Understanding Dr. Vanden Bossche's Analysis of the COVID-19 Immune Escape Pandemic

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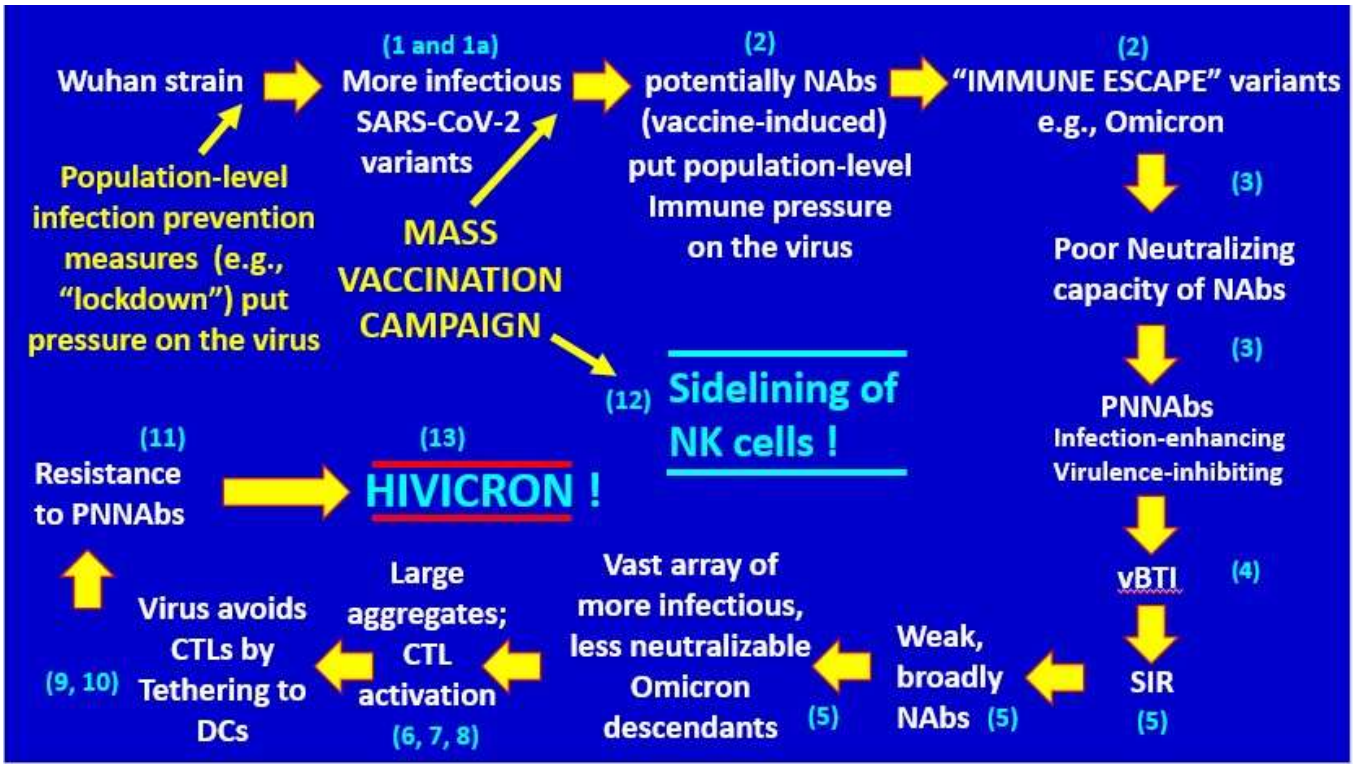
This article summarizes Dr. Geert Vanden Bossche's complex analysis of the COVID-19 situation. Figure 1 shows the sequence of events (1-13) that, according to Dr. Vanden Bossche, has predictably led to the imminent arrival of a **hi**ghly **vi**rulent Omicron variant ("HIVICRON"). A step-by-step explanation of each of the 13 events follows.

FIGURE 1



[Note to Readers: The article is composed of two parts, a MAIN TEXT and an APPENDIX. The Main Text, to the extent possible, uses language that is friendly to the general public. *Italicized sentences/paragraphs within the Main Text convey deeper scientific details that are primarily intended for readers who are already well-versed in immunology and virology.* The Appendix, which may be found at the very end of this article, provides background information for readers with limited knowledge of immunology and virology, including a helpful Table, and two Medical

Illustrations. The alphabetical footnotes in the Main Text indicate that more information may be found in the Appendix. The numerical footnotes refer to relevant articles in the medical literature (listed under REFERENCES).

ABBREVIATIONS:

- **NK cells:** Natural Killer cells. NK cells play an extremely important role in the first line of immune defense against viruses and other pathogens.
- **NAbs:** Neutralizing antibodies. NAbs "neutralize" virus by blocking entry of virus into susceptible host cells, thereby preventing infection and transmission. (It should be understood that when the immune system produces a NAb, that NAb is only potentially neutralizing. Depending on the time and situation, a NAb may prove to be truly and fully neutralizing, only partially or minimally neutralizing, or no longer neutralizing. A NAb that may initially be fully neutralizing, may later be only minimally neutralizing, due to immune evasive mutations in new variants. That is, the neutralizing capacity of a NAb can change.)
- **Abs:** Antibodies. (Not all antibodies are intended to be neutralizing Abs. Non-neutralizing antibodies serve in ways that do not involve direct blockage of viral entry into cells.)
- **RBD:** Receptor Binding Domain (on the S1 segment of the spike protein)
- **NTD:** N-Terminal Domain (on the S1 segment of the spike protein)
- **PNNAbs:** Polyreactive non-neutralizing antibodies. (They attach to the NTD)
- **BTIs:** Breakthrough Infections. (BTIs may occur in both unvaccinated and vaccinated individuals.)
- **vBTIs:** Vaccine BTIs. Most of the time we will be talking about vaccine-BTIs (vBTIs)---i.e., BTIs that occur in vaccinated individuals, despite their vaccination, even because of their vaccination.
- **OAS:** Original Antigenic Sin. (Also known as "immune imprinting" or "immune seniority.")
- **APCs:** Antigen presenting cells.
- **DCs:** Dendritic Cells.
- **CTLs:** Cytotoxic T Lymphocytes. (in this article we will be talking about "universal CTLs.")
- **CBIIS:** Cell-Based Innate Immune System. NK cells are a key component of the CBIIS.
- **URT:** Upper Respiratory Tract.
- **LRT:** Lower Respiratory Tract.
- **HIVICRON: Hi**ghly **Vi**rulent Omi**cron** variant. (It will also be referred to as "Highly Virulent replacement for Omicron.")

- **PBG:** Peptide binding groove
- **PSMP:** Pathogen-derived self-mimicking peptides
- **ADEI:** Antibody dependent enhancement of infection---not to be confused with antibody dependent enhancement of disease (ADED). ADED refers to Fc mediated phenomena---e.g., Fc/FcR mediated infection of phagocytes (e.g., macrophages). ADEI refers to PNNAb-mediated facilitation of viral entry into host cells that have ACE-2 receptors.

SUMMARY OF THE 13 SEQUENTIAL EVENTS:

For a quick summary of this article, one could simply read the bolded titles of each of the 13 "Events," as listed below. Also, there is a SUMMARY at the end of the article (page 29):

Event 1---The Wuhan strain appeared. Large-scale infection-prevention measures (e.g., "lockdown," including use of physical barriers) were implemented. These measures promoted the natural selection and dominant propagation of variants possessing mutations that rendered them more infectious than the Wuhan strain (e.g., Alpha and Beta variants).

Event 1a---At the beginning of the pandemic (when the Wuhan strain prevailed and the mass vaccination campaign had not yet been implemented) significantly infected individuals developed an innate immune response to the virus, including initial training of their Natural Killer cells (NK cells); and an adaptive immune response, including production of neutralizing antibodies (NAbs) against the Wuhan strain.[B-G]

Event 2---Then, the MASS VACCINATION CAMPAIGN was implemented. Vaccine-induced NAbs (while immature and suboptimal) placed great population-level immune pressure on the virus---because circulating virus was directly exposed to these suboptimal NAbs, which partially impeded infection but did not fully prevent infection. This population level immune pressure drove the natural selection and dominant propagation of "immune escape" variants that were better able to overcome the neutralizing effect of vaccine-induced NAbs. A prolonged series of progressively less neutralizable (and increasingly infectious) immune escape variants resulted, particularly during the Omicron era:

Event 3---Diminished neutralizing capacity of NAbs triggered the compensatory production of PNNAbs (polyreactive non-neutralizing antibodies), which had two different effects: a virulence-inhibiting effect and an infection-enhancing effect:

Event 4---Highly vaccinated individuals experienced frequent PNNAb-enhanced vaccine breakthrough infections (vBTI), caused by one new Omicron variant after another:

Event 5---The frequent vBTIs (with one Omicron variant after another) triggered the phenomenon of steric immune refocusing (SIR), which resulted in production of SIR-recalled, broadly but poorly cross-reactive neutralizing antibodies (SIR-recalled "pseudo-neutralizing" NAbs):

Event 6---As vBTIs cause high titers of immune-refocused antibodies to bind with increasingly weak affinity to mismatched epitopes on new circulating Omicron descendants, increasingly large aggregates of antibody-virus complexes are formed---Affinity vs Avidity:

Event 7---Large aggregates of antibody-virus immune complexes led to internalization of these aggregates into antigen presenting cells (APCs), which, in turn, activated "emergency use" cytotoxic T lymphocytes (CTLs):

Event 8---The compensatory immune response then shifted from a primarily NAb response to a primarily CTL response---from a humoral response to a cellular (CTL) response:

Event 9---New Omicron descendants (e.g., JN.1) developed capacity for increased inter-host transmissibility, as well as increased ability to adsorb onto dendritic cells (DCs) (which enabled avoidance of the CTL response). The stage was thereby set for the virus to develop increased capacity for intra-host transmissibility (the capacity for the virus to spread to different organs within the same host).

Event 10---To Review: First, the NAb response (including SIR-recalled NAbs) largely failed, then the CTL response began to fail:

Event 11---Then, failure of the virulence-inhibiting effect of the PNNAbs, but not of their infection-enhancing effect, became imminent:

Event 12---Since the beginning of the mass vaccination campaign, the extremely important cell-based innate immune system (CBIIS), particularly its NK cells (Natural Killer cells), have been continually sidelined in highly vaccinated individuals (but not in unvaccinated individuals). Accordingly, the NK cells of highly vaccinated individuals have not been sufficiently trained to protect those individuals from HIVICRON.

Event 13---The predictable arrival of HIVICRON (Highly virulent Omicron) is now imminent. The last remaining obstacle to the virus (the virulence-inhibiting effect of PNNAbs) will soon be overcome by a differently glycosylated new coronavirus (HIVICRON) that will replace the Omicron descendants. (FIGURE 12.) This places highly vaccinated individuals (fully vaccine-primed individuals) in highly vaccinated countries at high risk for enhanced severe disease and death:

MAIN TEXT

Event 1---The Wuhan strain appeared. Large-scale infection-prevention measures (e.g., "lockdown," including use of physical barriers) were implemented. These measures promoted the natural selection and dominant propagation of variants possessing mutations that rendered them more infectious than the Wuhan strain (e.g., Alpha and Beta variants).

First, the Wuhan strain of the SARS-CoV-2 virus appeared. it was recognized in Wuhan, China in December 2019, in the USA in late January 2020, and in Europe during February 2020.[A] In mid-March 2020, the World Health Organization (WHO) declared a global pandemic. In response, large-scale infection-prevention measures were implemented across the globe, stringent in some countries, less so in other countries---e.g., masking, social distancing, isolation, "lockdown" measures. These measures put population-level pressure on the virus. That is, these measures (essentially, physical barriers) made it more difficult for the virus to go (be transmitted) from one infected human to another (susceptible) human---i.e., inter-host transmission was made more difficult for the virus.

Mutations inevitably occur during viral replication. A virus that develops new mutations is a "variant" of preceding strains of that virus. It was predictable that a variant would emerge that had a mutation (or mutations) that enabled that variant to more easily overcome the physical barriers created by stringent large-scale infection-prevention measures, compared to the ability of the original Wuhan strain to overcome those barriers. That variant would be more infectious, would have a "fitness advantage" over the Wuhan strain, would be able to outcompete the Wuhan strain, and would eventually become the dominant variant, at a population level---until a new variant came along that had mutations that enabled it to outcompete the reigning variant and become the new dominant variant. This is the "natural selection" process that transpired during the first year of the pandemic and contributed to the rise of Alpha and Beta variants.

Event 1a---At the beginning of the pandemic (when the Wuhan strain prevailed and the mass vaccination campaign had not yet been implemented) significantly infected individuals

developed an innate immune response to the virus, including initial training of their Natural Killer cells (NK cells); and an adaptive immune response, including production of neutralizing antibodies (NAbs) against the Wuhan strain.[B-G]

When the Wuhan strain first appeared, people who became significantly infected mounted an innate immune response to the virus, including initial training of their Natural Killer cells (NK cells); and most also mounted an adaptive immune response, including production of neutralizing antibodies (NAbs) that were primarily directed against immunodominant (highly immunogenic) epitopes within the receptor binding domain (RBD) of the spike protein of the Wuhan strain.[B-G, 1-10] These NAbs would help protect such individuals when/if they encountered the Wuhan strain or a very similar variant in the future. These NAbs work by attaching to the RBD of the virus, thereby preventing (blocking) attachment of the RBD to the ACE-2 receptor on human cells.[D, 11] Successful attachment of the RBD to the ACE-2 receptor is what allows the virus to enter susceptible human cells. NAbs interfere with that successful attachment.

After initial significant infection with the Wuhan strain, the immune system does not just produce NAbs against immunodominant epitopes within the RBD.[C,] To a lesser extent the immune system normally also produces NAbs to subdominant (less immunogenic) more conserved (less variable, less mutable) epitopes elsewhere on the spike protein.[1-10] These additional NAbs have less neutralizing capacity than do the NAbs that bind to immunodominant epitopes, but they are valuable in that they are less variant specific---i.e., they can broadly cross-react against subdominant, conserved epitopes on a variety of variants, including future variants of the virus.

