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## Workshop Report

# **COVAX Clinical Development & Operations SWAT Team Workshop on “SARS-CoV-2 variants - Practical considerations for accelerated clinical development in light of current regulatory guidance”**

**March 25<sup>th</sup>, 2021**

Meeting report prepared by  
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## Executive summary

On 25<sup>th</sup> March 2021, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on “SARS-CoV-2 variants – Practical considerations for accelerated clinical development in light of current regulatory guidance.” The main aim was to address vaccine development pathways for COVID-19 vaccines adapted to variant SARS-CoV-2 strains.

Key points from the first part of the workshop included:

- Further COVID-19 vaccines are needed but must address new circulating virus variants.
- Pathways to approve new vaccines directed against novel variants, as well as authorised prototype vaccines adapted to new variants, need consideration.
- WHO has initiated a global consultation on a decision framework for assessing the impact of SARS-CoV-2 variants of concern (VOC) on public health interventions, including a coordinated decision framework for vaccine adaptation to variant strains.
- Regulatory alignment to assess adapted vaccines to new SARS-CoV-2 strains based on immunobridging to the authorised prototype vaccines, that have established clinical efficacy, is largely achieved.
- Further regulatory guidance is needed for new vaccine candidates that are in earlier stages of development.
- The Clinical Development Plan (CDP) for new vaccines includes various options for demonstrating vaccine efficacy, including for example immunobridging.
- Four different guidance documents regarding strain change have been made available recently from the United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), Access Consortium (consisting of regulatory agencies in Canada, United Kingdom, Switzerland, Singapore, and Australia), and the World Health Organization (WHO).

The second section of the workshop focused on two scenarios which were specifically addressed in two panel discussions.

Key points for approaches for vaccine candidates to variant SARS-CoV-2 strains adapted from **authorised prototype vaccines**, with clinical efficacy established based on conventional placebo-controlled trials, included:

- Immunobridging based on non-inferiority is recommended by regulators for adapted vaccine candidates from vaccine developers with a prototype vaccine that has previously demonstrated clinical efficacy,
- Developers are encouraged to implement international standards promptly.
- Regulators are at present more comfortable with the idea of using neutralising antibody assays for the purpose of bridging; however, are open to discussions if data could be generated in support of binding antibody assays.
- Use of fully validated assays for new SARS-CoV-2 strains may not be a prerequisite for immunobridging in the context of existing standards and validated assays against the original SARS-CoV-2 strain.

Key points for approaches for **new vaccines** against variant SARS-CoV-2 strains lacking clinical efficacy data based on conventional placebo-controlled trials included:

- In light of the increasing challenges regarding placebo-controlled vaccine efficacy trials, immunobridging is a potential pathway for new adapted vaccines from manufacturers without existing authorised prototype vaccines, particularly when adapted vaccine based on precedent class of authorised prototype vaccine is available. The likelihood of

acceptance depends on the difference between the new adapted vaccine candidate and the authorised prototype vaccine.

- Identifying an appropriate comparator for a large immunobridging study may be a challenge.
- Some experts have noted that attention should be exercised even when considering approaches supporting immunobridging within the same vaccine platform (i.e., various mRNA vaccines use different lipid nanoparticles).
- Non-inferiority efficacy studies likely may be required if immunobridging is not acceptable and an authorised adapted vaccine is available as a comparator.
- Data on breakthrough rates in individuals with different antibody titres will be important to development of a correlate of protection but thus far are not available.
- A new COVID-19 vaccine will likely require a safety database comparable to any vaccine for any pathogen under consideration for approval.
- Full characterisation of the immune responses elicited by each vaccine (including cell-mediated immunity) is important and could provide supporting information; however, regulators are at present prefer to use evaluations of antibodies for regulatory decisions.

