

Why should current Covid-19 vaccines not be used for mass vaccination during a pandemic?

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Prophylactic vaccines are for use in...a conventional prophylactic setting, NOT in a pandemic setting

- Prophylactic vaccines should be administered before infectious exposure to:
 - ensure full-fledged protection
 - prevent exacerbation of disease (cfr. Ebola – ring vaccination)
 - *prevent immune escape* and hence, enhanced infectiousness or even, resistance to the vaccine
- Several cases of severe disease due to highly infectious variants have already occurred in young people
- Several cases of fully Covid-19 vaccinated people shedding highly infectious variants have already been reported (some of which have even developed mild symptoms)



Aren't these cases compelling enough to demonstrate how easily Covid-19 viruses can escape host immunity?

General Rule: Virus replication on background of suboptimal immune response enables immune escape of highly mutable viruses.



Current Covid-19 vaccine technologies

- All of them are targeted at inducing specific Abs to S-protein (S1- RBD), so none of them prevents viral replication if Abs are too low in concentration or *affinity*
- ➔ They cannot control replication of more infectious CoV variants and may even drive immune escape (e.g., when fully vaccinated subjects are exposed to viral variants)
- Are they safe?
 - yes, at the level of the individual
 - absolutely not, for human populations exposed to Covid-19 pandemic
- Are they efficacious for protecting against disease?
 - yes, at the level of the individual
 - absolutely not, for human populations exposed to Covid-19 pandemic

Abs: Antibodies



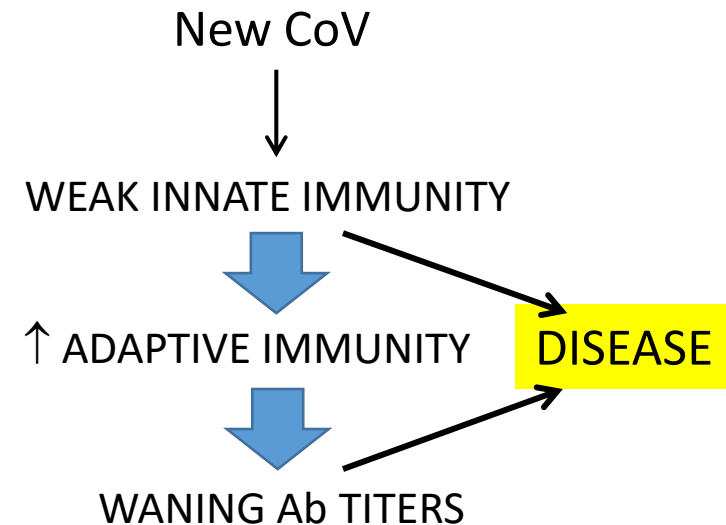
Gaps in our understanding of the natural course of viral pandemics

NACs*:

- Ag-nonspecific killing via natural Abs (NABs) and NK cells provide natural immunity

nonNACs**:

- Contract disease because of weak innate immunity
- Ag-specific killing (neutralization) via 'adaptive' Abs → protection
- Susceptible to disease when Ab titers wane



- Q: - Why does natural (i.e., w/o human intervention) viral pandemic comprise 3 waves?
- **Why does 2nd wave typically hit younger people?**
 - Why / how does the virus re-emerge to become seasonal?

