

COVAX



COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator

Workshop Report

COVAX Clinical Development & Operations and Enabling Sciences SWAT Teams Workshop on “COVID- 19 Correlates of Protection”

November 19th, 2020

Meeting report prepared by

Dr Julia Granerod

Executive summary

On 19th November 2020, the COVAX Clinical Development & Operations and Enabling Sciences SWAT Teams co-hosted a workshop on “*COVID-19 Correlates of Protection.*” The main aim was to review and discuss currently limited and scattered evidence on COVID-19 immune correlates.

The first section of the workshop focussed on evidence for existence of an immune correlate for COVID-19. Key points included:

- Correlates of protection (CoP), defined as an immune response that is statistically associated with protection, are important for many reasons including to enable the correct choice of vaccine antigen and to enable licensure when efficacy studies are not achievable for reasons of ethics or feasibility.
- Antibodies to spike protein are often neutralizing, while antibodies to nucleoprotein, non-structural proteins are non-neutralising.
- Fc-FcR interactions do not play a significant role in protection.
- IgM and IgA appear relatively short-lived, while IgG response appears normal/long-lived.
- Anti-spike glycoprotein immune responses after natural infection: mucosal antibody is present, neutralising antibodies correlate well with enzyme-linked immunosorbent assay (ELISA), and memory B cells present for >6 months.
- Neutralising antibodies are probably the most important predictor of protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but other antibody functions likely also contribute.
- Proof of principle data suggest monoclonal antibodies (mAbs) alone are sufficient for prevention.
- Preclinical models show evidence for some contribution of cell-mediated immunity to protection.
- From animal models, it is likely that infection provides protection against reinfection.
- Clinical follow-up from cases of COVID-19 globally suggest that re-infection can occur but is infrequent although duration of follow-up is limited.

The second section of the workshop focused on operational, statistical, and regulatory considerations for COVID-19 immune correlates. Key points included:

- Options to expedite contribution of data from early Phase 3 efficacy trials to correlates analyses are being explored.
- The context of use (e.g., “traditional” approval, accelerated approval, etc.) is the critically important feature that informs and frames each individual case in which a biomarker is proposed to accomplish a regulatory objective.
- Multiple assays have been selected, qualified, and validated for use in comparative immunogenicity and immune correlates analyses.
- Large volumes of sera are being secured for use as internal controls and reference standards for bridging, validation, trending, and external quality assessment.
- Standard and Reference Panel for anti-SARS-CoV-2 Antibodies developed by National Institute of Biological Standards and Control (NIBSC) is the subject of a World Health Organization (WHO) public consultation and review by the WHO Expert Committee on Biologicals Standardization in December 2020. Developers should access the Standard through NIBSC, and report results such that the community can understand comparability of results across studies.

- Coalition for Epidemic Preparedness Innovations (CEPI) Centralised Laboratory Network established: binding antibodies, neutralising antibodies, and T cells (Elispot) offered to CEPI funded and non-CEPI funded vaccine developers
- It is possible to learn something useful about correlates of risk/protection with only 15 breakthrough vaccine cases; however greater numbers are needed to achieve convincing precision.
- Despite recent positive results, it remains critical to continue to collect data on long term duration of protection and safety from these vaccines.

The slideset from the meeting can be found here:

https://media.tghn.org/medialibrary/2020/11/201119_COVAX_CoP_Workshop_Complete_Materials_vF.pdf

