Instead of generating herd immunity, C-19 mass vaccination triggers a chain reaction of new pandemics and epidemics with major impact on global health

Synopsis

The following predictions are distilled from an in-depth analysis of how the precipitated evolutionary dynamics of SARS-CoV-2 (SC-2) in highly vaccinated populations enable the virus to bypass the cell-based innate immune system (CBIIS) and exhaust the adaptive immune capacity in vaccinees while providing 'power training' to the CBIIS of the unvaccinated. Understanding the immunological consequences of this complex phenomenon provides new insights as to why sidelining of the CBIIS dramatically enhances the susceptibility of vaccinees to re-infection with more infectious variants. Furthermore, it explains how these individuals are now forming an asymptomatic reservoir of 'more virulent' SC-2 variants (BA.4 and BA.5), and to some extent other glycosylated viruses causing acute self-limiting (viral) infection (ASLVI) or disease (ASLVD). Highly vaccinated populations are now igniting new viral pandemics (e.g., the ongoing pandemic of 'more virulent' SC-2 variants [i.e., BA.4 and BA.5]; a pending pandemic of avian influenza; the ongoing pandemic of monkeypox virus).

Due to these asymptomatic reservoirs, many viruses may now begin to spill over into animal populations. This is especially true for highly infectious viruses in animals with close proximity to humans (e.g., livestock, zoo animals). Understanding the evolutionary viral dynamics and the corresponding shift in the host's immune response also provides a compelling explanation as to how the infection-enhancing antibodies in vaccinees enable the latter's enhanced susceptibility to SC-2 re-infection while paradoxically protecting them from severe disease. An analysis of the continuous interplay between viral infection and the subsequent immune response of the host also elucidates how high infectious pressure exerted by more infectious SC-2 variants increases the likelihood of temporary innate or adaptive immune suppression in a minority of young unvaccinated children or other unvaccinated age groups respectively. Understanding this phenomenon is key as it is likely responsible for the limited but unfortunate increase

in the incidence rate of severe disease (due to ASLVI [including SC-2], ASLVD or other acute or chronic microbial infections or immunopathology [hepatitis]) in young unvaccinated children. Whereas sidelining of the CBIIS (due to enhanced viral infectiousness) and sustained S(pike)-mediated activation of the adaptive immune system (AIS) is now igniting epidemics of other acute (i.e., other than ASLVIs or ASLVDs) and chronic microbial infections or immune-mediated diseases (e.g., cancer and immunopathologies) and affecting large numbers of vaccinees, only a limited number of unvaccinated elderly (or vulnerable[1]) people and young children will suffer from these epidemics.

When one grasps the above-summarized dynamics it becomes crystal clear that vaccinating young children against C-19 entails trading a highly ephemeral benefit (short-lived protection from severe C-19 disease) for an immense risk of severe disease from a multitude of other acute or chronic microbial infections or immunopathologies, the consequences of which are simply dramatic. As the forementioned ailments will primarily affect vaccinees and highly vaccinated countries, it is reasonable to assume that the unvaccinated and countries with low C-19 vaccine coverage rates will largely resist the pandemic storms as their capacity to build natural and herd immunity has not been compromised ('Africa will win'). The primary focus of highly vaccinated countries should now be early C-19 treatment of vaccinees and massive distribution of antivirals that are safe and effective and can be provided in sufficient quantities at affordable cost to these individuals.

My predictions are based on a multidisciplinary analysis drawing from fields of immunology, vaccinology, virology, evolutionary biology and biophysical sciences. The endpoint described by the convergence of the governing principles of these scientific disciplines coupled with an overwhelming body of evidence requires **that these conclusions be taken very seriously, even if they seem too dire to be true** ("*How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?*", Sherlock Holmes)

[1] For the purpose of this manuscript, 'vulnerable' people/ individuals refers to immunosenescent people/ individuals or people/ individuals with co-morbidities or who are otherwise immune suppressed

Pandemics and Epidemics of Concern or (?) of High Consequence

I. The ongoing pandemic of 'more virulent' SC-2 variants

Hospitalizations and mortality rates due to (not with!) SARS CoV-2 (SC-2) continue to decline as the unvaccinated increasingly train their innate immune response (primarily NK cell-based), while vaccinees are increasingly protected not only against severe C-19 disease (due to the inhibitory effect of high titers of infection-enhancing antibodies [Abs] that block viral *trans* infection in the lungs; https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic), but now even increasingly against mild-moderate C-19 disease (via strong activation [not priming!] of polyspecific MHC class I-unrestricted cytotoxic T cells[2], which naturally enable recovery from C-19 disease). However, as none of the immune mechanisms currently at play within these individuals can prevent productive infection (see figure 1), *vaccinees are now increasingly becoming asymptomatic shedders* of SC-2. This applies to all vaccinated subpopulations/ age groups. The immune mechanisms preventing *severe* disease are exclusively adaptive in nature (i.e., mediated by antigen [Ag]-specific infection-enhancing Abs and therefore independent of the innate immune status of the vaccinee).

