced by a higher frequency of encounters between the virus and subjects displaying suboptimal S-directed immune pressure. This will particularly apply if public health measures are relaxed for vaccinees (cfr. Covid passports/ green certificates etc.!) despite their capacity to serve as asymptomatic viral spreaders. This is to say that in countries currently experiencing low infectivity rates, stringent infection prevention measures will become increasingly ineffective as vaccine coverage rates will further increase. Ultimately, evolutionary dynamics will enable variants that are naturally selected for mutations capable of resisting S-specific Abs to become predominant. The

higher the vaccine coverage rate, the more viral resistance will include coverage of RBD-targeted Abs. This will eventually lead to a dramatic resurgence of cases. Moreover, as higher vaccine coverage rates imply higher vaccination rates in younger age groups, viral resistance will now also lead to more cases of severe disease in these age groups. It is unlikely that new vaccines that better match the S-directed mutations in more infectious variants are going to solve the issue of immune escape as they will primarily recall previously primed S-specific B memory cells due to the 'antigenic sin' effect. As this will result in a rapid Ab response directed against the S protein of the original wild strain, the recall effect will only amplify the mismatch between vaccinal Abs and circulating variants, the S protein of which will now have evolved new/ additional escape mutations within the receptor-binding domain (RBD).

Let's now consider the situation in countries in which the course of the Covid-19 pandemic is featured by a rather high to very high infectious pressure (e.g., the Americas, most European countries, Iraq, Iran, Turkey, Brazil, India, Kazakhstan, Mongolia, ...). Unless stringent infection prevention measures (i.e., lockdowns) are implemented, chances for preventing highly infectious variants (which are the cause of the high rate of infectivity in most of these countries) from abundantly spreading across the population are slim. Mass vaccination campaigns conducted on a background of high infectivity rates will dramatically increase the likelihood of previously asymptomatically infected subjects to get re-exposed to the virus shortly after previous natural infection (i.e. at a point in time where their natural CoV-nonspecific Abs are most suppressed). As their natural Abs will now more likely be outcompeted by suboptimal S-specific Abs for binding to the virus, the chances for these subjects to become susceptible to Covid-19 disease augment as well (as the more infectious variants are now more likely to break through their natural line of immune defense). Enhanced susceptibility to disease will, in turn, further promote spread of the more infectious circulating variants. So, once again, rising vaccine coverage rates will only lead to diminished effectiveness of infection prevention measures and cause plateaus of morbidity and mortality to stay at a relatively high level (i.e., higher than that of previous plateaus observed in-between previous waves) for a prolonged period of time. Again,

the more vaccination campaigns will include younger age groups, the higher will be the fraction of these age groups that will contract severe disease.

Conclusion: Countries which perform mass vaccination campaigns on a background of low infectivity rates will soon begin to see viral resistance to the current vaccines due to natural selection of S-Ab-resistant immune escape variants in asymptomatically infected vaccinees whereas countries performing mass vaccination campaigns on a background of rather high infectivity rates will face enhanced susceptibility/ vulnerability of previously asymptomatically infected age groups due to widespread suppression of innate, CoV-nonspecific immunity in these (younger!) age groups. Both situations are clearly at risk of taking a dramatic toll on human lives and causing health systems to collapse.

06: You suggest that the effect of vaccine-mediated immune escape could/can already be seen in a number of countries although their vaccine coverage rates are still fairly low. How do you explain?

As mentioned in my video lectures, some countries have already been witnessing a resurgence of cases within one to two months after they had brought the rollout of their Covid-19 vaccination campaign up to speed. Except for a few countries that have started rollout at the summit of an important peak of infection (e.g., UK, Israel, Portugal, ...), many countries have, indeed, seen a substantial increase in the number of cases after initiation of mass vaccination campaigns and this despite continued infection prevention measures. Even though one may argue that vaccine coverage rates between 5 and 10% do not suffice to substantially reduce the number of cases or morbidity and mortality rates, it remains difficult to understand why increasing vaccine coverage has been associated with a resurgence of cases in many countries, especially since the most vulnerable groups have been vaccinated first. Even countries with infection rates that had been quite stable over a prolonged period of time (e.g., Belgium) suddenly started to witness a substantial increase in cases about one month after the vaccine coverage rate had reached a level of about 5% (single dose of 2-dose vaccine). So, could

this already point to enhanced spread of more infectious immune escape variants?

First, it cannot be denied that during rollout of mass vaccination campaigns, several countries have been struggling with newly introduced infectious variants (e.g., UK variant) that were suddenly detected and may have been responsible for a surge in their number of cases. It seems plausible, though, that suboptimal S-directed immune pressure in vaccinees provides a competitive advantage to more infectious strains and, therefore, enhances their dominance and spread in the population. In this regard, mass vaccination may enhance circulation and hence, transmission of new, more infectious variants, thereby expediting the development of a new wave of infection and suddenly causing an important increase in morbidity and mortality rates. However, it is important to realize that even relatively low rates of vaccination with vaccines that are unable to stop transmission could lead to enhanced fitness and dominance of (spontaneously) emerging, more infectious immune escape variants. Whereas it has been postulated that high vaccine coverage rates (up to 70-80%) are required to generate (adaptive!) herd immunity against Covid-19, there is no threshold for vaccine coverage rates to promote 'training' of more infectious immune escape variants. Why? Mass vaccination campaigns initially target the elderly and people at risk and hence, even small vaccine coverage rates will already turn a fairly substantial percentage of *vulnerable* subjects in potential asymptomatic carriers. As asymptomatically infected people provide a breeding ground for more infectious immune escape variants to raise their fitness (as they are frequently subject to suboptimal S-targeted immune pressure in this population), every single vaccination contributes to strengthening this breeding ground. It's also important to realize that – as long as vaccines protect against *disease* - vaccination of vulnerable people does not only turn them into potential targets for asymptomatic infection but - at the same time - reduces the number of subjects endowed with an immune status the virus can easily (i.e., without experiencing any immune pressure) break through. This is to say that the effect of increasing vaccine coverage rates is much more dramatic in terms of enhancing adaptation of selected, more infectious Sars-CoV-2 variants than in terms of their contribution to achieving the putative threshold for (adaptive) herd immunity. As enhanced circulation of immune escape variants will only raise

the threshold required for vaccine coverage rates to achieve (adaptive) herd immunity, it is reasonable to conclude that vaccine coverage rates achieved as a result from mass vaccination campaigns using the current vaccines will never be high enough for the population to *acquire* herd immunity.