Memory B cells and T cells: When the B cells of the adaptive arm of the immune system produce these NAbs (against immunodominant and subdominant epitopes), B cells (and the T helper cells that enable those B cells) develop capacity for memory.[E,F] These "memory B cells" and "memory T helper cells" will be able to quickly re-produce (recall) these NAbs in the future (when the person is infected with the same virus or a variant of that virus). This capacity for memory and recall is key to understanding the concepts of "original antigenic sin (OAS),"[G, 12] which is discussed in Footnote G, and "steric immune refocusing (SIR)," which is discussed under Event 5.

Event 2---Then, the MASS VACCINATION CAMPAIGN was implemented. Vaccine-induced NAbs (while immature and suboptimal) placed great population-level immune pressure on the virus---because circulating virus was directly exposed to these suboptimal NAbs, which partially impeded infection but did not fully prevent infection. This population level immune pressure drove the natural selection and dominant propagation of "immune escape" variants

that were better able to overcome the neutralizing effect of vaccine-induced NAbs. A prolonged series of progressively less neutralizable (and increasingly infectious) immune escape variants resulted, particularly during the Omicron era:

In December 2020 (and the early months of 2021) the mass vaccination campaign was started, first in the elderly and most vulnerable, then across all age groups in most countries of the world. It was implemented more rapidly and more extensively in some countries than in others. In many countries the vast majority of the population became vaccinated against the SARS-CoV-2 virus. By 2023 over 70% of the global population had received at least one vaccine dose.

The vaccines were primarily designed to induce the immune system to produce neutralizing antibodies (NAbs) against immunodominant epitopes within the receptor binding domain (RBD) of the spike protein of the Wuhan strain.[C,D] The RBD of the spike protein is, indeed, an appropriate target for a vaccine against SARS-CoV-2, because, as explained in Footnote D and shown in Medical Illustrations A and B, the SARS-CoV-2 virus is able to infect human host cells by attaching the RBD of its spike protein to the ACE-2 receptor of the human host cell. The ACE-2 receptor is the "lock" to the host cell; the RBD is the "key" that opens that lock. When the RBD successfully attaches to the ACE-2 receptor, the "door is opened" and the virus enters the cell, where the virus replicates components of itself, assembles those components, releases progeny virions from the cell, and eventually lyses (kills) the cell.

As explained in Footnote D and shown in Medical Illustration B, when the immune system produces NAbs to immunodominant epitopes within the RBD of the spike protein, the goal is to have the NAbs tightly attach to epitopes within the RBD in such a way that the RBD can no longer attach to the ACE-2 receptor of the human host cell---i.e., so that the "key" will no longer successfully fit with the "lock."[11]

But one problem was that by the time the mass vaccination campaign was implemented, new variants (with mutations of immunodominant epitopes within their RBD) were circulating and the Wuhan strain was ceasing to be the dominant strain. So, there already was at least a slight mismatch between the anti-Wuhan NAbs and the RBD of the variants that were circulating in late 2020 and early 2021. The anti-Wuhan NAbs did not attach optimally tightly to the RBD of the new variants and thereby did not optimally interfere with attachment of the RBD to the ACE-2 receptor on human cells.

But even if the vaccine-induced NAb had been a perfect match for the RBD of the variant that was dominantly circulating at the time, there would still have been an even greater, much more

important problem:

That problem is that, after the first vaccine injection, it typically takes several weeks (4-6 weeks) for the immune system to provide sufficiently high titers of fully mature, tightly binding, fully functional (IgG) NAbs against the RBD of the spike protein (in the case of the SARS-CoV-2 pandemic). In the meantime, the NAbs are immature (IgM), suboptimal, and only partially and inadequately able to neutralize (block) the RBD from attaching to the ACE-2 receptor. Whereas sufficiently high titers of fully mature NAbs may be able to fully (optimally) neutralize the virus and fully (optimally) prevent infection (thereby optimally contributing to the death of the virus), immature (IgM) NAbs bind only loosely and suboptimally and are not able to fully prevent infection and thereby allow the virus to survive, replicate, and transmit to other individuals. **Suboptimal NAbs (i.e., either immature (IgM) NAbs or suboptimal titers of mature IgG NAbs) partially frustrate but do not fully prevent infection and transmission.**

This is a major problem because when a large percentage of the immunologically naïve population is vaccinated against the virus in the midst of an active pandemic, there is a large amount of virus circulating in the community, and this means that **the virus will predictably and frequently encounter immature (IgM) NAbs or suboptimal titers of affinity-matured IgG NAbs when the virus infects recently vaccinated individuals.** Although these suboptimal antibody responses are unable to prevent infection of host cells, they are able to make it more difficult for the virus to infect host cells. This being the case, if mutations occur that happen to enable a particular variant (the initial Omicron variant, for example) to better resist this partial (sub-optimal) neutralization, that variant will survive, propagate, have a competitive advantage, be naturally selected, and will become dominant.

It is this suboptimal population-level immune pressure (applied by the vaccine-induced immature IgM NAbs and/or insufficient titers of vaccine-induced mature IgG NAbs) that has driven the natural selection, and dominant propagation of a prolonged succession of more fit (i.e., less neutralizable) "immune escape" variants that have appeared since implementation of the mass vaccination campaign.

Immune escape variants particularly flourished during the Omicron era, one after the other, many of them co-circulating. The initial Omicron variant had over 30 mutations within the spike protein alone. These mutations enabled the initial Omicron variant and subsequent Omicron descendants to be sub-optimally neutralized by all previously produced NAbs, including the vaccine-induced anti-Wuhan NAbs. The many successive Omicron descendants have become increasingly difficult to neutralize and increasingly infectious. Current Omicron variants are far more infectious than the original Wuhan strain.

To summarize, the mass vaccination (of the majority of the immunologically SARS-CoV-2 naive population, across all age groups) in the midst of an active viral pandemic (like the SARS-CoV-2 pandemic) places the virus under hostile population-level immune pressure and will thereby predictably promote the natural selection and dominant propagation of variants that happen to have mutations that enable them to "escape" the immune pressure applied by suboptimal NAbs (suboptimal immature NAbs and/or suboptimal titers of mature NAbs). This results in a prolonged succession and vast array of less neutralizable and increasingly infectious co-circulating/co-emerging "immune escape" variants that would not have appeared in the absence of the mass vaccination campaign. This broadens the spectrum of immune escape variants, prolongs the pandemic, and sends it in a worrisome direction (as will be explained later).

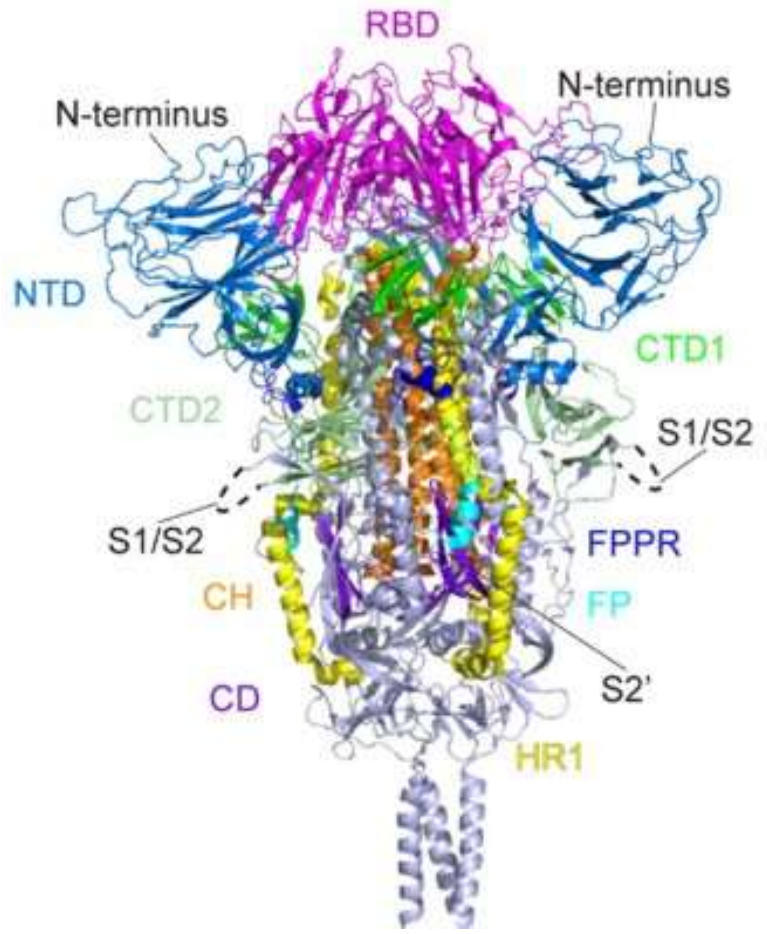
The mass vaccination campaign, particularly during the Omicron era, increasingly and progressively put population level immune pressure on the neutralizability, overall infectiousness, and transmissibility of the virus. If a mutation (or mutations) came along that enabled a new variant to be less neutralizable (by NAbs), and/or more infectious, or more transmissible, such new variants would be able to outcompete predecessor variants, would be naturally selected, and would become the new dominant variant(s).

Event 3---Diminished neutralizing capacity of NAbs triggered the compensatory production of PNNAbs (polyreactive non-neutralizing antibodies), which had two different effects: a virulence-inhibiting effect and an infection-enhancing effect:

When the neutralizing capacity of NAbs becomes markedly diminished (which certainly was the case when the anti-Wuhan NAbs to RBD epitopes became outdated), the immune system starts making Polyreactive Non-Neutralizing Antibodies (PNNAbs).[13-17] This is because the outdated, mis-matched NAbs bind to the RBD in such a way as to expose the N Terminal Domain (NTD) of the spike protein to the immune system. *(More scientifically stated, the outdated, mismatched NAbs engage in low-affinity, avidity-based interactions with immunogenic spike protein associated domains, thereby enabling immune recognition of the highly conserved, naturally immunosilent N-terminal domain (NTD) of the spike protein by the host immune system.)* Accordingly, the immune system produces PNNAbs that attach to the NTD.

See FIGURE 2, below, for an image of the spike protein, with the RBD at the top (in pink-purple) and the NTD on both sides (in blue). (The N-terminus is within the NTD.)

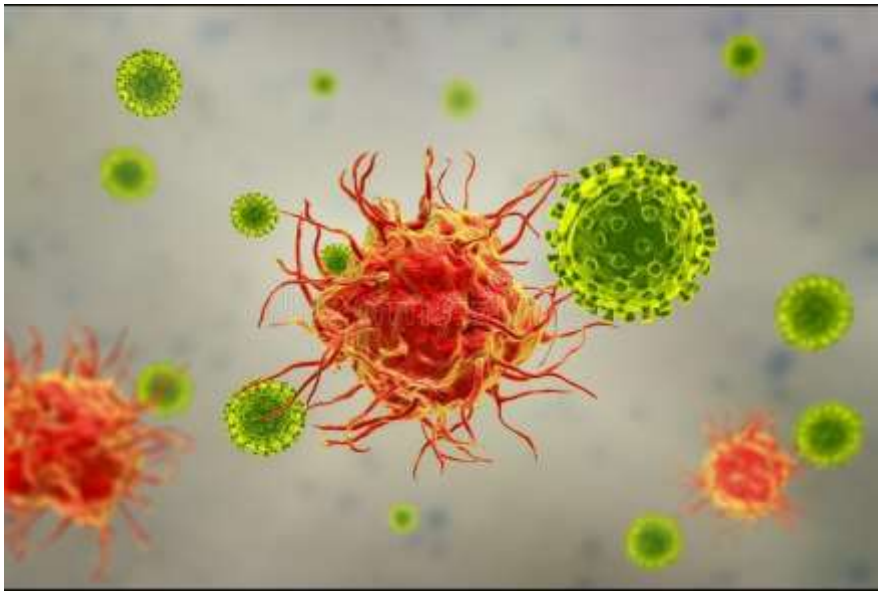
FIGURE 2



PNNAbs have two distinctively different immune effects: a virulence-inhibiting effect[13, 14] and an infection-enhancing effect.[15-17]

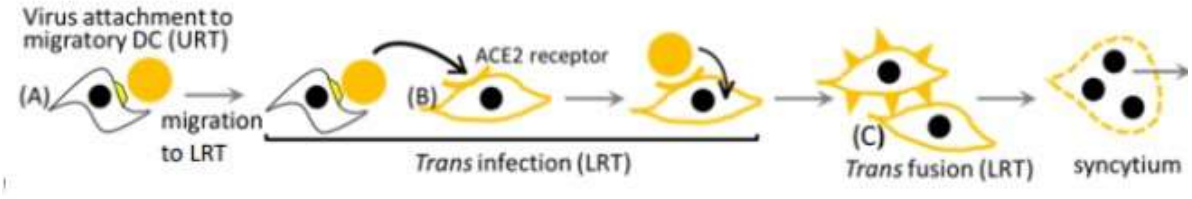
The virulence-inhibiting effect of PNNAbs: When the virus breaks through the innate immune system and produces a large load of progeny virus infecting the upper respiratory tract (URT), some of the freely circulating virions attach to the arms of migrating dendritic cells (DCs). See Figure 3, which shows two virions attached to the arms (tentacles) of a single dendritic cell.

FIGURE 3



These DCs, with virions tethered to them, can then migrate down to the lower respiratory tract (LRT), where the DCs can release the virus. (See Figure 4.) The released virus can then infect susceptible epithelial and alveolar cells (i.e., cells endowed with ACE-2 receptor) in the LRT. Those infected cells can then infect neighboring cells, causing them to fuse together and form syncytia. This process results in severe, even life-threatening infection and inflammation in the LRT and in other distal organs—i.e., severe disease and potential death.

