Foreword:

While preparing for the big bang, I felt compelled to share the attached article with the world. The intended audience primarily includes all scientists, public health authorities, medical doctors and so-called 'experts' who are still naïve or ignorant enough to believe that Covid-19 vaccine boosters can recall virus-neutralizing antibodies and therefore ensure prolonged protection against Covid-19 disease.

I am genuinely stunned at their intellectual laziness. Had they conducted thorough research, they would know what I know, which is that nothing has been more predictable than that mass vaccination against SARS-CoV-2 was doomed to breed more infectious immune escape variants, eventually leading to the dominant spread of a highly infectious variant capable of causing severe vaccine breakthrough infections in highly C-19 vaccinated populations (while sparing the unvaccinated).

I no longer care at this point whether this scientific and medical elite will even read the conclusions of my detailed immunological analysis. What is crucial now is that the scientific facts and truths behind this experiment are unequivocally documented in writing, leaving no room for excuses based on either naivety or willful ignorance. Their behavior has not only insulted the integrity of science but has also dealt a sledgehammer blow to those who got the jabs. History will undoubtedly remember their intellectual ignorance and moral indifference for many generations to come.

Scientists and self-proclaimed experts have been aligning their interpretation of serological data from updated COVID-19 vaccine boosters with the mainstream narrative, thereby conveying a dangerously misleading public health message.

List of abbreviations:

Ab: Antibody

Ag: Antigen

APC: Antigen (Ag)-presenting cell

Nab: Neutralizing antibody (Ab)

NTD: N-terminal domain

OAS: Original antigenic sin

PNNAb: Polymeric non-neutralizing antibody

RBD: Receptor-binding domain

S: Spike protein

SC-2: SARS-CoV-2

SIR: Steric immune refocusing

Th: T help

VBTI: Vaccine breakthrough infection

1. Summary

It should be emphasized that the alleged 'neutralizing' activity observed in post-boost or post-infection sera from previously mRNA-vaccinated individuals does not result from updated vaccines largely overriding immunological imprinting. On the contrary, it stems from the immunological recall of previously SIR (steric immune refocusing)-primed low-affinity anti-Spike (S) antibodies (Abs) towards more conserved S-associated epitopes. Unlike truly virus-neutralizing variant S-specific Abs, these infection-inhibiting, S variant-nonspecific Abs are a scourge, not a blessing!

I am perplexed at the growing lack of critical thinking in our universities and research institutes. As I am teaching in my course on the '*Immune Biology of Pandemics & Epidemics*' (https://www.anhinternational.org/health-creation-faculty/the-immune-biology-of-natural-and-immune-escape-pandemics-epidemics/) and describing in my book 'The Inescapable Immune Escape Pandemic' (https://braintrain.mykajabi.com/the-inescapable-immune-escape-pandemic), the 'ghosts' these scientists are revering are the multivalent interactions between SARS-CoV-2 (SC-2) particles and elevated concentrations of previously SIR-primed, cross S variant-reactive Abs. These heightened concentrations result from an Ab recall effect induced by updated vaccine boosters or vaccine breakthrough infections (VBTIs) caused by newly emerged SC-2 variants. When present at very high concentrations, these Abs enable infection-inhibiting activity. Given that the infection-inhibitory (or 'virus-neutralizing') effect occurs only at a very high concentration of these cross S variant-reactive Abs, I term this phenomenon '*pseudo*-neutralization'.

Large-scale immune refocusing events are initially triggered by VBTIs with Omicron or two doses of an mRNA-based Covid-19 (C-19) vaccine. These events occur when high concentrations of previously neutralizing anti-S Abs interact with antigenically distant viral variants. Alternatively, large-scale immune refocusing occurs when high concentrations of anti-S Abs interact with the neutralizing domains on the S protein with low affinity.

The immune refocusing towards increasingly cross S variant-reactive immune responses, coupled with subsequent VBTIs involving newly emerged SC-2 variants, results in the natural selection of progressively more infectious SC-2 variants. This process generates a self-perpetuating cycle of SIR-enabling Ab-dependent VBTIs. The continual occurrence of these SIR events eventually drives Ab-independent VBTIs, thereby leading highly C-19 vaccinated populations to collectively intensify immune selection pressure on viral infectiousness and subsequently on viral virulence.

Elevated titers of previously vaccine-primed, S variant-specific neutralizing antibodies (NAbs) or SIR-primed, cross S variant-reactive Abs, resulting from boosting following Ab-dependent VBTIs with Omicron or newly emerged S variants, respectively, collectively initiated SIR events in highly C-19 vaccinated populations. After a exhibiting a short-lived neutralization effect, high titers of previously SIR-primed, cross S variant-reactive Abs swiftly led to prolonged mitigation of infection, thereby promoting the natural selection and propagation of new, more infectious immune escape variants that subsequently triggered new SIR-enabling VBTIs. The arrival of Omicron thus set in motion a self-perpetuating cycle of SIR events. VBTIs with newly emerged SC-2 variants were initially facilitated by polymeric non-neutralizing antibodies (PNNAbs). These

(PNN)Ab-dependent VBTIs engendered widespread immune selection for increasingly infectious S variants while concurrently inhibiting viral virulence.

SIR gradually redirects population-level immune selection pressure exerted by *S-specific* infection-mitigating *Abs* to population-level immune selection pressure exerted by *non-S-specific* infection-mitigating *cytotoxic T lymphocytes* (CTLs). This is because SIR will ultimately prime Abs, the affinity of which for S variant protein is low enough to stabilize larger viral aggregates following Ab-dependent VBTI. These large Ab-virus complexes are readily taken up by Ag-presenting cells (APCs) and activate MHC[1] class I-unrestricted CTLs.

Collectively exerted non-S-specific immune pressure caused by CTL-mediated *mitigation* (instead of inhibition!) of infection has promoted natural selection and dominant propagation of a more infectious immune escape variant (i.e., JN.1) that incorporated non-S-specific infection-enhancing mutations (including replication-enhancing mutations in other viral proteins). As the non-S-specific, MHC class I-unrestricted CTLs result from strong activation of APCs by the universal peptide comprised within S2 (https://pubmed.ncbi.nlm.nih.gov/19439480/), it is reasonable to assume that the recruitment and stimulation of these T cells dominates the recall effect of S-specific T helper (Th) peptides on previously primed S-specific Th memory cells.

Deficient or insufficient recall of S-specific Th cells likely compromises the boosting of previously SIR-primed, cross S variant-reactive Abs. Decreasing concentrations of these previously SIR-primed low-affinity Abs, combined with their enhanced stabilization effect on multimeric viral aggregates, would reduce their interaction with individual virions of newly emerged variants VBTI or updated C-19 vaccine booster shots. This results in diminished recognition of the highly conserved enhancing domain within the N-terminal domain of the S protein (S-NTD), leading to a substantial decrease in the production of PNNAbs.

The dominant emergence of JN.1, therefore, serves as an indicator of an ongoing collective decline in PNNAb titers accompanying ongoing Ab-independent VBTIs. The shift from (PNN)Ab-dependent to (PNN)Ab-independent VBTIs causes highly C-19 vaccinated populations to collectively exert immune pressure on the enhancing site within S-NTD, promoting the selection of a new variant capable of preventing the attachment of virulence-inhibiting PNNAbs to highly infectious virions immobilized on the surface of migratory dendritic cells (DCs). This evolution is now paving the way for the dominant propagation of viral variants that may cause highly virulent VBTIs in highly C-19 vaccinated populations. As JN.1 currently dominates the global viral landscape and encounters steadily growing suboptimal immune pressure on its capacity to evade virulence-inhibiting PNNAbs when adsorbed on migratory DCs, the immune selection pressure on JN.1 offspring, acquiring mutations that prevent attachment to these Abs, is rapidly intensifying.

The foundation of our scientific institutions is rotten. Their reductionist approach to complex problems primarily benefits academic fame while leading to a socially irresponsible return on investment as illustrated by their pandemic unpreparedness and ignorance.

Scientists and so-called 'experts' who naïvely admire and worship sophisticated technologies without understanding the complexity of biology will be caught off guard and bare huge responsibility for

[1] MHC: Major Histocompatibility Complex

misleading our incompetent but highly influenceable public and global health authorities as it becomes increasingly evident how the mass C-19 vaccination program affects not only the health of individuals but even threatens that of entire C-19 vaccinated populations.

Despite repeated efforts of critical thinkers to warn them, the scientific and medical establishment continue to interpret their data along the lines of what the mainstream narrative has been dictating. Millions of tax dollars have been invested in an attempt to prove that the results of the artificial mass vaccination program surpass those of natural immunization. One can't help but think about how society will react if it turns out soon that this massive financial drain did anything but benefit it.

2. Introduction

I read the following article: The Updated COVID-19 Shot Works on the Newest Variants | TIME.

It refers to the following publication: "*XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against emerging SARS-CoV-2 variants*"

(https://www.biorxiv.org/content/10.1101/2023.11.26.568730v2.full.pdf).

I cannot help but feel that this manuscript may be considered an affront to scientific principles. It raises concerns that scientists may present observations described as 'surprising' or 'striking,' without a clear explanation, as robust support for the official recommendation to widely use updated C-19 vaccines to enhance public protection! It challenges the rigor and transparency expected in scientific discourse.

According to these scientists, updated C-19 vaccines are the magic bullet for 'conferring greater protection to the public'! Even well-known and highly esteemed experts and key opinion leaders from reputable academic and research institutions in this field have now started worshiping these mRNA vaccines almost the same way our ancestors worshipped the stars. They *blindly* applaud any data seemingly justifying continued C-19 vaccination (. However, they fail to provide a plausible explanation for how updated mRNA vaccine boosters or VBTIs could overcome immune imprinting such as to elicit 'robust neutralizing Abs (NAbs)' against a multitude of emerging, antigenically distant SC-2 variants *that the vaccine wasn't even specifically designed for*!

No wonder that their simplistic conclusions immediately caught my attention and, more importantly, my deep concern.

How on earth could immune responses triggered by updated C-19 vaccines readily neutralize infecting circulating variants while ignoring the concept of 'original antigenic sin' (OAS)?