As infection-enhancing Abs in vaccinees are boosted upon each re-exposure to the more infectious circulating virus, these Abs are raising the immune pressure on viral virulence which—for now—is still capable of preventing severe disease (although only for a limited amount of time!). However, this rising population-level immune pressure has already led to the enhanced intrinsic virulence of the virus (BA.4 and BA.5 are 'more virulent' variants; https://www.biorxiv.org/content/10.1101/2022.05.26.493539v1.full.pdf). The very last step the virus needs to take to fully escape the virulence-neutralizing effect of these Abs

[2] Sustained activation of these T cells can also protect vaccinees against C-19 disease in the presence of high titers of infection-enhancing Abs (see fig.1).

is to select a variant (of the conserved infection enhancing site[3]) which no longer sufficiently binds the infection-enhancing Abs when tethered to migrating dendritic cells (DCs; see fig. 1). Insufficient or deficient binding of these Abs to DC surface-tethered SC-2 virions will no longer allow them to prevent *trans* infection (leading to *trans* fusion, which is responsible for syncytia formation and severe disease; https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic), When this occurs, protection against severe disease will vanish. A similar process has already occurred with the 'more infectious' SC-2 variants of the S-RBD (receptor-binding domain of S protein) which were no longer sufficiently bound by previously neutralizing Abs. When this occurred, protection against (moderate) disease vanished.

I predict that it's only a matter of an additional few months (depending on booster shots[4]) before the virus overcomes this final hurdle, at which point highly vaccinated populations will be devastated by massive rates of C-19 morbidity and C-19 mortality if not massively treated with antivirals. Once SC-2 has become resistant to the virulence-inhibiting capacity of the infection-enhancing Abs, the latter will only contribute to precipitating and accelerating severe disease. Consequently, Ab-dependent enhancement of infection (ADEI) will now prompt Ab-dependent enhancement of disease (ADED). ADED will first manifest in vaccinees with high titers of infection-enhancing Abs and vaccinated at an early stage of the vaccination program (i.e., before they had an opportunity to train their CBIIS). Hence, elderly and vulnerable vaccinees will be affected first. Provided they had ample opportunity to train their innate immune system prior to vaccination, some vaccinees may have enough natural immune capacity left to survive—but will the hospitals still be able to treat them? Unless we make safe and effective antivirals immediately available in sufficient supply and at affordable cost[5] for prophylactic use of vaccinees at the first sign of this imminent wave, we're going to

[3] This infection-enhancing site is situated within the N-terminal domain of S (S-NTD)
[4] Booster shots are more effective in recalling infection-enhancing S-specific Abs than natural infection. This is because the bulk of viral load from natural infection can be eliminated by activated cytotoxic CD8+ T cells (for as long as the viral infection rate allows….)
[5] I am not aware of compounds exhibiting strong antiviral activity other than ivermectin and hydroxychloroquine that would fulfill all other conditions (safe, broadly available at low cost and at an affordable price)

face a massive loss of human life. The first sign to look for will be a return to improved protection of vaccinees against disease all together (but this time due to sustained activation of cytotoxic CD8+ T cells!) followed by a dramatic increase in the ratio of vaccinees hospitalized DUE to SC-2 to the unvaccinated hospitalized DUE to SC-2 (particularly in ages 20-60). In a following contribution, I will explain why this is the key parameter to monitor.

Upon exposure to more infectious SC-variants, unvaccinated individuals with a SC-2-trained innate immune system can still contract mild to moderate C-19 disease (depending on the enhanced infectiousness[6] of the variant and the strength and level of training of their cell-based innate immune system; CBIIS), but the frequency thereof will soon abate. Upcoming variants characterized by an antigenic shift (i.e., towards resistance to the virulence-inhibiting activity of infection-enhancing antibodies in vaccinees) will soon become dominant in highly vaccinated countries and will render the unvaccinated resistant to productive infection (https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic), However, in unvaccinated individuals with an immature CBIIS (young children), SC-2 infections are now causing a limited increase in the incidence of severe disease. The latter can only be explained by rapid re-exposure after primary asymptomatic infection which, in young children, enables short-lived non-neutralizing S-specific Abs (elicited as a result from such asymptomatic infection) to outcompete their innate, neutralizing Abs from binding to the virus.

