Infection-enhancing antibodies either ‘drain’ or ‘train’….

Abbreviations:

Ab: Antibody

Ag: antigen

ADED: Ab-dependent enhancement of disease

ADEI: Ab-dependent enhancement of infection

ASLD: Acute self-limiting disease

ASLI: Acute self-limiting infection

IEABs: Infection-enhancing Abs

LRT: Lower respiratory tract

SC-2: SARS-CoV-2

Weak immune activation by glycosylated ASLI- or ASLD-enabling viruses (that occurs, for example, during asymptomatic-mild natural infection) elicits low concentrations of non-neutralizing, short-lived IEABs. Upon subsequent re-exposure to a homologous or antigenically shifted[1] viral lineage these Abs are highly likely to enhance viral uptake by susceptible host cells and contribute to innate immune training of pre-primed NK cells. However, it’s important to note that individuals who contract asymptomatic/ mild infection provoked by a glycosylated ASLVI- or ASLVD-enabling virus can still experience disease. This can occur when re-exposure to the homologous or antigenically shifted viral lineage occurs at a point in time where the *short-lived* non-neutralizing IEABs are at their very highest level. As these Abs are immature (i.e., non-functional), their titers decline rapidly—they are no longer even detectable after 8 weeks. ADED after asymptomatic/ mild infection is therefore rare and the incidence rate thereof can only significantly increase in case of high viral infectiousness (which will substantially increase the likelihood for re-infection within just a few weeks after the previous asymptomatic-mild infection). In the case of SC-2, high viral infectiousness

[1] ‘Antigenically shifted’ relates to an antigenic shift in the viral surface protein that is responsible for initiation of infection

results from natural selection and dominant propagation of 'more infectious' SC-2 variants which is a direct consequence of mass vaccination (as previously explained).

On the other hand, immune priming by glycosylated ASLI- or ASLD-enabling viruses (for example, in people who contract the disease) induces virus-neutralizing Abs as well as non-neutralizing Abs (comprising IEABs). Upon subsequent re-exposure to an antigenically shifted viral lineage binding of the IEABs to a variant-nonspecific site[2] on the virus enhances viral uptake by susceptible host cells. This partially sidelines pre-primed NK cells and calls on cytotoxic CD8+ T cells to clear virus-infected cells, leading to more pronounced symptoms of disease. As the enhanced viral uptake does not usually lead to full drainage of the viral clearance capacity of cytotoxic CD8+ T cells, productive infection will not only enhance training of pre-primed NK cells but also enables priming of 'new' Abs directed at the surface protein that is responsible for initiation of infection by the antigenically shifted viral lineage.

This can explain why individuals who contracted disease induced by a glycosylated ASLVI- or ASLVD-enabling virus can still contract disease again (but rarely severe) up to several months after their recovery. This typically occurs when re-infection is caused by an antigenically shifted viral lineage and at a point in time where the naturally induced Ag-specific Abs are still fairly high. The phenomenon can also occur in the case vaccine-induced Abs are confronted with an antigenically shifted viral lineage before they have achieved full-fledged neutralizing capacity. Individuals who got partially vaccinated (e.g., only one shot) with a non-replicating Ab-based viral vaccine and become exposed to an antigenically shifted viral lineage shortly thereafter are prone to this risk.

Finally, strong immune priming by non-replicating Ab-based vaccines elicits high concentrations of both potentially neutralizing and non-neutralizing IEABs. Upon subsequent re-exposure to an antigenically shifted viral lineage the IEABs are highly likely to enhance viral uptake by susceptible host cells in a way that sidelines pre-

[2] In case of SC-2, this site is situated within the N-terminal domain of spike protein

primed NK cells and increasingly drains the flow capacity of viral clearance by cytotoxic CD8+ T cells (instead of training NK cells). This is likely to not only cause more severe disease and delay recovery, but also to prevent immune priming against the antigenically shifted epitopes (immunologically outcompeted by 'old' epitopes that benefit from 'antigenic sin'). Instead, natural re-exposure to either a homologous or antigenically shifted viral lineage will strongly boost the IEABs for lack of sufficient flow capacity of viral clearance by cytotoxic CD8+ T cells (as a result of deficient NK cell training). In case of re-infection with the same viral variant, this is likely to increase the severity of the disease (due to ADEI) whereas re-exposure to an antigenically shifted viral lineage that is resistant to the potentially infection-neutralizing vaccine-induced Abs (e.g., the more virulent Omicron BA.4 or BA.5 lineages in case of SC-2) will enable boosted IEABs to protect against *severe* disease (via inhibition of productive *trans* infection in the LRT).

In the meantime, viral lineages that are resistant to the potentially virulence-neutralizing vaccinal Abs are being selected. Once this has happened, the IEABs will facilitate ADEI-mediated ADED in vaccinees.

Conclusion in regard of SC-2 and Covid-19:

Whereas the unvaccinated are experiencing *increasing* and *durable* protection from C-19 *disease* caused by new variants through i) trained innate immunity (which is not susceptible to immune escape!) and ii) priming of new neutralizing Abs against those variants (as 'antigenic sin' is mitigated by trained innate immunity!), vaccinees now need to exclusively rely on boosting (as 'antigenic sin' is not mitigated by training of pre-primed NK cells) of IEABs (which are prone to immune escape!) to ensure a *fragile* and *provisional* protection from *severe disease*.

Whereas immune training is a blessing, immune drainage is a scourge! That's why only natural immunity can eventually fully protect you during a pandemic. That's why Africa will win!