

Q&As developed by the COVAX Regulatory Advisory Group (RAG): May2021

Background

Several NRAs and WHO have published considerations regarding the development and authorization of variant-adapted COVID-19 vaccines. These published statements are aligned in that they consider immunobridging (based on statistical non-inferiority assessments) as a way forward to authorize variant-adapted vaccines for which vaccine efficacy based on 'prototype' vaccines including the original SARS-CoV-2 strain has been demonstrated previously based on the identical platform technology and vaccine composition.

However, several aspects need further clarification, including but not limited to the following:

- 1. Immunobridging within same vaccine (same platform, dosing schedule, manufacturing process): Clarification on endpoints and trial populations to support immunologic non-inferiority**
2. Immunobridging to populations / age groups not included in Phase 3 vaccine efficacy trials / for which vaccine efficacy had not been established separately (including e.g. paediatric populations, older adults)/*No questions posed to the RAG at this time.*
3. Immunobridging across vaccines (similar / different platforms) to support authorization of new vaccines for which clinical vaccine efficacy / effectiveness will be established post roll-out/*Separate discussion- this was not be recorded or captured in minutes.*

With the present question to the RAG we would like to address aspect #1 and in particular highlighting the following issues / challenges:

- The NRA / WHO guidance documents provide different levels of details / different definitions with regards to the immunologic endpoint definitions. While there is consensus that immunologic non-inferiority should be demonstrated based on Geometric Mean Titres (GMTs), there is less clarity on the second primary endpoint based on proportionate immune response assessments. As developers may seek authorization / approval of variant-adapted vaccines in several different regions and will generate supportive data in one single Phase 3 immunologic non-inferiority trial, harmonized primary endpoints that can be adapted across vaccines (e.g. whole virion, full length spike gp / RBD) and platform technologies would be preferable.
- Vaccine efficacy for 'prototype' vaccines has been established in seronegative populations as per NRA / WHO requirements. When variant-adapted COVID-19 vaccines become available, the majority of people for whom the variant vaccine is intended, have been primed by prior SARS-CoV-2 infection (with the original virus, by a variant or both) or vaccination. It is not unlikely that these primed individuals will only require single dose booster. And even in seronegative persons, priming with a single dose of highly efficacious vaccines may be sufficient to at least protect against severe disease, followed by a booster 6-12 months later.

While a quantitative correlate of protection (CoP) has not been identified to date, there is a strong non-linear relationship between mean neutralizing antibody titres (calibrated to corresponding human convalescent sera panel titres) and vaccine efficacy. In the meantime, international standards have been established and should be used in the assessment of immune responses in clinical trials. Prospective analyses of antibody levels in breakthrough cases observed in vaccine efficacy trials are underway for several different vaccines and platform technologies.

In the absence of an established quantitative CoP, EMA, FDA as well as WHO have provided considerations with regards to the endpoints to be used for immunologic non-inferiority as summarized in Table 1.

Agency/ Organisation	Population	Primary objective: Interventions for immunobridging [assay]	Endpoint
EMA	Naïve	'Prototype' vaccine [original strain] → VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • SCR¹ (LB of 95% CI < -10%) • GMT (LB of 95% CI around the GM)
	Primed (single booster dose?)	'Prototype' vaccine administered previously (same / similar trial population) [original strain] → boost VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • GMT (LB of 95% CI around the GM) • SCR¹ as secondary EP
FDA	Naïve	'Prototype' vaccine [original strain] → VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • SRR² (NI margin of -10%) • GMT (LB of 95% CI around the GM)
	Primed (single booster dose?)	'Prototype' vaccine administered previously (same trial population) [original strain] → VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • SRR² (NI margin of -10%) • GMT (LB of 95% CI around the GM)
WHO	Naïve	'Prototype' vaccine [original strain] → VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • SCR[?] (LB of 95% CI < -10%) • GMT (LB of 95% CI around the GM)
	Primed (single booster dose?)	'Prototype' vaccine administered previously (same trial population) [original strain] → VOC-adapted vaccine [VOC]	<ul style="list-style-type: none"> • SCR[?] (LB of 95% CI < -10%) • GMT (LB of 95% CI around the GM)

- 1) SCR, seroconversion rate (EMA) = “≥4-fold increase in titre from pre-vaccination to post-vaccination. Since the primary will be in seronegative subjects, a nominal value should be applied to the pre-vaccination samples to calculate the seroconversion rate”
2) SRR, seroresponse rate (FDA) = not defined

Table 1.