Ag: Antigen; Abs: Antibodies

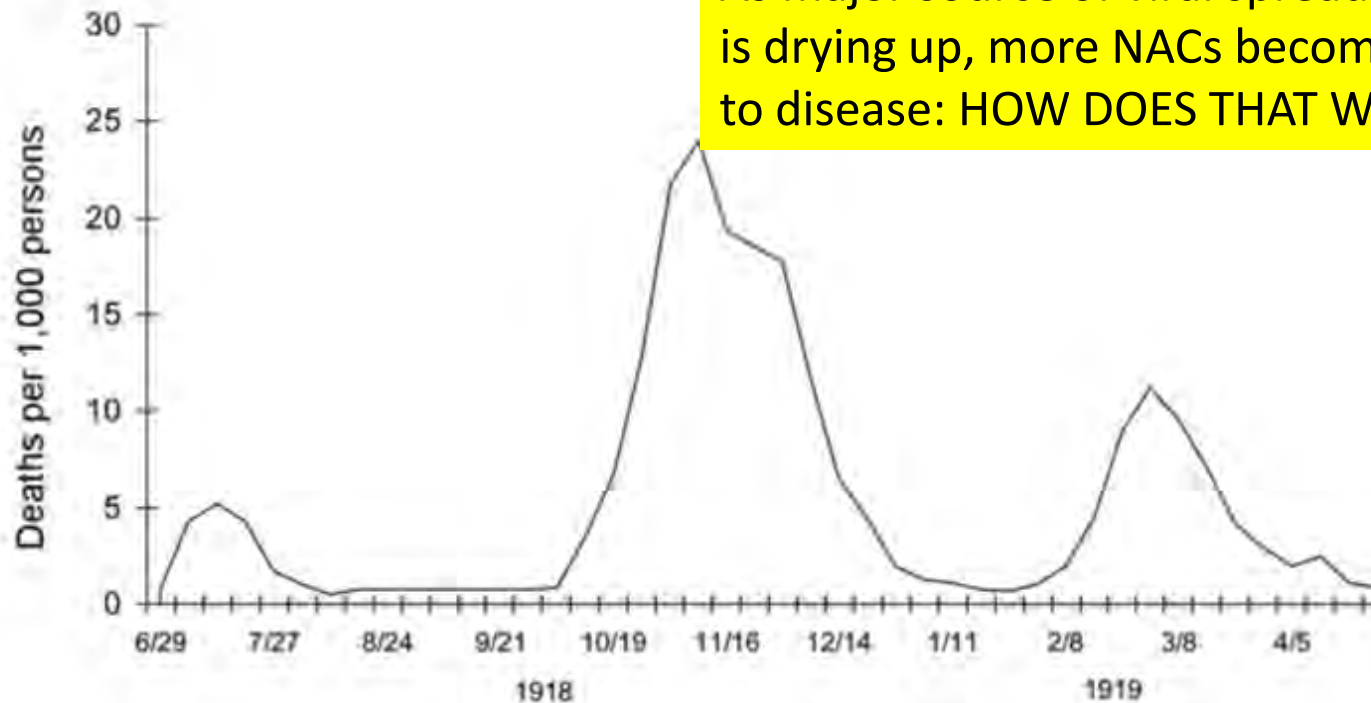
*NACs: Natural asymptomatic carriers ; refers to subjects who do not develop any clinical symptoms at all, or develop at most mild disease (involving upper respiratory airways only), after PRIMARY CoV infection - 4 -

**nonNACs: Relates to subjects who develop severe Covid-19 symptoms after PRIMARY infection



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.



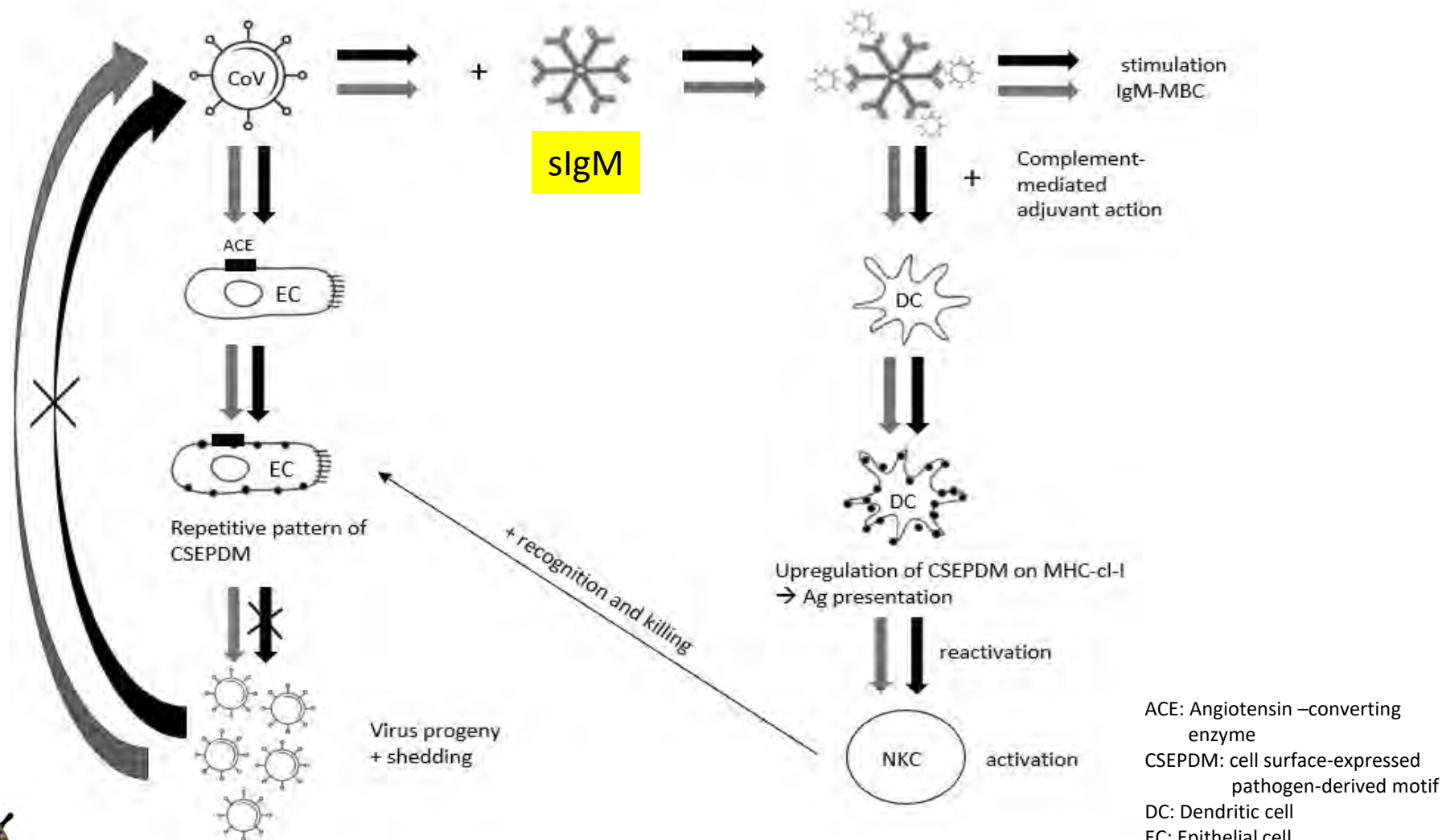
As major source of viral spread (nonNACs) is drying up, more NACs become susceptible to disease: HOW DOES THAT WORK?

