Immunological correlates of vaccine breakthrough infections caused by SARS-CoV-2 variants in highly C-19 vaccinated populations

by Geert Vanden Bossche PhD

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voiceforscienceandsolidarity.org

This article is dedicated to John Heathco

(Oct 29, 1982 - June 13, 2023)

'Johnny, this is for you. Without your help,

I struggled a lot to get the job done.

I am sure you would have loved to read it.'

– Geert

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Executive summary

In highly Covid-19 (C-19) vaccinated populations, an increase in IgG4 antibody (Ab) titers following steric immune refocusing (SIR)-enabling PNNAb[1]-dependent vaccine breakthrough infections (VBTIs) with infectious SARS-CoV-2 (SC-2) immune escape variants promoted generalized hyposensitization to 'foreign' and hypersensitization to 'self'. Whereas hyposensitization to 'foreign' has an anti-inflammatory effect, thereby mitigating disease symptoms, hypersensitization to 'self' promotes carcinogenicity and autoreactivity.

SIR-enabling VBTIs, but also mRNA vaccination, facilitates immune refocusing to more conserved, immune subdominant spike (S)-associated epitopes. Delayed maturation of these de novo primed, subneutralizing Abs into isotype-switched IgG4 anti-S Abs enables prolonged immune pressure on viral infectiousness, thereby promoting large-scale co-circulation of more infectious SC-2 immune escape variants. In other words, SIR-enabling VBTIs and delayed maturation of new, broadly cross-neutralizing anti-S Abs trigger a cascade of immune selection events that eventually mitigated disease caused by SC-2 and other unrelated viral pathogens (via anti-inflammatory IgG4) and thereby fostered viral spread. Upon subsequent VBTI, these very IgG4-switched anti-S Abs refocus the immune response to yet another set of S-associated epitopes with an even lower level of immunogenicity (i.e., immune recessive[2]). Their delayed maturation into isotype-switched IgG4 Abs eventually promoted co-circulation of a diversified spectrum of highly infectious immune escape SC-variants.

It is reasonable to assume that the lower the immunogenicity of a given epitope, the higher the likelihood it has functional homology with self-epitopes of the host. I therefore hypothesize that acute autoimmune disease and early-onset cancer in highly C-19 vaccinated populations are due to VBTI- or mRNA vaccine-mediated immune refocusing to more conserved, S-associated 'self-like' epitopes. Refocusing to S-associated, poorly immunogenic 'self-like' epitopes likely generates Abs that -after delayed maturation into isotype-switched IgG4 Abs in germinal centers- cross-react with 'self' or 'altered self' epitopes. Whereas Ab-mediated recognition of 'self' epitopes on the surface of healthy cells would entail failure of these self-epitopes to activate self-antigen (Ag)-specific regulatory T cells (Tregs) that downregulate activation/proliferation of self-reactive T cells such as to prevent recognition of

[1] PNNAb: Polyreactive non-neutralizing Ab
[2] 'Immune recessive' antigens are normally only poorly recognized or not recognized at all by the immune system and do not contribute significantly to the immune response against the pathogen.

'self', Ab-mediated recognition of 'altered self' epitopes expressed on the surface of malignantly transformed cells (i.e., cancer cells) would prevent their ADCC[3]-mediated immune recognition by Natural Killer (NK) cells. Whereas the former Abs promote autoreactivity, the latter promote carcinogenicity.

Both PNNAb-dependent VBTIs and mRNA vaccination fueled immune refocusing. The consequent shift of the anti-S Ab repertoire toward broadly cross-reactive virus-neutralizing or infection-inhibiting Abs led to large-scale immune escape in highly C-19 vaccinated populations. This, in turn, facilitated Ab-independent VBTIs with highly infectious Omicron descendants (e.g., BQ. 1- and XBB-derived variants) in C-19 vaccinees who had previously experienced PNNAb-dependent VBTIs and even in mRNA vaccinees who had not previously experienced such infections (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/).

Within the context of high titers of broadly cross-reactive IgG4 Abs, SIR-disabling, Ab-independent VBTIs involving highly infectious Omicron descendants hinder the re-stimulation of short-lived PNNAbs and cause generalized immune suppression of foreign- or self-centered CD8+ T cells while enabling asymptomatic viral transmission.

Collectively declining PNNAb titers in highly C-19 vaccinated populations drive natural selection of newly emerging variants that have the capacity to trigger enhanced severe C-19 disease in C-19 vaccinated individuals whereas suppression of foreign-centered CD8+ T cells can cause relapse of cancers that were previously in remission or lead to the reactivation of dormant chronic infections. On the other hand, suppression of self-centered CD8+ T cells can trigger a reawakening of underlying autoimmune disease. This likely accounts for the rising incidence of turbo cancers, accelerated autoimmune diseases and acute flare-ups of chronic infections that currently contribute to the alarming increase of excess mortality reported in several highly C-19 vaccinated countries.

In conclusion, the sequence of SIR-enabling PNNAb-dependent VBTIs followed by SIR-disabling VBTIs establishes a connection between widespread viral immune evasion and the concurrent emergence of non-Covid-19-related health issues and increased mortality. This connection is mirrored by the gradual increase of anti-S IgG4 Abs and attributed to their stimulation through either immune refocusing (SIR) or immune imprinting, respectively. A high prevalence of high IgG4 Ab titers in a highly C-19 vaccinated population should therefore be considered a poor prognostic sign for the outcome of this immune escape pandemic.

[3] Ab-dependent cell-mediated cytotoxicity

List of abbreviations

Ab: Antibody

ADCC: Ab-dependent cell-mediated cytotoxicity

Ag: Antigen

APC: Ag-presenting cell

BCR: B cell receptor

C-19: Covid-19

CTL: Cytotoxic T cell lymphocyte

DC: Dendritic cell

IgG4: Immunoglobulin G subtype 4

MHC: Major histocompatibility complex

NAb: Neutralizing Ab

NK cell: Natural Killer cell

PD-1: Programmed cell death protein 1

PNNAb: Polyreactive non-neutralizing Ab

RT-PCR: Reverse transcription polymerase chain reaction

S: Spike protein

SIR: Steric immune refocusing

TCR: T cell receptor

Th: T help(er)

VBTI: Vaccine breakthrough infection

RBD: Receptor-binding domain

SC-2: SARS-CoV-2

S-NTD: N-terminal domain of S protein

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1. SIR: A major game changer in the C-19 immune escape pandemic

1.1. Since the advent of Omicron, 'original antigenic sin' (i.e., imprinted immunity) alone can no longer explain the changes in viral behavior.

Immune imprinting (or: 'original antigenic sin') has been proposed to explain the loss of C-19 vaccine efficacy against newly emerging Omicron subvariants, such as BQ.1.1 and XBB.1, and thereby result in VBTIs (https://europepmc.org/article/med/37369369).

However, the notion of immune imprinting fails to offer a satisfactory explanation for the occurrence of VBTIs that do not result in severe C-19 disease. Additionally, this concept does not clarify why the emergence of new immune escape variants within a population that has achieved high C-19 vaccination rates is correlated with a reduced occurrence of C-19 disease and a decrease in viral shedding, even though sterilizing immunity is not achieved. It would also present a challenge to explain why significantly reduced viral shedding within a population retaining at least a "certain" level of virus-neutralizing Ab capacity (attributed to their presumed recall) wouldn't promptly result in the elimination of the virus (which is obviously not the case!). From the data published, it is obvious that the authors misinterpreted their data:

Graph 1D clearly indicates that VBTIs with BA.2 elicit broadly neutralizing capacity. The same has previously been reported to also occur upon VBTIs with BA.5 in humans. However, both the level and breadth of these Ab responses diminish with enhanced infectiousness of the virus (XBB.1 is more infectious than BQ.1.1 and the latter is more infectious than BA.2/5). This unambiguously indicates that the diminished neutralizing capacity (causing the VBTI) shifts the immune response towards more conserved, less immunogenic S-associated domains. This points to immune refocusing, a phenomenon that is more complex and very different from 'antigenic sin' and significantly contributes to viral immune escape (see sections 1.2. and 1.3. below).

1.2. The advent of Omicron triggered VBTI-mediated SIR-1. The latter resulted in delayed maturation of SIR-2-enabling IgG4 Abs. Since SIR drives viral immune escape, the advent of Omicron caused the pandemic to evolve into a self-catalyzing chain of large-scale immune escape.

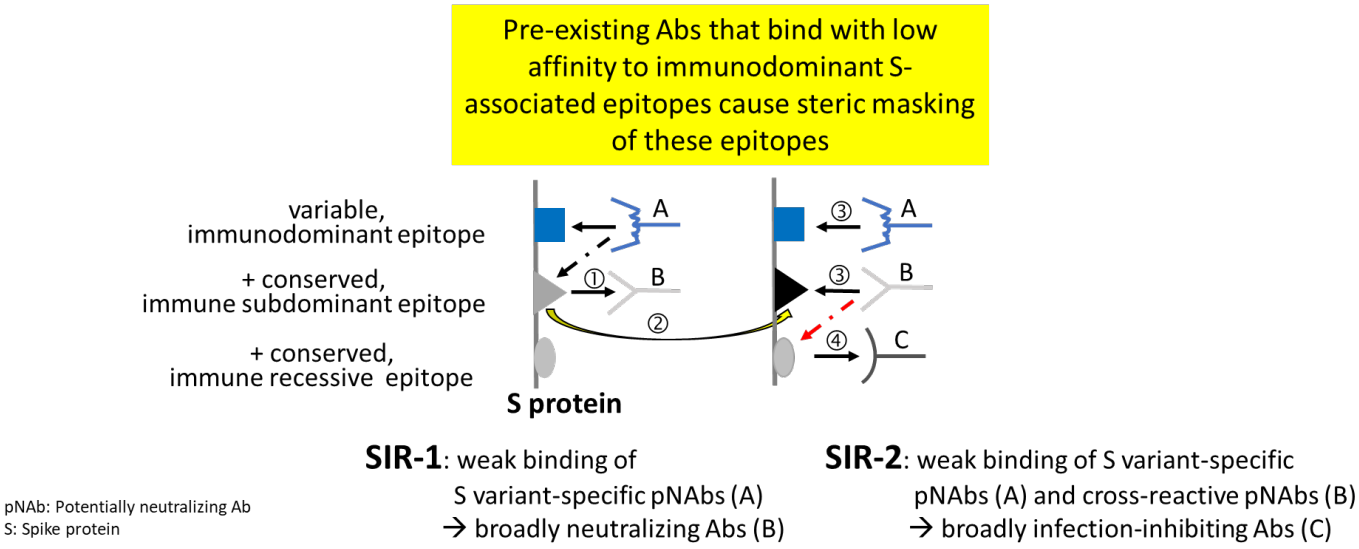

Fig. 1: VBTIs trigger immune refocusing and thereby elicit broadly cross-functional Abs and potentially pathogenic isotype-switched IgG4 Abs. **For detailed explanation, refer to p. 56.**

Immune refocusing (see Fig. 1) allows the host immune system to develop some new neutralizing capacity after multiple mutations in previously circulating pre-Omicron variants caused the neutralizing capacity of vaccine-induced S-specific neutralizing Abs (NAbs) to greatly diminish. Whereas the latter were directed at a diversified spectrum of dominant, variant-specific epitopes that are primarily situated within receptor-binding domain (RBD) of S (S-RBD), the newly primed NAbs target a limited subset of more conserved epitopes and have relatively low affinity. This explains why cross-neutralizing Ab titers elicited shortly after SIR-enabling VBTIs, or after mRNA booster immunizations in previously mRNA vaccine-primed individuals (see under 4.3.), rapidly declined (https://pubmed.ncbi.nlm.nih.gov/36548397/).

Before the advent of Omicron, priming of vaccine-induced NAbs directed against highly variable S-associated immunodominant epitopes on pre-Omicron variants was assisted by cognate T help. *Cognate* Th-dependent priming of anti-S Abs promotes their maturation into high-affinity Abs. Consequently, vaccinal Abs targeted at S-associated immunodominant epitopes (primarily situated within S-RBD) rapidly gained enhanced virus-neutralizing capability.

On the contrary, following the emergence of Omicron, SIR-mediated priming of broadly neutralizing Abs elicited against a limited set of epitopes comprised within a more conserved, S-associated subdominant domain is assisted by *noncognate* CD4+ T memory cells. Recall of the latter is probably aided by PNNAb-dependent enhancement of viral infectivity, which likely promotes the aggregation of progeny virions

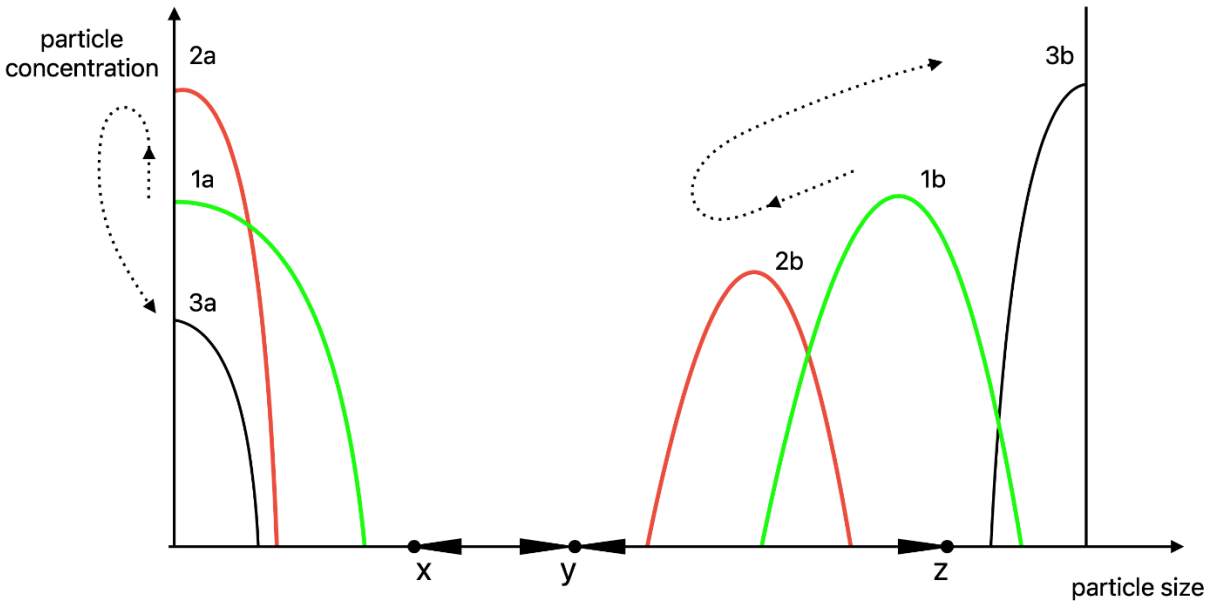

Fig. 2: Diagrammatic presentation of the size distribution of virus particles released from SC-2-infected target cells following VBTI by a new emerging variant. **For detailed explanation, refer to p. 57.**

after their release from infected cells (see Fig. 2). Increased uptake of viral aggregates (in the context of VBTI) or multimeric S protein (in the context of mRNA-based vaccination) into Ag-presenting cells (APCs) guarantees the immunogenic display of virus- or S protein-derived antigenic T helper cell peptides, respectively. On the other hand, poor uptake of monodispersed virions bound by high-affinity, non-neutralizing Abs into APCs allows the immune system to redirect its response to more conserved, weakly immunogenic domains. However, since these antigenic regions are not located on the viral particles (or on the S protein in the case of mRNA-based vaccination) that triggered the recall of previously primed T helper cells, the subsequent priming process for generating new broadly cross-neutralizing Abs cannot be assisted by *cognate* T help. Provision of weak, *noncognate* T help by previously primed Th cells would explain why these Abs have low neutralizing capacity[4]. It may also explain why it takes several months after SIR-enabling VBTI, or mRNA booster vaccination, for de novo primed memory B cells to mature in germinal centers and produce isotype-switched IgG4 anti-S Abs of high avidity (https://pubmed.ncbi.nlm.nih.gov/36548397/; see also under section 3.).

