How Has the COVID-19 Mass Vaccination Campaign Made the Natural Selection and Rapid Propagation of a HIGHLY Virulent Variant Highly Likely?

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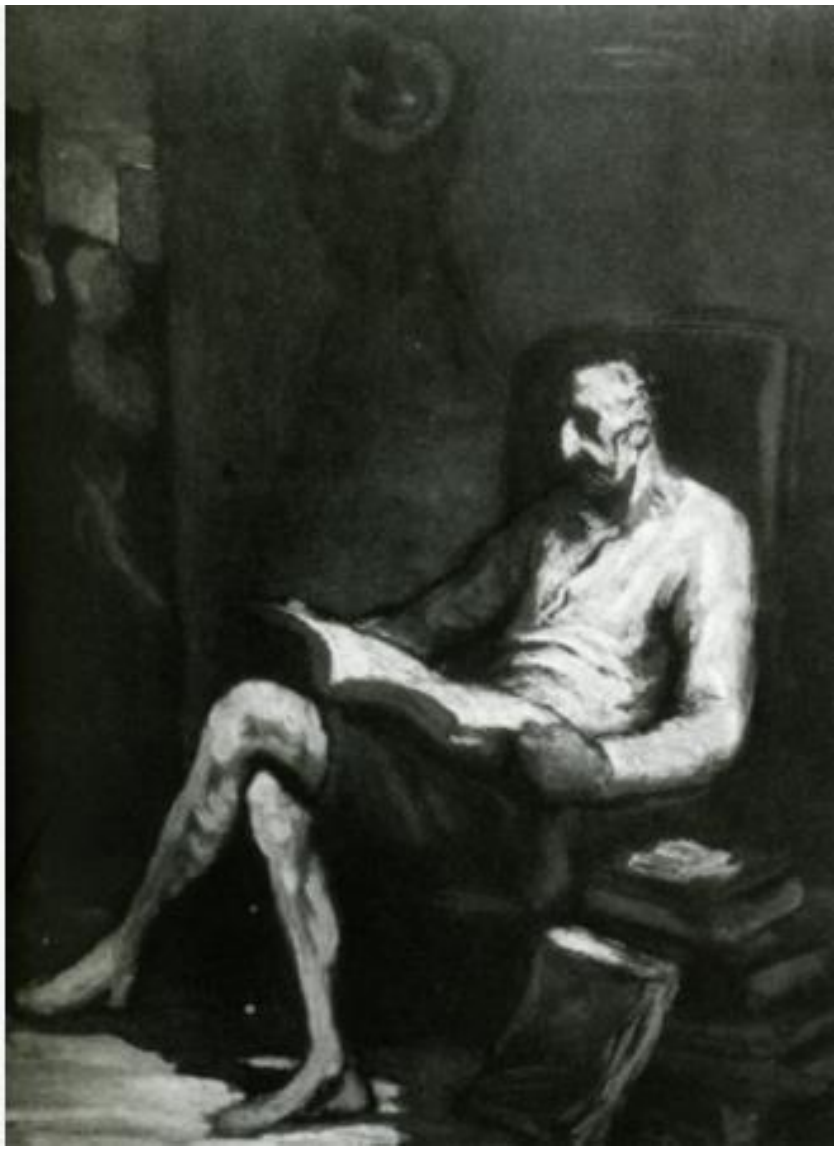
"I have tried to let Truth be my prejudice"
W. Eugene Smith, photojournalist (1918-1978)



ABSTRACT:

This article attempts to summarize Dr. Geert Vanden Bossche's scientific analysis of the COVID-19 mass vaccination campaign. Please bear in mind that Dr. Vanden Bossche's understanding of the COVID-19 situation is still evolving, as he studies the ongoing dynamic and complex interplay between the virus and our individual and collective immune systems, and the effects of the COVID-19 mass vaccination campaign on that interplay. He is still learning.

While temporarily protecting vaccinated individuals (vaccinees) from severe COVID-19, the COVID-19 mass vaccination campaign has, unfortunately, been placing tremendous suboptimal population-level immune pressure on the virus. This will inevitably and ultimately result in the emergence and propagation of SARS-CoV-2 variants that will be highly virulent when contracted by vaccinated individuals from/in highly vaccinated populations (though not highly virulent when contracted by healthy unvaccinated individuals). In the meantime (and beyond) the COVID-19 vaccines have been predisposing vaccinees to autoimmunity and malignancy, while also interfering with the ability of a vaccinee's immune system to control infections (acute and chronic) caused by non-SARS-CoV-2 viruses and other pathogens.

BRIEF SUMMARY:

To date, the immune systems of highly COVID-19 vaccinated individuals have been protecting vaccinees from severe disease via four main immune mechanisms: via **steric immune refocusing (SIR)**, which generates broadly neutralizing antibodies against the virus; via slow maturation of SIR-created antibodies into isotype-switched **IgG4 antibodies (Abs)**, which have an anti-inflammatory effect and thereby diminish disease severity; via mobilization of **MHC-Class I unrestricted cytolytic T lymphocytes (CTLs)**, which kill the virus and diminish inter-host transmission (transmission from an infected person to a new susceptible person); and via production of high levels of **virulence-inhibiting PNNAbs (polyreactive non-neutralizing antibodies)**, which protect against severe disease in the lower respiratory tract and other internal organs.

However, these protective immune mechanisms are unstable, unsustainable, will ultimately fail, and are creating serious problems. As explained in the main text of this article: SIR-created Abs are increasingly failing to protect and have spawned a vast array of "immune escape" variants; high titers of IgG4 Abs are predisposing vaccinees to autoimmunity and malignancy; high titers of IgG4 Abs and previously neutralizing, vaccine-induced Abs combined with exposure to highly infectious variants is now disabling SIR and triggering strong activation of APCs (antigen presenting cells), respectively. The resulting stimulation of MHC-unrestricted CTLs, while mitigating COVID-19 disease symptoms, is now causing generalized immune suppression. As titers of previously neutralizing, vaccine-induced Abs are now declining, the concentration of PNNAbs that effectively bind to the N-terminal domain of spike protein (Spike-NTD) is also declining; consequently, the virulence-inhibiting PNNAb levels are irreversibly dropping to levels that will not only fail to protect against severe disease but will also put suboptimal population-level immune pressure on viral virulence.

Soon the collective suboptimal PNNAb levels will create fertile conditions for the natural selection of more virulent variants in highly vaccinated populations. Under these circumstances, new variants that overcome the PNNAb-mediated inhibitory effect on viral virulence without compromising their intrinsic "fitness" (i.e., are just as infectious as other circulating variants) will become naturally selected and rapidly spread. This is because they will have a transmission advantage over current variants because they will cause severe systemic disease and, therefore, be massively shed in the environment instead of inducing CTL responses to virus-infected cells via enhanced viral uptake into APCs.

A highly infectious and highly virulent variant will have the potential to cause enormous numbers of hospitalizations and deaths, particularly in highly (and rapidly) vaccinated countries, particularly in vaccinated individuals whose innate immune training has been compromised, especially in frail and elderly individuals who have been vaccinated prior to viral exposure.

So, the "calming" of the pandemic over the past year (or so) has been largely due to a set of compensatory immune mechanisms (in vaccinees) that have temporarily protected vaccinees from severe COVID-19 but are unsustainable and seriously problematic. This "calm" has been falsely reassuring and will be followed by a "storm" caused by a new variant that is highly virulent when contracted by vaccinees whose cell-based innate immune system has been sidelined. Vaccinated individuals with such poorly trained innate immunity will be largely defenseless against this variant and are at high risk of succumbing to it. Healthy individuals who have not received the COVID-19 vaccine and live in a highly vaccinated population will be able to handle the variant well, because their innate immunity is robust, well-trained, and well-practiced.

This virulent variant will not survive long, however. It will cause a severe "storm," then die out relatively quickly, because it will quickly run out of accessible, susceptible hosts.

This sad outcome was predictable and preventable. The cascade of immune events and the ultimate outcome described in this article (and in related contributions) would not have occurred if the population had not exerted large-scale immune selection pressure on viral infectiousness. Because of the large-scale administration of spike-based vaccines during this pandemic, *the COVID-19 mass vaccination campaign* has led to vaccinated populations exerting significant immune selection pressure on viral infectiousness and now on viral virulence.

The scientific reality is that, because of laws of Nature, the mass vaccination campaign has transformed the initial COVID-19 pandemic into a far more serious, prolonged, and threatening pandemic, and, in addition, has created a tremendous amount of vaccine injury at the individual level—-such that far more cumulative deaths and morbidity will occur than would have occurred in the absence of the mass vaccination campaign.

INTRODUCTION:

Dr. Vanden Bossche's important analysis of the COVID-19 mass vaccination campaign has been largely ignored:

For more than two years Dr. Geert Vanden Bossche has been repeatedly explaining (to scientists, physicians, and the general public) why the implementation of a mass vaccination campaign (like the COVID-19 mass vaccination campaign) in the midst of an active pandemic of an acute self-limited viral infection (like SARS-CoV-2) will inevitably lead to the natural selection and rapid propagation of viral variants that are both highly infectious and highly virulent and will have the potential to cause a catastrophic number of hospitalizations and deaths. His analysis has been based on a deep understanding of the immunology, virology, vaccinology, and evolutionary biology involved; and on extensive, well-rounded, real world, interdisciplinary (non-"siloed") experience in these fields. His careful analysis has been scientifically sound, highly responsible, profoundly important, and has warranted the immediate attention of scientists, physicians, and public health officials---**but has been largely ignored**.

Dr. Vanden Bossche (GVB) has felt a professional and moral obligation to continue to share his honest, objective, deep, scientific analysis with the scientific/medical community and the public, so that all can be informed of and prepare for what is a very plausible and worrisome outcome (and in his view the inevitable outcome) of the COVID-19 mass vaccination campaign. He also shares his analysis in the hope that scientific and health policy mistakes will not be repeated in the future.