II. New pandemics of other glycosylated viruses (see fig. 2)

MHC class I-unrestricted cytotoxic T cells that—in the presence of high titers of infection-enhancing Abs—can protect vaccinees against C-19 disease are directed at a

[6] Enhanced SC-2 infectiousness may result from a higher intrinsic infectiousness of the virus or from enhanced susceptibility of the host to viral infection. The latter may occur in case a person becomes re-infected with SC-2 shortly after an asymptomatic primary infection. This is because short-lived, non-neutralizing Abs that were elicited following the asymptomatic primary infection are prone to bind to the virus and cause Ab-dependent enhancement of SC-2 infection.

conserved CTL epitope that is shared with other[7] glycosylated viruses causing acute self-limiting viral *infections*[8] (ASLVIs) or acute self-limiting viral *diseases*[9] (ASLVDs). Sustained activation of these T cells could, therefore, also protect C-19 vaccinees against disease upon their exposure to these other glycosylated viruses. In this case, however, the extent to which the vaccinated and unvaccinated control productive infection (i.e., the disease) will also depend on the level of additional viral clearance provided by their innate immune effector cells (i.e., NK cells, see fig. 1). Repeated re-infection will, therefore, turn *healthy*[10] C-19 vaccinees with a mature CBIIS into an *asymptomatic reservoir*[11] for these other glycosylated viruses[12] as well. However, vaccinees with a weakened CBIIS (fig.2: ④) will be more prone to *recurrent moderate disease* caused by these other glycosylated viruses. In a well-mixed and highly vaccinated population, enhanced transmission from the asymptomatic reservoir is therefore likely to significantly raise the incidence rate of *moderate disease* from ASLVI- or ASLVD-enabling glycosylated viruses in this C-19 vaccinated subpopulation. However, in vaccinees with an immature CBIIS and naïve adaptive immune system AIS (**young children**; fig. 2: ⑤), these other glycosylated viruses are likely to cause *severe disease*.

In contrast, healthy unvaccinated individuals with a mature innate immune system are more likely to develop *a transient episode* of *asymptomatic to mild* (fig.2: ①) or

[7] 'Other' means 'other than SC-2'

[8] Examples of glycosylated viruses [other than SC-2] causing ASLVIs: seasonal influenza, RSV and viruses responsible for vaccine-preventable infections: measles, mumps, rubella, varicella, rotavirus.
Note: Given the important asymptomatic reservoir, the occurrence of disease due to common influenza types may no longer be bound to seasonality!

[9] Examples of glycosylated viruses causing ASLVDs: zoonotic influenza (e.g., avian influenza virus), parapox virus (e.g., monkeypox virus)

[10] For the purpose of this manuscript 'healthy' is defined as 'without underlying diseases or immune suppressive conditions'

[11] As the cytotoxic Tc response has no memory and the infection-enhancing antibodies promote the susceptibility of vaccinees to re-infection, vaccinated people can repeatedly be re-infected and acquire mild or moderate disease. Because of frequent re-infection, CTL activation may be sustained and enable more rapid cytolysis of virus-infected cells (i.e., at an early stage of productive infection). Enhanced abrogation of productive infection is likely to lead to asymptomatic infection but will not provide sterilizing immunity (see fig. 1: B). Although asymptomatic vaccinees tend to shed less virus than unvaccinated individuals (https://www.medrxiv.org/content/10.1101/2022.01.28.22270044v1), they will shed and transmit virus over and over again while boosting their production of infection-enhancing Abs upon each re-exposure.

[12] A C-19 vaccinated population that during childhood has been largely vaccinated with live attenuated viral vaccines (e.g., measles, mumps, rubella, varicella) will not serve as a reservoir for these viruses but could still serve as asymptomatic transmitters of ***influenza virus and respiratory syncytial virus*** (RSV)

moderate to severe (fig.2: ②) *disease* from these other glycosylated viruses depending on their susceptibility[13] and the strength of their CBIIS. In a well-mixed and highly vaccinated population, enhanced transmission from the asymptomatic reservoir is therefore likely to significantly *diminish* the incidence rate of *severe* disease from ASLVI- or ASLVD-enabling glycosylated viruses in this C-19 *unvaccinated* subpopulation.

