Immediate cancellation of all ongoing Covid-19 mass vaccination campaigns should now become *THE most acute health emergency of international concern*

Introduction

So far, nobody has provided any kind of scientific evidence or rationale that massive human intervention (i.e., global implementation of infection prevention measures and mass vaccination) in the Covid-19 pandemic will lead to a decrease in mortality and morbidity rates in the human population. These large scale human interventions have been initiated without paying any attention to the population dynamics of a natural pandemic as caused by acute (self-limiting) viral infections. The best example of such a natural pandemic is probably the H1N1 Influenza pandemic that occurred during world war one (see fig 1). The natural course of this Influenza pandemic was not distorted by wide-spread implementation of infection prevention measures or mass vaccination programs. The pandemic was characterized by 3 waves before the virus became endemic.

How can we even consider intervening into a natural pandemic without any basic understanding of the evolutionary–shaped interplay between the virus and the population's immune status? Uninformed hygiene/ containment and immune interventions are at risk of disturbing the natural dynamics of a pandemic and hence, to prevent the virus and the population's immune defense from making a compromise that is 'viable' for both the virus and the immune system, and that naturally follows the 3 waves of mortality and morbidity. When the virus ultimately comes to terms with the immune system, herd immunity will prevent the virus from causing a further sequence of morbidity and mortality waves while being 'leaky' enough to not eradicate the virus. Any intervention that increases the population's immune pressure on the virus without eradicating the virus will inevitably lead to selective viral immune escape (see below).

Selective viral immune escape is, for example, known to occur when the neutralizing capacity of Ag (antigen-)specific serum antibodies (Abs) does not suffice to fully eliminate highly mutable viruses (e.g., Coronavirus; CoV) for lack of concentration or affinity. Due to large-scale infection prevention measures implemented as of the beginning of the pandemic, viral replication and spread have increasingly occurred on a background of high immune pressure and have, therefore, led to viral immune escape. The infectious variants that started to emerge end 2020 are a direct consequence of measures taken to prevent the virus from spreading.

Natural course of a pandemic caused by acute viral infection

The first wave of disease[1] (and mortality) primarily affects elderly people (or, more generally, subjects with weak innate immunity). Increasing viral spread causes this wave to transition into a more severe, second wave in younger age groups. Subsequently, declining Ab titers in seropositive subjects (i.e., those who recovered from disease contracted during the first wave) and increasing infectious pressure will trigger a third wave affecting both age groups. This third wave of disease (and mortality) comes to an end when those who are recovering from the disease will mount functional Abs against the circulating viral strain. The virus has, indeed, no chance to provoke an additional wave of morbidity and mortality in previously infected people whose Ab titers have meanwhile started to wane. Because of immunologic memory, seroconversion in this population segment will now occur very fast whereas those with sufficient innate immunity continue to resist the disease. This is to say that following the 3rd wave of a natural pandemic, viral spread will dramatically diminish as a result of strong herd immunity consisting of both, adaptive and innate immunity. It is interesting to note that during a natural pandemic (i.e., without human intervention), there is no need for the virus to select mutations that render it more infectious.

It is reasonable to assume that CoV can persist in the population despite herd immunity. Previously symptomatically infected subjects may spread the virus upon re-infection when their seroneutralizing Ab titers are no longer high enough to curtail viral replication at the mucosal portal of entry. Likewise, asymptomatically infected subjects[2] (i.e., the vast majority of young and middle-aged people) may also transmit virus upon (re-)infection. So, after the pandemic has come to an end, the virus continues to spread in the population, thereby causing endemic infection. However, as long as the majority of the population disposes of sufficiently high S-specific Ab titers or natural Abs (i.e., herd immunity!), waves of mortality and morbidity will no longer occur.

Asymptomatic carriers

CoV infection in asymptomatic carriers is abrogated after a short period of viral shedding. Viral clearance in these subjects is likely to occur through activation of NK cells. The latter are capable of recognizing CoV-associated, Ag-nonspecific patterns on the surface of CoV-infected

1 For the purpose of this manuscript, 'disease' refers to *severe* Covid-19 disease with involvement of lower respiratory airways

2 For the purpose of this manuscript, 'asymptomatic' infection refers to CoV infection which does not cause clinically relevant symptoms or only causes a mild level of disease (i.e., only involving upper respiratory airways)

epithelial target cells. As killing by NK cells is not Ag-specific, this immune mechanism is not susceptible to selective immune escape (cfr. below).

