Novel bivalent C-19 vaccines: What does common immunological sense predict in regard to their impact on the C-19 pandemic?

Bivalent mRNA booster candidates[1] have been developed as a next step in the development of C-19 vaccines to combat the virus; these new vaccines target the induction of a broader immune response than the original vaccines and have to some extent already been approved by regulatory authorities (e.g., FDA, MHRA).

One wonders though why studies conducted to test these new vaccines have only enrolled baseline seronegative participants whereas the new vaccines will predominantly be administered to people who have already been vaccinated with first generation C-19 vaccines. This is quite striking as usage of these updated C-19 vaccines to fight dominantly circulating Omicron variants *in previously C-19-vaccinated populations* is highly contra-indicated as it violates all basic principles of vaccinology. The latter dictate that infection-enhancing antibodies (IEABs), which are directed at a conserved antigenic site comprised within spike protein (S), will be rapidly re-stimulated by the Omicron-adapted S-based vaccine. While re-stimulation of these antibodies (Abs) will not require cognate T help (Th), priming of immune responses against variable and previously unrecognized antigenic motifs (so-called 'epitopes') of S is cognate T help-dependent and will therefore require uptake, processing, and presentation of the corresponding antigenic peptides (i.e., derived from those epitopes) by antigen-presenting cells (APCs).

As previously reported, C-19 disease in C-19 vaccinees is most likely mitigated by inhibition of *trans* infection of viral particles that are tethered to the surface of tissue-resident dendritic cells (which subsequently migrate to distant organs) and by strengthening activation of cytotoxic CD8+ T cells/ lymphocytes (CTLs) directed at a universal epitope comprised within S protein (https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic; https://www.voiceforscienceandsolidarity.org/scientific-blog/monkeypox). Both mechanisms are facilitated by IEABs that typically enhance receptor-mediated viral entry when anti-S Abs lose their neutralizing capacity due to growing resistance of SARS-CoV-2 (SC-2) variants. Sustained, Th-independent activation of CTLs will allow these lymphocytes to also recognize and kill APCs that cross-present (on MHC class I molecules) the universal, S-associated CTL epitope following uptake and processing of vaccinal antigen (Ag) by professional APCs (i.e., dendritic cells). This will prevent these APCs from priming Th-dependent Ab responses towards new (i.e., Omicron-specific) immunogenic B cell epitopes comprised within vaccinal Omicron-derived spike protein. More specifically, immune responses in healthy vaccinees not only sideline the innate immune response but also prevent APCs from inducing new adaptive immune responses either by blocking Ag uptake (i.e., due to adsorption of SC-2 particles to their surface) or preventing Ag presentation by killing professional APCs after they've internalized the vaccine-derived S antigen (comprising the conserved CTL epitope) as previously illustrated (see figure attached below).
Consequently, the immunological effect of vaccination in thoroughly C-19 vaccinated subjects is much

[1] Based on both the original Wuhan variant and either Omicron subvariant BA.1 or Omicron subvariant BA.4/5 lineage

different from that of a natural (breakthrough) infection. In the case of a breakthrough infection, the aforementioned defense mechanisms largely fail to result in APCs preventing *trans* infection or activating cytotoxic CD8+ T cells, and thus fail to protect the host against C-19 disease.
This implies that the immune system of a C-19 vaccinated person cannot rely on conventional Ag-presentation to enable immune recognition of new, S-associated epitopes unless the virus breaks through the host's (temporary) immune defense facilitated by short-lived IEABs. However, increased frequency of re-infection (i.e., as a result of enhanced susceptibility of vaccinees to infection; https://www.medrxiv.org/content/10.1101/2022.01.28.22270044v1) leads to a reduced likelihood that the virus will break through the fragile, Th-independent immune defense of vaccinees. This in turn will lower the chances for the vaccinees to generate natural immunity against any new variant, or for that matter any new S-derived vaccinal antigen (i.e., regardless of the antigenic characteristics of the Omicron (sub)variant it originates from).