07: The number of Covid-19 cases in India is currently exploding. This cannot be due to the effect of mass vaccination as the overall vaccination rate in India is still relatively low, correct?

This is true. It's important to understand that besides mass vaccination campaigns (using current vaccines in the midst of a pandemic) there are other interventions or influences that may give rise to viral immune escape during a Covid-19 pandemic!

Any situation that is prone to generating suboptimal S-directed immune pressure in a substantial part of the population is likely to promote selection and adaptation of variants that are featured by one or more mutations enabling higher viral infectiousness. Because vaccinees are frequently subject to suboptimal S-directed immune pressure, they will serve as a key target population for more infectious variants that may ultimately become resistant to S-targeted and hence, to vaccinal Abs. However, nonvaccinated asymptomatically infected people are also frequently subject to suboptimal S-directed immune pressure and can, therefore, serve as a breeding ground for more infectious and ultimately anti-S Ab -resistant variants. In areas where housing and hygienic conditions comply with good health standards, implementation of stringent infection prevention measures (including isolation of Covid-19-diseased patients) can dramatically diminish viral infectious pressure. However, provided mutual contacts are frequent enough, asymptomatically infected subjects will still serve as a source of continued viral transmission. In this population, virus replication and transmission will occur on a background of suboptimal S-directed immune pressure. Due to the relatively low infectivity rate in the population (infection prevention measures!), suppression of natural, CoV-nonspecific antibodies (Abs) will not usually suffice to cause severe disease in these subjects but is likely to promote selection and adaptation of more infectious variants. So, stringent infection prevention measures may promote enhanced circulation of more infectious

Sars-CoV-2 variants. It is reasonable to assume that preventing contact between the younger and older generation will expedite fitness and hence, dominance of more infectious variants.

In contrast, in areas where housing and hygienic conditions are poor (e.g., featured by overcrowding and poor sanitary conditions as in favelas [e.g., in Manaus, Brazil] or slums [in Mumbai, India]), the virus can spread quite easily and rapidly infect an extensive part of the population living in such conditions. This significantly increases the likelihood that a substantial percentage of the population becomes asymptomatically infected and that a significant proportion of previously asymptomatically infected subjects become re-infected by the virus shortly after their previous exposure, i.e., at a point in time at which their suboptimal S-directed Abs are still quite high. In case such previously asymptomatically infected subjects possess a level of innate CoV-nonspecific Abs that is still high enough to not succumb to the disease, their S-directed antibodies will exert strong immune pressure on the viral spike protein. This is likely to promote selection and adaptation of even more infectious variants in that mutations may be selected (e.g., in RBD domain) that prevent S-directed antibodies from outcompeting ACE-2 receptors for binding to Sars-CoV-2, thereby resulting in resistance of the virus to anti-S Abs. So, lack of prevention infection measures would dramatically enhance evolution of the virus towards variants that exhibit a level of infectiousness that is high enough to completely overcome binding of S-targeted Abs, especially if the latter are not of high affinity. It is reasonable to assume that the lower the average age of the population, the faster resistant variants will become fit enough to dominate other, less infectious viral variants.

In both cases described above, selective immune escape can occur in the absence of mass vaccination campaigns (with vaccines failing to block transmission). However, as mass vaccination further contributes to generating suboptimal S-directed immune pressure in vast parts of the population, there can be no doubt that these campaigns are ultimately going to cause huge waves of disease, comparable to the one currently ongoing in India. As the current vaccines are primarily targeted at the RBD within the spike protein, the immune pressure exerted will ultimately lead to the selection and adaptation

of viral variants that are even more infectious as they will ultimately succeed in overcoming binding of vaccinal Abs to the RBD of S.

One cannot imagine how mass vaccination on a background of circulating double or triple mutants is not going to lead to an even more dramatic wave of morbidity and mortality in India.

08: In countries that have now vaccinated most of the older generation, Covid-19 surges are increasingly observed in younger people. It makes sense, therefore, to vaccinate our youngsters as soon as possible, doesn't it?

This conclusion is completely wrong! I explained multiple times (see several contributions on my website) that the enhanced susceptibility of youngsters (who were protected during the previous wave(s)!) results from the combined effect of enhanced infection rates (e.g., as a result of important viral shedding by subjects who contracted the disease in previous waves and - more recently - also due to circulation of more infectious variants!) and suppression of variant-nonspecific, natural antibodies in these previously asymptomatically infected youngsters (as suboptimal post-infection anti-S Abs outcompete natural, CoV-nonspecific natural Abs). In order to avoid suppression of these natural Abs while increasingly being exposed to higher infectious pressure (because of circulation of more infectious variants), it has now become critical for youngsters to become or remain seronegative for S-specific Abs. This will enable their natural CoV-nonspecific Abs to deal with any kind of Sars-CoV-2 variant and even with other coronaviruses (CoV). As a sufficiently reliable serologic self-test is currently not commercially available, it is paramount for young people, but even for older people (e.g., < 65 y) who are in good health, to avoid re-exposure to the virus. This is because they may still have (suboptimal) S-specific Abs as a result of previous exposure. Upon re-infection, the level of these Abs might still be high enough to sufficiently suppress their innate immunity to cause (severe) disease. Since it is highly likely that we will be witnessing a decrease in vaccine efficacy as viral variants further evolve (which they will definitely do), there is a high risk that vaccinees will no longer be protected by their vaccinal S-specific Abs while the latter will

still be able to bind to the spike protein and hence, outcompete (at least to an important extent) their natural Abs. This would be particularly detrimental to children and young people in good health as they possess high(er) levels of these natural Abs that protect them against all Sars-CoV-2 variants.

09: Isn't it so that vaccines work, as we now see declining waves of infection and disease in several countries ramping up their mass vaccination campaigns?

