Workshop Report

COVAX Clinical Development & Operations and Enabling Sciences SWAT Teams Workshop on *"Immune correlates, SARS-CoV-2 variants, and 'mix & match': How vaccine developer approaches might be impacted by emerging data"*

February 25th, 2021

Meeting report prepared by

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Executive summary

On 25th February 2021, the COVAX Clinical Development & Operations and Enabling Sciences SWAT Teams co-hosted a workshop on "*Immune correlates, SARS-CoV-2 variants, and 'mix & match': How vaccine developer approaches might be impacted by emerging data.*" The main aim was to assess progress towards immune correlates for COVID-19 to enable accelerated vaccine development and investigate the impact of new variants.

The first section of the workshop focussed on how to make additional appropriate and impactful vaccines available. Key points included:

- Evidence supporting the establishment of an immune correlate of protection will be derived from different sources including breakthrough cases from large vaccine efficacy trials but also natural history and passive immunization studies (including animal studies).
- There are lessons to be learned from pneumococcal and meningococcal vaccine development for establishing correlates of protection for the next generation of severe acute respiratory disease coronavirus 2 (SARS CoV-2) vaccines.
- Several pre-clinical studies suggest that neutralising antibodies are sufficient to confer protection against SARS-CoV-2 infection. Clinical efficacy studies have also shown an associated between antibodies (as measured by neutralizing or binding assays) and disease protection.
- Short term protection after natural infection is robust and as good or even better than after vaccination.
- Correlate analyses are currently being undertaken by vaccine developers including Pfizer and Janssen.
- Data from the Pfizer efficacy trial showed that protection started prior to a substantial rise in antibodies. Protection at days 10-12 might be conferred by binding antibodies or very low neutralising antibody titre may be required for protection at virus entry into the mucosa.
- A wide array of T cell-based assays is being deployed in COVID-19 vaccine trials; gamma interferon ELISpot and intracellular cytokine staining are the most widely used but their correlation with efficacy is currently unknown.
- It will be important to understand correlates of protection also for other clinical endpoints such as asymptomatic infection or severe disease although current efficacy studies are not designed to support this analysis.
- Both neutralizing and binding antibodies, when standardized through use of a convalescent sera panel, show strong correlation with efficacy across seven vaccines representing four distinct vaccine platforms.

The second section of the workshop focused on new SARS-CoV-2 variants: how to evaluate the immune response and optimise the use of available vaccines against new variants. Key points included:

- The World Health Organization (WHO) International Standard exists and should be used for harmonising the assessment of immune responses to COVID-19 vaccine and assessing the impact of variants.
- 'Mix & match' strategies include heterologous priming (two different vaccines given for primary immunisation) and heterologous boosting (different vaccine given as a booster months after priming with for example two doses of the same vaccine).
- Heterologous prime / boost approaches for COVID-19 vaccines may lead to strengthening and broadening of immune responses and may also have

practical/operational benefits (interchangeability of different COVID-19 vaccines), adjuvant-/ antigen-saving strategies, preventing anti-vector immunity, and better tolerability following the second dose.

- CEPI has released a Call for Proposals (https://cepi.net/wp-content/uploads/2021/01/CEPICfPCallText.pdf) to address relevant clinical development gaps and to expand access to vaccines which also intends to support 'mix and match' programs.
- Stakeholders (NITAGs) will need evidence to implement heterologous prime / boost strategies at a program level.
- It is important to consider what data can be produced rapidly that will provide confidence regarding safety, dosing intervals, and clinical efficacy (particularly in the context of variants).
- Clear and consistent messages about the heterologous prime boost and why these are being recommended should be communicated from the outset to avoid public rumours and misinformation controversies.
- It will be a challenge to obtain the level of data needed to formally label a heterologous prime boost regimen by the regulators.
- The UK COM-CoV trial will assess 'mix and match' strategies for both heterologous priming and boosting.

