Nature will unambiguously demonstrate that neither the unvaccinated nor the vaccinated who refused to re-vaccinate can be blamed for the imminent transition of this immune escape pandemic to its final, hyperacute phase…

The emergence of cryptic lineages: Another example of how a lack of immunological insight leads to empty prejudices.

People often speculate that if my predictions come true (of which I remain 100% convinced), the unvaccinated will once again be scapegoated for exacerbating the public health damage caused by the virus. However, I firmly believe this won't be the case, as it will become unmistakably clear that cases of enhanced severe Covid-19 (C-19) disease will almost[1] exclusively occur among the C-19 vaccinated, leaving healthy unvaccinated individuals unaffected.

However, what is more probable is that public health authorities and self-proclaimed health experts will assert that the pandemic, which they believed was receding, has suddenly surged again due to the growing vaccine hesitancy. Consequently, they may argue that the immune system of people who decline updated C-19 vaccines is at risk of being overwhelmed by the current circulating, highly infectious SARS-CoV-2 (SC-2) variants and that many of them will therefore contract chronic SC-2 infections. As a result, they would persistently shed their own 'home-made' variants , so-called 'cryptic' lineages[2,3] that typically are very peculiar and always contained in one place (i.e., primarily localized where the allegedly chronically infected person resides).

Well, it's just going to be another significant misinterpretation on their part. This misinterpretation, however, conveniently suits them well as it could absolve them of any guilt (but not in the mind of those who read some of my more recent contributions to this topic[4]).

As a matter of fact, scientists specialized in virus surveillance in wastewater have unfortunately rushed to premature conclusions to explain the origin of these cryptic lineages, proposing the hypothesis that they are derived from unsampled chronic human C-19 infections or indicate the presence of a non-human animal reservoir! Instead of investigating the dynamics of population-level immune responses to the virus in highly C-19 vaccinated populations, they mistakenly suggest that these cryptic lineages can be traced back to single/ specific individuals living with Long Covid, a chronic disorder where individuals supposedly suffer from chronic SC-2 infection and persistently shed virus from various organ systems. However, for

[1] Unvaccinated individuals who experience SEVERE illness due to natural infection (a small percentage, particularly among the elderly and frail) develop very high antibody titers. Consequently, they could, like C-19 vaccinees, be susceptible to vaccine breakthrough infections (VBTIs) and immune refocusing.

[2] A "cryptic lineage" typically refers to a lineage the ancestry of which is difficult to trace because of genetic markers or mutations that are not usually observed in clinical samples, but can be identified by wastewater surveillance, since that technique picks up more people's infections than individual testing with PCR assays or antigen tests (which are no longer routinely performed anyway!). Unlike common variants that more or less rapidly spread through an entire population (Delta, Omicron, BA.5, XBB, JN.1 etc.), these lineages are typically found in a specific location and not recognized in GISAID's EpiCoV database.

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9176656/

[4] https://www.voiceforscienceandsolidarity.org/scientific-blog/reflections-on-the-ongoing-immune-escape-pandemic

these individuals to shed cryptic lineages in concentrations sufficient to be detected in wastewater, they would need to be shedding at least a thousand times more virus than an average acutely infected patient does! Despite all efforts, such super-shedders with chronic SC-2 infections who are active in society have not been found!

To comprehend the genuine science behind the cryptic lineages and the cases of Long Covid, one must understand the evolutionary population-level dynamics of the interactions between the virus and the host immune system that are characterizing the ongoing immune escape pandemic (i.e., a natural pandemic where herd immunity failed to establish as a consequence of the mass vaccination program).

In the initial phase of the C-19 pandemic, large-scale infection-prevention measures, including social restrictions, exerted non-selective '*containment*'-mediated pressure on viral infectivity. With the initiation of large-scale vaccination efforts, this pressure on the intrinsic infectiousness of the virus has rapidly been complemented by mounting selective immune pressure on virus neutralizability (as C-19 vaccines induce neutralizing antibodies [NAbs] against the virus).