Agenda

Time (CET)	November 19, 2020	Speaker(s)
15:00 – 15:05	Welcome & Meeting Objectives	Peter Dull (Clinical SWAT), Ivana Knezevic (Enabling Sciences SWAT)
Session 1: Evidence for Existence of an Immune Correlate for Covid-19		
15:05 – 15:20	Correlates of Vaccine-induced Immunity – An Overview <ul style="list-style-type: none"> • <i>Correlates nomenclature</i> • <i>Core principles in the approach to identification of immune correlates through key examples from past efforts</i> 	Stanley Plotkin (University of Pennsylvania)
15:20 – 15:40	SARS-CoV-2 immunity overview and risk factors for re-infection <ul style="list-style-type: none"> • <i>Accumulated evidence for immune responses to coronaviruses including SARS-CoV-2 to inform immune correlates assessment</i> • <i>Efforts to identify an association of re-infection risk with antecedent immune profile including an overview of ongoing and planned studies</i> 	Florian Krammer (Icahn School of Medicine at Mount Sinai)
15:40 – 15:55	PK/PD Considerations for SARS-CoV-2 Neutralizing Antibodies <ul style="list-style-type: none"> • <i>Proof of principle data to suggest mAbs alone sufficient for prevention, including dose-response in Rhesus prophylactic model to identify minimally effective level</i> 	Andrew Charles Adams (Eli Lilly & Company)
15:55 – 16:10	Non-human primate (NHP) passive transfer and vaccine studies <ul style="list-style-type: none"> • <i>NHP dose-titration protection data from convalescent sera & vaccine studies</i> • <i>Evidence for contribution of cell-mediated immunity to protection in pre-clinical models</i> 	Dan Barouch (Harvard University)
16:10 – 16:50	Panel Discussion Panel Members: <ul style="list-style-type: none"> • Meera Chand (PHE) • Robert Seder (NIH/NIAID) • <i>Other speakers from above also available to answer remaining questions and for any further discussion</i> 	Moderated by Karen Makar (BMGF)
Session 2: Operational, Statistical and Regulatory Considerations for Covid-19 Immune Correlates		
16:50 – 17:00	Opportunities for CoP Identification from Ongoing Phase III VE Studies <ul style="list-style-type: none"> • <i>Estimated timelines from OWS and other global Phase III efficacy studies</i> • <i>Key study design elements to support immune correlates analysis</i> 	Kristen Earle (BMGF)

17:00 – 17:15	<p>Regulatory Perspective: Approach to Acceptance of CoP for Licensure</p> <ul style="list-style-type: none"> • <i>Overview of the expectation from a regulatory perspective for adequacy of evidence for an immune correlates to support product registration</i> • <i>Tools to enable progress when evidence is incomplete</i> 	<p>Daniel Brasseur (Former EMA Expert)</p>
17:15 – 17:25	<p>COVID-19 Immunoassay Platform Overview</p> <ul style="list-style-type: none"> • <i>Overview of clinical immunoassays to support product registration of Operation Warp Speed candidates</i> • <i>Performance characteristics and interrelationship between assays</i> 	<p>Richard Koup (NIH/NIAID)</p>
17:25 – 17:35	<p>Development of the COVID-19 Research Standards and Global Immunoassay Network</p> <ul style="list-style-type: none"> • <i>Overview of CEPI Centralized Laboratory Network and WHO standardization efforts, including the establishment of the ECBS-endorsed International Standard for anti-SARS-CoV-2 antibody</i> 	<p>Valentina Bernasconi (CEPI)</p>
17:35 – 17:50	<p>Statistical Approaches for Assessment of Immune Correlates of Protection</p> <ul style="list-style-type: none"> • <i>Overview of Operation Warp Speed statistical analysis plan and approach in light of recent results of high short-term efficacy from interim analyses</i> 	<p>Peter Gilbert (Fred Hutchinson)</p>
17:50 – 18:25	<p>Panel Discussion <i>Including discussion on trial design approaches utilizing identified correlate</i></p> <p>Panel Members:</p> <ul style="list-style-type: none"> • Kathleen Neuzil (University of Maryland School of Medicine) • Ana Maria Henao-Restrepo (WHO) • Marco Cavaleri (EMA) • Jeff Roberts (CBER/FDA) • <i>Other speakers from above also available to answer remaining questions and for any further discussion</i> 	<p>Moderated by Peter Dull (BMGF)</p>
18:25 – 18:30	<p>Wrap Up & Next Steps</p>	<p>Paul Kristiansen (Enabling Sciences SWAT), Jakob Cramer (Clinical SWAT)</p>

Welcome and meeting objectives

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, and Dr Ivana Knezevic, Group Lead of Norms and Standards for Biologicals at WHO, welcomed participants and set the context for the workshop.