If the scientists and physicians who have promoted the mass vaccination campaign and have disagreed with GVB's analysis were as concerned as GVB is about understanding the complex COVID-19 situation as accurately as possible and were equally concerned about honestly educating and preparing the public, they would have provided, long ago, a point-by-point critique of GVB's analysis and would have engaged in respectful dialogue with him---dialogue that would be archived and made available for physicians and the public to view and study. That would have been in keeping with one of the most important fundamental principles of science and medicine---which is to welcome, honor, and critically evaluate all plausible, important, high priority hypotheses (which GVB's analysis certainly represents) and do so through respectful dialogue. Unfortunately, other scientists and physicians, particularly those who have most strongly promoted the prevailing COVID-19 narrative and its mass vaccination campaign, have remained silent about GVB's analysis and have avoided any discussion of his concerns---other than to ignore, dismiss, belittle, or demonize his analysis.

The only legitimate justification for scientists and physicians to not engage in constructive dialogue with GVB would be if his analysis were so irresponsible and so off the mark, scientifically, that it did not warrant comment. But his analysis is not irresponsible or wildly off the mark. To the contrary, his analysis is far more scientifically sound, far more sophisticated, and far more responsible than the simplistic, egregiously unscientific prevailing COVID-19 narrative, which has been based on "data" of astonishingly low scientific quality and whose key

promoters have been grossly violating fundamental principles of science, medicine, ethics, and democracy throughout the pandemic (as I have repeatedly explained and documented in many articles posted on my website). It is scientifically and intellectually untenable for those scientists and physicians to claim that GVB's analysis is so irresponsible and off that mark that it is unworthy of their comment. It is telling that the scientists and physicians who have strongly promoted the mass vaccination campaign have avoided any discussion of GVB's excellent analysis.

Misapplication of a "conventional view" regarding viral virulence:

I have tried to discuss GVB's concerns with scientists and physicians who have strongly doubted the accuracy of his analysis. This includes scientists and physicians who have been strongly opposed to the prevailing COVID-19 narrative and its mass vaccination campaign but have, nevertheless, been highly skeptical of GVB's prediction that a highly virulent variant will appear and cause devastating harm. The argument these scientists and physicians have typically put forth (an argument that I will call the "conventional view") is that ***"viruses normally do not evolve to become more virulent, because that would not be in the best interests of the virus---because if the virus kills its host, it will not be able to survive. Instead, it is in the best interest of the virus to, if anything, gradually become less virulent, not more virulent."*** This conventional view is largely correct when/if we are talking about a normal, usual, "naturally evolving" epidemic/pandemic (i.e., an epidemic that is not treated with a mass vaccination campaign in the midst of the active epidemic, using a suboptimal vaccine)---though I would hasten to add that the main reason a "naturally evolving" epidemic/pandemic ends is not because the virus gradually becomes less virulent---the main reason is that herd immunity develops and this results in the virus no longer having ample susceptible hosts to easily infect. I would also add that we should avoid the anthropomorphic notion that the virus has a conscious strategy. Evolution of the virus, evolution of the immune response, and evolution of the pandemic are determined by natural laws of nature---e.g., competitive binding, steric hindrance, conformational changes, other laws of physical chemistry, and the Darwinian principles of natural selection and fitness advantage.

What I think the "conventional view" fails to take into account is that this COVID-19 pandemic has not been treated in a normal, usual, natural way. Instead, it has been treated in a highly abnormal way---namely, with implementation of a mass vaccination campaign, across all age groups, in the midst of the active pandemic, using a suboptimal vaccine (i.e., a vaccine that thwarts but does not prevent viral replication and transmission). This highly abnormal intervention has profoundly changed the normal interplay between the immune system and the virus, at a population level---rendering that interplay to be highly abnormal. The COVID-19 mass vaccination campaign has forced the immune system to do things it normally does not need to do and has made it more difficult for the immune system to do what it needs to do. The mass vaccination campaign has profoundly and adversely affected the immune ecosystem---at both individual and population levels. Accordingly, the "conventional view" is not sufficient to explain what has been happening since implementation of the COVID-19 mass vaccination campaign, or to predict what will happen.

We have never before implemented a mass vaccination campaign (using a prophylactic non-live vaccine) in the midst of an active pandemic, for good scientifically-sound reasons. GVB feels very strongly (based on fundamental scientific principles---laws of nature) that this mass vaccination campaign will lead to the highly abnormal and highly unusual phenomenon of a variant emerging that is highly virulent when contracted by COVID-19-vaccinated individuals who lack a sufficiently trained CBIIS (cell-based innate immune system), due to deficient or insufficient previous exposure to natural infection---a phenomenon that would not have happened in the absence of such a campaign. One could argue that he cannot possibly know this "because we have never done this before." But he could similarly argue that, "because we have never done this before," the promoters of the mass vaccination campaign cannot possibly know that their campaign will not result in the natural selection and fulminant spread of highly virulent variants.

So, because we have never before implemented a mass vaccination campaign in the midst of an active pandemic, using a *prophylactic*, non-live vaccine---neither GVB, nor the promoters of the mass vaccination campaign, can provide definitive proof (at this point) that a highly virulent variant will or will not emerge and dominate. Instead, we are left to consider a spectrum of plausible hypotheses, including GVB's highly plausible hypotheses.

Frankly, in my opinion, GVB has more experience in and has taken a far deeper, more interdisciplinary, more well-rounded dive into the fields of immunology, virology, vaccinology, and evolutionary biology than have promoters of the mass vaccination campaign---and, more importantly, GVB, in my opinion, has been far more honest, objective, scientific, careful, ethical, and altruistic than have key promoters of the mass vaccination campaign, many of whom have obviously violated many fundamental principles of science, medicine, ethics, and democracy throughout the past three years, as I have explained in previously posted writings. Furthermore, GVB's scientifically plausible and highly responsible hypotheses are profoundly important and, therefore, need to be taken very seriously by other scientists and physicians, even if they are skeptical of them. Such is the tradition of science and medicine.

Below is a detailed **REVIEW** of my understanding of why GVB is so convinced that the COVID-19 mass vaccination campaign will, inevitably, result in the emergence, natural selection, and propagation of highly infectious and highly virulent SARS-CoV-2 variants that will have the potential to cause huge numbers of hospitalizations and deaths, particularly in highly (and rapidly) vaccinated countries, especially in highly vaccinated individuals.

For background information, consider viewing the video, ***Respecting the Immune Ecosystem---Concerns of an Immune System Ecologist,*** which is posted in the "Notes on COVID-19" section of my website (www.notesfromthesocialclinic.org) and provides numerous relevant and instructive medical illustrations.

Better yet, read GVB's recently published book, ***The Inescapable Immune Escape Pandemic,*** and access the many articles and videos on GVB's website: www.voiceforscienceandsolidarity.org,

particularly his recent article: https://www.trialsitenews.com/a/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-19-vaccinated-populations.-645407ab

NOTE TO READER: If the following detailed REVIEW seems too complex and confusing, the reader might want to skip to the section entitled A SUMMARIZING OUTLINE OF THIS ARTICLE (and maybe the SUPPLEMENTAL INFORMATION section), then return to the more detailed and nuanced REVIEW.] The FOOTNOTES at the end of the REVIEW might also be helpful, as might the BRIEF SUMMARY at the beginning of the article.

REVIEW:

WHY IS THE NATURAL SELECTION AND PROPAGATION OF HIGHLY VIRULENT SARS-CoV-2 VARIANTS AN INEVITABLE OUTCOME OF THE COVID-19 MASS VACCINATION CAMPAIGN?

The critically important difference between optimal and suboptimal immune pressure on the virus, at a population level:

In order to best appreciate the detrimental effects of the COVID-19 mass vaccination campaign on the immune ecosystem, it is important, first, to understand the critical difference between optimal and suboptimal immune pressure on viral infectiousness, at the population level.

Optimal immune pressure on viral infectiousness means that the immune response to the virus is so efficient and effective that the virus is quickly killed. The immune response puts so much immune pressure on the virus that the virus is unable to thrive. Optimum (population-level) immune pressure on viral infectiousness is characteristic of the "herd immunity" (collective sterilizing immunity) that develops during a naturally evolving pandemic of an acute self-limiting infection (a pandemic that is not treated with implementation of a mass vaccination campaign in the midst of the pandemic)

Suboptimal immune pressure on viral infectiousness means that the immune response to the virus is only partially and inadequately effective---such that the virus is put under sub-lethal pressure, as opposed to lethal pressure. The immune response thwarts viral replication and transmission but does not adequately prevent successful replication and transmission of the virus. This partial (suboptimal) immune pressure makes it difficult for the virus to survive and thrive but does not prevent survival. Under this circumstance, if a new variant appears on the scene and has a fitness advantage (i.e., is better able to overcome the suboptimal immune pressure on viral infectiousness), it will be able to thrive more easily than existing variants and will, therefore, outcompete other variants, be naturally selected, and dominantly propagate. In other words, suboptimal population-level immune pressure on viral infectiousness allows an incipient potentially threatening viral variant that has a fitness advantage (e.g., is more

infectious) to survive, reach its potential, and supplant variants that lack that fitness advantage. In fact, if suboptimal immune pressure is exerted at the level of the population (i.e., suboptimal 'population-level' immune pressure), it promotes the successful natural selection and dominant propagation (or co-circulation) of variants that are able to overcome the suboptimal immune pressure. In other words, suboptimal population-level immune pressure on a phenotypic characteristic of the virus (e.g., its infectiousness) inevitably results in immune selection pressure on that very viral characteristic.

Suboptimal population-level immune pressure on viral infectiousness is characteristic of a pandemic that is treated with large-scale use of spike-based vaccines (i.e., mass vaccination) that is implemented in the midst of the active pandemic. Since the advent of Omicron, highly COVID-19-vaccinated populations have been exerting suboptimal population-level immune pressure on more and more conserved, functional epitopes of the SARS-CoV-2 spike protein, thereby promoting natural selection and co-circulation of a diversified array/spectrum of increasingly infectious "immune escape" variants. In highly COVID-19 vaccinated populations, highly infectious variants are now facilitating a shift from immune selection pressure on viral infectiousness to immune selection pressure on viral *trans* infection (i.e., viral infection of the lower respiratory tract and other internal organs by virtue of virus transfer from migratory sentinel cells to susceptible organ cells) and, therefore, on the capacity of SARS-CoV-2 to trigger severe disease (as will be explained later).