In the current phase of the pandemic, the immune response of C-19 vaccinees has evolved in tandem with the immune evasion strategies of the virus. This evolution meanwhile caused highly C-19 vaccinated populations to exert non-selective immune selection pressure on the virus's transmissibility, driven by widespread cytotoxic T lymphocyte (CTL) responses targeting a highly conserved self-mimicking T cell epitope comprised within the S2 subunit of spike (S) protein (referred to as 'MHC [major histocompatibility complex] class I-unrestricted' CTLs). This explains why any viral variant spawned by the currently circulating highly infectious Omicron descendants and incorporating mutations in one or more viral proteins that amplify post-infection replication, will gain a competitive advantage in the face of immune responses that diminish viral transmissibility. However, only those emerging variants demonstrating the highest intrinsic infectiousness rates will gradually increase their prevalence over time (e.g., members of the JN.1 clan), while many others will only transiently benefit from their enhanced capacity to produce viral progeny, as they will eventually be outcompeted by the co-circulating, more infectious variants. Consequently, the latter can spread more widely, whereas the former propagate only as long as their transmissibility remains sufficiently competitive, achieved through various mutations in one or more viral proteins, against circulating variants that evolved to a higher level of intrinsic infectiousness.

In simpler terms, cryptic lineages only spread for a limited period before being overwhelmed by co-circulating variants that have incorporated additional mutations that confer an even higher level of infectiousness (e.g., mutations enabling non-ACE2[5]-receptor-dependent infection). Consequently, they can only spread to some extent within the subpopulation or small area where they originated. These lineages, competing for increased progeny production, often harbor highly divergent mutations in their viral proteins, resulting in very aberrant characteristics compared to widely circulating variants, hence earning them the label 'cryptic'[6]. This phenomenon explains why cryptic lineages can be shed by any host susceptible to productive infection of SC-2, particularly by C-19 vaccinees -whose productive infections

[5] ACE2: Angiotensin-converting enzyme 2
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9176656/

have now become increasingly asymptomatic-, regardless of whether they develop an immune pathological response upon re-exposure (see below).

The limited spread of cryptic lineages in the population, and their detection being confined to specific wastewater shed areas, is therefore *not due to intense shedding by specific individuals, but rather to nonselective population-level immune pressure on viral transmissibility*. Here are the key arguments supporting my analysis:

- If highly divergent cryptic lineages were shed by individual hosts, we would expect that the distinct intra-host immune selection mechanisms underlying these uncommon mutations would result from a diversified spectrum of immune-mediated disorders. The latter would likely be represented by a relatively small cohort of super-shedders, each contaminating a specific local sewershed. It would be unexpected for these individuals to remain healthy enough to avoid hospitalization or medical attention, where testing would reveal any underlying health issues. In fact, no socially active immunocompromised individual has been identified who persistently sheds a cryptic variant identical to those isolated from local sewersheds. Since the replication and shedding of this cryptic variant have been limited in duration, it is likely that its detection in wastewater occurred at a time when it had already been largely replaced by more infectious variants circulating in the population.
- The unusual mutations observed in the newly emerging cryptic variants not only perfectly align with the expected outcome of population-level nonselective immune pressure on viral replication but also their disappearance can be explained by the ongoing emergence of JN.1 descendants exhibiting an even higher level of intrinsic infectiousness.

To support the conclusion drawn from my analysis, I anticipate that researchers engaged in immune surveillance will soon report a decrease in the detectability of cryptic lineages. Meanwhile, mutation spotters will likely find that descendants of the JN.1 clan are acquiring additional mutations in the spike (S) protein, facilitating incremental enhancements in their intrinsic infectiousness.

Cryptic lineages transition from similar convergent to dissimilar divergent evolution and eventually disappear.

The selective immune pressure on the S protein, particularly on the S-RBD (receptor-binding domain of S protein), explains why cryptic lineages that emerged in the early stages of the Omicron era were less frequently observed and showed significant overlap with Omicron descendants. This confirms a similar pattern of ***convergent*** evolution due to similar immune selection pressure.