How is it possible that these Abs can even neutralize circulating variants that are adorned with a variant S protein that is antigenically very different from the one used in updated vaccines or displayed on variants causing VBTI? In other words, how could one explain that Abs in C-19 vaccinees continue to neutralize circulating immune escape variants and provide protection against C-19 disease, while deep mutational scanning (DMS) reveals profound immune evasive mutations in the S-associated neutralizing domains?

And what if they completely missed the point, and their observations reflected a kind of artefactual virus-neutralizing effect that can only be observed in their specific study setting—i.e., at very high Ab concentrations (i.e., in serum samples drawn shortly after the booster immunization or VBTI)—and rapidly transitions into a relatively stable infection-mitigating effect when the Ab titer decreases?

Could such a suboptimal sterilizing effect generate suboptimal immune pressure on the infectiousness of circulating variants, raising significant concerns about immune escape?

As the neutralizing effect extends across a multitude of circulating variants, could any transition from the inhibition of infection to the mitigation of infection not lead to large-scale immune escape and potentially hasten the emergence of more infectious variants?

Would evidence of prolonged suboptimal anti-infectious activity at lower concentrations of these Abs and/or the lack of recognition of monovalent S antigen (Ag) in Elisa undermine their optimism regarding the 'robust' neutralizing response elicited by updated mRNA booster doses? Consequently, does it not challenge their support for the public health recommendation to widely apply these updated C-19 vaccines for greater public protection?

3. The authors' assertion regarding the capability of updated vaccines to overcome original antigenic sin (OAS) and induce cross S variant-neutralizing Abs against circulating, antigenically distant variants can only be explained by SIR induced by mRNA vaccines.

The data in fig. 2 of this publication[2] indicate that immunological recall in individuals who previously received several doses of wildtype (D614G) monovalent mRNA vaccine, followed by one BA.5 bivalent mRNA booster dose prior to their XBB.1.5 booster dose (i.e., via XBB.1.5 monovalent vaccine or natural VBTI with XBB.1.5), reached a much higher titer of NAbs to D614G and BA.5 Ag than to XBB.1.5 itself. On the other hand, the increase in NAb titer to XBB.1.5 (and to a series of other newly emerged S variants) after the XBB.1.5 booster dose was significantly higher compared to the booster effect observed for NAbs to D614G and BA.5.

The authors are suggesting that the considerable "back boosting" of NAbs directed to prior SC-2 lineages (i.e., the ancestral lineage and the BA.5 variant) are the consequence of strong immunological imprinting resulting from prior vaccinations with the wildtype monovalent vaccine and the BA.5 bivalent vaccine, which also contains the ancestral D614G Ag. They conclude that the results from their experiment comparing the "*severity*" of immunological imprinting between the XBB.1.5 monovalent vaccine and the BA.5 bivalent vaccine (see fig. 2: B-D in the above-referenced publication) prove that the severity of immunological imprinting can be mitigated by removing the Ag that originally primed the immune response (i.e., D614G) from the booster vaccine such as to exclusively use updated *monovalent* booster vaccines.

[2] https://www.biorxiv.org/content/10.1101/2023.11.26.568730v2.full.pdf

I disagree with these conclusions. Firstly, there is no data comparing the booster effect between the XBB.1.5 monovalent vaccine and *monovalent* D614G or BA.5 vaccines. In my opinion, such a comparison would likely yield the same result, even with the absence of the ancestral S protein variant in the BA.5 vaccine.

Therefore, I do not concur with the authors' conclusion that the data generated indicate the *updated BA.5 bivalent booster vaccine exacerbates the problem of immune imprinting* due to the inclusion of the wildtype S protein and that *updated* booster vaccines in individuals previously primed with the wildtype S protein would therefore provide better stimulation of Abs if administered as *monovalent* booster doses.

The authors do not provide an explanation for how the increased antigenic distance of XBB.1.5 from the ancestral SC-2 lineage, compared to BA.5, could mitigate the severity of immunological imprinting in individuals previously primed and boosted with a monovalent wildtype vaccine. Considering the concept of OAS, I wonder whether anybody understands how an updated booster immunization with XBB.1.5 Ag, or a VBTI with the XBB.1.5 variant, could be more efficient in boosting NAb titers against XBB.1.5 and multiple antigenically distant variants than in recalling previously wildtype vaccine-primed Abs. The authors simply refer to the alleged mitigation of immune imprinting by heterologous monovalent XBB.1.5 vaccine boosters as 'striking'…

Due to these inconsistencies, it raises questions about whether primary vaccination (2 doses) with an *mRNA vaccine* targeting a specific S variant could account for the attenuated boosting effect observed when a subsequent booster dose using the same vaccine Ag was administered. Additionally, it prompts consideration of whether primary mRNA-based vaccination could also elucidate why the booster effect of a newly emerged S variant Ag was more pronounced, despite yielding an overall NAb titer lower than that achieved with a homologous prime-boost regimen.

These seemingly conflicting results can only be explained by the concept of steric immune refocusing (SIR). SIR occurs when high concentrations of non-neutralizing S-specific Abs interact with low affinity with an antigenically distinct variant S protein (see fig. I + see sections 1.2.1 and 1.2.2 from my book: https://braintrain.mykajabi.com/the-inescapable-immune-escape-pandemic). This occurs, for example, as a result of VBTIs with antigenically distant SC-2 variants, or in case vaccines directly induce elevated titers of low-affinity, non-neutralizing Abs towards the vaccinal target Ag (i.e., towards S-associated immunodominant epitopes in the case of mRNA-based C-19 vaccines).

In other words, the robust stimulation of NAbs against multiple newly emerged variants, observed after administering an XBB.1.5 booster vaccine or after a VBTI with the XBB.1.5 variant, in individuals previously mRNA-vaccinated with wildtype S protein and subsequently re-boosted with the BA.5 bivalent mRNA vaccine, can only be attributed to immune refocusing on more conserved S-associated domains.

Immune refocusing following a booster dose with the mRNA-based bivalent BA.5 vaccine likely resulted from the interaction of high titers of low-affinity Abs, previously induced to the immunodominant epitopes of the ancestral (D614G) and BA.5 S protein expressed on the surface of the mRNA-transfected host cells, with the immunodominant epitopes displayed on free circulating S protein released from mRNA-transfected host cells. Binding of the immunodominant epitopes of the ancestral (D614G) and BA.5 S protein by low-affinity Abs sterically hinders recognition of these epitopes, thereby enabling immune recognition of more conserved, S-associated subdominant domains (https://braintrain.mykajabi.com/the-inescapable-immune-escape-pandemic : see chapter 1.).

The above-described immunological mechanism would explain how SIR-enabling mRNA vaccines lead to priming of broadly cross-'neutralizing' IgM Abs of low affinity. I am, therefore, of the opinion that the recall of these previously SIR-primed Abs at very high titers was responsible for the 'striking' booster effect conferred by the XBB.1.5 monovalent mRNA vaccine or XBB.1.5 VBTI, as reported by the authors. As explained under sections 8 and 9 below**,** the neutralization activity of SIR-induced Abs is only short-lived because of their low affinity and lack of specificity. Updated vaccine boosters can, therefore, not durably protect against Covid-19 and instead promote viral immune escape.

In summary:

The authors misinterpret the effect of monovalent updated mRNA vaccine boosters as proof that these boosters can – at least partially – overcome the antigenic constraints imposed by immunological imprinting. However, *the 'neutralizing' Ab responses presented in this paper suggest, rather, that the updated XBB.1.5 mRNA vaccines (or VBTI with the XBB.1.5 variant) boost new, cross S variant-reactive Abs that have previously been induced as a result of SIR. Any subsequent updated mRNA booster dose or VBTI with circulating, antigenically more distant variants will facilitate boosting of these previously SIR-primed, cross S variant-reactive Abs (i.e., directed at multiple newly emerged variants) at high concentration.*

The difference in the magnitude of the booster effect on virus neutralization between the BA.5 bivalent vaccine and the XBB.1.5 vaccine cannot be due to a loss of sensitivity of the XBB.1.5 vaccine to immunological imprinting (or so-called OAS) but to a stronger recall effect of XBB.1.5 on previously SIR-primed Abs[3] directed at a more conserved S-associated domain. Any C-19 vaccine booster comprising this more conserved S-associated antigenic site would have recalled the previously SIR-primed Abs to the same extent.

The explanation, therefore, for the difference in the boost effect generated by the 2 different mRNA vaccines is not to be sought in a 'new edition' of the OAS[4] but in immune refocusing of the original, vaccine-primed Abs, directed at *immunodominant* S-associated target epitopes, to new, SIR-primed Abs, directed at *immune subdominant* S-associated epitopes. Some scientists are now finally starting to find out about the impact of VBTIs and mRNA vaccination on targeting the humoral immune response at newly emerged SC-2 variants without, however, explicitly labeling it as immune refocusing (https://pubmed.ncbi.nlm.nih.gov/38035879/; https://www.science.org/doi/10.1126/sciimmunol.adk5845).

As the authors erroneously conclude that monovalent updated vaccine booster doses largely overcome OAS and are, therefore, much better at recalling vaccine-primed NAbs towards variants comprising the updated variant S protein (i.e., the S protein from new emerging variants), *they mistakenly believe that continuing vaccination with updated booster doses will allow sustained protection against newly emerging variants with enhanced intrinsic infectiousness such as JN.1.*

[3] mRNA vaccination triggers steric immune refocusing (SIR; https://braintrain.mykajabi.com/the-inescapable-immune-escape-pandemic: see chapter 1). Hence, boosting of new, SIR-primed cross-'neutralizing' Abs to more conserved Ags in individuals previously vaccinated with wildtype monovalent vaccine (D614G) took already place upon the first immunization with the updated BA.5 bivalent booster vaccine.

[4] OAS refers to an immunological phenomenon whereby a new variant Ag inevitably recalls previously induced effector memory cells targeted at the original Ag used for priming.