Three waves of death: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919. The waves were 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

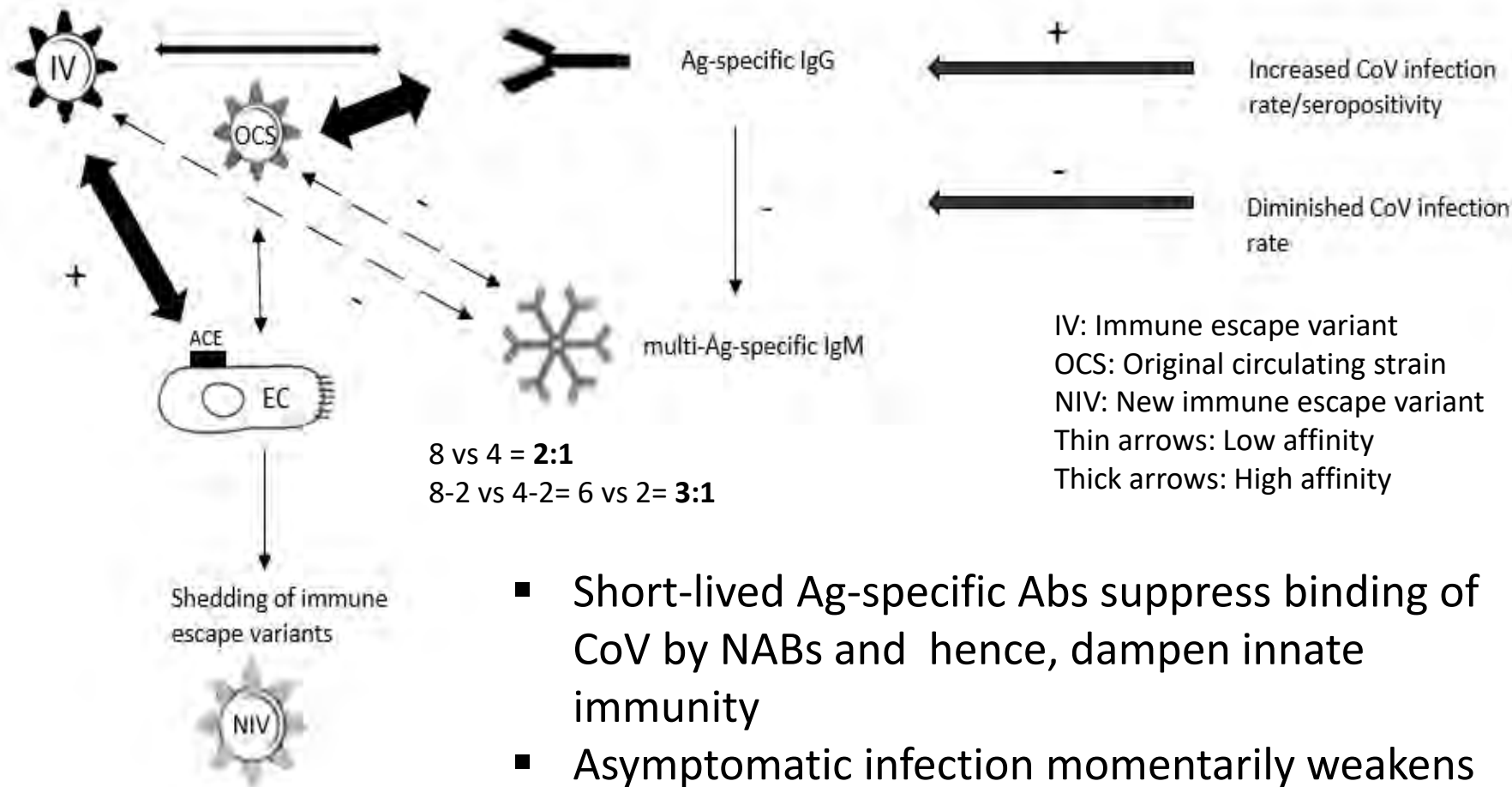
The current COVID-19 pandemic is often compared to the 1918 H1N1 influenza pandemic, which had three distinct waves over the course of a year. The proportion of influenza patients who were severely ill or died was much higher in the last two waves compared to the first.