Conversely, recently emerged cryptic lineages are now more frequently detected during wastewater surveillance, displaying dissimilar ***divergence*** from the prevailing circulating lineages, notably members of the JN.1 clan. Since these cryptic lineages originate from Omicron descendants previously selected due to immune pressure on virus neutralizability (i.e., on the S-RBD) followed by immune pressure on viral infectiousness i.e., on the S protein), all identified cryptic lineages have demonstrated increased intrinsic infectiousness and resistance to various classes of neutralizing monoclonal antibodies (Abs).

Below, in the appended figure 1 (an excerpt from the slide deck of my course: https://www.voiceforscienceandsolidarity.org/scientific-blog/the-immune-biology-of-natural-and-immune-escape-pandemics-epidemics---updated), I am summarizing the process wherein immune refocusing of S-directed Ab responses occurs in highly C-19 vaccinated populations, leading to a shift in the immune response towards a universally cross-reactive Cytotoxic T Lymphocyte (CTL) response (i.e., directed at a universal virus-derived peptide[7]). As enhanced universal CTL responses effectively abrogate productive viral infection by any variant, they exert growing non-selective immune pressure on viral transmissibility when mounted by an increasingly larger portion of the population.

This implies that any Omicron descendant, shed by a member of a highly C-19 vaccinated population, and possessing increased transmissibility due to mutational changes in its viral proteins, will benefit from a transmission advantage, thus being detectable in specific sewersheds. However, in highly C-19 vaccinated populations, variants that have evolved additional mutations enabling a higher level of intrinsic infectiousness will better facilitate enhanced transmissibility compared to those primarily evolving mutations that augment viral production rates only[8]. This is because the main source of viral transmission in these populations is vaccinated individuals, who largely act as asymptomatic shedders upon re-exposure. Consequently, in terms of viral transmissibility, *more infectious* variants will spread more rapidly and gradually outcompete *more productive* variants in highly C-19 vaccinated populations. It is, therefore, not surprising that as the immune pressure on viral transmissibility increases, several more infectious descendants spawned by the JN.1 clan exhibit a transmissibility advantage over other cryptic lineages and are now rapidly outcompeting the latter.

In summary:

All cryptic variants exhibiting enhanced transmissibility could sporadically and temporarily pop up in wastewater surveillance tracking from a particular sewershed. Mutations enabling enhanced transmissibility could include mutations that further enhance viral infectiousness (e.g., via a non-ACE2 receptor-dependent mechanism of viral entry and/ or any changes in SC-2 proteins resulting in enhanced production of viral particles). Given the enhanced protection of the unvaccinated and the vaccinated against productive infection, variants that are more infectious will eventually outcompete the less infectious ones. The latter are therefore referred to as cryptic.

What happens when the spectrum of more transmissible SC-2 variants is narrowing?

Increased viral infectiousness implies enhanced adsorption of viral particles to upper respiratory tract (URT)-resident dendritic cells (DCs), thereby reducing virus uptake, processing, and antigen (Ag) presentation by antigen-presenting cells (APCs). As a result, the elimination of virus-infected host cells gradually transitions to the accumulation of virus on Ag-presenting host cells (i.e., DCs), which transport the virus to various organ systems (see fig. 2 below). The combination of enhanced viral infectiousness and diminished abrogation of productive viral infection causes highly C-19 vaccinated populations to exert

[7] The universal peptide is comprised within the S2 fusion peptide: https://pubmed.ncbi.nlm.nih.gov/19439480/
[8] https://www.nature.com/articles/s41467-024-45274-3

growing immune pressure on the 'neutralizability' of viral *trans* infectiousness by polyreactive nonneutralizing Abs (PNNAbs).

I will now explain why this can be considered the final and most significant step in the virus's immune escape strategy, marking the beginning of the end of the immune escape pandemic:

First, as the virus gains the upper hand, the pain worsens for vaccinated hosts. This is because diminished Ag uptake may no longer allow universal pathogen-derived peptides to activate cytotoxic CD8+ T cell (Tc) responses (i.e., CTLs), but instead prime a diversified set of antigen-specific CD4+ T cells, some of which will be directed at self-mimicking virus-derived peptide. Priming of such self-directed CD4+ T cells may occur when promiscuous microbial T cell (Tc) peptides, sharing sufficient structural homology with particular self-peptides, are presented on upregulated MHC class II molecules. This phenomenon may, therefore, lay the foundation for the pathogenesis of autoimmune diseases via a phenomenon termed *degeneracy of Ag recognition of TCR* (T cell receptor) *recognition*[9,10,11,12].