However, a limited number of the unvaccinated with an immature CBIIS (young children; fig. 2: ③) are now more likely to develop severe disease from these other glycosylated viruses for the same reason as previously explained for SC-2 (see under section I.). In a well-mixed and highly vaccinated population, enhanced transmission from the asymptomatic reservoir is therefore likely to provoke a *limited increase* in the incidence rate of *severe* disease from ASLVI- or ASLVD-enabling glycosylated viruses in this C-19 *unvaccinated* subpopulation.

III. Ongoing epidemics of other microbial or immune-mediated diseases

In the meantime, depletion/ exhaustion of adaptive immune effector cells (i.e., IgG-producing B cells and cytotoxic CD8+ T cells) is now making healthy vaccinees more susceptible to recurrent *moderate disease* due to glycosylated pathogenic agents that can be broken down into three categories:

1. Glycosylated bacterial pathogens that normally cause other[14] acute self-limiting microbial infection (ASLMI) such as *Haemophilus influenzae* (Hib), meningococcal bacteria belonging to genus *Neisseria meningitidis* (e.g.,

[13] The host's susceptibility to contracting productive infection from these glycosylated pathogens may temporarily decrease as a result of enhanced SC-2 infectiousness. The latter may occur in case a person becomes re-infected with SC-2 shortly after an asymptomatic primary infection. This is because the short-lived, non-neutralizing Abs that were elicited following the asymptomatic primary infection are prone to bind to the virus and cause Ab-dependent enhancement of SC-2 infection, thereby causing a temporary activation of CD8+ T cells and thus entailing Ab-dependent mitigation of disease caused by glycosylated, ASLVI- or ASLVD-enabling viruses.
[14] i.e., other than ASLVIs or ASLVDs

serogroups A, C, W and Y; Men ACWY), and pneumococcal bacteria belonging to genus *Streptococcus pneumoniae.*

2. Glycosylated microbial pathogens that normally cause chronic self-controlled microbial infection (CSCMI) such as HSV-1/ HSV-2, EBV, CMV, HIV, and tuberculosis.
3. Glycosylated self-proteins that normally enable self-controlled tolerance of self-antigens

The anticipated rise in the incidence of these diseases simply reflects the extent of adaptive immune resources (in terms of S-specific Abs and cytotoxic CD8+ T cells) required of vaccinated individuals' immune systems to achieve the level of immune pressure necessary to prevent SC-2 from breaking through the protection conferred by the infection-enhancing Abs—which, for now, still provide protection against viral virulence (i.e., severe disease). Consequently, we will likely continue to witness a strong increase in the incidence rate of *moderate* disease from these pathogenic agents in vaccinated populations (as this subpopulation comprises most age groups).
However, in vaccinees with an immature (**young children**; fig. 2: ⑤) or weakened (fig. 2: ④) CBIIS, excessive SC-2-mediated stimulation of S-specific Abs and cytotoxic CD8+ T cells likely results in depletion of IgGs that are directed at other antigens and exhaustion of CD8+ T cells that are directed at pathogens other than those sharing the polyspecific CTL epitope comprised within S protein. It is reasonable to assume that this will entail a dramatic increase in the incidence rate of severe disease due to ASLMI- or CSCMI-enabling glycosylated viruses in vaccinated young children and elderly people. Incidence rates of severe disease are also likely to increase due to immunopathology- or cancer-enabling glycosylated self-proteins within vaccinated **young children** and the elderly respectively.

Although vaccinees serve as a breeding ground for these infections, they are not asymptomatic shedders and the spread of these glycosylated microbial infections can, therefore, ignite only epidemics and not pandemics. Upon exposure to the forementioned pathogenic agents, unvaccinated individuals with a mature innate immune system are more likely to develop *a transient episode* of *mild to moderate*

(fig.2: ①) or *moderate* to *severe* disease (fig. 2:②) from these other glycosylated viruses depending on their susceptibility[15] and the strength of their CBIIS. In a highly vaccinated population, the incidence rate of *moderate* to *severe* disease from glycosylated ASLMI- or CSCMI- or cancer-enabling pathogenic agents is therefore likely to increase.