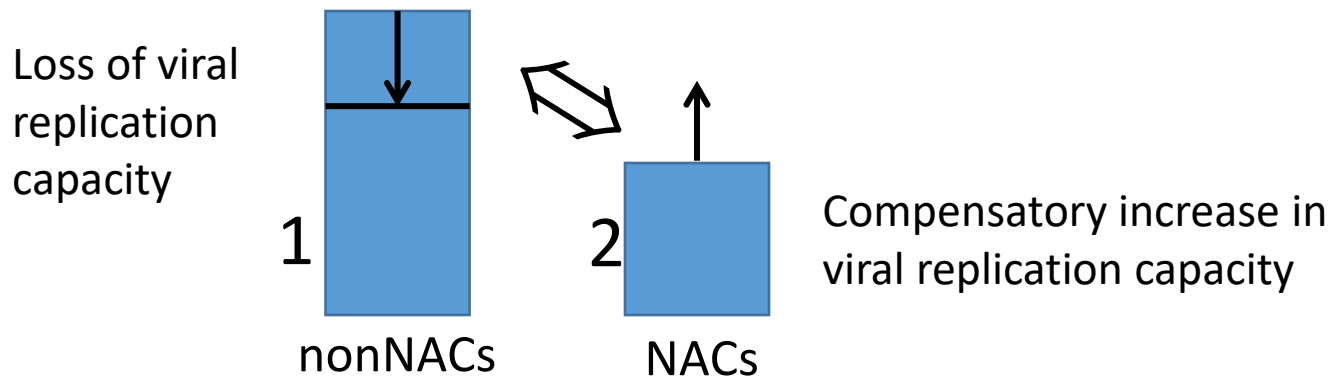
Abrogation of viral infection in NACs (after short-lived virus replication) is mediated by innate immunity



Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation



Increasing CoV infection rates promote enhancement of innate immune suppression in NACs (→ more susceptible to disease)

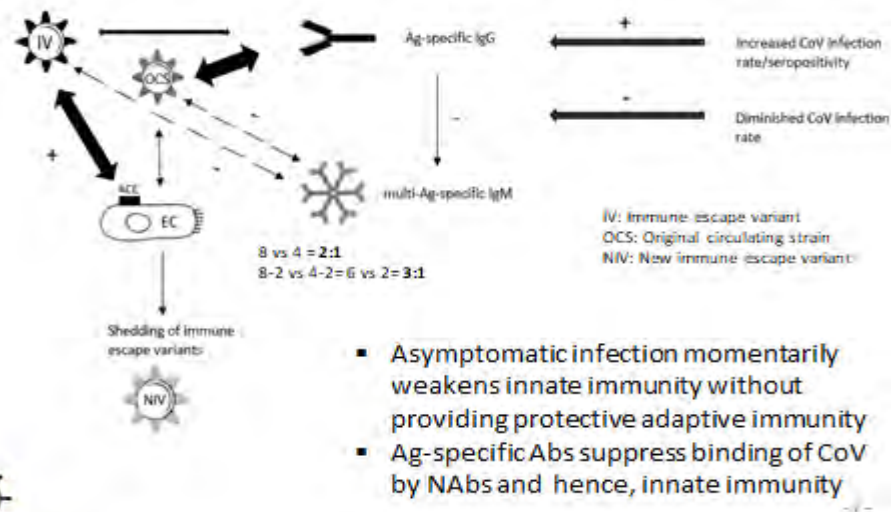


↑
susceptibility rate in NACs suffices to compensate for long enough....
until Ag-spec. Ab titers in nonNACs drop \Rightarrow virus can replenish replication capacity



Containment measures and vaccination of NACs jeopardize capacity for viral replication

Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation



Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation while leaving the door open for increasing its infectiousness when infection rates drop

Since virus replication in NACs is under control of (innate) immune system, the virus can compensate for loss of replication/transmission capacity by enhancing infectiousness through selective immune escape



↑ **viral infectiousness in NACs** suffices to compensate for long enough.... until Ag-spec. Ab titers in nonNACs drop



But what if these Ab titers don't drop??