Selective immune pressure and immune escape as a result of large-scale human intervention in the pandemic

Any intervention in the pandemic that directly (e.g., through mass immunization campaigns) or indirectly (i.e., through infection prevention measures) exerts significant pressure on viral infectiousness (and hence, exerts selective pressure on the spike [S] protein) will enable the virus to escape whenever it gets exposed to S-specific Abs that are suboptimal, either in concentration or affinity. This will inevitably allow the virus to rapidly unfold more infectious, immune escape variants. Mass vaccination campaigns conducted after a prolonged period of infection prevention measures will dramatically increase pressure on viral infectiousness because of broad selective immune pressure on S protein (due to S-specific Abs). Such additional immune selection pressure, especially when exerted during the second wave of a CoV pandemic, is likely to precipitate and amplify viral immune escape. It is reasonable to assume that the cumulative selective pressure on viral infectiousness may cause the second and third wave of the pandemic to dramatically increase and to merge into an even much bigger wave of disease and death that is ultimately going to affect all layers of the population (possibly, with the exception of small children).

Current mass vaccination campaigns comply with the above-mentioned conditions for dramatic enhancement of S-selective immune escape. When conducted in the midst of a pandemic, mass vaccination campaigns (using the current Covid-19 vaccines) exert an enormous amount of pressure on circulating virus strains.

However, as the S protein comprised within current vaccines does not properly match the S protein of the 'pre-selected', highly infectious variants and as the latter have now become dominant, use of these vaccines in mass vaccination campaigns will inevitably accelerate the emergence of even more infectious immune escape variants. This is because the number of vaccine recipients who are in the process of seroconverting while already being exposed to the virus will dramatically increase[3]. This leads to viral infection in the presence of a suboptimal immune response. Viral (re-)infection in the presence of suboptimal/ immature immune responses may also occur in vaccine recipients who are waiting for their second dose of a 2-shot vaccine or whose vaccinal Abs do not fully recognize the S 'edition' of the Covid-19 variants. Vaccination of subjects who are seropositive as a result of natural Covid-19 disease may have substantially prolonged S-specific Ab titers. These subjects may, therefore, serve as a

[3] Alike naturally infected subjects, vaccine recipients need time to mount a full-fledged Ag-specific Ab response

reservoir for sustained immune escape. The more the virus' S protein becomes immune pressurized, the more it will select escape mutations that converge towards the receptor-binding domain (RBD) of the S protein (as those are obviously more effective in escaping vaccine-induced Abs). This will inevitably lead to complete resistance of Covid-19 variants to any of the current vaccines and, therefore, further increase viral infectiousness.

Along the same lines of reasoning, it is not unthinkable that Covid-19 will, once again, cross species barriers. One can definitely not rule out that with growing immune-mediated selection of virus variants, Covid-19 is ultimately going to be able to jump to other animal species, especially industrial livestock (e.g., intensive pig and poultry farms with high stocking density) as i) these species are already known to host several different Coronaviruses and ii) variability/ mutations in the very spike protein, and particularly in the RBD, are known to be responsible for shifts in host tropism/ susceptibility. Similar to the situation with influenza virus, these animal species could then constitute a reservoir for SARS-COVID-2 virus. Depending on the prevalence of circulating animal CoVs in those farms (and hence, the level of trained immunity), those animals could now serve as asymptomatic carriers, thereby constituting a serious threat to humans.

Mass vaccination sidelines variant-nonspecific immunity in young and healthy individuals

S-specific, high affinity Abs induced by any of the current vaccines will outcompete natural, *broadly* protective natural sIgM antibodies as the latter only bind with low affinity to the spike protein of Covid-19. Even though the affinity of S-specific antibodies induced by these vaccines may no longer suffice to prevent S-mediated binding of Covid-19 variants to the RBD of CoV, they may still be able to hamper binding of sIgM. This is because natural sIgM Abs have low *affinity* for S protein (despite their high *avidity* for the virus surface). The ensuing suppression of the innate immune response will particularly affect natural resistance of younger age groups which - thanks to a well-trained innate immune system - resisted Covid-19 disease during the first wave. During the natural course of a pandemic, suppression of the innate immune system (and hence, potentially enhanced susceptibility to disease) in previously asymptomatically infected people (primarily the younger age groups) is only short-lived as they only experience a momentary increase in S-specific Abs after infection. Their vaccination, however, will lead to a long-lived suppression of their innate immune system while offering only limited or no protection against disease caused by highly infectious variants. It is, therefore, reasonable to assume that vaccination of young and healthy people will inevitably lead to long-lived suppression of their variant-nonspecific, innate immune defense at the mucosal portal of entry without offering a protective adaptive immune response. These age groups may, therefore, be

facing a prolonged increase of susceptibility to symptomatic infection and shedding, especially when exposed to more infectious variants.