As I previously explained in several of my lectures posted on the website, those declines are not to be considered an effect of the vaccination campaigns. Clearly, in the UK and Israel, the steep decline in cases could not be due to mass vaccination as a spectacular decrease in cases was already observed within a few weeks of vaccination and at a point in time where vaccination rates were still very low (e.g., in the UK, between 2 and 10% had only received a single dose over the course where a steep decline in cases was observed). Regardless of the percentage of vaccine coverage, a steep and substantial incline in cases will always be followed by a quite impressive decline down to a plateau that is situated at a higher level than the one observed after the previous wave (see for example the evolution of curves in Ukraïne, Hungary, Uruguay and soon also in India). As previously explained, the quite impressive decline in infection rates in those countries is due to the fact that people who developed the disease and survived are increasingly protected by S-specific Abs whereas those who didn’t still disposed of levels of functional natural Abs that were high enough to resist the disease. Due to their high level of acquired or innate immunity, these groups are able to control viral replication well enough to substantially reduce viral shedding and hence, viral spread and infectivity in the population. It’s merely because the vaccination campaigns in countries such as Israel and the UK coincided with a peak of infection that the subsequent decline in the number of cases is erroneously interpreted (by some) as a direct result of vaccination.

10: Does the Wuhan study prove that asymptomatically infected subjects are not a source of viral transmission?

The Wuhan study is often interpreted as an illustration of lack of viral shedding by asymptomatically infected people. However, one should bear in mind that this study was not set up to demonstrate the likelihood of viral transmission by asymptomatic cases but rather to assess the risk of Covid-19 cases in post-lockdown Wuhan. In addition, studies targeted at investigating infectious shedding and transmission should investigate shedding of viable virus as tested by viral infectivity assays and not by the occurrence of positive nucleic acid tests. Furthermore, the current publication reports about a cross-sectional screening study and hence, does not provide any information about the chronologic sequence of the infection chains. Consequently, there is no evidence that said asymptomatic positive cases got infected before their close contacts. In fact, the 1174 close contacts may have been the ones who were infected first but had already eliminated the virus and turned negative in the RT-PCR test by the time the screening study identified 300 asymptomatic positive cases as confirmed by said RT-PCR test. Given the short duration of viral shedding in asymptomatically infect subjects, it would not be unusual for subjects to test negative in a nucleic acid screening test at a cross-sectional point in time where some of the subjects to whom they transmitted the virus are still PCR-positive and possibly also seropositive (as was the case in 63.3% of asymptomatic positive cases).

Consequently, this study does not allow to conclude that asymptomatic positive cases are unlikely to be infectious and to serve as a source of transmission to close contacts. Although asymptomatic infected persons generally have low quantity of viral loads and a short duration of viral shedding when compared with symptomatic subjects, they can definitely serve as viral spreaders, not a least because they are asymptomatic (see - amongst others - supportive references from the literature: topic 2). Along the above lines of reasoning, it seems logical that the frequency of asymptomatic positive cases in this study correlated with the prevalence of previously infected confirmed cases. This is to say that the higher the infectious pressure, the higher the likelihood that positive cases of asymptomatic infection will still be detectable even up till a later post-lockdown timepoint.

11: If antigen-specific antibodies (Abs) suppress natural Abs, shouldn't vaccines other than Covid-19 vaccines suppress those as well?

No, in order for a vaccine to suppress the interaction of natural Abs with SARS-CoV-2 (including all its variants), it should induce Abs that bind to SARS-CoV-2. It is true that any vaccine that elicits Abs that are capable of binding to SARS-CoV-2 could serve a role of innate immune suppressor. Hence, even Abs that are specifically directed to a particular coronavirus causing the common cold could lead to suppression of CoV-nonspecific natural Abs as they may also be able to bind (but not neutralize!) other coronaviruses such as SARS-CoV-2 and all its variants. However, vaccinal Abs induced by vaccines that are not directed at a particular coronavirus will not compete with CoV-nonspecific natural Abs for binding to SARS-CoV-2.

12: Could more infectious variants cause more severe disease?

This is correct but not to be considered as a direct effect of altered intrinsic properties of the virus: when a more infectious variant becomes the dominant circulating strain, the degree of viral infectivity in the population will increase. As a result, the likelihood that a previously asymptomatically infected person will be re-exposed to the virus at a point in time where the level of suppression of his/ her natural CoV-nonspecific natural Abs by suboptimal (and hence, devoid of neutralizing activity) anti-S Abs is still significant will increase. Depending on the level of suppression of their natural Abs, some of these subjects (mostly younger age groups) may become highly susceptible to Covid-19 disease. Consequently, their likelihood of developing severe disease is not a direct consequence of the enhanced infectiousness of viral variants but results from the innate immune suppression that is more likely to occur in a number of subjects as a result of enhanced viral spread caused by the predominant circulation of such more infectious variants.

However, it has already been reported that more infectious variants may be endowed with additional mutations (i.e., other than those responsible for enhanced infectiousness). Some of these mutations are located in gene sequences that code for proteins other than S protein and are thought to be

responsible for a higher level of viral replication, thereby possibly causing a higher level of virulence.

Conclusively, higher infectiousness is not per se associated with a higher level of viral virulence.

13: How can it be explained that in Israel it seems that the massive vaccination has almost stopped the pandemic and no dramatic effects are being observed over people that have been vaccinated?

It's just a matter of weeks for a surge in Israel to occur due to resistance of the virus to vaccinal antibodies in vaccinees. I expect this surge to occur before summer.

14: How should the broader public be able to make a judgment by lack of an open scientific debate?

The truth about all this will soon come out. However, as I repeated on several occasions, this is not a matter of experts being wrong or right but a matter of making the science behind an extremely complex phenomenon accessible to the people who are told to get the current vaccine. As there is no public debate about this and as mass vaccination proponents refuse to address fundamental questions about the underlying population dynamics of the infection and the influence thereon of massive human intervention, chances are slim for the broader public to be able to make a sound judgment. I feel like this is simply a moral obligation but I am certainly not naïve in that I don't think that efforts of myself and others will suffice to stop this nonsense before the truth will become obvious to all… By then, all action may come much too late.

15: What are your expectations right now based on what you see in Israel and USA on the one hand and India, Ukraine and other countries on the other?