- Steady S-spec. Ab titers (VACCINATION!) in nonNACs will result in further increase in viral infectiousness in NACs.... until 'return' on escape mutations in nonNACs becomes relatively more profitable for the virus



- RBD-specific escape mutations enable virus to rebuild sufficient capacity for viral replication in nonNACs. The resulting immune escape variants are now resistant to the vaccine.

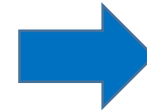


Increasing infection/ seropositivity rates in NACs and nonNACs promote immune escape

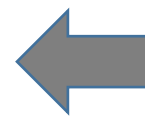
- Enhanced infection rates lead to increased rates of transient seropositivity in NACs; seropositivity suppresses innate immunity **because Ag-specific Abs outcompete NABs for binding to CoV and prevent training of innate immune system**



1. Selective (innate) immune escape in NACs



2. Increased infectiousness



3. Selective (adapt.) immune escape in nonNACs



Strange observations during ongoing Covid-19 pandemic..

- Untypical course/ waves of pandemic
- Emergence of several much more infectious strains
- Viral shedding (of more infectious variants) in fully vaccinated subjects



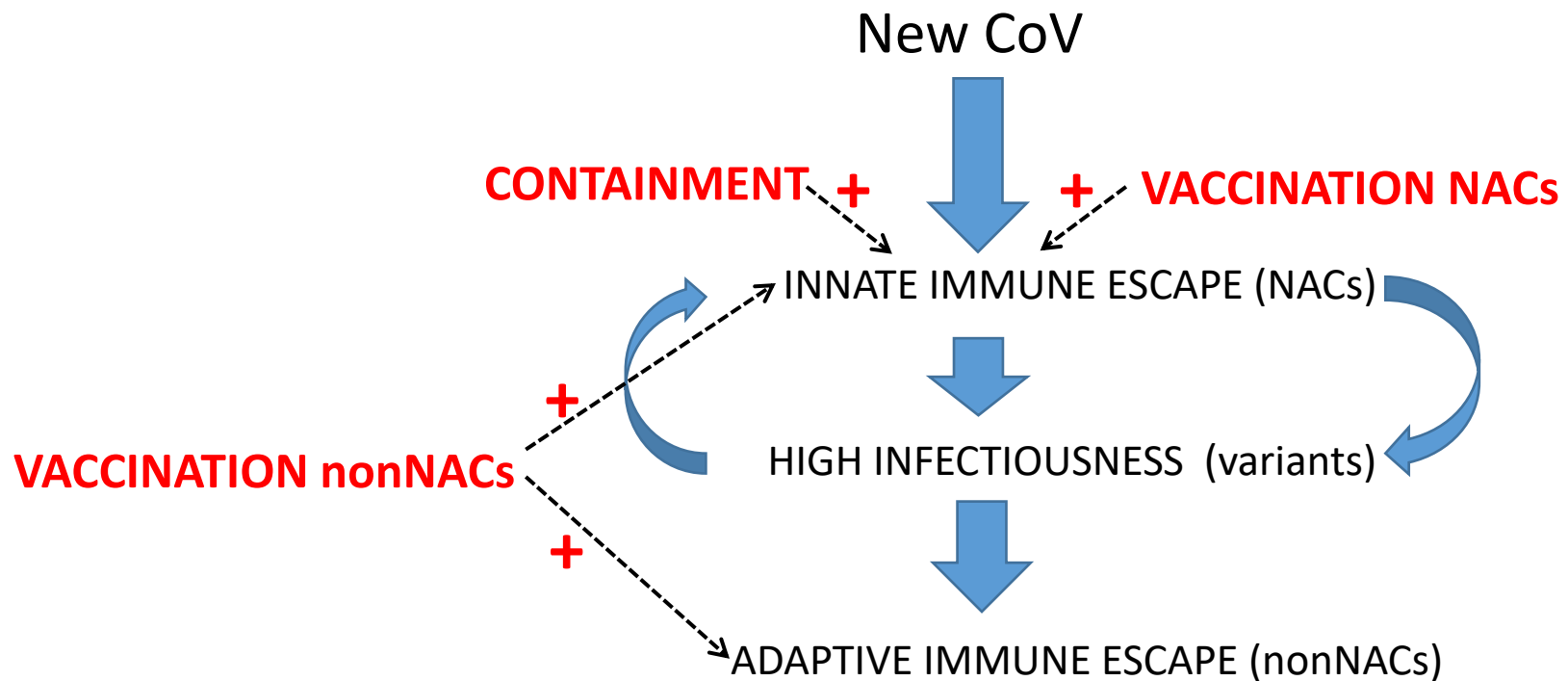
Selective (S/ RBD) protein-directed) immune escape