Recent positive results from large COVID-19 vaccine efficacy studies are important but multiple licensed products are required to have the necessary near-term global impact. Complexities for operational pathways for next vaccine registration highlights the urgent need to accelerate progress toward identification of an immune CoP. A correlate could accelerate access to additional COVID-19 vaccines through alternative study designs and support evaluation for durability of protection for each vaccine. There is currently limited and scattered evidence on COVID-19 immune correlates which would benefit from a consolidated review and dialogue.

Session 1: Evidence for existence of an immune correlate for COVID-19

The first session of the workshop aimed to:

- Review correlates nomenclature and highlight core principles in the approach to identification of immune correlates through key examples from past efforts;
- Present the accumulated evidence for immune responses to coronaviruses including SARS-CoV-2;
- Review efforts to identify an association of reinfection risk with antecedent immune profile including an overview of ongoing and planned studies;
- Share available non-human primate (NHP) mAb pre-exposure prophylaxis preclinical data dose-response results as well as recent early treatment clinical data to inform contribution of targeted antibodies for protection;
- Review NHP dose-titration protection data from convalescent sera and vaccine studies and discuss evidence for contribution of cell-mediated immunity to protection in pre-clinical models.

Correlates of vaccine-induced immunity – an overview

Dr Stanley Plotkin, University of Pennsylvania, provided an overview of correlates nomenclature and core principles in the approach to identification of immune correlates through key examples from past efforts.

A summary of the main points includes:

- CoPs, defined as an immune response that is statistically interrelated with protection, are important for many reasons including to enable the correct choice of vaccine antigen and the immune response induced by that antigen.
- Correlates can be determined in numerous ways, including analysis of immune responses in protected versus unprotected subjects in Phase 3 efficacy trials.
- There are numerous potential protective adaptive immune mechanisms induced by vaccination and any one of them can be a CoP.
- The 10 principles of CoPs include:
 1. Protection against what (infection/disease) must be defined – e.g. Killed/live polio vaccines induce IgG serum antibodies and protect against paralysis, but

protection against infection (from oral polio vaccine) is mediated by IgA and IgG antibody on the mucosal surfaces.

2. The mechanism of protection against infection is not necessarily the same mechanism as recovery from infection – e.g. antibody protects against measles infection but if infected individuals are deficient in T cells, they will develop severe measles.
 3. A large challenge dose can overcome immunity – e.g. challenge dose of cytomegalovirus (strain Toledo) infected $\geq 50\%$ of subjects in seronegative, naturally seropositive, and vaccinated seropositive groups.
 4. Most current vaccines protect through antibodies – e.g. hepatitis A.
 5. Correlates may be relative – e.g. low antibody levels may protect against influenza but some individuals with higher levels of antibody still developed disease.
 6. Antibodies must be functional – e.g. young children developed ELISA antibodies but not always bactericidal antibodies following group C meningococcal polysaccharide vaccine and remained susceptible to disease.
 7. More than one factor may protect as co-correlates – e.g. high protection if developed both serum haemagglutination-inhibition antibodies and nasal IgA following live intranasal influenza vaccine.
 8. Memory may be a mechanistic CoP – e.g. memory B cells are demonstrable in hepatitis B vaccinees and convalescents despite no protective serum antibody levels.
 9. T cell responses as correlates – e.g. correlate for varicella zoster (VZV) vaccine is varicella-specific CD4 T cells measured by lymphocyte proliferation.
 10. Non-mechanistic CoPs – e.g. VZV vaccine does induce VZV antibody, which can be used as a non-mechanistic correlate, but the actual correlate is varicella-specific CD4 T cells.
- CoPs become complicated with regards to mucosal pathogens.
 - Apart from neutralisation and cytotoxic T lymphocytes, additional protective immune mechanisms include for example binding antibodies that prevent attachment in Ebola and antibody dependent cellular cytotoxicity in human immunodeficiency virus.
 - Polytheism is preferable to monotheism with respect to CoPs by many vaccines.