As S-specific immune responses have immunological memory, the imprinted immunological 'program' of S-specific Ab generation and hence, innate immune suppression, will be recalled at every upcoming encounter with Covid-19 strains, or even with CoV strains at large (a phenomenon known as 'antigenic sin[4]'). This is at risk of inducing a persistent state of enhanced susceptibility to CoV-associated disease in vaccine recipients.

But mass vaccination campaigns will also have severe consequences for those who got vaccinated first (mostly the elderly, people with underlying disease or those who are otherwise immune compromised). In the highly likely event that mass vaccination will soon result in viral resistance to the vaccines, these people will have no arm of their immunity left to rely upon. In contrast to the infectious circulating virus, current vaccines do either not contain any critical killer cell motif or fail to activate dedicated killer cells. It goes, therefore, without saying that, vaccine-induced immune responses will inevitably result in a dramatic enhancement of morbidity and mortality rates in *all* of the vaccinated population when exposed to highly infectious Covid-19 variants.

Impact of continued infection prevention measures in non-vaccinated, previously asymptomatically infected subjects

Further to all of the above, insufficient exposure of non-vaccinated subjects to circulating CoV strains (e.g., due to stringent containment measures) will increasingly weaken their innate mucosal immunity for lack of training. Again, this is particularly relevant for those who - thanks to their sufficient and adequate innate immune defense – got away with asymptomatic infection during the first wave. Stringent and widespread infection prevention measures are now increasingly compromising their innate immunity and rendering them more susceptible to symptomatic infection. This comes on top of the increasing likelihood that these healthy subjects will become exposed to the virus while experiencing a short-lived surge in S-specific Abs (because of the current abundance of more infectious strains). So, even the population segment of non-vaccinated, previously asymptomatically infected healthy subjects may now end up with relatively higher morbidity and mortality rates, regardless of the type of variant they become exposed to. This is to say that sustainment of broadly implemented infection prevention measures will only amplify the already detrimental consequences of ongoing mass vaccination campaigns in the elderly and immunologically vulnerable segment of the

[4] Antigenic sin, also known as antigenic imprinting, refers to the propensity of the body's immune system to preferentially utilize immunological memory based on a previous infection when a second slightly different version of that foreign pathogen (e.g. a virus or bacterium) is encountered.

population. It is, therefore, reasonable to assume that – even in healthy, non-vaccinated people and younger age groups - mass vaccination in the elderly and vulnerable segment of the population, combined with containment measures, will cause morbidity and mortality rates to explode (see figure 2 below).

Vaccination of elderly and immune compromised (vulnerable) people followed by vaccination of younger, previously asymptomatically infected age groups

As mentioned above, mass vaccination campaigns in this group would dramatically deteriorate the situation as they will lead to a fast and massive increase in the number of asymptomatic subjects that are in the process of seroconverting on a highly infectious background and become, therefore, susceptible to severe disease and prone to promoting viral immune escape. As healthy people without a medical history of Covid-19 disease have no reason to isolate, there would be plenty of opportunity for highly infectious circulating variants to replicate and spread, thereby causing a further explosion in morbidity, mortality and S-selective immune escape in this population.

The more Covid-19 vaccination campaigns in the young and middle-age groups will be delayed (i.e., relative to their initiation in the elderly), the more they will enhance morbidity and mortality rates in this group. By the time mass vaccination campaigns are about to start in the young and middle-aged groups, a substantial number of these people will already have been re-infected with Covid-19 variants and have fallen victim to severe disease. This is because enhanced rates of infection due to circulating, highly infectious viral variants will significantly increase the likelihood for them to become re-infected while being in the process of seroconverting (cfr. above). So, by the time vaccinations in youngsters will be initiated, viral immune escape in this group may already be fueling a vicious circle of enhanced viral infectiousness. The latter would only result in more seroconversion and hence, more severe disease and accelerated immune escape. This is to say that the more vaccination campaigns in this group get delayed, the higher will be the speed at which even more infectious viral variants are selected. The ensuing exponential increase in the rate of viral immune escape would inevitably expedite resistance to the vaccine and hence, precipitate loss of vaccine-mediated protection in the vaccinated elderly.