S: Spike protein

RBD: Receptor-binding domain



Mass containment measures and mass vaccination in NACs accelerates INNATE immune escape whereas mass vaccination of nonNACs accelerates INNATE and ADAPTIVE immune escape



If needed, both NACs and nonNACs can serve as a potential source of immune escape upon human intervention in natural CoV pandemic



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

Executive summary (see also slide appended on p.6 below)

The manuscript, which is now in the process of being finalized, should shed some light on how the virus and especially its interaction with the host immune system determines the natural course (i.e., *without* human intervention) of a Coronavirus (CoV) pandemic. The interplay between host immune defense and viral immune escape determines the course of a natural CoV pandemic (including a natural Covid-19 pandemic).

In the clinic, viral immune escape is known to occur when the neutralizing capacity of serum antibodies (Abs) does not suffice to fully eliminate highly mutable viruses (e.g., CoV) for lack of their concentration or affinity. In a CoV pandemic setting, seroconversion occurs against a background of high infectious pressure and is, therefore, prone to promote viral immune escape.

The first wave of disease¹ (and mortality) primarily affects elderly people (or otherwise immunocompromised subjects). *Selective* (i.e., adaptive) immune escape is expected to cause this wave to transition into a more severe, second wave in younger age groups. Subsequently, *non-selective* (i.e., innate) as well as *selective* immune escape operated by increasingly infectious viral variants will trigger a third wave. The latter would primarily affect subjects who recovered from disease they contracted during the first wave as their seroneutralising Abs do no longer properly match the new circulating viral variants. This third wave of disease (and mortality) would come to an end when those who recovered from the disease will have mounted new functional Abs against these immune escape variants. As seroconversion in this population will now occur much faster (due to recall of cross-reactive T helper memory cells) and as the majority of the young and middle-aged population will either be seronegative or have seroconverted already by the time the third wave starts to expand, chances are slim for the virus to escape the host's Ab response. Asymptomatic², seronegative individuals (i.e., the vast majority of young and middle-aged people) may spread virus upon (re-)infection and hence, constitute a relevant source of viral transmission. However, CoV infection in these 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, antigen (Ag)-nonspecific patterns on the surface of CoV-infected epithelial target cells. As killing by NK cells is, therefore, not Ag-specific and as seroconversion

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

² For the purpose of the 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)

in asymptomatically infected subjects is only short-lived, viral immune escape does not normally occur. Consequently, new, more infectious, variants are unlikely to emerge from this population as long as viral infectiousness does not dramatically increase.

At the point of 'no immune escape', the pandemic will be under control and merge into an endemic infection. However, as long as the point of 'no immune escape' isn't reached, any additional immune selection pressure, for example as a result of suboptimal concentration or affinity of Ag-specific (e.g., spike protein-specific) Abs, will allow the virus to rapidly unfold more infectious, immune escape variants. Additional immune selection pressure, especially when exerted during the second wave of a CoV pandemic, is likely to precipitate and amplify viral immune escape. This might even cause the second and third wave to merge into a single huge wave of mortality and disease that affects all layers of the population (possibly, with the exception of small children).

Especially mass vaccination campaigns, particularly when conducted in the midst of a pandemic, are prone to exerting enormous immune pressure on circulating virus strains. This is because the vaccine is used in an increasingly infectious context (as escape variants are more infectious). Mass vaccination campaigns will accelerate the emergence of even more infectious immune escape variants. This because the number of vaccine recipients who seroconvert within a given time period will dramatically increase³. In addition, Ag-specific, high affinity Abs induced by any of the current vaccines will outcompete natural, *broadly* protective mucosal IgM antibodies as the latter only bind with low affinity to the receptor-binding domain of CoV (RBD). This will particularly affect natural resistance of younger age groups which - thanks to a well-trained innate immune system- resisted disease during the first wave. The new circulating CoV variants may now even be able to escape the host's CoV variant-nonspecific line of immune defense at the mucosal portal of entry. These age groups may, therefore, become more susceptible to symptomatic infection and shedding caused by more infectious variants.