SARS-CoV-2 immunity overview and risk factors for re-infection

Dr Florian Krammer, Icahn School of Medicine at Mount Sinai, presented accumulated evidence for immune responses to coronaviruses including SARS-CoV-2, to inform immune correlates assessment. He also discussed efforts to identify an association of reinfection risk with antecedent immune profile including an overview of ongoing and planned studies.

A summary of the main points includes:

- Many different vaccines in development focus only on the receptor binding domain (RBD) of the spike protein. There are however, many more proteins that these viruses express which may be important in natural infection and for some live-attenuated vaccines.
- The following is known about immunity, immune responses, and CoPs:
 - Antibodies to spike/RBD are often neutralizing.
 - Antibodies to nucleoprotein, non-structural proteins are non-neutralising.
 - Fc-FcR interactions have been shown to play a negligible role in protection.

- IgM and IgA appear relatively short-lived.
- IgG response appears normal/long-lived.
- Mucosal antibody is present after infection.
- Memory B cells may play an important role in protection from SARS-CoV-2 as these cells can be recalled, become plasmablasts, and start to actively secrete antibody during the long incubation period.
- A good CD4 T cell response against spike protein and a less pronounced CD8 response is evident.
- Data from other human coronaviruses (including historic challenge studies with 229E) show some evidence that infection may protect against reinfection and that antibodies may play a role, but durability may be limited and not cross protective.
- Neutralising antibodies were shown to correlate with protection against SARS-CoV-2 in humans during a fishery vessel outbreak with a high attack rate.
- A study (Protection Associated with Rapid Immunity to SARS-CoV-2 [PARIS]) is underway to investigate if reinfection is possible and to determine the protective titre.
- Major differences between immune responses to infection and vaccination include mucosal immunity and binding to neutralisation titre ratios.

Pharmacokinetic/pharmacodynamic considerations for SARS-CoV-2 neutralising antibodies

Dr Andrew Charles Adams, Eli Lilly & Company, presented pharmacokinetic (PK) and pharmacodynamic (PD) considerations for SARS-CoV-2 neutralising antibodies.

Main points included:

- In Eli Lilly's programs using monoclonal neutralising antibodies for COVID-19, antibodies which can disrupt the angiotensin-converting enzyme 2 spike protein interaction were screened and two antibodies were generated to progress through clinical testing.
- The lead antibody developed is LY-CoV555 (Bamlanivimab), which is now authorised for emergency use in the United States (US).
- Non-clinical PK/PD has been conducted in a rhesus prophylaxis model of SARS-CoV-2 infection to inform dosing.
- Risk assessment for first-in-human dosing concluded there was a low degree of an inherent risk of target organ toxicity and theoretical safety/efficacy concerns related to antibody-dependent enhancement of viral replication or disease and development of resistance/escape mutations.
- Viral dynamic PK/PD-based modelling and simulation and physiologically-based pharmacokinetic modelling were employed to increase the likelihood of finding an efficacious dose.
- The two independent approaches gave a dose range of 450-700mg, with 700 mg expected to result in maximum efficacy.
- Due to uncertainty in the translation of *in vitro* potency data to *in vivo*, a conservative approach was implemented to study higher doses to mitigate risk of underdosing.
- The Phase 2 clinical trial results showed that 700 mg was at a plateau and all dose levels were equally effective.

- These results present proof of principle data to suggest mAbs alone are sufficient for prevention, including dose-response in a Rhesus prophylactic model to identify the minimally effective level.

Non-human primate passive transfer and vaccine studies

Dr Dan Barouch, from Harvard University, discussed NHP dose-titration protection data from convalescent sera and vaccine studies and evidence for contribution of cell-mediated immunity to protection in preclinical models.