4. The virus-neutralizing effect towards a diversified spectrum of antigenically distant SC-2 variants, as measured in serum samples drawn shortly after an updated vaccine booster dose or VBTI with a newly emerged SC-2 variant, strongly suggests that the 'neutralizing' effect is short-lived and not variant S-specific.

Due to their multivalency, cross-'neutralizing' IgM Abs can engage multiple S Ags on multimeric particles (e.g., viral particles) and thereby enable multiple binding events to occur simultaneously. The strength of these interactions is referred to as avidity[5].

As the concentration of cross S variant-reactive Abs increases, for example because of re-exposure to newly emerged S protein variants, the likelihood of such multiple binding events occurring simultaneously also increases. This enhances the overall avidity of these Abs for the virus. Maximal avidity is achieved when the balance between Ab and Ag concentrations is optimal for the formation of stable immune complexes.

The capacity of low-affinity Abs (e.g., cross S variant-reactive IgMs) to engage in multivalent interactions with viral particles explains why these Abs can stabilize different-sized viral particulates, thereby generating stable virus-Ab complexes over a range of increasing dilutions. The binding kinetics of low-affinity Abs are therefore very different from those observed for high-affinity Abs as depicted in fig. IV below.

High concentrations of Abs that bind with low affinity to S-associated *immunodominant* domains increase the likelihood of multiple binding events occurring simultaneously and *extending to less immunodominant epitopes*. The increase in these multiple binding events enhances the overall avidity of low-affinity anti-S Abs for SC-2 particulates. When an optimal balance between low-affinity Ab and virus concentrations is achieved, stable virus-Ab complexes are formed and thereby maximize the avidity of these Abs for the virus.

If present in *excessively high* concentrations, for example as a result of an updated vaccine booster dose or a VBTI with newly emerged SC-2 variants, low-affinity Abs can enhance their interaction with their target binding site, thereby *maximally occupying all available target binding sites* on the virus. The ensuing saturation of virus particles explains the 'virus-neutralization' effect reported by the authors in the referenced publication (and confirmed by many other scientists publishing their research on the purported sustained vaccine-mediated protection against viral variants!).

This mechanism of neutralization is however fundamentally different from the one exhibited by high-affinity Abs that neutralize the virus by virtue of their high-affinity binding to a specific, immunodominant target epitope (so-called 'neutralizing' domain). The authors erroneously refer to this infection-inhibiting activity of Abs elicited upon updated vaccine boosters (or newly emerged VBTIs) as 'neutralizing' activity. In fact, the effect they are observing should be described as *pseudo*-neutralization effect.

[5] Avidity is a measure of the overall strength and stability of interactions between multiple binding sites on a bivalent or multivalent Ab and its corresponding multivalent Ag.

As Abs that interact with low affinity with their target epitopes[6] only acquire 'pseudo' virus-neutralizing activity when their concentration is high enough to saturate all the target binding sites on the viral particle, the neutralization effect will rapidly fall to suboptimal levels which merely *mitigate*, but do not neutralize, viral infectiousness (see under sections 8 and 9 below). This explains why it is crucial to distinguish between viral *pseudo*-neutralization and *authentic* viral *neutralization*. Pseudo-neutralizing Abs exert prolonged suboptimal immune pressure on newly emerging variants that have evolved to possess a higher level of viral infectiousness and are therefore prone to causing new VBTIs.

ID50 values (i.e., 50% inhibitory dilutions) are not a reliable metric for measuring durable protection from SC-2 when the prevailing Abs do not specifically interact with the neutralizing epitopes of the virus. This is because 'neutralizing' ID50 values for low-affinity, S variant-nonspecific Abs do not inform about the suboptimal infection-inhibiting Ab activity that rapidly ensues when the Ab titers decrease. They therefore inevitably fail to inform about the capacity of cross S variant-reactive Abs to drive immune escape. It is, therefore, completely misleading to suggest that acute Ab responses measured shortly after boosting[7] of SIR-primed Abs provide robust protection against newly emerging SC-2 variants. As the infection-inhibiting effect observed with cross S variant-reactive Abs can only be achieved in the presence of very high Ab titers, the pseudo-neutralizing effect is short-lived. This effect, therefore, can no longer be observed in follow-up serum samples.

5. The enhanced prevalence of co-circulating variants, including JN.1, is not related to diminished intrinsic neutralizability of these variants.

The interpretation of the authors that these emerging sublineages outcompete their precursors because of their intrinsic resistance to serum neutralization is not correct. The newly emerging sublineages outcompete their precursors because their precursors became resistant to previously primed NAbs and therefore triggered SIR upon administration of an updated vaccine booster or exposure to a new VBTI. The driving factor behind the natural selection and propagation of these newly emerged sublineages was the suboptimal immune pressure exerted by SIR-induced cross S variant-reactive Abs on these precursors!

In essence, the rise in prevalence of these newly emerged variants is not dictated by their reduced intrinsic neutralizability (i.e., resistance to the intrinsic neutralizing activity of boosted Abs). Instead, it is primarily determined by the immune selection pressure exerted by these Abs, stemming from the combined effects of their diminishing concentration and level of S variant-specificity.

[6] These Abs could be high-affinity anti-S IgG Abs (e.g., in the case of VBTI due to Omicron) or low-affinity anti-S IgM Abs (e.g., in the case of VBTIs caused by newly emerged , more infectious SC-2 variants)

[7] In the referenced study, boosting was achieved via a BA.5 booster vaccine in individuals previously vaccinated with a wildtype mRNA vaccine or via an XBB.1.5 booster vaccine or via exposure to XBB.1.5 in individuals previously vaccinated with a wildtype mRNA vaccine followed by a BA.5 bivalent mRNA booster dose.

6. State-of-the art serology is key to reveal immune refocusing and avoid misinterpretation of virus-neutralizing activity.

By promoting refocusing of the humoral immune response to increasingly conserved, 'self-mimicking' domains, VBTIs by more infectious immune escape variants, or repeated administration of updated mRNA vaccine booster doses, generate IgM Abs that recognize these conserved and less immunogenic S-associated epitopes.

These cross S variant-reactive IgM Abs eventually mature into isotype-switched, functionally monovalent IgG4 Abs that specifically bind with enhanced affinity to these new, more conserved, target epitopes. As antigenic domains with significantly reduced immunogenicity are more likely to include immunoquiescent 'self-resembling' epitopes, it is reasonable to assume that repeated VBTIs or updated mRNA vaccine boosters could make C-19 vaccinees more susceptible to immune pathology and cancers (https://www.voiceforscienceandsolidarity.org/scientific-blog/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-xx-vaccinated-populations).

An increase in relative IgG4 anti-S Abs indicates that the immune refocusing is mediated by Abs. This rise in IgG4 anti-S Abs will be nullified when Ab-mediated mitigation of infection transitions to CTL-mediated mitigation of infection (see under sections 11-13 below). This evolution may elucidate the reason behind the increased occurrence of early-onset cancers and immune pathology observed in extensively C-19-vaccinated populations following the emergence of Omicron, transitioning gradually to elevated mortality resulting from turbo cancers and the reactivation of pre-existing chronic conditions (https://www.voiceforscienceandsolidarity.org/scientific-blog/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-xx-vaccinated-populations).
As previously reported and reiterated in sections 12-14 below, this excess mortality rate likely precedes a transition to an even higher mortality rate due to the emergence of a new variant causing exacerbated severity of C-19 disease.

State-of-the-art serology would help determine the ratio of anti-S IgG4 Abs to anti-S IgG1 Abs and distinguish authentic neutralizing activity from pseudo-neutralization. As changes in avidity typically occur between multivalent Abs (e.g., IgM Abs) and multivalent Ags (e.g., repetitive patterns of virus surface-expressed S protein), the authors should have determined the isotype of the infection-inhibiting Abs and assessed their interaction with *monovalent* S-derived target Ags. Truly cross-neutralizing Abs are typically of the IgG class, binding to highly specific target Ags/epitopes. Conversely, Abs that neutralize via an "ensemble effect" do not commonly belong to the IgG class but to the IgM class and recognize *multivalent* Ags.

Elisa (Enzyme-Linked Immunosorbent Assay) using *monovalent* S protein cannot efficiently capture or cross-link IgM Abs because they have only one binding site. In contrast, *multivalent* Ags or Ag complexes may provide more binding sites for the multiple arms of IgM Abs[8]. Due to the low sensitivity of ELISAs using

[8] IgM Abs are pentameric, meaning they have five Ab subunits (monomers) linked together. Each monomer has two Ag-binding sites. This multivalency can lead to cross-linking of Ags, which is a characteristic feature of IgM binding.

monovalent S protein as the target Ag for detecting pseudo-neutralizing Abs, the high infection-inhibiting activity of these Abs will not be reflected by a high ELISA activity. This lack of correlation is atypical for truly neutralizing Abs. In the current study, however, neither ELISA assays nor Ig class/subclass characterization have been performed. *Conducting these analyses would have helped clarify that the Abs the authors are referring to are S variant-nonspecific and, therefore, not truly neutralizing*.

I am therefore proposing the following new definition of virus neutralization: "*Virus neutralization is the reduction in viral infectivity resulting from a decrease in the number of infectious viral particles due to their binding to highly Ag-specific Abs*, and typically occurs without the involvement of any other agent.

With regards to SC-2, this definition translates to the loss of viral infectivity resulting from a reduction in the number of infectious viral particles due to their binding to S variant-specific Abs. This definition specifically excludes any loss of infectivity caused by the binding of S variant-nonspecific (i.e., cross S variant-reactive) Abs to SC-2 lineages.

7. Very high concentrations of previously vaccine- or SIR-primed Abs trigger SIR and pseudo-neutralization whereas slightly lower concentrations trigger SIR and enhancement of infection.

I explain in my book how mass vaccination with mRNA-based C-19 vaccines (after the second dose) and large-scale VBTIs with Omicron promote SIR (see fig. I). SIR redirects the immune response towards more conserved, subdominant S-associated epitopes. This is because the second dose of an mRNA vaccine or a VBTI with a new, more infectious variant boosts the non-neutralizing, vaccine-induced, low-affinity anti-S Abs or, respectively, the previously neutralizing, vaccine-induced, high-affinity Abs.