The slideset from the meeting can be found here: https://epi.tghn.org/covax-overview/clinical-science/

Agenda

Time (CET)	February 25, 2021	Speaker(s)
15:00 – 15:05	**Welcome and meeting objectives**	**Peter Dull, BMGF**
15:05-15:15	**Introduction to Part 1: Progress toward immune correlates for COVID-19 to enable accelerated vaccine development**	**Peter Dull, BMGF Donna Ambrosino, USA**
15:15-15:30	Overview: Establishing a correlate from imperfect evidence – a historical perspective	**David Goldblatt**, University College London, United Kingdom
15:30-15:40	Evidence for a serological correlate of protection from animal models and planned future studies	**Cristina Cassetti**, NIAID, United States
15:40-15:50	Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains	**Florian Krammer**, Icahn School of Medicine at Mt. Sinai, United States
15:50-16:10	Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies	• **Stephen Lockhart**, Pfizer • **Dan Stieh**, J&J
16:10-16:25	Evidence of contribution of cell-mediated immunity to vaccine efficacy, and utility of T cell assays to correlates analyses	**Julie McElrath**, Fred Hutch Cancer Research Center, United States
16:25-17:00	Panel Discussion • Part I Speakers • George Siber (Affinivax, Inc., United States)	Moderated by: Peter Dull
17:00-17:05	**Break**	
17:05-17:10	**Introduction to Part 2: Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines**	**Jakob Cramer, CEPI Paul Kristiansen, CEPI**
17:10-17:20	International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants	**Paul Kristiansen**, CEPI
17:20-17:30	Neutralising Antibody assays against new variants: Overview of current activities	**William Dowling**, CEPI and WHO Assay Group
17:30-17:40	'Mix & Match': Heterologous primary vaccination and heterologous boosting regimens	**Jakob Cramer**, CEPI
17:40-18:25	Panel Discussion • Matthew Snape (Oxford Vaccine Group, United Kingdom) • Arnaud Didierlaurent (University of Geneva, Switzerland) • Adam Hacker (CEPI) • Helen Rees (University of the Witwatersrand, South Africa) • Farah Qamar (The Aga Khan University, Pakistan)	Moderated by: Jakob Cramer
18:25–18:30	**Wrap Up & Next Steps**	**Jakob Cramer**

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.

New data are continuously emerging regarding immune correlates and SARS-CoV-2 variants, while several vaccines against COVID-19 are being distributed in adult populations across the globe. An immune correlate of protection is urgently needed to advance additional COVID-19 vaccines rapidly towards approval as efficacy studies are increasingly operationally challenging. Evidence continues to accumulate in support of neutralising antibodies as the most suitable immune marker to infer efficacy, but the contribution of T cell response may also play an important role. Furthermore, it is important to assess and possibly improve the immune response of vaccines (both existing as well as under development) against the new variants.

Dr Dull and Dr Donna M. Ambrosino, MD (Independent Advisor) provided a summary of what is already known:

- There is a strong correlation between both neutralising and binding antibody responses and vaccine efficacy.
- Calibration to a human convalescent sera panel is necessary in the absence of International Units across studies as the relationship between efficacy and reported neutralising/binding titres is weak in the absence of this calibration.
- Calibration to the WHO International Standard may improve correlation.
- Nearly all variance is explained by antibody responses, leaving little room for impact of T cells on correlation.
- Determination of a threshold value for a protective correlate will require individual antibody distributions (i.e., reverse cumulative distribution function curves) and/or analysis of breakthrough infections and associated immune responses.

Session 1: Progress toward immune correlates for COVID-19 to enable accelerated vaccine development

The first session of the workshop aimed to:

- Review the accumulating evidence that a neutralising antibody response provides the primary contribution to protection against COVID-19 and discuss alternative supportive mechanisms.
- Discuss past approaches to advancing vaccine development despite imperfect evidence and lessons to mitigating the risks through confirmatory studies.

Overview: Establishing a correlate from imperfect evidence – a historical perspective

Professor David Goldblatt, University College London, discussed the use of correlates from a historical perspective in helping to license vaccines with a focus on imperfect evidence.

Main points included:

- An aggregate threshold derived from aggregated efficacy data defined a correlate of protection which led to the successful licensure of three (soon to be five) extended valency pneumococcal conjugate vaccines.
- All models are wrong, but some are more useful than others as is evident in the pneumococcal field.