All these populations will ultimately evolve towards resistance to the vaccine. Some populations like the UK and Israel are currently breeding resistant strains in asymptomatic people (so increasingly in vaccinees as vaccine coverage rates in these countries are quite high already) on a background of low infectivity (reduced number of new infections). I am saying this because the low infection pressure in the population will promote adaptation of variants with enhanced infectiousness. However, in order for the virus to acquire a much higher level of infectiousness in vaccinated people, it has to completely overcome the pressure placed by vaccinal Abs. As its spread has been dramatically reduced due to high vaccine coverage rates, this has now become a condition sine qua non for the virus to ensure sufficient propagation.

In countries where the level of infectivity is still quite high (e.g., USA), the virus will most likely evolve to resistance using one or more intermediary steps of enhanced infectiousness before full resistance to the vaccine will occur. This is to say that I first expect one or more even more infectious variant(s) to emerge and adapt and to cause more or less important wave(s) of infection and disease. The steeper and more important these waves, the more impressive their decline will be and the (relatively) lower plateau they will reach (e.g., Ukraïne, Hungary, Uruguay, India as compared to USA, France, Chile, Brazil etc).

16: What is going on in India? Why is the pandemic there so aggressive although they haven't been vaccinated - so according to your explanation the natural immune system should have been able to fight the virus and its mutants due to its non-specific character?

I presume that there has been massive spread of the virus amongst asymptomatically infected people. I am quite sure that the vast majority of these asymptomatic infections went unnoticed. Asymptomatic infections fuel spread of more infectious Sars-CoV-2 variants (see my related lecture on the website) due to increasingly frequent re-exposure of previously infected subjects experiencing suppression of their natural antibodies as a result of suboptimal S-specific antibodies (Abs). The more widespread the immune

pressure, the more likely the selection of immune escape variants is going to promote their enhanced infectiousness. The most effective way for the virus to replicate in the presence of widespread immune pressure on the spike (S) protein is to overcome the effect of antibodies targeted at S protein. This is to say that widespread immune pressure on S protein is likely to drive selection of viral variants that enable binding of the ACE-2 receptor to the virus to an extent that fully outcompetes binding of S-specific Abs to the virus. When this occurs, the virus is per definition resistant to S-specific antibodies. In an extreme situation of abundant asymptomatic transmission as presumably occurred in India prior to full implementation of mass vaccination campaigns, resistance to S-specific antibodies could, indeed, occur in the course of a natural pandemic. There can be no doubt, however, that ongoing mass vaccination campaigns provide a competitive advantage to S-Ab-resistant variant(s). Because vaccinees – alike nonvaccinated asymptomatically infected people – are frequently subject to suboptimal S-directed immune pressure, they will serve as a key target population to variants that are resistant to S-targeted and hence, vaccinal Abs. Consequently, previously asymptomatically infected subjects (i.e., infected during the first wave) as well as vaccinated subjects are now becoming highly susceptible to (severe) disease as is currently observed by the important second wave of infection and disease.

17: Do you think that if the pandemic had been treated differently, it would have been extinguished by itself? Is that what happened in other pandemics in the past (such as the Spanish flu or the polio pandemic)? And if so, is it expected that many people would die before the pandemic fades away? (What is exactly the difference between natural pandemic and artificial pandemic as you call the current situation?)

Please see my lecture on this topic. Due to its potential to spread through asymptomatic carriers and the high prevalence of asymptomatically infected subjects, the ‘natural’ evolution of Sars-CoV-2 towards more infectious variants is in my opinion inevitable. Unless overcrowding and poor personal and environmental hygienic conditions prevail (as is, for example, the case in India), infection prevention measures are more likely to lead to selection and

adaptation of more infectious variants. Under all circumstances mass vaccination campaigns will further expedite the infectiousness of circulating variants and ultimately result in resistance to vaccinal Abs or to Abs induced as a result of previous natural infection. In contrast to a natural pandemic, an artificial pandemic is featured by unprecedented massive human intervention such as large scale infection prevention measures and mass vaccination campaigns. Unlike the natural Flu pandemic of 1918 or the SARS-CoV-1 pandemic of 2002-2004 (which was in fact more of an epidemic than a pandemic), a natural Sars-CoV-2 pandemic would in my opinion take a much higher toll on human lives before it gets extinguished. Because of the self-perpetuating cycle of enhanced infectiousness, such a pandemic may only come to an end when the vast majority of the remaining population has a level of innate immunity that even highly infectious variants can no longer break through. However, the evolution of a natural Sars-CoV-2 pandemic would definitely leave more time for vaccines inducing sterilizing immunity to be developed (as the number of more infectious variants and the level of their infectiousness viral infectiousness would increase less rapidly).
As far as polio and smallpox are concerned, one should not forget that the success of these vaccination campaigns was to a large extent due to the deployment of LIVE attenuated vaccines. None of the current vaccines used in the fight against this Covid-19 pandemic are live vaccines.

18: You mentioned that a preventative vaccine should not be used when the virus is already circulating in the population. Is this indeed the definition for the Pfizer vaccine? What then is the difference between this vaccine and a therapeutic one? And what was used in the fifties during the Polio pandemic? The vaccine was given during the pandemic, isn't it, and actually stopped the pandemic? Was that a therapeutic vaccine?

A preventive/ prophylactic vaccine is a vaccine that you receive before being exposed to the pathogen. That’s important because you may not be protected as an individual when you get exposed to the pathogen before you got (a full course of) the vaccine. On a population level, however, the risk of using prophylactic vaccines while already being exposed to the virus is much more

dramatic as it may promote fitness of selected immune escape variants. The risk is especially relevant in case of a pandemic of a highly mutable virus combined with mass vaccination campaigns! People comparing this with the successful use of prophylactic vaccines for polio or seasonal influenza are comparing apples and oranges as these infections relate to outbreaks/ epidemics, i.e., they occur on a background of herd immunity that can be rapidly recalled upon re-exposure to the virus (which is, of course, not the case for a pandemic). This is to say that upon re-exposure 'optimal' immunity can be recalled in the vast majority of the population, thereby leaving no chance to the virus to promote survival and propagation of viral immune escape variants. However, if we were facing a real influenza pandemic (i.e., not due to antigenic drift but to antigenic shift, meaning the occurrence of a 'new' virus for which no herd immunity exists), we would be struggling as well to control it if prophylactic vaccines were to be used (although with Flu, the situation is a bit more favorable in that viral shedding by asymptomatically infected people is negligible).

