Conclusions

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Conclusions

Neutralizing antibody responses are generally predictive of protection against symptomatic infection, and also play some role in protecting against severe disease.

The virus is constantly evolving, this highlights the importance of up to date information about effectiveness of new vaccines and consideration of how new variants will affect efficacy of new vaccines.

Most vaccines evaluated to date include entire spike protein, some with stabilizing mutations.

T cell responses are durable, protect against severe disease, preserve recognition of VOCs. Non-spike proteins are important T cell targets. For spike-only vaccines, CD4 responses may be more important than CD8.

Binding antibody responses wane more slowly than neutralizing responses and are more robust to variants (though less so to BA.2 vs BA.1). RBD and S2 binding responses may play a dominant role in protection.

Where preexisting vaccine responses exist, mucosally delivered antigen can induce strongly protective responses in animals.
Conclusions

Breadth of antigenic composition is important. Adjuvants may be able to overcome narrower breadth. Difficult to argue that any arm of immune response to vaccines is unimportant—so vaccines that induce broad immune responses—cellular, mucosal, neutralizing, binding are most likely to be robust. Pan-sarbecovirus vaccines may require additional antigens.

Protection against infection requires neutralizing responses (including mucosal). Protection against severe disease is more mediated by combinations of neutralizing responses, non-neutralizing binding responses, T cells, and memory B cells, though strong neutralizing responses by themselves may be adequate. Variants (not just sequence, also incubation time) increase complexity.

mRNA vaccine Nab responses wane more rapidly than Ad-vectored. CD4 responses similar, CD8 better with Ad-vectored. In people who do not maintain Nab responses, other responses mediate protection against severe disease. CD8 responses are highly cross-reactive to omicron, with some drop-out.
Conclusions

Most CMI assays are labor intensive. Standardization is difficult, but harmonization is possible. Availability of naïve cells may become an issue. Innate responses can be assessed using cytokines. Additional work is merited.

Humoral responses may predict other protective responses, though relationship of neutralizing to non-neutralizing protective response may depend to some degree on demographics. Especially in the elderly, balanced responses (including neutralizing responses) are important.

WHO TPPs set R&D targets for funders and developers. Desired attributes of preferred and minimally acceptable COVID vaccines are included. TPP is currently under revision. Current draft suggests effectiveness attributes for severe disease: Preferred 90%, acceptable: 70-80%.

Uncertainties in effectiveness of comparator and in applicability of the biomarker, risks inherent in non-inferiority comparisons support conservative approach to immunobridging.

Information about effectiveness of the comparator is very important, especially in the face of variants.
Conclusions
Information about effectiveness of the comparator is very important, especially in the face of variants. Non-clinical data may provide additional support for decision-making. Finding the right comparator will be critical. Could consider using multiple comparators in some cases. Strong support for finding a way to get promising vaccines into the field.

There are many drivers both of transmission and of impact of the pandemic. We don’t yet know if virus will take on a seasonal pattern or will evolve to another pattern. Continued flare-ups are likely. There is variability by country in estimates of seroprevalence.

In-deployment studies could rapidly provide reliable information about how well vaccines work against severe disease and be used to assure that decisions made based on immune markers are correct.

Other creative approaches can provide useful information, on durability and relative efficacy from ongoing studies, including in-deployment studies, though variability in attack rates and impact of variants on efficacy can make things more difficult.

Human challenge studies are feasible and could provide supportive information about vaccine efficacy and potentially provide support for immune markers of protection. About half resisted infection. New challenge strains take ~ 6 months and might not yield results applicable to severe disease.
Conclusions

Safety evaluation of new vaccines, even for EUA, is expected to be robust.

General agreement with key elements of the proposed framework- and clinical development based on immunobridging is already proceeding. All regulators support use of immunobridging using neutralizing responses for modified vaccines (primary or booster), and all but one regulator on the panel for new vaccines (either as primary or booster). Characterization of comparator and new vaccine in terms of CMI and humoral response to VOCs. Comparator selection is important, where ideally the most robust comparators are used. Criteria should depend on effectiveness of the comparator that is authorized or listed. Pre-clinical data, including challenge studies, can also help to support use of immune response data in specific circumstances. Post-authorization effectiveness studies will also be important.

New vaccines remain desperately needed and their development should be incentivized. Clear guidance will help. Supply, resource considerations will be critical as pandemic and responses evolve. Over the long term, more data on immune mechanisms of protection will be helpful, along with implementable assays to measure different aspects of the immune response. More variant-specific research. Develop clinical data to address different settings. Recommend explanation in framework to address scope.