- Standardization of assays and reagents allowed multiple manufacturers to license using correlates of protection and therefore use head-to-head non-inferiority trials. This is at an early stage with COVID-19 and needs to be accelerated.
- There are lessons to be learned from pneumococcal and meningococcal vaccine development for establishing correlates of protection for the next generation of SARS CoV-2 vaccines.

Evidence for a serological correlate of protection from animal models and planned future studies

Dr Cristina Cassetti, National Institute of Allergy and Infectious Diseases, discussed existing data regarding a serological correlate of protection from animal models, including non-human primates (NHP) and hamsters, and further ongoing studies.

Summary points included:
- Several pre-clinical studies suggest that neutralising antibodies are sufficient to confer protection against SARS-CoV-2 infection.
    - Purified IgG protects macaques against SARS-CoV-2 in a dose-dependent fashion, with a neutralising antibody threshold titre of ~1:50.
    - A system serology study of NHPs immunised with the Novavax vaccine showed that both neutralising and Fc-effector functions contribute to protection, potentially through different mechanisms in the upper and lower respiratory tract. Both macaque and human vaccine-induced antibodies exhibit altered Fc-receptor binding to emerging mutants.
    - A Clover vaccine passive transfer and challenge study in hamsters showed that higher circulating neutralising antibodies correlated with better protection from SARS-CoV-2 challenge.
    - Passive transfer of monoclonal antibodies into NHPs to assess correlates of protection showed high monoclonal antibody levels post challenge and that prophylactic administration of two monoclonal antibodies reduces viral shedding in the upper and lower respiratory tract.
- Other immune responses (Fc-effector functions, CD8+) may contribute to protection, but their relative importance is still under investigation.
- A large ongoing NHP study will compare correlates of protection in different vaccine platforms (i.e., Janssen, Moderna, Novavax, Sanofi).

Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralising titres, variant strains

Dr Florian Krammer, Icahn School of Medicine at Mount Sinai, presented data on observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms and the impact of neutralising titres and variant strains.

Main points included:
- First evidence that neutralising antibodies correlate with protection from SARS-CoV-2 came from a fishery vessel outbreak with a high attack rate.
- Since then, many further studies with larger sample sizes have shown that antibodies are largely protective against infection. For example, a study of healthcare workers in the United Kingdom (UK) showed a prior history of SARS-CoV-2 was associated with an

83% lower risk of infection, with median protective effect observed five months following primary infection.

- Protection after natural infection is robust and as good or even better than after vaccination.
- Protection is correlated with antibody responses to spike protein.
- Studies that determine the impact of variants on neutralising activity of post-vaccination sera side by side are urgently needed. Comparisons conducted in different laboratories do not help to understand the definitive impact of different variants.

Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies

Dr Stephen Lockhart, Pfizer, and Dr Dan Stieh, Johnson & Johnson, discussed approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies.

Key points are summarised as follows:

- Pfizer correlates analyses:
    - Pilot work is planned to assess cases in the vaccine cohort; however, as of November 2020 only eight breakthrough cases without evidence of prior infection have been identified. More cases are likely to be identified following subsequent unblinding. Post-second dose neutralisation titres are currently being assessed. Peripheral blood mononuclear cells (PMBC) have not been collected from subjects so T cell analysis cannot be performed.
    - An unexpected relationship was evident in the Pfizer efficacy study between vaccination date and degree of protection. Onset of protection commenced around day 10/12; however, only very low levels of neutralising antibody were present at the 21-day bleed (i.e., after the first dose but immediately before the second dose). Antibody levels increased quite markedly after the second dose. Thus, protection started prior to a substantial rise in antibodies. This has also been seen with other vaccines.
- Janssen correlates analyses:
    - ENSEMBLE study is a study of Ad26.COV2.S vaccine for the prevention of SARS-CoV-2-mediated COVID-19 in adults in the United States (US), South Africa, and parts of South America including Brazil.
    - Planned correlates analyses focus on binding and neutralising antibody to the vaccine strain and the endpoint COVID-19 with any strain.
    - Correlates analyses are planned for each region separately to assess whether correlates may differ by viral lineage.
    - Sufficient vaccine breakthrough cases exist for correlates analyses; sample selection and distribution are in process. Correlates analyses will be conducted as soon as the data set is available from one of the assays (e.g., correlates analyses for binding antibody might be conducted first to accelerate time to results).
    - The lack of the same set of major variants in the same region/trial is a challenge.
    - Similar and durable humoral immune responses are evident after a single dose of vaccine in adults aged 18-55 and ≥ 65 years. The observed neutralising antibody response was 96% of Ad26.COV2.S group (Day 29) and the response lasted ≥ 85 days in both age groups.
    - CD4+ and CD8+ T cell responses are elicited by the vaccine, with a strong Th1 bias in all participants.

