FINAL REPLY TO DR. GERSTENBLUTH AND DR. DUITS
- Geert Vanden Bossche, DVM, PhD

Let me first of all emphasise that, contrary to what dr. Gerstenbluth apparently stated in his press conference on April 20 and what *Het Antilliaans Dagblad* reported on April 29, I have never accused him (nor doctor Duits) of engaging in a kind of genocide, as he calls it, and I challenge him to either prove these allegations or to publicly withdraw them.

Next, I want my comments and critics to their letter from April 27th to reflect the complexities and challenges of the pandemic and to warn all those who blindly advocate for conducting mass vaccination campaigns in the heat of this pandemic about the risk and consequences of short-sighted interpretations and conclusions. Those who think that they will find the manual on how to deal with this pandemic in peer-reviewed journals clearly lack a sense of reality in that even the most enlightening publications can only shed *some* light on a limited number of aspects of this pandemic. The major piece of work remains with those who are determined to unveil the dynamics of the complex interplay between the infectious pressure mounted by a steadily increasing number of more infectious variants and the immune response mounted by subpopulations endowed with different types and levels of immunity. Without having completed this tough exercise, it's simply impossible to gain a true understanding of how extreme conditions or interventions (e.g., overcrowding, stringent infection prevention measures, mass vaccination campaigns) are now fueling the pandemic to an extent that nobody dares to predict any longer how and when it is going to come to an end.. Let me be very clear that a such exercise takes more than applying conventional textbook knowledge and citing quotes and references from the literature. It is much more about a meticulous exercise in putting the many pieces of a complex puzzle together in ways that match the science and enable to explain the current evolution of the pandemic as it unfolds in different features in different countries. Only when the pieces adequately match will the puzzle allow to make meaningful interpretations and predictions. If they don't match, any prediction and promise is simply at the mercy of speculation and guesses.

That is what I am calling 'doing a decent homework'. Given the multifaceted dimension of this viral pandemic and the unprecedented large scale human intervention, both pharmaceutical and nonpharmaceutical, one needs to be able to draw from different fields such as evolutionary biology, immunology, virology, vaccinology and even biophysics and environmental hygiene to gain enough of a knowledge base to then further build upon.

I am, therefore, getting upset when bold but baseless statements are made about the benefits of these mass vaccination campaigns. 'Bold' in a sense that they are aimed at putting poorly or misinformed laymen under pressure to agree upon subjecting themselves to a medical intervention with life-long consequences; 'baseless' as their approach is short-sighted instead of holistic and in that their rhetoric refers to situations from the past whereas it should be clear by now that we are experiencing a situation that is completely unprecedented in the history of mankind.

So, I am not all impressed by dr Gerstenbluth's and dr. Duits's textbook citations related to immunology, vaccination and public health intervention. From the references they are citing, I have to conclude that they continue to ignore that Sars-CoV-2 has the capacity to also spread and evolve through asymptomatic carriers (hence, including vaccinees!), and that because of human intervention the course of this pandemic now considerably deviates from that of a natural pandemic, let alone that of an outbreak or epidemic (known to occur on a background of herd immunity!). Consequently, the number of references cited does not always reflect the level of one's credibility. In no way have the doctors been

taking into account some of the key shortcomings I've been highlighting such as the completely neglected role of natural immunity as the key contributor to herd immunity against acute infection caused by highly mutable viruses and the critical importance of viral immune escape as facilitated by suboptimal S-directed immune pressure in asymptomatically infected vaccinated or nonvaccinated individuals. Ignoring this is not taking into consideration a steadily growing number of 'yes', ... peer-reviewed publications!

I will now deal - as announced in my reply of April 30 - with every single argument in the letter of dr. Gerstenbluth and dr. Duits to demonstrate that it does not provide scientifically sound evidence that the ongoing mass vaccination campaigns hold any legitimate promise for bringing this pandemic under control.

Dear dr. Gerstenbluth and dr. Duits

> **"Vaccination programs are essential for solving the SARS-COV2 pandemic"**

Can you please explain how vaccination programs will 'solve' the pandemic: whether and when herd immunity will be achieved, highly infectious variants will be under control and Covid-19 cases will abate and degrade into yet another 'common cold'?

> ***"Unmasking misinformation"***

I assume this title relates to the information you are spreading.

> **"Willemstad, April 27 2021**
> Dear Dr. Vanden Bossche
>
> Below please find our response to your letter dated April 19 2021. We received your comments on the informative video we made (https://youtu.be/Izb3IOkJJfY). We deemed our video necessary as your personal opinion expressed on YouTube was causing unnecessary hesitancy in locals for participating in the vaccination program on our islands as well as creating unwarranted confusion among medical professionals in the Dutch Caribbean. First of all it should be made clear that we adhere strictly to our scientific code of conduct based on rigor, respect (of each individual person) and responsibility (1). To this end, argumentation on issues should be based on sound data published in peer reviewed journals, not baseless opinion. Pursuing the truth is more than creating knowledge as it also entails fighting untruths in an ethical way (2). There should be no room for denigrating or condescending remarks and it would fit you well to adhere to this code and avoid future diatribe."

As your preaching does not serve the truth it will inevitably foster hesitancy in those who want to find out about the scientific rationale behind these campaigns. First, how can you be so short-sighted in thinking that the truth and all of the truth can only be found in peer-reviewed journals whereas there is no single journal that ever dealt with a pandemic comparable to the one we are currently facing? Are you aware of any peer-reviewed articles even suggesting that mass vaccination campaigns conducted in the heat of a pandemic of a highly mutable virus and using vaccines unable to block viral transmission are going to have a happy ending? So according to your viewpoints, any invention, novel insight or creation of new knowledge ought to be 'baseless' as it is not described in a peer-reviewed journal!

Secondarily, let me be very clear that you are all but well-placed to educate me on your codes of ethics. Your 'informative video' was clearly aimed at making fun of critics and their insights without leaving them any possibility to correct your cheap interpretations of the science involved. I am not sure whether a performance as despicable as your mocking interview is covered by the codes of ethics for scientists that you pretend to adhere to? I am saying this because in your video you are, indeed, not just mocking me but in fact all scientists who are doing the utmost to express their critical views on the massive, highly questionable type of human interventions that are currently taking place in this pandemic. If one thing is truly unethical, it is definitely the completely irrational and unfounded mass vaccination campaigns that are currently conducted and the push from those with conflicts of interest to get uninformed or confused people vaccinated, no matter what and how. As far as I am concerned, I am not bound by any code other than the unconditional respect for human life.This code does not prohibit me from labeling statements as 'nonsense' when they are not scientifically correct.

> "1. A code of ethics for scientists. Pang CL. Lancet. 2007 Mar 31; 369(9567): 1068.
> 2. A code of ethics to get scientists talking. Nature. 2018 Mar 1; 555(7694): 5., WEF Code of ethics 2018
> Several arguments you brought forward in defense of you advocating natural infection as the only effective approach for a pandemic, and insisting on vaccination and public health interventions being high-risk procedures during a pandemic with grave effects, can certainly not be supported by scientific data (neither public health, immunological nor virological)."

In a very 'unethical' way, you are twisting my words to an extent that is beyond worrisome. It is certainly correct that I do believe that ongoing large-scale human interventions are going to have a negative impact on the course of this pandemic, especially because they will drive adaptation of a steadily increasing number of even more infectious immune escape variants endowed with selected, S-associated mutations (currently *the* most troublesome issue). However, in contrast to what you are trying to make people believe, I am not advising to let the pandemic run its natural course but to intervene in a scientifically rational way using, amongst others, immune intervention strategies that provide sterilizing immunity (i.e., using transmission-blocking vaccines). My proposal and recommendation in this regard are clearly stated on my website. The endgame at this stage should be *eradication* of the virus.

