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

Workshop Report

Workshop on *"Emerging Challenges to the Development of COVID-19 Vaccines"* organised by the COVAX Clinical Development & Operations SWAT Team

January 28th, 2021

Meeting report prepared by
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Executive summary

On 28th January 2021, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on "*Emerging Challenges to the Development of COVID-19 Vaccines.*" The main aims were to discuss developer needs and propose solutions for the progression of "Wave 2" vaccines towards emergency use authorisation (EUA)/licensure in the setting of the introduction and limited availability of new vaccines, to review recently emerging data on severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) variants to better understand the potential relevance for existing vaccines, and to review research opportunities and data gaps based on immunological principles and previous vaccine experience to understand how to better use available vaccines.

The first part of the workshop focused on the path to approval of additional COVID-19 vaccines.

Key points included:
- Multiple sources of data will contribute to identification of a correlate of protection, including data from Phase 3 efficacy studies, natural history studies including re-infection studies, and passive immunisation (human and animal studies), and early evidence supports the relationship between neutralizing antibodies and protection.
- Sponsors and owners of primary data from efficacy studies are encouraged to share information on breakthrough cases and correlates analyses as soon as possible. The World Health Organization (WHO) International Standard should be used for respective analyses.
- Placebo-controlled trials can still be performed ethically when an effective vaccine exists but requires careful justification and communication with relevant regulatory and ethical bodies.
- Various paths to licensure are still available including Phase 3 trials assessing superiority of clinical efficacy versus a partially effective vaccine with disease endpoint, non-inferiority with disease endpoint, and immuno-bridging when justified and supported with confirmatory efficacy/effectiveness evaluations.
- Post-introduction studies for COVID-19 vaccines are needed, and a best practice guidance document on evaluating COVID-19 vaccine effectiveness is being prepared by WHO and will be available on their website in February 2021.
- The increasing complexity of conducting placebo-controlled trials was acknowledged. Developers may favour conducting a comparative study; however, the selection of comparator will be challenging.
- There are promising signs of an immunological correlate of protection based on humoral immune response; a correlate of protection based on cell-mediated immunity is more difficult to achieve based on practical complexities of obtaining the correct samples linked to efficacy readouts.
- The strength of the immune data package submitted for the original EUA or conditional approval will determine the extent of post-marketing commitments to provide confirmation of that vaccine effectiveness.

The second part of the workshop focused on clinical development gaps, specifically optimising vaccination schedules for currently available COVID-19 vaccines.

Key points included:
- The United Kingdom (UK) variant (B1.1.7) was only modestly more resistant to neutralisation by convalescent plasma (~3 fold) and mRNA vaccine induced immune responses (~2 fold), whereas the South African variant (N501Y.V2) was >10-30 fold and ~6.5-8.6 fold more resistant to neutralisation by convalescent plasma and sera from mRNA vaccines, respectively.

- Heterologous prime-boost regimen does not always improve the immune response. The importance of selecting the right vaccine for priming was highlighted. The type of vaccine used for booster dose influences the quality of the immune response.
- Increasing the interval between first and second dose may favour a broader repertoire and increase affinity of antibodies but may require an interval of months rather than weeks.
- Future studies will have to assess the immune response in previously infected individuals. Variant adapted vaccines given after previous immunisation with original vaccines may broaden antibody repertoire further. Antigenic sin needs to be considered.
- The Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) study is commencing in the UK in February 2021 and aims to assist flexibility in vaccine delivery. The primary outcome is non-inferiority of immunogenicity of heterologous with homologous prime/boost schedules administered at four-week intervals. Prolonged intervals of 12 weeks will also be assessed. The two vaccines to be included are the AstraZeneca/Oxford and Pfizer/BioNTech vaccines, with scope to add additional vaccines as they are approved.
- It is critical to further our understanding of potential correlates of protection or immune responses which could be linked to protection in order to facilitate the interpretation of data.
- The proposed Com-COV study is important to assess immune responses across different platforms using a heterologous strategy; however, discussions will be required about whether this will suffice for a claim for use for any of the vaccines. Knowledge about correlates of protection will be important. Animal models could provide supporting data as could effectiveness studies in the field. As confidence in the use of immune markers increases, regulatory agencies may be more willing to consider granting approval on that basis, with the collection of effectiveness data post-approval.
- It is important to acquire extra samples to assess as broad an array of immune markers as possible, including cell-mediated responses, as it is not known what response is important for protection.
- The Coalition for Epidemic Preparedness Innovations (CEPI) has released a Call for Proposals (CfP) to support clinical trials / trial amendments addressing significant gaps in clinical development and to expand access to COVID-19 vaccines.