Therapeutic vaccines are vaccines that are capable of curing people who have already contracted the disease. This is because the immune response elicited by such a vaccine is capable of killing cells that are already infected or pathologically altered (the latter in the case of cancer, for example). Provided they induce immunologic memory, such vaccines could also be used to prevent disease.

19: Several countries claim they are beginning to see the success of their mass vaccination campaign and that enhanced vaccination rates are opening a bright perspective for people to plan their summer holidays. (How) can I verify whether this promise/ prediction holds true?

Let me first be clear that I am not playing the panic-monger but simply prefer to be realistic instead of irrationally optimistic.

Based on the dynamics of infectious pressure and the impact thereof on the likelihood of disease or exertion of suboptimal immune pressure in previously asymptomatically infected subjects, one can make a more rational estimate of

how the pandemic is going to evolve in a particular country/ region (see 'Predictions on outcome of mass vaccination campaigns during a pandemic of more infectious Sars-2-CoV variants'). There can be no doubt that ongoing mass vaccinations are now diminishing infection and disease rates in the population. However, we need to be very cautious as the decrease in infectious pressure primarily relates to people who have not been vaccinated yet! This is because testing is not routinely, let alone systematically, performed on vaccinees. However, there is meanwhile ample evidence that asymptomatic people can shed virus as well. It has been shown on multiple occasions that especially vaccinees who become infected with variants shed and transmit Sars-CoV-2. Consequently, reported infection rates are currently underestimated. And, of course, the more the mass vaccination program progresses, the more this is going to be the case. So, the underestimation pertains to unreported infection of healthy, i.e., asymptomatic subjects, an ever increasing part of whom consists of vaccinees. This critical element is missing from the forecast currently proposed by a number of national health authorities. In my previous contribution ('Predictions on outcome of mass vaccination campaigns during a pandemic of more infectious Sars-2-CoV variants'), I highlighted the importance of declining infectious pressure on the likelihood of the virus to escape suboptimal S-directed pressure in previously asymptomatically infected subjects and vaccinees. I have emphasized how more frequent exposure of the virus (due to MASS vaccination) to suboptimal S-directed immune pressure builds a fertile breeding ground for more infectious variants and how the latter will evolve towards a higher level of infectiousness till full resistance to vaccinal antibodies is achieved. This also means that the introduction of more infectious variants (e.g., double mutant from India) will enjoy a competitive advantage and, therefore, expedite their propagation. In the context of mass vaccination, it is important to understand that 'more infectious' variants are merely to be seen as an intermediate stage in the evolution towards full resistance to vaccinal Abs.

In my home country (Belgium), for example, public health authorities recently reported an important decrease (20-30%) in infection, morbidity and mortality rates. This 'favorable' evolution would now substantiate their decision to continue further relaxing of social measures and opening up the economy while providing a hopeful perspective for the summer holidays. However, as

long as viral transmission by vaccinated people and concomitant breeding of more infectious variants in this population are ignored, it is impossible to make rational or reliable predictions on how this pandemic of ‘variants’ will evolve. It goes without saying that more social contacts amongst healthy people (to a large extent consisting of previously asymptomatically infected persons and a steadily increasing number of vaccinees) is only going to enhance exposure of Sars-CoV-2 variants to suboptimal S-directed immune pressure. It is, therefore, fair to conclude that the current perspective as depicted by health authorities and blindly adopted by politicians, only relates to the bright, sun-drenched tip of the iceberg, the dark but more representative portion of which lies beneath the surface and cannot yet be seen or easily understood. This especially applies when authorities decide to not systematically monitor vaccinees for viral shedding and sequence the virus they shed to investigate potential evolutionary convergence of mutations towards viral domains targeted by vaccinal Abs (i.e., the virus’ receptor-binding domain; RBD). CDC, for example, recently decided to restrict their monitoring or reporting of Covid-19 vaccine breakthrough cases to those that result in hospitalisation or death. There can be no doubt, therefore, that the number of cases of infection and the reproductive rate they are now reporting are largely underestimated and hence, misleading. Back to the situation in my home country, it can reasonably be predicted that recently reported cases are soon going to level off at a kind of plateau (only slightly declining or inclining) from which a new wave of morbidity and mortality will take off within the next coming weeks or months. The lag time and magnitude thereof as well as the age groups affected (younger versus older; i.e., nonvaccinated versus vaccinated) will depend on the speed and extent of the ongoing mass vaccination campaign and how fast ‘more infectious’ immune escape variants will ultimately evolve into vaccine-resistant variants. As already mentioned on repeated occasions, enrolment of increasingly younger age groups will only expedite the evolution of variants towards full vaccine resistance. Hence, higher vaccine coverage rates will promote these evolutionary dynamics and thus, not at all contribute to establishing herd immunity.

20: Surges in Covid-19 morbidity and mortality primarily affect nonvaccinated people, so why then would one urge that mass vaccination campaigns be stopped?

The mantra that vaccination diminishes viral infectious pressure makes us believe that the more people we vaccinate, the fewer will get infected and hence, the fewer will contract the disease. Although misleading, this reasoning – at first glance – seems, indeed, to make sense. So, why is it misleading to the point that it is simply wrong?