> "The same holds true for several unjust fundamental immunological and virological mechanisms you describe in your comments.From the start it should be clear that in an immune response both innate and adaptive pathways are intricately involved in a fine tuned and highly integrated system that, over the course of humankind, has proven itself to be extremely successful. Stratifying immune functions has its explanatory benefits but its effectivity is better understood in the cooperative functionality of different cells."

Is this a textbook citation? To what extent do you want these 'philosophical' considerations to contribute to the discussion or to counter 'several unjust fundamental immunological and virological mechanisms' I am describing in my comments? I can only work with concrete statements, not with meditationary ideas about immunology in general.

> **"Public Health measures and vaccination are essential for curbing pandemics**
> Public health data and a myriad of scientific publications have unequivocally proven that vaccination is a fundamental step for eliminating viral threats during pandemics and for preventing ongoing viral mutation and immune escape variants (3,4)."

Where have you read that vaccination prevents immune escape variants? It is not mentioned in the literature you are citing; on the contrary, (3) highlights the problem of antigen variability and the lack of solutions to overcome it whereas (4) states: "*In the case of the current pandemic of the virus SARS-CoV-2, a vaccine that prevents severe disease and disease-driven hospitalization could have a substantial public health impact.* ***However, a vaccine that could also block acquisition of the virus, and thus prevent both asymptomatic and mild infection, would have much larger impact by reducing transmission in the community and potentially establishing herd immunity*****."!**

In these publications, no pandemic other than the current Covid-19 pandemic is mentioned! The Flu pandemic of 2009 is only mentioned in the context of recipients who developed narcolepsy as a consequence of vaccination! (Reference 3).

Regardless of the irrelevance of the references you cited, your adherence to the mantra of mass vaccination that the more one vaccinates, the less the virus will replicate and the fewer variants will emerge is particularly simplistic and dangerous as it does not take into account selection and adaptation of more infectious variants as a result of frequently encountered suboptimal S-targeted immune pressure due to mass vaccination (again, you may want to educate yourself on this issue and watch my recent interview with Bret Weinstein; it's posted on my website).

> "Pursuing herd immunity as you propose through infection should be rejected in view of the related high mortality and morbidity.
>
> The futility of such an approach in the SARS-CoV2 pandemic has for instance painfully been shown in the unmitigated outbreak in Manaus, Brazil (5) and the current disastrous COVID-19 outbreak in India. Furthermore recent reports have also shown substantial burden of health loss for COVID-19 survivors of up to 6 months after initial infection (6). Clearly, acquiring herd immunity by infection is not an option."

Where or when did I say that we should be pursuing herd immunity through natural infection? Herd immunity through natural infection would only yield adaptive immunity! I have been repeating on multiple occasions that the major contributor to herd immunity is innate immunity (between ca 50 and 80% of the population is 'naturally' protected against disease upon introduction of a new coronavirus in an immunologically naïve population) and that herd immunity can never be achieved through adaptive immunity only, even regardless of vaccination. Knowing that priming by natural infection is more efficient than priming by any mRNA vaccine (see below), I am curious to learn which arguments you're going to put forward in trying to make people believe that mass vaccination is going to be much more efficient than widespread natural infection (cfr. Manaus) in generating protective herd immunity? Again, I have not been advocating for letting the current pandemic run its natural course but to stop ongoing mass vaccination campaigns as they will worsen things dramatically.

> "Achieving protective immunity through vaccination has proven safe and very effective (3,4)."

None of the pathogens mentioned in these publications have been vaccinated against in the context of a pandemic!

> "Also recent results of the SARS-CoV2 vaccination program in Israel using mRNA vaccines show an impressive reduction in SARS-CoV2 related mortality and morbidity and further accentuate the necessity of combining Public Health Measures with effective vaccines in addressing the SARS-CoV2 pandemic (7,8)."

I have repeatedly addressed the erroneous interpretation of the data in Israel and the UK in my video messages and documents posted on my website. The observed decline in cases was clearly not due to vaccination as extensively explained in these messages/ lectures posted. Instead of misleading people with your simplistic but erroneous interpretation of the evolution of the pandemic in these countries, you may want to take a deeper dive in the data to conclude that the steep decline in both Israel and the UK was merely due to the fact that mass vaccination campaigns were brought up to speed at a point in time where the number of cases had peaked.

> "The importance of combining both approaches for achieving protection and saving lives is further accentuated in the current dire public health situations faced in Sweden that is in stark contrast to its neighboring countries of Denmark, Norway and Finland (9). This as Sweden chose to minimally implement public health measures and let natural infection run its course (an approach you propose)."

Again, I am not proposing to let the pandemic run its course but I am certainly even less so proposing to make it worse by baseless, large-scale interventions (an approach you propose).
Alike Sweden, Denmark has been facing a large peak of cases between the end of Oct 2020 and the end of Jan 2021. Both peaks were followed by a steep decline in cases before vaccine coverage rates became more significant (i.e., with less than 3.5% of the population having received a single dose in both countries). As Sweden's mass vaccination campaign was brought up to speed on a background of a rising number of cases, it is likely to have contributed to the overall amplitude of the third wave that is currently still in the process of declining. In Denmark however, the mass vaccination campaign was brought up to speed on a relatively low infection rate background, thereby leading to a relatively lower increase in cases and causing the curve to merge into an elevated plateau rather than a clear-cut peak (i.e., the plateau of infection cases is now situated at a level that is relatively higher than the one observed for previous plateaus in-between the first, second and third wave). In addition, the biggest peak in Sweden has not been any more pronounced than those observed in Israel, UK, USA, France etc. Or did these countries not adhere to the disinfection prevention measures either?
It may also be useful to realize that the course of the pandemic is now primarily determined by the level of circulation of more infectious variants. It would suffice for any of these other Scandinavian countries to host a highly infectious variant in order for a surge in cases to occur. This being said, I do not think it makes a lot of sense to think of the pandemic as a local event that can durably be controlled by the country's strategy and policy, even when living on an island.

> "As a Caribbean island with direct Latin American connections we are certainly aware of the discrepancy of the ongoing SARS-CoV2 outbreak in Chile in spite of achieving a relatively high population vaccination percentage. Probable scientific explanations provided for these observations by Chilean scientist themselves include low adherence to public health measures (10) and primarily use of the less effective inactivated virus Coronavac SARS-CoV2 vaccine for their vaccination program. Studies performed by the University of Chile and the Chilean Department of Health show only 3% and 16% vaccine effectivity after priming and 54 and 67% respectively after a booster shot for documented infectivity (11,12). These results are much poorer than the ones observed in vaccine programs making use of the BNT162b2 mRNA vaccine (46% and 92% respectively) (13)."

This explanation is too simplistic! Even before the summit of the peak in Chile was reached, 20% of the population got *fully* vaccinated! This is three times the rate of the full regimen vaccination that was associated with a steep decline of cases in the UK. Even a coverage rate of 24% (single dose of mRNA vaccine) and of 13% by a full vaccine regimen did no protect the US population from a resurgence in cases between mid March and mid April 2021! In all countries, deployment of mass vaccination campaigns on a background of a plateau or rising infection rates seems to lead to a (further) increase in the number of cases. This especially applies if more infectious strains are circulating (e.g. Chile, Brazil, Uruguay, India…).