The priming of autoreactive T cells can be attributed to cross-reactivity between pathogen-derived and self-antigens (molecular mimicry). The chronic antigenic stimulation of circulating autoreactive T cells directed towards tissue-specific self-antigens, likely underlies the pathogenesis of Long Covid. The severity of this chronic T cell-mediated autoimmune disease presumably hinges on the extent of virus internalization into APCs and subsequent presentation of promiscuous Tc peptides on cell surface-expressed MHC class II molecules. This suggests that both the prevalence and severity of Long Covid cases are poised to rise alongside the evolution of the virus towards an increasingly narrow range of more transmissible variants causing vaccine breakthrough infections (VBTIs) in highly C-19 vaccinated populations. Since the pathogenesis of Long Covid likely involves the degenerate recognition of a promiscuous self-like Tc peptides, it's not surprising to observe that the occurrence and severity of Long Covid are independent of the patient's genetic MHC background.

Anticipating that the potent and universal CTL activation (coupled with exhaustion of Ag-specific CD8+ T cells!) will be mitigated due to enhanced adsorption of more infectious variants to DC-tethered virions (see fig. 2), we may witness *a surge in T cell-mediated autoimmune diseases replacing the surges of turbo cancers*. Given that the onset or exacerbation of Long Covid is likely triggered by re-exposure to circulating virus, the diagnosis of Long Covid often correlates with a positive PCR assay or Ag test. However, correlation does not necessarily imply causation, and there's no evidence to support the notion that the chronicity of this condition stems from persistent viral replication.

Based on the proposed dynamics of the interaction between the virus and population-level immunity, it seems reasonable to attribute the chronicity of this condition to the recall of previously induced Ab responses in previously C-19 vaccinated individuals. Therefore, I would prefer to designate this chronic disease as *vaccine-associated autoimmune disease* rather than Long Covid, as the former better underscores the immune pathological nature of this condition and its prevalence among C-19 vaccinees.

[9] https://pubmed.ncbi.nlm.nih.gov/11359825/;
[10] https://pubmed.ncbi.nlm.nih.gov/10490973/;
[11] https://pubmed.ncbi.nlm.nih.gov/9155643/;
[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7133435/

Finally, it is crucial to recognize that the days of the JN.1 descendants are numbered. With an increasing trend towards the adsorption of viral particles to URT-resident DCs, the concentration of Ab-virus complexes capable of recalling PNNAbs is declining while stimulation of foreign-centered CD4+ T cells by strongly activated APCs may generate autoreactive CD4+ T cells (see further below), but no longer assist recall of previously primed anti-S Abs. Consequently, PNNAbs titers gradually become rate-limiting for inhibiting viral *trans* infection. As a result, highly C-19 vaccinated populations are exerting increasing immune pressure on the 'enhancing' antigenic site within the N-terminal domain of S protein (S-NTD) responsible for binding the PNNAbs[13] in highly C-19 vaccinated populations.

It is reasonable to assume that the decreasing recall of PNNAbs gradually renders the binding of these Abs to the enhancing site on DC-tethered virions rate-limiting in preventing severe C-19 disease[14]. As this enhancing antigenic site within S-NTD is highly conserved, highly C-19 vaccinated populations are now exerting increasing non-selective immune pressure on viral *trans* infectiousness (i.e., viral virulence). Since the virus can no longer alleviate this mounting immune pressure through further changes in S-associated epitopes or mutations in other viral proteins, the only way to mitigate the rising immune pressure on viral virulence is through the incorporation of a specific glycosylation profile. The crucial aspect of this glycosylation profile is its ability to obstruct PNNAb binding to the DC-tethered virions, regardless of the amino acid composition or arrangement of the S protein[15]. As a result, the incorporation of a uniform glycosylation profile would lead to the emergence of a completely novel, antigenically very divergent, non-neutralizable viral lineage. This lineage, termed 'HIVICRON', would possess the ability to sterically evade binding of the virulence-inhibiting PNNAbs to their DC-tethered virions (the phenomenon I refer to as 'steric immune silencing'). Consequently, this new Coronavirus would exhibit a high level of viral virulence in fully C-19 vaccinated individuals and swiftly outcompete all previously circulating SC-2 variants in highly C-19 vaccinated populations.