But mass vaccination campaigns will also have severe consequences for those who got vaccinated first (mostly the elderly or people with underlying disease or those who are otherwise immunocompromised). In the highly likely event that mass vaccination will soon result in antiviral resistance (see below), these people will have no single bit of 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 human population (except for small children?).

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

Further to all of the above, low exposure to circulating CoV strains (e.g., due to stringent containment measures) will increasingly weaken 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. Especially the younger age groups may, therefore, end up with relatively higher morbidity and mortality rates, even regardless of the emergence of more infectious viral variants. This is to say that broadly implemented infection prevention measures will only amplify the already detrimental consequences of ongoing mass vaccination campaigns. It is reasonable to assume that the combination of non-selective and selective immune escape will cause morbidity and mortality rates in younger age groups to explode (see figure attached on p.6 below).

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 infected with Covid-19. Enhanced rates of infection by highly infectiousness viral variants have now significantly increased the likelihood for them to become re-infected while being in the process of seroconverting. So, by the time vaccinations will be initiated, viral immune escape in this group may already be fueling a vicious circle of enhanced viral infectiousness resulting in more seroconversion and hence, more immune escape. Mass vaccination campaigns in this group will only 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 against a highly infectious background and, therefore, are prone to promoting viral immune escape. As there is naturally no reason for them to isolate, there will be plenty of opportunity for the highly infectious circulating strains to replicate in the presence of suboptimal Ab titers and, therefore, to escape the host's immune control.

Hence, the more vaccination campaigns in this group get delayed, the more selection of even more infectious viral variants will be expedited. The ensuing exponential increase in viral immune escape rates will ultimately enable viral variants to even break through vaccine-mediated protection in the vaccinated elderly. As their Abs increasingly mismatch the ever more infectious emerging variants, they will no longer manage to control viral replication and shedding and rapidly allow for massive viral immune escape. Because seroprotective Abs primarily confer protection through targeting Covid-19's RBD, the virus will now increasingly select mutations in this particular part of the spike protein as those most readily enable the virus to escape vaccine-induced Abs. This will inevitably precipitate resistance to the vaccine. As

a result of mass vaccination, people who got the vaccine first will suddenly no longer be protected and, despite vaccination, fall prey to a wave of catastrophic morbidity and mortality.

There can, therefore, be no doubt that current vaccination strategies are rendering the impact of mass vaccination campaigns even more catastrophic and only adding to the magnitude of a pending global health disaster. However, mass vaccination also harms individual health as vaccine-induced variant-specific Abs will outcompete natural variant-nonspecific mucosal Abs for binding to CoV variants and thereby deprive individuals from their broadly protective natural (life)line of immune defense.

As large scale vaccination campaigns combined with the sustained implementation of several containment measures will only expedite the occurrence of viral escape mutations, the illusory hope that current Covid-19 vaccines could generate herd immunity should once and for all be thrown overboard. Along the same line 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 same 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-COV-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.

Conclusion:

The combination of mass vaccination 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 raise 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., immunocompromised people and elderly first, followed by the younger age groups).