The slides from the meeting can be found here:

[https://media.tghn.org/medialibrary/2021/04/20210325\\_Workshop\\_MASTER\\_DECK\\_FINAL\\_VERSION.pdf](https://media.tghn.org/medialibrary/2021/04/20210325_Workshop_MASTER_DECK_FINAL_VERSION.pdf)

## Agenda

Time (CET)	March 25, 2021	Speaker(s)
<b>14:00 -14:20 (20 mins)</b>	<b>Part 1: Welcome and meeting objectives</b> <ul style="list-style-type: none"> <li>• <b>Highlights from previous workshops in context of recent developments</b></li> <li>• <b>Progress on correlates of protection and late breaking key data</b></li> </ul>	<b>Peter Dull, BMGF</b>
<b>14:20-14:35 (15 mins)</b>	General Overview: <ul style="list-style-type: none"> <li>• Current landscape of programs (prototype vaccine +/-VOCs)</li> <li>• Regulatory framework for variant vaccines (approved and non-EUA vaccines)</li> </ul>	<b>Jakob Cramer, CEPI</b>
<b>14:35-14:55 (20 mins)</b>	WHO Guidance: <ul style="list-style-type: none"> <li>• Variants and Vaccines: Global Public Health Implications- Sylvie Briand</li> <li>• Regulatory preparedness on adapting, if needed, vaccines for strain changes- David Wood</li> </ul>	<b>Sylvie Briand, WHO &amp; David Wood, Independent Consultant</b>
<b>14:55-15:10 (15 mins)</b>	Regulatory convergence: Review of available guidance documents from US FDA, EMA and the Access Consortium <ul style="list-style-type: none"> <li>• Label expansion studies</li> <li>• Immuno-bridging vs. efficacy -- biomarkers / CoP</li> </ul>	<b>Adam Hacker, CEPI</b>
<b>15:10-15:15</b>	<b>Break</b>	
	<b>Part 2: Use Cases &amp; Panel Discussions</b>	
<b>Approach for vaccines with acceptable efficacy data (with or without EUA / full registration)</b>		
<b>15:15-15:30 (15 mins)</b>	Overview by International Vaccine Institute (IVI) <ul style="list-style-type: none"> <li>• Clinical Development Plan approach for variant vaccines – among developers with vaccines already authorized</li> </ul>	<b>Anh Wartel, IVI</b>
<b>15:30-15:50 (20 min)</b>	Panel Discussion: Products with or without EUA, full registration <ul style="list-style-type: none"> <li>• Regulators representing the recently available variant vaccine guidance</li> <li>• Gustavo Mendes Lima Santos, ANVISA (Brazil)</li> <li>• Phil Krause, US FDA</li> <li>• Marco Cavaleri, European Medicines Agency EMA</li> </ul>	<b>Moderated by Jakob Cramer</b>
<b>Approach for vaccines lacking efficacy data</b>		
<b>15:50-16:10 (20 mins)</b>	Overview by PATH <ul style="list-style-type: none"> <li>• Clinical Development Plan approach options for variant vaccines - based on non-EUA products</li> <li>• Statistical discussion of success criterion for immuno-bridging comparisons <ul style="list-style-type: none"> <li>○ Immuno-bridging and CoP</li> <li>○ Seroresponse, GMTs, Reverse cumulative distribution curves</li> </ul> </li> </ul>	<b>Jorge Flores / David Kaslow, PATH</b>
<b>16:10-16:50 (40 mins)</b>	Panel Discussion: Products in development without path to efficacy / EUA <ul style="list-style-type: none"> <li>• Same Panel as above</li> </ul>	<b>Moderated by Peter Dull</b>
<b>16:50-17:00 (10 mins)</b>	<b>Wrap Up &amp; Next Steps</b>	<b>Jakob Cramer, CEPI</b>

## **Part 1: Welcome and meeting objectives**

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, welcomed participants and set the context for the workshop.

At present, 14-15 COVID-19 vaccines have received emergency authorisation / accelerated approval. Additional vaccines, however, are needed as current models predict insufficient vaccine supply to cover the world's population, expansion limits exist on manufacturing capacity for current vaccines, and there is concern over evolving variants. Identification of a biomarker that is reasonably likely to predict protection against COVID-19 would enable accelerated evaluation of new vaccine candidates. As data accumulate, the critical question remains whether a sufficiently confident relationship has been established between biomarker(s) and vaccine efficacy based on clinical endpoints. Recent data to further support a correlate of protection include:

- Two recent, independent studies have reported a strong correlation between antibody titres and clinical efficacy, suggesting a potential correlate of protection.
- In one of these studies, a strong non-linear relationship ( $\rho=0.905$ ) between neutralising antibodies and efficacy predicted 50% protective neutralisation level at 20% average human convalescent sera titre.
- Post-hoc analyses of the Janssen and Novavax Phase 3 trials showed that adjusting for efficacy against the prototype (ancestral) strain (D614G) strengthened the relationship between SARS-CoV-2 neutralisation and vaccine efficacy.