As GMTs do not provide any information on proportionate vaccine effects in clinical trials, several different endpoints are commonly used to assess proportionate immune responses post vaccination. Seroprotection rate (SPR) is commonly used to describe the proportion of subjects with post vaccination antibody levels above a specific quantitative antibody titre established as disease-specific CoP. Seropositivity rate describes the proportion of subjects with quantifiable post vaccination titres and is sometimes used synonymically with seroprotection rate for vaccines where the presence of antibodies is considered protective (e.g. poliomyelitis). Like GMTs, seroprotection and seropositivity rates can be assessed independent of baseline titres. However, these endpoints would not allow the assessment of vaccine-attributable effects in mixed seronegative / seropositive populations unless their assessment (e.g. as primary objective) is restricted to seronegative subjects only. In contrast, seroconversion rate (SCR) is generally defined as the proportion of subjects seronegative at baseline turning positive (antibody titre above lower limit of quantification, LLoQ). To assess vaccine-attributable effects in the entire trial population (subjects seronegative and seropositive at baseline), a second part can be added to the SCR definition for seropositive subjects – for example requiring a ≥4-fold increase of pre-vaccination titres (see for example WHO guidelines for IPV vaccine development). Seroresponse rate (SRR) could be all of the above.

The EMA definition of SCR requires a ≥ 4 -fold titre increase and – since the primary analysis is to be done in seronegative subjects – a nominal value should be applied to the pre-vaccination sample. Half the LLoQ could, for example, be used as such a nominal value. Hence, the post vaccination titre would be at least twice the LLoQ. Seroresponse rate required by FDA is not defined any further. The WHO guidance document does not mention a specific proportionate endpoint for non-inferiority assessments in addition to GMTs – but seroconversion rate (without further definition) is mentioned in the document.

EMA requests the assessment of immunologic non-inferiority to be done separately in SARS-CoV-2 naïve subjects (with neither previous vaccination nor natural infection) and in previously vaccinated subjects. In the FDA guidance it is stated that immunologic non-inferiority should be assessed separately for primary vaccination series and booster dose of the variant-adapted vaccine. WHO recommends that data should as much as possible be generated in a naïve population. WHO acknowledges that data from a non-naïve population can also be generated if there is difficulty in identifying a naïve population in light of widespread natural infections and current efforts to roll-out vaccines widely.

Even if recruitment is restricted to unvaccinated subjects, clinical trials representative of the general population will nowadays include increasing proportions of seropositive subjects unless specifically restricted to seronegativity upon recruitment. Proportions of previously infected subjects vary by region. Of note: Some that may have experienced (mild) disease may remain or turn seronegative a few months later and may be recruited into vaccine trials as seronegative subjects despite previous natural infection (and possibly pre-existing primed B-/T-memory cells).

If recruitment into vaccine trials is not restricted to seronegative subjects at baseline (defined as exclusion criterion) and the primary objective is immunologic non-inferiority in seronegative subjects, a relevant proportion of trial subjects would not contribute to the primary objective of the trial.

We, therefore, propose to consider a proportionate endpoint definition which can be applied for primary series and booster vaccination / in both, seronegative and seropositive (either post natural infection or vaccination) trial subgroups. The Clin Dev & Ops SWAT team would be interested in the RAG's considerations on the following endpoint proposed for discussion (in addition to GMTs):

Seroresponse rate (absence of a quantitative CoP):

- For seronegatives, proportion of subjects with $\geq x$ -fold (TBD*, e.g. ≥ 4 -fold) titre increase calculated based on the $\frac{1}{2}$ LLoQ
- For seropositive, proportion of subjects with $\geq x$ -fold (TBD*, e.g. ≥ 4 -fold) baseline titre increase

Seroresponse rate (with an established quantitative CoP):

- For seronegative, subjects with antibody titre considered as protective or above
- For seropositive, proportion of subjects with $\geq x$ -fold (TBD*, e.g. ≥ 4 -fold) baseline titre increase

*) to be justified by the vaccine developer and agreed by the regulator / WHO – preferably aligned across regulators / WHO

Developers may chose i) to assess primary series or booster vaccination (single dose) in separate trials with immunologic non-inferiority as primary objective in unvaccinated / naïve subjects and previously

vaccinated subjects, respectively, or ii) to assess primary series / booster vaccination in one single trial. The latter approach, however, would result in multiple (at least 2: GMTs, SCRs) non-inferiority assessments performed separately for primary and booster vaccination.

Based on the considerations and definitions above, SCRs (and GMTs) could also be assessed combined in seronegative and seropositive subjects post single dose as secondary endpoint.

Descriptive reverse cumulative distribution curves will also be provided as additional endpoints.