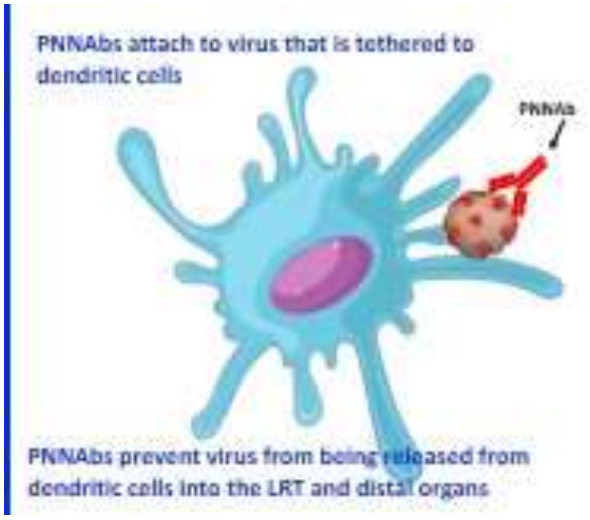
FIGURE 4



Fortunately, PNNAbs are able to inhibit the above process. They do so by binding to the NTD of virions that are tethered to the arms of dendritic cells (DC). (See Figure 5.) This binding impairs release of the virions from the DCs. The virions are kept out of harm's way; they are prevented from infecting the LRT and other internal organs. PNNAbs, therefore, prevent DC-tethered

virions from becoming virulent. This virulence-inhibiting effect protects the person from severe disease and death.

FIGURE 5



The infection-enhancing effect of PNNAbs: These same PNNAbs enhance the infectiousness of free virions. How are they infection-enhancing? When the PNNAbs attach to the NTD of the spike protein, this causes a conformational change in the RBD---namely, the RBD flips from the "closed" position to the "open" position. (See Figures 6 and 7.) When the RBD is in the open position, it is much easier for the RBD to successfully attach to the ACE-2 receptor and, thereby, enter and infect host cells. When the RBD is in the closed position, it is much more difficult for the RBD to successfully attach to the ACE-2 receptor. This is how PNNAbs are infection-enhancing.

FIGURE 6

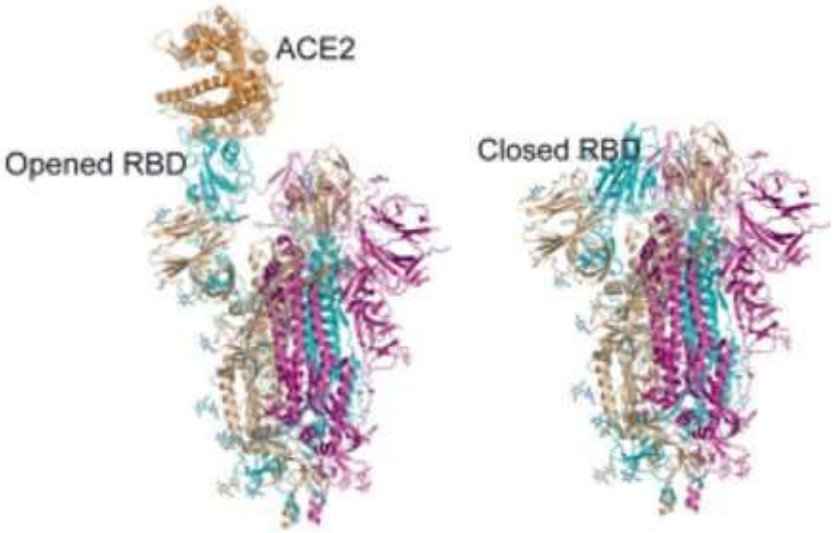
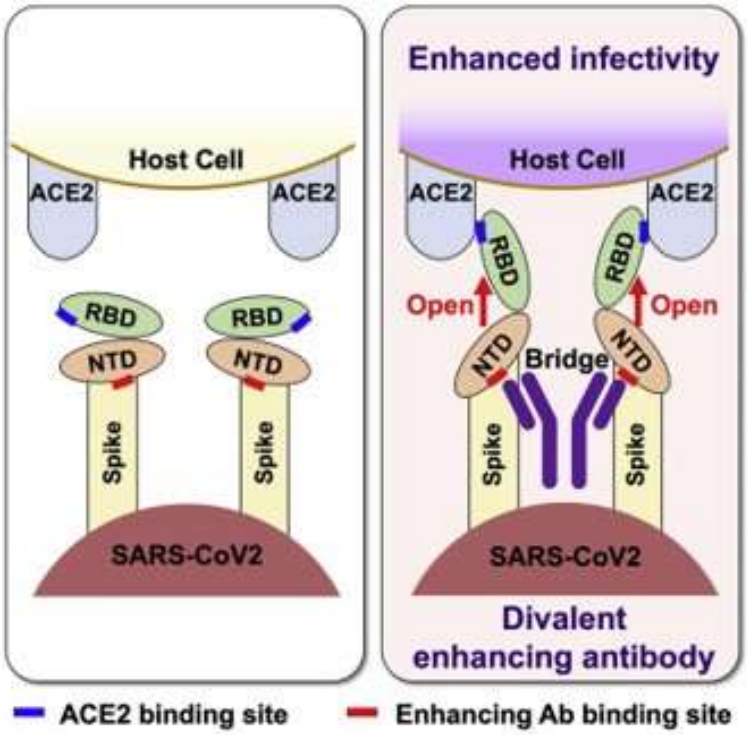


FIGURE 7
Infection-enhancing effect of PNNAb (in purple)



<u>Event 4</u>---Highly vaccinated individuals experienced frequent PNNAb-enhanced vaccine breakthrough infections (vBTI), caused by one new Omicron variant after another:

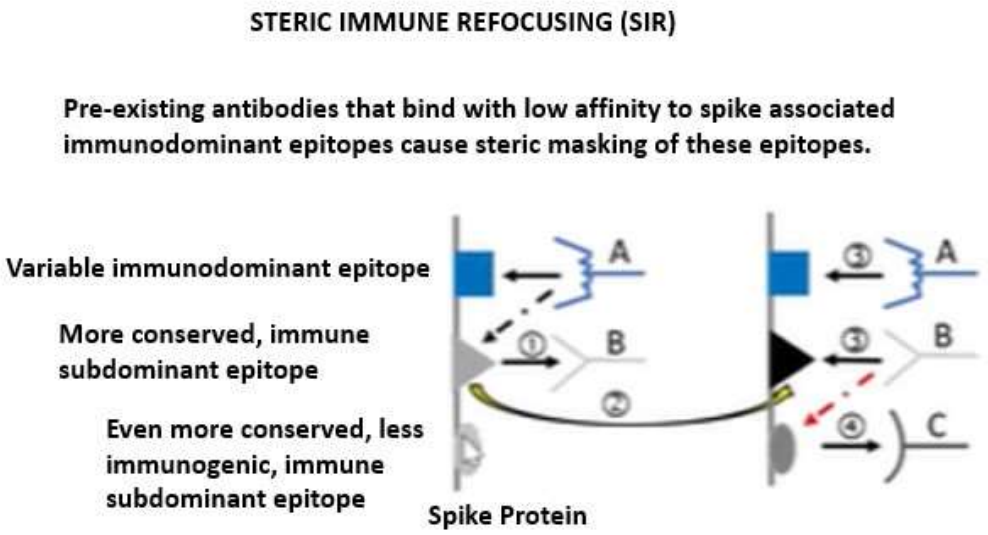
As the mass vaccination campaign led to large-scale PNNAb-mediated enhancement of viral infectiousness, <u>vaccinees experienced frequent vaccine breakthrough infections (vBTIs)</u>, despite their vaccination. Not only has viral immune escape led to a high incidence of PNNAB-mediated vBTIs, but also the immune-refocused "pseudo-neutralizing" antibodies ("SIR-recalled NAbs" directed against subdominant and increasingly conserved epitopes, as will be explained in Event 5) have become rapidly and increasingly ineffective as their suboptimal functionality promotes natural selection of immune escape variants. For these reasons, throughout the Omicron era, vBTIs in vaccinees has fueled additional subsequent vBTIs with one Omicron variant after another.

Whereas highly vaccinated individuals regularly develop PNNAbs and BTIs, unvaccinated individuals only develop PNNAbs upon re-exposure to a very different variant shortly after

infection with a previously circulating variant. Unvaccinated individuals have also developed frequent BTIs during the Omicron era, but in most cases their immune system handles these BTIs in a different and more effective way than does the immune system in vaccinated individuals---namely, in unvaccinated individuals, increasingly trained NK cells (Natural Killer cells) handle BTIs quite well and prevent those BTIs from triggering steric immune refocusing (SIR). (More on this later.)

Event 5---The frequent vBTIs (with one Omicron variant after another) triggered the phenomenon of steric immune refocusing (SIR), which resulted in production of SIR-recalled, broadly but poorly cross-reactive neutralizing antibodies (SIR-recalled "pseudo-neutralizing" NAbs):

FIGURE 8



Explanation of the SIR phenomenon: Each time a highly vaccinated individual develops a PNNAb-enhanced vBTI with yet another increasingly infectious Omicron variant, the immune system of that individual recalls previously primed antibodies (Abs)[F] that are directed at increasingly conserved immune subdominant spike-associated epitopes. This results from the epitope masking of the more variable immunodominant spike-associated epitopes by high titers of recalled pre-existing (but now outdated and mismatched) neutralizing Abs (e.g., anti-Wuhan NAbs directed at RBD epitopes)---which have also been recalled because of original antigenic sin (OAS). The recalled antibodies that are progressively directed at increasingly conserved immune subdominant epitopes will not only comprise antibodies that recognize the new Omicron variant that is currently infecting the person (Omicron variant X, for the sake of discussion) but will also recognize other variants that have not yet emerged. This is because

these antibodies are cross-reactive with conserved immune subdominant epitopes that are shared by past, present, and future Omicron variants.

Stated in a different way: Each time a highly vaccinated individual develops a PNNAb-enhanced vBTI with yet another increasingly infectious Omicron variant, the immune system of that individual recalls several different NAbs, due to the phenomenon of original antigenic sin (OAS). It recalls the original long-ago-outdated vaccine-induced anti-Wuhan NAbs that are directed at variable immunodominant epitopes on the RBD of the spike protein. It also recalls previously produced NAbs to increasingly more conserved immune subdominant epitopes on the spike protein, and these NAbs broadly cross-react with the new Omicron variant that is currently infecting the person (which we are calling Omicron variant X, for the sake of discussion).

The problem is that although the recalled vaccine-induced anti-Wuhan NAbs that bind to immunodominant epitopes within the RBD fail to adequately bind to the ACE-2-competitive domain within the RBD of the spike protein of the new Omicron variant X (and thereby fail to neutralize the virus), these NAbs, nevertheless, still bind, loosely, to their respective epitopes. These outdated NAbs bind loosely to the virus via multivalent binding to surface-expressed epitopes within that variant's RBD. These NAbs thereby sterically mask immunodominant and variable epitopes on the variant's RBD, shielding them from the view of the immune system. (See Figure 8.) This steric hindrance re-directs the immune system's attention to less immunogenic, more conserved epitopes located elsewhere on the spike protein (e.g., epitope B, for the sake of discussion). Accordingly, the immune system is "refocused" (or re-directed) to recall NAbs to epitope B, because the more immunodominant and variable epitopes are now sterically hidden from the immune system's view. These previously primed NAbs to the more conserved epitope B are recalled due to this steric immune refocusing (SIR). Although these SIR-recalled NAbs to epitope B are broadly cross-reactive (meaning that they react against conserved epitopes on a wide array of Omicron variants) they have poor neutralizing capacity because their binding to spike-associated epitopes is primarily avidity-based, not affinity-based. This implies that they rapidly lose their virus-neutralizing (i.e., infection-inhibiting) capacity over time. These SIR-recalled NAbs help to inhibit infection, but only modestly and briefly.

At a population level, a collective decrease in the neutralizing capacity of NAbs places suboptimal pressure on the infectiousness of the virus and thereby promotes the natural selection of new even more infectious variants, causing vaccinated individuals to develop yet another vBTI, this time due to a highly infectious Omicron variant Y.

When a vaccinated individual is then infected with Omicron variant Y, previously produced (but no longer effective) anti-RBD NAbs (directed against immunodominant epitopes), as well as

recently recalled NAb to epitope B, still bind to their respective epitopes, despite their failure to adequately neutralize the virus. This, again, sterically masks/hides the relevant epitopes (including epitope B) and directs the immune system's attention to an even more conserved and even less immunogenic epitope (epitope C). The refocused immune system then recalls NAbs that bind with even lower affinity to epitope C and thereby have a short-term infection-inhibiting effect (which could preferentially be called "pseudo-neutralizing" because these antibodies bind to non-ACE-2 competitive spike-associated domains). These NAbs to epitope B and C are examples of SIR-recalled NAbs.

Then, another vBTI occurs (due to Omicron variant Z), new steric hindrance occurs, and the immune system re-directs (re-focuses) to recall NAbs against epitope D, an even more conserved epitope. And so it goes after each of multiple vBTIs. During this cascade of events, SIR-recalled NAbs are successively recalled against increasingly conserved/less immunogenic epitopes, and these NAbs increasingly and progressively have less neutralizing capacity. Indeed, they become "pseudo-neutralizing" rather than truly neutralizing.

During the above-described SIR phenomenon, recall of NAbs against subdominant epitopes represents the dominant response, because the immunodominant epitopes are sterically masked.