What worries me enormously is the complacency of health authorities when it comes to evaluating the effectiveness of mass vaccination in the course of the pandemic. When morbidity and mortality rates increase despite enhanced vaccination rates, the latter are simply deemed insufficient to have a positive impact whereas an abrupt decline in cases is readily considered a successful result of vaccination even if vaccination rates are low (e.g., < 10%) and relate to a single dose (as has, for example, been observed in the UK, Israel and more recently in Turkey and Brazil). Instead of taking a deeper dive in the complex population dynamics of the pandemic, some experts seem to prefer to take things easy and to blame poor performance of certain vaccines and lack of people's adherence to infection prevention measures when the curves go up and the opposite when they come down. As I stated: that is too simplistic! The more 'more infectious' variants are circulating and the pandemic is evolving, the less we will see an impact of the public health measures (except for complete lockdown scenarios).

"3. A guide to vaccinology: from basic principles to new developments. Pollard AJ, Bijker EM.Nat Rev Immunol. 2021 Feb; 21(2): 83-100.
4. Estimating the health impact of vaccination against ten pathogens in 98 lowincome and middle-income countries from 2000 to 2030: a modelling study. Li X, Mukandavire C, Cucunubá ZM et al. Vaccine Impact Modelling Consortium.Lancet. 2021 Jan 30; 397(10272):398-408.
5. Three-quarters attack rate of SARS-CoV-2 in the Brazilian **Amazon** during a largely unmitigated epidemic. Buss LF, Prete CA Jr, Abrahim CMM et al. .Science. 2021 Jan 15; 371(6526): 288-292.
6. High-dimensional characterization of post-acute sequalae of COVID-19. Al-Aly Z, Xie Y, Bowe B.Nature. 2021 Apr 22. doi: 10.1038/s41586-021-03553-9. Online ahead of print.
7. Signals of hope: gauging the impact of a rapid national vaccination campaign. Shilo S, Rossman H, Segal E.Nat Rev Immunol. 2021 Apr; 21(4): 198-199.
8. COVID-19 dynamics after a national immunization program in Israel. Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E.Nat Med. 2021 Apr 19. doi: 10.1038/s41591-021-01337-2. Online ahead of print.
9. The Swedish COVID-19 strategy revisited. Claeson M, Hanson S.Lancet. 2021 Apr 19:S0140-6736 (21) 00885-0.
10. Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile G. E. Mena *et al*., *Science* 10.1126/science.abg5298 (2021).
11. Vacunas contra el SARS-CoV2 muestran 56,5 por ciento de efectividad en la prevención de contagios - Universidad de Chile, Martes 6 de abril 2021. https://www.uchile.cl/noticias/174186/resultados-primer-estudio-de-efectividad-delas-vacunas-en-chile
12. Ministerio de salud. Gobierno de Chile. 16 de abril 2021. https://www.minsal.cl/wp-content/uploads/2021/04/20210416_ESTUDIOEFECTIVIDAD-CORONAVAC.pdf
13. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. Dagan N, Barda N, Kepten E. et al. N Engl J Med. 2021 Apr 15;384(15):1412-1423.

Avoiding viral mutation and vaccine resistance by allowing natural infection

According to your opinion asymptomatic infected persons with suboptimal antibody titers are selected by stringent public health interventions facilitating viral mutation and vaccine resistance. You also state that "a natural pandemic of an acute viral infection does not generate variants"."

What do you mean by 'asymptomatic infected persons with suboptimal antibody titers are selected by stringent public health interventions?' This doesn't make any sense. You seem, once again, to be twisting my words in that I am not saying that nonpharmaceutical intervention facilitates viral mutation or vaccine resistance but that it may promote selection and adaptation of more infectious variants and that this may have caused such more infectious variants to increasingly circulate even before mass vaccination started. Likewise, and as explained under the next § below, the opposite extreme (e.g., overcrowding in slums or favelas) may promote selection and adaptation of more infectious variants as well. As already reiterated on several occasions, there has been no such evolution (i.e., towards circulation of more infectious variants) during the Influenza pandemic of 1918, despite a high infection rate in the population. Clearly, the Flu pandemic was not subject to either pharmaceutical or nonpharmaceutical human intervention.

> "As already mentioned, the published Manaus data clearly demonstrate the opposite to be true (5, 14). Mutations have arisen causing variants of concern (P.1) with increased transmissibility, higher morbidity and mortality in a population lacking implementation of public health measures and effective vaccination programs. To put this more clearly, most current detected variants have arisen prior to vaccination initiation."

Surges of cases (i.e., waves) during a pandemic find their rational explanation in changes of the dynamic interplay between the virus (by means of viral infectious pressure) and the host immune system (by means of the population's innate and adaptive immune status). Public health measures may contribute to changes in those dynamics. As you may learn from the Q&A below (posted on my website), stringent as well as poor public health measures may, however, result in a similar effect in that both may enhance training of more infectious immune escape variants resulting in a new wave of infection, disease and mortality. That is why I am cautioning against simplistic interpretations of the data and for jumping to conclusions. Or do you think that the convergence of the mutations carried by the more infectious variants towards several domains of S (responsible for viral infectiousness) or even to particular amino acids within the RBD (responsible for binding of anti-S antibodies) simply occurred accidentally?

***Q**: 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?*

A: 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 under 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 where 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.

> "14. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Faria NR, Mellan TA, Whittaker C. et al. Science. 2021 Apr 14:eabh2644. doi: 10.1126/science.abh2644. Online ahead of print.
>
> **An effective immune response**
> It should be clear that for an effective immune response both humoral (e.g. antibodies) and cellular (innate cells, T-cells and B-cells) pathways are of importance. Antibodies primarily protect against cells becoming infected by blocking viral entry whereas innate cells and T-cells are responsible for effective virus containment and removal after cellular infection (effectively preventing clinical complications; as correctly mentioned in our informative video at 14:56!). (15)"

Author: Geert Vanden Bossche, DVM, PhD (May 3 2021) – www.geertvandenbossche.org

OK, this is textbook knowledge!
But interesting to learn about your citing ref. 15 as it confirms a number of things you seemed to ignore or not to know:

- Covid-19 vaccines do not protect against transmission and cannot prevent asymptomatic infection in all subjects.
- CD8+ T cells are largely absent (or not even measured) in Covid-19-induced immune responses and
- CD8+ memory T cells (which take time to develop) only fulfill a role in protecting previously infected subjects against symptomatic disease and severe symptoms (and thus, not against infection!) :
- see the attachment at the end for further evidence of shortcoming of current vaccines and the role of CD8+ T cells in protecting against (severe) disease at a later stage of infection

> "In contrary to your stated opinion, several recent publications show asymptomatic SARS-CoV-2–infected individuals to have strong antiviral immunity characterized by a highly functional virus-specific cellular immune response and stable antibody neutralization titers regardless of infection symptomatology (16,17).
>
> It is also consistent with the hypothesis that there may be ongoing affinity maturation in response to residual antigen after viral clearance, leading to improved quality of the antibody over time (17)."