Key points are summarised as follows:

- An NHP model for COVID-19 was developed and showed that 1) SARS-CoV-2 infection protects against re-challenge in rhesus macaques and pseudovirus neutralising antibody titres correlate with protection with prototype DNA vaccines.
- These correlate studies were expanded through study of Ad26 vaccine which is currently in clinical trials with Johnson & Johnson. SPP showed complete protection in bronchoalveolar lavage (BAL) and still very good protection in nasal swabs.
- Numerous humoral and cellular parameters were investigated, and neutralising antibody titre was shown to be the best correlate for both pseudovirus and live virus.
- Other parameters also correlated with protection, including antibody-dependent natural killer cell activation and antibody-dependent cellular phagocytosis.
- Neutralising antibodies are probably the most important CoP, but other antibody functions likely also contribute.
- Dose-reduction Ad26.COV2.S study
 - Low-dose Ad26.COV2.S vaccine protected rhesus macaques in BAL (2×10^9 vp) and nasal swabs (1×10^{10} vp)
 - Sub-protective vaccine responses resulted in reduced protection but no evidence of enhanced disease.
 - Neutralising antibody titres correlated with protective efficacy in three independent vaccine studies in rhesus macaques.
- IgG adoptive transfer and CD8 depletion studies
 - Purified IgG protects macaques against SARS-CoV-2 challenge in a dose-dependent manner.
 - Threshold neutralising antibody titres for protection in this model are low (~ 50).
 - CD8 depletion reduced protection against re-challenge in convalescent macaques with waning neutralising antibody titres.
 - These data suggest that neutralising antibodies alone protect, but cellular immune responses may also contribute when neutralising antibody titres are borderline or sub-protective.

Panel discussion

A panel discussion included the following key points:

- Neutralizing antibody appears to be a CoP, but other factors may also contribute. Vaccine studies should follow the immune responses over longer periods of time to determine which factors wane and whether waning is accompanied by decreased efficacy. Thus, factors identified with acute infection may change as individual immune responses decline.

- Public Health England (PHE) is conducting a natural immunity study (SIREN) which aims to assess the risk of infection in seropositive individuals. A large cohort of healthcare workers has been set up with over 35,000 already enrolled and the study still recruiting. Around 30% of participants are found to be seropositive at baseline by commercial ELISAs that are in approved clinical use in the United Kingdom (UK). Seropositive individuals undergo PCR testing every two weeks in their hospital lab and serology testing by commercial ELISA in their local lab every two to four weeks and complete a clinical questionnaire every two weeks. It is important to note that not only disease but also infection is detected in this study and monitoring will continue for a year in the first instance. Viral genomics and other investigations are used to confirm reinfection and detailed immunological characterization with matched controls alongside from the cohort can be carried out as needed.
 - Natural infection in animal studies or humans are different in two ways. The route of infection may increase mucosal responses in upper and lower airways which could be different than vaccines given intramuscularly. Immune responses for antibodies and T cells may be “broader” following primary infection than with vaccines encoding only the spike protein. However, “certain” vaccines by focusing on the spike can induce significantly higher antibody responses than primary infection.
 - Reinfection is unlikely to be a high frequency event (at least over a period of six months), as only anecdotal cases have thus far been reported. It is likely that infection provides some protection against reinfection, but more robust data are needed.
 - However, these are care reports only; systematic surveillance for reinfection is challenging to conduct using national data sets as individuals can remain PCR positive for up to 90 days. This is best addressed using a cohort study design.
 - Confirmation of reinfection is scientifically challenging. A large proportion of reinfection might be asymptomatic and short, making viral detection difficult. Reinfection may boost antibody titres in people who already have some immunity.
- *What are the key learnings from preclinical models about the relative contribution of non-antibody mediated protection?*
 - Data strongly suggest that antibodies, likely neutralising antibodies, are the principal determinant for protection. Strong correlations have been seen with >100 monkeys across studies for correlates.
 - Pre-clinical studies show most vaccines protect against lower airway. Only some vaccines rapidly control against upper airway and these are associated with higher antibody titres. The latter may have implications for a transmission effect.
 - It is likely that vaccines (RNA and especially protein vaccines) which induce much higher neutralizing antibody responses would have higher and more durable protection.
 - The role of T cells by vaccines is not clear. It may have a role following primary infection in animal models in upper airway, but there is no evidence for T cells in vaccine protection or how they affect re-infection in humans.
 - Subclinical infection may provide immunity to individuals against serious disease.
- *Vaccines predominantly protect the lung, somewhat the throat, and less effectively protect the nose. However, surveillance for infection in the population is*

predominantly conducted through nasal or nasopharyngeal swabbing. What are the challenges of reconciling the two?