Evidence of contribution of cell-mediated immunity to vaccine efficacy and utility of T cell assays to correlates analyses

Dr Julie McElrath, Fred Hutch Cancer Research Center, discussed the contribution of cell-mediated immunity to vaccine efficacy.

Key points are summarised as follows:

- A wide array of T cell-based assays is being deployed in COVID-19 vaccine trials, which will illuminate differences in immune responses to various vaccine platforms, particularly those that are primarily just using neutralising antibodies and those that have the capacity to induce both CD4 and CD8 T cells.
- Gamma interferon ELISpot and intracellular cytokine staining are the most widely used, but their correlation with efficacy is currently unknown. These can be validated assays and can provide substantial information.
- There is a lack of validated SARS-CoV-2-specific assays across the trials, and difficult sample collection remain challenges for the utility of T cell assay-based biomarkers in large scale trials.
- There is a requirement for T cell durability to be determined. This can be learnt from infection; however, assessing this in vaccine trials over time will be important to determine how long both CD4 and CD8 cells circulate in the blood.

Panel discussion

A panel discussion included the following key points:

- *Dr George Siber, Affinivax, Inc., US –*
    - There is increasing evidence that antibody to spike strongly correlates with protection by vaccines in most circumstances. Interestingly, neutralising titre values as published by the manufacturers correlate poorly with efficacy; however, when these are related to human convalescent sera as a standard the correlation becomes very evident and strong.
    - The use of human convalescent sera as a standard is not ideal. The WHO International Standard should be used to confirm this finding. Ultimately, standardised assays that have gone through inter laboratory comparisons should be used.
    - Mechanisms exist (i.e., reverse cumulative distribution curves) to define the protective threshold level of antibody using studies that have already been conducted, as has been applied to other pathogens. The threshold level, along with the geometric mean, are the main basis for comparing new vaccines with existing vaccines with efficacy trials using non-inferiority criteria that have been well established.
    - Neutralising antibodies correlate with binding assays at a high level with rare exception. Thus, it may be possible to use binding assays rather than neutralising antibodies, as neutralising antibodies are difficult to standardize and preliminary analyses from vaccine trials show higher correlation of binding assays with efficacy.
    - Regulators want to compare vaccines within platforms, as immune responses between platforms may differ (especially T cell responses) and complicate comparisons. The quality of antibody response could also differ (neutralising versus certain Fc effector function differences, cellular phagocytosis, etc.). The

high correlation seen with binding antibodies may enable non-inferiority studies across platforms, as well as within platforms.

- *Prof Andrew Pollard, University of Oxford –*
    - The neutralisation assay is problematic; it is difficult to conduct and roll out into multiple laboratories and is further complicated by the emergence of new variants. If strong correlations are evident with binding antibody, the latter will be easier to help bridge to new vaccines and use from a regulatory perspective as the critical standardised assay.
    - All trials have measured protection differently with varying clinical endpoints. Thus, it is unlikely that the same factor is being measured when levels of antibody and their correlate are considered. The absence of head-to-head studies complicates bridging. It is important to re-assess data from the trials to make them more similar and improve correlations across platforms.
    - It is unknown what to measure in the T cell compartment that relates to COVID-19 vaccine protection. Even if this was known, standardising potential assays across different laboratories would be an even bigger challenge.
    - The important correlation in COVID-19 in the future will focus on severe disease, hospitalization, and death. Prevention of infection will eliminate severe disease; however, SARS-CoV-2 will likely continue to vary in circulating human populations given the nature of RNA viruses. Thus, it is important to understand what is needed to prevent severe disease, hospitalization, and death as this will determine whether an annual update to the coronavirus vaccine is administered or whether people continue to live with upper respiratory tract infections in the years ahead.