Whereas optimal population-level immune pressure on viral infectiousness ends a pandemic relatively quickly, prolonged suboptimal immune pressure exerted on viral infectiousness by the population promotes natural selection of new, more infectious immune escape variants. This fuels enhanced immune escape and therefore prolongs a pandemic while driving it in a more dangerous direction.

For further discussion of optimal versus suboptimal population-level immune pressure, please see SUPPLEMENTAL INFORMATION at the end of this article.

Why are highly vaccinated individuals, in particular, experiencing frequent breakthrough infections (BTIs)?

Throughout the COVID-19 pandemic, all of us, vaccinated and unvaccinated, have been frequently exposed (and are still being exposed) to more infectious SARS-CoV-2 variants---most recently, many Omicron variants and subvariants, all of which are highly infectious, all of which represent "immune escape" variants. As a result, both previously infection-primed individuals (individuals whose immune response to SARS-CoV-2 was triggered by natural SARS-CoV-2 infection) and previously vaccine-primed individuals (individuals whose first immune response was artificially triggered by COVID-19 vaccination) have been experiencing breakthrough infections (BTIs). Vaccinated individuals, in particular, have been frequently experiencing breakthrough infections (which we will call "vaccine-BTIs"), for the following three main reasons:

1. Their vaccine-induced potentially neutralizing antibodies (pNAbs), which are directed against epitopes in the receptor binding domain (RBD) of the spike protein, have been unable to neutralize the many "immune escape" variants that have successively appeared---because these variants have mutated in a way that enables them to "escape" from (be resistant to) these vaccinal pNAbs. (These immune escape variants appeared on the scene because their resistance to pNAbs gave them a competitive "fitness advantage" which, in turn, led to the natural selection and dominant propagation of these variants.)
2. Their polyreactive non-neutralizing antibodies (PNNAbs), which were stimulated into binding to the N-terminal domain of the spike protein (Spike-NTD) because of the substantially diminished neutralizing capacity of vaccine-induced anti-spike Abs, have been facilitating viral entry into susceptible epithelial host cells (i.e., these PNNAbs are infection-enhancing) and have thereby accelerated production of viral progeny. This infection-enhancing effect of the PNNAbs is due to the fact that binding of PNNAbs to a highly conserved antigenic region within the N-terminal domain of the spike protein (Spike-NTD) causes a conformational change in the spike protein that flips the receptor binding domain into the "open position" thereby making it easier for the virus to enter susceptible host epithelial cells.)
3. Their innate immune system has been sidelined because non-replicating vaccines do not train the cell-based innate immune system and many vaccinees received their vaccination prior to exposure to natural infection (especially in countries that implemented a fast-track mass vaccination program).

Why have BTIs (in both unvaccinated and vaccinated individuals) been relatively mild (at least since the initial appearance of Omicron variants)? What protective immune mechanisms have been at play?

During the Omicron era, BTIs (in both unvaccinated and vaccinated individuals) have, so far, either been asymptomatic or have usually caused only mild or moderate symptoms. To date, BTIs have not usually caused severe COVID-19 disease, for the reasons mentioned below:

In the case of heathy unvaccinated individuals: Healthy unvaccinated individuals have been able to handle re-exposure increasingly well, primarily because of their robust, fully participating, and increasingly trained innate immunity. Their innate immune system is able to quickly lower viral loads and kill virus-infected cells (via trained, i.e., epigenetically re-programmed, natural killer cells) without needing to prime the adaptive immune system for help (although MHC class I-unrestricted CTLs may be triggered in the case of symptomatic infection).

In the case of vaccinated individuals: Vaccinated individuals, on the other hand, have been heavily relying on four major protective immune mechanisms to deal with their frequent vaccine-BTIs. As will be explained, these protective immune mechanisms, though temporarily helpful, are unstable, unsustainable, will ultimately fail, and are problematic.

1. **The SIR phenomenon (Steric Immune Refocusing)**:[1-3] First, vaccinated individuals, via the SIR phenomenon, developed broadly neutralizing antibodies to immunosubdominant spike-associated domains.

In the context of SARS-CoV-2, SIR refers to the redirection of the immune system to produce neutralizing antibodies against conserved immune-subdominant epitopes[2] of the spike protein when pre-existing poorly neutralizing Abs sterically hinder (physically block) immune recognition of the variable immune-dominant epitopes of the spike protein.

These SIR-created high avidity antibodies have temporarily provided efficient cross-neutralizing activity. However, there have been downsides associated with the beneficial protective effects of these SIR-created antibodies. Titers of these SIR-created neutralizing antibodies, which were initially already at relatively low levels, declined and rapidly reached a point where they fell below the optimal threshold for providing protection from infection (i.e., fell into the suboptimal range). Because of the suboptimal neutralizing titers of these antibodies and their delayed maturation (in germinal centers) into affinity-matured, isotype-switched IgG4 antibodies, prolonged large-scale (population-level) immune pressure has been exerted by these antibodies in highly COVID-19 vaccinated populations. In these populations, suboptimal SIR-created population-level immune pressure on viral infectiousness led to the natural selection and co-circulation of a vast array of more infectious Omicron descendants. In short, while providing some protection to vaccinees, the SIR phenomenon spawned a succession of increasingly infectious "immune escape" variants and ultimately led to co-emergence of highly infectious Omicron descendants. (Note: Because of the diminished production of viral progeny, re-exposure of *unvaccinated*, infection-experienced individuals to Omicron-derived descendants did not trigger SIR and, therefore, did not promote viral immune escape!)

A second downside of the SIR phenomenon is that it increasingly refocuses the immune system on more immunorecessive epitopes, ones that have greater similarity to "self" and "altered self." This predisposes to autoimmunity and malignancy, respectively.[2, 3]

2. **The anti-inflammatory effect of isotype-switched IgG4 antibodies:** SIR-created neutralizing antibodies eventually underwent isotype-switching---i.e., matured (in delayed fashion) into IgG4 antibodies. IgG4 antibodies have an anti-inflammatory effect. Accordingly, when vaccinated individuals with high titers of SARS-CoV-2 specific IgG4 antibodies (i.e., those who experienced a SIR-enabling vaccine-BTI) are exposed to newly emerging immune escape variants, their symptoms have been reduced by the anti-inflammatory effects of these IgG4 antibodies. As not only vaccine-BTI but also mRNA vaccination facilitates SIR, it stands to reason that IgG4 antibodies can also be induced after mRNA -vaccination.

   Indeed, Irrang et al documented that "several months after the second vaccination [with mRNA COVID-19 vaccine], SARS-CoV-2 specific antibodies were increasingly composed of non-inflammatory IgG4, which was further boosted by a third mRNA vaccination and/or

SARS-CoV-2 variant BTI." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9847566/. (These unusual levels of SARS-CoV-2 specific IgG4 antibodies have not been documented in unvaccinated individuals.)

However, there is an unfortunate trade-off for the protective anti-inflammatory effect of vaccinee's high levels of IgG4 antibodies---namely, they predispose those individuals to autoimmunity and malignancy, as explained in the FOOTNOTES of this article[2,3] and in GVB's recent article: https://www.trialsitenews.com/a/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-19-vaccinated-populations.-645407ab

3. **Activation of CTLs (Cytolytic T Lymphocytes):** Despite the functional monovalency of isotype-switched IgG4 antibodies, elevated titers of these Abs result in strong cytolytic activation of MHC Class I unrestricted T lymphocytes but no longer promote SIR upon vaccine-BTIs with highly infectious Omicron descendants. This is because high concentrations of IgG4 Abs bound to progeny virions of these variants will expedite viral uptake by APCs (antigen presenting cells). SIR-disabling vaccine-BTIs therefore not only enhance CTL-mediated elimination of virus-infected cells, thereby rapidly abrogating viral shedding and safeguarding vaccinated individuals from COVID-19 disease altogether, but also prevent *de novo* priming of new, broadly cross-neutralizing Abs and thus, promote propagation of viruses with higher intrinsic infectiousness. High viral infectiousness can ultimately cause activated CTLs to kill the APCs that activated them in the first place. Strong activation of APCs and insufficient or deficient presentation of non-SARS-CoV-2-related Ags may lead to generalized immune suppression and increased prevalence of other, non-Covid-19-related diseases.

4. **The virulence-inhibiting effect of PNNAbs (polyreactive non-neutralizing antibodies):** PNNAbs bind to Spike-NTD exposed on free infecting virions as a result of diminished neutralizing capacity of potentially neutralizing vaccine-induced antibodies (pNAbs) and thereby enhance viral infectiousness. These Abs have also a virulence-inhibiting activity in that they attach to virus that is tethered to migrating dendritic cells (DC) and thereby prevent transfer of virus from dendritic cells to cells in the lower respiratory tract (LRT) and other internal organs---i.e., high levels of PNNAbs adsorbed on DC-tethered virions inhibit *trans* infection in the LRT and other internal organs and, thereby, protect vaccinated individuals from *severe* COVID-19 disease (fig. 1). However, as the infectiousness of the circulating variants increases, hyperactivation of CTLs not only leads to generalized immune suppression but also causes highly vaccinated populations to exert immune selection pressure on viral *trans* infectiousness and, therefore, promote natural selection of new variants that are likely to exhibit enhanced virulence (as explained below).

In these ways, SIR-created neutralizing antibodies, anti-inflammatory IgG4 Abs, and CTLs have been enhancing recovery from disease, in vaccinees, (after providing some short-lived

protection from infection) or have been mitigating or even preventing disease symptoms, while PNNAbs have been protecting vaccinated individuals from severe COVID-19 disease, when these individuals have experienced vaccine-BTIs with more infectious variants. However, while this "immunologic rescue operation" (GVB's phrase) has been protecting vaccinated individuals from severe disease, it has meanwhile been facilitating asymptomatic transmission (to both vaccinated and unvaccinated individuals) of a diversified array of highly infectious SARS-CoV-2 immune escape variants; it is, therefore, now causing highly COVID-19 vaccinated populations to exert large-scale immune selection pressure on viral virulence (as will be further explained later); it has predisposed vaccinees to autoimmunity and malignancy; and it has adversely affected the ability of vaccinees to normally handle other pathogens.