Wait a minute! First, there is compelling evidence (see references compiled on my website) that NK cells play a critical role in eliminating Sars-CoV-2 in asymptomatically infected subjects. So, my opinion is all but contrary to acknowledging that a highly functional cellular immune response is involved (more about this follows below). Your extrapolation to 'stable neutralizing Ab titers' is in fact copied from R. Kedl's interpretation but not from the authors of the study (I;e., ref. 16) he is referring to. So it seems like you didn't even read the original study authored by Le Bert et al.? Indeed, in the reference you are citing (17), R. Kedl is merely giving his own interpretation of the original study published by Le Bert et al. (your reference 16). Clearly, the key purpose of this study was not to study the kinetics of the antibody response in asymptomatic subjects but to investigate the functionality of antiviral cellular immune responses (see title of this paper!). As far as Ab responses are concerned, the author acknowledges:

"Despite their ability to efficiently control the infection, asymptomatic individuals who clear SARS-CoV-2 have been hypothesized to mount a reduced antiviral adaptive immune response (Long et al., 2020b). This hypothesis is supported mainly by measurement of SARS-CoV-2–specific antibodies (Atyeo et al., 2020; Long et al., 2020b; Henss et al., 2021) and B cell quantity (Woodruff et al., 2020)."
So, the above references cited by Le Bert et al. point, indeed, to significant waning of Ab responses in asymptomatically infected subjects. In Le Bert's study, the purpose of measuring antibodies was merely to determine the timepoint of seroconversion to then characterize cellular responses as a function of the timepoint of infection! ("*More importantly, by evaluating the period of SARS-CoV-2 antibody seroconversion, we could separate individuals who were likely infected >6 wk before sampling from those who were likely infected within the last 4 wk*"). The hypothesis about affinity maturation of **Abs** in response to residual antigen is definitely not part of the conclusions drawn by Le Bert et al. ("*An alternative explanation could be that SARS-CoV-2–specific **T cells** persist longer at a higher frequency in COVID19–recovered patients, since viral antigen might persist more in symptomatic patients who usually have higher quantity of viral replication (Wang et al., 2020)".*

In addition, within the cohort studied by Le Bert et al., there was very active transmission of Sars-CoV-2, thereby increasing the likelihood that subjects got repeatedly asymptomatically infected and hence, mounted, once again, short-lived Abs (instead of recalling memory B cells): "*We therefore selected 85 asymptomatic individuals, from a cohort of male workers living in a* ***densely populated dormitory*** *with* ***active spread of SARS-CoV-2 infection*** *(Fig. 1 A), who, based on their kinetics of appearance and disappearance of antibodies against nucleoprotein (NP) and S, were likely* ***exposed to SARS-CoV-2 at different time points***"

> "Such a general antiviral mechanism is known to be important for protection against re-infection through the generation of long-lived antibody secreting plasma cells and memory B cells that can be quickly reactivated to secrete potent neutralizing antibodies. B cells undergo a process of somatic hypermutation (SHM) to generate the best virus-binding Abs. (18) (as mentioned in our informative video a powerful and effective way our immune system adapts and obtains more capability to address current and future mutated viruses)."

First, the above Ab recall effect is your personal interpretation of what happens in asymptomatically infected subjects. Again, there is no evidence whatsoever that asymptomatic infection generates B cell memory and this is certainly not what is reported in the study conducted by Le Bert et al. (nor is this even suggested by R. Kedl in ref. 17!). Le Bert et al. are primarily referring to the antiviral effect of IFN-γ and IL-2 (and linked secretion of IL-10) by Th1 cells ("*We suggest that this could be the functional signature of protective virus-specific cellular immune responses in asymptomatic SARS-CoV-2 infection*"). Similar cytokines are also secreted by activated NK cells. They do, indeed, have an antiviral effect. However, there is also compelling evidence that viruses are capable of developing strategies to bypass the effect of these cytokines. It is, therefore, paramount to activate cells that can directly eliminate CoV-infected cells by virtue of killing them. This is what cytotoxic NK cells do in asymptomatically infected subjects whereas CD4+ Th1 cells cannot kill virus-infected cells!

> "This fundamentally known process has now also been extensively described as occurring in natural SARS-CoV2 infections (19,20). Even small changes in SHM may be biologically relevant, as somatically mutated clones can exhibit higher degrees of cross-protection against different mutant strains of the virus (20). We would suggest for you to familiarize yourself with this mechanism for a better understanding of the viral-immune interaction."

This is the ultimate joke! As you seem, however, having noticed: This study (20) is dealing with natural infection and not with vaccination! As already mentioned in my first letter, your conclusion that the beneficial effect of vaccination equals that of natural infection (and is 'combining the best of both worlds') is overtly at odds with decades of immunology research! You may be the ones who need to educate yourselves on the difference between priming by natural Sars-CoV-2 infection as compared to vaccination. The enhanced breadth of Ab response can only be achieved in case of priming by natural infection! (https://science.sciencemag.org/content/sci/early/2021/03/24/science.abg9175.full.pdf).
In addition, the study reported under reference 19 had only a follow-up of a few weeks and hence, did not investigate whether B cell clones evolved and underwent further SHM as occurs after natural Sars-CoV-2 infection. Further SHM as described in the previously mentioned study (20) takes, indeed several months. So, today there is no evidence whatsoever that mRNA vaccines in their own right are capable of inducing memory B cell clones that evolve towards recognition of a broader spectrum of variants. In fact, this seems very unlikely. Last, as there is compelling evidence that (a substantial amount of) asymptomatically infected subjects do not develop immunological B cell memory, even vaccination of

previously exposed but asymptomatically infected subjects will not result in antibodies with increased neutralizing potency and breadth of vaccinal Abs.

> "15. Adaptive immunity to SARS-CoV-2 and COVID-19. Sette A, Crotty S.Cell. 2021 Feb 18; 184(4): 861-880.
> 16. Highly functional virus-specific cellular immune response in asymptomatic SARSCoV-2 infection Nina Le Bert, Hannah E. Clapham, Anthony T. Tan. Et al. J. Exp.Med. 2021 Vol. 218 No. 5 e20202617
> 17.Down but far from out: The durability of SARS-CoV-2 immunity after asymptomatic infection. Kedl RM.J Exp Med. 2021 May 3; 218(5): e20210359. doi: 10.1084/jem.20210359.
> 18. Dual Nature of Type I Interferons in SARS-CoV-2-Induced Inflammation. King C, Sprent J.Trends Immunol. 2021 Apr; 42(4): 312-322.
> 19. Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination. Goel RR, Apostolidis SA, Painter MM, et al. Sci Immunol. 2021 Apr 15; 6(58): eabi6950. doi: 10.1126/sciimmunol.abi6950.
> 20. Evolution of antibody immunity to SARS-CoV-2. Gaebler C, Wang Z, Lorenzi JCC, et al. Nature. 2021 Mar; 591(7851): 639-644.
>
> **Effectivity mRNA vaccines**
> From a practical perspective, several studies have shown the effectivity of mRNA vaccines for several mutated strains. This is based on the presence of neutralizing antibodies, memory B cells and T cell activity. This is again contradictory to your opinion that vaccine-induced responses are antigen-specific and hence, not properly recognizing mutated S protein, "especially not when originating from highly infectious variants"."

We know about your excitement about mRNA vaccines. However, this is no excuse for committing an immunological faux pas so egregious that it shocks me when you are saying that vaccine-induced responses are not antigen-specific! First, enhancement of Ab affinity through maturation and SHM does not imply a change in specificity (although antigenic shift has been described for viruses it has not for recognition by neutralizing antibodies!). Secondarily, we're not talking about monoclonal Abs but polyclonal sera! Furthermore, the real test is protection *in vivo.* There can be no doubt that even these mRNA vaccines do not block viral transmission and that their impact on reducing viral shedding strongly depends on the type of S-variant vaccinal Abs will have to deal with. There is meanwhile a myriad of publications confirming this! Consequently, there can be no doubt either that mass vaccination generates a substantial pool of potential viral spreaders. Why on earth would health authorities otherwise advise vaccinees to continue wearing face masks? The higher vaccine coverage rates, the more likely the virus will spread amongst asymptomatic vaccinees (i.e., at least as long as the vaccines protect against (severe) disease) and the higher the likelihood circulating variants will further evolve to a higher level of infectiousness and ultimately resistance to the vaccine.