- *Different levels of antibody may be necessary for protection against carriage and invasive pneumococcal disease. Also, the level of antibody required for protection from different pneumococcal serotypes varies but the protection mechanism is the same. Might there be a different mechanism and therefore a different path to licensure for a COVID-19 vaccine?*
    - *Prof David Goldblatt* - The mechanism may not be that difficult but achieving a consensus and agreement might be.
    - For pneumococcal disease, a high antibody level is required to reach the correlate for carriage and thus the Food and Drug Administration was resistant to license vaccines using correlates of protection against carriage. There is likely a mixed mechanism of protection against carriage with both antibody and cellular immunity. The simplest way to progress pneumococcal vaccine development was to use antibodies that would protect against invasive disease and hope that prevention of colonization would also occur, which is exactly what happened. The antibody might not be the effector molecule but if the antibody is correlated with the effector molecule, then it becomes a correlate of protection rather than a surrogate of protection.
    - There is increasing evidence (from Israel, England, and Scotland) of efficacy following the first dose the Pfizer and Oxford vaccines; however, focus has been on antibodies and neutralisation activity after the second dose and this needs consideration.

- *Data has shown protection with the Pfizer vaccine starts (day 10/12) well before a substantial rise in neutralising antibodies. How can this be explained?*
    - It is possible that only a very low neutralising antibody titre may be required for protection at virus entry into the mucosa; however, this needs further discussion. Data following a single dose of human papillomavirus vaccine show very low

levels of antibody may be sufficient for durable protection if the virus is encountered at the time of entry.
    - Alternatively, protection at day 10/12 might be conferred by binding, rather than neutralising, antibodies which reach decent titres at that time point.

- *It is thought that ~95% of neutralising antibodies target the receptor binding domain. Is there a reason that a correlate of protection would differentially apply to a spike-based vaccine versus a receptor binding domain-based vaccine or can a similar level be achieved from both these protein-based vaccine types?*
    - Around 50% of neutralising antibodies target the receptor binding domain and 50% target the N-terminal domain following mRNA vaccination. Too much emphasis is placed on the receptor binding domain when whole spike vaccines are used.

- *For meningococcal group B, bactericidal antibodies are derived from a protein-based vaccine or a conjugate vaccine with CRM or tetanus conjugate. If the end goal is neutralisation, does it matter how this is achieved (i.e., which platform etc.)?*
    - *Prof David Goldblatt* – Neutralising live virus is the gold standard test if the end goal is neutralisation.
    - Neutralising live virus has been used to link back and functional antibodies have been critical to development of vaccines against other pathogens. There is good correlation between neutralisation and binding antibodies, but binding antibodies tend to persist while neutralising antibodies appear to reduce over time, so if the focus is solely on binding antibodies, some non-functional antibodies may be missed.
    - With pneumococcal vaccination, binding antibodies that are non-functional are found in adults. Thus, binding antibodies per se cannot be used unless there is a tight correlation at various points in life at time points after vaccination.
    - If live virus neutralisation is the laboratory endpoint, the vaccine antigen is not important. If the laboratory endpoint is refined (i.e., binding assays, ACE2 receptor inhibition) problems will be encountered when cross platform evaluations are done.

Session 2: Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines

The aims of the second part of the workshop included:

- Review the available international standard in the context of new variants.
- Provide an overview on the development of neutralising antibody assays against new variants.
- Introduce and discuss a practical approach for the assessment of vaccine 'mix & match' strategies (i.e., heterologous primary vaccination, heterologous boosting regimens).

International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants

Dr Paul Kristiansen, Coalition for Epidemic Preparedness Innovations (CEPI), discussed the International Standard for SARS-CoV-2 immunoglobulins and the use of the existing International Standard to address new variants.