Late-breaking data from a mouse immunogenicity study from Clover showed that a heterologous prime boost (wildtype prime plus South Africa boost) did not induce additional neutralisation to the South African (B.1.351) pseudovirus compared to two doses of wildtype vaccine. In addition, "back-neutralization" of the original strain by vaccination with a variant vaccine based on B.1.351 was also shown in the pre-clinical study.

This workshop aimed to address vaccine clinical development pathways for COVID-19 vaccine for variant strains.

### ***General overview of 'adapted prototype' versus 'adapted new' COVID-19 vaccines***

Dr Jakob Cramer, Coalition of Epidemic Preparedness Innovations (CEPI), gave an overview of 'adapted prototype' versus 'adapted new' COVID-19 vaccines.

Main points included:

- Authorised prototype COVID-19 vaccines protect at least against severe disease caused by circulating SARS-CoV-2 variants, although severe cases included/detected in clinical programs are rare and the certainty of the evidence level is weak.
- Further vaccines are needed but must consider new circulating virus variants. New vaccines directed against new variants, and pathways to authorise both, prototype vaccines adapted to new variants and new vaccines targeting new variants need consideration.
- Different terminology is used across regulatory guidance and scientific publications (e.g., *prototype* versus *parent*, *original*, or *current* vaccine; *adapted* vaccines should not be *modified* in terms of changing any other vaccine characteristic) which presents challenges.
- A CDP for new vaccines may consider various options for demonstrating vaccine efficacy for example:

- Vaccine efficacy demonstrated based on superiority to inactive comparator (placebo) when there is no evidence of correlation between immune response and vaccine efficacy.
- Vaccine efficacy demonstrated based on clinical non-inferiority in case placebo-controlled trials are no longer acceptable. However, this approach would go in line with large sample sizes and hence relatively long timelines.
- Vaccine efficacy demonstrated based on immunobridging (non-inferiority) with post-authorisation vaccine effectiveness when there is evidence of correlation between the immune response and vaccine efficacy available which is accepted by National Regulatory Authorities (NRA)/WHO Pre-qualification (PQ).
- An adequate seroprotection rate should be demonstrated to prove vaccine efficacy when a quantitative immune correlate of protection is available and accepted by NRAs/WHO PQ.
- Vaccine roll-out and increasing seropositivity rates will impact the feasibility of placebo-controlled clinical trials compared to 2020 which is why COVID-19 vaccines can be grouped as either:
  - Wave 1 – where a prototype vaccine is authorised with clinical efficacy data. Immunobridging to develop vaccines adapted to new variants is possible.
  - Wave 1a – where Phase 3 vaccine efficacy data are expected soon.
  - Wave 2 – where a vaccine candidate is advancing through early-stage clinical development, but Phase 3 trials have not yet started or will not start in the next few months. Conventional vaccine efficacy trials may no longer be an option and vaccine efficacy for these vaccines may have to be based on immunobridging. The question of whether to shift to variant rather than the original SARS-CoV-2 strain directly and if so, which variant should be selected, should be considered.
- Protein-based COVID-19 vaccines is the largest group of COVID-19 vaccines still in development, but vaccines differ in terms of construct (i.e., nanoparticle, S-trimer, VLP), adjuvants, and dosing schedules. This must be considered in the appropriate selection of a potential comparator for immunobridging assessment.
- Placebo-controlled trials are preferred to demonstrate vaccine efficacy but will be increasingly difficult to conduct due to vaccination campaigns targeting high-risk groups, practical challenges of recruiting younger population groups, and an increasing proportion of seropositivity in the trial population.

### ***Variants and vaccines: global public health implications***

Dr Sylvie Briand, WHO, discussed WHO guidance in the context of global public health implications of variants and vaccines.