After infection prevention measures have already bred a series of highly infectious variants in previously asymptomatically infected people, mass vaccination in the elderly and vulnerable group now forces the young and previously asymptomatically infected population to breed even more variants that are even more infectious. That is the stage many European countries are in right now. For the reasons mentioned above, vaccination of the young and previously

asymptomatically infected population would make the situation much worse in that this population would fall prey to a wave of catastrophic morbidity and mortality.

Covid-19 vaccination and herd immunity

As large scale vaccination campaigns combined with sustained implementation of several containment measures will only expedite the occurrence of S-targeted viral escape mutations, the illusory hope that current Covid-19 vaccines could generate herd immunity should once and for all be thrown overboard. On the contrary, shedding and transmission of highly infectious variants due to insufficient neutralizing capacity of vaccinal Abs are increasingly turning vaccine recipients into asymptomatic virus spreaders. Those will constitute a substantial source of infection for non-immunized segments of the population instead of (indirectly) protecting them. Meanwhile, there is a broad consensus that – unlike immunization of the population during the natural course a pandemic – ongoing mass vaccination campaigns will never succeed in generating sufficient herd immunity to bring the pandemic under control.

Conclusion:

The combination of mass vaccination (using current vaccines) and infection prevention measures is a recipe for a global health disaster. Following the science, one has to conclude that all age groups (possibly with the exception of small children?) will be heavily affected and subject to rates of morbidity and mortality that rise much faster and much higher than those expected to occur during the *natural* course of a CoV pandemic. This will particularly apply if the sequence of mass vaccinations following the first infectious wave parallels that of natural infection (i.e., immune compromised people and elderly first, followed by the younger age groups).

Mass vaccination in the heat of a pandemic that is now dominated by a multitude of highly infectious variants is particularly harmful as these variants readily escape to vaccine-induced S-specific Abs while still being capable of outcompeting variant-nonspecific natural Abs for binding to Covid-19 (variants), thereby depriving individuals from their broadly protective, natural (life)line of immune defense against Covid-19 (variants) in particular and CoVs in general.

No one, for that matter, should be granted a right to implement large-scale pharmaceutic and non-pharmaceutic immune interventions during a viral pandemic without having gained an in-depth understanding of the immune pathogenesis of the virus and the intrinsic

population dynamics of infection and immunity that naturally result from the introduction of a new virus in large parts of the human population.

When one follows the science, and nothing but the science, it becomes extremely difficult to not label ongoing mass vaccination campaigns as a massive blunder, not only to public health but also to individual health.

Substantiation for the reasoning put forward above can be drawn from my slides at the Ohio Vaccine Summit (March 1-3; 2021) and several interviews posted on
https://www.geertvandenbossche.org/

These interviews shed some light on

i) how components of the innate immune system can protect against Covid-19 and render infections asymptomatic

ii) why and how, in an immunologically Covid-19-naïve population, specific Ab-mediated suppression of the innate immune system shifts the first wave of disease and death from (predominantly) the elderly (and immunocompromised) subjects to those who at the outset of the pandemic got away with asymptomatic infection (i.e., predominantly, the younger and middle-aged population segment).

iii) how declining adaptive immunity in seropositive subjects and enhancement of specific Ab-mediated suppression of innate immunity in the asymptomatically infected population finally causes a third wave of morbidity and mortality in substantial parts of the overall population

iv) how the population eventually controls the pandemic by building herd immunity

All of the above illustrates the critical contribution of both, the innate and adaptive immunity in bringing the viral pandemic under control and to eventually shift its course into that of an endemic infection.

v) how our understanding the population dynamics of a natural pandemic (i.e., without human intervention) caused by an acute viral infection such as Covid-19 helps to comprehend the sophisticated interplay between the virus on the one hand and population immunity on the other during a natural CoV pandemic

vi) why large-scale human intervention has a highly detrimental impact on the refined interplay between the virus and its host and how perturbation thereof leads to a

dramatic increase of viral infectiousness, morbidity and mortality, primarily in S-Ab seropositive subjects.

vii) why containment/ hygiene measure drive the emergence of highly infectious strains and why subsequent mass vaccination campaigns with 'leaky' vaccines (protecting against disease, but not preventing infection) dramatically aggravate selective immune escape and hence, viral infectiousness

viii) how enhanced viral infectiousness leads to a dramatic increase in morbidity and mortality rates

ix) why abrogation of viral infection in asymptomatically infected subjects provides a sound rationale for developing NK cell-based immune interventions and why a such approach would not be prone to immune escape and has the potential of providing sterilizing immunity