As immune refocusing and pseudo-neutralization can only take place when the Abs interact with the virus as dispersed single particles, it can be concluded that both effects can only occur when the low-affinity Abs reach a concentration high enough to saturate all target binding sites on the virus. Nevertheless, a slight deviation from these excessively high concentrations will quickly lead to the engagement of low-affinity Abs in multivalent binding. This involves occupying all available dominant or subdominant immunogenic domains, allowing for a stronger and more stable interaction when their concentration falls below the saturation level of the specific target epitope.

Binding of single virions by high concentrations of low-affinity Abs that engage in multivalent binding with immunogenic S-associated domains (i.e., *including immunodominant and subdominant antigenic domains)* refocuses the immune response towards immunoquiescent/ immunosilent S-associated epitopes that are conserved across all SC-2 variants (e.g., the enhancing site within S-NTD; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8142859/pdf/main.pdf; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128678/pdf/main.pdf).

It is reasonable to assume that presentation of the conserved antigenic site within S-NTD in repetitive arrays at the surface of the virus elicits Th-independent, polymeric, non-neutralizing IgM Abs (PNNAbs) towards

this conserved antigenic site. Non-neutralizing Abs that bind to highly conserved enhancing site within S-NTD have been reported to enable Ab-dependent enhancement of infection (https://pubmed.ncbi.nlm.nih.gov/34384810/; https://www.sciencedirect.com/science/article/pii/S0092867421006620), thereby helping the virus to bypass the cell-based innate immune system (CBIIS) and facilitating VBTI.

It is reasonable to hypothesize that, when present in high concentrations, even *high-affinity IgG Abs* interacting with antigenically distant variants may participate in strong multivalent interactions capable of stabilizing *individual* virions. This, in turn, could lead to an infection-enhancing effect. This phenomenon was likely at the core of the initial wave of VBTIs caused by Omicron.

Lastly, it is reasonable to assume that achieving the pseudo-neutralization and Ab refocusing effect is contingent upon the presence of high concentrations of low-affinity Abs that are not (re-)directed to S-associated target epitopes *antigenically too distant*. (Re-)directing these Abs to epitopes that are too distant would reduce their affinity for these target epitopes below the minimum threshold required for interacting with individual virions (see fig. IV). Therefore, it can be expected that booster vaccination, or VBTIs in individuals who have already experienced several SIR events due to previous VBTIs, will no longer elicit acute Ab responses with immune refocusing or pseudo-neutralization capacity.

8. Short-lived pseudo-neutralization or enhancement of infection rapidly transitions into a more stable and therefore prolonged infection-mitigating effect.

SIR-enabling VBTIs lead to the priming of polymeric IgM Abs towards less immunodominant S-associated domains. As these anti-S Abs exhibit reduced binding affinity for the targeted S-associated epitopes, their binding strength per particle surface unit decreases to a level insufficient for stabilizing individual virions (see fig. II below). A reduction in the concentration or affinity of these Abs will consequently enhance their stabilizing effect on *multimeric* viral particulates, leading to a rapid shift in the size distribution of stabilized viral particulates. This shift manifests from a predominant presence of single/individual virions to a predominant presence of multimeric virus-Ab, as illustrated in fig. III below. With the increased prevalence of infection-incompetent, multimeric virus-Ab complexes in the serum, their influence surpasses that of monomeric virus-Ab complexes with infection-enhancing activity. Consequently, the infection-inhibiting activity ('pseudo'-neutralization) of the tested sera transforms into an infection-mitigating activity.

The lower the intrinsic affinity of the newly generated Abs for the new, more conserved target epitopes, the higher the concentration of stabilized multimeric viral particulates and the more rapidly the latter will dominate as the concentration of these Abs decreases. In other words, the lower the intrinsic affinity of the newly generated anti-S Abs, the more quickly the pseudo-neutralizing effect will transition into an infection-mitigating effect (see fig. IV).

All of the above suggests that the observed pseudo-neutralizing effect of boosted Abs towards newly emerged viral variants, as described in the referenced study, is likely to be *short-lived and will rapidly*

transition into a prolonged, infection-mitigating effect. It also indicates that for virions of newly emerged, more infectious variants to benefit from the short-lived stabilization conferred by previously SIR-primed cross S variant-reactive Abs and thereby enhance their infectiousness, these new variants need to have sufficiently high transmissibility to ensure a short average lag time to viral re-exposure. In this way, they can infect a sufficiently large part of the vaccinated population at a point in time where the remaining Ab titers will stabilize a sufficiently important part of the overall viral particle population as single, infection-enhancing virions (i.e., able to produce PNNAbs) to ensure a sufficiently high number of VBTIs, enabling a sufficiently high rate of viral immune escape.

The requirement for a higher level of infectiousness in the newly emerging viral variants is assured by the growing contribution of larger viral aggregates following repeated VBTIs. Their growing contribution leads to an escalating level of immune selection pressure on viral infectiousness exerted by broadly cross S variant-reactive Abs with decreasing affinity. It is, indeed, reasonable to assume that anti-S Abs with lower affinity exert a stronger and more prolonged infection-mitigating effect on antigenically distant SC-2 variants when compared to the effect exerted by the same concentration of anti-S Abs with higher-affinity (see fig. IV). It is therefore obvious that repeated VBTIs with newly emerging variants or additional boosters with updated vaccines will only expedite natural selection of more infectious immune escape variants.

As the authors of this publication ignore the impact of infection-mitigating titers on generating suboptimal immune pressure, they inevitably ignore the impact of boosting previously SIR-primed Abs to more conserved S-associated Ags on driving natural selection of new variants with ever-increasing infectiousness.

In summary:

The authors do not grasp that the updated monovalent boosters do NOT mitigate the impact of previously primed immunological memory but instead largely mitigate viral infectiousness. This is because the recall of previously SIR-induced Abs will rapidly lead to Ab titers that can no longer inhibit viral infectiousness. By mitigating viral infectiousness, these Abs exert suboptimal immune pressure on the very variants they initially neutralized when boosted at high concentrations. *In other words, the neutralizing activity of these Abs is characteristic only of the 'acute' Ab response and conceals their substantial capacity to subsequently exert suboptimal immune pressure on viral infectiousness.*

Consequently, the authors appear not to realize that the more frequently updated booster vaccines are used, the more rapidly the virus will evade the Abs these updated booster vaccines recall, despite their neutralizing activity in serum samples drawn shortly after the booster dose.

9. Updated vaccine boosters and VBTIs with newly emerged SC-2 variants expedite SIR. SIR combined with immunological imprinting[9] promotes large-

[9]Pseudo-neutralization and suboptimal anti-infectious activity of Abs following VBTIs or updated booster shots in previously mRNA-vaccinated individuals is due to immunological imprinting of new Abs, previously primed as a result of SIR-enabling mRNA vaccination (after 2 doses) and directed at more conserved, immune subdominant S-associated domains.

scale selection of more infectious immune escape variants, thereby initiating an escalating self-perpetuating sequence of SIR-enabling Ab-dependent VBTIs.

Because high concentrations of refocused, cross S variant-reactive Abs tend to stabilize viral particulates in ways that mitigate, but do not prevent viral infection, they drive immune escape and fuel new SIR-enabling VBTIs that cause the spectrum of co-circulating variants to expand (so-called 'large-scale immune escape).

As continuing VBTIs drive the refocused immune response towards increasingly conserved and therefore increasingly immune recessive S-associated epitopes, boosted Abs sacrifice their specific affinity[10] for the S-associated target Ag in exchange for higher avidity[11] towards viral particles displaying a multimeric array of S protein.

It follows that the 'magic' bullet allowing C-19 vaccinees to 'neutralize' newly emerged SC-2 variants merely results from the lack of *specificity* exhibited by the previously primed refocused Abs, combined with their high concentration resulting from boosting. Due to their decreased epitope-specificity, these Abs can engage in multivalent interactions with multimeric viral particulates. These multiple interactions collectively enhance the avidity of these Abs for multimeric arrays of the S protein, as presented on viral particulates. (see fig. III). This contrasts with monovalent interactions, where there's only one binding site on each molecule, leading to weaker overall binding**.**

As individual viral particles can only be stabilized by high concentrations of low-affinity, S variant-nonspecific Abs, the pseudo-neutralizing effect of these Abs will rapidly decrease after their recall at high concentration following a booster dose[12] or VBTI. As the avidity of these Abs at a given Ab concentration decreases with diminished affinity of the Abs for the targeted S variant-specific epitope, the level of the infection-inhibitory dilution allowing to reduce viral infectivity by 50% (so-called neutralizing ID_{50}) also decreases with diminishing affinity of the Ab for the targeted S variant-specific epitope (https://www.biorxiv.org/content/10.1101/2023.11.26.568730v2.full.pdf: fig. 2: B-D).

Repeated VBTIs with antigenically distant variants or updated booster immunizations in previously mRNA-vaccinated individuals recall previously SIR-primed Abs. These Abs target increasingly immune subdominant, less variant domains of the S protein. Consequently, C-19 vaccine recipients undergoing new VBTIs or receiving booster shots with more antigenically distant S variants undergo additional immune refocusing events. This clarifies the reason why repeated SIR-enabling VBTIs or updated vaccine boosters (e.g., based on S protein from XBB.1.5) redirect the immune response towards Abs with progressively lower affinity for the S-associated immunogenic epitopes. Consequently, this phenomenon also accounts for the expanded spectrum of pseudo-neutralization exhibited by these Abs (i.e., including all newly emerged

[10] Affinity refers to the strength of the binding between a single antigenic determinant and a single antigen-binding site on an antibody.
[11] Avidity refers to the overall strength and stability of interactions between multiple binding sites on a bivalent or multivalent antibody and its corresponding *multivalent* or *multimeric* antigen (i.e., an Ag with multiple epitopes).
[12] It has been extensively documented that titers of broadly cross'neutralizing' Abs generated after the 2nd dose of an mRNA vaccine rapidly decrease to subneutralizing concentrations.

variants tested including XBB.1.5. itself but also EG.5.1.; HV.1; HK.3; JD.1.1, and to a lesser extent JN.1) as shown in the referenced publication (see fig. 2).