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

Agenda

Time (CET)	January 28, 2021	Speaker(s)
15:00 – 15:10	**Welcome & Meeting Objectives**	**Jakob Cramer**, CEPI
15:10-15:15	**Part 1: Path to approval of additional Covid-19 vaccines** *Study Design Considerations for Advanced Development*	**Peter Dull, BMGF**
15:15-15:35	Status of EUA/Licensure and vaccine use globally and key updates from previous workshops, including correlates of protection	Peter Dull, BMGF
15:35-15:45	The ethics of placebo-controlled COVID-19 efficacy studies when vaccines are available	Joe Millum, NIH
15:45-16:05	Placebo-controlled efficacy studies: Possibilities and Challenges *Alternative trial designs based on clinical endpoints* *Non-inferiority assessment based on immunogenicity*	Alan Fix, PATH & Dean Follmann, NIH
16:05-16:15	Phase 4 clinical studies: post authorization study designs to support accelerated or conditional approvals	Daniel Feikin, WHO
16:15-16:45	**Panel Discussion: Practical paths to approval of vaccines still in development** *Speakers from Part I + Invited guests* • *Ralf Clemens, GRID* • *Adam Hacker, CEPI* • *Anh Wartel, International Vaccine Institute (IVI)*	Moderated by: Peter Dull
16:45-16:50	**Break**	
16:50-17:00	**Part 2: Clinical development gaps - optimizing vaccination schedules of currently available Covid-19 vaccines to** *1) address delivery barriers* *2) optimize durability of protection* *3) improve breadth of protection against new variants*	Jakob Cramer
17:00-17:15	Post-infection and vaccine-induced immune reponses against SARS-CoV-2: summary of impact of new variants	Shabir Madhi, University of the Witwatersrand
17:15-17:30	Heterologous prime-boost, prolonged dosing interval: Immunologic considerations for improving the immune response	Arnaud Didierlaurent, University of Geneva, Switzerland
17:30-17:45	Comparing COVID-19 Vaccine Schedule Combinations (com-COV)	Matthew Snape, University of Oxford
17:45-18:15	**Panel Discussion: Optimizing vaccine impact** *Speakers from Part II + Invited Guests* • *Phil Krause, US FDA* • *Marco Cavaleri, European Medicines Agency* • *Andrew Pollard, University of Oxford*	Moderated by: Jakob Cramer
18:15-18:25	Expanding access to vaccine / filling-in clinical development gaps: CEPI new Call For Proposals (CFP) on clinical trials	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 to the workshop.

The workshop aimed to address emerging challenges in COVID-19 vaccine development and was divided into two sections, increasing vaccine availability and improving the use of available vaccines. Specific workshop objectives included:
- To discuss developer needs and propose solutions for the progression of "Wave 2" vaccines towards EUA/licensure in the setting of the introduction and limited availability of new vaccines;
- To review recently emerging data on SARS CoV-2 variants to better understand the potential relevance for existing vaccines;
- To review research opportunities and data gaps based on immunological principles and previous vaccine experience to understand how to better use available vaccines.

Part 1: Path to approval of additional COVID-19 vaccines

Status of EUA/Licensure and vaccine use globally and key updates from previous workshops, including correlates of protection

Dr Peter Dull provided an update from previous COVAX workshops, including correlates of protection, and summarised the status of EUA/Licensure and vaccine use globally.