> "Both mRNA vaccines (Pfizer, Moderna) generate significant neutralizing antibody titers, B cell memory and virus-specific T cell responses (19, 21).
>
> To further elaborate on the mechanism, vaccines require a pathogen-specific immunogen as well as an adjuvant —the latter stimulates the innate immune system and provides the necessary second signal for T cell activation. An optimal adjuvant stimulates innate immunity without inducing systemic inflammation that could elicit severe side effects (hence simulating infection without systemic inflammation; a possible culprit for natural infection sequalae). For mRNA vaccines, the mRNA can serve as both immunogen (encoding the viral protein) and adjuvant, owing to intrinsic immunostimulatory properties of RNA (21)."

You copied this from the cited publication. However, I am not aware of any study showing that the mRNA contained within Covid-19 mRNA vaccines serves an adjuvant function. There is no reference

backing up the statement made in that publication. It's not like any type of ss RNA will serve as a TLR3 or TLR7 ligand. In addition, in order for this mechanism to enhance antigen (Ag) presentation, it is critical that both the Ag and the adjuvant are taken up by the same APC. I don't think there is any evidence that APCs translate the mRNA into S protein while at the same time triggering an mRNA-mediated TLR pathway. Lipid or polymer-based nanoparticles serve as a kind of adjuvant for mRNA vaccines in that they protect and stabilise the fragile mRNA and enhance its delivery into target cells.

> "21. COVID-19 vaccines: modes of immune activation and future challenges. Teijaro JR, Farber DL.Nat Rev Immunol. 2021 Apr; 21(4): 195-197.
>
> Next you vehemently present as a fact that there can be no pressure on the virus after natural infection, as "the protection is not provided by adaptive immunity but solely by natural immunity."

Again, you are twisting my words! What I am really saying is that there is no selective pressure on the virus when it gets under attack by NK cells as is likely the case in asymptomatically Sars-CoV-2- infected subjects.

> "Being non-specific, it cannot put selective immune pressure on the virus!" This opinion stands corrected by several studies demonstrating an important role for adaptive immunity in natural infection and vaccine generated protection. Saine et al. (22) show COVID-19 disease to drive substantial T cell activation, with T cell recognition of a large number of SARS-CoV-2-derived peptides. Of interest is the observation by the authors that considerable Tcell recognition of such peptides exists in healthy donors, arguing for crossrecognition, potentially from T cells raised against other coronaviruses (considered by you as "nonsense" (sic)), likely influencing immune response to SARS-CoV2."

I maintain that your reasoning re: T cell recognition of SARS-CoV-2-derived peptides is completely irrelevant in the context of protection against INFECTION, which is what is of paramount concern for the further evolution of a pandemic. Also, you seem - once more - to suggest that immune responses from natural infection will translate into similar responses upon vaccination. And even though cross-reactive T cells do exist, there is absolutely no evidence that those contribute to preventing viral infection or abrogating it at an early stage. In terms of their capacity to kill virus-infected cells at a later stage of infection, it seems like you are confusing cross-reactivity ('cross-recognition') with cross-protection! As far as vaccine-induced immunity is concerned, none of the current vaccines have been shown to induce *protective* T cells (i.e., CTLs)

> "Regarding B cells, convincing published data present an important role in natural infection. Ogega et al (23) show most SARS-CoV-2-infected individuals to develop SRBD–specific, class-switched resting memory B cells that resemble germinal center–derived B cells induced by effective vaccination against other pathogens, providing evidence for durable B cell–mediated immunity (antibodies and memory B cells) against SARS-CoV-2 after mild or even severe disease (19)."

I am not sure I understand how the above citation about the durability of B cell immunity contributes to the discussion. The problem of the Abs secreted by these B cells is not their longevity/ durability but their lack of blocking transmission of the steadily growing number of highly infectious variants. I have highlighted several times the link between the resulting increase in infectious pressure and the likelihood

for previously asymptomatically infected subjects to get re-infected while having their innate, CoV-nonspecific Abs suppressed by suboptimal S-specific Abs.

> "Continuing on the topic of T cells in SARS-CoV2 infection, you are mistaken again for referring as a fact that "vaccines do not induce cytotoxic T cells". Several studies clearly show mRNA vaccines to induce virus-specific helper T cells and cytotoxic Tcells, both of which might be involved in protection against challenge. (22,24)"

Reference 22 does not relate to vaccine-induced cytotoxic T cells (CTLs) but merely to their induction upon natural infection. On the other hand, reference 24 literally states:

"*mRNA vaccines also induce virus-specific helper T cells and cytotoxic T cells, both of which <u>might</u> be involved in protection against challenge*".

Seriously, is this the best evidence you could find? There isn't even any reference backing up this statement. In addition, CTL responses are MHC class I-restricted. So even if such responses would be induced by mRNA vaccines, there is no way they could be induced broadly. Indeed, CD8+ T cells elicited by conventional vaccines only protect individuals who are already genetically predisposed to T cell-mediated viral control by virtue of expression of protective MHC class I alleles! Again, this relates to basic knowledge of immunology and is a too well-known conundrum for vaccinologists.

> "22. SARS-CoV-2 genome-wide T cell epitope mapping reveals immunodominance and substantial CD8+ T cell activation in COVID-19 patients. Saini SK, Hersby DS, Tamhane T, et al. .Sci Immunol. 2021 Apr 14; 6(58): eabf7550. doi: 10.1126/sciimmunol.abf7550.
> 23. Durable SARS-CoV-2 B cell immunity after mild or severe disease. Ogega CO, Skinner NE, Blair PW, et al. J Clin Invest. 2021 Apr 1; 131(7): e145516. doi: 10.1172/JCI145516.
> 24. SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants. Moore JP, Offit PA.JAMA. 2021 Mar 2; 325(9): 821-822.
>
> Finally on the topic of anti-S antibodies, one should consider the breadth of polyclonal antibody response against specific epitopes of the Spike protein. A mutation in the RBD does not imply that all polyclonal blocking/neutralizing antibodies directed against that specific epitope become ineffective. mRNA vaccines, in particular, induce such a strong neutralizing antibody response that there seems to be enough "spare capacity "to deal with reductions in the sensitivity of the variant viruses to neutralizing antibodies" (24)."

Did you even realize that the very publication you are citing is raising the issue of immune escape as a result of suboptimal immune pressure? Did you even read it? Let me share an excerpt from this reference (24):

"*Variants in the S-protein that increase the amount of virus shed from an infected person or that increase its affinity for the ACE2 receptor are likely to increase virus transmission, an important problem in the context of a pandemic. Furthermore, the same or similar alterations can change the shape of the S-protein and impair or even destroy NAb binding sites. Hence, by extrapolation, vaccine efficacy might be compromised. These "escape mutations"* ***typically arise when the virus is put under selective pressure by antibodies that limit but do not eliminate viral replication****. Under these conditions, the virus might then find a way to escape this pressure and restore its ability to reproduce more efficiently.* ***The scenario of virus evolution in the face of suboptimal immunity is one reason extending the interval between the first and second dose of a SARS-CoV-2 vaccine might be problematic"****.*

> "This is in stark contrast to your simplified representation of polyclonal antibody failure to effectively block viral activity. Your one-dimensional perspective on infection induced antibody response is only applicable when considering use of monoclonal antibodies for passive immunization and treatment of early COVID-19, which is not the addressed topic (25,26)."