New broadly anti-S NAbs will mature into anti-S IgG4 Abs and thereby acquire functional monovalency. Because IgG4 Abs are functionally monovalent and have reduced Fc-mediated effector function (https://pubmed.ncbi.nlm.nih.gov/36548397/), they are optimally suited to prevent enhanced aggregation of progeny virus upon its release from virus-infected cells (see under section 1.3.1.2.). Opsonization of monodispersed

[4] In case *cognate* T help were provided, these Abs would be endowed with strong virus-neutralizing capacity. This would prevent them from placing suboptimal immune pressure on viral neutralizability and therefore hamper immune escape into more infectious Omicron descendants.

progeny virions by IgG4 Abs is likely to facilitate a new immune refocusing event (i.e., SIR-2) when C-19 vaccinees are subsequently exposed to VBTIs caused by more infectious immune escape variants (see fig. 2 and section 1.3.1.2.).

As avidity maturation of broadly cross-neutralizing Abs into IgG4 Abs takes several months, repeated re-exposure to circulating variants ensures prolonged suboptimal immune pressure on virus neutralizability and thereby promotes the emergence of new, more infectious, immune escape variants. Similar to SIR-1, SIR-2 likely results in delayed affinity maturation of the induced anti-S Ab-producing B cells into IgG4-switched memory B cells and would therefore allow broadly infection-inhibiting Abs to exert prolonged suboptimal immune pressure on viral infectiousness (see under section 1.3.1.2.).

In summary:

SIR-1-enabling VBTIs in highly C-19 vaccinated populations seem to provide optimal conditions for generating large-scale immune selection pressure on viral infectiousness (https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic: chapters 1.2.3.-1.2.8.). Delayed maturation of SIR-1-induced cross-neutralizing Abs into isotype-switched IgG4 Abs enables highly C-19 vaccinated populations to place large-scale immune selection pressure on viral infectiousness (see under sections 1.3.1. and 1.3.2.). By triggering SIR-2, elevated titers of high-avidity IgG4 Abs cause VBTIs to self-catalyze large scale immune escape. It is, therefore, fair to state that these Abs aid in the amplification of natural selection for variants that possess even higher infectiousness. This ultimately paves the way to the emergence of new Omicron-derived variants that have the capacity to enhance viral virulence in C-19 vaccinees, as explained below in section 1.3.2.

1.3. Immunological correlates of viral immune escape in highly C-19 vaccinated populations.

1.3.1. Immunological correlates of SIR-enabling VBTIs and SC-2 immune escape in highly C-19 vaccinated populations.

1.3.1.1. VBTI-mediated SIR-1 results from binding of anti-S Abs with poorly neutralizing capacity to the immunodominant epitopes of monovalent S antigen, thereby facilitating immune recognition of immune subdominant domains and priming broadly functional anti-S Abs of low affinity.

First, VBTI-mediated SIR in vaccinated individuals resulted in low-affinity binding of previously vaccine-induced Abs to the S-associated immunodominant domains displayed on single progeny virions. This allowed the host immune system to re-orient its immune response to *subdominant* S-associated immunogenic domains and rapidly elicited broadly neutralizing, low-affinity Abs to said domains (see fig. 1). Due to their relatively low affinity, the titers of these Abs rapidly fell below the optimal threshold required for providing protection from infection and reducing viral transmission while still mitigating C-19 disease upon re-exposure.

The combination of their suboptimal neutralizing activity and their delayed maturation (in germinal centers) into functionally monovalent Abs (i.e., IgG4; see under section 3) resulted in prolonged large-scale immune selection pressure on virus neutralizability. The latter promoted natural selection and co-circulation of a broad spectrum of poorly neutralizable immune escape variants, whose infectiousness was therefore prone to being enhanced by PNNAbs.

It is worth noting that broadly neutralizing Ab titers are not only induced by SIR-enabling VBTI but also by mRNA vaccination (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9886553/; see under section 4.3.). I have previously explained why and how mRNA vaccination is likely to induce SIR (https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic: chapters 1.2.1. and 1.2.2.). It is therefore fair to conclude that both SIR-enabling VBTI and mRNA vaccination foster enhanced viral immune escape (see also under section 5.).

1.3.1.2. Maturation of broadly cross-functional Abs into isotype-switched IgG4 Abs allows an additional SIR event (SIR-2). The latter further improves the vaccinee's anti-viral immune response and thereby enables natural selection and co-circulation of highly infectious immune escape variants in highly C-19 vaccinated populations.

The intriguing aspect of affinity maturation in SIR-induced, broadly functional antibodies is that it takes several months before it produces 'functionally monovalent' antibodies with high avidity (see under section 3.5.-3.7.).

After the first SIR event (SIR-1), maturation of broadly cross-neutralizing Abs into broadly neutralizing, bispecific IgG4s of high avidity eventually allows for a second SIR (SIR-2) event to occur upon subsequent

exposure of C-19 vaccinees to newly emerging, more infectious immune escape variants (see fig. 1). Recall of IgG4 anti-S Abs generates elevated levels of these Abs and thereby allows the host immune system to effectively prevent enhanced aggregation of more infectious progeny virions that are released in high density from virus-infected cells (see fig. 2). The subsequent monovalent binding of anti-S IgG4 Abs to the immunodominant epitopes on S protein Ag displayed on offspring virions is believed to trigger SIR-2. SIR-2 re-orients the humoral immune response to S-associated antigenic regions of SC-2 that are more conserved, therefore even less immunogenic, and presumably comprise infection-facilitating epitopes. New, broadly cross-reactive Abs of low affinity targeted at these immune recessive epitopes rapidly exert suboptimal immune pressure on viral infectiousness. Because of the delayed maturation of these Abs (in germinal centers) into new, isotype-switched anti-S IgG4 Abs, SIR-2-enabling VBTIs in highly C-19 vaccinated populations likely resulted in *prolonged* large-scale immune selection pressure on the (intrinsic) viral infectiousness of the circulating variants. It is reasonable to assume that this explains the rapid and successive emerοence of a diversified spectrum of dominantly circulating, highly infectious Omicron-derived immune escape variants.

It is important to note that elevated titers of IgG4 Abs trigger SIR-2 without compromising viral shedding as they hamper the interaction of IgG4-coated virions with Fc receptors on APCs and NK cells (see under section 3.1.). Impaired internalization of progeny virions into APCs and their failure to interact with NK cells prevent cytotoxic activation of CTLs (cytotoxic T cell lymphocytes) or ADCC-mediated activation of cytolytic NK cells and thereby prevent rapid killing of virus-infected epithelial cells. This likely explains why IgG4 Abs initially mitigated disease symptoms while promoting shedding in C-19 vaccinees exposed to more infectious variants.

1.3.1.3. Enhanced evolution of immune escape variants toward more infectious Omicron descendants parallels a growing incidence of autoreactive and tumor diseases.

As already mentioned, SIR-enabling VBTIs eventually result in elevated levels of anti-S IgG4 Abs. The latter in turn triggered another SIR event while preventing virus internalization into APCs, thereby avoiding immune inflammatory symptoms and rapid abrogation of viral shedding. This resulted in a type of *'pseudo' tolerance*[5] toward the circulating variant, granting the mismatched anti-S IgG4 Abs plenty of opportunity to bind

[5] In section 3.7., I explain why IgG4 Abs do not induce tolerance *sensu* stricto.

with low affinity to S Ag on variant progeny virus and re-orient the host's humoral immune response to more conserved, infection-facilitating S-associated epitopes. The resulting suboptimal immune pressure on these epitopes caused highly C-19 vaccinated populations to exert prolonged immune selection pressure on viral infectiousness. The latter eventually culminated in natural selection and rapidly successive sequence of dominantly circulating, highly infectious Omicron descendants in these populations.

Since maturation of IgG4 Abs results in immune refocusing to immune recessive S-associated domains, it is rational to anticipate that circulation of increasingly infectious Omicron variants will result in more frequent instances of immune activation (i.e., immune 'unsilencing') of more conserved, 'self-like' epitopes associated with the S protein found within these antigenic regions. Maturation of the newly elicited Abs into high-avidity isotype-switched IgG4s, along with subsequent reactivation, could eventually generate high IgG4 Ab titers that enable recognition of 'self' or 'altered self' antigens expressed on the surface of healthy or malignantly transformed host cells, respectively.

1.3.2. Immunological correlates of SIR-disabling VBTIs and SC-2 immune escape in highly C-19 vaccinated populations.

1.3.2.1. Co-circulation of highly infectious Omicron descendants results in frequent VBTIs that are largely asymptomatic and mitigate viral shedding while raising population-level immune pressure on viral trans infectiousness.

When viral progeny is abundantly produced in virus-infected host cells following VBTIs with newly emerging, highly infectious Omicron descendants (e.g., XBB.1.5; XBB.1.16; XBB.1.9.2; EG.5, …), the yield of viral progeny per infected cell is high and likely results in formation of large viral aggregates. This is due to the fact that functionally monovalent IgG4 Abs might not possess the necessary binding potency to hinder most individual progeny virions from forming large viral aggregates, even when these Abs are present in high concentrations. Consequently, the viral offspring released from epithelial cells infected by a highly infectious variant would primarily consist of large viral aggregates instead of monodispersed, IgG4-bound virions (see fig. 2). The uptake of such large viral aggregates by APCs likely results in enhanced Ag presentati¬¬on and thereby triggers MHC[6] class I-unrestricted cytotoxic activity of CD8+ T cells. Cytolytic elimination of both virus-infected cells and activated APCs

[6] MHC: Major Histocompatibility Complex

will not only halt C-19 disease and abrogate viral shedding (leading to reduced levels of SC-2 in the environment, like in wastewater), but it may also curtail effective immune presentation of other antigens that challenge the vaccinee's immune system. Failure to present foreign antigens could lead to lack of protection upon natural exposure to several other pathogens or upon vaccination with several distinct Ags.

This already implies that vaccination with updated S-based C-19 vaccines matching the circulating variants will inevitably fail to elicit protective cognate Abs. In other words, neither VBTIs with highly infectious Omicron descendants nor C-19 vaccines using updated variant S Ag in the context of highly infectious circulating variants will be able to elicit new virus-neutralizing Abs.

However, abrogation of professional Ag presentation also prevents recall of previously virus- or vaccine-primed Th cells and therefore disables SIR. This is because failure to recall these Th cells will prevent priming of new, cross-functional anti-S Abs. Instead, being re-exposed to highly infectious variants likely boosts the levels of functionally monovalent anti-S IgG4 Abs, resulting in high titers of these Abs due to immune imprinting.

It is reasonable to assume that functionally monovalent IgG4 Abs impede formation of multimeric viral colloids in the upper respiratory tract upon subsequent exposure to circulating virus. Consequently, production of new, short-lived PNNAbs by peripherally circulating B cells is no longer stimulated. Diminished production of short-lived PNNAbs will result in a rapid and population-wide decline in PNNAbs in highly C-19 vaccinated populations.

It appears, therefore, that VBTI following exposure to highly infectious Omicron descendants in a context of high concentrations of IgG4 Abs indirectly causes PNNAb concentrations in vaccinees to collectively decrease while promoting asymptomatic transmission. There can be no doubt that this situation generates enhanced suboptimal immune pressure on the highly conserved (i.e., SC-2 variant-nonspecific) antigenic site within S-NTD that serves as a binding site for *trans* infection-inhibiting PNNAbs. As explained under 1.3.2.2., suboptimal titers of *trans* infection-inhibiting PNNAbs cause highly C-19 vaccinated populations to exert immune selection pressure on viral *trans* infectiousness and hence, on the capacity of SC-2 to cause severe C-19 disease (as PNNAb-mediated inhibition of viral *trans* infectiousness prevents the occurrence of severe C-19 disease).

However, diminished production of PNNAbs does not reduce viral infectivity of currently circulating variants. This is because the latter have high intrinsic infectiousness and do not rely on PNNAb-mediated enhancement of viral infectiousness to cause VBTI. The latter are, therefore, referred to as 'Ab-independent VBTI'.

1.3.2.2. The level of immune pressure exerted by highly C-19 vaccinated populations determines the evolutionary path to PNNAb-mediated enhancement of viral virulence in C-19 vaccinees.

Due to the continued viral transmission resulting from asymptomatic infection caused by highly infectious variants among C-19 vaccinees, declining PNNAb titers within highly C-19 vaccinated populations will progressively exert immune selection pressure on the conserved antigenic site within the N-terminal domain (NTD) of S (S-NTD). This pressure will however not allow for natural selection of variants that picked up mutations within the conserved antigenic peptide itself. This is because such mutations would obstruct binding of PNNAbs to the conserved antigenic site on *free* virions. Failure of PNNAbs to bind to this conserved antigenic site would prevent such variants from compensating a potential fitness cost and thereby prevent them from competing with other circulating, highly infectious variants that did not pick up virulence-enabling mutations[7].