Conclusion:

Updated C-19 vaccines comprising new mRNA- or protein-derived S-associated sequences of one or more Omicron (sub)variants will only further deteriorate the already dire consequences of C-19 mass vaccination—abundant cell surface-expressed and/ or free circulating S protein will cause a unilateral and potentially protracted recall of IEABs without priming neutralizing Abs against new Omicron-specific antigenic sequences in the vast majority of healthy vaccinees. Whereas the purpose of these novel vaccines is to enhance protection against continuously evolving variants, they will have exactly the opposite effect, in that they will enhance the evolutionary dynamics of the virus. Continued mass vaccination with novel Omicron-adapted vaccines will only increase population-level immune pressure on viral virulence by the IEABs (which currently have a virulence-inhibiting effect at the level of the lower respiratory tract). *Large scale vaccination with these updated vaccines will merely expedite natural selection and expansion of SC-2 variants that will exhibit a high level of virulence and infectiousness in vaccinees*, while sparing the unvaccinated from this impact.

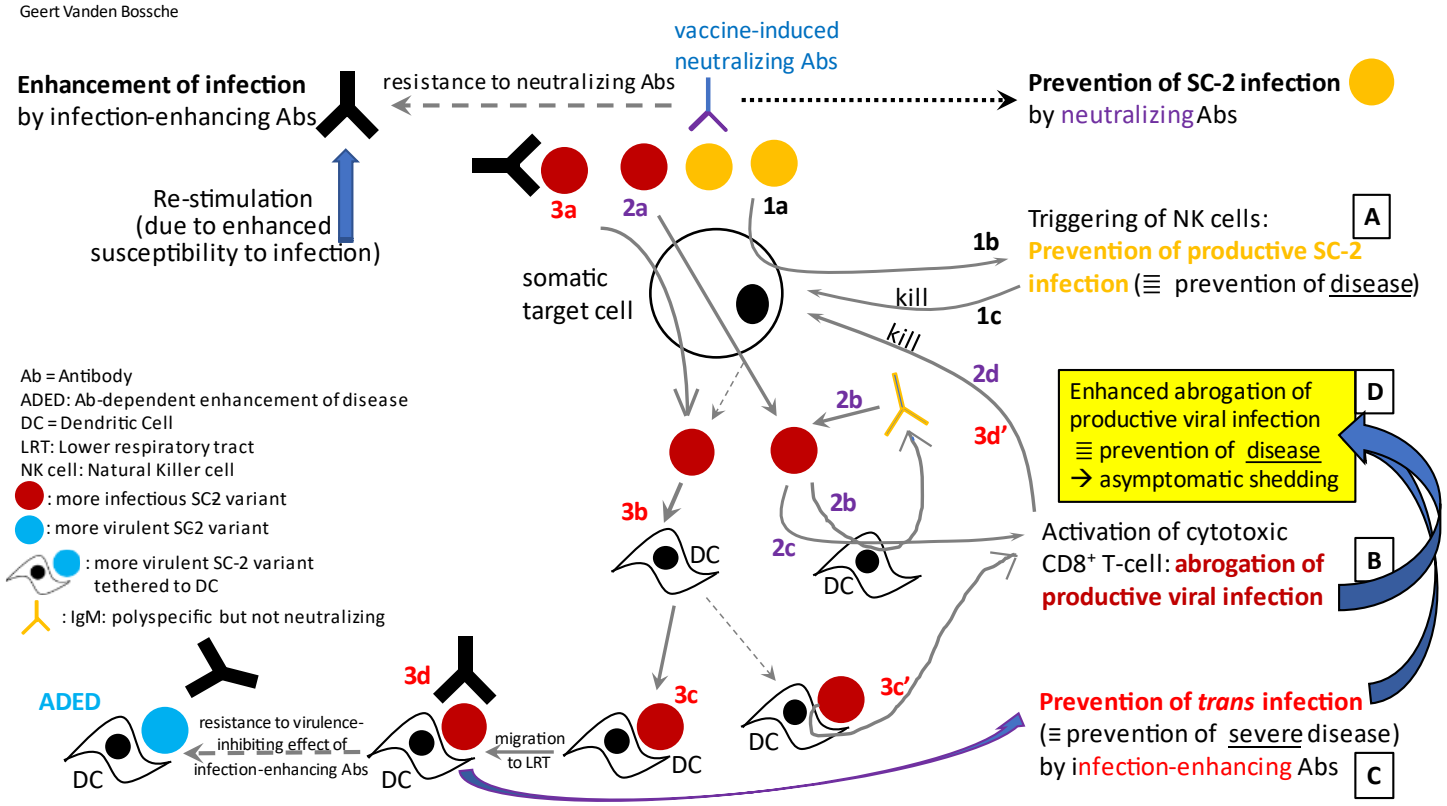
Figure:
(from https://www.trialsitenews.com/a/epidemiologic-ramifications-and-global-health-consequences-of-the-c-19-mass-vaccination-experiment-a212bb47):