When their affinity for specific, S-associated target epitopes falls below a certain threshold, the capacity of low-affinity Abs to enable an infection-inhibitory ('pseudo'-neutralizing) effect may become too low, regardless of their concentration. This clarifies why broadly cross S variant-reactive Abs, generated through multiple SIR events, lose significant virus-neutralizing capacity (fig. 2: B-D in: https://www.biorxiv.org/content/10.1101/2023.11.26.568730v2.full.pdf and fig. 1: H-I in: https://www.biorxiv.org/content/10.1101/2023.12.08.570782v1.full.pdf:)

Concentrations that are optimally suited to promote the formation of stable multimeric viral particulates in the aqueous phase hinder the contact of these Ab-virus complexes with susceptible host cells over a range of increasing dilutions, thereby inhibiting the infectivity of the virions comprised within these complexes. Enhanced stabilization of multimeric viral particulates diminishes the contribution of individual virions, including those capable of triggering Th-independent production of PNNAbs (see fig. III). This reduction in infection-competent viral particles prolongs the infection-mitigating impact of previously SIR-induced Abs following updated booster vaccination or new infection (see fig. IV). Prolonged mitigation of infection intensifies population-level immune pressure on viral infectiousness, while the decreased production of Th-independent PNNAbs eventually weakens the virulence-inhibiting effect of VBTIs (see under section 12 below).

In summary:

The inhibition of viral infectivity is not driven by sustained intrinsic neutralizability of specific S-associated epitopes but by the avidity of previously SIR-primed cross S variant-reactive Abs for multimeric S protein expressed on viral particulates. The infection-mitigating effect, following pseudo-neutralization by high concentrations of previously SIR-primed Abs, therefore exerts immune selection pressure on immunogenic epitopes that are shared across S protein variants. As S protein is responsible for viral infectiousness, prolonged mitigation of infection contributes to enhanced immune selection pressure on viral infectiousness.

Repeated VBTIs or mRNA vaccinations with an antigenically distant S protein trigger immune refocusing towards increasingly conserved, antigenically more distant S-associated domains. Nevertheless, as long as the immune refocused Ab response involves S-associated domains that are not fully conserved, the newly produced Abs will retain a certain level of S variant specificity. This explains why the pseudo-neutralization effect conferred by the XBB.1.5 vaccine booster was superior for XBB.1.5 and EG.5.1 as compared to that observed for antigenically more distant variants [e.g., HV.1, HK.3 JD.1.1, JN.1] (see fig. 2 in the referenced publication). The fact that the booster effect on pseudo-neutralization titers was comparable across multiple more distant variants confirms the more conserved nature of the newly targeted S-associated epitopes. It also explains why pseudo-neutralization will rapidly be followed by large-scale, i.e., less selective, viral immune escape. This implies that new variants will be chosen among the progeny of all co-circulating variants, *based on infection-enhancing mutations across the entire S protein*. As the selected subvariants gain a growth advantage in the population over their immediate precursors, they replace them, thereby triggering new SIR-enabling VBTIs and further facilitating large-scale viral immune escape (see fig. V below).

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Based on the above, it is reasonable to assert that the referenced study is misleading for two primary reasons. First, following the administration of an updated vaccine booster dose or re-exposure to an antigenically distant variant, the authors only examined acute Ab responses (i.e., ID50 titers measured within 2 weeks after the booster dose or viral re-exposure). Secondly, while boosted titers of SIR-primed Abs can initially bind with sufficient affinity to S-specific epitopes and saturate all available binding sites on the virus, this may no longer be the case after an additional mRNA immunization with a more updated mRNA vaccine or a subsequent VBTI with a more recent SC-2 variant, resulting in a dramatically reduced seroneutralization titer.

10. Recurrent SIR events, resulting from updated C-19 vaccine boosters or VBTIs caused by newly emerged, antigenically distant variants, expand the spectrum of selected immune escape variants while enhancing their infectiousness. The divergent evolution of more infectious SC-2 variants shortens the duration for new, more infectious variants to successively increase in prevalence and outpace their precursors.

VBTIs in C-19 vaccinees enable SIR. Subsequent exposure to new, antigenically more distant variants boosts new, previously SIR-primed Abs. Boosting of new, previously SIR-primed Abs causes suboptimal immune pressure on viral infectiousness and drives natural selection and propagation of more infectious variants. Whereas exposure to early Omicron descendants caused VBTIs and thereby boosted previously *vaccine-primed S-specific* Abs (i.e., due to PNNAb-mediated enhancement of infection), VBTIs by currently circulating Omicron are now boosting previously *SIR-primed cross variant S-reactive* Abs (see fig. V below).

The higher the antigenic distance between the circulating variants and the original SC-2 lineage (or vaccinal S Ag) that initially primed the immune system, the higher the frequency of new SIR-enabling VBTIs in highly C-19 vaccinated populations and the lower the infection-neutralizing effect of previously SIR-primed Abs towards newly emerging, more infectious SC-2 variants. On the other hand, more antigenically distant variants will broaden the scope and prolong the duration of their infection-mitigating effect. This, in turn, increases the collective immune pressure on viral infectiousness as explained above. The increase in immune selection pressure on viral infectiousness drives the emergence of new, more infectious variants that rapidly outpace their predecessors. Consequently, the probability of a subsequent VBTI occurring shortly after the previous SIR-induced priming of cross-S variant-reactive Abs is high. This ensures a robust, large-scale boost effect, leading to large-scale pseudo-neutralization, followed – once again- by prolonged immune selection pressure on the infectiousness of circulating variants. Recurrent VBTIs induced by more infectious variants or updated booster vaccinations therefore accelerate successive natural selection and the propagation of new SC-2 variants with higher infectiousness (see fig. V below).

As the infectiousness of these newly emerged variants increased, the frequency of new VBTIs also rose, gradually leading to a higher incidence of new immune refocusing events after the initial wave of SIR-enabling VBTIs triggered by Omicron. *The resulting large-scale immune escape led to an ever-faster succession of more infectious SC-2 variants. The latter rapidly augmented their prevalence due to a gradually growing intrinsic infectiousness.*

In summary:

Repeated booster immunizations and/ or recurrent VBTIs with newly emerging SC-2 variants drive immune selection and propagation of increasingly infectious SC-2 variants.

The boosting of SIR-primed cross S variant-reactive Abs upon re-exposure to a circulating infecting variant enables these Abs to initially exert a short-lived infection-neutralizing effect, which then rapidly transitions into an infection-mitigating effect. However, the mitigation of infection inevitably results in suboptimal immune pressure on viral infectiousness. Suboptimal population-level immune pressure, exerted by cross S variant-reactive Abs on viral infectiousness, promoted natural selection of more infectious variants within an expanding spectrum of new, less S variant-specific Omicron descendants, thereby facilitating the co-circulation of increasingly infectious variants and expediting the sequence of progressively less symptomatic, yet SIR-enabling VBTIs in highly C-19 vaccinated populations.

11. Non-S-specific immune selection pressure on viral infectiousness exerted by MHC class I-unrestricted CTLs likely explains the dominant propagation of JN.1

(https://www.voiceforscienceandsolidarity.org/scientific-blog/the-fulminant-spread-of-jn-1-is-a-highly-worrisome-prognostic-indicator).

Once the affinity for specific S-associated target epitopes drops below the threshold needed to maintain an optimal balance between Ab and Ag concentrations, ensuring the formation of stably hydrophilized immune complexes[13], Ab avidity is no longer sufficient to prevent these Abs from stabilizing larger viral particulates, thereby promoting their uptake by APCs. This, in turn, stimulates MHC class I-unrestricted CTLs. The enhanced activation of CTLs enables the continuation of the infection-mitigating effect on viral infectiousness, achieved through the improved abrogation of viral productivity. Large-scale activation of CTLs intensifies the immune selection pressure exerted on viral infectiousness.

As the activated CTLs lack immunological memory, and there is no evidence supporting their infection-mitigating effect being MHC class I haplotype-restricted, one could speculate that their stimulation is prompted by the enhanced presentation of a universal epitope within S2 (https://pubmed.ncbi.nlm.nih.gov/19439480/). This occurs following the internalization of a high concentration of viral virions, typically in the form of viral aggregates. This hypothesis gains credence as heightened MHC class I-unrestricted CTL activity could lead highly C-19 vaccinated populations to exert non-S-specific immune selection pressure on viral infectiousness. This, in turn, could enable the dominant propagation of a newly emerging variant that incorporates non-S-specific infection-enhancing mutations, not confined to the S protein. It's not surprising, therefore, that the rapid and global spread of the JN.1 variant is marked by the incorporation of additional infection-enhancing mutations in other viral proteins (https://www.forbes.com/sites/williamhaseltine/2023/10/26/jn1-the-odd-man-out-among-omicron-sublineages/?sh=74aa039b3e47&s=03). By assimilating these additional, non-S-specific infection-

[13] i.e., stabilized in the aqueous phase

enhancing mutations, SC-2 has enhanced its reproduction capacity in response to the increasing elimination of virus-infected cells by CTLs.

In summary:

As the titers of previously SIR-primed Abs decline, the pseudo-neutralizing effect rapidly dissipates, transitioning into a more stable infection-mitigating effect that decreases gradually. The rate of decrease depends on the affinity of the elicited Abs for S-associated target epitopes.