Binding of PNNAbs to the conserved antigenic site within S-NTD of free virions would enhance viral infectiousness of new emerging virulent variants that potentially paid a fitness cost (i.e., in terms of lowered intrinsic infectiousness) in exchange for lifting the blockade on PNNAb-mediated inhibition of high virulence. This, however, requires the conserved antigenic site within S-NTD to stay clear of mutations. Mutations within this conserved antigenic site would block binding of PNNAbs to *free* virions and therefore prevent PNNAb-mediated enhancement of their infectiousness.

I postulate that once highly infectious variants start to dominate, highly C-19 vaccinated populations are bound to exert suboptimal immune pressure on the antigenic site within S-NTD and promote selection of

[7] New, naturally selected variants that emerge in highly C-19 vaccinated populations are likely to pay an intrinsic fitness cost in exchange for their capacity to lift the blockade on viral virulence.

variants able to provoke PNNAb-mediated enhancement of severe C-19 disease[8] in C-19 vaccinees.

Once the immune selection pressure exerted on viral *trans* infectiousness collectively reaches a threshold that is high enough to select an O-glycosite variant capable of collectively lifting the blockade of PNNAbs on viral *trans* infectiousness, highly C-19 vaccinated populations will likely witness a massive surge in highly virulent VBTI.

At any given time following a VBTI, the overall immune pressure on viral infectiousness or *trans* infectiousness is higher in C-19 vaccinated populations that underwent a fast-track mass vaccination program compared to populations which achieved a similar vaccine coverage rate at a much slower pace. Consequently, the suboptimal immune pressure capable of exerting immune selection pressure on viral infectiousness or *trans* infectiousness is also higher the faster the speed of the mass vaccination program. It follows that the time required for newly emerging, highly infectious variant to circulate or to effectively lift the blockade on PNNAb-mediated inhibition of severe C-19 disease is likely to increase with the speed of mass vaccination.

I therefore postulate that in countries which vaccinated their population at a relatively slower pace, the mortality wave will manifest as a more protracted surge and be characterized by a much lower peak. The latter would be preceded by a steadily increasing (excess) death rate, which is primarily due to collateral, non-Covid-19-related disease, and gradually transitions into a protracted surge in C-19 mortality (see under section 1.3.1.3. and 1.3.2.3.). In contrast, in countries that opted for fast-track mass vaccination, I expect the wave of (excess) mortality to be delayed. After being selected, though, these newly emerging variants can reasonably be expected to rapidly unfold their highly virulent properties in a large portion of the highly C-19 vaccinated population and disseminate to different organs within the bodies of C-19 vaccinees. This would inevitably trigger a wave of hyperacute systemic C-19 disease that is higher, larger

[8] As previously reported (https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic), growing O-glycosite chains at selected O-glycosites are thought to possess sufficient conformational versatility to dampen the trans infection-inhibiting effect triggered by binding of PNNAbs on the conserved antigenic site of DC-tethered virions while not impeding viral infectiousness of free virions. Adequate O-glycosite mutations would therefore allow to abolish the PNNAb-mediated, suboptimal population-level immune pressure exerted on viral trans infectiousness without obstructing entry of free virions into susceptible cells. I can only envision this virulence-inhibiting effect being surmounted by a mechanism that modifies the conformation of the conserved antigenic site within S-NTD. A such mechanism has been postulated to involve a change in the interaction of this antigenic site with glycan chains on mutated O-glycosites. This change would need to occur upon attachment of highly infectious virions to migratory DCs that patrol the upper respiratory mucosa. Note: Migratory DCs are DCs that have a unique capacity to capture antigens across mucosal barriers and migrate to different organs or to the draining lymph nodes via afferent blood vessels or lymphatics, respectively.

and has a steeper slope. This is because, at any given moment, a larger number of vaccinated individuals would contribute to the alteration in immune pressure. Therefore, I hypothesize that these countries will likely witness a significant increase in their mortality rates due to severe non-Covid-19-related diseases overlapping with the wave of Covid-19-related deaths (see also under section 2.).

In conclusion:

The epidemiological scenario within populations that have been extensively vaccinated against Covid-19 is presently marked by significantly reduced viral shedding, comparatively lower rates of Covid-19-related illness and death, and a growing incidence of non-Covid 19-related (excess) deaths. The latter are particularly due to acute cases of cancer and autoimmune disease or reactivation of pre-existing health issues such as underlying autoimmune disease, dormant cancers, or chronic infections. Taken together, these observations reflect an imminent shift toward immune selection pressure on viral *trans* infectiousness and hence, dramatically increase the likelihood for a new emerging variant to cause enhancement of severe C-19 disease in highly C-19 vaccinated populations. Asymptomatic transmission of the currently circulating, highly infectious Omicron descendants are greatly favoring this evolution.

The current evolutionary dynamics of SC-2 in highly C-19 vaccinated countries are transforming the above-described epidemiological landscape into a scenario where individual case fatalities due to severe C-19 disease will steadily increase and pave the way to a substantial wave of C-19 mortality. I anticipate that this wave will manifest as a prominent and substantial peak in countries that have vaccinated their populations very rapidly. On the other hand, I anticipate that this wave will be of a smaller magnitude, reaching its peak with a significantly lower mortality rate and preceded by a gradually increasing slope of non-Covid-19-related case fatalities in countries that took more time to reach their high Covid-19 vaccination rate. Eventually, the high mortality rate in C-19 vaccinees combined with broadly protective innate immunity in the unvaccinated is likely to diminish viral transmission down to a level where SC-2 can no longer survive in the affected population and will therefore be eliminated from these populations.

1.3.2.3. Enhanced evolution of immune escape variants toward highly infectious Omicron descendants parallels a growing prevalence of turbo cancers and acute flare-ups of underlying autoreactive diseases and chronic infections.

Hyperactivation of APCs upon exposure to highly infectious Omicron descendants upregulates expression of programmed cell death protein 1 (PD-1) on DCs/ APCs. Upregulated expression of PD-1 on DCs/ APCs suppresses CD8+ T cell effector function and puts C-19 vaccinees at risk of acute reactivation and possibly exacerbation of underlying autoimmune or cancerous diseases or productive chronic infections (https://www.nature.com/articles/s41577-023-00871-z; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/). Whereas suppression of foreign-centered CD8+ T cells causes reactivation and potential exacerbation of pre-existing cancers and underlying chronic, non-SC-2-related infections, suppression of *self*-centered CD8+ T cells likely promotes reactivation of underlying autoimmune disease.

Summary of 1.3.2.

PNNAb-dependent VBTIs with early Omicron variants triggered immune refocusing toward less immunogenic S-associated domains while preventing these variants from causing severe disease[9] without jeopardizing viral shedding.

SIR is key for populations to 'clinically' recover from VBTIs. This is because SIR primes broadly cross-reactive anti-S Abs that expedite recovery from C-19 disease or mitigate symptoms from Covid-19, and potentially other unrelated viral diseases[10], due to their broadly neutralizing, infection-inhibiting, or anti-inflammatory effect (the latter after maturation of these Abs into isotype-switched IgG4 Abs). In this way, SIR-enabling VBTIs turned C-19 vaccinees in a breeding ground for increasingly infectious immune escape variants and thereby promoted training of the innate immune system in the unvaccinated.

With the advent of highly infectious Omicron descendants, PNNAb-independent VBTIs activated broadly cross-reactive CTLs and thereby promoted asymptomatic viral transmission by C-19 vaccinees while preventing *de novo* Ag presentation upon re-exposure. The latter is critical since poor Ag presentation prevents VBTI by highly infectious variants from triggering SIR while allowing them to boost previously primed IgG4 Abs to heightened levels through immune imprinting.

[9] As VBTIs were initially facilitated by PNNAbs and as the latter inhibit high viral virulence, early VBTIs did not cause severe C-19 disease.
[10] Mitigation of symptoms caused by other unrelated pathogens likely depends on the antigenic characteristics of the subdominant domains comprised within the S protein of the variant causing the VBTI.

Elevated titers of isotype-switched IgG4 Abs likely prevent continued stimulation of short-lived PNNAbs. In a highly C-19-vaccinated population, failure to sustain PNNAb titers translates into suboptimal population-level immune pressure on viral *trans* infectiousness. This triggers natural selection of a new variant that can surmount the capacity of a highly C-19 vaccinated population to prevent highly infectious SC-2 variants from causing severe disease in C-19 vaccinees who are devoid of trained cell-based innate immunity.

A high mortality rate among C-19 vaccinees will substantially reduce viral transmission. As the surviving fraction of the population (i.e., all those with adequately trained cell-based innate immunity) possesses sterilizing immunity, viral transmission could even be diminished below the minimum level required to establish herd immunity and drive the virus into endemicity.

In other words, in highly C-19 vaccinated populations, the C-19 pandemic will likely end by eradication of the virus. However, before this happens, highly C-19 vaccinated populations may already face a substantial amount of severe morbidity and excess death due to an increased incidence of autoimmune diseases, cancer, underlying chronic infections or acute diseases caused by other, non-CoV-2-related infectious pathogens.

1.3.3. SIR delayed the timeline I predicted for new variants to cause highly virulent VBTIs in C-19 vaccinees.

Back in 2022, I was worried that imminent VBTIs with more infectious SC-2 variants would cause severe C-19 disease in vaccinees devoid of trained innate immunity. Back then, I did not realize that if these VBTIs were highly virulent in C-19 vaccine recipients, the small subpopulation of unvaccinated individuals would never acquire sterilizing immunity quickly enough to control the more infectious variants. With the advent of Omicron, the predicted VBTIs did indeed occur. However, as previously vaccine-primed Abs largely lost their neutralizing capacity when confronted with Omicron, Omicron's infectiousness benefited from the production of PNNAbs. As the latter enhanced Omicron's infectiousness, they expedited the production of viral progeny, consequently triggering SIR while protecting vaccinees from severe C-19 disease.

SIR reorients the vaccinee's immune response to subdominant S-associated epitopes (see fig. 2). As explained above (see under section 1.3.1.), SIR-enabling VBTIs with early Omicron variants triggered a self-catalyzing chain of large-scale viral immune escape in highly C-19

vaccinated populations. Although delaying the immune escape dynamics of SC-2, this evolution promoted natural selection and co-circulation of increasingly infectious immune escape variants while also improving mitigation of C-19 disease. Repeated exposure of the unvaccinated to more infectious Omicron descendants has been key to enabling immune adaptation of their cell-based innate immune system.

Based on the above, it is fair to conclude that the advent of Omicron in highly C-19 vaccinated populations has been responsible for delaying the timeline I predicted for more infectious variants with highly virulent properties in C-19 vaccinees to emerge. This delay has allowed the unvaccinated to improve their control over the circulating variants.

1.3.4. SIR is the key to establishing herd immunity and ending the immune escape pandemic in highly C-19 vaccinated countries/regions. The frequency of SIR-enabling VBTIs determines the pace at which natural immune selection of more infectious variants evolves.

SIR proves to be a tool highly C-19 vaccinated populations have been using to establish herd immunity after mass vaccination prevented vaccinees from acquiring sterilizing immunity. To make that happen, vaccinees who suffered a SIR-enabling VBTI (while being protected from severe C-19 disease) first progressed to improve their immune defense such as to develop milder symptoms, thereby facilitating viral transmission. This ensured that the unvaccinated individuals were adequately and continuously exposed to the circulating variants, thereby allowing for prolonged and intensified training of their innate immune system.

In the next step of the evolutionary dynamics of the immune escape pandemic, C-19 vaccinees further reshaped their adaptive immune response such as to prevent *de novo* production of short-lived PNNAbs while curtailing Ag presentation and promoting asymptomatic viral transmission. As explained in section 1.3.2.1., this will eventually allow SC-2 to become highly virulent in C-19 vaccinees[11] and therefore remove the portion of the 'herd' that is unable to develop sterilizing immunity and, as a result, unable to contribute to herd immunity.

[11] For the purpose of this manuscript, the term 'C-19 vaccinee' only refers to those vaccinees who did not have the opportunity to adequately train their innate immunity prior to C-19 vaccination (primarily due to SIR-enabling VBTI or mRNA vaccination) and are therefore at risk of developing enhancement of severe C-19 disease upon exposure to future viral variants. This risk primarily pertains to those who were vaccinated first, mainly the elderly (aged > 60) and individuals with underlying health conditions.

The higher the number of individuals experiencing a VBTI at any given time in any given C-19 vaccinated population, the higher the population-level immune pressure on the virus and the slower the dynamics of viral immune escape will evolve. It therefore follows that the higher the number of VBTIs at any given time in any given C-19 vaccinated population, the more the emergence of highly infectious Omicron descendants will be delayed and the more time it will take for SIR-disabling VBTIs to drive natural selection of newly emerging variants that are able to lift the PNNAb-mediated blockade on high viral virulence in C-19 vaccinees.

As the frequency of VBTIs at any given time is likely promoted by the speed of mass vaccination, it is reasonable to postulate that countries which conducted their mass vaccination program at high speed will experience the highest mortality rate from enhanced severe C-19 disease. It also follows that the wave of C-19 mortality in countries with comparable demographics, vaccination strategies, and vaccine coverage rates may still exhibit distinct shapes, contingent on the pace at which mass vaccination was executed. I therefore anticipate that countries which rapidly proceeded with their mass vaccination program will witness a wave of C-19 mortality that is much higher and larger compared to that of other countries which implemented their mass vaccination program at a slower pace. As already mentioned under 1.3.2.2., it is also reasonable to assume that once highly infectious variants start to co-circulate, the delay in the onset of the C-19 mortality wave will be greatest in countries that were the quickest in implementing their mass vaccination program.

Based on the above reasoning, one concludes that the evolutionary dynamics of the current immune escape pandemic in highly C-19 vaccinated countries are targeted at allowing the host species to control viral replication and transmission.

The immune selection pressure exerted by the population and the resulting co-circulation of more infectious immune escape variants should, therefore, be considered a catalyst for allowing the host species to control viral transmission and not as a result of the virus' strategy to prolong its transmission and survival.

1.3.5. SIR-enabling PNNAb-dependent VBTIs drive viral immune escape while enabling cross-reactivity with other unrelated foreign Ags on other pathogens or with 'self' or 'altered self' Ags on the body's own host cells.