However, a limited number of the unvaccinated with an immature CBIIS (young children; fig. 2: ③) are now more likely to develop severe disease from these glycosylated pathogenic agents for the same reason as previously explained for SC-2 (see under section I.) In a highly vaccinated population, one can therefore expect *a limited increase* in the incidence rate of *severe* disease from glycosylated ASLMI- or CSCMI- or immunopathology-enabling pathogenic agents in this C-19 unvaccinated subpopulation.

IV. How will these pandemics/ epidemics evolve, and which populations will they affect?

While emerging pandemics of other ASLVIs (e.g., influenza, RSV) or ASLVDs (e.g., monkeypox and avian flu) will inflict relatively little damage to populations that—except for young children—are highly vaccinated (as there is cross-protection from cytotoxic CD8+ T cells), more significant damage will come from epidemics of *other microbial diseases and cancer* as they become more prevalent due to relative exhaustion of the adaptive immune system in these populations. ***However, if communities proceed with vaccination of young children, all emerging pandemics and ongoing epidemics will cause incredible damage to this part of the population***, possibly even before the pandemic of 'more virulent' SC-2 variants transitions into its final

[15] The host's susceptibility to contracting productive infection from these glycosylated pathogenic agents may temporarily increase as a result of enhanced SC-2 infectiousness. The latter may occur in case a person becomes re-infected with SC-2 shortly after an asymptomatic primary infection. This is because the short-lived, non-neutralizing Abs that were elicited following the asymptomatic primary infection are prone to bind to the virus and cause Ab-dependent enhancement of SC-2 infection, thereby causing a temporary depletion/ exhaustion of IgGs and CD8+ T cells needed to fight off other glycosylated pathogenic agents and thus entailing Ab-dependent enhancement of disease caused by glycosylated ASLMI- or CSCMI- or immunopathology- or cancer-enabling pathogenic agents.

dramatic stage of ADED. Given my predictions on the timeline for the latter to happen, this would particularly apply to C-19 vaccination of children in countries with a relatively low vaccine coverage rate.

Meanwhile, many animal species have also become susceptible to *highly infectious* SC-2 and other 'antigenically shifted' glycosylated viruses (e.g., avian influenza) *for lack of Ag-specific antibodies and adequately trained cell-based innate immunity*. This situation is likely to not only threaten zoo animals but even livestock due to its close proximity with humans and short lifespans that do not allow for the development of robust innate (and thus herd) immunity (owed to lack of endemic circulation of glycosylated viruses). In addition, high stocking density or other unfavorable management or environmental conditions may produce stressors which can negatively impact innate immune function (e.g., within poultry, cattle, pigs).

Countries with low vaccine coverage rates, well-trained innate immunity and younger populations will do best (*Africa will win*!). Loss of human life is likely to be most severe in highly SC-2 vaccinated countries, while unvaccinated individuals in these regions will have trained their innate immunity adequately to resist emerging SC-2 variants well-adapted to the immune status of vaccinees. The situation will be dire in countries like China, for example, where not only a high percentage of (elderly) people have been vaccinated, but where the unvaccinated are also at risk due to poorly trained innate immunity as a result of stringent infection-prevention measures.

<u>Overall conclusion</u>

Massive suboptimal immune pressure exerted by highly C-19 vaccinated populations on the life cycle of SARS-CoV-2 drives natural selection and dominant propagation of highly infectious variants that sideline the cell-based innate immune system while subverting and eroding the adaptive immune system in ways that ignite new pandemics and epidemics with dramatic consequences. Both human and animal populations are at significant risk, particularly in countries with high C-19 vaccine coverage rates and especially within vaccinated children. These countries will severely suffer from the

pandemic of 'more virulent' SC-2 variants once the latter have become resistant to the virulence-inhibiting activity of vaccine-induced infection-enhancing Abs.