Your misleading enthusiasm about the omnipotence of mRNA vaccines can only be explained by the fact that you are still not understanding the theory of Darwin and the power of natural selection. Not understanding how natural selection promotes survival and propagation of the fittest prevents you from understanding that the Sars-CoV-2 variants have been selected in ways to successfully escape 'your' polyclonal immune response. When the latter will be induced as a result of vaccination, variants that succeed in escaping this immune response will be trained to more easily overcome this immune pressure. Mutations selected in these variants will be such that they enable the virus to escape from the vaccine-induced immune response, no matter the breadth of that response. So, it's not a matter of which and how many epitopes can be targeted by the vaccine but how the virus can escape the overall S-targeted immune response such as to survive and reproduce more efficiently. So, natural evolutionary selection will not 'spare' a 'strong' neutralizing antibody response. But as a more practical way of getting convinced of how badly these vaccines perform against the variants, you may want to take a somewhat deeper dive in the literature to learn how easily the South-African variant breaks through the immunity of mRNA-vaccinated people.

> "25. Neutralizing monoclonal antibodies for treatment of COVID-19. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL.Nat Rev Immunol. 2021 Apr 19:1-12.
> 26. FDA NEWS RELEASE 16-04-2021 Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab
>
> As of today we have reached a grim milestone worldwide of more than 3 million direct COVID-19 deaths and the pandemic has set us back in many ways within healthcare and has resulted in devastating effects on the socio-economical level. Countries like India in which neither public health measures, nor vaccination, are adequately implemented are facing the catastrophic brunt of 'the virus running its course' Furthermore it is becoming increasingly clear that post initial SARS-CoV2 infection long term sequelae will have high morbidity impact on a sizable group of persons (6) further increasing the necessity for vaccinations in preventing natural infections."

You are obviously depicting this grim milestone of 3 million Covid deaths to conclude on the need for mass vaccination campaigns. But where is your evidence proving that those are actually having a beneficial effect on the course of the pandemic? You can help limiting the damage by doing the science instead of blindly adhering to the mantra of vaccination and completely ignoring the premises for adequate use of these vaccines! Again, the conditions for these vaccines to be useful are not fulfilled when deployed in mass vaccination campaigns in the midst of a pandemic of a highly mutable virus! Having studied and analyzed in depth the course of the pandemic in several different countries, I cannot see any evidence whatsoever that ongoing mass vaccination campaigns are having a beneficial effect on the evolution of this pandemic! On the contrary! As already explained on multiple occasions, the spectacular declines of cases observed in some countries (Israel, UK, Portugal, Hungary, Uruguay,…) cannot be attributed to a beneficial impact of these vaccination campaigns!

> **"Conclusion**
> The internet and social media have changed the world as we know it. In their strength, they are now also a platform easily used for spreading misinformation sometimes with disastrous consequences. Using social media to reach millions with inaccurate unfounded personal opinion and thereby causing distractions and vaccination hesitancy, potentially contributing to unnecessary loss of life, is condemnable."

I fully agree. This could not be illustrated any better than by your misinformative video (https://youtu.be/Izb3IOkJJfY) Since 'experts' like you and others refuse to enter in a public scientific debate, there is no other way for independent scientists to convey their important scientific insights but to also use these channels.

> "To end the pandemic as soon as possible, we must collectively continue to rigorously focus on essential public health interventions and aggressive and effective vaccination programs. These are based on sound science supported by published data in peer reviewed journals from the fields of public health, immunology and virology. Not baseless misinformation."

I hope it has become very obvious from the comments above as well as those inserted in your 'take home messages for laymen' below that you have not been providing any sound scientific arguments to back up 'aggressive' mass vaccination campaigns. The panoply of peer-reviewed journals are not supportive of your claims and many times even inconsistent with those. This is not at all to say that the science in these publications is not of good quality but rather that even peer-reviewed journals can at most merely provide some pieces of a complex puzzle. Given the fact that, in many regards, we are dealing with a completely unprecedented situation, there is still some homework to be done in order to put these pieces together. This homework can only considered being finished when it provides a scientifically sound explanation for the observations made and the evolution to be expected. Your story does not match these criteria. This is worrisome as all rhetoric based on extrapolation of conventional wisdom, misinterpretation of data and simplistic reasoning will only create a breeding ground for even more uncertainty and confusion.

> "We have no conflicts of interest to disclose."

In that case, the future will unveil how to reconcile your scientific integrity with your fanatic enthusiasm about moving these mass vaccination campaigns forward, regardless of all shortcomings I highlighted above.

> "Sincerely,
> Prof. Dr. AJ Duits, PhD, I Gerstenbluth, MD, MSc
> Medical Immunologist Public Health Physician & Epidemiologist"

Geert Vanden Bossche, DVM, Phd.

> **"Take home messages for laymen**
> **Is vaccination the solution for successfully addressing a pandemic?**
> Yes. All scientific evidence shows that a vaccination program combined with stringent public health measures will end the SARS-CoV2 pandemic."

Where is this evidence? How could this evidence even exist, given that the extent of human intervention in this pandemic is simply totally unprecedented and that there is no data on the long-term effect of these vaccines? Where are the publications proving that this is not just a large scale *experiment*, the outcome of which is fully unknown but a rational approach, based on sound scientific grounds and, therefore, ensuring a successful outcome? Are you taking full responsibility for the statement you make above in that you would at least quit your position in case mass vaccination with the current vaccines (e.g., mRNA vaccines) combined with stringent public health measures are not going to end this pandemic in a saving-lives way? And what is the timing for your optimistic scenario?

> "It is very important to make use of a vaccine proven to be effective and adhere to public health measures. This approach is supported by the WHO and by studies done by scientists of different renowned institutes like University of Oxford, Imperial College of London, London School of Hygiene and Tropical Medicine, University of Singapore, University of Hong Kong."

Big names are no guarantee for success. WHO miserably failed when Ebola struck Africa and world-class institutes failed in designing an effective vaccine against HIV. This is not to say that I do not respect the efforts of the scientists involved. It is just that finding solutions to complex problems takes more than having reputational institutes or organizations work on it.

> **"Is letting the virus spread through natural infection to successfully address the SARS-CoV2 pandemic advisable?**
> No. This should be firmly rejected given the disastrous consequences; overwhelming health care capacity, loss of life. This is currently seen in for example Brazil and India. Furthermore, it is now known that persons recovered from the initial disease episode of COVID-19 can suffer from debilitating
> symptoms that persist for months (post covid syndrome), without effective treatment. The economic consequences are dire."

I never said we should let the pandemic run its natural course. What I am saying is that the unthoughtful deployment of current vaccines in the heat of a pandemic is going to promote the spread of highly infectious variants and ultimately lead to resistance to the vaccines. You seem to pretend that doing something, even if unproven to be beneficial and likely to be harmful, is better than not doing anything. We need to be more innovative in that we focus more on novel concepts of immune intervention than on new (manufacturing) technologies of conventional vaccines.

> **"What examples do exist of successful vaccination and public health programs for addressing the COVID-19 pandemic?**
> Several well-documented examples have been published on institutional, regional and country level. We mention two:
> Israel

> Israel was one of the first countries to introduce a vaccine program (using mRNA vaccine from Pfizer) combined with stringent public health measures in December 2020. They have documented and published their data. These show an impressive reduction of persons getting infected, sick and/or dying."

As abundantly explained in several different contributions on my website, this spectacular drop in cases was certainly not a result of the vaccination campaign that only started around the time when the infection peaked.