While VBTIs caused by Omicron prompted *steric immune refocusing* [SIR] (i.e., a shift in immune response focus) and led to mitigation of C-19 disease (i.e., prevention of severe C-19 disease), the emergence of HIVICRON is believed to induce 'steric immune silencing' (see further below) while restoring binding of PNNAbs to the enhancing site on *freely circulating viral particles*), thereby leading to PNNAb-dependent enhancement of severe C-19 disease.

I have proposed that the most probable method for a new variant to develop resistance against PNNAb-mediated inhibition of viral virulence is through the addition of elongated carbohydrate chains at specific O-glycosylation sites[16] . The mutated O-glycosites within HIVICRON are expected to be grafted on an S protein structure that is markedly distinct and highly divergent from those found on currently circulating Omicron descendants, despite originating from them. Consequently, highly C-19 vaccinated regions may suddenly witness the proliferation of a 'cryptic' viral lineage characterized by a combination of mutations conferring *resistance to neutralization as well as heightened infectiousness and virulence*, representing a

[13] https://pubmed.ncbi.nlm.nih.gov/34139176/

[14] PNNAbs are believed to play a crucial role in restraining viral virulence by binding to the conserved antigenic site within S-NTD: https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic

[15] https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic

[16] https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic

substantial departure from all previously circulating SC-2 variants. It is therefore highly likely that the combination of significant alterations in viral proteins along with extensive changes in the S-associated glycosylation profile of these new viral lineages will prompt public health authorities and experts to attribute the emergence of this new Coronavirus to a chronic infection in a single (unidentified!) individual who persistently fails to control viral replication due to inadequate immunity (and consequently, according to their assessment, due to insufficient C-19 vaccination!).

Hence, due to their misunderstanding of the pathogenesis of chronic infection/ shedding and Long Covid along with their ignorance regarding the escalating immune pressure on viral virulence, public health authorities may conveniently attribute the increasing prevalence of these disorders in highly C-19 vaccinated populations to the perceived inadequacy of the population's coverage rate by updated C-19 vaccines*.

Conclusion:

I hope this report unequivocally demonstrates that *Long Covid patients bear no responsibility for the emergence of presently detected highly transmissible cryptic lineages, nor will they serve as a breeding ground for a future new Coronavirus with high virulent potential in populations with high C-19 vaccination rates.* Instead, these patients suffer from immune pathological consequences stemming from SIR-enabling VBTIs within highly C-19 vaccinated populations. SIR-enabling VBTIs, and thus the sporadic and temporary emergence of cryptic SC-2 lineages and the accompanying so-called *Long Covid cases, are merely the consequences of escalating immune escape and immune pressure originating from mass vaccination and eventually driving the virus to evolve with remarkable gain-of-function* (see fig. 1).

Mass vaccination, rather than the lack of acceptance of updated C-19 vaccinations, is the sole cause of the seemingly perpetual cycle of viral immune escape and the accompanying rise in chronic viral shedding and immune pathology (referred to as 'Long Covid'). However, *the increasing incidence of Long Covid cases, coupled with the evolution of JN.1 descendants towards higher levels of dominance and adsorption to URT-resident DCs, serves as the harbinger of a dramatic wave of highly virulent VBTIs that will ultimately put an end to the large-scale gain-of-function experiment conducted in highly C-19 vaccinated populations*.

There shall be no doubt that the responsibility of this unprecedented gain-of-function experiment on the very human species solely lies with those who orchestrated this mass vaccination program. Neither patients dealing with Long Covid nor individuals who declined the C-19 vaccination or rejected the updated boosters, can be blamed for chronic shedding of cryptic variants and the increasing incidence of Long Covid, let alone for the looming disaster that could have been prevented if the principle of "First, do no harm" had been honored.