Recurrent VBTIs followed by updated vaccine booster doses or VBTIs with newly emerged circulating variants entail a cascade of immune refocusing events, thereby generating prolonged suboptimal immune pressure on viral infectiousness in highly C-19 vaccinated populations. As widespread elicitation of suboptimal infection-inhibiting immune responses causes collective immune selection pressure on viral infectiousness, the viral landscape has been increasingly characterized by divergent evolution of co-circulating variants into a diversified spectrum of SC-2 variants that rapidly replace their immediate precursors based on their enhanced intrinsic infectiousness. As newly mounted immune responses eventually shift from targeting cross S variant-reactive epitopes to a highly conserved S-associated epitope, it's not surprising that rapidly emerging variants, which are quickly replacing less infectious predecessors, incorporate a set of less commonly observed infection-enhancing mutations, not only in their S protein but also in other viral proteins. This undoubtedly drives the dominant propagation of JN.1, a SC-2 lineage that has incorporated mutations no longer specific to one or more S protein variants and enabling enhanced viral entry (e.g., in the S protein) or enhanced viral productivity (e.g., in other viral proteins). Because these mutations confer a growth/ fitness advantage, the JN.1 variant is now rapidly outpacing other co-circulating variants (https://www.everydayhealth.com/coronavirus/covid-19-variant-jn1-variant-drives-new-wave-of-illness/; https://www.cdc.gov/nwss/rv/COVID19-nationaltrend.html; https://www.cidrap.umn.edu/covid-19/us-covid-activity-jumps-jn1-expands-brisk-flu-and-rsv-levels-continue; https://www.cdc.gov/respiratory-viruses/whats-new/SARS-CoV-2-variant-JN.1.html).

12. Large-scale activation of MHC class I-unrestricted CTLs promotes large-scale stabilization of viral particulates by previously SIR-primed Abs of decreasing affinity. By collectively shifting Ab-mediated mitigation of infection to CTL-mediated mitigation of infection, highly C-19 vaccinated populations will eventually exert immune selection pressure on viral virulence (see figs. VI and VII).

At present, the productive infection of highly infectious circulating virus is significantly hindered. This is due to the fact that highly infectious virus creates an immunological environment favoring the adsorption of viral virions onto dendritic cells (DCs) resident in the upper respiratory tract (URT) while low-affinity Abs facilitate the uptake of larger viral aggregates by APCs. DCs that adsorb, rather than internalize, viral particles fail to mature and migrate to the lungs instead of the tissue-associated lymph nodes. The binding of PNNAbs to DC-tethered virions prevents the *trans* infection of the virus to susceptible alveolar cells (fig.

VI). Meanwhile, the uptake of viral aggregates into APCs activates MHC class I-unrestricted cytotoxic T lymphocytes (CTLs), which rapidly eliminate virus-infected cells, thereby abrogating productive viral infection.

Enhanced CTL activity not only mitigates infection but also dampens Th-dependent boosting of previously SIR-primed S variant-nonspecific Abs, leading to diminished production of PNNAbs. This development is worrisome as PNNAbs not only serve a role of enhancing viral entry in case of strongly diminished NAb capacity but also prevent the *trans* fusion and productive infection of susceptible host cells in distal organs by curtailing the *trans* infection of highly infectious virions adsorbed on URT-resident DCs. As the CTL activity *collectively* increases, significant immune selection pressure is likely exerted on the specific conserved enhancing site within S-NTD. This site facilitates the inhibition of *trans* infection by attaching to PNNAbs, consequently inhibiting viral virulence upon VBTI.

It is reasonable to assume that suboptimal immune pressure confined to a specific antigenic site will rapidly intensify, compelling the virus to undergo a significant mutational change to counter the immune pressure on this specific site, thereby abolishing the virulence-inhibiting effect of the PNNAbs. These changes, however, should not compromise the infection-enhancing activity of these Abs as this activity will likely be essential to compensate for the fitness cost associated with the significant mutations necessary for a new variant to overcome the virulence-inhibiting effect of the PNNAb.

13. New emerging, highly infectious variants do not rely on PNNAbs to provoke VBTIs and, therefore, cause highly C-19 vaccinated populations to place immune selection pressure on the infection-enhancing site within S-NTD to release the brakes on viral virulence.

The more immune refocusing directs the Ab response to more conserved S-associated epitopes, the lower the affinity of the newly produced Abs for these epitopes. Consequently, these Abs tend to stabilize particulate progeny viruses in ways that facilitate their uptake in Ag-presenting cells (APCs), thereby promoting the activation of MHC class I-unrestricted cytotoxic T lymphocytes (CTLs) upon re-exposure to highly infectious circulating SC-2 variants.

The more SIR directs the Ab response to more conserved S-associated epitopes, the lower the affinity of the newly produced Abs for these epitopes and the more these Abs tend to stabilize particulate progeny virus in ways that facilitate their uptake in APCs. Enhanced uptake of viral aggregates in APCs promotes activation of MHC cl I-unrestricted CTLs upon re-exposure to highly infectious circulating SC-2 variants.

As immune refocusing shifts from S variant-nonspecific humoral to non-S-specific cellular immune effectors, the infection-mitigating effect strengthens, and the immune pressure on viral infectiousness increases *across all circulating variants*. The enhanced activation of these CTLs promotes the dominant propagation of new immune escape variants that incorporate an increasing number non-protein S-restricted infection-enhancing mutations, exemplified by JN.1.

The growing intrinsic infectiousness of newly circulating variants eliminates the necessity for infection-enhancing PNNAbs to interact with the virus. Consequently, *Ab-dependent* VBTIs caused by increasingly infectious circulating variants rapidly evolve into a self-perpetuating cycle of *Ab-independent* VBTIs. As highly infectious immune escape variants do not rely on PNNAbs to enhance their infectiousness and provoke VBTIs, their infection in the presence of collectively declining PNNAb concentrations lead highly C-19 vaccinated populations to exert suboptimal immune pressure on the virus' capacity to resist the virulence-inhibiting effect of PNNAbs.

In other words, *the accelerated chain of SIR events triggered by VBTIs with increasingly infectious S variants will eventually cause highly C-19 vaccinated populations to exert growing immune selection pressure on the virus' capacity to resist the virulence-inhibiting effect of PNNAbs, thereby preventing PNNAb-mediated inhibition of severe C-19 disease and causing highly virulent Ab-independent VBTI.*

14. Society in highly C-19 vaccinated populations will be caught off guard.

When the population-level immune pressure on virulence inhibition surpasses a certain threshold, any circulating SC-2 progeny variant that picks up the predicted O-glycosite mutations in the S protein can prevent the conserved enhancing site within S-NTD of dendritic cell (DC)-tethered virions from binding to virulence-inhibiting PNNAbs. I have previously explained how substantial changes in the (O-) glycosylation profile of the virus could unleash viral *trans* infectiousness and systemic dissemination (https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic).

Any potential fitness cost incurred due to the virulence-enhancing mutations would be compensated by the infection-enhancing activity of the same PNNAbs. This scenario seems plausible as the binding of these Abs to the enhancing site on free virions would remain unaffected and because even suboptimal concentrations of virulence-inhibiting PNNAbs would still be sufficient to enhance the infectivity of any variant with diminished intrinsic infectiousness, regardless of the mutations it incorporates.

Consequently, this newly emerging variant could swiftly establish dominance while nullifying the virulence-inhibiting effect of PNNAbs across the entire C-19 vaccinated population. Such an emerging variant could unleash unrestrained virulence, triggering a sudden and dramatic surge in severe C-19 disease and mortality within highlyC-19 vaccinated populations.

Regrettably, the recent surge in C-19-related hospitalizations and deaths in highly C-19 vaccinated countries has not alerted our health experts or public health authorities. While there is no evidence suggesting that JN.1 causes more severe illness or poses an increased risk to public health compared to other currently circulating variants (e.g., HV.1), its rapid spread is highly concerning. This is because the escalating prevalence likely indicates a decline in S-specific T-helper activity, signaling a reduction in the boosting of PNNAbs. Hence, the emergence of JN.1 likely marks the beginning of selective immune pressure being exerted by highly vaccinated populations on the conserved (i.e., S variant-nonspecific) infection-enhancing site within S-NTD.

As discussed earlier, the impact of JN.1's high level of viral infectiousness on the immune systems of C-vaccinees is such that it could eventually unleash a 'mysterious' (i.e., not yet understood by our scientific experts or public health authorities!) blockade of viral virulence, disrupting the protection previously enjoyed by C-19 vaccinees.

Society has been 'pleasantly' (according to the opinion of many but not to mine) surprised by Omicron when it bypassed the infection-inhibiting effect of anti-S-RBD (receptor-binding domain) Abs while triggering the production of virulence-inhibiting Abs. This time, however, society will be 'unpleasantly' caught off guard by a new variant (in my book called "HI-VI-CRON") bypassing the *trans* infection-inhibiting effect of the anti-S-NTD Abs, thereby triggering the unrestrained virulence of the virus.

In summary (sections 12-14):

Because high concentrations of refocused, cross S variant-reactive Abs tend to stabilize viral particulates in ways that mitigate -but do not prevent- viral infection, they drive immune escape and fuel new SIR-enabling VBTIs that cause the spectrum of co-circulating variants to expand (so-called 'large-scale immune escape).

As SIR events progressively steer humoral responses toward more conserved S-associated epitopes, the avidity, and consequently, the infection-neutralizing effect of these newly produced Abs upon a subsequent updated booster dose or new VBTI likely diminishes, while their functional breadth expands. This expedites natural selection of more infectious immune escape variants which increasingly rapidly account for a growing portion of the circulating SC-2 virus population.

After immune refocusing has transitioned from variant S-nonspecific humoral responses to non-S-specific cellular responses (i.e., MHC class I-unrestricted CTLs), any circulating variant that acquires new mutations, regardless of whether they are in the S protein or other viral proteins, and subsequently enhances its productive infectiousness, will gain a competitive advantage over all other co-circulating variants.