Summary points included:

- Three VOC have been defined to date, with more likely to emerge over the coming months. The importance of a strong monitoring system to assess evolution of these variants was highlighted.
- Distinguishing variants of interest from VOC is important. VOC are the variants that will likely trigger further decision-making processes, including potentially changing vaccines.
- The co-circulation of variants is evident in some countries. This has future implications in terms of determining the predominant circulating viruses and finding the best match between vaccine and circulating viruses at a given time.
- A good response to any epidemic or pandemic is impossible without public trust.
- A framework is required to address questions raised by the emergence of variants (e.g., length of immunity, re-infection).

- WHO has initiated a global consultation (29<sup>th</sup> March) on a decision framework for assessing the impact of SARS-CoV-2 VOC on public health interventions. The aims are to establish a global forum for harmonised coordination and communications regarding VOCs and their impact on public health interventions, produce a decision-making framework that outlines the critical triggers, roles and responsibilities, and information needs and standards to guide policy recommendations regarding the impact of VOCs, and establish a common understanding of the current evidence, challenges, and solutions for VOCs and their impact on current and future COVID-19 vaccines.

### ***Regulatory preparedness on adapting, if needed, vaccines for strain changes***

Dr David Wood, Consultant to WHO, discussed regulatory perspectives on adapting vaccines to strain changes.

Key points included:

- A globally coordinated response is essential for identifying VOC, their impact on vaccines, and any adaptations to vaccine composition.
- Regulatory alignment to assess authorised prototype vaccines with established efficacy adapted to new SARS-CoV-2 strains based on immunobridging is largely achieved.
- Further regulatory guidance is needed for vaccine candidates that are in earlier stages of development.
- Careful messaging is essential on variants and the impact they will have on vaccines so as not to disturb public trust in COVID-19 vaccines.

### ***US, EU, ACCESS, and WHO guidance on strain change***

Dr Adam Hacker, CEPI, reviewed available global guidance documents regarding strain change.

Main points included:

- Four different guidance documents regarding strain change are available, including US FDA, EMA, Access Consortium, and WHO.
- The scope for all guidance documents is similar with a requirement for the parent/prototype vaccine to be approved and the variant/adapted vaccine to use the same manufacturing process and sites, and with the assumption that there is no correlate of protection.
- Different terminology is being used across the various guidance documents. This should be addressed to achieve some consistency.
- Similarities and differences exist between the various guidance documents in terms of chemistry, manufacturing and control, non-clinical considerations, clinical considerations, and safety data requirements.

### **Part 2: Use cases and panel discussions**

#### ***Approaches for authorised prototype vaccines adapted to variant SARS-CoV-2 strains with vaccine efficacy established based on conventional placebo-controlled trials***

#### ***Vaccine clinical development plan - approaches in the context of products with EUA***

Dr Anh Wartel, International Vaccine Institute, provided an overview of the CDP approach for variant vaccines among developers with vaccines already authorised.

Summary points included:

- Guidelines from EMA/US FDA/ACCESS/WHO have been issued early in the process and are helpful for vaccine developers.
- For vaccine developers with a prototype vaccine and demonstrated efficacy, immunobridging based on non-inferiority is recommended by regulators. Immunogenicity assumptions will drive the size of the trial.
- Generation of additional safety data should be discussed with regulators.
- Further clarity is required regarding specific assay types needed and interpretation of non-inferiority of the immune response using different assays and potentially testing prototype and adapted vaccines in different populations.
- The following must be considered where new variant vaccines are tested and deployed:
  - Pharmacovigilance must be strengthened to assess the safety of these adapted vaccines.
  - Surveillance of emerging variants under immune pressure is crucial.
  - Virus sieve analysis of breakthrough infections should be conducted.