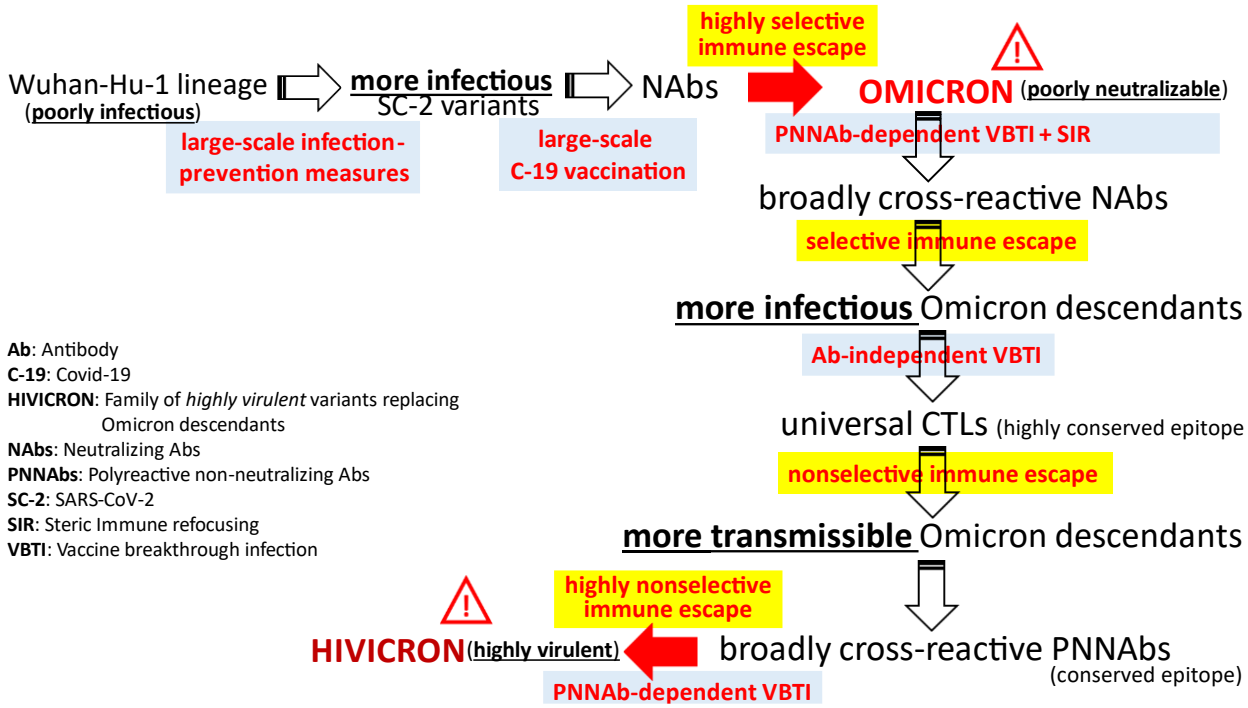

Fig. 1: The immune escape pandemic in a nutshell. Large-scale infection-prevention measures combined with mass C-19 vaccination resulted in large-scale gain-of-function (from asymptomatic-mild infection by Wuhan-Hu-1 lineage to (PNN)Ab-dependent enhancement of severe C-19 disease by HIVICRON).