It is well known that molecular homology involving cross-reactive microbial peptide epitopes can enable protection between heterologous pathogens (https://pubmed.ncbi.nlm.nih.gov/11359825/.)

It is also well known that molecular mimicry involving a given microbial epitope and a pool of cross-reactive self-peptides can lead to autoimmune disease (https://pubmed.ncbi.nlm.nih.gov/9151902/).

It therefore seems that the host's immune response to an unrelated 'foreign' or 'self' Ag may be triggered by a previous experience of the host immune system with an infectious pathogen.

This particularly applies to pathogens that induce *productive chronic infections* and, consequently, trigger a prolonged immune inflammatory response due to continuous antigen presentation. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7133435/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5774991/; https://www.mdpi.com/1999-4915/15/3/782).

Hence, it is not surprising to find that when the immune system f*ails to control* an *acute self-limiting infection*, it can equally trigger pathogen-specific immune responses that cross-react with unrelated antigens.

Whereas in the case of productive chronic infection, immunological cross-reactivity occurs at the CD4+ Th cell level, it is not surprising to find that immunological cross-reactivity elicited in the case of acute self-limiting infections typically occurs at the Ab level. In this case, the shift in Ag recognition is not determined by B cell receptor (BCR) plasticity (i.e., in analogy to T cell receptor [TCR] plasticity) but by the antigenic versatility of the immune subdominant or recessive domain that is activated/unsilenced as a result of immune refocusing. The latter is a hallmark of PNNAb-dependent VBTI.

By refocusing the immune response, previously C-19 vaccine-induced Abs triggered priming of new Abs targeted at immune subdominant or recessive epitopes on variant S protein exposed on the surface of newly emerging SC-2 immune escape variants. Similar to productive chronic infections, when an individual is re-exposed to distinct immune escape variants of a specific pathogen that would typically cause /*acute self-limiting infection, it entails repeated or prolonged exposure and antigen presentation to the host immune system.

Depending on the antigenic properties of the immune subdominant or recessive epitopes unsilenced by SIR, new Abs that target these epitopes

can recognize other antigenic peptides that possess some homology in their amino acid composition and are either expressed on the surface of unrelated pathogens or on the surface of healthy or pathologically altered host cells (see under 3.5.).

Immune refocusing resulting from SIR-1-enabling PNNAb-dependent VBTIs likely enabled immunological cross-reactivity among antigenic peptides that share some homology and are comprised within infection-facilitating proteins of viruses causing acute, self-limiting infection. I therefore hypothesize that immune refocusing in C-19 vaccine recipients prevented or, at the very least, mitigated diseases caused by other phylogenetically unrelated viruses, such as avian influenza virus (H5N1), and possibly even monkeypox virus or respiratory syncytial virus (RSV). This could explain the enhanced spread of these infections and, therefore, explain

2. **In highly C-19 vaccinated populations, the likelihood for C-19 vaccinees to contract immune pathology or early-onset cancers following VBTI with Omicron descendants is not primarily determined by genetic predisposition, external environmental influences, or demographic characteristics but by the time elapsed since the first wave of SIR-enabling VBTIs or SIR-enabling mRNA vaccination. The type of pathology and organs/ tissues affected likely depends on the Ag specificity of the induced IgG4 Abs.**

It is important to note that the incidence of autoreactive disease or early-onset cancer in highly C-19 vaccinated populations strongly depends on the time required for SIR-induced Abs to mature into isotype-switched IgG4 Abs as well as on the frequency of VBTIs in those populations. The more time elapses since the first wave of SIR-enabling VBTIs or SIR-enabling mRNA vaccination, the more VBTIs will have occurred and thus the higher the likelihood for unsilenced immune recessive epitopes to generate pathogenic IgG4 Abs (see also under section 3.5.2). On the other hand, the type and location of organ disease are likely determined by the Ag specificity of the IgG4 Abs induced.

Considering the increasing occurrence of autoimmune and cancer-related conditions in extensively C-19 vaccinated populations, I am inclined to believe that the impact of other variables, such as individual immunogenetic diversity, disparities in host demographics, or external environmental influences, is subordinate to that stemming from the aforementioned factors.

While they may be identical or share significant similarity in their naturally selected *immunodominant* S epitopes and their 'official' classification based on WHO or CDC criteria, SC-2 variants circulating in highly C-19 vaccinated countries can exhibit a wide range of diverse *immune recessive* peptides.

Consequently, VBTIs involving distinct variants within a specific C-19 vaccine recipient, or VBTIs with a particular variant among different C-19 vaccine recipients, exhibit differing probabilities of triggering autoreactive or carcinogenic IgG4 Abs and affecting a varying spectrum of organs, depending on the time elapsed since the first SIR event (i.e., SIR-1-enabling mRNA vaccination or VBTI).

The above line of reasoning explains why only a portion of highly C-19 vaccinated populations develops autoimmune diseases or early-onset cancers. It also clarifies why the spectrum of affected organs can be highly diversified.

It remains to be seen, however, to what extent the growing wave of these diseases will be overshadowed by the anticipated wave of enhanced severe C-19 disease. As explained in section 1.3.2.2. , this probability may be particularly relevant to countries that adopted a fast-track mass immunization program.

Meanwhile, the rate of newly reported cases of autoimmune diseases and cancer is anticipated to continue increasing, even though VBTIs associated with presently circulating variants are currently mostly asymptomatic in terms of C-19 disease.

3. The evolutionary significance of elevated IgG4 Ab titers: Good, bad or….misunderstood?

3.1. Immunological properties of IgG4 Abs

(summarized in https://www.nature.com/articles/s41577-023-00871-z and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/)

IgG4 undergoes Fab (fragment antigen binding)-arm exchange, rendering it bi-specific for Ag binding and operationally univalent. Due to their weak affinity for Fc receptors, IgG4 Abs are largely unable to activate Ab-dependent immune effector responses (e.g., complement activation, ADCC responses) and diminish the capacity for Fcγ-mediated antigen uptake and APC activation.

Diminished activation of APCs results in reduced immune signaling and stimulation of T cells (e.g., T helper cells or CTLs). Class switch to IgG4 may therefore have an anti-inflammatory effect while promoting continued viral replication and transmission in the case of exposure to infectious pathogens (https://pubmed.ncbi.nlm.nih.gov/24648341/; https://www.science.org/doi/10.1126/sciimmunol.ade2798).

Because of their functional monovalency, IgG4 Abs in circulation prevent Ag cross-linking and therefore hamper formation of immunological complexes with antigens (https://www.science.org/doi/10.1126/sciimmunol.adg7327).

Fab-arm exchange, combined with the generally diminished capability of IgG4 to trigger Fcγ-mediated effector functions, explains why IgG4 Abs are frequently considered a naturally occurring form of 'immune-blocking' Abs.

3.2. High levels of IgG4 Abs result from failure to eliminate foreign pathogenic agents.

There has been a lot of controversial debate and speculation on whether the induction of IgG4 Abs in infectious or immune-mediated diseases is good (i.e., protective) or bad (i.e., pathogenic) or….just misunderstood (https://pubmed.ncbi.nlm.nih.gov/37191589/; https://www.science.org/doi/10.1126/sciimmunol.adg7327).
I very much opt for the third possibility!

High IgG4 Ab titers have been shown to correlate with dampening of pathogen-induced inflammatory reactions, which is beneficial, but also with diminished protection from the pathogen, which is detrimental (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/; https://www.nature.com/articles/s41577-023-00871-z). Likewise, elevated IgG4 concentrations have been shown to mitigate clinical manifestation of allergies, which is beneficial, but are also associated with autoimmunity (presumably due to lack of activation of self-antigen-specific regulatory T cells), which is detrimental (https://pubmed.ncbi.nlm.nih.gov/6600252/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8534225/).

It seems therefore that elevated IgG4 titers associated with chronic disease either result from a weak and inadequate T helper response (e.g., in the case of infection or allergy) or a weak and inadequate regulatory T cell response (e.g., in the case of tumor disease or autoreactivity; https://pubmed.ncbi.nlm.nih.gov/32819973/;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8534225/;
https://www.science.org/doi/10.1126/sciimmunol.adg7327;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/).

Little is still known regarding the factors responsible for inducing and ensuring prolonged production of IgG4 Abs. Nevertheless, there is a consensus that prolonged or repetitive Ag exposure can lead to a rise in IgG4 Abs.

When the host immune response to a specific infectious pathogen is delayed (e.g., in the case of acute self-limiting infections) or fails to eliminate the pathogen or pathogen-infected host cells (e.g., in the case of chronic infections), the exposure to the infectious pathogen is prolonged. In this case, elevated IgG4 Ab titers may not only mitigate inflammatory reactions to the specific infectious pathogenic agent but also decrease an individual's susceptibility to other unrelated pathogenic agents.

Whereas researchers report in detail about the structure of IgG4 Abs and the mechanism of their interaction with immune effector cells, they all seem to be puzzled about the evolutionary significance of these 'imperfect' Abs as the latter don't seem to provide any evolutionary advantage to the host (https://www.science.org/doi/10.1126/sciimmunol.adg7327).

I am surprised that the duology of 'infectious pathogen' and 'prolonged or repeated antigen exposure' doesn't ring the alarm for pathogen immune escape with them! However, both conditions are fulfilled when an infectious pathogen subverts the host immune system and thereby induces suboptimal immune responses that promote natural selection and dominant propagation of immune escape variants.

3.3. What triggers sustained IgG4 Ab responses in the case of acute self-limiting infections?

Similar to productive chronic infections, acute self-limiting infections necessitate prolonged or repeated antigenic challenge to initiate and sustain the production of IgG4 Abs. In the context of acute self-limiting infections, the repetition of antigenic exposure usually arises from immune escape mechanisms. However, the continuity of immune escape is contingent upon the redirection of host immune responses toward epitopes that generate Abs with reduced infection-inhibiting capabilities. This shift in immune focus to less immune protective epitopes occurs when the potency of high-affinity Abs to neutralize the pathogen diminishes

significantly, granting the pathogen the opportunity to breach the host's adaptive immune defenses.

This likely happens when the immune system is confronted with an antigenically shifted variant of the pathogen while solely relying on Ag-specific, high-affinity IgG Abs, I.e., without the support of trained innate immunity.

In the case of SC-2, this scenario typically unfolds when an individual has been administered a C-19 vaccine before encountering such antigenically shifted variant (for example in instances where a C-19 vaccine recipient experiences an infection caused by an Omicron-derived immune escape variant). As the immune system of the vaccine recipient struggles to control the pathogen, the latter breaks through the vaccinee's immune defense. Such VBTI subsequently ensures repeated exposure to the pathogen due to the delayed class switching of low-affinity, broadly neutralizing Abs to IgG4 Abs, thereby creating an extended period in which new variants can be selected—such that can evade the suboptimal neutralizing immune pressure exerted by the C-19 vaccinated population (see under section 1.3.1.).

Upon subsequent VBTI involving a newly emerging variant, IgG4 Abs facilitate a new cycle of immune refocusing, thereby guaranteeing the sustained production of IgG4 Abs.

3.4. Failure of vaccines to confer sterilizing immunity is known to drive pathogen immune escape and therefore VBTIs. The latter have been reported to lead to high levels of IgG4 Abs. (https://pubmed.ncbi.nlm.nih.gov/24648341/; https://www.science.org/doi/10.1126/sciimmunol.ade2798).

Pathogen immune evasion may occur as a result of deficient or insufficient functioning of the innate and/ or adaptive immune system due to external immune suppressive influences or immunogenetic factors. Alternatively, pathogen immune evasion may also be due to intrinsic immune subversive properties of the pathogen. Nonetheless, prolonged and extensive immune evasion by a pathogen causing acute, self-limiting infection within a genetically diverse population can only transpire through continuous and widespread impairment of the host immune response.

Mass vaccination during a pandemic generates an immune status that is reminiscent of other vaccination strategies that fail to induce sterilizing immunity. Vaccination against target pathogens which typically cause chronic infection (e.g., HIV, Malaria) has typically been associated with elevated IgG4 Ab titers in populations exposed to these pathogens (https://www.nature.com/articles/s41577-023-00871-z; https://www.science.org/doi/10.1126/sciimmunol.adg7327; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/).

It is reasonable to assume that even prophylactic vaccination against infections with a typical chronic course will eventually trigger SIR-enabling VBTIs upon post-vaccination exposure and thereby enable the free-circulating pathogen to evade vaccine-induced humoral immune responses. It is therefore likely that mass vaccination with current candidate vaccines against such typically chronic infections will only enhance pathogen transmission and therefore promote *large-scale* immune escape of the targeted pathogen.

If the above postulate applies, one can reasonably expect mass vaccination during a pandemic of a virus causing acute, self-limiting infection to repeatedly cause suboptimal population-level immune pressure on the virus. When the vaccination targets infection-enhancing proteins (e.g., S protein in the case of C-19 vaccines), the vaccinated population will exert selective immune pressure on viral infectivity.

In the case of C-19 mass vaccination, immune selection pressure is repeatedly generated because of re-exposure to VBTIs. mRNA vaccination (conducted prior to natural exposure) accelerated the occurrence of the first wave of VBTIs in highly C-19 vaccinated populations (see under section 4.). Exposure to circulating SC-2 variants in the presence of immune selection pressure on viral infectiousness results in natural selection and propagation of new immune escape variants that are characterized by a level of infectiousness that is higher than that of previously circulating variants.

Elevated titers of IgG4 Abs following VBTI, or following full mRNA vaccination prior to natural exposure, are indicative of SIR. On the other hand, high titers of IgG4 Abs are also prone to triggering new VBTIs as they facilitate new SIR events while mediating an anti-inflammatory effect. This provides elevated titers of IgG4 Abs with a license to protect C-19

vaccinees from C-19 *disease*[12] but not from productive viral infection and transmission. As a result, the immune selection pressure on the variant S protein presented by newly emerging immune escape lineages persists, leading to an ongoing process of viral immune evasion.

In other words, high titers of IgG4 Abs indicate the transition of a natural pandemic into an immune escape pandemic (i.e., a pandemic of immune escape variants). As explained in my book "The Inescapable Immune Escape Pandemic[13]", large-scale vaccination with S-based C-19 vaccines during the initial, natural SC-2 pandemic eventually prevented highly C-19 vaccinated populations from developing 'herd immunity' and thereby converted a natural pandemic into a pandemic of immune escape variants.