First, it's important to understand that mass vaccination campaigns (in the context of a pandemic of a highly mutable virus) enables breeding of more infectious variants. Because suboptimal S-directed immune pressure will select mutations within the S protein that are capable of resisting this immune pressure, variants comprising such mutations will be more infectious and, therefore, reproduce more efficiently. Since suboptimal S-directed immune pressure is inherently associated with large scale vaccination during a pandemic, 'more infectious' variants will increasingly circulate and become dominant. As a result, the infection rate in the host population will equally increase. As long as S-specific antibodies (Abs) protect against (severe) DISEASE, people who got fully (!) vaccinated or naturally immunized (i.e., as a result of natural infection) will enjoy better clinical protection than those who have not been vaccinated or previously symptomatically infected. HOWEVER, it is paramount to realize that mass vaccination campaigns conducted in the heat of a Sars-CoV-2 pandemic have the capacity to push the virus to evolve towards developing full resistance to S-directed Abs. As mass vaccination progresses, the infectious pressure will decline (especially due to prevention of [severe] disease!) while the immunization status of the population will get strengthened (as Ab titers in an ever growing number of vaccinees will increase). This combination will enable selection and adaptation of increasingly infectious variants or increasingly promote the propagation of newly introduced, more infectious variants (such as the Indian mutant). As none of the vaccines used is capable of blocking viral transmission and as the currently circulating variants are already more infectious (than the original wild type strain), selection and adaptation of even more infectious variants or

circulation of newly introduced, highly infectious variants will be promoted, thereby enabling more or highly infectious variants to become dominant. The dynamics of this natural evolution will be greatly expedited upon enrolment of more and more younger age groups in the mass vaccination campaigns. While mass vaccination of younger age groups will barely contribute to diminishing infectious pressure and disease, it will significantly contribute to growing the reservoir of asymptomatic spreaders and, therefore, expand the breeding ground for more infectious variants. As long as the evolutionary dynamics of this pandemic continue to be shaped by mass vaccination, we should get prepared for full vaccine resistance to occur. If mass vaccination and flanking infection prevention measures are going to be continued as the only approach to diminishing infectious pressure and disease, the endgame of this pandemic will inevitably be determined by the consequences of vaccine resistance. When vaccine resistance occurs, the situation for both vaccinees and nonvaccinated persons will dramatically change as vaccinal Abs will now merely suppress the functionality of natural, variant-nonspecific Abs and, therefore, block natural/ innate Ab-mediated viral clearance. *Consequently, the larger vaccine coverage rates will grow (including more and more younger age groups), the more 'more infectious' variants will evolve towards resisting vaccinal, S-specific Abs and the more we'll see non-vaccinated people being better protected than vaccinees.* Even though resistance to vaccinal, S-specific Abs would likely affect functionality of Abs acquired after natural infection, it is reasonable to assume that those who recovered from acute Covid-19 disease will still be able to resist (severe) Covid-19 disease upon re-infection, even if they got vaccinated. In contrast to vaccinees who did not previously contract acute, self-limiting Covid-19 disease, previously symptomatically infected subjects will also have developed functional memory T cells capable of targeting virus-infected cells and hence, abrogating viral infection. It is true that in order for memory CTLs (cytotoxic T lymphocytes) to be recalled upon re-exposure to Sars-CoV-2, S-specific Abs may be required. However, even though these Abs may no longer be able to fully neutralize vaccine-resistant Sars-CoV-2 variants, they will still be able to bind to S protein and, therefore, enable Ab-mediated uptake and processing of virions by Ag-presenting cells.

21: How long will it take until full-fledged vaccine resistance occurs? In the meantime, what is the risk for non-vaccinated as compared to vaccinated subjects to contract (severe) Covid-19 disease?

There is no equation to precisely predict this as it will essentially depend on several factors such as

> i) the effective reproduction number (as a measure for the 'infectious pressure'). This number is largely determined by the infectiousness of the viral variant and the level of deployment of infection prevention measures
>
> ii) the speed and extent of the mass vaccination program in general and of the enrolment of younger age groups in particular
>
> iii) the level of adoption of early treatment protocols such as proposed (and to some extent already implemented) by Dr. Peter McCullough and others

In (smaller) countries that rolled out their mass vaccination campaign on a background of a rather low infectious pressure and that have already achieved large vaccine coverage rates, we are currently witnessing an important wave of morbidity and mortality (e.g. Seychelles, Maldives, Bahrain). It cannot be ruled out that this evolution has been favored by enhanced propagation of more infectious variants as a result of mass vaccination. As declining infectious pressure combined with rising suboptimal S-directed immune status of the population is likely to promote reproduction and spread of more infectious variants, it is reasonable to expect that a similar evolution will become increasingly manifest in larger countries that are now achieving high vaccine coverage rates on a background of low infectious pressure (e.g., United Kingdom, Israel, Portugal). As these countries are much larger and hence, demographically more heterogeneous than the islands mentioned above, it may well be that a similar evolution will first be restricted to certain regions/ cities before becoming more generally observed.

When a highly infectious variant (e.g., Indian mutant) gets introduced in a country that already provides a fertile breeding ground for more infectious variants according to the conditions described above, further evolution of these variants towards full vaccine resistance will likely be expedited. The current issue with the Indian mutant spreading rapidly in the UK will tell us whether this is effectively the case.

In order for variants to evolve towards vaccine resistance in countries which are now proceeding with mass vaccination campaigns on a background of a rather elevated infectious pressure (primarily due to high morbidity), more time may be required. This is because the infectious pressure will first need to sufficiently come down (via mass vaccination) before the conditions for enhanced propagation of more infectious variants will be fulfilled. I, therefore, expect that high vaccine coverage rates in countries which high infectious pressure will first lead to one or more additional waves of morbidity and disease caused by more infectious variants before vaccine-resistant variants will make their advance (e.g., Brazil, Chile, Uruguay, United states). The more the morbidity rate and hence, the infectious pressure will decrease, the more mass vaccination will contribute to expanding the population's reservoir of 'suboptimal S-directed immune pressure' and the less it will contribute to further diminishing the population's reservoir of 'disease' (causing optimal infectious pressure). In other words, at low infectious pressure asymptomatic spreaders will increasingly serve as a breeding ground for more infectious variants. The more one turns people into asymptomatic spreaders (which is what mass vaccination does), the larger this breeding ground gets. The younger the vaccinees, the more and also the faster the balance will tilt towards growing variants than to diminishing morbidity (and mortality) rates. More infectious variants will initially pose a higher risk of severe disease to non-vaccinated as compared to vaccinated subjects. However, the opposite will hold true once vaccine resistance has been established as the non-vaccinated will still be able to rely on their natural/ innate CoV-nonspecific antibodies (Abs) whereas vaccinees cannot.