- Recent data from Moderna is supportive of this; there were zero cases of severe infection and five (out of 90) cases of milder infection. Thus, vaccines in humans are likely more effective at protecting against severe pneumonia and less effective against milder upper respiratory cold-like symptoms and potentially even less effective against asymptomatic disease although that remains to be seen.
- It is important to note that a vaccine that might not be 100% effective in protection against upper respiratory infection might significantly reduce the time of viral shedding and viral titres which impacts transmission. Vaccine that do not provide sterilizing immunity might still impact transmission. This is supported by data from primate models where vaccines that do not lead to sterilizing protection in the nose almost all give a substantial reduction in magnitude and duration of virus replication in the nose compare with controls.
- *What is the utility of the hamster model, which has a more severe disease phenotype, to answer some of these questions?*
 - The NHP model is a good model of the asymptomatic and mild disease category, but there is no NHP model that gives consistent severe disease. Thus, there is an importance for other models, including small animal models. The hamster model is used in addition to the NHP model for testing of monoclonal antibodies and vaccines and in pathogenesis studies. Both models are relevant, and effects with vaccines and monoclonal antibodies are seen in both models. In the high-dose hamster model, vaccines do not appear to give sterilizing protection but give substantial protection against clinical disease. In the primate model, vaccines appear to give sterilising protection.
- *What are thoughts regarding up or downward translation in age to non-target populations such as paediatrics?*
 - Vaccines that reduce, but might not eliminate, nasopharyngeal infection in all individuals would still have a major effect on transmission both to the young and elderly.
 - Reactogenicity may be a hurdle in the young for some vaccine candidates.
- *What viral load thresholds are considered for transmission of the virus and where are those viral loads being measured?*
 - Preclinical NHP data have shown effective protection of the lower respiratory tract by the majority of all vaccine formulations. However, the ability to confer protection in the upper respiratory tract is limited to those vaccines with the highest neutralizing antibody responses and also may be dependent on the challenge dose used.
 - Protection of the upper respiratory tract is required to prevent transmission, likely with a CT threshold higher than 30.
 - Data from a post-exposure prophylaxis study in nursing homes will help inform amount of protection from the neutralizing antibody component of the response.
- *How will correlates defined in these preclinical models be quantitatively transitioned to help the development of follow-on vaccines?*
 - Based on data from two vaccines, neutralizing antibodies are the most likely correlate with an effect on virus excretion as well as protection. Other candidates may have additional mechanisms of action. We are some way towards establishing neutralizing antibodies as an important CoP for COVID-19; however, more needs to be learnt, also about CoPs against infection.

Session 2: Operational, statistical, and regulatory considerations for COVID-19 immune correlates

The aims of the second part of the workshop included:

- Review estimated timelines from Operation Warp Speed (OWS) and other global Phase 3 efficacy studies and highlight critical study design elements and limitations in supporting immune correlates analysis;
- Provide an overview of regulatory expectations for adequacy of evidence for an immune correlate to support product registration and discuss tools to enable progress when evidence is incomplete;
- Discuss clinical immunoassays to support product registration of OWS candidates and review performance characteristics and interrelationship between assays;
- Share information about the CEPI Centralized Laboratory Network and WHO standardization efforts, including the establishment of the Expert Committee on Biological Standardization (ECBS)-endorsed International Standard for anti-SARS-CoV-2 antibody;
- Present an overview of the OWS statistical analysis plan and approach considering recent results of high short-term efficacy from interim analyses.

Opportunities for CoP identification from ongoing Phase 3 vaccine efficacy studies

Dr Kristen Earle, Programme Officer at the Gates Foundation, discussed estimated timelines from OWS and other global Phase 3 efficacy studies and key study design elements to support immune correlates analysis.

