I think it's about time we come up with an emergency plan!

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I may be wrong, but I now feel that we are finally approaching the end phase of this pandemic!

Until recently, highly COVID-19 (C-19)–vaccinated populations have primarily exerted *adaptive immune pressure* on *viral infectiousness*, leading to the emergence of variants capable of evading virus-neutralizing antibodies (Abs) targeting *specific* spike (S) protein *peptide epitopes*. However, highly C-19-vaccinated populations now appear to be shifting toward exerting *innate immune pressure* on viral *trans infectiousness* [1], resulting in the emergence of variants (e.g., NB.1.8.1) that can–at least to some extent–evade *virus-inhibiting* interactions with dendritic cell-expressed lectins, which *nonspecifically* recognize S-associated *glycan motifs*. While earlier (adaptive) immune escape variants primarily caused *vaccine breakthrough infections* resulting in *enhanced viral infection rates*, these newer (innate) immune escape variants are more likely to cause '*high-viral-load' breakthrough infections* in individuals with poorly trained cell-

mediated innate immunity, potentially leading to *increased rates of highly virulent infections*—associated with severe disease and death—in highly C-19-vaccinated populations.

So I wouldn't be surprised if we start the summer with a nasty surprise…

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1 Viral *trans* infectiousness refers to the ability of a virus to infect new host cells indirectly via interactions with host immune cells, such as dendritic cells, rather than through direct infection of target cells. It typically implies a process where:
Antigen-presenting cells (especially dendritic cells or macrophages) capture viral particles at mucosal surfaces via lectin receptors (e.g., DC-SIGN), not to become productively infected themselves, but rather to transfer the virus to permissive target host cells. This lectin-mediated transfer mechanism is often referred to as viral *trans* infection. *Trans* infection facilitates intra-host transmission of SARS-CoV-2 and promotes cell-to-cell fusion (so-called *trans* fusion), leading to the formation of syncytia—structures that are considered pathognomonic of viral virulence. In the context of SARS-CoV-2, migratory dendritic cells (DCs) patrolling the upper respiratory tract can bind spike protein–associated glycans via cell surface-expressed, nonspecific pattern recognition receptors (e.g., C-type lectins), facilitating indirect viral transmission to ACE2-expressing host cells.
This mechanism would bypass traditional neutralization by anti-spike antibodies targeting *peptide epitopes*, contributing to *innate immune escape*.
The distinction from *viral infectiousness* is important when discussing immune escape, as the current evolution of SARS-CoV-2 appears to reflect a shift from *adaptive immune evasion* (antibody/epitope specificity) toward *innate immune evasion*. In the case of SARS-CoV-2,

innate immune evasion is thought to be due to the diminished capacity of circulating escape mutants to induce inflammatory cytokines and/or interferons (particularly type I interferons such as IFN-α and IFN-β), which are known to upregulate the expression of C-type lectins on the surface of migratory DCs (pattern recognition receptor evasion).

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