The false impression that the pandemic is currently subsiding, heading into endemicity, and becoming less worrisome:

The above four protective mechanisms, upon which vaccinated individuals have been relying to diminish viral pathogenicity, have given the impression that the pandemic is subsiding, becoming milder, and heading into a relatively benign endemic phase. But, as explained below, this is a false impression. These protective mechanisms will ultimately fail and result in the natural selection and propagation of new emerging variants that have the capacity to become highly virulent in COVID-19 vaccinees. These mechanisms have been providing false reassurance. The current "calm" will, unfortunately, be followed by a severe "storm." The latter will primarily affect those who were vaccinated prior to experiencing natural infection (e.g., the elderly and those considered vulnerable because of underlying disease or immune suppressive conditions) .

Why will the protective immune mechanisms upon which highly vaccinated individuals have been relying inevitably fail and promote the "successful" emergence of a highly virulent variant?

As long as the concentration of PNNAbs bound to DC-tethered progeny virions remains high enough (i.e., are at optimal levels, or close to being optimal, and are putting optimal immune pressure on viral *trans* infection), the virulence-inhibiting effect of the PNNAbs and the APC-mediated activation of CTLs will adequately protect the vaccinated individual from severe disease (or even from COVID-19 altogether) and will diminish viral shedding. Although high levels of PNNAbs bound to DC-tethered progeny virions (via Spike-NTD) are able to prevent or mitigate viral *trans* infectiousness at the level of the LRT and internal organs, the infectiousness of the virus at the URT (upper respiratory tract) remains unaffected and promotes asymptomatic transmission. Thus far, h**igh levels of PNNAbs bound to DC-tethered virions have been preventing natural immune selection of new variants capable of escaping from the virulence-inhibiting effect exerted by these antibodies** (fig. 1).

However, since the circulating variants have increased infectiousness, their progeny virus is released in high density from the cells they infect and thereby cause substantial inflammation. The latter promotes enhanced adsorption of progeny virions onto patrolling, migratory dendritic cells and thereby fosters opsonization of free progeny virus by vaccine-induced anti-Spike Abs. Enhanced uptake of these virus-Ab complexes into APCs have been strongly activating cytolytic

T lymphocytes (CTLs), which in turn eventually kill the APCs that activated them in the first place. This killing of APCs hinders the recall of previously vaccine-primed T helper cells, thereby preventing further SIR, or the production of new antibodies targeting new, more conserved spike-derived antigen, despite the presence of elevated titers of functionally monovalent Ig-G4 Abs. Failure of vaccine-BTIs to prime new, broadly neutralizing anti-Spike Abs leads to failure to reduce viral infectiousness. Consequently, elevated IgG4 -Ab titers in highly vaccinated populations link enhanced protection of vaccinees from Covid-19 disease and diminished viral shedding to enhanced infectiousness of the circulating immune escape variants and their asymptomatic transmission. Enhanced viral infectiousness lowers the concentration of PNNAbs that bind to Spike-NTD on DC-tethered virions in vaccinees as shown in fig. 2. This inevitably leads to suboptimal PNNAb-mediated immune pressure on viral *trans* infectiousness in Covid-19 vaccinees.

When levels of immune pressure on viral *trans* infectiousness collectively decline into the suboptimal range, Spike-NTD-binding PNNAbs will place large-scale immune selection pressure on the *trans* infectiousness of DC-tethered progeny virions produced by the currently circulating, highly infectious Omicron descendants. In other words, diminished viral shedding, which is now threatening viral transmission in highly COVID-19 vaccinated populations, is indirectly causing suboptimal immune pressure on viral virulence while enabling asymptomatic transmission of highly infectious variants. Collectively exerted, suboptimal population-level immune pressure drives natural selection. That is, any emerging variants that are able to overcome the virulence-inhibiting effect of the PNNAbs while maintaining a high level of viral infectiousness will have a transmission advantage, will be naturally selected, and propagate (as enhanced severe disease will not enable timely isolation of the affected individuals). In short, **diminished viral inter-host transmission** (transmission from an infected person to a new susceptible person) is promoting natural selection of highly infectious immune escape variants that have **capacity to enhance systemic intra-host viral replication and dissemination to distal organs** such as to enable enhanced, but lethal viral transmission. When this happens, a major wave of exacerbated severe COVID-19 disease cases is likely to occur among the highly vaccinated. In the absence of herd immunity, it is reasonable to assume that this will ultimately allow Nature to control viral transmission. Elimination of those unable to mount a sterilizing immune response to the virus (i.e., primarily vaccinated individuals) would allow those who do mount a sterilizing immune response to contribute to establishing herd immunity and thereby durably protect the human species from new SARS-CoV-2 pandemics.

In the past, booster doses of vaccine and/or reinfection (BTIs) were resulting in periodic boosting of previously vaccine-primed NAbs or *de novo* production of new, cross-functional neutralizing antibodies (via SIR)---up to optimal levels. However, booster doses of vaccine, or vaccine-BTIs with highly infectious Omicron descendants, are now failing to boost or prime neutralizing antibodies (again, because APCs are so preoccupied with removing highly infectious virus from vaccine-BTIs that they succumb to the killing by the CTLs they activate or cause other antigens to be outcompeted for uptake into their antigen processing and presentation machinery). At the same time, these SIR-disabling vaccine-BTIs fail to stimulate new, broadly neutralizing anti-Spike Abs. Consequently, both (updated) booster doses and ongoing

(asymptomatic) vaccine-BTIs fail to reduce viral infectiousness. It follows that the PNNAb-mediated immune pressure on viral *trans* infection will drop into a suboptimal range.

A large-scale decrease in PNNAb titers in the context of circulating highly infectious variants is now increasing immune selection pressure on viral *trans* infection. Upon mounting beyond a certain threshold, the immune selection pressure will likely trigger natural selection of a new SARS-CoV-2 variant(s) displaying mutational changes (presumably in the glycosylation profile of spike protein) that enable the variant to collectively lift the blockade on viral virulence. However, mutational changes in the Spike-associated glycosylation profile may bear a substantial fitness cost. In order for these newly emerging variants to not be outcompeted by other currently circulating, highly infectious variants (which cannot lift this blockade), it is critical that they maintain a high level of infectiousness by enabling PNNAbs to bind to the conserved antigenic site comprised within Spike-NTD. This implies that mutations targeted at evading the PNNAb-mediated inhibitory effect on intrinsic viral virulence cannot occur within this antigenic site and that manifestation of a high level of virulence by these newly emerging variants will likely depend on the presence of suboptimal concentrations of PNNAbs bound onto DC-tethered virions. In other words, the newly emerging immune escape variants are likely to provoke PNNAb-dependent enhancement of severe disease.

In short, because of the laws of nature, newly emerging immune escape variants exhibiting highly infectious, highly virulent properties (in COVID-19 vaccinees) will be selected and rapidly transmitted, and thereby cause PNNAb-dependent enhancement/exacerbation of systemic disease (most likely not only affecting the lower respiratory tract but a multitude of different internal organs), particularly in highly vaccinated countries, particularly in vaccinated individuals who have weak and/or untrained innate immunity (e.g., those who were vaccinated prior to experiencing natural infection, i.e., the elderly and frail). This would not have happened in the absence of the COVID-19 mass vaccination campaign.

Of course, this virulent variant will not be able to survive for long. Healthy unvaccinated individuals (with robust, uninhibited innate immunity that has become increasingly trained to deal with more and more infectious SARS-CoV-2 variants) will be able to eliminate this variant by virtue of sterilizing immunity, despite its virulence in COVID-19 vaccinees. (Group 1). Our hope is that many vaccinated individuals will have been sufficiently exposed to natural infection prior to vaccination to allow for enough training of their innate immune system to weather the storm, especially if they also receive excellent medical management (Group 2). Individuals who received at least two or three vaccine doses (i.e., in the case of mRNA-based or non-mRNA-based vaccine, respectively) prior to natural infection and subsequently experienced a vaccine-BTI (i.e., primarily those who were vaccinated first, i.e., the elderly and vulnerable individuals) are at greatest risk of succumbing to the new emerging variant(s) that can overcome the PNNAb-mediated virulence-inhibiting effect (Group 3). Groups 1 and 3 will prevent the highly virulent variant from circulating for long, because they will either fail to shed the variant (in the case of group 1) or soon run out of accessible susceptible hosts (in the case of group 3), and the pandemic will finally end, not thanks to herd immunity but thanks to eradication of the virus.

Note: Healthy vaccinees who only received a single injection of an mRNA-based COVID-19 vaccine or no more than 2 injections with a non-mRNA-based vaccine prior to developing a

symptomatic vaccine-BTI are thought to have preserved their capacity to train their cell-based innate immune system.

Why is it important to take Dr. Vanden Bossche's excellent analysis very seriously?

For the above reasons, Dr. Vanden Bossche has been extremely worried about the COVID-19 mass vaccination campaign. This is why he has felt obligated to warn scientists, physicians, and the general public about this highly likely outcome---so that all can prepare for such an outcome. Even if his prediction turns out to be wrong (which he greatly doubts, based on his understanding of the science involved), he wants people to have a chance to prepare in case he is correct (which he thinks is highly likely). Even if other scientists and physicians doubt that GVB's analysis is correct, they must acknowledge that his analysis represents a responsible and scientifically sound analysis about which physicians and citizens deserve to know and for which physicians and citizens deserve opportunity to prepare.

In my opinion, GVB's concerns and the conclusion of his analysis are correct. The most likely reason for the unwillingness of the promoters of the mass vaccination campaign to engage in dialogue about GVB's concerns and conclusion is that they know (or at least worry) that their understanding of the virology, immunology, vaccinology, and evolutionary biology of the COVID situation is not nearly as deep and wise as GVB's understanding. Compared to GVB's understanding, their understanding, in my opinion, has been simplistic, far less scientific, and less accurate. They should learn from GVB, not ignore or belittle his excellent analysis.