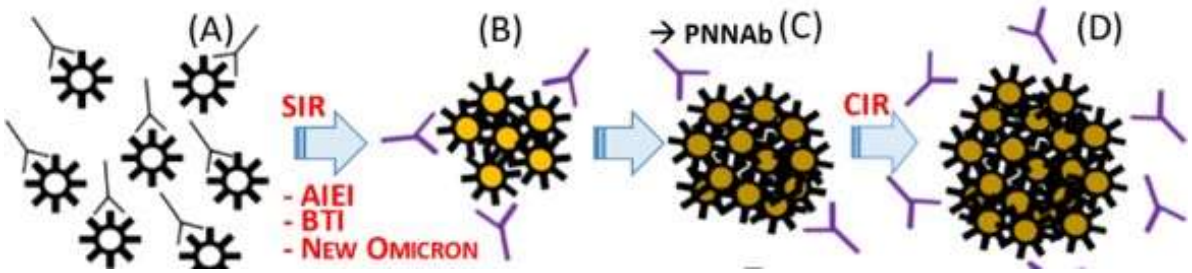
The reason for emphasizing that epitopes B, C, D, and so on represent increasingly conserved epitopes is that the more conserved an epitope is, the more closely that epitope mimics self-antigens. Normally, the adaptive immune system is able to recognize the difference between self-antigens and foreign antigens and has learned to assiduously avoid reacting to self-antigens. However, the adaptive immune system is not good at distinguishing between self-antigens (on normal human cells) and self-mimicking antigens (on viruses or other pathogens). Consequently, antibodies against pathogen-derived epitopes that very closely mimic self-antigens are prone to accidentally attack self-antigens on normal healthy cells. That is, these SIR-recalled NAbs (which have been progressively directed at increasingly conserved epitopes), especially once they mature into IgG4 antibodies, can lead to autoimmune disease.

Event 6---As vBTIs cause high titers of immune-refocused antibodies to bind with increasingly weak affinity to mismatched epitopes on new circulating Omicron descendants, increasingly large aggregates of antibody-virus complexes are formed---Affinity vs Avidity:

The next concept to understand is that when the neutralizing capacity of NAbs increasingly diminishes, due to vBTI-mediated immune refocusing to more conserved, less immunogenic spike-associate epitopes, their interaction with progeny virus from subsequent vBTIs results in

the formation of progressively/increasingly larger aggregates of antibody-virus complexes, as shown in FIGURE 9 and as explained below:

FIGURE 9



When a NAb is a close match with its intended epitope, that NAb strongly and tightly attaches to that epitope---i.e., the NAb has "high affinity" for the epitope. For example, at the very beginning of the pandemic the immune system of naturally infected individuals produced anti-Wuhan RBD NAbs and those antibodies had high affinity for (bound tightly to) immunodominant epitopes within the RBD of the spike protein of the Wuhan strain and, thereby, were initially effective---until mutations occurred in those same epitopes, resulting in an imperfect match (mismatch).

When a NAb becomes mismatched with its intended target epitope (because mutations have occurred within that epitope in the new variant), the NAb will have lower affinity for that epitope, will bind less strongly/tightly to that epitope. Low affinity interactions of high titers of NAbs at the surface of viral particles promotes viral aggregation to decrease the overall surface area involved. This minimizes the energy interaction at the virus-liquid interface and therefore stabilizes virus-antibody interactions. High titers of low affinity antibodies will therefore engage in multivalent, avidity-based interactions, rather than monovalent, affinity-based interactions with breakthrough virus.

Stated another way:

Particularly during the Omicron era, many of the epitopes on new Omicron variants were different from the epitopes towards which preceding NAbs had been directed. That is, the anti-Wuhan NAbs and post-Wuhan NAbs, including SIR-recalled NAbs, increasingly became mismatched with, and had lower and lower affinity for, the latest circulating Omicron variant.

When a NAb's affinity for its target epitope decreases, that NAb becomes less able to single handedly neutralize (even partially neutralize) single virions. However, high titers of these NAbs

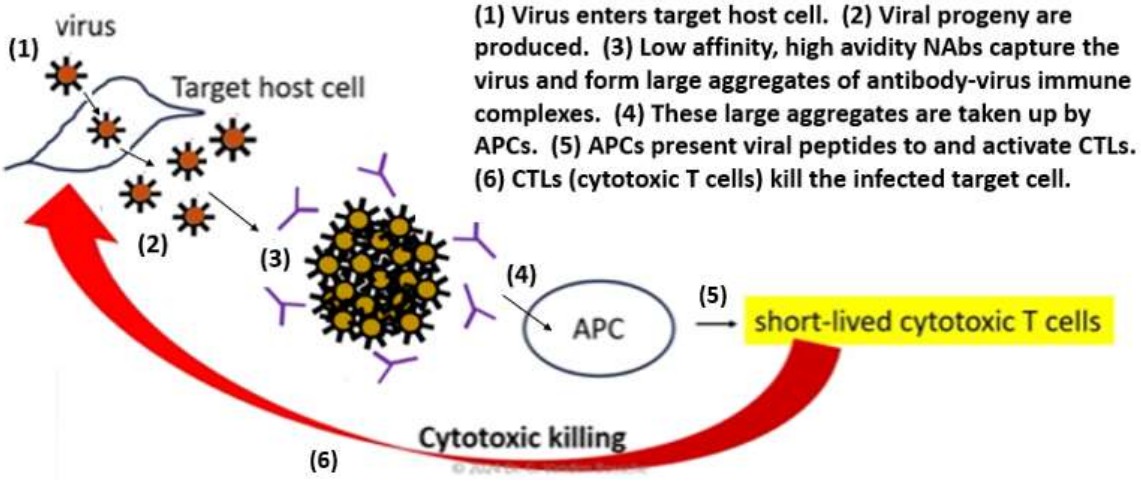
can still control the progeny virus following a new vBTI by having these low affinity NAbs work together to engage in multivalent, avidity-based interactions with the virus, thereby preventing the latter from spreading to other organs. In this situation, the immune system tries to neutralize the virus by having a team of low affinity NAbs work together to neutralize the virus. Members of this antibody team have low affinity for specific, spike-associated epitopes, but by working together and interacting via weaker, but multivalent interactions with a repetitive array of these epitopes on the surface of viral particles, the NAbs can stabilize viral aggregates in the aqueous phase, thereby preventing or mitigating viral infection.

At first, these aggregates are small. But as the affinity (and neutralizing capacity) of NAbs continues to diminish, the aggregates become larger and larger. (See Figure 9.) In other words, during the post-Omicron era, repeated immune refocusing events resulted in recall of NAbs of decreasing affinity for spike-associated epitopes, and thereby enabled (pseudo) neutralization of progeny virus from subsequent vBTIs (i.e., vBTIs caused by newly emerging immune escape variants) by forming larger and larger aggregates of antibody-virus complexes.

Event 7---Large aggregates of antibody-virus immune complexes led to internalization of these aggregates into antigen presenting cells (APCs), which, in turn, activated "emergency use" cytotoxic T lymphocytes (CTLs):

As the neutralizing capacity (and affinity) of NAbs increasingly diminished, and as new vBTIs yielded larger and larger aggregates of antibody-immune complexes, humoral immune refocusing eventually transitioned into cellular immune refocusing. This is because large aggregates are more readily taken up by APCs, thereby promoting activation of MHC-Class I unrestricted CTLs. These activated CTLs then killed virus infected host cells. (See FIGURE 10.)

FIGURE 10



It is important to know that these CTLs are different from the NK cells of the innate immune system. They are also different from the antigen-specific CD8+ MHC Class I restricted cytotoxic T cells that the immune system may activate in response to a specific pathogen. And they are different from so-called NK-like CTLs. They represent a sort of "emergency use" troop of CTLs that the immune system can quickly call upon to kill infected cells when the NK cell response has been inadequate (or absent, or sidelined) and before antigen-specific CD8+ MHC Class I restricted cytotoxic T cells would have time to respond. These emergency use CTLs that we are referring to are relatively non-specific; they are CD8+, but they are MHC class I unrestricted; they are directed against "universal peptides."

[*Note to immunologists: These "universal" CTLs recognize the same universal, self-mimicking peptides (presented on the MHC-Class I PBG) that NK cells recognize. (PBG=Peptide Binding Groove.) However, in the case of NK cells these peptides are being presented outside of the MHC-Class I PBG---and the CTLs are recognizing these peptides at a later stage of infection (i.e., in the case of insufficient or deficient NK killing at an earlier stage of infection). In the case of an insufficient/deficient universal CTL response, MHC-Class I restricted T cells are produced. The latter have no direct cytotoxic effect on infected cells.*]

Event 8---The compensatory immune response then shifted from a primarily NAb response to a primarily CTL response---from a humoral response to a cellular (CTL) response:

As already discussed, the NAb approach increasingly failed to adequately neutralize the frequently evolving Omicron variants that were becoming increasingly mutated, increasingly infectious, therefore increasingly difficult to neutralize, and were continuing to cause large-scale frequent PNNAb-enhanced vBTIs in highly vaccinated populations.

To review: First, the vaccinal anti-Wuhan-spike NAbs failed to prevent infection with the Wuhan strain in freshly vaccinated individuals; then they failed to prevent infection in increasingly larger portions of the population upon subsequent exposure to Alpha, Beta, Gamma, and Delta variants, despite a significant increase in NAb titer due to OAS. This led to the emergence of a highly immune evasive variant, Omicron, which triggered large-scale vBTIs, which resulted in large-scale SIR. SIR enables the recall of previously primed broadly cross-reacting Abs which rapidly reached suboptimal neutralization levels due to low affinity, thereby promoting further large-scale viral immune escape. Co-circulation of a multitude of more infectious immune escape variants dramatically increased the prevalence of vBTIs and promoted the formation of larger and larger aggregates of progeny virus complexed by low affinity Abs. Because such antibody-virus complexes are readily taken up by APCs, the immune response increasingly refocused to universal CTLs, rather than to broadly reactive NAbs. Consequently, the antiviral immune response of vaccinees shifted from NAb-mediated control of vBTIs to CTL-mediated control of vBTIs.

This CTL response worked well for a while. In fact, it worked so well that many people with vBTIs were either asymptomatic or only mild-moderately ill and that viral shedding diminished. This even gave the illusion (a false impression) that the highly infectious Omicron descendants were becoming increasingly mild and that the pandemic was coming to an end. But this was an erroneous interpretation. (More on this later.)

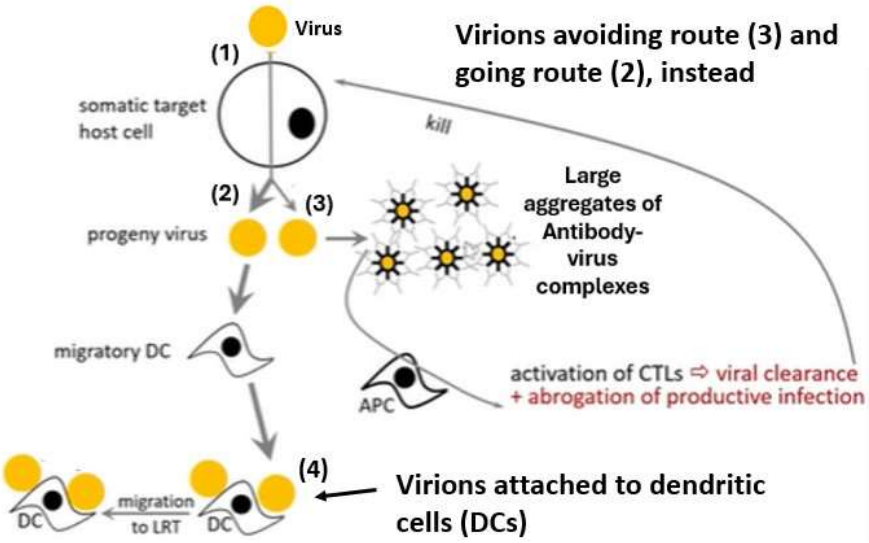
<u>Event 9</u>---New Omicron descendants (e.g., JN.1) developed capacity for increased <u>inter-host</u> transmissibility, as well as <u>increased ability to adsorb onto dendritic cells (DCs)</u> (which enabled avoidance of the CTL response). The stage was thereby set for the virus to develop increased capacity for <u>intra-host</u> transmissibility (the capacity for the virus to spread to different organs within the same host).

As the CTL response following vBTIs increasingly frustrated viral transmission, new Omicron variants that were more transmissible were naturally selected (because of their fitness advantage). At the same time, some of these more transmissible variants developed increased capacity to adsorb onto the arms of URT-resident DCs. [*These new variants (JN-1 and its descendants, for example) generate a cytokine environment that facilitates adsorption onto the arms of migratory DCs. (See FIGURE 11.) JN-1, for example, is capable of producing Open Reading Frame 8 (ORF-8), which results in increased cytokine-mediated inflammation, which, in turn, upregulates lectin on the surface of the arms of DCs.*[18] *These "sticky" lectins make it easier for the glycosylated virus to adsorb onto the arms of the DCs.*] This increased capacity of the virus to adsorb onto the arms of DCs increasingly resulted in less virus being taken up by APCs

and presented to CTLs. [Note: Adsorption of viral progeny onto DCs more effectively mitigates productive infection compared to killing of virus-infected cells by CTLs following uptake of progeny virus into APCs.]

As an increasing proportion of freely circulating virus got adsorbed onto DCs, less virus was available to become complexed with NAbs and fewer large aggregates were formed. Fewer large aggregates of antibody-virus complexes meant that fewer CTLs were being activated. That is, there was a shift from the virus going the CTL route to the virus going the route of adsorption onto DCs. This adsorption of virions onto the arms of DCs, coupled with the virulence-inhibiting effect of PNNAbs, temporarily resulted in a steady and increasing control of vBTIs and an improved control over viral transmission. However, **it set the stage for the virus to develop increased capacity for <u>intra-host</u> transmissibility (the capacity for the virus to spread to different organs within the same host), if the virus could overcome the virulence-inhibiting effect of the PNNAbs. (As will be discussed under Events 11 and 13.)**

FIGURE 11



<u>Event 10</u>---To Review: First, the NAbs response (including SIR-recalled NAbs) largely failed, then the CTL response began to fail:

As already discussed, first the NAb approach increasingly failed in that it drove the propagation of more infectious variants, then the CTL response also increasingly failed in that it drove the propagation of more transmissible variants. The immune system had deployed these two mechanisms, plus the virulence-inhibiting PNNAbs, to compensate for the failure of the COVID vaccines, including failure of the "updated" vaccines. It has been these three compensatory protective immune mechanisms, not the COVID vaccine, that has been preventing severe disease and death in highly vaccinated individuals (https://notesfromthesocialclinic.org/do-the-covid-19-vaccines-protect-against-severe-disease-and-death/). However, mitigation of productive infection by SIR-recalled NAbs or by CTL activation further drove viral immune escape and were, therefore, not sustainable, while immune refocusing also caused harmful/unfortunate side effects (e.g., predisposition of highly vaccinated individuals to autoimmunity, malignancy, and other chronic immune-pathology, including probable immune-mediated "long COVID").