The described dynamics explain why despite similarly high vaccine coverage rates the evolution of the pandemic can be very different from one country to another. In some countries (e.g., Brazil, Chile, Uruguay, United states,…),

advanced vaccination campaigns have substantially reduced mortality and morbidity rates in vulnerable people whereas in other countries, mass vaccination has led to enhanced circulation of more infectious variants (best documented in the UK). The latter inevitably increase morbidity and mortality rates in non-vaccinated people with weakened immunity (as already seen on small islands such as Seychelles, Maldives, Bahrain). The latter include the elderly, people with underlying diseases or otherwise immune suppressed individuals as well as subjects who got more susceptible to Covid-19 disease due to suboptimal levels/ quality of S-specific Abs (e.g., due to recent asymptomatic infection, incomplete vaccination or waning Ab titers after natural infection). Only when variants become increasingly resistant to vaccinal Abs will this situation begin to reverse and render vaccinees more susceptible than non-vaccinated people (as explained above).

Last, it may be important to consider that mass vaccination campaigns or large-scale implementation of stringent infection prevention measures or over-crowding (due to mass gatherings or high concentration of people in refugee camps/ slums/ favelas) in certain countries/ regions can have severe repercussions on infection and morbidity/ mortality rates in countries that have not yet achieved high vaccination rates. This is because all of the above-mentioned interventions/ conditions are prone to breeding more infectious variants that can be introduced in those countries and subsequently give rise to large waves of morbidity and death.

22: Why does mass vaccination preclude herd immunity?

The short answer is that mass vaccination promotes asymptomatic spread of more infectious variants.

Several experts are speculating that some countries (e.g., Sweden) or some states in the US, for example, are well on their way to developing herd immunity. Their speculation is primarily based on a decline in cases and morbidity/ mortality rates following a recent/ previous wave. I consider this interpretation being erroneous as it completely ignores the darker part of the iceberg that’s under the surface and where more infectious variants are bred.

That part of the iceberg consists of asymptomatic spreaders. The latter population is steadily growing as vaccine coverage rates increase. The consequences of this growth is now especially worrisome as more and more younger age groups are enrolled in these mass vaccination campaigns. In some countries the effect of high-speed mass vaccination campaigns conducted in the vulnerable part of the population synergized with a fast increase in herd immunity in all non-vaccinated subjects who didn't manage to naturally resist Covid-19 disease (e.g., UK, Israel, Portugal). These countries missed the opportunity to bring the pandemic under control as they further expanded their mass vaccination campaign to also include younger age groups. Instead of intensifying their mass vaccination campaign, they should have continued stringent prevention infection measures (or even impose a lock-down) for about 2 months to prevent previously asymptomatically infected subjects from being infected while still possessing suboptimal S-specific antibodies. It is highly likely, indeed, that decreasing the reservoir of susceptible subjects (i.e., those with recent asymptomatic infection) combined with stringent infection prevention measures would have prevented Sars-CoV-2 from causing further cases of disease and raising the infectious pressure to a level high enough to cause re-infection in previously asymptomatically infected subjects shortly enough after their primary infection. This can reasonably be assumed as it is generally acknowledged that viral shedding by asymptomatically infected subjects is short-lived and that the concentration of virus shed is much lower than in people who contract Covid-19 disease. However, expanding mass vaccination to age groups that are at much lower risk of contracting Covid-19 disease will only expand the reservoir of subjects combining the capacity of asymptomatic spreading with a prolonged duration of suboptimal S-directed immune pressure (both due to vaccination). The expansion of this reservoir combined with a sustained (pandemic!) but low infectious pressure is what's going to drive the propagation of more infectious variants. However, as long as the declining morbidity and mortality rates in the vaccinees are exceeding the incline of those rates in the non-vaccinated, nobody will become aware of what's going on at the breeding ground under the water unless…vaccinees are monitored for virus shedding and viral samples are sequenced for monitoring evolutionary changes in infectiousness, regardless of whether vaccinees are symptomatic or not. The same applies to non-vaccinated persons who contract Covid-19 disease

(here, infection by more infectious circulating strains is now increasingly reported!).

In conclusion: Dropping mortality and morbidity rates do not indicate growing herd immunity if in the meantime an ever increasing part of the population serves as a growing incubator for more infectious variants because of their increasing enrolment in mass vaccination campaigns during a pandemic. Any rhetoric about memory T cells as a foundation for herd immunity is completely irrelevant. Memory T cells will protect individuals from contracting (severe) Covid-19 disease a second time. The problem, however, is the lack of control over viral infectiousness. Since vaccinees will not only serve as an important reservoir for virus transmission but also for exposure of the virus to suboptimal S-directed immune pressure, vaccinees will basically constitute *a source of transmission of more infectious variants*. This is why mass vaccination precludes herd immunity. In addition, more infectious variants will come with a higher risk of (severe) Covid-19 disease, first in the non-vaccinated and later in the vaccinated population. It is reasonable to expect that this switch will be expedited by enrolling younger age groups in mass vaccination campaigns. When this occurs, it can be expected that the moderate benefit of vaccination in terms of decreased morbidity and mortality rates in the vulnerable groups will be countered by a disastrous incline of those rates in all vaccinees (including all vaccinees belonging to the younger age groups). So, the mantra that mass vaccination protects the elderly from Covid-19 disease and hence, should also better protect the younger age groups* while enhancing herd immunity is a myth! It is completely wrong!

* increasing morbidity rates in the younger age groups are caused by more infectious variants, the breeding of which is enhanced by continuing mass vaccination campaigns beyond the stage where they have lowered the infectious pressure down to a critical level.

23: If asymptomatically infected people spread the virus, why do countries with no lockdowns and no obligatory face masks (e.g. Sweden and Florida) have results that are similar to those with lockdowns?