In my opinion, their unwillingness to engage in dialogue is not only scientifically, medically, and intellectually irresponsible, but also cruel. It is cruel to leave the public dangling, confused, miseducated, and misled about the realities of the COVID-19 situation. It is cruel to leave the public unprepared to deal with the profoundly worrisome situation the mass vaccination campaign has created. It is cruel and dishonest to not inform the public of the mistakes the promoters of the mass vaccination campaign have made and what can be done at this point to proactively and optimally address the threatening situation that has resulted.

The reality is, the mass vaccination campaign has transformed the initial COVID-19 pandemic into a far more serious, prolonged, and life-threatening pandemic, and, in addition, has created a tremendous amount of vaccine injury at the individual level—-such that far more cumulative deaths and morbidity will occur than would have occurred in the absence of the mass vaccination campaign. Enormous mistakes have been made and have resulted in enormous threats to huge numbers of people.

Good physicians admit their mistakes, take responsibility for them, work to ensure that damage done is optimally addressed, and take steps to ensure that mistakes are not repeated. The promoters of the mass vaccination campaign have not performed these tasks.

What, specifically, can be done, if GVB is correct and a highly virulent, highly threatening variant appears?

Many important proactive steps can be taken. For details, please see the following article (and an ADDENDUM to it), which is posted on my website: In Anticipation of a Highly Virulent SARS-CoV-2 Variant

FOOTNOTES:

[1]**Steric Immune Refocusing (SIR):** For a detailed explanation of the SIR phenomenon (and the IgG4 situation), please see GVB's book and his most recent article: https://www.trialsitenews.com/a/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-19-vaccinated-populations.-645407ab.

In the context of SARS-CoV-2, SIR refers to the redirection of the immune system to produce neutralizing antibodies against conserved immune-subdominant epitopes[2] of the spike protein when pre-existing poorly neutralizing Abs sterically hinder (physically block) immune recognition of the variable immune-dominant epitopes of the spike protein.

The SIR phenomenon, which became evident during the Omicron era, has contributed greatly to delaying natural selection of immune escape variants while expanding the scale thereof. This explains why loss of protection from moderate disease (Omicron) has not abruptly shifted to enhanced virulence (as GVB initially predicted) but first transitioned to mitigation and subsequently even to prevention of Covid-19 disease altogether. It seems as though the immune system, at a population level, first needs to mount a high level of immune selection pressure on viral pathogenicity in order for the virus to unleash a highly virulent variant. As currently circulating, highly infectious variants have induced a nearly unparalleled level of immune protection in vaccinees, second only to protection induced in unvaccinated individuals by natural infection (!), it is reasonable to assume that the virus has now entered the final stage of evolving toward variants combining high intrinsic infectiousness with highly virulent properties in vaccinees.

SIR is a hallmark of PNNAb-dependent vaccine-BTIs and results from binding of non-neutralizing antibodies to the immunodominant epitopes of a monovalent antigen, thereby facilitating immune recognition of immunosubdominant or immunorecessive domains and priming broadly neutralizing antibodies with high avidity but low affinity (note: induction of such antibodies have also been reported upon mRNA vaccination: https://www.ncbi.nih.gov/pmc/articles/PMC9886553/)

SIR appears to be a tool nature uses to shape the evolutionary dynamics of the interaction between the virus and the host immune system such as to leave the host's adaptive immune system a chance to adapt to vaccine-BTIs and gradually optimizing protection from disease in exchange for granting the virus a license to prolong its propagation and spread (at the benefit of improving sterilizing immune capacity in the unvaccinated before eliminating those devoid of this capacity). GVB had not anticipated (and could not have anticipated) this phenomenon when he initially predicted that a highly virulent variant would likely appear by the early fall of 2022. By now, the new SIR-induced Abs are ceasing to be involved in shaping the evolution of

highly infectious variants into highly infectious variants with highly virulent properties in COVID-19 vaccinees. At this stage, Ab-independent vaccine-BTI caused by highly infectious variants in the context of (declining titers of) pre-existing vaccine-induced Abs are educating the immune system to re-orient its target from an immunorecessive S-associated domain to an immunosilent antigenic site within Spike-NTD.

[2]**What is an epitope?** An epitope is a part of an antigen (a part of the spike protein, in the context of SARS-CoV-2) that the immune system recognizes and reacts to. It is an immunogenic part of the antigen---a part that triggers an immune response. On the spike protein, for example, there are dominant, highly immunogenic epitopes and there are many subdominant, much less immunogenic epitopes.

[3]**How do SIR and high levels of IgG4 predispose to autoimmunity and malignancy?** As the SIR phenomenon continues, antibodies are produced against epitopes that are increasingly more conserved and less immunogenic and more closely resemble "self" epitopes and "altered self" epitopes. These SIR-created antibodies slowly and ultimately mature into SARS-CoV-2-specific isotype-switched IgG4 antibodies.

High titers of these IgG4 antibodies tend to cross-react with "self" epitopes (on our healthy cells) and "altered self" epitopes on cells that are becoming malignant.

When IgG4 antibodies attach to "self" epitopes on healthy cells, this results in failure of self-epitopes to normally activate self-epitope-specific regulatory T cells (T regs) that, in turn, normally and protectively down-regulate the activation and proliferation of self-reactive T cells. That is, normally, these T regs protect healthy cells from autoimmune destruction by self-reactive T cells---but the IgG4 antibodies interfere with that protective process, and autoimmunity results.

When previously healthy cells become malignant, the normal "self" epitopes that are expressed on their surface become altered and become "altered self" epitopes. When IgG4 antibodies attach to "altered self" epitopes on the surface of malignantly transformed cells, this prevents ADCC (antibody dependent cellular cytotoxicity)-mediated immune recognition of these malignant cells by NK cells. This results in failure of NK cells to kill malignantly transformed cells.

So, the high levels of IgG4 antibodies that follow the SIR phenomenon predispose highly vaccinated individuals to autoimmunity and malignancy. This may be one mechanism by which highly vaccinated individuals are developing new cancers (i.e., early onset cancers) and new autoimmune diseases. On the other hand, "turbo cancers" (or rampant relapse of previously controlled cancer) or relapse of previously controlled autoimmune disease are thought to be triggered by hyperactivation of APCs and downstream suppression of CD8+ T cells following vaccine-BTI with highly infectious variants (that are asymptomatic in terms of Covid-19)..

ACKNOWLEDGEMENTS:

It is important to acknowledge that the immunology involved in the COVID-19 situation is extraordinarily complex and incompletely understood. GVB is still learning and still improving the accuracy and breadth of his understanding of that complexity.

I would like to acknowledge and thank Geert for the generous help and patient teaching he has extended to me, as I have tried to understand his analysis and the COVID situation in general. My understanding of GVB's analysis is incomplete and represents, at best, a simplified version of his analysis. My intention and hope is that this simplified version will make it easier for the reader to appreciate and understand GVB's more complex and complete analysis. My hope, too, is that this article will stimulate and facilitate much needed scientific dialogue about the COVID mass vaccination campaign and the COVID situation in general.

Also, I would like to acknowledge the extraordinary work of the human immune system itself. **The real hero of the COVID-19 pandemic is the immune system**, which has ingeniously and tirelessly worked to protect both vaccinated and unvaccinated individuals from the consequences of the misguided mass vaccination campaign.

The vaccinated and unvaccinated have needed to be protected in completely different ways. Because the innate immune system of vaccinees has, unfortunately, been sidelined by COVID vaccination, the immune system has tried to protect the vaccinated by employing the four main mechanisms reviewed in this article. Simultaneously, the immune system's efforts to protect the vaccinated have resulted in valuable training experiences for the innate immune system of unvaccinated individuals.

The immune system has used its thousands of years of experience and adaptation to protect Humanity. And, of course, the immune system has kindly done all of this work for free---despite being marginalized and insulted by the arrogant and erroneous claims made by promoters of the mass vaccination campaign that "vaccine-induced immunity is superior to natural immunity."

Unfortunately, many people will pay a huge price for what the mass vaccination campaign has wrought. The immune system will not be able to save everyone. In order to save Humanity as a species, the immune system has had no choice but to allow the final step (emergence and propagation of a more virulent variant) to occur. (Read Geert's article to see what I mean.) Even if the immune system could figure out a way to prevent the propagation of a highly virulent variant (when contracted by vaccinees), the price to pay would undoubtedly be too high, especially in the longer run. Accordingly, the immune system has done the best that is possible under the difficult/challenging circumstances created by the mass vaccination campaign. It has been doing what it needs to do to save Humanity from a misguided mass vaccination campaign.

My hope is that people, globally---both the vaccinated and the unvaccinated---will come to appreciate the heroic and altruistic work the immune system has been doing—and, then, more importantly, try to emulate that wise behavior by working kindly together to carefully protect

each other, correct the mistakes that have been made, ensure that these mistakes not be repeated, and apply lessons learned from the COVID-19 pandemic to the other grave problems that are currently facing Humanity.

A SUMMARIZING OUTLINE OF THIS ARTICLE:

- For three main reasons highly vaccinated individuals, in particular, have been experiencing frequent SARS-CoV-2 breakthrough infections (BTIs). (BTIs are infections that occur when the virus "breaks through" the immunity that a previously infection-primed individual had developed by that point in time. When a virus breaks through naturally-acquired immunity, a "natural BTI" occurs; when a virus breaks through vaccine-acquired immunity, a "vaccine-BTI" occurs). Highly vaccinated individuals are experiencing frequent vaccine-BTIs because:

    - Their vaccine-induced potentially neutralizing antibodies (pNAbs)---e.g., the vaccine-induced pNAb against the original Wuhan strain of SARS-CoV-2---have been unable to neutralize the many new "immune escape" variants that have subsequently appeared, because these variants have mutated in a way that enables them to "escape" from (be resistant to) extant pNAbs. These immune escape variants appeared on the scene because their resistance to existing pNAbs gave them a competitive "fitness advantage" which, in turn, led to the natural selection and dominant propagation of these variants.