Figures

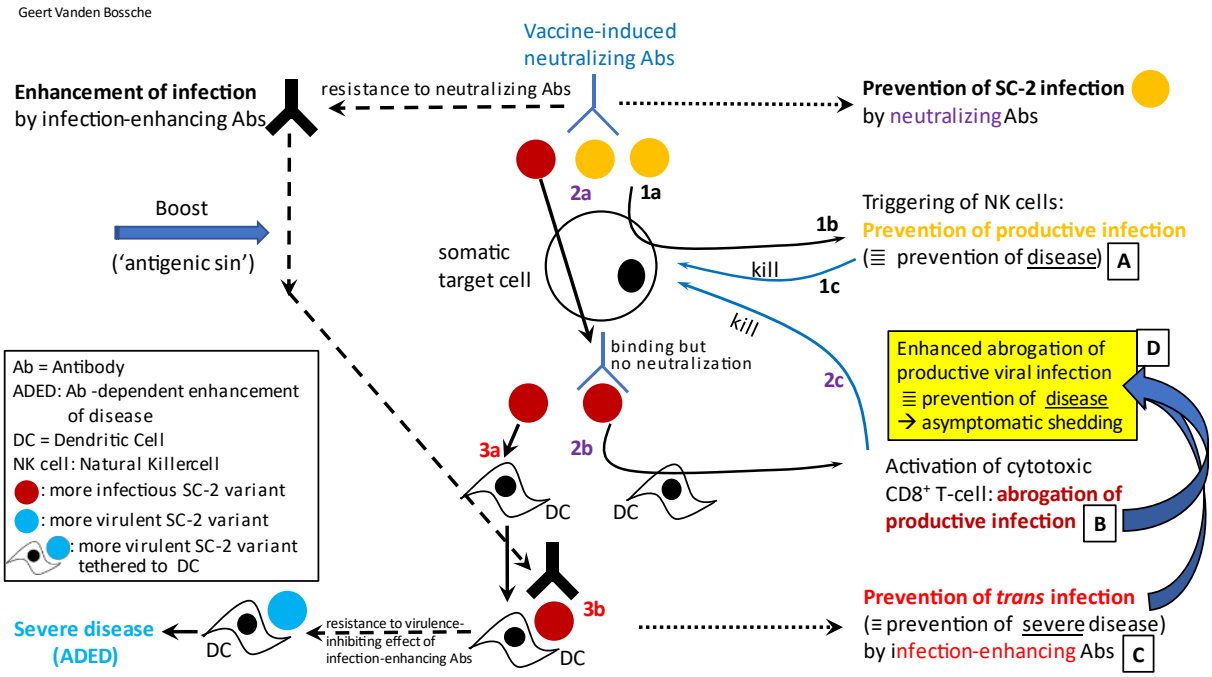


Fig. 1: *Acute, self-limiting viral infections that don't lead to systemic/ severe disease (and possibly death) are terminated by **M**(ajor) **H**(istocompatibility) **C**(omplex)-unrestricted, cytotoxic CD8+ T cells that have no memory and the activation of which is triggered by a universal, pathogen-nonspecific Tc epitope comprised within the spike (S) protein. Unless an infected person progresses to developing severe disease, this is what allows a fairly rapid recovery from disease after primary productive infection (and certainly before fully functional virus-neutralizing Abs peak) [according to **2a-2b-2c** pathway]. However, rather than stimulating de novo generation of new neutralizing Abs towards variants that escaped the neutralizing activity of vaccine-induced Abs, exposure of vaccinees to these immune escape variants will rapidly boost the non-neutralizing, infection-enhancing Abs (those are directed against an antigenic site that is conserved within the N-STD of all SC-2 variants and, therefore has a license to commit 'antigenic sin' once it has primed the host's immune system).*

*In vaccinees with poor experience in fighting productive infection (and hence, poor training of their innate immune defense) prior to C-19 vaccination (cfr. A: **1a-1b-1c**), infection-enhancing Abs[16] (cfr. C:) that are responsible for preventing severe disease by binding to DC-tethered virus (according to **3a-3b** pathway) can synergize with continuously activated cytotoxic CD8+ Tc-mediated killing (cfr. B) to even prevent disease all together and hence, render vaccinees asymptomatic despite their high susceptibility to re-infection (cfr. D). As prevention of disease is not due to prevention of productive infection but to accelerated abrogation of infection, these vaccinees will continue to shed and transmit SC-2 upon re-infection. Whereas innate immune effector cells are MHC-unrestricted and polyspecific (i.e., NK cells) and, therefore, don't drive immune escape, the infection-enhancing-Abs are Ag-specific (i.e., S-specific) and – if produced at high titers by a large part of the population – will promote natural selection of immune escape variants that can resist the virulence-inhibiting capacity of these Abs. This is because vaccinees cannot prevent productive viral infection; consequently, the immune pressure they exert on viral virulence is suboptimal in that it cannot prevent dominant propagation of immune escape SC-2 variants that have the capacity to overcome this immune pressure. Resistance of viral variants to the virulence-inhibiting activity of infection-enhancing Abs will inevitably cause ADEI-mediated ADED.*