In summary, high titers of anti-inflammatory IgG4 Abs enable SIR (i.e., SIR-2) while attenuating disease symptoms in C-19 vaccinees experiencing VBTI. This combination turns C-19 vaccine recipients into breeding and transmission grounds for new emerging immune escape variants. IgG4 Abs play therefore a crucial role in fueling viral immune evasion.

Based on the above reasoning, it seems fair to assume that measuring IgG4 Ab titers in the blood of asymptomatic C-19 vaccinees, possibly complemented by measuring infectious shedding in nasopharyngeal mucosal swabs (via SC-2 Ag test or reverse transcription polymerase chain reaction [RT-PCR]), is a good proxy for diagnosing or confirming the 'inescapable' nature of viral immune escape. The increase in IgG4 levels explains the failure of SIR-enabling VBTI and mRNA vaccination to provide durable protection and control viral transmission (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00089-7/fulltext).

I therefore postulate that a high prevalence of high titers of IgG4 Abs in a highly C-19 vaccinated population is to be considered a poor prognostic sign for the outcome of this immune escape pandemic.

3.5. High levels of anti-S IgG4 Abs link enhanced rates of autoimmune disease or cancer to broad, self-centered immune refocusing following SIR-enabling VBTI or mRNA vaccination in highly C-19 vaccinated populations.

[12] As explained in section 1.3.2.2., advanced SIR-mediated immune escape in highly C-19 vaccinated populations may lead to autoreactivity or carcinogenicity and, therefore, cause clinical symptoms even though the SC-2 infection itself is asymptomatic or only causes mild symptoms.
[13] https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic

3.5.1. High titers of anti-S IgG4 Abs mediate enhanced viral immune escape while promoting acute autoimmune disease and early-onset cancer in highly C-19 vaccinated populations. High titers of IgG4 Abs therefore link the increasing incidence of these diseases to enhanced viral immune escape.

The emergence of highly infectious immune escape variants is paralleled by enhanced immune selection pressure exerted on S-associated immune recessive domains. The less immunogenic, the greater the degree of conservation of the targeted epitopes, and the closer they resemble self-epitopes.

It follows that circulation of highly infectious immune escape variants is inevitably accompanied by increasing titers of avidity-matured, functionally monovalent IgG4 Abs that bind to 'self'-antigens or 'self-like' (e.g., 'altered self') epitopes that share functional homology with the unsilenced immune recessive epitopes. Pathogenic IgG4 Abs could either prevent self-epitopes from signaling B cells to activate self-Ag-specific regulatory T cells that downregulate the activation/ proliferation of self-reactive T cells, or prevent altered self-epitopes from being recognized by ADCC Abs.

It is therefore not surprising that the current circulation of highly infectious Omicron variants has been accompanied by a rapidly increasing incidence of autoreactive diseases (e.g., autoimmune Ab-associated myocarditis, diabetes mellitus or neuropathy) and early-onset cancers.

Autoreactivity and carcinogenicity should be viewed as side effects resulting from SIR-2-enabling VBTIs and, consequently, from immune evasion, rather than being a direct outcome of C-19 vaccination.

It is also intriguing to observe that alterations in non-SC-2-related pathology mirror the evolutionary dynamics of the virus. Consequently, the non-SC-2-related pathology evolved from inflammatory diseases (e.g., inflammatory myocarditis and immune thrombotic thrombocytopenia) to autoreactive and cancerous diseases.

3.5.2. The likelihood for a C-19 vaccinee to contract acute autoreactive or early-onset cancerous disease increases with time elapsed after the first VBTI or after full mRNA vaccination. The type of pathology and organs affected depends on the Ag specificity of the pathogenic IgG4 Abs elicited upon exposure to SIR-enabling VBTI with a specific 'pathogenic' variant.

Overall, cases of severe disease or (excess) death due to immune-mediated, non-SC-2-related pathology only affect a certain portion of highly C-19 vaccinated populations. This has led some parties to believe that different types of formulations of C-19 vaccines - and even placebos – have been used in mass vaccination campaigns.

Since the advent of Omicron, highly C-19 vaccinated populations have witnessed a wave of VBTIs. It is therefore not surprising that -since the advent of Omicron- the incidence of autoimmune diseases and cancers in highly C-19 vaccinated populations has significantly increased over time.

The probability for any given C-19 vaccinee to develop pathogenic titers of 'self'- or 'altered self'-reactive Abs not only depends on the probability of contracting a second SIR-enabling event (i.e., after a first SIR-enabling VBTI or SIR-enabling mRNA vaccination[14]) but also on the time required for maturation of 'self-like'-reactive IgG1 Abs into IgG4 Abs of high avidity. It is therefore reasonable to assume that for any given individual who has received a C-19 vaccine, the probability of contracting autoreactive or cancer disease increases with time elapsed after the first VBTI or full mRNA vaccination. Consequently, the incidence of pathogenic side effects in highly C-19 vaccinated populations is also likely to increase with time elapsed after the first wave of (symptomatic) SIR-enabling VBTIs or after mass administration of the second (SIR-enabling!) mRNA-vaccine dose.

As explained in section 2., the more SIR-enabling VBTIs and the higher their frequency, the higher the probability for unsilenced epitopes to generate pathogenic IgG4 Abs. In other words, the more SIR-enabling VBTIs and the higher their frequency, the higher the incidence of acute autoimmune diseases and early-onset cancers. On the other hand, the type and location of organ disease are likely determined by the Ag-specificity of the IgG4 Abs induced.

The longer the time that has passed since the initial wave of SIR-enabling VBTIs or SIR-enabling mRNA vaccination, the more frequent VBTIs

[14] Only C-19 vaccinees who did not experience SC-2 infection prior to C-19 vaccination and who are, therefore, devoid of pre-existing trained innate immunity, are susceptible to SIR-enabling VBTI.

occur in heavily C-19-vaccinated populations. Consequently, unsilenced immune recessive S-associated antigenic regions will more frequently encompass epitopes that exhibit functional homology with 'self' or 'altered self' epitopes expressed on the surface of either healthy or pathologically transformed host cells.

However, since the duration until exposure to a VBTI resulting in sufficiently elevated levels of pathogenic IgG4 Abs can vary significantly among different C-19 vaccine recipients within the same population, it is not surprising to witness that only a segment of C-19 vaccine recipients experience IgG4-induced pathogenic effects. Furthermore, the nature of the pathology and the specific organ affected are also likely influenced by the range of 'self' or 'self-like' Ags recognized by pathogenic anti-S IgG4 Abs. Consequently, the antigenic characteristics of the co-circulating (sub) variant responsible for the pathogenic VBTI play a role in determining the type of pathology and the location of organ disease (see also under section 2.).

Due to the influences mentioned above on IgG4-mediated pathogenicity in a specific C-19 vaccine recipient, differences in the antigenic repertoire of currently co-circulating variants do not allow the ranking of these variants based on epidemiologically significant risks or concerns. Circulating variants are usually ranked according to different criteria enabling health authorities to assess the risk they pose to public health (e.g., in terms of virulence, infectiousness, transmissibility, resistance to neutralizing Abs etc.).

These criteria do not encompass S-associated peptide sequences that are typically immune recessive or immunosilent but can gain considerable immunogenicity due to SIR-enabling VBTI.

While SIR-1-enabling mRNA vaccination or VBTIs led to the generation of broadly virus-neutralizing Abs, they also triggered the development of broadly inflammatory anti-S Abs, which eventually matured into broadly anti-inflammatory IgG4 Abs (i.e., alleviating inflammatory symptoms by preventing uptake into APCs). On the other hand, SIR-2-induced responses not only produced broadly infection-inhibiting Abs but also generated broadly 'self-like'-reactive Abs. These Abs eventually matured into high-avidity IgG4 Abs with the potential for autoreactivity or carcinogenicity. Consequently, highly C-19-vaccinated populations are presently witnessing a gradual increase in the prevalence of acute autoreactive diseases and early-onset cancers.

3.6. High levels of anti-S IgG4 Abs link increased rates of turbo cancers and resurgence of underlying autoimmune diseases, or chronic non-SC-2-related infections in highly C-19 vaccinated populations to generalized immune suppression following SIR-disabling VBTI.

3.6.1. High titers of anti-S IgG4 Abs mediate enhanced immune selection pressure on viral trans infectiousness while increasing the prevalence of turbo cancers and promoting resurgence of underlying autoimmune diseases or chronic non-SC-2-related infections. High titers of IgG4 Abs therefore link the increasing incidence of these diseases to enhanced immune selection pressure on viral trans infectiousness.

This postulate is based upon the following line of reasoning:

Upon VBTI with a highly infectious Omicron-derived immune escape variant, high titers of isotype-switched IgG4 Abs no longer enable SIR-mediated induction of new, broadly cross-protective Abs to the S protein of these new variants. This is because the avidity of functionally monovalent IgG4 Abs no longer suffices to prevent formation of large viral assemblies when progeny virions are released in high density from virus-infected target host cells (see fig. 2). The uptake of these large viral aggregates into tissue-resident APCs leads to strong activation of APCs. Hyperactivation of APCs enables abrogation of viral shedding and Ag presentation (including the presentation of new variant S Ags and non-SC-2 Ags), presumably via cytotoxic activation of short-lived MHC-unrestricted CTLs (https://pubmed.ncbi.nlm.nih.gov/11535638/).

Whereas abrogation of Ag presentation prevents recall of previously induced virus-specific (or S-specific[15]) T helper cells, and therefore prevents IgG4 Abs from triggering SIR, upregulation of PD-1 on DCs/ APCs suppresses CD8+ T cell effector function.

Reduced antigen-presenting capacity, coupled with T cell immune suppression, results in widespread immune suppression. Generalized immune suppression likely increases susceptibility of C-19 vaccinees to novel infectious agents while fostering the abrupt reactivation of latent autoimmune conditions, cancer, or persistent/ chronic infections (as explained under 1.3.2.3.).

[15] 'S-specific' would apply in case T helper cells have been vaccine-primed.

Furthermore, elevated titers of functionally monovalent IgG4 Abs will impede the formation of multimeric viral particles when they interact with circulating virus in the upper respiratory tract. As multimeric viral particles trigger production of anti-S PNNAbs, diminished aggregate formation will cause titers of these short-lived Abs to decline. When the levels of PNNAbs in highly C-19-vaccinated populations collectively drop, they exert immune selection pressure on the highly conserved, PNNAb-binding site within S-NTD. In other words, collectively declining anti-S PNNAb titers exert high immune selection pressure on the capacity of the virus to become highly virulent in C-19 vaccinees. This will inevitably lead to natural selection of new immune escape variants that are able to provoke PNNAb-dependent VBTI while lifting the blockade on viral virulence. These variants could therefore cause PNNAb-mediated enhancement of severe C-19 disease.

Based on the above postulate, a high prevalence of elevated IgG4 Ab titers combined with reduced PNNAb titers in highly C-19 vaccinated populations would indicate a transition in the non-SC-2-related pathology from acute autoreactivity or early-onset carcinogenicity to acute reactivation of other, chronic infectious or noninfectious conditions (such as cancer). It would also create conditions conducive to the emergence of novel, highly infectious immune escape variants that can swiftly exhibit a significant level of virulence in C-19 vaccinees.

The rise in anti-S IgG4 Abs and concomitant shift to an enhanced rate of chronic infectious or other immune suppression-mediated diseases in highly C-19 vaccinated populations is therefore extremely alarming.

However, our authorities and key opinion leaders do not understand the significance of the increased morbidity and mortality rate from these non-SC-2-related diseases on a background of relatively low C-19 morbidity and mortality rates. They don't grasp that the rising prevalence of turbo cancers and severe illness due to resurgence of chronic infections or underlying autoimmune diseases indicates that the host immune system has shifted from adapting to *symptomatic*, SIR-disabling VBTIs caused by more *infectious* variants to adapting to *asymptomatic*, SIR-enabling VBTIs caused by *highly infectious* variants. The latter promote viral transmission and shift the target of the immune selection pressure exerted by highly C-19 vaccinated populations from functional antigenic sites on S protein displayed on *free* virions to a highly conserved, non-functional antigenic site on S-NTD displayed on *DC-tethered* virions.

In conclusion:

The above-described activation of chronic infectious and non-infectious immune-mediated diseases combined with the seemingly comforting epidemiological situation of SC-2 (i.e., low C-19 hospitalization and mortality rates and diminished shedding of SC-2 into the environment) are to be considered a *poor prognostic sign* as they indicate an imminent threat of a major health disaster in highly C-19 vaccinated countries.

To emphasize the insidiousness of this evolution, I can only re-iterate the (sub)title of my book[16]: "*Society in highly C-19 vaccinated populations will be caught by surprise*".

3.6.2. High titers of IgG4 Abs link excess mortality from non-C-19-related disease to large-scale immune escape of SC-2 virus.

Unless the old dogmas are revisited, the C-19 pandemic will erroneously go down in history as *'an extremely insidious pandemic that even allowed highly infectious SC-2 virus to 'silently' pursue its immune escape trajectory until it ultimately evolved into an immune escape variant that – for some mysterious reason- proved to be highly virulent in C-19 vaccine-primed individuals'.*

SIR-enabling PNNAb-dependent VBTIs followed by SIR-disabling VBTIs link large-scale viral immune escape to concomitant SIR- or immune suppression-mediated non-C-19-related pathology via their stimulation of elevated titers of anti-S IgG4 Abs.

However, as scientists and health authorities do not seem to understand the underlying evolutionary dynamics of the adaptive immune response in C-19 vaccinees, they cannot understand that enhanced rate of cancers, autoimmune disorders or exacerbations of other, chronic infections are to be considered *side effects of large-scale VBTIs* that will ultimately enable the population to establish herd immunity.

The excess mortality rate due to non-C-19 disease in the context of low C-19 morbidity and mortality rates is therefore the only and last *clinical* alert left to warn highly C-19 vaccinated countries about an imminent and dramatic viral immune escape event. However, as the origin of the above-described side effects in highly C-19 vaccinated populations is obviously not debatable and as their nature is not considered by scientists and health

[16] https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic

authorities to mirror dangerous immune escape, I keep shouting that society in highly C-19 vaccinated countries will be caught off guard!

3.7. IgG4 Abs have erroneously been labeled as 'immune suppressive'.

IgG4 Ab do not cause immune exhaustion, they do not induce tolerance[17] nor do they make individuals more susceptible to disease. These misinterpretations are rooted in a poor understanding of the immunological mechanism of action of IgG4.