      Note: Neutralizing antibodies work by attaching to the receptor binding domain (RBD) of the spike protein on the SARS-CoV-2 virus, thereby blocking/preventing the RBD from attaching to the ACE-2 receptor on the surface of the human cell, thus preventing (or at least thwarting) viral entry into the cell. The reason for calling these antibodies "potentially" neutralizing antibodies (pNAbs) is because they are able to neutralize the virus provided the antibodies match with the viral lineage the immune system is exposed to.

      It may be helpful to realize that "neutralizing antibodies" may vary regarding the extent to which they are neutralizing. Some neutralizing Abs, theoretically, might be 100% neutralizing (optimally neutralizing) and able to totally prevent viral entry into cells (and thereby prevent viral replication within that cell and prevent transmission of virus from that infected person to a new susceptible person); other neutralizing Abs might be more weakly neutralizing and allow at least some viral entry (i.e., allow at least some viral replication and transmission). More importantly, even if a vaccine-induced pNAb were 100% neutralizing, it takes a few weeks for that optimal pNAb to mature to the point of being 100% neutralizing. In the meantime, the immature version of that pNAb is only suboptimally neutralizing. This is important because when a mass vaccination campaign is implemented in the midst of an active pandemic, the virus, which is

ubiquitously circulating in the population, will be exposed to the immature, suboptimally neutralizing pNAb. It is exposure to these suboptimally neutralizing pNAb, at a population level, that leads to the natural selection and dominant propagation of new variants that are able to overcome these immature pNAbs and therefore have a fitness advantage. By the time a potentially optimal pNAb matures, a variant has already emerged that is resistant not only to the immature pNAb but also to the mature pNAb, rendering the mature pNAb to be suboptimally effective, if effective at all.

- Their polyreactive non-neutralizing antibodies (PNNAbs), which were stimulated into binding to Spike-NTD because of the diminished neutralizing capacity of the pNAbs, have been infection-enhancing (i.e., they have been facilitating entry of virus into susceptible host epithelial cells) and have thereby accelerated production of viral progeny.

  Note: PNNAbs do not bind to the RBD of the SARS-CoV-2 virus. Instead, they bind to the N-terminal domain (NTD) of the spike protein (the Spike-NTD). When PNNAbs bind to the NTD of the spike protein, this results in a conformational change in the spike protein---specifically, the RBD is flipped into the "open" position and this makes it easier for the RBD to attach to the ACE-2 receptor on the host cell, which, in turn, results in easier entry of virus into the host cell. This is how PNNAbs are "infection-enhancing."

- Their cell-based innate immune system (CBIIS) has been sidelined because: non-replicating (non-live virus) vaccines do not train the cell-based innate immune system; and SIR (see below), which is a hallmark of mRNA vaccines and vaccine-BTIs, sidelines the cell-based innate immune response.

  Note: The cell-based innate immune system provides the extremely important first line of defense against viral infection. Natural killer (NK) cells, in particular, provide excellent and broad protection. NK cells quickly kill cells that have become infected, killing the virus in the process. Sidelining of the cell-based innate immune system severely impairs a person's ability to control viral infection. The COVID-19 vaccines sideline the cell-based innate immune system and render the vaccinee dependent on the adaptive immune system (the part of the immune system that produces virus-specific antibodies).

- Highly vaccinated individuals have been heavily relying on four main immune mechanisms to protect them from their frequent vaccine-BTIs (breakthrough infections that have occurred despite or even because of vaccination). Although these mechanisms have been providing significant temporary protection from severe disease, these mechanisms are unstable, unsustainable, will inevitably fail, and are causing serious problems, especially for vaccinees devoid of trained innate immunity:

- **The SIR phenomenon (Steric Immune Refocusing):[1-3]**

  In the context of SARS-CoV-2, SIR refers to the redirection of the immune system to produce neutralizing antibodies against conserved immune-subdominant epitopes[2] of the spike protein when pre-existing poorly neutralizing Abs (outdated pNAbs) sterically hinder (physically block) immune recognition of the variable immune-dominant epitopes of the spike protein. That is, steric hindrance occurring at the level of immune-dominant epitopes forces the immune system to refocus on immune-subdominant epitopes.

  SIR-created broadly neutralizing, cross-neutralizing antibodies have been providing temporary protection. These SIR-created neutralizing antibodies have partially compensated for the absence of effective pNAbs. The trade-off, however, is that these SIR-created antibodies have been suboptimally neutralizing (particularly as their titers have rapidly fallen because of low antibody affinity) and this has triggered large-scale immune escape involving co-emergence and co-circulation of increasingly infectious "immune escape" variants. Indeed, the vast array of highly infectious Omicron variants has come about because of the suboptimal population-level immune pressure associated with the SIR phenomenon.

  Note: BTIs in unvaccinated individuals (i.e., natural-BTIs) do not trigger SIR and, therefore, do not promote viral immune escape. It is vaccine-BTIs that trigger SIR and thereby promote viral immune escape. Natural-BTIs do not trigger SIR because of the contribution of cell-based innate immunity, which diminishes the production rate of viral progeny, thereby enabling abundant opsonization of progeny virions by pNAbs. This promotes fast uptake of progeny virus into APCs (antigen presenting cells).

  Another trade-off is that the SIR phenomenon has ultimately predisposed vaccinees to autoimmunity and malignancy.[3] Please see GVB's recent article: https://www.trialsitenews.com/a/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-19-vaccinated-populations.-645407ab

- **The anti-inflammatory effect of isotype switched IgG4 antibodies:** SIR-created neutralizing antibodies have undergone isotype-switching and matured (in delayed fashion) into IgG4 antibodies. IgG4 antibodies have an anti-inflammatory effect. Accordingly, when vaccinated individuals with high titers of SARS-CoV-2 specific IgG4 have experienced vaccine-BTIs, their disease symptoms have been reduced by the anti-inflammatory effects of these IgG4 antibodies.

  Unfortunately, there is a particularly worrisome trade-off for the protective anti-inflammatory effect of a vaccinee's high levels of IgG4. High levels of IgG4

predispose vaccinees to autoimmunity and malignancy.[2, 3] Please see GVB's recent article: https://www.trialsitenews.com/a/immunological-correlates-of-vaccine-breakthrough-infections-caused-by-sars-cov-2-variants-in-highly-c-19-vaccinated-populations.-645407ab

Note: Whereas low levels of low-affinity, cross-neutralizing anti-spike antibodies trigger additional SIR events in the context of more infectious Omicron descendants thereby amplifying viral immune escape, eventual high levels of IgG4 in the context of highly infectious Omicron descendants disable the SIR phenomenon.

- **Activation of CTLs (Cytolytic T Lymphocytes):** Vaccine-BTIs with *highly infectious* Omicron descendants facilitate viral uptake by APCs (antigen presenting cells), which, in turn, results in activation of MHC Class I unrestricted cytolytic T lymphocytes (CTLs) and eventual inhibition of SIR. These CTLs quickly kill virus infected cells, rapidly abrogate viral shedding and can protect vaccinated individuals from COVID-19 disease altogether. This CTL-mediated reduction of viral inter-host transmission (transmission from an infected host to a new susceptible host) has been thwarting the opportunity of the virus to optimally replicate via inter-host transmission, thereby, threatening viral survival. This threat to the virus is accompanied by immune selection pressure on viral *trans* infectivity (the ability of the virus to easily transfer from dendritic cells to cells in the lower respiratory tract and other internal organs) and will thereby favor natural selection of future variants that are able to cause enhanced severe disease in vaccinees. More on this later.

  Furthermore, The CTLs that have been killing virus-infected cells will also ultimately kill the APCs that activated the CTLs in the first place. Moreover, hyperactivation of APCs and/or their elimination by activated CTLs will eventually lead to generalized immune suppression and the emergence or resurgence of other, non-COVID-19-related acute or chronic infectious diseases.

- **The virulence-inhibiting effect of PNNAbs:** The PNNAbs, which bind to Spike-NTD as a result of diminished neutralizing capacity of vaccine-induced antibodies (pNAbs), have a virulence-inhibiting effect (in addition to their infection-enhancing effect). PNNAbs attach to virus that is tethered to migrating dendritic cells, thereby preventing transfer of virus from dendritic cells (DC) to cells in the lower respiratory tract (LRT) and other internal organs---i.e., when at high levels PNNAbs inhibit *trans* infection in the LRT and other internal organs and, thereby, protect vaccinated individuals from *severe COVID-19 disease.*

  Unfortunately, as vaccine-BTIs cease to trigger SIR and previously SIR-induced, broadly neutralizing Ab titers wane, increasingly infectious variants will successively dominate and concentrations of virulence-inhibiting PNNAbs bound

to DC-tethered virions will inevitably drop into the suboptimal range (as explained in the REVIEW section of this article), at which point they will become less effective; will cause a sufficiently large fraction of the population to place sub-optimal immune pressure on the virus; and will eventually make highly vaccinated populations exert immune selection pressure on viral virulence. This will drive natural selection of new emerging variants that have the capacity to overcome the virulence-inhibiting effect of these PNNAbs and cause PNNAb-enhanced severe disease in highly vaccinated individuals. (Such highly virulent variants could offset any fitness cost resulting from additional glycosylation by binding to PNNAbs via their unaltered, conserved enhancement site located within Spike-NTD.) These variants would therefore not be outcompeted by currently circulating, highly infectious (but not highly virulent) variants. In addition, they would spread more rapidly as enhanced *trans* infection of progeny virus would result in diminished internalization of virus-pNAb complexes into APCs, and therefore impair cytolytic CD8+ T cell activity. Diminished killing of virus-infected cells will enhance viral transmission and rapidly enable a highly infectious and highly virulent variant to prevail.

- The above four protective immune mechanisms have created an impression that the pandemic is subsiding, becoming milder and less threatening, and is heading into a relatively benign, or at least easily manageable, endemic phase. But this is a false impression. This "calming" of the pandemic has been falsely reassuring and will be followed by a "storm" of severe disease, particularly affecting the highly vaccinated---because these four protective mechanisms are unstable, unsustainable, will ultimately fail and a highly virulent (as well as highly infectious) variant will successfully emerge and prevail in highly vaccinated populations. In addition, increased IgG4 levels combined with more infectious or highly infectious immune escape variants will predispose highly vaccinated individuals to autoimmunity and early-onset cancers or generalized immune suppression (resulting in turbo cancers or flare-ups of chronic infectious or underlying autoimmune diseases), respectively.