**Panel discussion: Variant vaccines adapted from prototype vaccine which already achieved authorisation based on clinical efficacy**

A panel discussion included the following key points:

- *Dr Gustavo Mendes Lima Santos, ANVISA, Brazil* –
  - There is no guidance specific to Brazil on variant vaccines adapted from a prototype vaccine which already received authorisation.
  - With regards to immunobridging, concerns exist about developing a correlate based on the prototype vaccine. The P1 variant, which is now widespread, was not observed in clinical trials for prototype vaccines in Brazil.
  - Preliminary studies have been conducted by some developers to support the possibility of immunobridging trials in Brazil, but the lack of international standards remains a challenge to be addressed.
  - Concerns exist on how to avoid large clinical trials to obtain rapid answers regarding the performance of vaccines against new variants.
- *Dr Phil Krause, US FDA* –
  - Two advantageous facts when considering immunobridging in the context of a prototype vaccine that has already achieved authorisation include:
    - Variant vaccines being considered are adapted from prototype vaccines that already achieved authorisation based on a clinical endpoint efficacy trial.
    - Variant vaccines likely result in similar types of immune response as the prototype vaccine that was evaluated in the clinical endpoint efficacy trial as they have been adapted from that prototype vaccine and are based on the exact same platform.
  - Regulators are willing to accept that the magnitude of the neutralising response will likely be proportional to the magnitude of other immune responses. If the neutralising response is as high as what was originally observed, the efficacy of the variant vaccine is likely equal to that demonstrated in the clinical trial.
  - In this context, assay validation and international standards may be less important so long as the samples from the prototype and variant vaccines can be studied in the same assays and the assays are robust.
  - A quantitative correlate of protection may be unnecessary as the overall immune response (as represented by one component of that immune response) is being bridged from one situation to another.
- *Dr Marco Cavaleri, EMA* –



- The immunogenicity of the variant vaccine should be bridged to the prototype vaccine. As this will be the key readout, the assay should be validated, and an international standard used.
  - A potential limitation is the difficulty comparing neutralisation assays to two different viruses (original versus variant strain). To ensure bridging can be done in a trustworthy way, a non-inferiority margin for the geometric mean titre and seroconversion will still be required. Where there is doubt about the neutralizing assays as they relate to different strains, additional important supportive data may be provided by animal studies.
  - Guidance documents may evolve as more data are gathered.
- *Please comment on importance of international standard.*
    - It is technically possible to assign unitage to the international standard for the variants. This is one option being evaluated by WHO and will be a data driven decision.
    - Another option is to develop additional international standards specific for the different VOC. An announcement will soon be posted, as a preparedness step, to solicit materials that could be potentially useful to develop such additional standards.
    - Assays are important in terms of immunobridging based on non-inferiority. Vaccines that have read out vaccine efficacy have all tested the immune response without using international standards. Developers are encouraged to implement international standards promptly.
- *Some difficulties exist in functional/neutralizing assays and for immunobridging there might be a preference for functional assays. Please comment on neutralizing compared to binding antibodies, in particular in terms of new variants?*
    - Regulators are at present more comfortable with the idea of using neutralising antibody assays for the purpose of bridging; however, are open to discussions if data could be generated in support of binding antibody assays (particularly binding assays to specific epitopes shown to be important).
    - More evidence is required on binding antibodies and on the correlation between binding antibodies and neutralizing antibodies, particularly in the context of new variants.
- *It will be increasingly difficult to recruit populations seronegative to both the original and the variant strain. For two-dose vaccines, immunobridging will be assessed post-second dose. Please comment on immunobridging post-first dose in seropositives (to possibly establish single dose regimen in previously vaccinated/infected persons)?*
    - Comparison needs to be made under as clean a set of conditions as possible. If the efficacy study showed efficacy based on seronegative individuals, that is the group in which the primary bridging needs to be done.
    - Testing in naive individuals is preferable from an immunogenicity standpoint to ascertain immune responses from the two different vaccines. Thus, this is at present a clear-cut requirement from regulators.
    - Regulators are aware that studies in seronegatives may be increasingly difficult once there is broad seropositivity in the population. Consideration will then be given to how immunobridging can be done (i.e., whether in the context of a booster study only and not testing of primary series in subjects that had never encountered the virus either via vaccination or natural infection).
    - Regulators have considered the scenario of boosting with the same platform (i.e., boosting with the same vaccine but just changing the strain). They should, however, be ready to discuss a broader boosting concept (i.e., boosting

individuals that received other vaccines or those naturally infected). Such a scenario will likely be encountered, and it is important to consider how to make this happen in a way where data could still be interpreted, and a regulatory decision reached.