As already described under section 1.2. and 1.3., the monovalent binding of high-avidity IgG4 Abs to the S protein present on progeny virions subsequent to VBTI hinders Fc-mediated effector functions, consequently obstructing the uptake of single viral particles into APCs. This allows IgG4 Abs to trigger SIR (i.e., SIR-2) and elicit broadly cross-functional Abs towards immune recessive epitopes comprised within S protein expressed on the new immune escape variant. These newly primed Abs will initially curtail viral infectiousness. However, because of their low affinity, their titer rapidly declines. When their titer falls below the minimal threshold required to prevent infection, these Abs will still be able to bind to the virus. The resulting virus-Ab complexes will be taken up by APCs, thereby activating short-lived, broadly cross-reactive cytotoxic T cells. These CTLs kill virus-infected cells and thereby abrogate viral shedding while allowing vaccinees to rapidly recover from C-19 disease.

In other words, IgG4 Abs *do not cause tolerance* towards the pathogen and the immune system does *not* become *exhausted* either. However, as IgG4 Abs enable SIR-2-enabling VBTI upon exposure to more infectious variants, they ensure continued viral immune escape. Because of their anti-inflammatory effect, isotype-switched IgG4 Abs also render C-19 vaccinees *less susceptible to disease*.

While appearing paradoxical at first glance, exposure to highly infectious variants further improves immune protection in C-19 vaccinees and will even protect them from contracting C-19 disease altogether. This is presumably due to the highly infectious nature of the immune escape variant causing the VBTI. Massive production and release of high concentrations of progeny virions from the infected cells likely promote clustering of progeny virions into large aggregates that largely prevail over

[17] Tolerance refers to the state of immune unresponsiveness or reduced responsiveness to a specific foreign antigen that the immune system would normally recognize as 'non-self' or potentially harmful.

monodispersed virions bound by functionally monovalent IgG4 Abs (see fig. 2). As explained in sections 3.6.1. and 1.3.2.1., these aggregates likely facilitate massive uptake and internalization of progeny virus into tissue-resident APCs and thereby trigger strong cytotoxic activity of CTLs towards both, diseased virus-infected cells and the APCs that stimulated these CTLs.

As VBTIs generate high levels of IgG4 Abs and hyperactivation of APCs triggers stimulation of MHC-unrestricted CTLs while facilitating suppression of CD8+ T cells, *generalized immune suppression is paralleled by elevated IgG4 Ab titers*. However, correlation does not imply causation! Therefore, it would be incorrect to infer that elevated IgG4 Ab titers in extensively C-19-vaccinated populations possess inherent immune suppressive properties!

It is important to emphasize that instances of acute autoreactivity or early-onset cancer driven by IgG4 following SIR-enabling mRNA vaccination or VBTI are not attributable to an inherent immunological shortcoming. These pathologic immune responses are simply due to immune refocusing (i.e., SIR-2) caused by low-affinity binding *of isotype-switched IgG4 Abs upon their interaction with previously targeted, immune subdominant epitopes on S protein exposed on the surface of a new, more infectious variants. As explained in section 3.5., SIR-2 may facilitate priming of new, broadly reactive Abs that bind to 'self' or 'altered self' epitopes expressed on the surface of the host's own body cells or on pathologically altered (e.g., transformed) host cells, respectively. Binding of these Abs to 'self' or 'altered self' epitopes prevents signaling of cognate B lymphocytes to self-Ag-specific regulatory T cells that downregulate the activation/ proliferation of self-reactive T cells or prevent signaling of cognate Abs to functional, self-centered immune effector cells (i.e., via ADCC Abs facilitating cognate recognition by NK cells).

3.8. IgG4 are ideally suited to trigger SIR upon exposure of more infectious Omicron descendants.

Because of their high specificity for monovalent antigen, the capacity of isotype-switched IgG4 Abs to stabilize monodispersed virions is much higher than that of SIR-induced, broadly cross- neutralizing, low-affinity Abs from convalescent patients.

Monovalency of isotype-switched anti-S IgG4 prevents antigen cross-linking and multimerization of viral particles and would thereby reduce viral uptake into APCs. IgG4 Abs are therefore ideally suited to trigger

SIR, even though the progeny virus is more likely to aggregate because enhanced viral production following VBTI with more infectious variants is likely to increase the concentration of progeny virions released from infected epithelial host cells (see fig. 2).

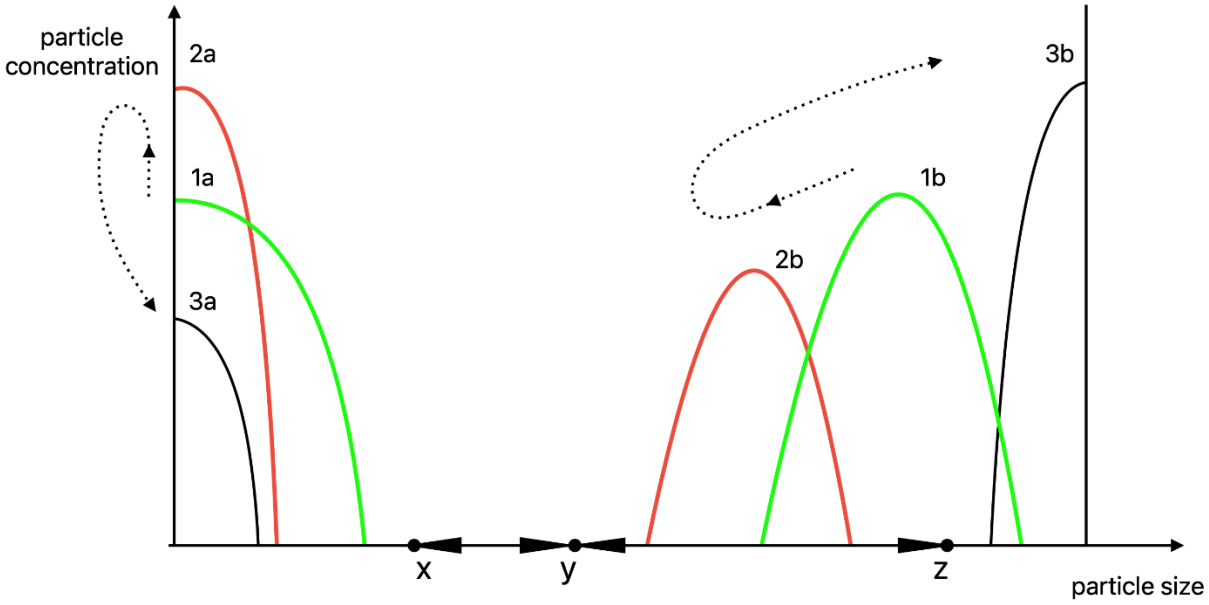

Fig. 2: Diagrammatic presentation of the size distribution of virus particles released from SC-2-infected target cells following VBTI by a new emerging variant.

Consequently, anti-S IgG4 Abs interact with 'more infectious' progeny virus in ways that enable sufficient dispersion of the offspring population into smaller aggregates and monodispersed virions (see fig. 2). Limited uptake of IgG4-opsonized, monodispersed virions by antigen-presenting cells (APCs), alongside significant uptake of viral aggregates by APCs, would redirect the immune response toward less immunogenic, infection-facilitating domains.

Immune refocusing triggered by VBTI or mRNA vaccination facilitates priming of newly generated, broadly cross-reactive Abs within the context of *noncognate* T help. Provision of suboptimal, noncognate T help may explain why these newly primed Abs have low infection-inhibiting capacity. They are, therefore, prone to exerting suboptimal immune pressure on viral infectiousness and fueling viral immune escape[18].

[18] Assistance by cognate T help would strengthen the infection-inhibiting capacity of these Abs and thereby prevent them from placing suboptimal immune pressure on viral infectiousness. This would obstruct the emergence and immune escape into highly infectious Omicron descendants.

3.9. High titers of anti-S IgG4 Abs are optimally suited to drive sustained viral immune escape following VBTIs. The combination of high titers of anti-S IgG4 Abs and exposure to highly infectious Omicron descendants will eventually increase the susceptibility of highly C-19 vaccinated populations to contracting enhanced severe C-19 disease and thereby enable viral eradication.

As already mentioned, SIR-1-enabling VBTIs with early Omicron variants or SIR-1-enabling mRNA vaccination eventually result in increased levels of isotype-switched IgG4 Abs. Upon exposure to circulating variants, IgG4 Abs will trigger a second SIR event (SIR-2). The latter eventually results in maturation of other, broadly functional anti-S Abs (presumably with 'infection-inhibiting' activity) into functionally monovalent IgG4 Abs. Whereas SIR-1-induced anti-S IgG4 Abs have an anti-inflammatory effect and mitigate C-19 disease, high titers of SIR-2-induced anti-S IgG4 Abs may trigger acute autoimmune disease or early-onset cancers.

I hypothesize that even in the presence of elevated titers of functionally monovalent IgG4 Abs, VBTI caused by highly infectious variants primarily leads to the formation of large aggregates of viral progeny, which are readily internalized by APCs (see under sections 3.6.1. and 1.3.2.1.). While strong activation of CTLs allows for efficient (i.e., asymptomatic) transmission of highly infectious virus, high titers of functionally monovalent IgG4 Abs obstruct re-stimulation of short-lived PNNAbs. These conditions are ideally suited to allow highly C-19 vaccinated populations to exert significant immune selection pressure on the *trans* infectiousness of DC-tethered virions. This will promote natural selection of newly emerging immune escape variants that are able to collectively lift the inhibitory effect of PNNAbs on viral *trans* infectiousness while taking advantage of the enhancing effect of PNNAbs on *viral infectiousness*. It is fair to assume that exposure to a such variant will result in PNNAb-mediated enhancement of severe C-19 disease in vaccinees (as explained under section 3.6.1.).

It can be reasonably anticipated that a high mortality rate among C-19 vaccine recipients could eventually diminish the extent of viral transmission to a point where SC-2 can no longer survive in its host population.

In summary:

IgG4 fuels immune escape while mitigating symptoms from PNNAb-dependent, SIR-enabling VBTIs (i.e., caused by more infectious Omicron variants) or rendering Ab-independent, SIR-disabling VBTIs (i.e., caused by highly infectious Omicron descendants) asymptomatic.

An increase in prevalence of elevated IgG4 titers is paralleled by diminished viral shedding in the environment[19] (erroneously interpreted by health experts and authorities as an indicator of diminished viral transmission and therefore of growing herd immunity!) and an increased incidence of autoimmune disease, cancer, and flare-ups of chronic infections.

Elevated IgG4 titers and growing rates of autoimmune and cancerous disease in highly C-19 vaccinated populations are particularly worrisome as they unambiguously indicate that immune selection pressure exerted by the population is now increasingly placed on the *trans* infectiousness of *DC-bound virions* instead of on the infectiousness of *free virions*.

This translates into a shift from immune refocusing on a distinct type of S-associated epitopes (i.e., with a different level of immunogenicity) to immune stimulation of anti-S Abs with a distinct isotype (i.e., IgG4 Abs).

Whereas immune selection pressure on viral infectiousness promotes the co-circulation of more infectious variants while mitigating disease, immune selection pressure on viral trans infectiousness is thought to favor the co-emergence of new variants that may evolve to maintain a high level of viral infectiousness (thanks to PNNAb-mediated enhancement) while lifting the blockade on viral trans infectiousness. This would enable such variants to provoke PNNAb-mediated enhancement of severe disease[20].

The transition phase between immune selection pressure on *viral infectiousness* and immune selection pressure on *viral trans infectiousness* is characterized by the failure of VBTIs to provoke SIR. SIR-disabling VBTIs are typically triggered by exposure to highly infectious Omicron descendants.

[19] However, measurement of virus concentrations in the environment (e.g., in wastewater samples) does not inform on the evolution of viral transmission of a highly infectious virus that can be efficiently transmitted among asymptomatically infected C-19 vaccinees.
[20] This evolution is similar to the one that prompted the emergence of Omicron, which lifted the blockade on viral neutralizability and, therefore, on the virus' capacity to cause moderate C-19 disease (while conferring protection from severe C-19 disease).

In conclusion:

At this stage of the pandemic, there is only one way for highly C-19 vaccinated populations to control the virus and to end the pandemic. This pandemic can only be brought to an end if highly C-19 vaccinated populations shift their immune selection pressure away from the functional (i.e., infection-inhibiting), moderately conserved antigenic sites within the S protein expressed on free SC-2 virions to the nonfunctional, highly conserved PNNAb-binding site within the S-NTD displayed on SC-2 virions that are attached to migratory dendritic cells. (https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic: chapter 3.). This is because such a shift will eventually enable natural selection of newly emerging variants that are capable of collectively lifting the blockade on viral trans infectiousness while taking advantage of residual PNNAbs to enhance their infectiousness. I therefore anticipate that these new variants will be able to provoke PNNAb-mediated enhancement of severe C-19 disease in C-19 vaccinees. The resulting surge in the C-19 case fatality rate would involve the most extreme type of herd immunity[21] as it would reduce viral transmission below the minimum threshold needed for the virus to ensure its replication and transmission. In highly C-19 vaccinated countries, the C-19 immune escape pandemic is therefore thought to result in the eradication of SC-2.

4. mRNA vaccines promote IgG4-mediated immune escape.

4.1. mRNA vaccination is prone to inducing IgG4 Abs (after at least 2 vaccinations) in previously uninfected individuals.

SC-2-uninfected people who received at least 2 injections with an mRNA vaccine develop high IgG4 Ab titers (https://pubmed.ncbi.nlm.nih.gov/36548397/) and are, therefore, at risk of developing acute autoreactive or early-onset tumor disease or contracting generalized immune suppression upon subsequent VBTIs. Whereas cytolytic destruction of APCs hampers Ag presentation, suppression of CD8+ effector T cells likely leads to re-activation of underlying autoimmune diseases or dormant cancers or enables resurgence of chronic infections. Since all of these

[21] Classical epidemiology misinterprets the evolutionary dynamics of a pandemic as being steered by the self-protective strategy of the virus rather than by the complex evolutionary constraints governing the survival of the higher vertebrate species. Hence, the simplistic but erroneous explanation as to why herd immunity ends a pandemic (of an acute, self-limiting viral disease) would be that herd immunity enables endemicity of the virus and therefore ensures its survival. This notion would, however, be contradicted in case herd immunity leads to viral eradication.

immune disorders are initiated by irreversible viral immune escape via VBTI, their occurrence indicates the susceptibility of C-19 vaccinees to potentially succumbing to a highly virulent VBTI in the near future.