As we will describe further in Events 11 and 13. increased adsorption of more transmissible viral progeny onto the surface of tissue-resident DCs will reduce the concentration of PNNAbs bound per adsorbed virion. Suboptimal concentrations of PNNAbs will eventually cause highly vaccinated populations to exert immune pressure on viral trans-infection, the phenomenon that triggers virus transfer to susceptible host cells in the lungs and other internal organs. Viral trans-infection triggers viral trans-fusion, which facilitates virus dissemination to other organ cells, thereby promoting viral virulence and the appearance of severe COVID-19 disease. Syncytia formation is the histopathologic hallmark of this virulence. See FIGURE 4.

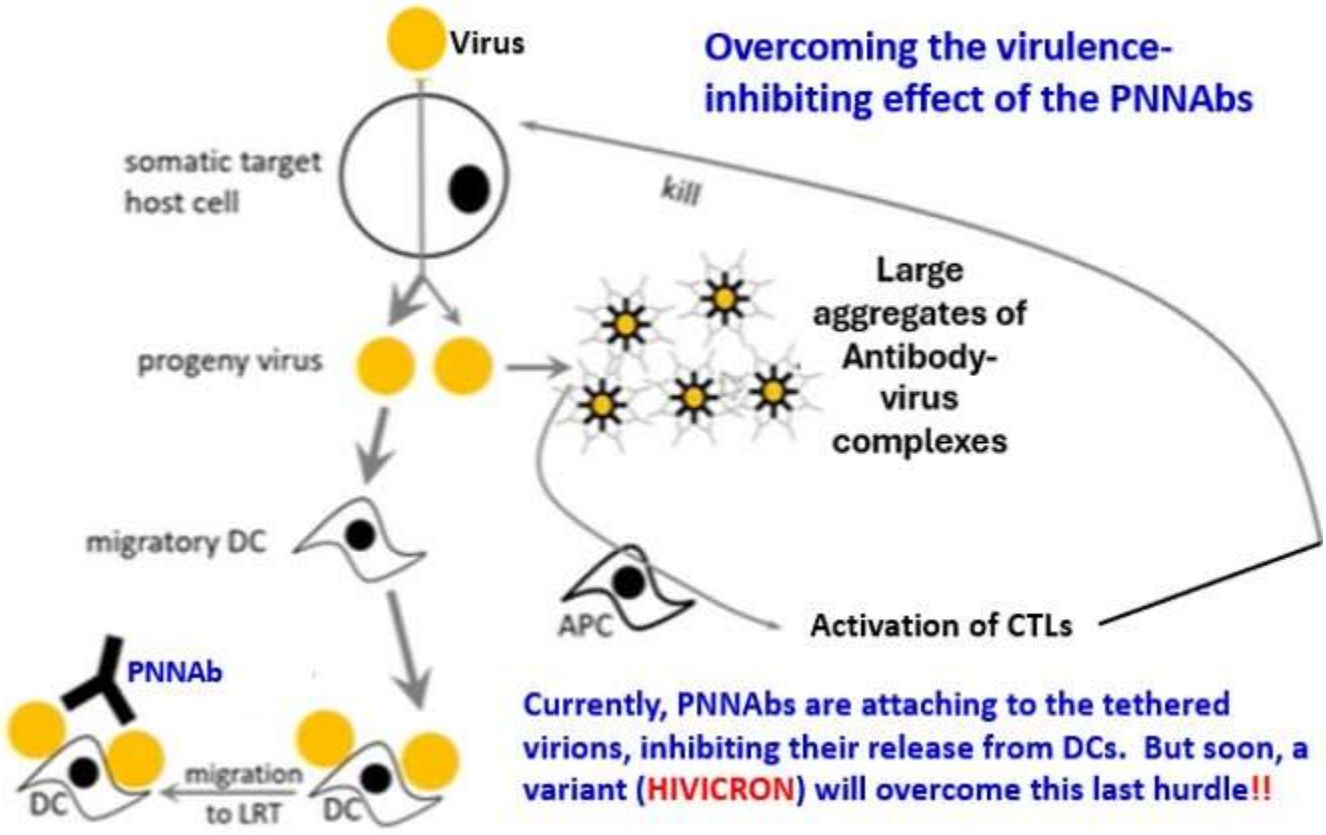
Event 11---Then, failure of the virulence-inhibiting effect of the PNNAbs, but not of their infection-enhancing effect, became imminent:

With the NAbs (including SIR recalled antibodies) and the CTL response increasingly failing to provide protection, and as more and more virus was being tethered to the arms of DCs, highly vaccinated individuals became increasingly dependent on the virulence-inhibiting effect of PNNAbs.

As explained earlier, PNNAbs protect by attaching to virus that is tethered to DCs, thereby impairing release of tethered virus into the LRT where the virus can cause severe disease and potential death. (FIGURE 5.) Given the collectively raising immune pressure exerted by PNNABs on a small and highly conserved domain of the Spike protein (comprised within the NTD), **it is, unfortunately, only a matter of time before a viral variant will be selected that is able to overcome this virulence-inhibiting effect of the PNNAbs**. (See FIGURE 12.) According to Dr. Vanden Bossche's analysis, this newly emerging coronavirus lineage will be characterized by specific changes in the glycosylation profile of the Spike protein, such as to shield the conserved domain within the NTD from PNNAB attachment when the virus is absorbed onto the surface of

DC, but not when free viral particles infect the URT. This implies that upon exposure to this new SARS-CoV-2 lineage, PNNAbs can still attach to the conserved antigenic site within the NTD of free virus and thereby trigger PNNAb-enhancement of infection (antibody-dependent enhancement of infection or ADEI). [*This may be required as it is reasonable to assume that more abundant glycosylation of Spike protein will come with a fitness cost that would enable this new SARS-CoV-2 variant(s) to unfold it virulence–enhancing effect by enabling absorption of viral progeny to migratory DCs and thus preventing PNNAbs from successfully attaching to the NTD of tethered virus.]* This will make it easy for the virus to be released into the LRT and other internal organs where it will threaten to cause multisystemic viral dissemination, resulting in severe disease and death.

FIGURE 12



For two reasons the virulence-inhibiting effect of PNNAbs will increasingly diminish. First, as mentioned earlier, recent more transmissible viral variants (e.g., JN-1) have been increasingly attaching to DCs and decreasingly going the route of immune-complex aggregation and CTL activation. As a larger quantity of virus adsorbs onto DCs, a larger quantity of PNNAbs are

consumed as the PNNAbs attach to tethered virus. This consumption increasingly/progressively reduces the titers of PNNAbs to suboptimal levels. Secondly, the interaction between recalled broadly cross-reactive Abs and the newly emerging variants becomes too weak to build immune complexes that are capable of triggering production of new PNNAbs; this also contributes to a decline in PNNAb titers.

Due to the extensive changes already exhibited by the JN.1 clan, combined with the predicted significant changes in the glycosylation profile, a new type of coronavirus will likely be generated. Once a new coronavirus lineage is able to overcome the virulence-inhibiting effect of PNNAbs, that variant (HIVICRON) will be extremely threatening. (This is further discussed in Event 13.)

Event 12---Since the beginning of the mass vaccination campaign, the extremely important cell-based innate immune system (CBIIS), particularly its NK cells (Natural Killer cells), have been continually sidelined in highly vaccinated individuals (but not in unvaccinated individuals). Accordingly, the NK cells of highly vaccinated individuals have not been sufficiently trained to protect those individuals from HIVICRON.

Although I have listed this event as Event 12, it is actually an event that starts soon after an individual becomes vaccinated and continues throughout the rest of the pandemic. **This sidelining of the NK cells is an extremely important component of Dr. Vanden Bossche's analysis**. Why and how do NK cells become sidelined in highly COVID-19 vaccinated individuals, and what are the consequences of this sidelining? Several factors contribute to the sidelining:

Initially, sidelining of NK cells occurs primarily when high titers of infection-enhancing PNNAbs are accelerating the speed of the infectious process in individuals whose first immune defense line of viral clearance is not sufficiently strong/trained to reduce the viral load.

To review: *PNNAbs are likely generated as a result of exposure of high titers of outdated NAbs to an antigen-shifted variant. Sufficiently high titers of these pre-existing antibodies with poor neutralizing capacity (i.e., directed at an antigen-shifted variant) can engage in multivalent, avidity-based interactions with viral particulates entering the URT before the virus has a chance to infect a large number of susceptible host cells. Despite their low affinity for the spike-associated immunogenic epitopes, these antibodies can synergize to capture a large amount of freely circulating virus, collectively masking the immunogenic epitopes from recognition by the host immune system and forming antibody–virus complexes that triggered the production of cognate T help–independent PNNAbs, directed at the highly conserved (i.e., variant non-specific) immunosilent domain comprised within the spike-NTD. Binding of these PNNAbs to this conserved antigenic site has been reported to promote a confirmational change in the spike RBD, thereby facilitating binding of the RBD binding site to the ACE-2 receptor on susceptible epithelial Cells and enhancing viral entry into epithelial cells of the URT.*

During the further course of the immune pandemic, extraordinarily infectious omicron descendants have been selected to dominate in prevalence. Although the strength of interaction between the pre-existing vBTI-boosted NAbs with these newly emerging descendants was no longer sufficient to form virus-antibody complexes capable of triggering PNNAB production, the extraordinary intrinsic infectiousness of these new variants was high enough to ensure continued sidelining of the CBIIS. **This extraordinary infectiousness results in such a rapid process of infection/release of viral progeny that NK cells do not have time to become involved**.

The above factors result in NK cells not having an opportunity to become involved in the killing of infected host cells at an early stage of infection (before progeny is produced). They are robbed of this opportunity to become involved and increasingly trained.

What are the consequences of the sidelining of the NK cells? Normally NK cells critically contribute to the first line of cell mediated immune defense against viral infection. (See Table 1 in Appendix.) This is because NK cells recognize and kill host cells at an early stage of altered self-molecule expression on their surface. Specifically NK cells recognize PSMP (pathogen-derived self-mimicking peptides) that appear early on the surface of infected cells. These PSMPs indicate that the cell has become infected. If the cell surface-expressed density of these PSMPs is too low, the infected cell will not be killed at this early stage, and the intracellular virus reproduction cycle will be completed with all viral components, migrating to the surface of the cell prior to being assembled and released as complete progeny virions.

Strong acceleration of the above-described viral reproduction cycle will not leave sufficient time for pre-primed NK cells to recognize and kill virus infected cells at an early stage of infection.

Normally, NK cells are so efficient that they are often able to end the infection without need for involvement of the adaptive arm of the immune system (production of antigen-specific immune effectors such as antibodies or T cells, e.g.). Better, yet, NK cells are educable and even have some adaptive memory (of unclear duration). NK cells can learn from their experience with each more infectious (i.e., more "challenging") SARS-CoV-2 variant that they encounter. This results in cumulative "training" of the NK cells, via epigenetic reprogramming.

Unvaccinated individuals who have been exposed to more and more infectious circulating variants, have a thoroughly trained innate immune system. Their NK cells have not been sidelined during the COVID pandemic. In fact, during the pandemic their NK cells have encountered several different SARS-CoV-2 variants, particularly during the Omicron era, and this has provided excellent, ongoing, cumulative training of their NK cells. Their NK cells, currently, are better prepared to handle SARS-CoV-2 variants than ever before.

Unfortunately, the NK cells of highly vaccinated (fully vaccine-primed) individuals have been sidelined since shortly after vaccination and have remained sidelined ever since, for the reasons mentioned earlier. Since vaccination, their NK cells have had no opportunity for involvement or

training. Consequently, fully vaccine-primed individuals have been totally dependent on NAbs (including SIR-recalled NAbs), virulence-inhibiting PNNAbs, and CTLs to protect themselves from disease or hospitalization (i.e., severe disease) and potential death. They have not been (and will not be) able to rely on their NK cells to kill SARS-CoV-2 infected cells and, thereby, have not established (and will not establish) sterilizing immunity and have not contributed (and will not contribute) to herd immunity.

[Note: It is important to know that even in unvaccinated individuals who previously developed severe COVID-19 disease, the conditions for sidelining of the cell-mediated innate immune system (CBIIS) (e.g., NK cells) upon exposure to an antigen-shifted variant are fulfilled. This is because development of severe disease, following exposure of unvaccinated individuals largely results from weakened innate immunity (for example, in immunocompromised individuals). and is known to generate high titers of NAbs. Binding of the latter to an antigen-shifted variant will therefore not only cause PNNAb-mediated enhancement of infection but even lead to BTI. This is similar to how high titers of vaccine-primed, poorly neutralizing antibodies trigger VBTI in vaccinees who become exposed to new variants while their NK cells have not been sufficiently trained by previous infection. BTIs, regardless of whether they are caused by infection or vaccine-primed humoral immunity will promote immune refocusing while boosting previously elicited NAbs. As immune refocusing, eventually promotes selection and propagation of more infectious variants, high titers of boosted, but miss-matched antibodies will continue facilitating PNNAb–mediated BTIs upon subsequent exposure to newly emerging variants while their NK cells have not been adequately prepared/trained to deal with enhanced viral infectiousness.]

But, is this sidelining of the NK cells irreversible? Is it possible that the NK cells in highly vaccinated individuals could eventually become un-sidelined and have opportunity for involvement and training, regarding SARS-CoV-2?