- **Why has the mass vaccination campaign resulted in the set of adjustments described above?**

  Why has the mass vaccination campaign resulted in the above-described set of immune adjustments? The bottom line is that the human immune system is designed to protect the human species, including up to the point of protection from extinction.

  Normally, populations of natural host species develop herd immunity (collective sterilizing immunity) in the course of a pandemic of a (new) virus causing acute self-limiting infection (like SARS-CoV-2 virus). That herd immunity brings the pandemic to an end. Unfortunately, the mass vaccination campaign prevents development of herd immunity. Individuals who were vaccinated prior to experiencing productive infection do not develop sterilizing immunity and therefore do not contribute to herd immunity.

Unvaccinated infection-primed individuals develop sterilizing immunity and thereby contribute to herd immunity.

By preventing the development of herd immunity, the mass vaccination campaign presented the immune system with a huge problem, because without development of herd immunity the COVID-19 pandemic would continue indefinitely and become increasingly threatening to the human species. Given the fact that the mass vaccination campaign prevents herd immunity, the best option for the immune system and for the human species, at least in the long run, has been to: optimize opportunity for the unvaccinated (Group 1) and for those vaccinated individuals who got productively infected prior to vaccination so as to sufficiently train their cell-based innate immune system (Group 2) to develop sterilizing immunity; and ultimately, eventually allow those who are heavily vaccinated and devoid of trained cell-based innate immunity (Group 3) to succumb to a virulent variant. That is certainly a terribly sad and tragic reality for Group 3, but this appears to be what the set of immune adjustments described in this article accomplishes, in the immune system's effort to save the human species from the existential threat posed by the mass vaccination campaign.

The four protective immune adjustments have, indeed, temporarily protected vaccinated individuals left with untrained cell-based innate immunity from severe COVID-19---though not without predisposing them to autoimmunity, malignancy, and increased susceptibility to infection. In the meantime, the vast array of highly infectious variants spawned by the mass vaccination-mediated SIR phenomenon has provided the cell-based innate immune system of unvaccinated individuals with valuable training, practice and experience, so that they will be able to adapt to variants exhibiting different levels of infectiousness, including highly infectious variants, regardless of their virulence. Also, the four immune adjustments have ultimately provided fertile opportunity for the eventual and inevitable natural selection and rapid propagation of highly infectious variants capable of triggering enhanced virulence in vaccinees devoid of trained cell-based innate immunity. Once these variants emerge, the pandemic will end because the unvaccinated (Group 1) and the vaccinated who---prior to their vaccination---had already started the training of their cell-based innate immune system (CBIIS) will have sterilizing immunity, whereas the other vaccinees (Group 3) will no longer transmit virus to the population once they become hospitalized because of their enhanced severe disease. Sterilizing immunity, combined with the isolation and/or removal of individuals who cannot clear the viral infection, will cause the pandemic to end because this combination will reduce transmission to a level where the virus can no longer survive.

Unfortunately, because of the mass vaccination campaign, the sacrifice of group 3, sadly and tragically, gives the human species the best chance for long term survival.

- The immune system would not have needed to make the above-described set of adjustments if the pandemic had been managed in a natural way---i.e. without introduction of mass vaccination in the midst of an active pandemic. **The immune**

system should never have been put in this position! The immune ecosystem should never have been violated in this way, or in any way! The human species should never have been subjected to the COVID-19 mass vaccination campaign!

- The reality is, the mass vaccination campaign has transformed the initial COVID-19 pandemic into a far more serious, prolonged, and threatening pandemic, and, in addition, has created a tremendous amount of vaccine injury at the individual level—-such that far more cumulative deaths and morbidity will occur than would have occurred in the absence of the mass vaccination campaign. Enormous mistakes have been made and have resulted in enormous threats to huge numbers of people.

<u>SUPPLEMENTAL INFORMATION</u>: ABOUT MUTATIONS, FITNESS ADVANTAGE, NATURAL SELECTION, DOMINANT PROPAGATION, AND THE DIFFERENCE BETWEEN OPTIMAL AND SUBOPTIMAL IMMUNE PRESSURE:

Viruses normally develop random mutations. Some viruses mutate more quickly, frequently, and greatly than others. The SARS-CoV-2 virus is highly mutable---as we have clearly seen, especially during the Omicron era.

Some mutations might render a particular variant more (or less) intrinsically infectious; other mutations might render a variant more (or less) intrinsically virulent. Some mutations provide a fitness advantage; others do not.

I hasten to add that the extent to which a given virus/variant is highly infectious or highly virulent depends not only on the intrinsic infectiousness and intrinsic virulence of the virus/variant, but also on the status of the exposed person's immune system. For example, the "highly virulent" variant that GVB worries about will be extremely threatening to an individual who is fully vaccinated and was vaccinated before becoming productively infected with SARS-CoV-2; but will not be a threat to healthy unvaccinated individuals living in highly vaccinated populations whose innate immune systems are robust, well-trained, and well-practiced.

A new emerging variant that has a mutation(s) that has been naturally selected based on collective immune selection pressure on viral infectiousness or neutralizability give(s) it a "fitness advantage" and will be better equipped to potentially survive, compete, and thrive in that particular immunological environment. This is because those mutations give that variant a fitness advantage to successfully outcompete other variants, which did not incorporate such mutations. The naturally selected variant may therefore become the dominantly circulating variant (in the case of natural selection of mutations situated within a variable antigenic domain) or co-circulate with other selected variants (in the case of natural selection of mutations situated within a more conserved antigenic domain). Such a variant will likely emerge if the immune selection pressure exerted by the population on viral fitness exceeds a given threshold.

If a sufficient percentage of an immunized population (e.g., 70% in the case of some pandemics) has the immune capacity to exert sufficient immune pressure on the virus to efficiently kill it,

none of viral variants that are randomly generated upon viral replication will enjoy a large-scale fitness advantage in the context of the collective immune response of the host population. None of these 'fitter' (i.e., more infectious) incipient variants will therefore experience immune selection pressure and hence, none of them will be naturally selected to dominantly (co-)circulate. Consequently, all of them will be outcompeted by the ancestral viral lineage. If a high percentage of the population is only capable of mounting a suboptimal immune response against viral infection, the circulating virus will experience large-scale immune *selection* pressure on its infectiousness and immune escape variant(s) exhibiting a higher level of viral fitness/ infectiousness become naturally selected. This will drive dominant propagation and (co-)circulation of that/those variant(s). In fact, it is suboptimal population-level immune pressure on viral infectiousness or viral *trans* infection that triggers immune selection pressure on viral infectiousness or virulence, respectively and drives the natural selection of immune escape variants that are able to overcome the suboptimal immune pressure on viral infectiousness and virulence. It's important to note that in order for a more virulent variant to qualify for natural selection, it should exhibit a level of infectiousness that is comparable with that of the circulating virus. In other words, immune escape variants that are highly virulent but not sufficiently infectious will never be subject to natural selection, even if the host population exerted high immune selection pressure on viral virulence.

In short, optimal population-level immunity puts lethal (optimal) immune pressure on an incipient, emerging, potentially threatening viral variant and prevents it from spreading or becoming virulent, while suboptimal population-level immunity puts immune *selection* pressure on an emerging threatening variant and provides opportunity for it to thrive in ways that may or may not cause severe disease.

What typically happens during a naturally evolving pandemic?

During a naturally unfolding pandemic (i.e., a pandemic that is not treated un-naturally by implementing a mass vaccination campaign in the midst of the active pandemic), an increasing percentage of the population develops sterilizing immunity to the virus after having contracted . productive, asymptomatic or symptomatic infection. Those individuals who develop sterilizing immunity (after an initial exposure to the virus) will be able to kill the virus when that virus subsequently tries to infect them. Once a sufficient percentage of the population develops sterilizing immunity (e.g., 70% in the case of some pandemics, depending on the basic reproduction number (Ro) of the virus as assessed in a particular host population), "herd immunity" is established, i.e., viral transmission, is too low to cause symptomatic infection in the not yet exposed part of the population, and the pandemic transitions into the endemic phase (due to the herd immunity).

What is described above represents "optimally protective immunity" that puts "optimal immune pressure" on the virus, at both an individual and a population level. This optimally protective immunity competently and quickly deals with emerging, potentially threatening new variants. In other words, optimal immune pressure prevents incipient potentially threatening new variants from being selected and spreading.

What happens when a mass vaccination campaign is implemented in the midst of an active pandemic?

In contrast, when a pandemic is treated by implementing a mass vaccination campaign using Spike-based vaccines in the midst of the active pandemic, the immune system becomes only suboptimally protective (rather than optimally protective) and puts suboptimal immune pressure (as opposed to lethal optimal immune pressure) on the virus. When this happens at a population level, immune selection pressure is exerted on the virus.

Large-scale suboptimal immune pressure therefore drives the natural selection and dominant propagation of "immune escape" variants. Natural immune selection occurs, for example, when suboptimal immune pressure partially thwarts viral replication and transmission but without preventing the virus from generating and transmitting viral progeny. Under circumstances wherein collective, suboptimal immune pressure is threatening viral replication, a new *more infectious* immune escape variant will be selected; because of its higher level of infectiousness, it will readily outcompete the less infectious, previously circulating viral lineage and dominantly propagate. That is what we have seen following massive implementation of *infection-prevention* measures and *infection-prevention* immune interventions (with Spike-based vaccines) during the pandemic ---a succession and vast array of naturally selected new dominant variants, each being more infectious than preceding variants.