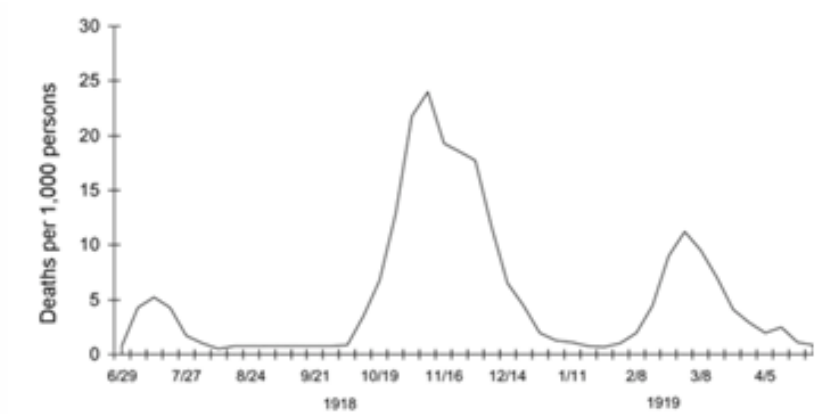
x) why immune interventions enabling sterilizing immunity will be required to eradicate all of the steadily emerging highly infectious Covid-19 variants

xi) how CoV-nonspecific, innate immunity can be trained by regular exposure to CoV and promoted by a healthy lifestyle (see fig. 3 below)

xii) how a rapid and user-friendly serodiagnostic assay could potentially help healthy, non-vaccinated subjects who have experienced asymptomatic Covid-19 infection to measure their (short-lived) S-specific Abs such as to enable them to protect themselves against disease (when seropositive) while giving them the opportunity to train their innate immune system (when seronegative).

The current COVID-19 pandemic is often compared to the 1918 H1N1 influenza pandemic

For example, the 1889-92 influenza outbreak had three distinct waves, which differed in their virulence. The second wave was much more severe, particularly in younger adults.



Three waves of deaths: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919. The waves are broadly the same globally during the pandemic. Taubenberger JK, Morens DM. 1918 Influenza: the Mother of All Pandemics. Emerg Infect Dis. 2006;12(1):15–22. CC BY

The current COVID-19 pandemic is often compared to the 1918 H1N1 influenza pandemic, which had three distinct waves over the course of a year. The proportion of influenza patients who were severely ill or died was much higher in the last two waves compared to the first.