In the initial guidance released by WHO and FDA on placebo-controlled vaccine efficacy trials, it was stated that the primary efficacy endpoint point estimate should be at least 50% with a lower bound alpha-adjusted confidence interval of >30%. We propose to discuss with the developer if stricter non-inferiority margins or immunologic superiority can be considered for immunobridging for 'prototype' vaccines with established efficacy of less than 60%. Alternatively, and if further evidence supports the correlation between nAb titres and proportionate clinical protection, a minimum antibody titre predicting at least 50% (TBD) protection (with a corresponding 95% CI) may be defined in addition to non-inferiority margins.

Question:

#1. Immunobridging within same vaccine (same platform, dosing schedule, manufacturing process): Clarification on endpoints and trial populations to support immunologic non-inferiority

Problem statement / summary/question:

The proportionate endpoint used for immunobridging (in addition to GMTs) should be harmonized to allow developers generate the respective evidence based on one core Phase 3 trial protocol. In light of increasing proportions of seropositive population (previous natural infection / vaccination) it is important to have a single proportionate endpoint definition applicable to seronegative and seropositive subgroups. Immunobridging after single dose of variant-adapted vaccine given as a booster vaccination in previously vaccinated subjects should also be assessed based on the proportionate endpoint. The approach for vaccines with an established efficacy of 60% or less should be discussed with the developer.

- Does the RAG agree with the proposed approach and endpoint definition for the proportionate immune response in addition to GMTs which is applicable to both, initially seronegative and seropositive populations? Please provide comments and / or subsequent items that are missing.

RAG Feedback:

- RAG members welcomed the proposal and agreed with the overall objective of achieving harmonized endpoints.
- It was noted that discussions are still ongoing within regulatory authorities as to how these endpoints should be defined. As more data arise and the level of knowledge increases, harmonization is more likely to occur.
- It was proposed that regulators should have further discussions in regulatory forums with NRAs/cluster teleconferences with the aim of achieving harmonization of endpoints.

- Awareness was raised about the benefit to vaccine developers of harmonized endpoints, as developers generally conduct a single clinical trial that will gather data to make informed decisions and filings in different world regions.
- Multiple elements need to be considered such as the type of assays used for these endpoints; the population, in particular previously infected individuals or seropositive at baseline; or the appropriate minimum factor for titre increase post- vs. pre-vaccination.
- It was mentioned that for other types of vaccines a minimum of 4-fold titre increase (post- vs. pre-vaccination) had been deemed adequate.
- With regards to single-dose booster vaccination strategies assessed via immunobridging, it was noted that this will become the most likely scenario as vaccination rates continue to increase and hence the available pool of naïve individuals, and in particular elderly, decreases. The existing reflection papers/guidelines on variants include this kind of scenario (and the desired primary outcome). It is anticipated that this will evolve as more data and knowledge are gathered.
- The importance of gathering data via conducting “exploratory” clinical studies (i.e. studies with a cohort of vaccinees receiving a booster of variant vaccine) was highlighted as these data will be helpful in further refining the endpoint definitions and statistical criteria and will aid global harmonisation. Characterization of the immune response elicited by the vaccine variant and of the baseline status are regarded as key components in these exploratory studies.
- RAG agreed that the clinical assessment strategy for vaccines with 60% (or less) efficacy should be discussed with regulators.

List of attachments and/or references

- FDA. [US Emergency Use Authorization for Vaccines to Prevent COVID-19 APPENDIX 2: EVALUATION OF VACCINES TO ADDRESS EMERGING SARS-COV-2 VARIANTS](#) ver 22 February 2021
- EMA. [EU Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain\(s\) of SARS-CoV-2](#) ver 25 February 2021
- ACCESS (UK, Australia, Canada, Singapore and Switzerland), [Guidance on strain changes in authorised COVID-19 vaccines](#) ver 4 March 2021
- WHO. [WHO ADDENDUM to Considerations for Evaluation of COVID-19 Vaccines for Prequalification or Emergency Use Listing. Considerations for evaluation of modified COVID-19 vaccines](#) ver 12 March 2021
- WHO. Considerations for evaluation of COVID-19 vaccines. ver 25 November 2020
- WHO. https://www.who.int/biologicals/expert_committee/WHO_TRS_993_web_FINAL.pdf
- WHO. https://www.who.int/biologicals/WHO_TRS_1004_web.pdf
- Khoury et al. 2021. What level of neutralizing antibody protects from COVID-19? medRxiv doi: <https://doi.org/10.1101/2021.03.09.21252641>;
- Earle K et al. <https://www.medrxiv.org/content/10.1101/2021.03.17.20200246v1>