Unfortunately, even if the levels of PNNAbs, vaccine-induced NAbs, and SIR-recalled NAbs were to greatly decline, and even if CTL activity were to greatly diminish, a major remaining problem is the ***speed*** of the infection/production of progeny process. The newest variants are not just extraordinarily infectious. **In addition, those variants have developed extraordinary capacity to rapidly replicate new viral components, rapidly send them to the cell surface, and rapidly assemble those components into full progeny virions.** To repeat, this entire process, from initial entry of virus into a susceptible host cell to the final assembly and release of progeny virions is now occurring so rapidly, that untrained (due to prolonged sidelining) NK cells would not have time to carefully evaluate and react to the virus infected cells, even if untrained NK cells were given opportunity to participate. The untrained NK cells could only watch, while this astonishingly rapid process proceeds without affording untrained NK cells an opportunity to get involved, much less become trained. In particular, **it is the rapidity of the process of infection/production of progeny virus that irreversibly sidelines the NK cells**, because that rapidity will not slow down. Hence, the untrained NK cells will remain uninvolved and untrained, regarding SARS-CoV-2.

Note: One conceivable way to help highly vaccinated individuals, whose NK cells have been sidelined and have thereby lacked opportunity for training, would be to try to offer some

training of their NK cells (prior to arrival of HIVICRON) by giving these individuals the MMR vaccine. The MMR, being a live-attenuated vaccine, is capable of stimulating and training NK cells to recognize and react to the "universal peptide" on the measles virus (and mumps virus, too). Since the measles virus possesses a universal peptide that is similar to the universal peptide possessed by SARS-CoV-2, it is conceivable that the MMR vaccine could stimulate and train the NK cells to recognize and react to not only the measles virus but also the universal peptide of SARS-CoV-2. The MMR vaccine would need to be given in advance of the arrival of HIVICRON. This is only a suggestion for consideration by patients and their physicians. (See Dr. Vanden Bossche's article about this consideration:
https://www.voiceforscienceandsolidarity.org/scientific-blog/training-is-gaining
https://www.voiceforscienceandsolidarity.org/scientific-blog/this-is-what-i-would-do-if-i-were-vaccinated-against-covid

Event 13---The predictable arrival of HIVICRON (Highly virulent Omicron) is now imminent. The last remaining obstacle to the virus (the virulence-inhibiting effect of PNNAbs) will soon be overcome by a differently glycosylated new coronavirus (HIVICRON) that will replace the Omicron descendants. (FIGURE 12.) This places fully vaccine-primed individuals (highly vaccinated individuals) in highly vaccinated countries at high risk for enhanced severe disease and death:

Because of the series of events that has resulted from the COVID-19 mass vaccination campaign (and would not have occurred in the absence of that campaign), fully vaccine-primed individuals (highly vaccinated individuals) have been placed in the following threatening situation:

The current Omicron variants are extraordinarily infectious---more infectious than ever before. They are far more infectious than the original Wuhan strain. Until now, virulence-inhibiting PNNAbs, CTLs, and NAbs (including SIR-recalled NAbs) produced or recalled upon repeated vBTIs have usually enabled fully vaccine-primed individuals to control the vBTIs and thus protect them from (severe) disease, despite the infection-enhancing effect of vaccine-induced PNNAbs. These three protective immune mechanisms, which the immune system has provided to partially compensate for the failure of the ill-advised mass vaccination campaign and to prolong viral transmission across the population, has often been sufficiently effective to render a vBTI to be only mild, even asymptomatic. This has given the illusion, the false impression, that the Omicron variants are only mild and that the pandemic is almost over, whereas in reality it has enabled sustained viral spread and therefore continued selection of more transmissible Omicron descendants.

As mentioned earlier, these three protective mechanisms never fully substituted for the insufficient virus-neutralizing effect of vaccine-induced antibodies, nor were they sustainable; they have been failing one by one. The SIR-recalled NAbs have ceased to have a significant vBTI-

mitigating effect. The CTLs are now playing a less protective role. And the effect of the virulence-inhibiting PNNAbs will soon be overcome by a new coronavirus lineage (HIVICRON). In addition, the NK cells of fully vaccine-primed individuals have been irreversibly sidelined due to the newly emerging extraordinarily infectious immune escape variants and will not be able to provide protection against a new threatening variant. It is important to note that the above also likely applies to the NK cells of unvaccinated infection-primed individuals who contracted severe COVID-19 disease, or who got vaccinated shortly after productive natural infection.

In other words once a new coronavirus lineage emerges that is able to overcome the virulence-inhibiting effect of the PNNAbs, individuals whose NK cells have not been adequately trained (for example, fully vaccine-primed individuals and infection-primed individuals who contracted severe disease or got vaccinated shortly after their recovery from symptomatic infection) will be almost completely defenseless against such a variant and at risk of developing enhanced severe life-threatening disseminated disease. Dr. Vanden Bossche has called this variant **HIVI**CRON (**Hi**ghly **Vi**rulent replacement for Omicron).

Although HIVICRON will be highly virulent when contracted by individuals whose NK cells have not been adequately trained (i.e. predominantly fully vaccine-primed individuals) HIVICRON will not be highly virulent when contracted by healthy previously exposed unvaccinated individuals because the NK cells of these individuals have not been sidelined during the pandemic and in fact have gained great experience and training in fighting off a diversified spectrum of more infectious variants. Accordingly the excellently trained NK cells of healthy unvaccinated individuals will be able to handle HIVICRON quite well by recognizing the same PSMPs at an early stage of infection. Unvaccinated individuals would not be able to handle HIVICRON, if their NK cells had not had the time and practice to become as highly trained as they now are. (Again, highly vaccinated individuals were denied such opportunity for training and practice, because their NK cells have been sidelined.)

Fortunately not all vaccinated individuals will be as vulnerable to HIVICRON as described above. There is a spectrum of vulnerability. If a fully vaccine-primed individual happened to have been infected by the SARS-CoV-2 virus one or more times before becoming vaccinated, that Individual's NK cells might have gained sufficient experience and training to participate effectively when HIVICRON infection occurs. As already mentioned this would only apply provided the previous infection did not lead to severe disease, and the vaccination did not occur immediately after the recovery phase. Immunologically naïve individuals who have received two or more doses of an mRNA vaccine or three or more doses of a non-mRNA vaccine will be at higher risk of enhanced severe disease than those who received less than two or three doses, respectively. The higher risk attributed to messenger RNA vaccines results from their capacity to

trigger immune refocusing (SIR) on their own, even in the absence of PNNAb–enhanced vBTI. (See Chapters 7.1 and 7.2 in Dr. Vanden Bossche's book: ***The Inescapable Immune Escape Pandemic.***)

SUMMARY:

The COVID-19 mass vaccination campaign was an enormous mistake. Predictably, it transformed what would have been a relatively brief and manageable pandemic (probably lasting 9-12 months, involving 1-2 waves during that time) into a prolonged "immune escape" pandemic that has become far more dangerous and **will cumulatively claim far more lives than if the mass vaccination campaign had never been implemented**. And I am not even including the extremely unacceptable number of deaths from vaccine-caused injury (severe adverse events experienced by individuals who were vaccinated).

When a mass vaccination campaign is NOT implemented in the midst of an active pandemic, "immune escape" variants do not occur; prolonged and high titers of NAbs do not occur; therefore, SIR does not occur; and because SIR does not occur, adaptive immune protective effectors do not collectively shift from highly antigen-specific Abs to broadly cross-reactive Abs or CTLs, nor does sidelining of NK cells occur upon re-exposure.

So, the mass vaccination campaign has been responsible for: the prolonged succession of increasingly infectious dominant "immune escape" variants; the SIR-triggering PNNAb-mediated BTI; the SIR phenomenon; the repeated recall of broadly but poorly cross-neutralizing Abs or short-lived CTLs; and the sidelining of NK cells. In highly vaccinated (fully vaccine-primed) individuals the immune system has partially compensated for vaccine failure by providing immune mechanisms (namely, PNNAbs, SIR-recalled NAbs, and CTL activation) that have been temporarily protecting vaccinees against severe COVID-19 disease and death (and even against symptomatic COVID-19). But those compensatory protective immune mechanisms were always suboptimal in that they were too weak or short-lived/unsustainable, and were therefore predictably driving natural selection of a new type of coronavirus (HIVICRON) that will likely use PNNAbs to enhance its infectiousness while overcoming the virulence-inhibiting effect of these PNNAbs. That variant will be highly virulent for fully vaccine-primed individuals, and individuals with a weakened CBIIS (e.g., poor NK cell functionality) in general, in highly vaccinated countries.

Pandemics end when herd immunity is established. Sterilizing immunity in a sufficient majority of the population is essential for herd immunity to occur. Natural infection provides sterilizing

immunity; the COVID-19 vaccines do not enable sterilizing immunity. The mass vaccination campaign has not only failed to contribute to herd immunity, but it has even prevented development of herd immunity.

Unfortunately, an additional problem with the mass vaccination campaign is that the temporarily protective immune mechanisms that the mass vaccination campaign has forced the immune system to deploy have worrisome side effects, including potential autoimmune disease, potential malignancy, and other immune pathology.

Again, the COVID-19 mass vaccination campaign has been a colossal blunder. Its consequences were predictable.

NEXT STEPS:

If Dr. Vanden Bossche's analysis is correct, what can we do, how can we prepare?

A primary purpose of this article is to alert readers to Dr. Geert Vanden Bossche's (GVB's) analysis so that the general public can appreciate GVB's concerns, take them seriously, and have an opportunity to prepare for the highly virulent variant that he anticipates.

People will not have an opportunity to prepare if they are unaware of GVB's concerns or have been inclined or encouraged to summarily dismiss his concerns without adequately considering the complex science involved.

I have attempted to explain GVB's analysis in sufficient scientific detail and with sufficient clarity, so that readers will at least vaguely understand his analysis, recognize why they need to take his analysis seriously and, with appropriate urgency, make preparations.

Several related articles and videos provide detailed explanations of what specific anticipatory action steps individuals, physicians, and public health officials can take in response to GVB's analysis. Links to these articles and videos are provided at the end of this article. (See **Related Articles and Video-Discussions**).

Personally, I think GVB's analysis is the most scientifically sound, insightful, important, and helpful of any analysis that has been shared publicly by any scientist or physician during the course of the COVID pandemic.

Regarding Geert's predictions of when HIVICRON will arrive:

Throughout the pandemic, GVB has, for three main reasons, wanted to share his best opinion as to how likely he thought the emergence HIVCRON would be, when it would likely appear, and how devastating it will likely be. First, he has wanted to be honest in answering the obvious questions, "How certain are you that HIVICRON is inevitable, when do you think it will arrive, and how severe will its consequences be?" He could have routinely provided vague and "safe" answers, for example: *"It certainly is a possibility that we must take very seriously. It's impossible to predict when such a variant might arrive; possibly in several months, or a year, or even longer, hopefully never (because I could be wrong); but we need to prepare for the possibility that such a variant could exact a considerable toll."* But those answers would not have been fully honest answers. His honest answers are: He feels very certain that HIVICRON is inevitable. He thinks it will suddenly arrive within the next several weeks. He thinks an enormous number of people will suffer severe disease and die (often quickly).

Second, one of his major purposes has been to give people an opportunity to properly prepare for the situation he predicts, and this has necessitated conveyance of an honest message of urgency. Thirdly, he deeply cares about Humanity and feels an obligation to provide honest, scientifically accurate information and stimulate important dialogue about the predictable consequences of the COVID-19 mass vaccination, especially if such information and dialogue is not being offered by other scientists or physicians.

Yes, it is true that in the past GVB has been wrong regarding prediction of when a highly virulent variant would arrive. His initial timeline was wrong because he had not anticipated the SIR phenomenon. He must be excused for this because the SIR phenomenon had never before occurred during human pandemics or epidemics as it directly results from large-scale vaccine breakthrough infections (vBTIs) and/or large scale use of mRNA vaccines. GVB's recognition of the SIR phenomenon during the COVID-19 pandemic represents the first time that such a phenomenon in a human pandemic has been recognized and discussed. Also, his timeline was wrong because he did not know, and could not have known, how long the SIR phenomenon (or the CTL response) would continue---that is, he could not have known that vBTIs would cause a repetitive cycle of immune refocusing events that would significantly prolong the duration of the pandemic, thereby extending the duration of viral transmission in the population and improving innate immune protection in those whose an immune system remained responsive to training upon repeated exposure to more infectious variants.

GVB's current prediction, that a highly virulent variant will appear within the next several weeks, is based on his careful observations that the pandemic has evolved beyond the broadly cross–

reactive NAbs or CTL response, and now the most recent highly transmissible variants (KP.2 and KP.3) have characteristics that distinguish them from the previously dominant JN.1 clan by natural selection of newly emerging mutations that again concentrate on the spike RBD. Given the critical role of spike protein in facilitating, viral infection or *trans* infection (virulence), GVB assumes that the immune pressure on viral transmissibility is now on the brink of driving natural selection of a new type of coronavirus; the latter would exhibit a dramatic, structural change in the very spike protein that is largely facilitated by a mutated, more extensive glycosylation pattern, thereby enabling this new coronavirus to overcome the last hurdle that currently still largely protects COVID-19 vaccinees against severe COVID-19 disease. That last hurdle is the virulence-inhibiting effect of the PNNAbs.

GVB's timeline could again be wrong. But it is best to now make anticipatory plans and do so with considerable urgency.

FINAL COMMENT---LAWS OF NATURE:

It is important to emphasize the great extent to which GCB's analysis is based on Laws of Nature: laws of biophysics, physical chemistry, and biochemistry; laws of immunology, virology, and vaccinology; and laws of genetics, evolutionary biology, and natural evolution. For example, he pays close attention to conformational changes, competitive binding, steric hindrance, affinity/avidity, aggregate formation, dynamically changing ratios, relative concentrations, balance/imbalances, a continuum of processes, population-level pressures, fitness advantage, natural selection, and dynamic evolutionary change.

Management of the COVID-19 pandemic is not just about antibodies and making antibody levels higher. In fact, as GVB's analysis points out, excessively high antibody levels can be detrimental. Management of a pandemic requires a far deeper understanding of the extremely complex immunology, virology, vaccinology, and developmental biology involved.