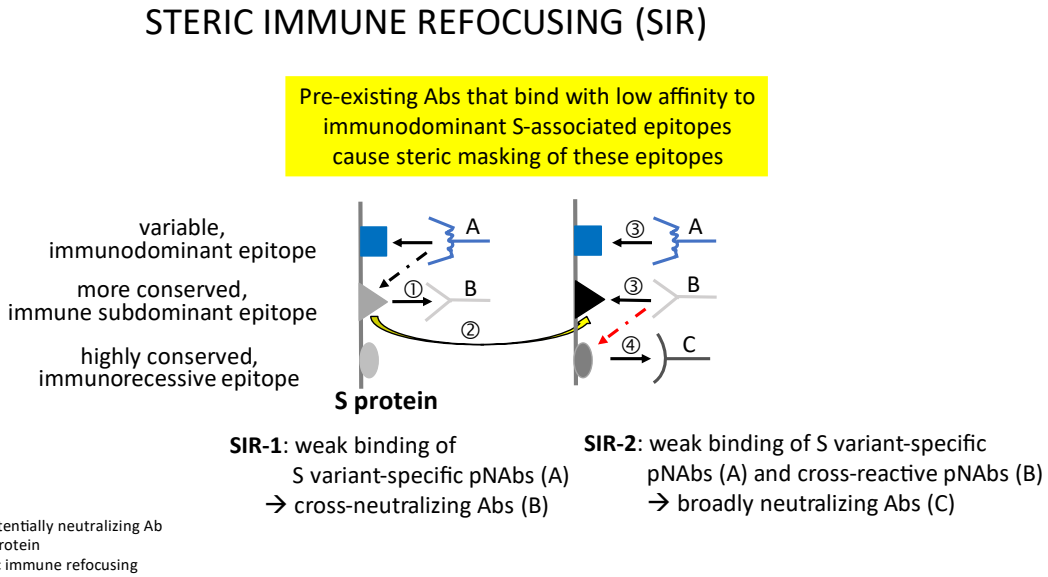
This phenomenon explains the rapid increase in dominance observed with the JN.1 variant. Its incorporation of several non-S-associated mutations improving its reproduction is reflecting heightened non-S-specific immune selection pressure on viral infectiousness. This corroborates my theory that advanced immune refocusing will ultimately lead to enhanced uptake of stabilized virus-Ab aggregates into APCs, thereby activating MHC cl I-unrestricted T cells. These CTLs are likely triggered by high concentrations of a universal (i.e., non-S-specific MHC cl I peptide) following massive internalization of viral aggregates into APCs. Immune selection pressure collectively exerted on productive viral infectiousness would therefore fit with the mutational changes exhibited by JN.1, a variant that quickly gained speed in recent weeks.

More importantly, the significant growth of JN.1, reflecting enhanced activity of MHC class I-unrestricted T cells, indirectly suggests a decline in the recall of S-specific Th memory cells. This phenomenon may be attributed to the hyperactivation of APCs during intensified Ag presentation to T cells, likely triggering negative PD-1/PD-L1-mediated co-stimulation while not impacting T cell activation by universal peptides (https://www.nature.com/articles/s41467-020-18570; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6199356/).

In the absence of a sufficient booster effect, virulence-inhibiting PNNAbs in highly C-19 vaccinated populations will collectively decline below the optimal threshold required for inhibiting viral virulence.

The current heightened activity of CTLs is not only mitigating C-19 disease and viral transmissibility in C-19 vaccinated individuals but also responsible for diminishing protection against viral trans infection by the highly infectious JN.1 variant. As a result, societies in highly vaccinated C-19 countries, including public health authorities and purported 'experts,' may find themselves caught off guard.

15. Figures



Boosting of cross S variant-reactive Abs will quickly result in suboptimal immune pressure on viral infectiousness, allowing highly C-19 vaccinated populations to exert *large-scale immune selection pressure* on viral infectiousness.

Fig. I: SIR 1 triggers induction of broadly neutralizing Abs of low affinity (A) that are directed at more conserved, immune subdominant epitopes (①). This drives large-scale immune escape of SC-2 variants that have poor neutralizability (②) and are responsible for new VBTIs that boost previously SIR-primed Abs (③) to bind to their subdominant epitopes, thereby triggering SIR 2. SIR-2 primes broadly cross S variant-reactive Abs towards highly conserved, immunorecessive domains (④). Due to their low affinity, these Abs will rapidly exert high, large-scale immune selection pressure on viral infectiousness in highly C-19 vaccinated populations. This will eventually result in the emergence of highly infectious SC-2 variants capable of triggering PNNAb-independent VBTIs.

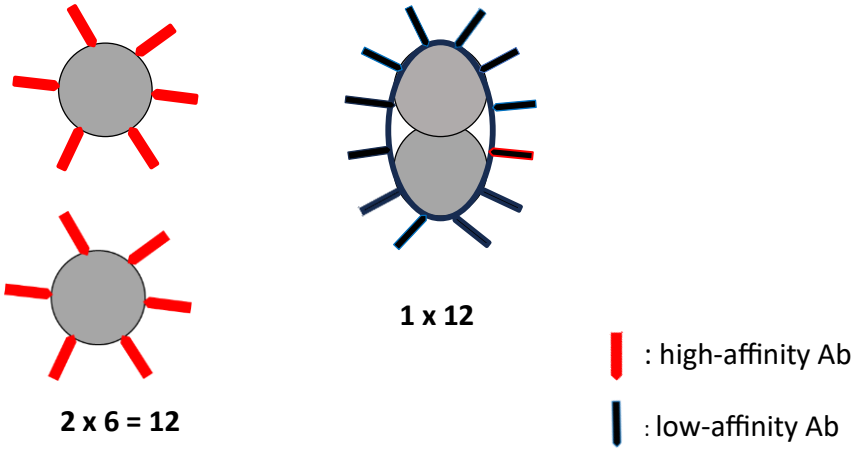


Fig. II: Low-affinity Abs stabilize viral complexes/ aggregates

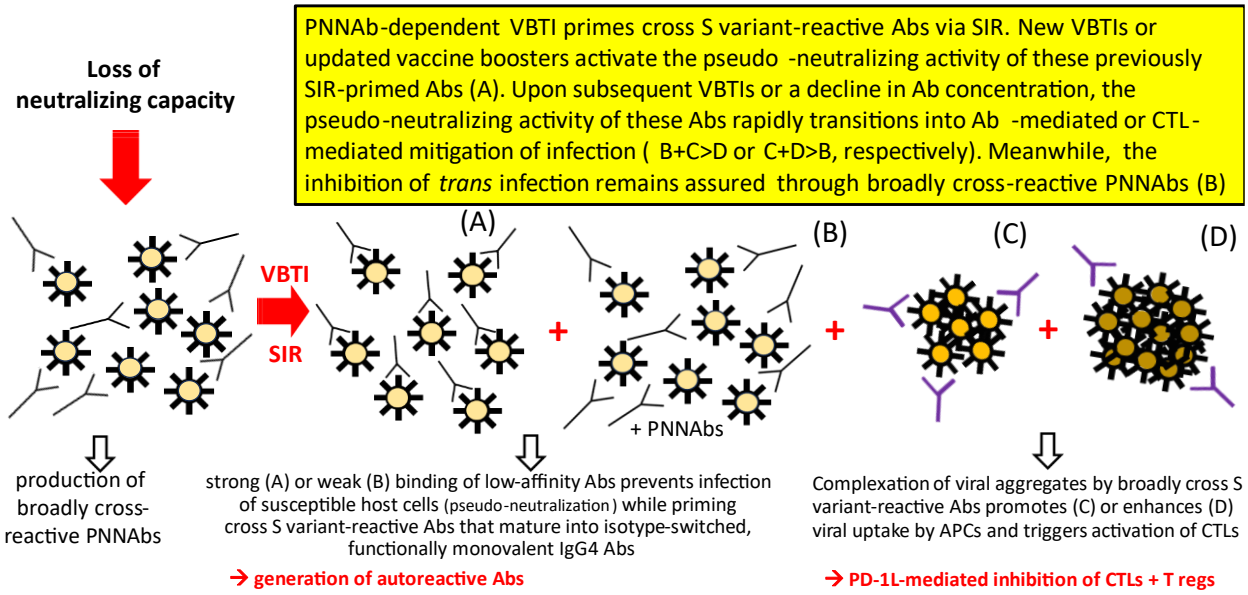


Fig. III: VBTI with Omicron or more infectious Omicron descendants enable (transient) protection from infection or *trans* infection, respectively.

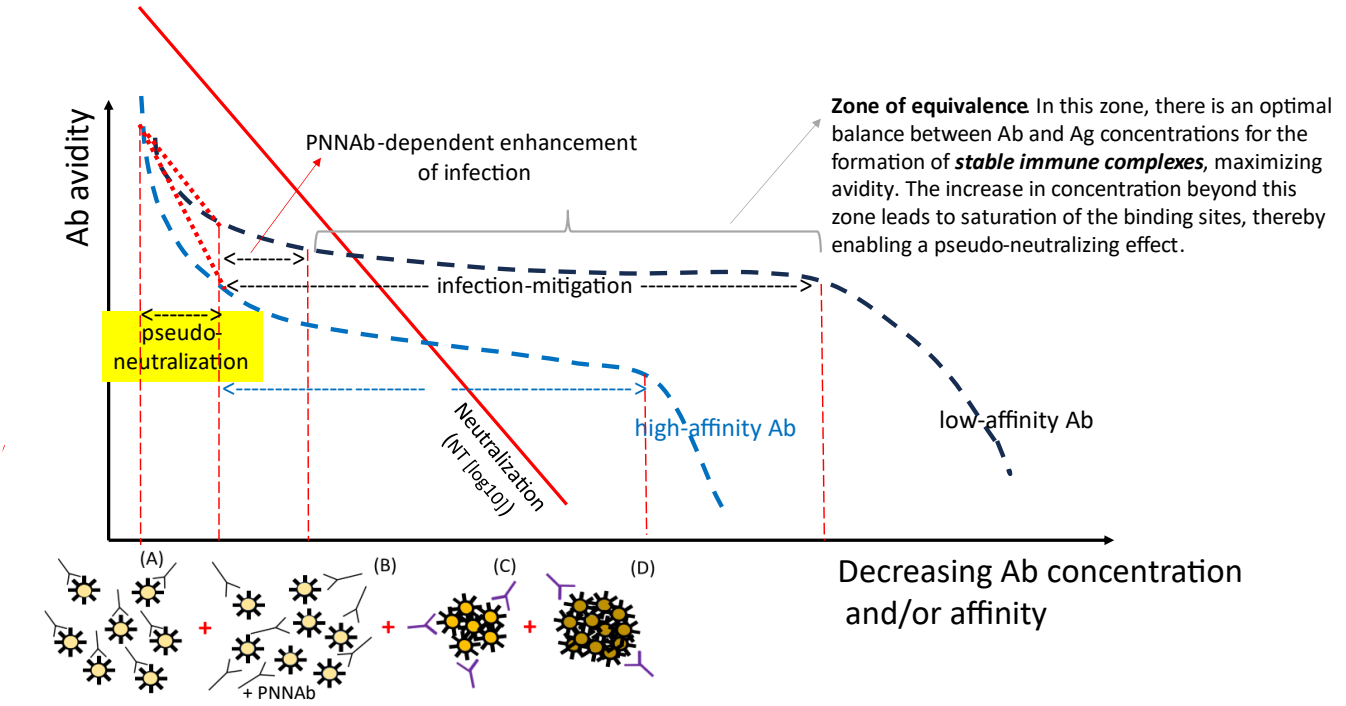


Fig. IV: Avidity is a measure of the overall strength and stability of interactions between multiple binding sites on a bivalent or multivalent Ab and its corresponding multivalent Ag. Low-affinity Abs cover a broader scope of variants and can stabilize viral particulates over a broader range of dilutions. These Abs can, therefore, exert much broader and stronger immune selection pressure on viral infectiousness (via their prolonged infection-mitigating activity) compared to high-affinity Abs. At excessively high concentration, though, the latter have much higher pseudo-neutralizing capacity than low-affinity Abs.