*Acute, self-limiting viral infections that don't lead to systemic/severe disease (and possibly death) are terminated by **M**(ajor) **H**(istocompatibility) **C**(omplex)-unrestricted, cytotoxic CD8+ T cells that have no memory and the activation of which is triggered by a universal, pathogen-nonspecific Tc epitope comprised within the spike (S) protein. Unless an infected person progresses to developing severe disease, this is what allows a fairly rapid recovery from disease after primary productive infection (and certainly before fully functional virus-neutralizing Abs peak) [according to **2a-2b-2c-2d** pathway]. However, rather than stimulating de novo generation of new neutralizing Abs towards variants that escaped the neutralizing activity of vaccine-induced Abs, exposure of*

vaccinees to these immune escape variants will rapidly recall their non-neutralizing, infection-enhancing Abs (those are directed against an antigenic site that is conserved within the N-STD of all SC-2 variants).

*In vaccinees with poor experience in fighting productive infection (and hence, poor training of their innate immune defense according to pathway **1a-1b-1c**) prior to C-19 vaccination, infection-enhancing Abs[2] that are responsible for preventing severe disease by binding to DC-tethered virus (according to **3a-3b-3c-3d** pathway) can synergize with strongly activated cytotoxic CD8+ Tc-mediated killing (**3c'**) to even prevent C-19 disease all together and hence, render vaccinees asymptomatic despite their high susceptibility to re-infection (B + C → D). As prevention of disease is not due to prevention of productive infection but to accelerated abrogation of infection, these vaccinees will continue to shed and transmit SC-2 upon re-infection. Whereas innate immune effector cells are MHC-unrestricted and polyspecific (i.e., NK cells) and, therefore, don't drive immune escape, the infection-enhancing-Abs are Ag-specific (i.e., S-specific) and – if sustained at high enough titers for a long enough time by a large part of the population – will promote natural selection of immune escape variants that can resist the virulence-inhibiting capacity of these Abs. This is because vaccinees cannot prevent productive viral infection; consequently, the immune pressure they exert on viral virulence is suboptimal in that it cannot prevent the expansion in prevalence of immune escape SC-2 variants that have the capacity to overcome this immune pressure. Resistance of viral variants to the virulence-inhibiting activity of infection-enhancing Abs will inevitably cause Ab-dependent enhancement of severe disease (ADESD).*

[2] As previously explained, the non-neutralizing, infection-enhancing Abs are currently hampering *trans* infection at the level of distant organs such as the lower respiratory tract; this is what's currently exerting population-level immune pressure on viral virulence: https://www.voiceforscienceandsolidarity.org/scientific-blog/predictions-gvb-on-evolution-c-19-pandemic).


Geert Vanden Bossche
vaccine-induced neutralizing Abs
Enhancement of infection by infection-enhancing Abs
resistance to neutralizing Abs
Prevention of SC-2 infection by neutralizing Abs
Re-stimulation (due to enhanced susceptibility to infection)
3a
2a
1a
1b
1c
kill
kill
somatic target cell
Triggering of NK cells: A
Prevention of productive SC-2 infection (≡ prevention of disease)
2d
2b
3d'
Enhanced abrogation of productive viral infection ≡ prevention of disease → asymptomatic shedding D
Ab = Antibody
ADED: Ab-dependent enhancement of disease
DC = Dendritic Cell
LRT: Lower respiratory tract
NK cell: Natural Killer cell
: more infectious SC2 variant
: more virulent SC2 variant
: more virulent SC-2 variant tethered to DC
: IgM: polyspecific but not neutralizing
3b
2b
2c
DC
DC
Activation of cytotoxic CD8+ T-cell: abrogation of productive viral infection B
ADED
3d
3c
3c'
resistance to virulence-inhibiting effect of infection-enhancing Abs
migration to LRT
DC
DC
DC
Prevention of trans infection (≡ prevention of severe disease) by infection-enhancing Abs C