4.2. However, previous SC-2 infection prevents mRNA vaccination from generating elevated levels of IgG4 Abs.

Repeated injection of C-19 vaccines, even including mRNA vaccines, fails to trigger SIR and therefore fails to raise IgG4 Ab titers when administered after previous SC-2 infection (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10222767/). This is because mRNA vaccination post infection recalls previously infection-primed T helper memory cells. The latter are dedicated to assisting recall of previously infection-primed neutralizing anti-S Abs but not to assist *de novo* priming of non-neutralizing Abs targeted at S protein expressed on the surface of mRNA-transfected host cells.

In other words, mRNA vaccination following natural infection will not trigger SIR and therefore not generate an increase in IgG4 Ab levels.

4.3. As mRNA vaccines elicit a significant increase in IgG4 Abs, large-scale immunization with mRNA-based vaccines enhances pathogen immune evasion.

Increased levels of IgG4 Abs have been reported to occur after the second vaccination with mRNA-based vaccines. Drawing from the mechanism explained above and the observation that mRNA booster doses elicited a broadly neutralizing Ab response (https://pubmed.ncbi.nlm.nih.gov/11535638/), it is reasonable to infer that an mRNA booster dose has the potential to induce immune refocusing, thus resulting in elevated IgG4 Ab titers. This inference rests on the rationale that an mRNA booster dose might stimulate the recall of low-affinity Abs[22] previously generated against immunodominant epitopes presented on the S protein expressed on the surface of mRNA-transfected cells. As mentioned above, immune refocusing promotes noncognate T help-assisted priming of poorly functional, broadly cross-neutralizing Abs that slowly mature into isotype-switched IgG4 Abs. As explained in section 3.8, high titers of functionally monovalent, isotype-switched IgG4 Abs enable SIR, even upon VBTI

[22] As priming of these Abs upon the first mRNA injection is assisted by noncognate T help, they bind with low affinity to immunodominant S-associated epitopes (primarily situated within the RBD) and thereby reorient the immune response to immune subdominant domains exposed on *in vivo* synthesized S protein that is released from mRNA-transfected host cells (https://www.voiceforscienceandsolidarity.org/scientific-blog/the-inescapable-immune-escape-pandemic: chapters 1.2.1. and 1.2.2.).

caused by more infectious SC-2 variants. As a result, they indirectly enable noncognate Th-assisted priming of broadly cross-protective, infection-inhibiting Abs that are directed at more conserved infection-facilitating S-associated epitopes.

Like SIR-enabling VBTIs, mRNA-based immunization in uninfected individuals is therefore thought to enhance large-scale viral immune escape.

From an immunological perspective, it is reasonable to assume that SIR-1 and SIR-2 equally manifest in individuals previously primed with an mRNA vaccine and are subsequently exposed to an updated mRNA booster dose (i.e., adapted to the circulating, more infectious Omicron-derived variant).

However, in the case of vaccination with adenovirus (Ad)-based C-19 vaccines, boosting did not lead to an increase in IgG4 Abs or a shift in the anti-S Ab repertoire toward broadly cross-neutralizing Abs[23] (https://www.frontiersin.org/articles/10.3389/fimmu.2022.1020844/full; https://pubmed.ncbi.nlm.nih.gov/36548397/). In the case of non-replicating viral vector vaccines, the S-encoding mRNA is directly transcribed from the DNA insert without exogenous chemical modification. It is therefore likely that the viral intracellular mRNA is degraded before the secreted, free-circulating S protein is presented to Ag-specific CD4+ T cells after uptake into APCs. Adeno-vector-infected cells would therefore not enable prolonged cell surface expression of S protein. Consequently, these vaccines do not allow for immune refocusing and de novo priming of new, broadly cross-neutralizing Abs that subsequently mature into isotype-switched IgG4 Abs of high avidity.

5. The ultimate gateway to finishing the Omicron pandemic consists of….herd immunity!

5.1. Viral immune escape following VBTIs is not driven by a 'strategy' of the virus to survive but by evolutionary pressure on survival of the human species.

IgG4 Abs following SIR-enabling VBTIs allow the host immune system to improve its immune defense against SC-2 from *protection against severe C-19 disease over mitigation of C-19 disease to full-fledged protection from C-19 disease and abrogation of viral shedding*.

[23] Boosting with these vaccines resulted in a substantial drop of the neutralizing capacity of vaccinal Abs toward newly emerged Omicron-derived sublineages.

However, in the absence of herd immunity, highly C-19 vaccinated populations remain highly susceptible to asymptomatic re-infection by highly infectious variants and thereby gradually exhaust the capacity of PNNAbs to protect vaccinees from severe C-19 disease. This ultimately triggers a shift from enhanced *inter-host* viral transmission to enhanced *intra-host* dissemination of the virus. The latter will ultimately lead to eradication of the virus from highly C-19 vaccinated populations (see under section 3.9.).

Viral immune escape following VBTI should therefore be considered the consequence of population-level immune dynamics targeted at ensuring survival of the host species.

This is how these dynamics work during an *immune escape pandemic* (i.e., a pandemic of immune escape variants):

The stronger the immune protection, the greater the potential infectiousness of newly emerging immune escape variants, leading to a higher incidence rate of VBTIs and, consequently, an increased rate of viral transmission. Although a high viral transmission rate ensures adequate training of the innate immune system in the unvaccinated, it prevents a highly C-19 vaccinated population from developing herd immunity! Nevertheless, herd immunity is the only mechanism that can ensure survival -and therefore long-lived protection- of a human population against acute self-limiting infections[24].

Nature will establish herd immunity for the benefit of the host species' survival. In order to achieve this, it will preserve individuals capable of making effective contributions to it while relinquishing those who are unable to do so (i.e., due to inadequate, deficient, or weakened innate immunity).

Thus, it is not surprising that once the innate immunity of the unvaccinated has been trained strongly enough to possess sterilizing capacity against highly infectious circulating variants, the strong protection from C-19 disease in vaccinated individuals will suddenly transition to a heightened susceptibility to enhanced severe C-19 disease.

To build efficient herd immunity during a natural pandemic, it suffices when the vast majority of the population acquires natural immunity. However, in the case of an immune escape pandemic (i.e., in a highly

[24] Examples of acute self-limiting infections are viral infections caused by coronaviruses, influenza viruses, enteroviruses, parvoviruses, rotaviruses.

C-19 vaccinated population) that remains untreated[25], the portion of the population that is unable to sterilize the steadily emerging immune escape variants will inevitably succumb to the disease. This will automatically diminish viral transmission to a level where the virus can no longer survive, thus strengthening herd immunity (in the remainder of the population) beyond a threshold that would allow the virus to become endemic in the human population.

This implies that it is the host species, not the virus, that will ultimately triumph!

Based on the above, it can already be inferred that the human cost in lives during an immune escape pandemic is significantly greater than during a natural pandemic, where the selective loss of lives aids in preserving the overall population's health. While herd immunity serves as the solution to end both a natural pandemic and an immune escape pandemic, the processes of its establishment and the resulting outcomes differ. In the context of a natural pandemic, it will lead the virus into endemicity, while in the case of an immune escape pandemic, it will lead to virus eradication.

In the case of a natural pandemic, endemicity allows for a regular boost of herd immunity. Meanwhile, SC-2 has likely become endemic in several animal populations. Endemicity in animal populations could potentially play a role in establishing endemicity in the surviving human population. Nevertheless, this can only occur when the protective effect of innate immune adaptation has sufficiently waned, and the surviving population has grown large enough to facilitate continuous asymptomatic transmission.

5.2 The time has come for epidemiologists to delve into immunology rather than adhering to outdated epidemiological dogmas.

All of the above should illustrate that viral immune escape dynamics following VBTIs are driven by an immunological rescue operation that is collectively steered by natural selection pressure and aimed at establishing herd immunity, thus protecting the population. It is not driven at all by a kind of 'survival strategy' of the pathogen as old epidemiological dogmas

[25] The only conceivable approach to manage a pandemic involving immune escape variants would be to carry out extensive treatment campaigns using antiviral drugs. Regrettably, the implementation of such a treatment program is highly improbable.

claim. These dogmas are incorrect in teaching that viral immune escape reflects the pathogen's intention to manipulate or subvert the host's immune response to ensure its survival.

According to the classical school of thought, viral immune escape dynamics during this pandemic have been driven by evolutionary pressure on the virus to survive and it is therefore compulsory for the virus to evade population-level immune pressure. The classical epidemiological school of thought always considers the virus to be in the driver's seat, even when herd immunity is eventually established, and the virus has become endemic. A natural pandemic would therefore always lead to endemicity, but not eradication of the virus. A low rate of asymptomatic transmission would fulfill the objective of ensuring viral survival in the context of population-level immune protection from disease. Under no circumstances would the virus become highly virulent as this could lead to the elimination of a substantial part of the host population and therefore diminish the virus' chances to survive.

This misinterpretation of viral evolutionary dynamics has prevented the scientific community from understanding that 'self-fueling' VBTIs during an immune escape pandemic of a virus causing acute self-limiting infection aims at protecting the population, not the virus, and thereby proceeds in two transitioning steps.

It first improves the immune response of those who have the capacity to develop natural, sterilizing immunity (i.e., the unvaccinated). This process sets the stage for the second step, which involves removing the segment of the population that irreversibly lost that capability (i.e., the vaccinated) after viral immune escape advanced to the point where it largely evaded vaccine-induced NAbs (i.e., since the emergence of Omicron in highly C-19 vaccinated populations or since the start of large-scale vaccination with mRNA vaccines, whichever occurred earlier).

In conclusion:

Epidemiologists and health authorities lack an understanding of the evolving immunological mechanisms that drive the evolutionary dynamics of the virus. Consequently, they do not grasp the fact that VBTIs involving highly infectious Omicron descendants enable highly C-19 vaccinated populations to reduce C-19 pathogenicity and viral shedding, even in the presence of high (yet asymptomatic) viral transmission rates and thus, a complete lack of herd immunity.

At some point, though, the population must let go of individuals who have reached the limits of their contribution to driving natural selection of more infectious variants (which benefits the training of the innate immune system in the unvaccinated!).

Preserving the human species will require Nature to eliminate significant numbers of vaccinated individuals from highly C-19 vaccinated populations. This will enable those with strong trained innate immunity (primarily the unvaccinated) to control the virus through sterilizing immunity, ultimately leading to virus eradication.

6. **mRNA-based C-19 vaccination *before*[26], but not after, SC-2 infection, raises IgG4 Ab levels. Immune protection acquired through natural disease is superior to that provided by C-19 vaccines[27].**

All C-19 vaccinees who experienced symptomatic VBTI or largely remained asymptomatic but received at least 2 injections of an mRNA vaccine prior to natural SC-2 infection should consider taking antiviral medication.

In both cases, serum levels of IgG4 Abs are likely to have increased. Elevated IgG4 Ab titers in C-19 vaccinees could indicate high susceptibility to PNNAb-mediated enhancement of severe C-19 disease upon exposure to a new type of SC-2 variants, the emergence of which is now thought to be imminent in highly C-19 vaccinated populations.

7. Conclusions

Every seasoned vaccinologist should have known that mass vaccination programs conducted during a pandemic cannot produce herd immunity. It's irresponsible and a disgrace to the world that the WHO recommended mass vaccination in an unreasonable and irrational effort to control the SC-2 pandemic, and that numerous key opinion leaders, including vaccine experts, supported their advice.

Meanwhile, there is abundant evidence demonstrating that widespread C-19 vaccination actually facilitated immune escape and consequently resulted in VBTIs (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9047157/; https://pubmed.ncbi.nlm.nih.gov/34596015/).

[26] https://pubmed.ncbi.nlm.nih.gov/36713457/
[27] https://academic.oup.com/cid/article/75/1/e545/6563799

VBTIs with Omicron led to SIR and thereby re-oriented the host immune response to conserved, immune subdominant S-associated domains. SIR[28] uniquely illustrates how the host immune response can effectively adapt to more infectious SC-2 variants, or SIR-enabling mRNA vaccination, and thereby drive large-scale viral immune escape.

SIR-enabling mRNA vaccination and VBTIs have been shown to result in elevated titers of IgG4 Abs, but neither the evolutionary significance nor the etiological trigger of isotype-switching to IgG4 Abs has been elucidated. High IgG4 Ab titers have been inaccurately construed as reflecting an independent immune mechanism capable of alleviating the adverse immunological effects triggered by any situation that results in prolonged or repeated exposure to foreign Ags (e.g., in the case of prolonged exposure to infectious pathogens or repeated exposure to allergens, respectively). However, prolonged, or repeated exposure of this nature has also been documented to potentially trigger the production of IgG4 Abs with adverse consequences, as they may react with 'self' antigens present on the surface of healthy host cells or with 'altered self' antigens expressed on the surface of pathologically altered cells (e.g., cancer cells). The seemingly 'beneficial' effect is inaccurately termed 'tolerance' (towards foreign), while the adverse effect is erroneously labeled as 'intolerance' (towards self). Nonetheless, the mechanism responsible for the differential impact of elevated IgG4 Abs has remained enigmatic.

While the presence of elevated IgG4 Ab titers has been extensively documented and is recognized to be associated with either facilitating '(pseudo)tolerance' or '(pseudo)intolerance', no investigation has yet explored the importance of elevated IgG4 Ab titers in the context of an evolving immune escape pandemic.

The sole plausible causal explanation for the evolutionary patterns of anti-S IgG4 Ab titers and the accompanying broadly protective or pathogenic immune response in C-19 vaccine recipients is large-scale immune refocusing and viral immune escape.

Immune refocusing resulted from SIR-enabling VBTIs with Omicron. SIR events re-directed the immune response to a completely different, more conserved set of S-associated epitopes in a way that generates suboptimal

[28] Immune refocusing allows the host immune system to develop some new neutralizing capacity after multiple mutations in previously circulating pre-Omicron variants diminished the neutralizing capacity of vaccine-induced S-specific NAbs. Whereas the latter were directed at a broad and diversified spectrum of dominant, variant-specific epitopes that are primarily situated within S-RBD, de novo primed NAbs targeted a limited subset of more conserved epitopes and exhibited relatively low affinity. This explains why cross-neutralizing Ab titers elicited shortly after SIR-enabling VBTIs, or after mRNA booster immunizations in previously mRNA vaccine-primed individuals, rapidly declined.

immune pressure on these epitopes. In highly C-19 vaccinated populations, SIR-enabling VBTIs led to natural selection of a broad and diversified range of less neutralizable immune escape variants while also concurrently giving rise to increased levels of anti-S IgG4 Abs.