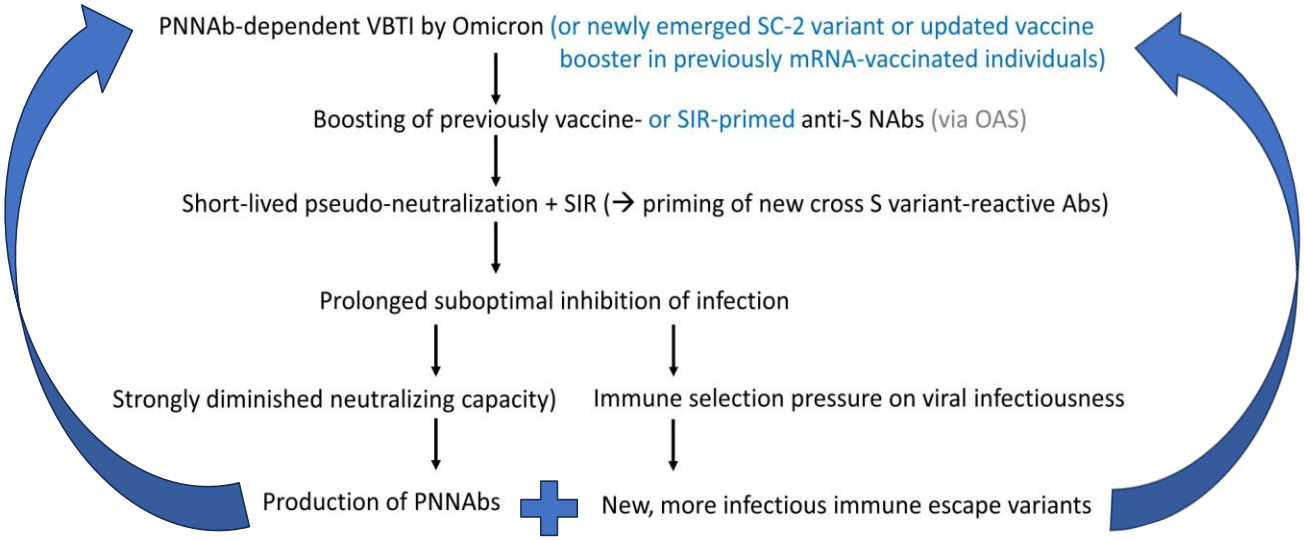


Fig. V: Boosting of previously vaccine- or SIR-primed Abs by updated vaccine boosters (in previously mRNA-vaccinated individuals) or VBTIs with newly emerged SC-2 variants respectively initiate or continue a self-perpetuating cycle of SIR-enabling PNNAb-dependent VBTIs.

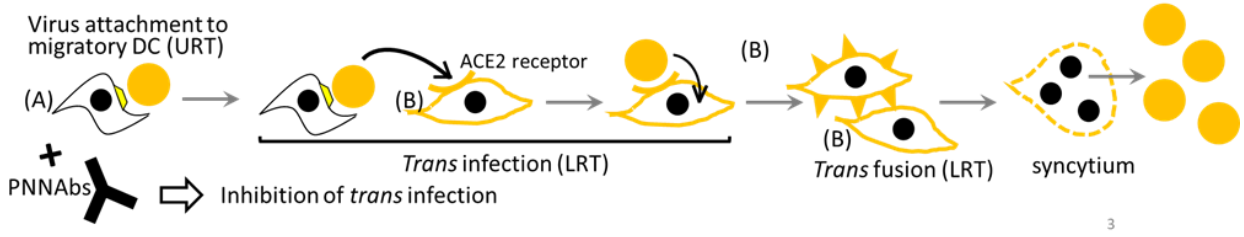


Fig. VI: **A**: Productive infection triggers innate inflammatory stimuli such as interferons. The latter upregulate lectin expression on DCs. Lectins are attachment receptors for SC-2.

B: Lectins on DCs enable viral adsorption in the upper respiratory tract (URT); virions tethered to DCs promote viral dissemination as activated tissue-resident DCs do not support productive infection but migrate and facilitate infection in *trans* of epithelial cells (low expression of ACE-2) in the lower respiratory tract (LRT) https://www.nature.com/articles/s41586-021-03925-1

C: S-mediated membrane fusion and formation of syncytia. The latter is pathognomonic for severe C-19 disease

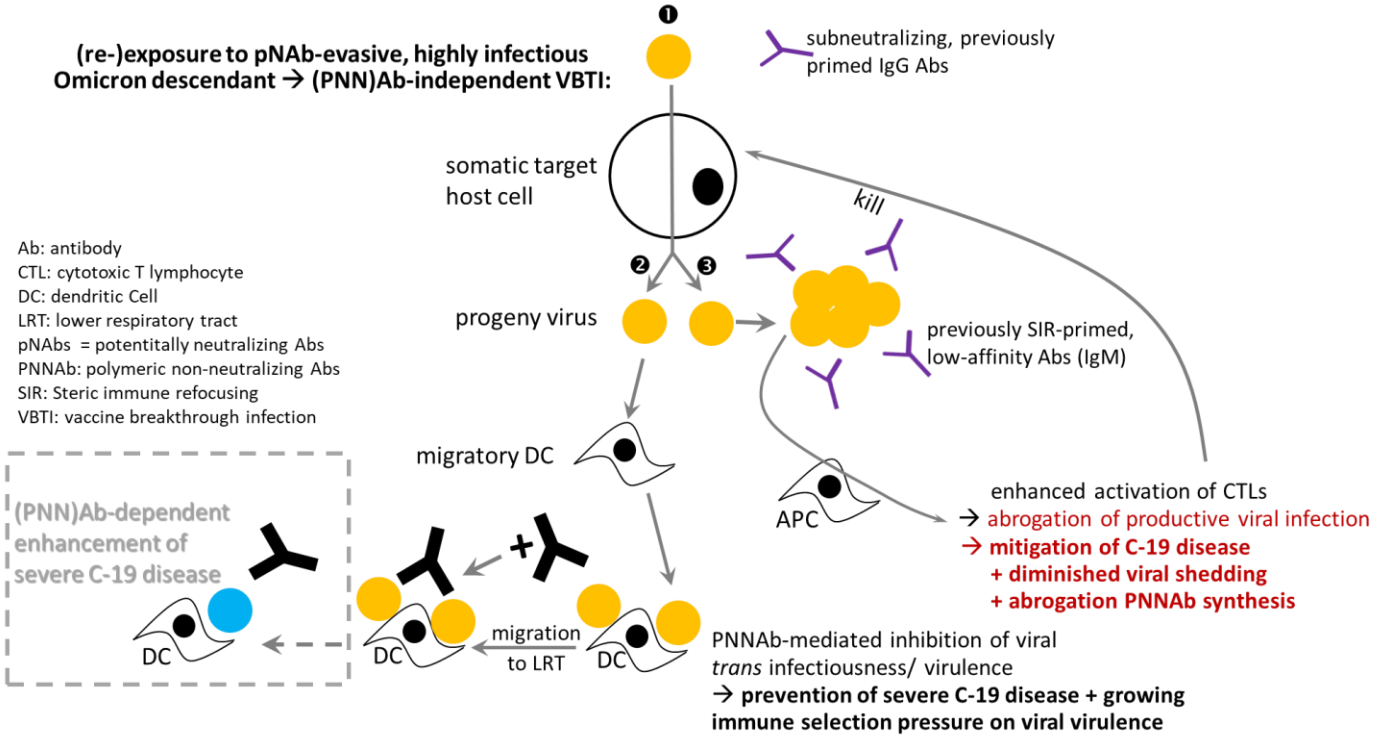


Fig. VII: Newly emerged, highly infectious Omicron descendants do not rely on PNNAbs to infect target host cells (❶). Replication of highly infectious variants generates an immunological environment that promotes their adsorption onto tissue-resident DCs. PNNAbs bind in high quantities to progeny virus tethered to these DCs, which subsequently migrate to the lungs and other distal organs (❷). Diminished production of these virulence-inhibiting PNNAbs, combined with their enhanced binding to DC-tethered virions, leads to increasing immune selection pressure on viral virulence in highly C-19 vaccinated populations. As previously SIR-primed Abs bind with low-affinity to the highly infectious, antigenically more distant immune escape variant, large Ab-virus complexes 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 while impeding T help to assist in boosting previously SIR-primed Abs. As explained in the text, diminished boosting of previously primed anti-S Abs, combined with their enhanced binding to migratory DCs, drives large-scale immune selection pressure on viral virulence upon subsequent VBTIs with newly emerged immune escape variants. The dominant circulation of the highly infectious JN.1 variant is currently likely to increase immune selection pressure on viral virulence beyond the threshold for triggering the selection of a new variant that has the capacity to cause highly virulent VBTIs in highly C-19-vaccinated populations due to PNNAb-dependent enhancement of severe C-19 disease.