Summary points included:

- A tool (WHO International Standard) exists for harmonising the assessment of immune responses to COVID-19 vaccine and assessing the impact of variants and should be used.

- The International Standard is available at the National Institute for Biological Standards and Control (NIBSC) and can be accessed at:
    - First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/136)
    - First WHO International Reference Panel for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/268)
- A workshop will be held on the CEPI Centralized Laboratory Network on 12th March 2021. The Centralized Laboratory Network was set up to facilitate rapid evaluation, approval, and dissemination of the most effective vaccine candidates and to standardize immunological testing of COVID-19 vaccines.
- A meeting was held by the WHO Assays Working group in January 2021 on how to implement the International Standard and this will be done again by the end of March 2021.

Neutralising antibody assays against new variants: Overview of current preclinical activities

Dr William Dowling, CEPI, provided an overview of current activities to assess neutralising antibody assays against new variants and evidence on heterologous prime boost from preclinical studies.

Key points included:

- Studies from different laboratories involving new variants have used distinct viral isolates or pseudoviruses and diverse assay formats, which makes direct comparison of the data difficult; use of the WHO International standard could be useful in this regard.
- In general, there is a slight reduction in neutralisation of convalescent or vaccine sera observed with variant of concern (VOC) B.1.1.7 and more significant reductions in neutralisation observed with VOC B.1.351. This was seen in both live virus and pseudovirus assays.
- VOC P.1 and P.2 have recently been used in pseudovirus assays and neutralising titres fell between B.1.1.7 and B.1.351.
- Neutralisation of variants after a single dose is low versus post-second dose.
- Convalescent plasma from B.1.1.7 patients neutralises B.1.351 more efficiently than pre-B.1.1.7 plasma.
- Heterologous prime-boost is an approach that has been successful in other contexts, including the Gamalaya Gam-COVID-Vac vaccine.
- Heterologous prime-boost approaches for COVID-19 vaccines may lead to strengthening and broadening of immune responses.
- Binding and neutralising antibody responses in mice were highest for modified vaccinia virus Ankara (MVA) vectors with receptor binding domain protein boosts rather than MVA boosts.
- Heterologous prime-boost with small activating RNA and ChadOx1 led to stronger T cell responses than homologous boosts with either ChAD or RNA and higher antibody responses than ChAd prime boost.
- Heterologous prime-boost of spike and receptor binding domain proteins led to higher neutralising antibody titres in mice; however, there was no advantage over homologous boost in NHPs.

'Mix & Match': Heterologous prime-boost regimens

Dr Jakob Cramer, CEPI, summarised evidence and some considerations around heterologous primary vaccination and heterologous boosting regimen.

Summary points included:

- Options for managing new variants include optimal use of currently available vaccines, vaccine adaptation against new variants, and bi-/multivalent vaccines.
- 'Mix and match' can be applied to heterologous priming vaccination (i.e., two different vaccines given as first and second dose for primary vaccination [e.g., 4-12 weeks apart]) or heterologous boosting regimen (i.e., different vaccine given 6-12 months after homologous primary vaccination).
- There is evidence from other vaccines (e.g., Ebola vaccine) that 'mix and match' strategies may improve both the breadth and duration of the antibody response.
- There are additional potential benefits including practical/operational aspects, adjuvant-/ antigen-saving strategies, anti-vector immunity, and better tolerability following the second dose.
- Numerous theoretical 'mix and match' combinations could be considered given the various vaccine platform technologies and vaccine products in use. In general, limited evidence is available on combining different vaccine platform technologies and to optimise the immune response based on heterologous priming / boosting.
- Some vaccines, particularly mRNA and protein-based vaccines, may be good for priming due to strong T-follicular helper cell induction. Immunological, economical, logistical, and political considerations and potentially associated contraindications will help determine the most suitable platform for priming.
- Potential strategies to investigate 'mix and match' include prospective clinical trials, either as a partnership between two different developers or alternatively by recruiting subjects that have received a first dose / full primary immunisation and providing a heterologous second dose (→ heterologous priming) or booster dose (→ heterologous boosting). Core elements are encouraged in terms of trial design, endpoints, and use of WHO international reference standards.
- CEPI has released a Call for Proposals (https://cepi.net/wp-content/uploads/2021/01/CEPICfPCallText.pdf) to address relevant clinical development gaps and to expand access to vaccines which also intends to support mix and match programs.