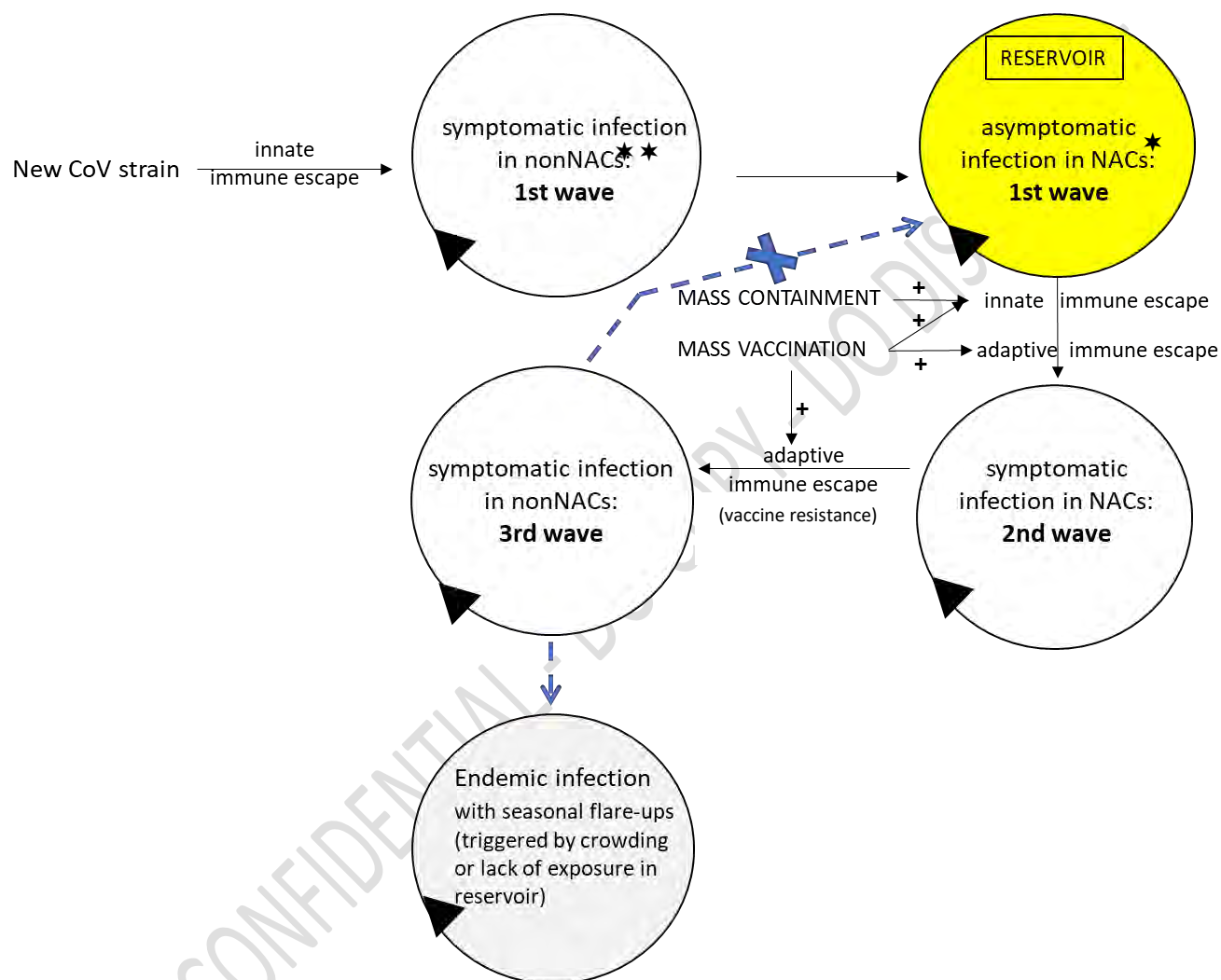
No one, for that matter, should be granted a right to implement large-scale pharmaceutical and non-pharmaceutical immune interventions, especially not during a viral pandemic, and certainly not without an in-depth understanding of the immune pathogenesis of a viral pandemic. When one follows the science, and nothing but the science, it becomes extremely difficult to not label

ongoing mass vaccination campaigns as a crime, not only to public health but also to individual health.

To substantiate the reasoning above, the manuscript will first explain how components of the innate immune system can protect against Covid-19 and render infections asymptomatic. It will then go on to explain in more detail why and how, in an immunologically Covid-19-naïve population, selective (i.e., adaptive) immune escape shifts the first wave of disease and death from the elderly (and immunocompromised) subjects to those who at the outset of the pandemic got away with asymptomatic infection (i.e., the younger and middle-aged population segment). Similarly, it will be explained how accelerated viral immune escape in the asymptomatically infected population finally shifts back the burst of morbidity and mortality to the elderly, and how the population eventually controls the pandemic by controlling viral immune escape. This will already illustrate the critical importance of dissecting the changing contribution of innate and adaptive immunity to the population's overall immune defense against a viral pandemic. Understanding these dynamics helps to comprehend the sophisticated course of a natural CoV pandemic, how it eventually merges into an endemic infection and why human intervention has a highly detrimental impact on the refined interplay between the virus and its host. In regard of the latter, the devastating global health impact of ongoing mass vaccination campaigns and accompanying stringent and widespread containment measures will be explained in more detail as the global and individual health consequences could simply be unbearable for many years to come.

After the introductory section on innate immune defense mechanisms relevant to Covid-19, other relevant topics will be addressed in form of questions and answers. Last, a section will be dedicated to the scientific rationale for using NK cell-based vaccines that could provide sterilizing immunity and hence, wipe out Covid-19 and related variants all together.

The natural course of a CoV pandemic is controlled by the population's innate and adaptive immunity and dramatically aggravated by antibody-based vaccines when used in mass vaccination campaigns conducted in the course of the pandemic and flanked by stringent containment measures



★NAC: Natural asymptomatic carrier : for the purpose of this manuscript, NAC is defined as a subject disposing upon a level of innate immunity high enough to resist disease

★★nonNAC: For the purpose of this manuscript, nonNAC is defined as a subject who is not endowed with a level of innate immunity high enough to be able to resist disease when exposed to infectious virus during the first wave

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