Fig. 2: *The table below summarizes the type of disease the pandemics described in the text are expected to cause in a well-mixed highly vaccinated population and how the incidence rate of the different types of severe disease (and hence, the hospitalization rate) is expected to evolve in the vaccinated as compared to the unvaccinated part of the population, depending on the maturity/strength of the CBIIS and the level of immune experience of the AIS. Enhanced viral transmission from the asymptomatically infected group of C-19 vaccinees to other parts of the population will cause 3 new types of pandemics[17], i.e., a pandemic of antigenically shifted **, 'more virulent' immune escape SC-2 variants enabling ADEI in vaccinees (P1),** a pandemic of **acute, self-limiting viral infections** (**P2**), a pandemic of **acute, self-limiting***

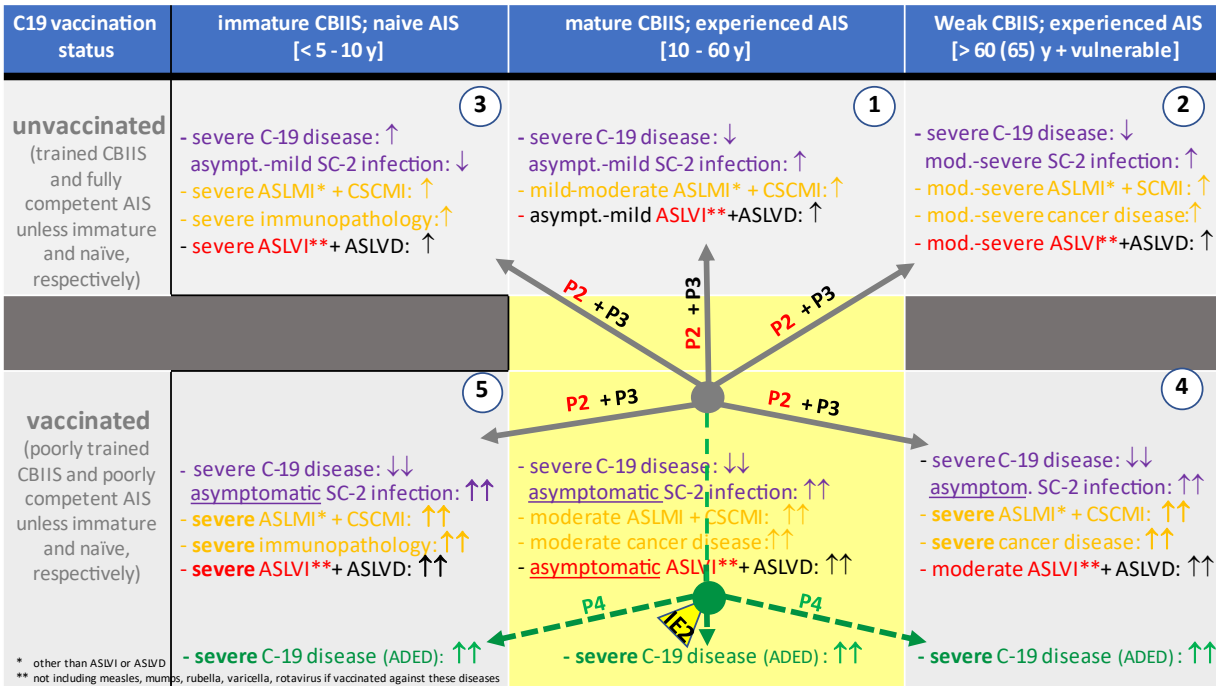
[16] As previously explained, the non-neutralizing, infection-enhancing Abs are currently hampering *trans* infection at the level of distant organs such as the lower respiratory tract; this is what's currently exerting population-level immune pressure on viral virulence: https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic).