A panel discussion included the following key points:

- *What is the real-world practical impact of 'mix and match' approaches?*
    - *Dr Helen Rees, University of Witwatersrand, South Africa* – It is important to generate evidence and guidance regarding mix and match approaches and not leave programs to make their own choices. Guidance will most likely come from regulatory authorities or advisory committees on COVID-19 vaccines, and both will require evidence.
    - Potential challenges of mix and match might include dosing intervals (i.e., use interval of the prime or boost?) and implications for pharmacovigilance and monitoring of safety signals (how to attribute?).
    - It is important to consider what data can be produced rapidly that will provide confidence regarding safety, dosing intervals, and clinical efficacy (particularly in the context of variants).

- *Is there an opportunity to generate this evidence for example in South Africa and / or in Pakistan and will clinical trials be approved on 'mix and match' strategies?*

- *Dr Helen Rees* – There is a real interest in many African countries to become involved in clinical trials. South Africa has developed a good infrastructure over many years and has so far been involved with trials for five different vaccine candidates.
- Data interpretation (i.e., laboratory data, whether neutralising antibodies are the gold standard or T cells etc.) is a challenge. In the absence of robust data interpretation, programs will make their own decisions, as happened in South Africa when the rollout of the Astra Zeneca vaccine was halted (due to little effect on mild/moderate disease). The Janssen vaccine is now being rolled out in a Phase 3B trial and hospitalisation as a surrogate for severity is being considered.
- Literature-based data on the vaccines are being used to inform decisions regarding purchase and efficacy; however, there is lack of knowledge on how to interpret these data. Rapid identification of robust answers in the absence of huge clinical trials needs consideration.
- *Dr Farah Qamar, The Aga Khan University, Pakistan* – Stakeholders will need evidence to implement heterologous prime boost or mix and match strategies at a program level. The more evidence generated for different combinations the better; however, complexities (i.e., logistical and storage challenges) will arise if the heterologous prime boost is very tightly prescribed, particularly in the context of low- and middle-income countries. At the community level, further challenges including public rumours using the mixed approach, misinformation controversies, and questions about the different regimens may arise as has already been seen in India and other countries. Clear and consistent messages about the heterologous prime boost and why these are being recommended should be communicated from the outset.

- *Some vaccines may be rolled out in the public sector while others are rolled out in the private sector. Would it be an issue if a heterologous priming regimen is used in some parts of the population but not in others?*
  - *Dr Farah Qamar* - Once evidence is generated on vaccine combinations available in the private, as well as public, sectors, there should be no issues with the regulatory approvals, but in the initial phase this will differ.

- *Discuss the difference between formally licensing a heterologous priming regimen and generating data that would allow NITAGs to simply recommend certain vaccines to be used in a heterologous regimen.*
  - *Dr Adam Hacker, CEPI* - Regulators are facing challenges at present with new variants and increasing difficulty to conduct vaccine efficacy studies, at least within the homologous prime boost regimen. Data are needed, with emphasis on using national standards to generate comparable data and understanding what level of immune response is required to provide protection.
  - Data could be generated quickly on immediate local reactions following vaccines administered in a heterologous regimen in error and provide some level of reassurance regarding immediate potential concern. It is important to give the public at least some level of comfort that mix and match strategies are possible from a safety point of view.
  - It will be a challenge to obtain the level of data needed to formally label a heterologous prime boost by the regulators.
  - Vaccine availability and NITAG/government recommendations will play a role.