On a background of (relatively) high infectious pressure (i.e., due to relatively high morbidity rate), enhanced viral transmission by asymptomatically infected people (e.g., Florida, Sweden) and hence, enhanced viral infectiousness has only relatively little impact on morbidity and mortality ‘results’. However, the lower the infectious pressure, the more viral transmission dynamics occur in the asymptomatically infected part of the population and thus, the more predominant more infectious variants will become. Mass vaccination campaigns will only accentuate this trend. This is because asymptomatically infected vaccinees will be more likely to shed ‘more infectious’ variants (as their S protein differs in antigenicity from the vaccinal S) than non-vaccinated, asymptomatically infected subjects (the latter efficiently deal with all variants thanks to their CoV-nonspecific natural antibodies). In addition, vaccinees will exert suboptimal S-directed immune pressure for a prolonged period of time because it takes time for their vaccinal antibodies to mature and to grow to sufficiently high levels. Especially when conducted on a background of low infectious pressure will mass vaccination campaigns make more infectious variants evolve and spread more rapidly in countries with stringent infection prevention measures (potentially including lockdowns) than in those with loose public health and social measures. This is to say that the extent to which vaccinees from countries with stringent infection prevention measures build a breeding ground for highly infectious, even up to vaccine-resistant variants is much more important, as is the pace at which they evolve variants with enhanced infectiousness. On the other hand, it is reasonable to assume that the propagation of newly introduced, more infectious variants (e.g., Indian mutant) will considerably be expedited in these vaccinees. Unfortunately, as public health authorities don’t show much appetite to measure viral shedding in vaccinees and monitor evolutionary changes in the sequence of the viral variants they shed, breeding of more infectious variants in vaccinees goes largely unnoticed. Hence, differences in those evolutionary dynamics are not monitored and can, therefore, not be compared between populations that are subject to different conditions of viral exposure/ containment.

24: A number of countries are now reporting 'growing herd immunity as a successful result of their mass vaccination campaigns’. If mass

vaccination campaigns expedite herd immunity, why should we oppose them?

It is true that herd immunity has been proposed as the end goal of mass vaccination campaigns. However, it seems like health authorities need to revisit the definition of herd immunity. Herd immunity is defined as a form of indirect protection from infectious disease that is conferred to non-immune individuals due to diminished disease transmission by immune people. When the contribution of the immune population that is capable of blocking transmission is high enough to disrupt the chain of transmission, the virus can no longer replicate and propagate and hence, the disease stops spreading. So, the mantra of herd immunity dictates that the greater the proportion of immune individuals in a community, the smaller the probability that non-immune individuals will come into contact with an infectious individual and the higher the likelihood that herd immunity will be achieved. It is important to note, though, that herd immunity directly relates to diminished viral transmission and not per se to immunity. Only when the type of immunity is such that is leads to significant reduction of viral shedding will the immune status of the population be a reliable correlate for viral transmission. Although there is no doubt that people who get the disease and are vaccinated shed less virus than those who are not vaccinated, this does not hold true for healthy people. I am convinced that healthy people who get infected but are vaccinated shed more virus that those who’re not vaccinated. There is an increasing number of publications reporting about viral shedding in vaccinated individuals, especially in those who get infected by variants. In contrast, healthy, asymptomatically infected subjects, only shed virus in low concentration and for a short period of time. Even more importantly, they are capable of abrogating viral infection and shedding, regardless of the type variant they get infected with. In other words, vaccinal S-directed antibodies (Abs) do not equal reduction of viral transmission in healthy people. So, measuring the rate of S(spike)-directed Abs in a population with an ever increasing part of vaccinees does not allow to assess the level of herd immunity. The more younger people are vaccinated, the more this applies (they normally shed less virus when not vaccinated because they’re relatively less likely to get Covid-19 disease!). This situation is in sharp contrast to S-directed immunity that results from natural infection. In case of natural

infection, the immune mechanisms, including the S-directed Ab response itself, is much more diversified and hence, S-specific Abs mirror a type of immune response that is more potent than the one induced by Covid-19 vaccines. This already explains why immune responses induced upon natural infection have the capacity to significantly diminish viral transmission in healthy people who get re-infected. This is to say that the more people get vaccinated, the less S-specific Abs will reflect a genuine growth in herd immunity. This trend will only augment upon enhanced enrolment of younger and younger age groups in the mass vaccination campaigns. It is, therefore, undeniable that the ongoing mass vaccination campaigns will not at all enable herd immunity! If health authorities would not have decided to no longer report about cases of viral shedding in vaccinated people (unless vaccinees are hospitalized or come down with severe disease!), even the broader public would readily understand that the rising number of people with S-specific Abs as a result of mass vaccination does not reflect a growth in herd immunity. In other words, people would realize that the current narrative that mass vaccination induces herd immunity is a myth!

25: Contradictory messages are circulating about the effectiveness of Covid-19 vaccines towards variants (including the double mutant from India). Who is wrong and who is right?

Stakeholders of the ongoing mass vaccination campaigns claim good effectiveness towards variants but don’t always mention that this relates to the capacity of these vaccines to prevent *severe disease* and hence, hospitalization and death. It is clear, however, that all Covid-19 vaccines fail in blocking viral transmission, especially transmission of more infectious variants. This is a huge problem as viral transmission is now increasingly taking place among healthy people in general and vaccinees in particular (as their S-specific Abs do not sufficiently neutralize S variants). The resulting suboptimal S-directed immune pressure serves as a breeding ground for even more infectious variants. As more and more people are now getting their second shot and as more and more younger age groups are getting vaccinated, suboptimal immune pressure on viral infectiousness is only

increasing. This will eventually lead to full resistance of Sars-CoV-2 to these vaccines.

In conclusion: Although decreasing the burden on the health care system, success in fighting the Covid-19 pandemic should not be anticipated based on good vaccine effectiveness in terms of prevention of severe disease and hospitalizations only, but also on reduction of transmission among healthy vaccinees. The latter criterion can no longer be verified as health authorities are now no longer reporting about breakthrough infections in vaccinees unless they are coming down with severe disease. Precisely due to the lack of effectiveness of Covid-19 vaccines in blocking viral transmission continued mass vaccination campaigns will only promote dominant propagation of more infectious variants and eventually cause Sars-CoV-2 to become fully resistant to Covid-19 vaccines. Even if the already announced ‘updates’ of these vaccines would manage to overcome the problem associated with ‘antigenic sin’ (this will require substantial adjuvantation), the issue with more infectious immune escape variants will remain. There can be no doubt, therefore, that the updated vaccines as well will fail to prevent viral resistance. It goes without saying that circulation of a vaccine-resistant virus in populations with a high vaccine coverage rate will be highly problematic.