In turn, these IgG4 Abs triggered another SIR event, thereby causing prolonged but suboptimal population-level immune pressure on intrinsic viral infectiousness. This provided a fitness advantage to all new Omicron-derived variants sharing the same immune escape mutation within the conserved infection-facilitating domain of S protein. Therefore, their natural selection promoted a rapid succession of distinct, dominantly circulating highly infectious immune escape variants.

In the context of the ongoing pandemic involving Omicron-derived descendants, we have witnessed how large-scale immune escape has been paralleled by immune responses in C-19 vaccine recipients that gradually evolved from being broadly inflammatory (encompassing multiple SC-2 Ags) to becoming broadly anti-inflammatory (extending to other viral pathogens) in the majority of vaccine recipients. Subsequently, these immune responses have shifted towards being broadly autoreactive or carcinogenic (potentially involving various organs) in a steadily increasing subset of the vaccinated individuals.

It is important to note that also mRNA vaccination can trigger SIR, but the mechanism is different. mRNA vaccines trigger SIR (SIR-1) by priming low-affinity Abs to immunodominant epitopes on S protein expressed on the surface of mRNA-transfected cells. This explains why full mRNA vaccination (i.e., after booster dose) also induces broadly neutralizing Abs that ultimately mature into functionally monovalent anti-S IgG4 Abs. The latter promote another SIR event (i.e., SIR-2) upon VBTI with more infectious virus. Hence, it is justifiable to infer that widespread immunization using mRNA-based C-19 vaccines expedited large-scale SC-2 immune evasion while gradually shifting the immune response from broadly protective and inflammatory in a decreasing majority of C-19 vaccine recipients, to broadly anti-inflammatory but potentially broadly autoreactive or carcinogenic in an expanding subset of C-19 vaccinated populations.

It is even reasonable to assume that mass vaccination with *any mRNA-based vaccine* will drive large-scale immune evasion of the targeted pathogen and therefore also lead to broad-spectrum autoreactivity and carcinogenicity.

In addition, exposure to highly infectious variants in the presence of elevated IgG4 Ab titers triggers SIR-disabling VBTIs that result in largely asymptomatic cases of C-19 disease and entail rapid abrogation of viral shedding. However, SIR-disabling VBTIs caused by highly infectious Omicron descendants are now failing to prime new NAbs in previously vaccinated individuals. This is due to the fact that highly infectious variants cause strong activation of APCs. These APCs are so preoccupied with removing highly infectious virus from VBTIs that they succumb to the killing by the CTLs they activate. *This phenomenon also explains why booster doses with updated C-19 vaccine will fail to prime new NAbs in previously C-19 vaccinated individuals*. Concurrently, these SIR-disabling VBTIs boost pre-existing IgG4 Ab levels. Elevated titers of functionally monovalent IgG4 Abs obstruct the aggregation of viral particles when exposed to circulating variants in the upper respiratory tract, despite the presence of long-lasting but poorly neutralizing vaccine-induced Abs. This leads to a reduction in the production of short-lived, trans infection-inhibiting PNNAbs (i.e., preventing severe C-19 disease).

In summary, both, (updated) booster doses and ongoing (asymptomatic) VBTIs are ineffective in generating new NAb capacity while levels of PNNAbs are currently steadily dropping into a suboptimal range.

Enhanced activation of APCs upon exposure of C-19 vaccinees to VBTIs caused by highly infectious Omicron descendants also explains why high levels of IgG4 Abs correlate with generalized immune suppression and, therefore, with an increased incidence of turbo cancers and flare-ups of underlying chronic infections or immune-mediated diseases.

In conclusion, the sequence of SIR-enabling PNNAb-dependent VBTIs followed by SIR-disabling VBTIs establishes a link between widespread viral immune evasion and the concurrent manifestation of health issues and increased (excess) mortality not directly associated with Covid-19. This link is mirrored by the gradual increase of anti-S IgG4 Abs. These Abs are generated or recalled during SIR-enabling or SIR-disabling VBTIs as a result of immune refocusing or immune imprinting, respectively.

Lastly, the collective decline in PNNAb titers in highly C-19 vaccinated populations exerts growing immune selection pressure on viral trans infectiousness. This likely promotes natural selection of newly emerging variants that are able to collectively lift the blockade of these Abs on the virus' potential to cause severe C-19 disease while preserving their infection-enhancing capacity.

In other words, such new Omicron-derived variants will acquire both highly infectious and highly virulent properties within highly C-19 vaccinated populations.

Consequently, the resulting enhancement of severe C-19 disease through PNNAbs is believed to lead to swift systemic virus spread and replication across various organs in C-19 vaccine recipients.

In the meantime, growing immune selection pressure on viral trans infectiousness translates into a shift from an increased prevalence of early-onset cancers and acute autoimmune diseases to a rising prevalence of turbo cancers and resurgence of pre-existing autoimmune diseases and reactivation of underlying chronic infections because of generalized immune suppression.

The final and definitive message is that key opinion leaders and health experts are mistakenly interpreting decreased C-19 pathogenicity as a signal that the virus is transitioning into endemicity. They fail to grasp that, without herd immunity, decreased pathogenicity is intrinsically tied to enhanced immune evasion of SC-2 and to non-Covid-19 illnesses.

Therefore, considering the increasing IgG4 Ab titers, the currently observed low rates of C-19 hospitalization and mortality should be seen as an unfavorable prognostic indicator. They merely point toward an impending risk of a substantial healthcare crisis in highly C-19 vaccinated countries.

Figures

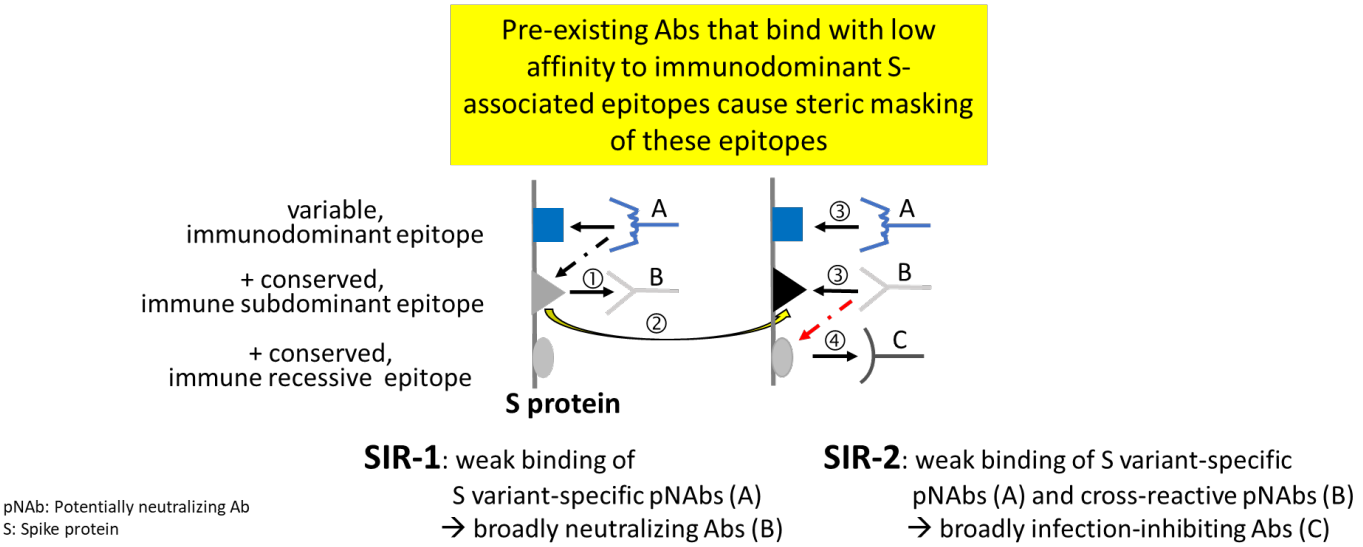

Fig. 1 VBTIs trigger immune refocusing and thereby elicit broadly cross-functional Abs and potentially pathogenic isotype-switched IgG4 Abs.

SIR-enabling VBTIs drive large-scale viral immune escape in vaccinees by reorienting the immune response to S-associated antigenic sites that prime broadly functional antibodies (Abs) with low affinity. SIR occurs when pre-existing Abs (A) bind with low affinity to their target epitopes on progeny virus or in vivo synthesized vaccinal antigen (i.e., in the case of mRNA transfection), respectively. SIR-induced Abs to subdominant S-associated antigenic domains have low affinity and therefore enable highly C-19 vaccinated populations to place high immune selection pressure on these more conserved domains. SIR therefore allows for fast and large-scale immune escape. SIR-1 triggers induction of broadly neutralizing Abs of low affinity (B) that are directed at more conserved, immune subdominant epitopes
(①). This drives large-scale immune escape of variants that have acquired a higher level of viral infectiousness due to their diminished neutralizability (②) and therefore provoke new VBTIs; the latter allow pre-existing potentially NAbs to bind with low affinity to both the S-associated immunodominant and mutated, subdominant epitopes expressed on the new progeny virus (A and B, respectively). This triggers SIR-2, which allows other, immune recessive S-associated epitopes to prime broadly infection-inhibiting Abs of low affinity (C) and potentially also Abs that will mature into broadly reactive IgG4 Abs. Whereas the former drive large-scale emergence of highly infectious Omicron descendants that trigger SIR-disabling VBTIs, the latter may react with self or altered self Ags expressed on the surface of healthy or malignantly transformed host cells, respectively.

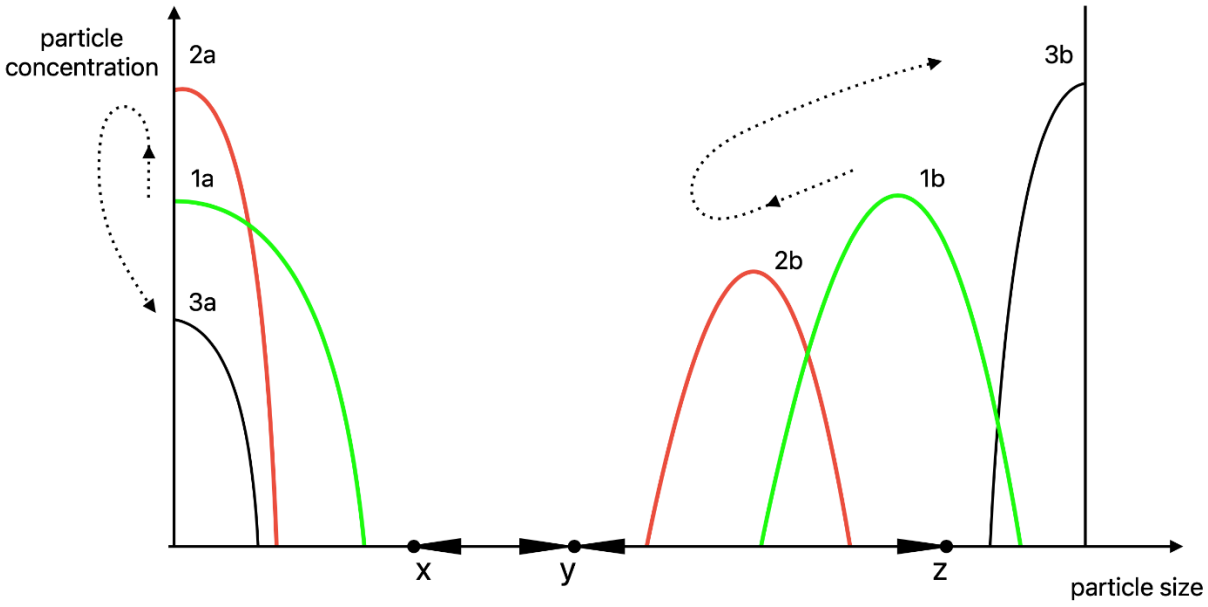

Fig. 2 Diagrammatic presentation of the size distribution of virus particles released from SC-2-infected target cells following VBTI by a new emerging variant. The y-z interval represents a theoretical range of size distribution comprising viral aggregates of a size that is optimally suited for uptake by APCs and, therefore, for recall of noncognate T helper memory cells. The latter are required to prime new, broadly cross-reactive Abs to the variant S protein.

Curves 1a and 1b depict the size distribution of progeny virus released from SC-2-infected target cells following a VBTI caused by SC-2 virions whose infectiousness is enhanced by PNNAbs (i.e., in the presence of vaccine-primed Abs with greatly diminished neutralizing capacity). High titers of poorly neutralizing, low-affinity Abs have the capacity to stabilize relatively low concentrations of single progeny virions (1a) while aggregates (1b) cannot be stabilized and are partially taken up by APC (1b). This combination enables SIR-1.

Curves 2a and 2b depict the size distribution of progeny virus released from SC-2-infected target cells following a VBTI caused by more infectious SC-2 in the presence of isotype-switched IgG4 Abs. As the latter are functionally monovalent, they have a higher capacity to stabilize single progeny virions (2a). However, most of the remaining progeny virus clusters in aggregates (2b) that will be taken up by APCs, thereby facilitating SIR-2.

Curves 3a and 3b depict the size distribution of progeny virus released from SC-2-infected target cells following a VBTI caused by *highly infectious* SC-2 in the presence of isotype-switched IgG4 Abs. Although the latter have a high capacity to stabilize single progeny virions (3a), they

cannot prevent clustering of most of the progeny virus in large aggregates (3b). As the latter will trigger MHC-unrestricted CTLs instead of recalling previously primed Th cells, the VBTI fails to trigger SIR. Such VBTI is therefore referred to as 'SIR-disabling'.

The dotted arrows indicate the shift in particle size distribution as SIR-enabling VBTIs transition to SIR-disabling VBTIs.

Note: Whereas the y-z interval represents the optimal range of particle size for activation of memory T helper cells following VBTI, the x-z range could represent the ideal size spectrum of multimeric viral particles, which effectively trigger stimulation of short-lived PNNAbs through the interaction of poorly neutralizing Abs with a variant carrying a distinct S protein Ag in the upper respiratory tract (e.g., in the case of exposure of C-19 vaccinees to Omicron).

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