> "As they have reached about 70% of their population vaccinated, the country is now finally starting to relax its measures and allowing its citizens a more normal way of life.
>
> *Data reported among others by Clalit Research Institute, Innovation Division, Clalit Health Services, Tel Aviv, the School of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Be'er Sheva, Weizmann Institute of Science, Rehovot, Israel."*

The level of vaccination should not determine the level of relaxation of measures. One needs to understand that vaccinees are to be considered asymptomatic spreaders, thereby enabling the virus to evolve to overcome suboptimal immune pressure imposed by S-targeted antibodies in a steadily growing population of vaccinees. Those who do not believe this will have to witness how vaccinees will ultimately breed highly infectious, 'home-made' or imported variants or even resistant variants (the latter applies to countries where mass vaccination campaigns are progressing on a background of low infectious pressure).

> "Curaçao
> On the Caribbean island of Curaçao an immense COVID-19 outbreak (at a certain point the highest new cases per 100.000 inhabitants in the world) was successfully halted by stringent public health measures and then showed rapid decline after implementation of an aggressive mass vaccination program (using
> mRNA vaccines by Pfizer and Moderna) after 2 weeks (reaching almost 50% of the population vaccinated with minimally 1 shot).
>
> *Data reported by the Epidemiology and Research Unit, Government of Curaçao."*

Again, mass vaccination in Curaçao was only brought up to speed in the first week of April, which was exactly at the summit of the wave of cases. As repeatedly mentioned, the steep decline following such a peak is not to be considered an effect of mass vaccination. It barely took 2 weeks for the peak to decline by 50%. This can, indeed, not be attributed to the vaccination campaign as this was exactly the time it took Curaçao to ramp up its vaccine coverage by a single dose from 10% to around 25% of the population (and from 3 to 8% of the population for the 2 doses).

> **"What do we know of countries that have chosen for an approach based on natural infection?**
> The results have been devastating with a high number of patients with COVID-19 related complications and deaths. The hospitals and medical staff have been under extreme pressure to help each and every patient and in several countries the system has been completely overwhelmed. This also results in people suffering from other health issues not getting needed access to care."

It is likely that overcrowding and poor personal and environmental hygienic conditions resulting in abundant asymptomatic infection during and following the first (mild) wave have led to enhanced

selection and adaptation of highly infectious mutants in the Indian population (see Q & A above). Whereas you believe that enhancement of mass vaccination in India will control the number of cases, I am expecting that increasing vaccination rates will merely provide a huge competitive advantage to the semi-resistant, highly infectious mutant(s) that are currently circulating in India, thereby causing a further increase in cases.

> "India
> On 24/04/2021 India reported 349,691 new cases of Covid-19 during the coronavirus pandemic (with 2627 deaths) according to official reports. Hospitals don't have sufficient intensive care units, oxygen, ventilators and supplies. The country has struggled with implementing public health measures and setting up a mass vaccination program (based on Covaxin (an Indian vaccine (inactivated virus based) and Covidshield (Astra-Zeneca vaccine produced locally)). On 24/04/2021 only 8.5% of the population had been vaccinated with minimally 1 shot. The country has also been facing the emergence of a SARSCoV2 variant that seems more infective (B1.617 is however still only present in a relative small proportion of cases).
>
> *Data from the Johns Hopkins institute, University of Oxford, University of California*
>
> Manaus, Brazil
> The effects of the SARS-CoV2 pandemic in Manaus, Brazil (population 2 million) has been well documented. Despite achieving at first a high percentage of persons naturally infected in October 2020 (76%), with no effective public health measures implemented and no effective vaccination program, uncontrolled resurgence of COVID-19 was subsequently observed with dire consequences. These results show that aquiring herd immunity by infection is not an option.
>
> *Data reported among others by Departamento de Molestias Infecciosas e Parasitarias and Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo , Imperial College London"*

How does this relate to the case you want to make about mass vaccination campaigns?
If even a rate of infection as high as 76% (based on seroconversion) as a result of natural infection does not suffice to provide sufficient herd immunity to protect the population against subsequent, even more dramatic, waves of morbidity and mortality, how then could mass vaccination be successful? Or do we think that vaccine coverage rates beyond this percentage will provide herd immunity as the threshold for herd immunity may suddenly be reached at a somewhat higher coverage rate? Where is the science? In the light of these data, what is your rationale for assuming that (slowly) progressing vaccine campaigns will perform dramatically better than rapidly spreading natural infection? Please go on my website and educate yourself on how high infection rates are likely to re-expose previously asymptomatically infected subjects at a time when their natural Abs are heavily suppressed (i.e., shortly after their previous infection). It is more than time to move away from the idea that mass vaccination campaigns with vaccines that are unable to block transmission are going to help us hit some illusive threshold of herd-immunity that will make this pandemic go away for good!

> "Sweden
> Sweden also supported a natural infection program based on voluntary public actions. This has resulted in a much higher patient infectivity, burden of hospitals and deaths in comparison to neighboring countries. Our World in Data COVID-19 statistics, with 606 new infections per million per day, with its neighbors Denmark, Finland, and Norway reporting 115, 62, and 112 new infections per million per day, respectively (April 15, 2021).
>
> *Data reported by Results for Development, Washington, DC 20036, USA (MC); Spånga Transkulturella Läkarmottagning, Spånga, Sweden (SH)"*

Alike Sweden, Denmark has been facing a large peak of cases between the end of Oct 2020 and the end of Jan 2021. Both peaks were followed by a steep decline in cases before vaccine coverage rates became more significant (i.e., with less than 3.5% of the population having received a single dose in both countries). As Sweden's mass vaccination campaign was brought up to speed on a background of a rising number of cases, it is likely to have contributed to the overall amplitude of the third wave that is currently still in the process of declining. In Denmark however, the mass vaccination campaign was brought up to speed on a relatively low infection rate background, thereby leading to a relatively lower increase in cases and causing the curve to merge into an elevated plateau rather than a clear-cut peak (i.e., the plateau of infection cases is now situated at a level that is relatively higher than the one observed for previous plateaus in-between the first, second and third wave). In addition, the biggest peak in Sweden has not been any more pronounced than those observed in Israel, UK, USA, France etc. Or did these countries not adhere to the disinfection prevention measures either? As from now, the impact of infection prevention measures will increasingly vanish as plateaus are now reflecting the ongoing infection and transmission chains occurring amongst asymptomatic carriers who increasingly serve as a breeding ground for more infectious variants that suffer much less from infection prevention measures.

> "Chile
> The recent data presented by Chilean scientists and the government show escalating COVID-19 infections, medical complications and deaths while implementing a mass vaccination program reaching a high percentage of the population vaccinated (41%). One of several possible explanations is the lack of effectivity of the mainly used vaccine for the program (Sinovac; inactivated virus based vaccine). The data from Chile show only 3% or 16% effectivity after the first shot (in comparison Pfizer mRNA shows 46% effectivity after the first shot in Israel).
>
> *Data reported among others by Universidad de Chile, Santiago, Chile, , Ministerio de Salud, Gobierno de Chile., Clalit Research Institute, Innovation Division, Clalit Health Services, Tel Aviv"*

This explanation is too simplistic! Even before the summit of the peak in Chile was reached, 20% of the population got *fully* vaccinated! This is three times the rate of the full regimen vaccination that was associated with a steep decline of cases in the UK. Even a coverage rate of 24% (single dose of mRNA vaccine) and of 13% by a full vaccine regimen did no protect the US population from a resurgence in cases between mid March and mid April 2021! In all countries, deployment of mass vaccination campaigns on a background of a plateau or rising infection rates seems to lead to an increase in the number of cases. This especially applies if more infectious strains are circulating (e.g., Chile, Brazil, Uruguay, India…)

> **"Does a program based on vaccination lead to viral mutations whereas a program based on natural immunization does not?**
> Studies show that the emergence of viral mutations is related to unbridled virus reproduction in a community; the earlier we stop availability of hosts for the virus the less chance the virus has to mutate."