[17] 'Pandemics' and not 'epidemics' as the spread and transmission of these infectious pathogens will not be restricted to highly vaccinated countries

viral diseases *(**P3**) and one 'pseudo-pandemic' of* ***'more virulent' immune escape SC-2 variants enabling ADEI-mediated ADED in vaccinees*** *(**P4**).*

P1 *and* ***P4*** *(will) only affect* ***highly vaccinated countries****. The health impact of the ongoing pandemics (i.e.,* ***P1****,* ***P2****,* ***P3****) and the imminent pseudo-pandemic (i.e.,* ***P4****) on immunologically distinct groups of a well-mixed, highly vaccinated population are described in the text.*

Abbreviations:
ADED: Antibody-dependent enhancement of disease
AIS: Adaptive immune system
ASLMI: Acute self-limiting microbial infection (other than ASLVI or ASLVD)
ASLVD: Acute self-limiting viral disease
ASLVI: Acute self-limiting viral infection
C-19: Covid-19
CBIIS: Cell-based innate immune system
CSCMI: Chronic self-controlled microbial infection (i.e., self-controlled by the host immune system)
IE2: 2nd immune escape event (triggering resistance of 'more virulent' SC-2 to the virulence-neutralizing/ inhibiting activity of infection-enhancing Abs and thereby rendering vaccinees highly susceptible to severe disease)
P1: new C-19 *pandemic of* antigenically shifted, *'more virulent' immune escape SC-2 variants enabling ADEI in vaccinees* (i.e., BA.4 and BA.5)
P2: ongoing *pandemic of ASLVIs*
P3: ongoing *pandemic of ASLVDs (Avian influenza virus; Monkeypox virus and Respiratory Syncytial Virus [RSV])*
P4: imminent *'pseudo-pandemic'*[18] *of new, 'more virulent' immune escape SC-2 variants enabling ADEI-mediated ADED in vaccinees.* This is the C-19 (pseudo-)pandemic of SC-2 immune escape variants exhibiting 'highly viral infectiousness' and 'high viral virulence' in vaccinees.
SC-2: SARS-COV-2



Note:

[18] For the purpose of this manuscript, a 'pseudo-pandemic' is defined as a global epidemic of an infectious agent that is so virulent that it is no longer able to spread

- *The age groups don't exactly correspond to the status of the CBIIS and AIS described and only provide a ballpark figure on the age range of groups comprising the majority of people with the indicated immune status*
- *For the purpose of this manuscript, the term 'vulnerable' refers to the CBIIS status of people/ individuals with co-morbidities/ underlying diseases are who are otherwise immunosuppressed or immunodeficient*
- *For the purpose of this manuscript, the term 'elderly' refers to people/ individuals with a more or less immunosenescent CBIIS (i.e., alteration of its immune function due to aging).*
- *For the purpose of this manuscript, the term 'young children' refers to people/ individuals with a more or less immature CBIIS*
- *A dramatic increase (↑↑) in '**severe**' disease is highlighted in **bold** as the incidence and evolution thereof will provide guidance on the need for hospitalization*
- *Asymptomatic is underscored if the asymptomatic (sub)population serves as a reservoir of viral transmission:*
- ***Purple fonts** indicate the asymptomatic reservoir responsible for initiation of the P1 pandemic and the types of disease caused by transmission of 'more infectious' and 'more virulent' SC-2 variants to the different unvaccinated groups of a well-mixed, highly vaccinated population. Because 'more infectious' variants raise the infection rate in the population, they compromise innate immunity in young unvaccinated children whereas they improve innate immune training in the remainder of the unvaccinated population. As 'more infectious' variants become more and more resistant to potentially neutralizing vaccinal Abs, they bind more readily to infection-enhancing Abs. The latter are capable of blocking trans infection and trans fusion in vaccinees and thereby enable abrogation of productive infection (via cytotoxic CD8+ T cells) which first results in prevention of severe disease and eventually (i.e., with enhanced activation of cytotoxic CD8+ T cells) in prevention of disease all together, but not in prevention of productive infection (see fig. 1).*
- ***Red fonts** indicate the asymptomatic reservoir responsible for initiation of the P2 pandemic and the types of disease caused by asymptomatic transmission of glycosylated, ASLVI-enabling viruses to the different groups of a well-mixed, highly vaccinated population*
- ***Black fonts** indicate the asymptomatic reservoir responsible for initiation of the P3 pandemic and the types of disease caused by asymptomatic transmission of glycosylated, ASLVD-enabling viruses to the different groups of a well-mixed, highly vaccinated population*
- ***Green fonts** indicate the type of disease (i.e., ADEI-mediated ADED) caused by natural selection and dominant propagation of new, 'more virulent' immune escape SC-2 variants in vaccinees*
- ***Gold fonts** indicate the types of disease caused by sustained (vaccinees) or transient (unvaccinated) depletion of IgGs and CD8+ T cells required to fight off glycosylated pathogens causing ASLMIs or CSCMIs or immune-mediated diseases (i.e., cancer or immunopathologies)*