Above all, Dr. Vanden Bossche appreciates the complexity of the COVID-19 situation, especially the complexity of the dynamic, continually changing interplay between the immune system and the virus and how this interplay is affected, at both an individual and a population level, by a misguided mass vaccination campaign.

Unfortunately, the scientists, physicians, public health officials, and other health authorities who were entrusted with the management the COVID-19 pandemic have not applied the same degree of scientific rigor and appreciation of complexity that Dr. Vanden Bossche has exhibited. They have violated many of the most fundamental and important principles of science, medicine, public health, ethics, and democracy: https://notesfromthesocialclinic.org/eight-

fundamental-principles-of-science-and-medicine/ The result has been enormous mistakes that have already caused enormous unnecessary suffering and death and will continue to do so. We must never again make such mistakes. .

ACKNOWLEDGEMENTS:

I would like to thank Dr. Geert Vanden Bossche for so generously and graciously helping me to at least partially comprehend his complex analysis. He has extensively reviewed this manuscript, suggested important changes, and contributed greatly to improving the scientific accuracy of the manuscript. Despite his help, I worry that my attempt to explain his analysis falls short of doing justice to his work. In that spirit I take full responsibility for any shortcomings in my explanation of his analysis. With those shortcomings in mind, I certainly welcome corrections and alternative understandings from readers. Rigorous, respectful scientific dialogue is necessary for optimal correction and improvement of our individual and collective thinking. Unfortunately, in the scientific and medical communities, there has been a dearth of dialogue about GVB's analysis.

I also thank GVB for his permission to include some of his published diagrams, which I have modified for the sake of simplicity. I would also like to thank Blaine Keigley, MD for his careful review of the manuscript and his helpful suggestions.

REFERENCES:

1. Hastie, K. M. et al. Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: a global consortium study. Science 374, 472–478 (2021). https://www.science.org/doi/full/10.1126/science.abh2315
2. Barnes, C. O. et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature 588, 682–687 (2020). https://www.nature.com/articles/s41586-020-2852-1
3. Qi, H., Liu, B., Wang, X. *et al.* The humoral response and antibodies against SARS-CoV-2 infection. *Nat Immunol* **23**, 1008–1020 (2022). https://doi.org/10.1038/s41590-022-01248-5. https://www.nature.com/articles/s41590-022-01248-5
4. Piccoli L, Park YJ, Tortorici MA, et al. Mapping Neutralizing and Immunodominant Sites on the SARS-CoV-2 Spike Receptor-Binding Domain by Structure-Guided High-Resolution Serology. Cell. 2020 Nov 12;183(4):1024-1042.e21. doi: 10.1016/j.cell.2020.09.037. Epub 2020 Sep 16. PMID: 32991844; PMCID: PMC7494283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7494283/

5. Wec AZ, Wrapp D, Herbert AS, et al. Broad sarbecovirus neutralizing antibodies define a key site of vulnerability on the SARS-CoV-2 spike protein. bioRxiv [Preprint]. 2020 May 16:2020.05.15.096511. doi: 10.1101/2020.05.15.096511. PMID: 32511337; PMCID: PMC7241100.
Broad sarbecovirus neutralizing antibodies define a key site of vulnerability on the SARS-CoV-2 spike protein - PMC (nih.gov)
6. Oliveira JR, Ruiz CMR, Machado RRG, et al. Immunodominant antibody responses directed to SARS-CoV-2 hotspot mutation sites and risk of immune escape. Front Immunol. 2023 Jan 5;13:1010105. doi: 10.3389/fimmu.2022.1010105. PMID: 36685521; PMCID: PMC9849925.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9849925/
7. Haslwanter D, Dieterle ME, Wec AZ, et al. A Combination of Receptor-Binding Domain and N-Terminal Domain Neutralizing Antibodies Limits the Generation of SARS-CoV-2 Spike Neutralization-Escape Mutants. mBio 12:10.1128/mbio.02473-21.
https://journals.asm.org/doi/10.1128/mbio.02473-21
8. Du, L., Yang, Y. & Zhang, X. Neutralizing antibodies for the prevention and treatment of COVID-19. *Cell Mol Immunol* **18**, 2293–2306 (2021). https://doi.org/10.1038/s41423-021-00752-2
https://www.nature.com/articles/s41423-021-00752-2
9. Yuan, M., Liu, H., Wu, N. C. & Wilson, I. A. Recognition of the SARS-CoV-2 receptor binding domain by neutralizing antibodies. Biochem. Biophys. Res. Commun. 538, 192–203 (2021).
https://www.sciencedirect.com/science/article/pii/S0006291X20319215
10. Lasrado, N., Ai-risk, Y. C., Hachmann, N. P., Miller, et al. (2023). Neutralization escape by SARS-CoV-2 Omicron subvariant BA. 2.86. *Vaccine*, *41*(47), 6904-6909.
https://www.sciencedirect.com/science/article/pii/S0264410X23012537
11. Jackson, C.B., Farzan, M., Chen, B. *et al.* Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* **23**, 3–20 (2022). https://doi.org/10.1038/s41580-021-00418-x
https://www.nature.com/articles/s41580-021-00418-x?fromPaywallRec=false
12. Roitgen et al., Immune imprinting , breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination; 2022, Cell 185, 1025–1040 March 17, 2022, ª 2022 The Authors. Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2022.01.018.
13. Lempp, F.A., Soriaga, L.B., Montiel-Ruiz, M. *et al.* Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. *Nature* 598, 342–347 (2021).
https://doi.org/10.1038/s41586-021-03925-1
https://www.nature.com/articles/s41586-021-03925-1

14. Perez-Zsolt, D. et al. Siglec-1 on dendritic cells mediates SARS-CoV-2 *trans*-infection of target cells while on macrophages triggers proinflammatory responses. Preprint at *bioRxiv* https://doi.org/10.1101/2021.05.11.443572 (2021).
15. Yahi N, Chahinian H, Fantini J. Infection-enhancing anti-SARS-CoV-2 antibodies recognize both the original Wuhan/D614G strain and Delta variants. A potential risk for mass vaccination? J Infect. 2021 Nov;83(5):607-635. doi: 10.1016/j.jinf.2021.08.010. Epub 2021 Aug 9. PMID: 34384810; PMCID: PMC8351274. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8351274/
16. Liu Y, Soh WT, Kishikawa JI, et al. An infectivity-enhancing site on the SARS-CoV-2 spike protein targeted by antibodies. Cell. 2021 Jun 24;184(13):3452-3466.e18. doi: 10.1016/j.cell.2021.05.032. Epub 2021 May 24. PMID: 34139176; PMCID: PMC8142859. https://pubmed.ncbi.nlm.nih.gov/34139176/
17. Guerin P, Yahi N, Azzaz F, et al. Distinct evolution of infection-enhancing and neutralizing epitopes in the spike protein of SARS-CoV-2 variants (from alpha to omicron) : a structural and molecular epidemiology study. Research Square; 2021. DOI: 10.21203/rs.3.rs-1054360/v2. https://europepmc.org/article/ppr/ppr431495
18. Wu, X., Manske, M. K., Ruan, G. J., Witter, T. L., Nowakowski, K. E., Abeykoon, J. P., ... & Witzig, T. E. (2023). Secreted ORF8 induces monocytic pro-inflammatory cytokines through NLRP3 pathways in patients with severe COVID-19. *iScience*, *26*(6). https://www.cell.com/iscience/pdf/S2589-0042(23)01006-4.pdf

RELATED ARTICLES AND VIDEO-DISCUSSIONS:

Please see the many articles and video-discussions on Dr. Geert Vanden Bossche's website: www.voiceforscienceandsolidarity.org

Also, please consider accessing Dr. Vanden Bossche's 12 week online course on ***The Immune Biology of Natural and Immune Escape Pandemics/Epidemics.*** Details about the course may be found on his website.

And consider reading Dr. Vanden Bossche's book: ***The Inescapable Immune Escape Pandemic.*** Published by Pierucci Publishing, 2023; Paperback ISBN: 978-1-956257-69-4; Ebook ISBN: 978-1-956257-68-7

The articles and video-discussions listed below are posted in the "Notes on COVID-19" section of Dr. Rennebohm's website: www.notesfromthesocialclinic.org

Note: If you click on the desired article and the article does not "load" quickly or at all (i.e., the "loading" just spins and spins and is "taking too long"), scroll down on that same page and click on the option to "open in a new tab." (That option may not be visible unless you scroll down.) The article will open quickly when you click on "open in a new tab."

In Anticipation of a Highly Virulent SARS-CoV-2 Variant: An ADDENDUM
https://notesfromthesocialclinic.org/in-anticipation-of-a-highly-virulent-sars-cov-2-variant-an-addendum/

Dr. Vanden Bossche's Analysis of the COVID-19 Situation---in a Nutshell
https://notesfromthesocialclinic.org/in-a-nutshell-dr-vanden-bossches-analysis/

The General's Memos—Simplified
https://notesfromthesocialclinic.org/the-generals-memos-simplified/

An Armed Forces Analogy: The Immunologic Consequences of the COVID-19 Mass Vaccination Campaign
https://notesfromthesocialclinic.org/an-armed-forces-analogy/

Respecting the Immune Ecosystem---Slide by Slide Written Transcript.
https://notesfromthesocialclinic.org/respecting-the-immune-ecosystem-slide-by-slide-written-transcript/ The actual video may be found by accessing the *Notes From the Social Clinic* website (www.notesfromthesocialclinic.org), going to the *Table of Contents (TOC)*, and scrolling through the *Notes on COVID-19* section. The video-presentation is located just above the Slide by Slide Written Transcript.

Video-Discussion: Clinical Implications of Geert's Predictions
https://notesfromthesocialclinic.org/video-discussion-clinical-implications-of-geerts-predictions/

Video-Discussion: *Clinical Implications of Geert's Predictions*
https://www.youtube.com/watch?v=UAblCGtVzVo

Prophylactic Use of Ivermectin—In Anticipation of a Highly Virulent SARS-CoV-2 Variant
https://notesfromthesocialclinic.org/prophylactic-use-of-ivermectin/

Ivermectin in the Prevention and Treatment of COVID-19—A Summary Statement
https://notesfromthesocialclinic.org/ivermectin-a-summary-statement/

How Has the COVID-19 Mass Vaccination Campaign Made the Natural Selection and Rapid Propagation of a HIGHLY Virulent Variant Highly Likely?
https://notesfromthesocialclinic.org/2315-2/

An Open Letter to Physicians and Physician Organizations
https://notesfromthesocialclinic.org/an-open-letter-to-physicians-and-physician-organizations/

Who or What is Most Responsible for the COVID-19 Pandemic and its Mismanagement?
https://notesfromthesocialclinic.org/who-or-what-is-most-responsible-for-the-covid-19-pandemic-and-its-mismanagement/
Eight Fundamental Principles of Science and Medicine
https://notesfromthesocialclinic.org/eight-fundamental-principles-of-science-and-medicine/

Rennebohm RM. An Open Letter to Parents and Pediatricians Regarding COVID Vaccination---Part I (Posted in March 2022, with 1078 references). https://notesfromthesocialclinic.org/an-open-letter-to-parents-and-pediatricians-2/

Do the COVID-19 Vaccines Protect Against Severe Disease and Death?
https://notesfromthesocialclinic.org/do-the-covid-19-vaccines-protect-against-severe-disease-and-death/

APPENDIX:

Footnote A: Timeline of Events during the COVID-19 Pandemic:

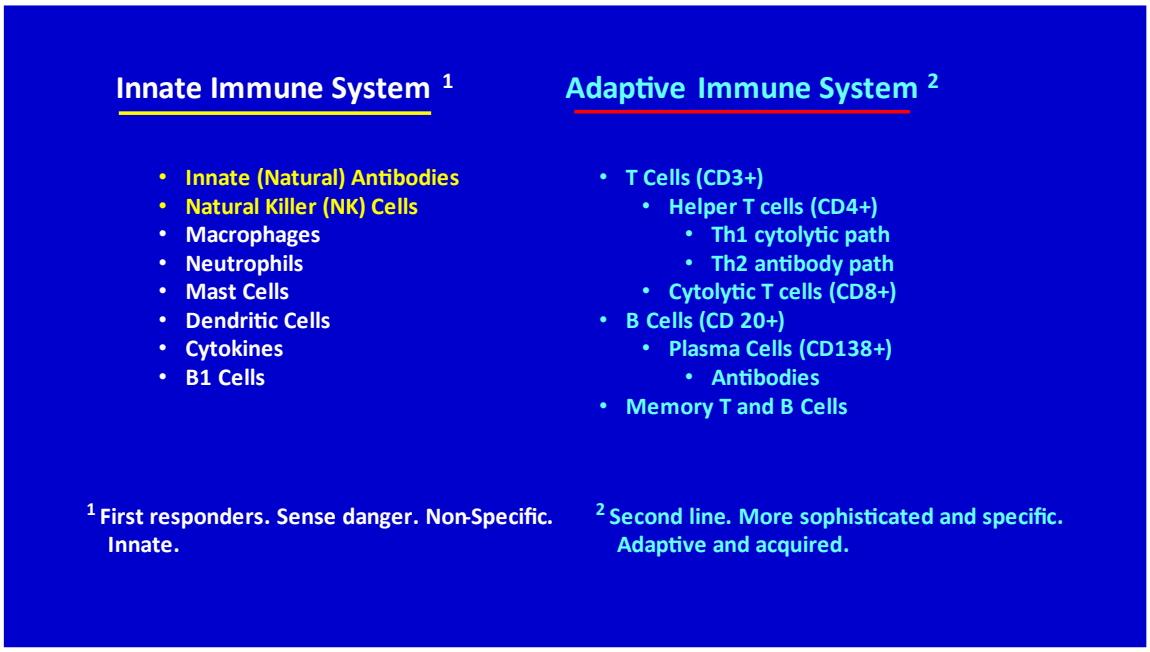
- December 2019: Wuhan strain first recognized
- Late January 2020: first case of COVID recognized in US.
- February 2020: COVID cases recognized in Europe
- Mid-March 2020: WHO declared a COVID Pandemic
- Mid-March 2020: Population-level infection prevention measures (e.g., “lockdown”) were implemented, putting pressure on the virus
- November 2020: Alpha (B.1.1.7) variant was first identified
- End of 2020: Beta (B.1.351) variant was first identified and quickly spread but was not common in the US.
- Late 2020: Delta (B.1.617.2) variant was first identified and became the dominant variant until Omicron took over.
- Mid-late December 2020: Vaccine roll-out was started. By the time of large-scale roll-out, Alpha, Beta and Delta had already appeared.
- Mass vaccination occurred throughout 2021 and beyond.