This is the 'cheap' mantra of vaccination as proclaimed by the WHO. This is ignoring the basics of evolutionary biology which dictate that harsh conditions (in this case suboptimal immune pressure) will lead to natural selection, adaptation and hence, survival and more efficient reproduction and, therefore, dominance of the fittest.

> "Obviously a program based on natural infection would prolong the period of virus reproduction in a population and lead to mutations (as shown for example in Manaus). As a fact most known SARS-CoV2 viral mutations of growing concern were described before the start of massive vaccination programs."

Your statement in the first sentence is not based on any plausible scientific rationale. It can also not be denied that since implementation of mass vaccination campaigns a myriad of additional more infectious strains have started to circulate. I have never been saying that more infectious variants were not already circulating before mass vaccination campaigns were initiated. On the contrary! But mass vaccination campaigns promote selection and adaptation of more infectious variants or provide newly introduced variants with a competitive advantage. Both phenomena are resulting in enhanced viral spread and infection rates and, therefore, lead to enhanced susceptibility of previously asymptomatically infected subjects.

> **"Are mRNA vaccines effective and safe?**
> Several studies and data garnered on millions of persons vaccinated with mRNA vaccines have shown a high grade of protection against infection and or disease with no safety issues of concern.
>
> *Data provided among others by Centers for Disease Control, USA."*

I am leaving this topic to the sound judgment of other experts. The point I am criticizing is not vaccine safety and efficacy as evaluated on an individual and short-term basis but rather the mid- and long-term consequences of mass vaccination campaigns conducted in the midst of a pandemic of a highly mutable virus. No single report, publication or document provides any kind of sound scientific rationale for the effectiveness and safety thereof in terms of controlling the pandemic and the ever increasing number of more infectious variants, let alone for assessing the risk of vaccine-resistance evolution.

> **"Does mRNA vaccination give a higher degree of protection than natural infection?**
> Studies have shown convincingly that vaccinated persons have a higher degree of protection based on higher levels of protective antibodies and protective cells (T and B cells). Furthermore in Manaus a high degree of naturally infected persons (70%) did not provide sufficient protection for COVID-19 resurgence. Thus, ...
>
> *Data provided among others by Cedars-Sinai Medical Center, Los Angeles, CA, USA.,*
> *Icahn School of Medicine at Mount Sinai New York, NY"*

Thus what? Thus, 'be nice and get yourself vaccinated', correct? See my comments above: Mass vaccination campaigns are not going to perform any better than widespread natural infection. You're simply substituting nonvaccinated asymptomatic carriers by asymptomatic vaccinated carriers as a breeding ground for more infectious – or even vaccine-resistant variants. Alike widespread and uncontrolled natural infection, ongoing vaccination campaigns in the midst of a pandemic are going to lead to high rates of suboptimal S-directed immunity and will thereby create selective pressure, which will favor dominant propagation of variants that are able to infect people who have been immunized. And where is the scientific evidence that mRNA vaccines induce protective T cells (protective T cells are to be understood as cytolytic T cells); as already mentioned- there is no single antigen that confers broadly protective CTL-mediated protection due to MHC class I-restriction of CD8+ T cell responses. Hence, your statement is simply wrong.

Author: Geert Vanden Bossche, DVM, PhD (May 3 2021) – www.geertvandenbossche.org

ATTACHMENT

15. Adaptive immunity to SARS-CoV-2 and COVID-19. Sette A, Crotty S.Cell. 2021 Feb 18; 184(4): 861-880.

As mentioned above your cited reference 15 contains a number of things you seemed to ignore or not to know. In bold you will discover further evidence of shortcoming of current vaccines and the role of CD8+ T cells in protecting against (severe) disease at a later stage of infection.

Adaptive immunity to SARS-CoV-2 and COVID-19.

An ideal COVID-19 vaccine would elicit long-lasting high titer neutralizing antibody titers and **would provide sterilizing immunity to prevent disease and onward transmission**.

Priming of the immune system by a vaccine happens **well in advance of virus exposure**. **One key feature of vaccines is that immunization occurs well in advance of infection, giving the adaptive immune system time to respond, expand, and mature**

Although lung infection is a major component of severe COVID-19 (and relatively slow), URT infection is important for transmission. **Notably, a vaccine that can prevent severe disease, or even most URT symptomatic diseases, would not necessarily prevent transmission of virus**. For example, the current pertussis vaccine prevents clinical disease but not infection, and probably not transmission (Warfel et al., 2014), and **much SARS-CoV-2 transmission occurs early, during the pre-symptomatic phase** (He et al., 2020). Several non-human primate COVID-19 vaccine studies are consistent with the possibility of COVID-19 vaccines preventing severe disease in humans but possibly **not preventing URT infection** (Corbett et al., 2020; van Doremalen et al., 2020; Gao et al., 2020; Guebre-Xabier et al., 2020; Mercado et al., 2020; Tostanoski et al., 2020; Vogel et al., 2020; Yu et al., 2020). **It is plausible that SARS-CoV-2 infection may elicit better protective immunity in the URT than any of the major current COVID-19 vaccine candidates**, because infection occurs at that site and is therefore more likely to elicit tissue-resident memory

Prevention of transmission is also an important topic. The Pfizer and Moderna clinical trials were not designed to test this, but in the Moderna trial there were swab tests on the day of the second immunization. There were substantially fewer asymptomatic infections detected in the vaccinated group after a single immunization (**67% reduced**) (U.S. Food and Drug Administration, 2020a). For the AstraZeneca/Oxford ChAdOx1 vaccine efficacy against asymptomatic SARS-CoV-2 infection was **27%**

CD8+ T cell responses to candidate COVID-19 vaccines in humans or non-human primates are either largely absent or not measured in the current literature (e.g., the CanSino Ad5 vector-based vaccine did not distinguish between CD4+ and CD8+ T cells by ELISPOT) (Zhu et al., 2020).

The relatively slow course of severe COVID-19 in humans (median 19 days PSO for fatal cases) (Zhou et al., 2020a) **leaves open the reasonable possibility that protective immunity against symptomatic or severe 2 COVID-19 may very well involve memory compartments such as circulating memory T and B cells** (Altmann and Boyton, 2020; Baumgarth et al., 2020).

In a natural infection, the adaptive immune response takes time to develop, and many cells are already infected by the time an antibody response develops. Frequently antibodies alone cannot clear an ongoing infection, it also takes T cells. This may be why SARS-CoV-2 neutralizing antibody titers have

not correlated with lessened disease severity in primary COVID-19 (Baumgarth et al., 2020; Rydyznski Moderbacher et al., 2020; Tan et al., 2020a).

In SARS-CoV-2 infections, **the presence of virus-specific CD8+ T cells has been associated with better COVID-19 outcomes** (Rydyznski Moderbacher et al., 2020; Peng et al., 2020). **Overall, circulating SARS-CoV-2-specific CD8+ T c2222ells are less consistently observed than CD4+ T cells** (Grifoni et al., 2020; Rydyznski Moderbacher et al., 2020; Sekine et al., 2020).