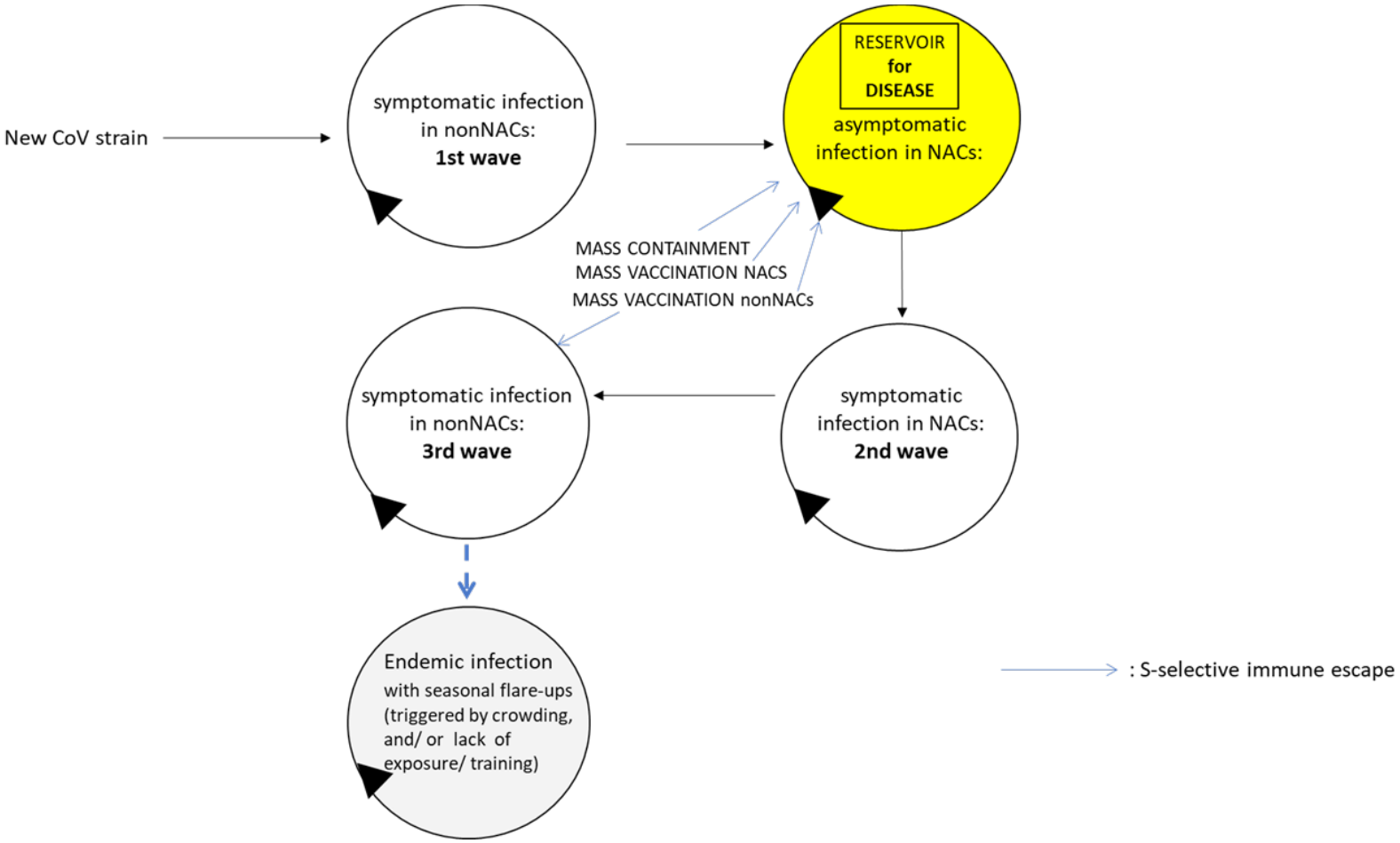
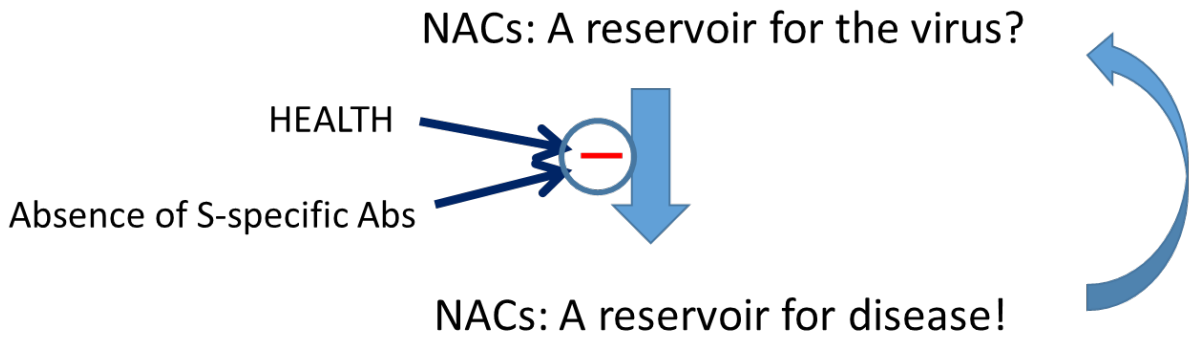


Fig. 2: The natural course of a CoV pandemic is controlled by the population's innate and adaptive immunity and dramatically perturbed by vaccines inducing S-specific antibodies when used in mass vaccination campaigns conducted in the course of the pandemic and flanked by stringent containment measures

*NACs: Natural asymptomatic carriers ; refers to subjects who do not develop any clinical symptoms at all, or develop at most mild disease (involving upper respiratory airways only), after PRIMARY CoV infection (i.e., during first wave)

**nonNACs: Relates to subjects who develop severe Covid-19 symptoms after PRIMARY infection (i.e., during first wave)

The crucial role of NACs…….



I only take responsibility for the statements and scientific papers that I have published myself. I want to emphasize that what I am trying to convey goes beyond various beliefs and opinions. They are irrelevant to what concerns us as humans. In fact, they are an obstacle. Above all I want to safeguard my integrity and insist on absolute independence. The response to my appeal should remain only and purely scientific and in no occasion ever be used or abused by any non-scientific rhetoric.