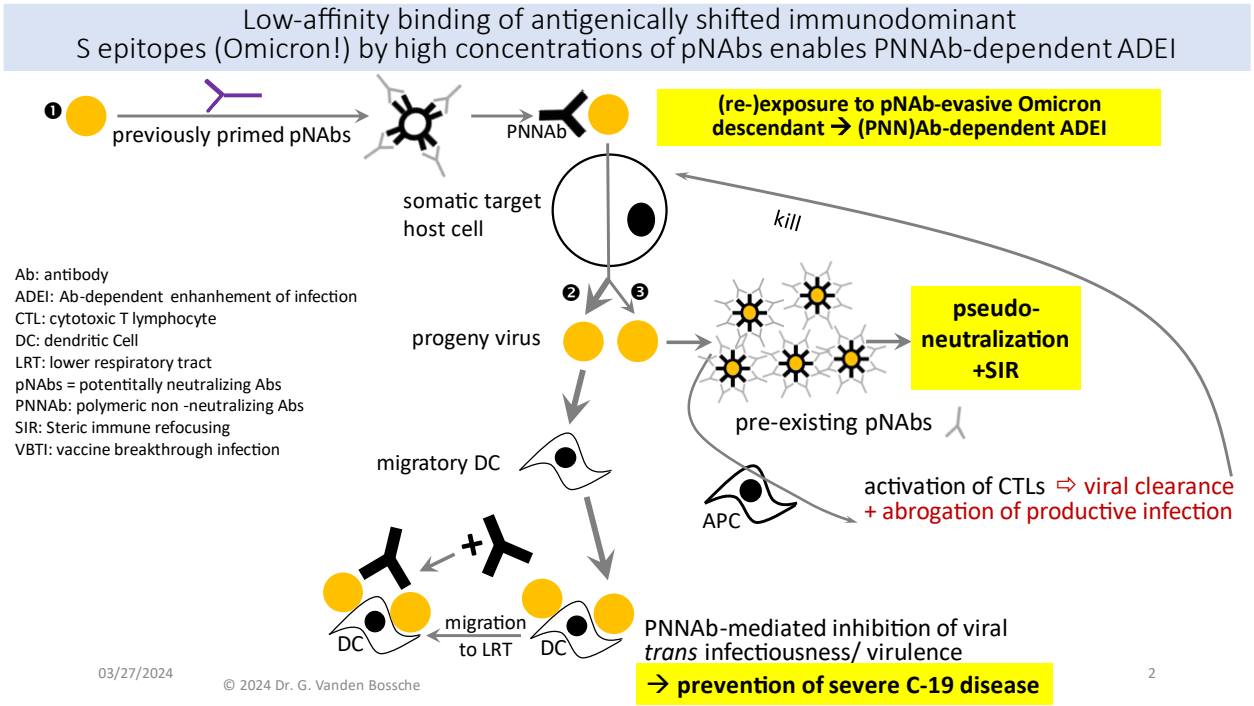

Fig. 2: Early Omicron descendants enter target host cells via PNNAb-dependent enhancement of infection (❶). PNNAbs bind to progeny virus tethered to these DCs, which subsequently migrate to the lungs and other distal organs (❷). On the other hand, previously SIR-primed Abs bind with low-affinity to the antigenically more distant immune escape variant, thereby generating Ab-virus complexes that are taken up into patrolling APCs (❸). Enhanced uptake of large Ab-virus complexes into APCs facilitates strong activation of CTLs, thereby enabling the elimination of virus-infected host cells.

Highly infectious Omicron descendants do not rely on PNNAb-dependent enhancement of infection to enter target host cells. Replication of highly infectious variants generates an immunological environment that promotes their adsorption onto tissue-resident DCs. Due to their high level of intrinsic infectiousness, newly emerging, more transmissible Omicron descendants (e.g., members of the JN.1 clan) will therefore enhance the adsorption of progeny virions on migratory DCs and thereby reduce viral uptake by APCs. Reduced viral uptake by APCs will promote the priming of CD4+ T cells. Some of these T cells may be self-reactive, while others are foreign-centered but fail to serve as T helper cells to assist in boosting of previously SIR-primed Abs due to a lack of immune recognition of the corresponding B cell epitopes. Diminished boosting of previously primed anti-S Abs results in diminished production of PNNAbs.

As these highly infectious variants are steadily growing in prevalence, diminished production of PNNAbs, combined with their enhanced binding to highly infectious DC-tethered progeny virions leads to a steadily increasing immune pressure on viral virulence in highly C-19 vaccinated populations. This is thought to eventually trigger the selection of a new Coronavirus lineage that has the capacity to cause PNNAb-mediated enhancement of VBTIs in highly C-19-vaccinated populations, thereby causing a massive wave of enhanced severe C-19 disease.