Summary points included:

- The COVAX Clinical SWAT are exploring options to expedite contribution of data from early Phase 3 efficacy trials to correlates analyses. These options include:
 - “Real time” analysis with cases analysed as they accrue prior to unblinding through Data and Safety Monitoring Board
 - Minimise time between primary efficacy and correlates analyses
 - Pool data from breakthrough cases within platforms to increase power
- The breadth of the global response presents both challenges and opportunities to identification of a correlate. Some challenges unique to such a large-scale effort include breadth of platforms and variability in antigens. However, similarities in protocols (timepoints, inclusion/exclusion criteria, common assays, and international standard) may facilitate analysis across studies.

Regulatory perspective: approach to acceptance of CoP for licensure

Dr Daniel Brasseur, a former European Medicines Agency (EMA) expert, presented an overview of the expectation from a regulatory perspective for adequacy of evidence for an immune correlate to support product registration and tools to enable progress when evidence is incomplete.

Key points included:

- Biomarkers are a critical part of vaccine discovery, development, licensure, and implementation.

- Vaccine-associated biomarkers can include measures of immune response correlated with protection from disease and nonimmune biomarkers related to safety and effectiveness (field studies).
- Most biomarkers (directly linked to the vaccine mechanism of action) are based on the humoral response and their use requires validation particularly when linked to efficacy.
- From a regulatory perspective, biomarkers can be used for many different objectives, the most important one being immune bridging to avoid repetition of field trials for vaccines targeting the same disease.
- Context of use (e.g., “traditional” approval, accelerated approval, etc.) is the critically important feature that informs and frames each individual case in which a biomarker is proposed to accomplish a regulatory objective.

COVID-19 immunoassay platform overview

Dr Richard Koup, National Institutes of Health’s National Institute of Allergy and Infectious Diseases (NIAID), presented an overview of clinical immunoassays to support product registration of OWS candidates and performance characteristics and interrelationship between assays.

Summary points included:

- OWS Immune Assays Working Group has selected, qualified, and validated multiple assays for use in comparative immunogenicity and immune correlates analyses in support of OWS Phase 3 trials.
- To build capacity and redundancy, contracts are being awarded to contract research organisation laboratories that will tech transfer and validate the assays from the developer laboratories.
- NIAID is working with multiple contractors and partners to identify and secure large volumes of sera for use as internal controls and reference standards for bridging, validation, trending, and external quality assessment.

Development of the COVID-19 Research Standards and Global Immunoassay Network

Dr Valentina Bernasconi, CEPI, presented an overview of CEPI Centralized Laboratory Network and WHO standardization efforts, including the establishment of the ECBS-endorsed International Standard for anti-SARS-CoV-2 antibody.

Summary points included:

- Two initiatives to improve assay standardisation include the development of WHO International Standards and reference reagents at NIBSC (WHO collaborating centre) and CEPI Centralised Laboratory Network.
- The International Standard will be available in small quantities and labs will be expected to create their own secondary standard for calibration.
- Reference reagents and reference panel aim to create a communal language between laboratories worldwide and improve comparability of results.
- The CEPI 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.
 - Qualified assays include: Full length S,RBD, N ELISA; Pseudo virus and wild type virus neutralization assays; IFN- γ , IL-5 ELISPOT

- All COVID-19 vaccine developers are invited to apply to use the network for preclinical samples up to samples from clinical Phase 2a studies

Statistical approaches for assessment of immune CoPs

Dr Peter Gilbert, Fred Hutch, presented an overview of the OWS statistical analysis plan and approach in light of recent results of high short-term efficacy from interim analyses.

Summary points included:

- Standardization of labs/assays/Statistical Analysis Plans is needed for interpreting results across Phase 3 trials and for meta-analysis.
- Phase 3 trials need to collect baseline prognostic factors as correlates of risk and CoPs analyses should adjust for potential confounders.
- Nonparametric correlates of risk analyses that integrate machine learning provide robust answers (e.g. threshold searching).
- A synthesis of multiple types of CoPs analyses, with distinct interpretable outputs, can provide a more complete understanding of CoPs.
- CoPs analyses need sensitivity analyses to understand robustness to departures from causal assumptions.
- Meta-analysis of CoPs evaluation will be needed.
- There is an opportunity for an open process for immune correlates assessment for the global community of biostatisticians.
- It is possible to learn something useful about correlates of risk/protection with only 15 breakthrough vaccine cases; however greater numbers are needed to achieve convincing precision.
 - Over 25-50 vaccine breakthrough cases are projected across Pfizer and Moderna trials over the next 2-3 months.
 - If placebo recipients are crossed over to the vaccine arm, they can be followed to capture additional cases.
- Active comparator arm trials pre- and post-approval would provide data for additional vaccine breakthrough cases.