### **Approaches for new vaccines against variant SARS-CoV-2 strains lacking efficacy data based on conventional placebo-controlled trials**

#### **Pathways for approval of COVID-19 vaccines based on SARS-CoV-2 variant strains**

Dr Jorge Flores, PATH, discussed pathways for approval of COVID-19 vaccines based on SARS-CoV-2 variant strains.

Summary points included:

- Immunobridging is a potential expedited pathway for new adapted vaccines from manufacturers without existing authorised prototype vaccines, particularly when adapted vaccine based on precedented class of authorised prototype vaccine is available.
- The likelihood of acceptance depends on the difference between the new adapted vaccine candidate and the authorised prototype vaccine (e.g., platform, adjuvant, etc.).
- A sufficiently large safety database will be required.
- Post-approval pharmacovigilance and effectiveness studies should be planned in advance and initiated at introduction.
- If immunobridging is not acceptable and an authorised adapted vaccine is available as a comparator, then non-inferiority efficacy studies may be the next best alternative; however, the study size may not be feasible.
  - If immunobridging is not acceptable and no approved vaccine is available with demonstrated efficacy against the VOC, then clinical efficacy trial design will depend on the circulating strains and efficacy of the available authorised prototype comparator(s). In rare instances, a placebo-controlled trial might be feasible to conduct.
- Additional research, including for example characterisation of immune response to variant strains and development of standard reagents and assay validation, is needed to inform decisions regarding immunobridging versus clinical efficacy trials.

#### **Panel discussion: Pathway for variant vaccines for which no prototype has been authorised**

A panel discussion included the following key points:

- *Dr Marco Cavaleri, EMA* –
  - EMA has not officially agreed a way forward for the approval of second-generation vaccines. Regulators will need to know that any efficacy study is not feasible or problematic to the point that it is not an option. Immunobridging needs consideration, specifically the type of immunobridging and what bridging to.
  - All the COVID-19 vaccines appear to elicit neutralising antibodies with a certain degree of correlation with protection. However, there is concern regarding how immunogenicity can be compared in a way that is solid and acceptable for a regulatory decision.
  - Identifying an appropriate comparator for an immunobridging study may be a challenge, and the mechanism of protection and viral aspects of protective immunogenicity that is derived from the vaccine need consideration.
  - An immunobridge with a mucosal vaccine would be difficult. Immunogenicity in terms of systemic neutralising antibody will likely be low. The route that could lead to potential approval of such a vaccine remains unknown.

- Defining a comparator that belongs to the same platform technology should be possible for other vaccine types; however, a sufficient quantity of comparator vaccine must also be available. The protective efficacy of the vaccine shown in the field, mechanism of protection, and level of neutralizing antibodies should be considered.
- Regulators will require a good understanding of pros and cons and the various variables around immunobridging to a vaccine that is intrinsically different.
- *Dr Phil Krause, US FDA –*
  - COVID-19 vaccine development has thus far been fast without sacrificing confidence. Thus, it is crucial that any next steps retain these levels of confidence, especially as vaccines that may be made available under these new regimes are more likely to be deployed in the low- and middle-income countries.
  - Neutralizing antibodies appear to correlate with efficacy where the vaccine sequence corresponds to the sequence of the circulating virus. Data, however, are lacking where the vaccine sequence differs from the circulating virus.
  - Caution should be exercised even when immunobridging within the same vaccine platform. For instance, various mRNA vaccines use different lipid nanoparticles, which play an important role in innate immune responses and subsequent adaptive immune responses.
  - Data on breakthrough rates in individuals with different antibody titres are critical to development of a correlate of protection but thus far are not available.
  - Passive immune response studies (i.e., passively administered antibodies shown to be protective) would provide further evidence in neutralising titre as a correlate of protection.
  - Randomised data are preferred over observational data. This could include randomised data in non-inferiority studies, human challenge studies, and post exposure prophylaxis studies. Defining a robust control group is complicated in observational studies as the decision to receive a COVID-19 vaccine is time and risk factor dependent.
  - Randomised data may also be preferred over correlates of protection. The correlates pathway is associated with difficulties, placebo-controlled randomised trials remain feasible in some places, and other ways to randomize to non-placebo could still provide useful information.
- *Dr Gustavo Mendes Lima Santos, ANVISA, Brazil –*
  - COVID-19 vaccines have been developed rapidly; however, knowledge of the disease is still growing, hence many questions remain unanswered (i.e., correlate of protection, immunobridging studies).
  - Vaccine roll-out is slow in Brazil as a result of the current situation. Thus, it is still feasible to conduct studies including individuals who have yet to receive the vaccine.
  - Brazil is likely to move towards observational and effectiveness studies for approval of variant vaccines for which no prototype has been authorised as a result of aforementioned limitations regarding knowledge.
- *Safety database: Studies have been very large for initial efficacy studies driven by the need to accumulate sufficient cases rapidly. Presuming a licensure pathway is found acceptable based on immunogenicity, is 3,000 vaccine-exposed subjects a reasonable target for an adult indication with a known vaccine platform?*
  - Any new COVID-19 vaccine is unlikely to require a safety database that is larger than what would be expected for any vaccine for any pathogen that could be