In this context of suboptimal population-level immune pressure (as opposed to the context of optimal immune pressure), what happens when highly infectious **and** highly virulent variants emerge---variants that are able to spread and overcome the virulence-inhibiting effect of the PNNAbs and thereby enhance *trans* infection in the LRT (lower respiratory tract) and other internal organs? For one thing, this variant is not quickly killed. Its replication and transmission is partially thwarted (diminished) by CTL-mediated abrogation of viral shedding. This mechanism, however, fails to enable the collective imposition of immune selection pressure on the virus's potential for shedding, as the ongoing asymptomatic transmission of a highly infectious virus ensures adequate viral replication and transmission. These highly infectious, highly virulent immune escape variants have the capacity to naturally select individuals that have a 'fitness advantage' in that they generate sterilizing immunity and thereby contribute to herd immunity. Because herd immunity is critically important for the preservation/survival of the host species, these highly virulent immune escape variants are naturally selected to spread and cause enhanced severe disease in those who can't contribute to herd immunity for lack of sterilizing immunity (i.e., a large part of the C-19 vaccinees). As mentioned earlier, selection of immune escape variants that are capable of causing PNNAb-enhancement of severe disease would not have succeeded under conditions of a naturally evolving pandemic as the vast majority of the population would have acquired sterilizing immunity naturally.

The bottom line is that the suboptimal population-level immune pressure created by the COVID mass vaccination campaign resulted in conditions that, first, allowed the successive (co-)emergence and (co-)circulation of increasingly infectious immune escape variants and, now, is about to allow highly virulent variant to be naturally selected and spread. This would not have happened if the pandemic had been allowed to evolve naturally. The optimal immune pressure

during a naturally evolving pandemic would have resulted in massive sterilizing immunity and thereby prevented natural selection of immune escape variants.

The eventual appearance of new immune escape variants that acquire a sufficiently high level of viral infectiousness to spread and incorporate adequate mutations to acquire a high level of viral virulence in COVID-19 vaccinees is an inevitable (and predictable) outcome when a mass vaccination campaign with vaccines targeted at preventing infection (i.e., Spike-based) is implemented in the midst of an active pandemic---because large-scale suboptimal population-level immune pressure on spike protein initially generates immune selection pressure on viral infectiousness and subsequently (i.e., since the advent of vaccine-BTIs with Omicron) on viral virulence.

FIGURE 1 (per GVB):

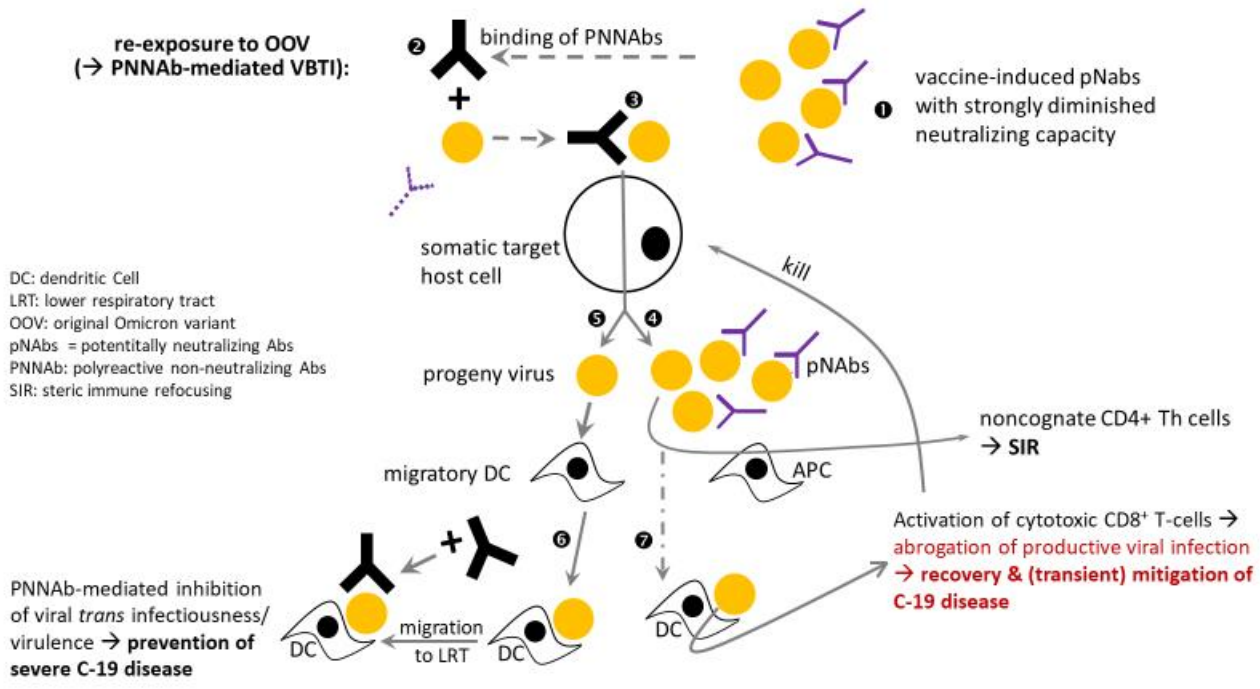


Fig. 1: Pathogenesis of PNNAb-dependent VBTI (vaccine-BTI). Diminished neutralizing capacity of pNAbs to OOV triggers binding of PNNAbs (❶,❷); binding of PNNAbs to OOV provokes PNNAb-dependent VBTI (❸). pNAbs bind in relatively low concentration to progeny virus because of the enhanced viral production rate in target host cells (❹). As this likely delays uptake of progeny virions into APCs, PNNAb-dependent VBTIs are thought to trigger SIR.

PNNAb-mediated enhancement of viral infectiousness further promotes adsorption of infectious progeny virus onto migratory DCs (❺, ❻), thereby enabling PNNAbs to prevent severe disease. Abundant uptake of non-adsorbed virus in patrolling DCs/APCs (❼) ultimately triggers cytotoxic killing of virus-infected host cells and promotes recovery and mitigation of disease.

FIGURE 2 (per GVB):

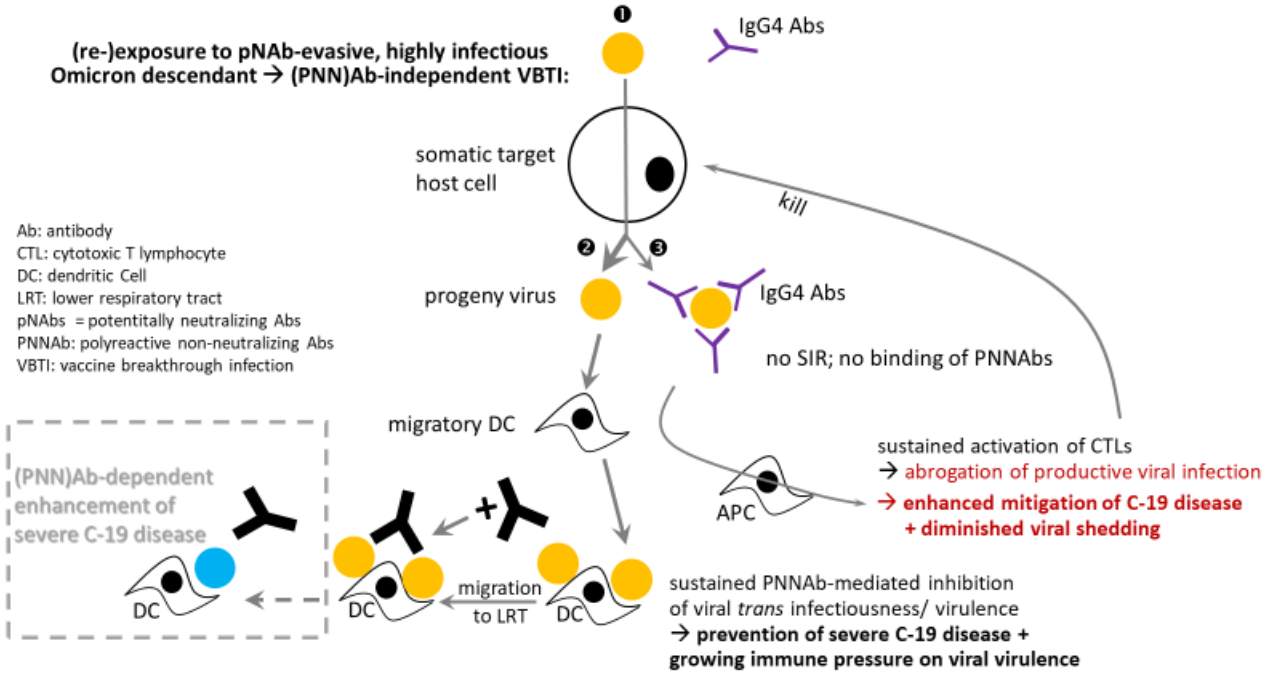


Fig. 2: Pathogenesis of (PNN)Ab-independent VBTI. High intrinsic infectiousness of co-circulating Omicron descendants precipitates infection of target host cells (❶) and enhances the production rate of highly infectious progeny virus. The latter predominantly adsorbs onto tissue-resident DCs and thereby causes pre-existing PNNAbs to only bind in relatively low concentration to progeny virus tethered to migratory DCs (❷). Diminished virulence-inhibiting capacity of pre-existing PNNAbs causes highly C-19 vaccinated populations to raise immune selection pressure on viral

virulence while still protecting vaccinees from severe disease. As enhanced virus adsorption to DCs results in relatively low concentrations of free/non-adsorbed progeny virions, IgG4 Abs bind to the latter in relatively high concentration and thereby expedite uptake of IgG4 Ab-virus complexes into patrolling APCs (❸). Enhanced uptake of IgG4 Ab-virus complexes into APCs facilitates strong activation of cytotoxic T cells (CTLs) and thereby enables elimination of virus-infected host cells while preventing SIR. As a result, PNNAb-mediated population-level immune selection pressure on viral virulence will gradually increase upon subsequent VBTIs caused by circulating, highly infectious variants. Dominant circulation of immune escape variants with an ever-increasing intrinsic infectiousness will ultimately cause the highly vaccinated population to raise the immune selection pressure on viral virulence beyond the threshold triggering selection of new, highly virulent variants that enable large-scale occurrence of PNNAb-dependent enhancement of severe disease (ADESD).

Note: The artwork on the front page is Honore Daumier's depiction of Don Quixote, who was undaunted in his determination to right wrongs and create Social Beauty, despite the insistence of most that he was a fool to try.

Rob Rennebohm, MD

September 30, 2023