# Answered Questions ONLY

**Workshop Q&A: 25 March, 2021 SARS-CoV-2 variants – Practical considerations for accelerated clinical development in light of current regulatory guidance**

| Webinar ID | Actual Start Time | # Question | | |
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| **Question** | **Asker Name** | **Answer 1(s)** | **Answer 2** | **Answer 3** |
| Why is the COVAX team in the Earle paper proposing that the future gold-standard assay for immunobridging should be "most likely" be a VNA if binding antibodies showed an even better correlation across the studies? | Nadine Salisch | Regulators may prefer a functional read-out (nAb). That said, if high correlation with binding Ab in naives, bAb may well be acceptable. High correlation between nAb and bAb seems to break down with variants | great question. binding looks better if you simply look at the correlation. Dr. Plotkin reminds us frequently that antibodies dont only neutralize. Let's discuss in the panel. | |
| Regulators may prefer a functional read-out (nAb). That said, if high correlation with binding Ab in naives, bAb may well be acceptable. High correlation between nAb and bAb seems to break down with variants (nAb drops but bAb stays high). May also want to consider if full Spike versus RBD antigen. | David Vaughn | | | |
| Why is there so little use of the WHO standards for comparaison of neutralization titers? | Michel De Wilde | Harmonization is essential and a lot of teams are briding to the set of reagents that are available | We eagerly await linkage data from all the developers / sponsor of their historical testing results to the IS as now available. We would expect future public discussion of vaccine response or immune readouts to always | |
| Is that better to use Immunobridging (NI) with post-authorization "effectiveness" or "(confirmatory) efficacy" ? | Chien-hui Hsu | Not seeing use of immunogenicity NI plus efficacy to generatie evidence of expectation of protection to date. Bharat in India had a form of approval while awaiting efficacy but consent was still required. NI to post-EUA effectiveness in an environment | Well, it's by the experience of accelerated approval that confimartory efficacy is expected after surrogate enpoint is satisfied. One previous case is 10-valent pneumococcal conjugate vaccine. But indeed the difficulty | We will take this up in the panel. Thx for the question. Confirmatory efficacy has its own operational challenges and effectiveness studies are inevitable (it appears). |
| How would you deal with a finding that a serological correlate predicted lower airway protection, but a more complex mixed correlate better explained virus replication in upper airway? | bgraham@mail.nih.gov | One approach: address through the labelled indication for use, e.g. a narrowed indication; that is, from an indication for prevention of COVID-19 to an indication for prevention of lower respiratory tract COVID-19. | I think even if mixed is the "truth" (and I think our guess would be yes, its mixed), we are aiming for a regulatory pathway that we're sufficiently comfortable with to enable a risk-mitigated road to | |
| One more reason for (young) people to not participate in vaccine studies is that they may not receive a vaccination pass (green card, license) that allows them to travel in the near future (and other restrictions?) | Geert Leroux-Roels | Thx Geert. Highlights the fast evolving world where even well-planned trials can get surprised by external events that can undermine | very good point - certainly relevant for an increasing no. of countries.. | If “unblinded” in the UK and a trial participant received the verum, then a certificate is produced, at least for |

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| Influenza is a slightly misleading example for how to handle variants as there tends to be one new variant all over the world at a time. covid currently has at least three in different degrees in different areas. How do yourecommend the inclusion of a new strain in a vaccine against covid? | Philip | i used this comparison to show that we have to define the composition of the vaccine based on the circulating virus at a given time. There are many influenza strains ( and clades) circulating at a given time ( H1N1, H3N2, and B ) and the decision is based on genetic and phenotypic characteristic of viruses as well as data on population immunity. The influenza vaccine compostion process involves regulators. i put the link to the influenza process to illustrate the results of the vacine composition meeting. | | |
| Further to Michel De Wilde's question/suggestion, would use in live viral neuts of a hyperimmune globulin which is even more standardized than CCP improve the definition of a COP? | Theodore Tsai | | | |
| For David Wood: Regarding the WHO IS: will WHO assign International Units for variants (VoC) | Svein Rune Andersen | Thanks Svein. WHO is assessing options to address this question. It could be done through assignment of unitages for each VoC to the existing IS. Or it may need the development of additional ISs for the variants. As a | | |
| How will the requirement for studies in seronegative subjects evolve in the context of expanding vaccination campaigns accross the world? a lot of countries are running out of sero negative individuals | Tobias Kamphuis | This topic becomes important to address if immunobridging is an acceptable regulatory pathway for a vaccine candidate--specifically if seroresponse response to a comparator is the preferred comparison. A single fold-rise | | |
| Do you feel that CHIM studies could play a role? | Han van den Bosch | The timing of available data, including with variants, is a challenge relative to the other streams of supportive data that should be | | |
| What are the criteria for "naive" individuals, and what are the expectations on pre-screening of subjects? | Douglas Holtzman | Hi Doug!! relevant point. Does seronegative mean negative for original and new variant? what about previous mild natural infection which has turned seronegative again over | | |

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| The NI margin for the lower bound for the GMT ratio of 0.67 seems problematic. Moderate efficacy has been shown for the B.1.351 variant where the neutralizing antibody response for the variant is more than 4-fold lower than for the prototype strain. If the NI GMT margin is rigourously applied effective vaccines may not | Raburn Mallory | Important point. Let's discuss live in the panel. I believe that one has been pre-socialized with them. | Great - additional variability will likely be intrdouced through the neeed to evalute responses using 2 different neutralization assays which may also make it difficult to achieve the margin. | But also you run a risk of approving relatively ineffective vaccine that could be basis for more approvals.... |
| EUA vaccines in the US are not approved vaccines. | Jean L Hu-Primmer | EUA vaccines in the US are not approved vaccines. | correct. Unlike the conditional marketing authorisation in the EU. This underslines the | |
| Are the conditionally authorized vaccines in EU considered "approved" - does that infer full marketing authorization? | Jean L Hu-Primmer | Are the conditionally authorized vaccines in EU considered "approved" - does that infer full marketing | unlike EUA in the US, a conditional marketing authorisation in the EU is an | |
| There seems to be a common thread in todays discussion around "neutralizing" responses which implies that neutralizing assays trump antibody binding assays (where both may be validated) but there is indeed rate-limiting considerations on the choice of assay for consideration of variant-specific vaccine | Chris Ockenhouse | Can you be more explicit in your concern?<br>Are you worried about assay throughput or ability to reliably validate a neut assay with sufficient LLOQ or assay performance across | | |
| we are really not going to have access to "placebo' non-exposed or non vaccinated individuals | Anonymous Attendee | Almost 20% of exposed individuals (tested positive, but asymptomatic) are seronegative. Or people who were covid-positive last year who haven't been vaccinated yet. Plenty | not for a large efficacy study | give it a year. If people are still seropositive for over a year hooray we dont even need a new vaccine yet. That is not my guess as to |
| After a correlate of protection becomes available for a given first generation vaccine, could sponsors use this information to support an approval of a variant vaccine based on immunogenicity relative to the COP - rather than NI? | Ruben Donis (BARDA) | the quantitative threshold correlate will likely, if agreed upon, be for the original strain. So its complicated. | | |
| If animal study demonstrates that binding antibody to the variant better correlates with protection from that variant, would binding antibody be acceptable for immuno bridging study | Anonymous Attendee | I would say yes and , if so, again Standard reagents are paramount. | | |
| Thank you Jorge. A number of intranasally delivered vaccines are advancing. Potentially using existing technologies delivered by IM. How does one argue bridging in this case ? | Nick | Thanks Marco, had the same sense that this immunological bridge is far more challenging. | | |