- approved in the EU (n=3,000 for vaccine-exposed subjects). If a signal of concern emerges, regulators may require the safety database be expanded.
- A large safety database is not required (hundreds) for variants of a vaccine that has already demonstrated both safety and efficacy; however, it is important to ensure the reactogenicity profile is not different to that of the prototype vaccine. A robust post-approval surveillance system is required due to the concern over rare events (1/100,000 or 1/1,000,000).
  - Uptake of vaccines may be enhanced if safety databases were larger. Thus, it is important to achieve a balance between this and the minimal regulatory requirement.
- *How does concern around enhanced disease now (March 2021) compare to that three to six months ago?*
    - All current vaccines appear to protect against disease, which means they also protect against enhanced disease. It is unknown what will happen as immune responses wane and thus, if there is a concern for enhanced disease it is likely to come with waning immunity rather than initial vaccination. Thus, there is a need to remain vigilant.
    - It is no longer an FDA requirement that a minimum of five severe cases be included to rule out enhanced disease.
  - *If two vaccines are compared whose efficacy is far above the clinical efficacy requirements of at least 50%, and stringent non-inferiority or even superiority criteria are defined, would that increase regulators' comfort to consider immunobridging of two products that are a bit further away in terms of immune response characteristics?*
    - Regulators are open to discuss how to immunobridge in a way that is conservative, stringent, and would minimise the potential to make any mistake in estimating the level of protection of any new vaccine. They are also open to discuss the option of superiority or comparing to the most immunogenic or protective vaccines based on currently available information.
  - *There are practical challenges to acquiring an appropriate comparator vaccine for non-inferiority studies. If the 'appropriate' comparator is not accessible, can a different accessible comparator be used, and a bigger non-inferiority margin be considered?*
    - A developer may not enter a trial with a superiority requirement unless they were confident it could be met.
    - Regulators would consider a study if much greater immune responses were demonstrated to a new vaccine than to any other vaccine.
    - Regulators usually decide the required criteria prospectively, resulting in minimum (rather than maximum) acceptable criteria.
  - *Would other immune evaluations apart from neutralising antibodies (e.g., T cell immune response, cell-mediated immune response) potentially add to an assessment, in addition to the non-inferiority assessment?*
    - Full characterisation of the immune responses elicited by each vaccine is important and could provide supporting information; however, regulators are at present resistant to use evaluations other than antibodies for regulatory decisions.
    - As there is no universal correlate of protection at present, more research needs to be conducted and cell-mediated immune response assays are an important part of that research. The knowledge that the overall cell-mediated response for a given vaccine correlates reasonably with a prototype vaccine may be an important qualitative finding that could support immunobridging.

## Wrap-up and next steps

Dr Jakob Cramer thanked attendees for their participation in the workshop and outlined the next steps as follows:

- The COVAX Clinical Dev & Ops and Enabling Sciences SWAT Teams plan to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines.
- Resources will be shared at the following website (<https://epi.tghn.org/covax-overview/>) and a workshop report will be distributed.
- Workshop attendees are invited to join post-workshop discussions on the [COVAX hub](#).
- COVAX Enabling Sciences Workshop: Global and local approaches to detect and interpret SARS-CoV-2 variants will be held on April 16<sup>th</sup>.