A panel discussion included the following key points:

- Prof Kathy Neuzil, Co-Principal Investigator in Vaccines for COVID-19 Prevention Trials Network, emphasized:
 - Results from the first two efficacy trials indicate these vaccines are highly efficacious against non-severe disease and appear to be highly efficacious with a smaller sample against severe disease.
 - The timing of the results suggests potential protection with one dose or at least very soon after the second dose.
 - Both protocols included multiple blood draws, although not at the same time points. These resources (i.e. blood) from Phase 3 are important and developers planning new trials are encouraged to include multiple blood draws in their protocols for potential correlates analyses.
 - The window for placebo recipients, particularly in high risk groups in certain locales, is narrowing and needs to be discussed and carefully considered.

- Dr Ana Maria Henao-Restrepo, Medical Officer at WHO, highlighted the following points:
 - A workshop took place at WHO on November 6th about next steps for COVID-19 vaccines. Three clear messages emerged:
 - It is important to continue to acquire randomized placebo-controlled data and it is ethically acceptable to not unblind the placebos.
 - Despite recent positive results, more vaccines are needed to reach the global population. Thus, placebo-controlled trials should continue while non-inferiority trials will be challenging and difficult.
 - Longer term information on the duration of protection and on the safety of these vaccines are required.
 - A validated immune CoP may provide important insights regarding the new vaccines but there are two challenges:
 - The Pfizer and Moderna vaccines have very high efficacy, thus more individuals need to be vaccinated to get enough breakthrough cases to be confident about this correlation.
 - It is likely that CoPs are vaccine or platform specific, and generalisability to all platforms remains a challenge.
 - Long-term evaluation is critical as kinetics of potential correlates may change over time.
 - Despite recent positive results, it remains critical to continue to collect data on long term duration of protection and safety from these vaccines.

- Dr Jeff Roberts, Food and Drugs Administration, noted:
 - The importance of maintaining the blind in placebo-controlled trials was reiterated.
 - Global interaction is required to discuss collection of data types to facilitate bridging efficacy across populations and potentially across platforms.
 - Most regulatory authorities have some version of a conditional approval, the FDA's being the accelerated approval. It is however important to think about how to get additional field efficacy data to fill the gaps.

- Dr Marco Cavaleri, EMA, reported:
 - It is important to acquire longer term data from these trials. Efforts from CEPI and OWS to achieve a common platform for antibody testing, particularly neutralising antibodies, will be helpful.
 - Manufacturers in the most advanced phase of vaccine development should ensure efforts around CoPs is done in the fastest way possible.
 - Validated CoPs following rigorous biostatistical approaches are appreciated by regulators. However, often regulators make decisions using new unvalidated markers. Thus, it is important to understand how new markers can be used in a way that would still allow conclusions to be drawn about a vaccine's level of protection.
 - Comparison of markers of protection will likely have to be done across a certain type of platform technology as the extent to which extrapolation from one platform to another can be done remains unknown.
 - How to conduct an efficacy study in the paediatric population and which immune marker strategy to use should be considered.

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.
- The Clinical Dev & Ops SWAT Team plans to host two additional workshops in December:
 - December 16: Maternal immunization
 - December 17, TBC: Pre-/post-licensure assessments of infection and transmission
- The Enabling Sciences SWAT Team will continue to develop and make available tools for the whole vaccine development community. Developers are encouraged to use WHO International Standards, available at NIBSC, as well as the CEPI Centralised Laboratory Network to make results comparable across programmes.
- Resources will be shared at the following website (<https://epi.tghn.org/covax-overview/>) and a workshop report will be distributed.