- *Three vaccines are currently rolled out in the UK, and the COM-CoV trial will generate data to support potential interchangeability or improve heterologous priming strategies. It will also address the issue of prolonging the dosing interval. Discuss the rationale, design aspects, and interval selection for the COM-CoV program.*

- *Dr Matthew Snape, Oxford Vaccine Group* - The COM-CoV trial is designed as a non-inferiority trial. The aim is not necessarily to identify the optimal immunization schedule but the one(s) to avoid from an immunogenicity and reactogenicity point of view.
- The ChAdOx and Pfizer vaccines are being considered in different combinations to ensure the immune response to a mixed schedule is not inferior to the licensed schedule. Data are being generated primarily for the Joint Committee on Vaccination and Immunisation, the UK NITAG, rather than for regulatory purposes, to provide flexibility in the immunisation schedule.
- Evaluation at different intervals was a pragmatic decision. Initially, only second doses administered at a four-week interval were to be included. The UK subsequently recommended delaying the second dose to 12 weeks, thus this interval was also included to obtain data that reflected current UK practice.
- Protein-based vaccines will be included at a later stage. To obtain data as quickly as possible that is relevant to the UK, an eight-week interval will be considered for these.
- To date, 820 participants have been enrolled.
- It is hoped that in addition to identifying any schedules to avoid, a more immunogenic combination might be found.

- *The main focus of the UK COM-CoV trial is heterologous priming, and the trial protocol has been made publicly available. An additional program for heterologous boosting is planned. How will those interested in doing similar programs in other countries be able to cooperate?*
  - *Dr Matthew Snape* - In a separate protocol, the UK COM-CoV trial will enrol individuals who received either two doses of Pfizer or two doses of ChAdOx as priming. These individuals will then be given a range of different vaccines in a randomized manner as a third dose.
  - This part of the study will run from mid-2021 (i.e., June/July) to generate data long enough after the first two doses to be considered a later booster but not so late that the data are no longer of use.
  - Increased reactogenicity has been seen following the second dose of the Pfizer vaccine. It will be interesting to assess what happens after three doses of Pfizer and whether this will be an appropriate strategy.
  - The potential issue of anti-vector immunity, particularly after the third dose of the ChAdOx vaccine, will also be assessed.
  - One aspect that might need consideration in heterologous boosting is whole virus vaccines and their range of different antigens. If a whole virus vaccine is administered as a third dose in an individual who received two doses of a spike protein-based vaccine previously, this would be the third exposure to the spike protein but first exposure to the nuclear capsule. Thus, the individual would have a boosted response to some antigens and an initial response to others. The impact of this is not known but it is important to consider as there are whole virus vaccines currently in use.
  - These studies are currently being conducted independently of the manufacturers. It is hoped going forward that communication will be directly with the manufacturers and they will be able to cooperate and supply vaccines directly.

- *Due to lack of pre-existing evidence, it is not possible to define the optimum heterologous priming regimen. What aspects should be considered in choice of priming and boosting vaccines?*
  - *Dr Arnaud Didierlaurent, University of Geneva* - It may be worth administering the stronger vaccine as a prime; however, vaccine choice will also depend on the desired outcome. A broader antibody repertoire may be more advantageous in

terms of sterilizing immunity, but CD8 T-cells may be useful for preventing severe disease.
    - Evidence on quality of memory B-cells is lacking at present. It may be misleading to only consider antibody levels as it is memory B cells that are boosted after the second dose. It will be important to generate data across platforms on memory B-cells to help decide which vaccine is most suitable for priming.
    - The vaccine type received as prime may be important when considering a boost based on variants.
    - It will be important to determine if any vaccine platforms can overcome antigenic sin.
    - Data are needed to further elucidate advantages and disadvantages.

- *These platform technologies do not only have different immunogenic characteristics, but also differ in terms of storage conditions, shipping conditions, and contraindications. Will the latter impact heterologous priming even if vaccines had an immune response advantage against new variants?*
    - *Dr Helen Rees* – Multiple regimens should not operate in parallel within a country as this will lead to confusion.
    - Clarification is urgently needed on how to proceed in countries with emerging (or established) variants. At present, there is confusion for example over whether to prime with an original vaccine and then boost with a modified vaccine that has been tailored to an appropriate variant, or not to prime at all and wait for a new vaccine against the VOC.
    - *Dr Farah Qamar* - An approved regimen will vary by country and will be dependent on capacity for vaccine storage and rollout. Inactivated vaccines should be tested in mix and match strategies and evidence generated as they do offer broader immunity and better immunity against variants.

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.