- Late November 2021: Omicron (B.1.1.529) was first identified. Omicron became prominent by Dec 2021, dominant by mid December 2021, and a vast array of Omicron co-circulating Omicron variants have dominated the scene ever since.
- September 2023: JN.1 variant was first documented in the US. It accounted for 21% of cases by mid-December 2023 and accounted for more than 85% by late January 2024.

Footnote B---Innate immune system versus adaptive Immune system: Please see TABLE 1. The innate immune system represents the first line of immune defense against viral infection. Natural Killer cells (NK cells) are particularly important because they are capable of quickly recognizing that a host cell has become infected, and they can quickly kill infected cells (early in the course of the cell's infection), thereby killing the virus (whose survival depends on replicating within living cells).

The adaptive arm of the immune system is the second line of immune defense. The adaptive arm is responsible for antigen-specific actions, including production of virus-specific antibodies. Whereas the NK cells recognize and react to cells that have been infected by any one of a broad and vast array of viruses (or other pathogens), the adaptive arm recognizes and reacts against specific viruses (or other pathogens). Often, the innate immune system (which reacts against a broad range of viruses) is able to control viral infection without needing the specific, more sophisticated (and more slowly acting) adaptive arm to become involved. More information about NK cells is provided under Event 12.]

TABLE 1

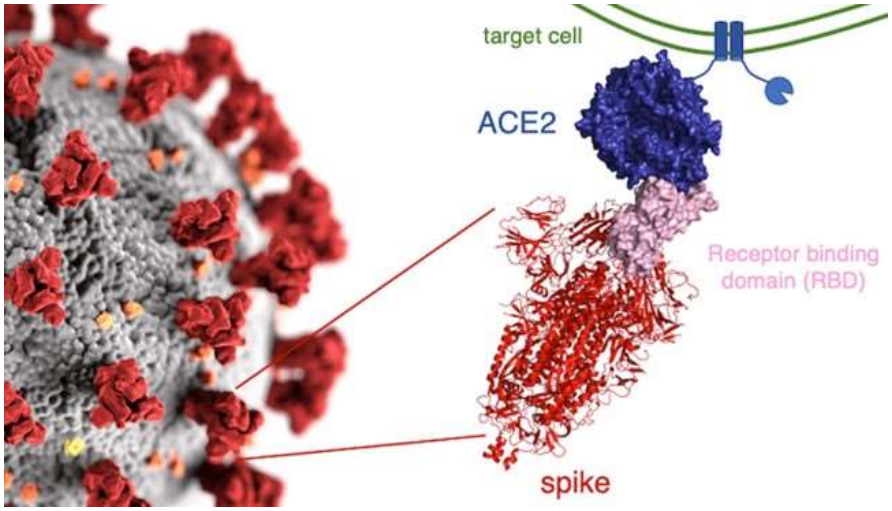


Footnote C---definition of "antigens" and "epitopes:" An antigen is any substance that triggers the body to make an immune response (e.g., production of antibody) to that substance. Antigens can be proteins, peptides, polysaccharides, lipids, nucleic acids, etc. There are foreign antigens, self-antigens, and altered self-antigens. Foreign antigens include "self-mimicking" antigens on viruses. Viruses use self-mimicking antigens to encourage the immune system to leave them (the virus) alone. Early in life, the immune system learns how to distinguish between obviously foreign antigens, self-antigens, and altered self-antigens. (Altered self-antigens, for example, occur when a cell becomes malignant.) Normally, the immune system attacks foreign antigens and altered self-antigens but leaves self-antigens alone. Although the immune system is good at recognizing obviously foreign antigens, it is not good at distinguishing "self-mimicking" foreign antigens from true self antigens.

An epitope, also known as an antigenic determinant, is the part of an antigen that is recognized by the immune system, specifically by antibodies, B cell receptors, or T cell receptors. There are highly variable, highly immunogenic, immune dominant epitopes; and there are more conserved, less immunogenic, immune subdominant epitopes.

Footnote D---Neutralizing Antibodies (NAbs) and Neutralizing Capacity: A primary mechanism by which the SARS-CoV-2 virus enters (and infects) a human host cell is for the receptor binding domain (RBD) of the virus to attach to the ACE-2 receptor on the surface of a human host cell. (See Medical Illustration A.)[11] The ACE-2 receptor is the "lock" to the door that allows virus to enter the cell; the RBD is the "key" that opens that lock. When the RBD successfully attaches to the ACE-2 receptor, "the door is opened" and the virus is able to enter the cell and replicate within that cell. (Viruses are able to survive and propagate only if they can replicate within host cells.)

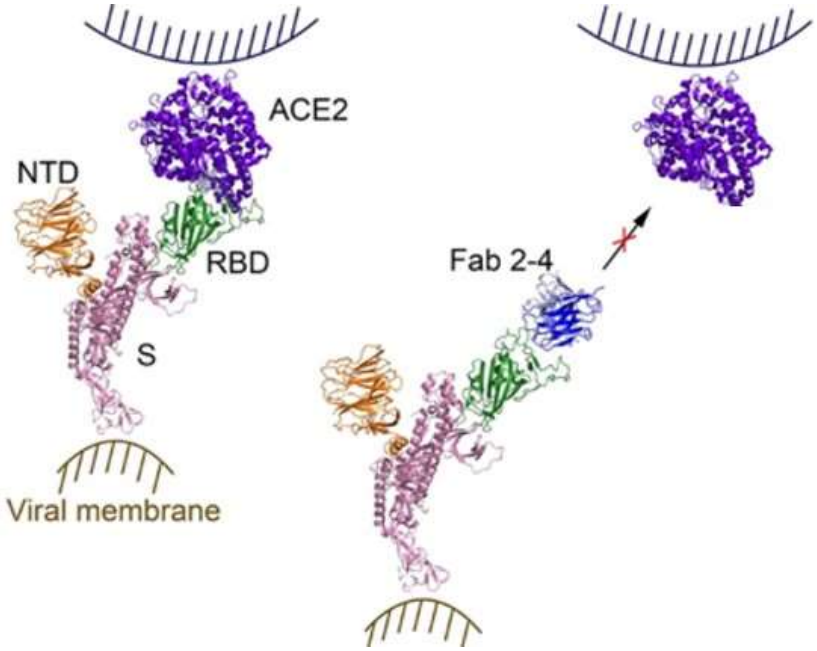
MEDICAL ILLUSTRATION A



Medical Illustration A shows the SARS-CoV-2 virus on the left, with its multiple spike proteins protruding from its surface. On the right is a close-up view of a single spike protein, with the spike protein's receptor binding domain (RBD) in pink-purple and the rest of the spike protein in red. In this drawing, the RBD has successfully attached to the ACE-2 receptor on the target (human host) cell. This attachment "opens" the door to the cell and allows the virus to enter and infect the cell.

Among the most important antibodies that people developed after natural infection with the Wuhan strain, or after receiving a vaccine that exposed them to the Wuhan strain spike protein, are the neutralizing antibodies (NAbs) that work by attaching to the most immunodominant epitopes within the receptor binding domain (RBD) of the spike protein of the virus. (See Medical Illustration B.) The binding of these NAbs to the RBD blocks attachment of the RBD to the ACE-2 receptor on human cells, thereby interfering with entry of virus into these human cells. This is what is meant by a "neutralizing" antibody (NAb).

MEDICAL ILLUSTRATION B



Medical Illustration B shows, on the left, the spike protein of the virus, with its RBD (in green) successfully attached to the ACE-2 receptor of a host cell. On the right side, a **neutralizing antibody** (Fab 2-4, in blue) is attached to the RBD (in green) of the spike protein. This neutralizing antibody (NAb) is blocking attachment of the RBD to the ACE-2 receptor on the surface of the host cell, thereby preventing entry of the virus into the host cell.

When a person is naturally infected with the SARS-CoV-2 virus (Wuhan strain, e.g.), or is exposed to the Wuhan strain spike protein through vaccination, the immune system produces multiple different NAbs, each directed at a different epitope on the spike protein of the virus. In

addition to producing NAbs to the most immunodominant epitopes within the RBD (which are also the most variable, least conserved epitopes), the immune system also produces NAbs to more conserved, immune subdominant epitopes of the spike protein (but to a far less extent, in unvaccinated individuals). These NAbs to more conserved, less variable epitopes have less neutralizing capacity than the NAbs to the most immunodominant epitopes, but they have valuable broadly cross-reactive potential (i.e., may cross-react with a broad range of potential SARS-CoV-2 variants, including future variants).

Although the NAbs against immunodominant epitopes on the RBD of the Wuhan strain would work well when/if the individual again encountered the Wuhan strain, these NAbs would not work equally well against a new viral variant (Alpha variant, e.g.) that has developed mutations in epitopes within its RBD that render it to be at least somewhat resistant to the NAbs against the Wuhan strain. That is, the NAbs against the immunodominant epitopes on the RBD of the Wuhan strain (anti-Wuhan RBD NAbs) will not optimally block attachment of an Alpha variant's RBD to the ACE-2 receptor on human host cells. Because of this mis-match, the neutralizing capacity of the anti-Wuhan RBD NAbs will not be as strong against a new (Alpha) variant. However, since the RBD of the Alpha variant was only slightly different from the RBD of the Wuhan strain, the anti-Wuhan RBD NAbs will cross-react fairly well against the mutated RBD of the Alpha variant.

So, what happens when a person who has produced anti-Wuhan NAbs (due to infection in early 2020, e.g.) then becomes significantly infected with the Alpha variant in late 2020? When the Alpha variant breaks through the innate immune defense (because the anti-Wuhan NAbs are declining in titer) the immune system (because of "original antigenic sin," as explained below) recalls not only the anti-Wuhan RBD NAbs that are directed against the immunodominant epitopes of the RBD, but also recalls the NAbs to more conserved, immune subdominant epitopes. These latter NAbs, which the initial Wuhan infection primed/prepared the immune system to produce, are broadly cross-reactive and will thereby help to partially neutralize the new Alpha variant. [See discussion of memory B cells, immune priming, and original antigenic sin (OAS), below.] The combination of recalled anti-Wuhan RBD NAbs to immunodominant epitopes (though slightly mismatched with mutated epitopes on Alpha) and recalled NAbs to subdominant epitopes results in adequate control of Alpha infection. (Of course, NK cells of the innate immune system normally contribute early on and deserve most of the credit for controlling the infection.) **Note:** Upon infection with the Alpha variant, the immune system does not produce new high affinity NAbs that are specific for (highly matching with) the mutated immunodominant epitopes within the RBD of the Alpha variant.

Footnote E---Memory B cells: When the immune system develops virus-specific antibodies, like the NAbs against immunodominant epitopes within the RBD of the Wuhan strain and NAbs to subdominant epitopes, it also develops memory B cells and memory T cells that will be able to re-produce (recall production of) these same antibodies when/if that person again becomes infected with that virus (or a closely related, similarly looking, variant of the virus, like the Alpha or Beta variant).

Footnote F---Immune Priming and Recall: "Immune priming" refers to the preparing of immune cells (primarily T cells and B cells) for the capacity for memory and potential recall. Both natural infection and vaccination prime the immune system to produce antibodies and to be able to recall production of those antibodies in the future when needed. Whereas the initial full priming takes 4-6 weeks, previously produced antibodies can be recalled quickly. (In this article, "highly vaccinated individuals" are also referred to as "fully vaccine-primed individuals.")

Footnote G---Original Antigenic Sin (OAS):[12] OAS refers to the fact that, normally, when a person who, for example, has been primed by the Wuhan Strain in the past, then (later) encounters a new distinct variant (e.g., the Alpha variant), their immune system will predominantly recall anti-Wuhan RBD NAbs that are directed against immunodominant epitopes within the RBD. (These antibodies are recalled via previously primed memory B cells that specifically bind to these epitopes and previously primed cognate memory T cells.) These NAbs are predominantly recalled because (with the help of memory T helper cells) memory B cells that already know how to produce anti-Wuhan NAbs are stimulated by the Alpha variant, dominantly proliferate, and quickly recall those Abs. As a result, infection of previously Wuhan S-primed individuals with the Alpha variant primarily results in high titers of slightly outdated anti-Wuhan NAbs directed against immunodominant S-associated epitopes. Due to the immunodominant nature of the epitopes and the previously induced immunological memory, the recall of these anti-Wuhan NAbs will overshadow the recall of previously primed memory B cells recognizing subdominant Wuhan S-associated epitopes or the *de novo* priming of naïve B cells specifically recognizing Alpha Spike-specific epitopes.

Note: The above-described situation will be exactly reversed in individuals experiencing BTI-mediated SIR, due to masking of the immunodominant S-associated epitopes. These individuals will primarily recall previously primed cross-reactive NAbs against subdominant epitopes that are shared among several different variants (including, but not limited to, the currently circulating variant). Any individual possessing high titers of NAbs will proceed to SIR upon exposure to an antigenically very distinct variant (i.e., resulting in poorly neutralizing capacity of the pre-existing Abs). However, SIR is a rather rare event in unvaccinated individuals and primarily occurred in C-19 vaccinees after the advent of Omicron. Hence, large-scale SIR events resulted from large-scale vBTIs with Omicron variants in highly C-19 vaccinated populations.

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June 19, 2024