Key points included:
- Multiple sources of data will contribute to identification of a correlate of protection, including data from Phase 3 efficacy studies, natural history studies (i.e., longitudinal reinfection studies), and passive immunisation in both humans and animals.
- Early evidence supports the existence of a serological correlate of protection:
    - Increasing neutralisation titres relatively to convalescent sera across vaccines from Phase 1/2 studies suggest a positive relationship to increasing Phase 3 efficacy and a modest threshold for protection across platforms with the non-variant strains.
    - Neutralising antibodies from prior infection protect against infection as evident in a ship outbreak.
    - Adoptive IgG transfer protects macaques from challenge with evidence of a threshold effect.
- Sponsors and owners of primary data from Phase 3 efficacy studies are encouraged to share information on breakthrough cases and correlates analyses as soon as possible, using the WHO International Standard.
- United States Food and Drug Administration (US FDA) guidance states that an accelerated approval of a COVID-19 vaccine may be considered if vaccine immune responses are "reasonably likely to predict protection" against COVID-19; however, companies are still required to conduct studies to confirm the anticipated clinical benefit.
- A statistical analysis plan has been made available on how correlates analyses may be conducted (https://figshare.com/articles/online_resource/CoVPN_OWS_COVID19_Vaccine_Effic acy_Trial_Immune_Correlates_SAP/13198595).
- The pipeline of COVID-19 vaccines is robust, with multiple products having received EUA and have the potential to contribute to correlates analyses.
- Vaccine introductions have started, and countries are strategically rolling out limited supply of approved products to high-risk populations.

- Resources for future Phase 3 site selection are provided by COVAX-supported clinical sites and dashboard (https://epi.tghn.org/covax-overview/clinical/) as vaccine rollout advances.

The ethics of placebo-controlled COVID-19 efficacy studies when vaccines are available

Dr Joe Millum, Bioethicist at the National Institute of Health, provided an insight into the ethics of placebo-controlled COVID-19 efficacy studies when vaccines are available.

Key points included:
- Placebo-controlled trials are sometimes ethical when an effective vaccine exists.
- Providing placebo instead of effective vaccine as a control requires justification.
- Any risk imposed by withholding an effective vaccine must be minimized, not excessive, and justified by the social value of using placebo rather than an alternative.

Placebo-controlled efficacy studies: possibilities and challenges

Dr Alan Fix, Deputy Director of the Vaccine Clinical Team at the Center for Vaccine Innovation and Access PATH, and Dr Dean Follmann, Assistant Director of Biostatistics at the National Institute of Allergy and Infectious Diseases, discussed alternative trial designs based on clinical endpoints and non-inferiority assessment based on immunogenicity.

Summary points included:
- Various paths to licensure are still available including superiority versus a partially effective vaccine with disease endpoint, non-inferiority trials with disease endpoint, and immuno-bridging.
- Trials using clinical endpoints are more difficult without placebo groups as case rates are lower implying longer and bigger trials.
- Non-inferiority designs rely on applying an estimated vaccine efficacy for a comparator to a new setting. A conservative choice of margin and formulation of the non-inferiority trial is important.
- Immuno-bridging based on a vetted correlate of protection is appealing, promising, and the path to licensure it is hoped will work.
    o Such analyses are planned for Operation Warp Speed vaccine trials.
    o The successful Eli Lily trial demonstrated that monoclonal antibody prevents acquisition of disease, providing support that antibody is reasonably likely to predict vaccine efficacy.
    o Animal studies can be conducted with down-dosing to demonstrate the protective role of antibodies.
    o Aggregated evidence can be used to support use of antibody for licensure.

Phase 4 clinical studies: post-authorization study designs to support accelerated or conditional approvals

Dr Daniel Feikin, Department of Immunizations, Vaccines, and Biologics at the World Health Organization, discussed post-authorisation study designs to support accelerated or conditional approvals.

Key points included:
- Post-introduction studies for COVID-19 vaccines are needed for the following reasons:

- o Vaccine efficacy in randomised controlled trials differs from effectiveness in the real world.
  - o If EUL/EUA is granted based on interim results, vaccines are rolled out before all study outcomes have been assessed (e.g., efficacy in risk groups, against infection). This is the case for COVID-19 vaccines at the present time.
  - o If a vaccine is approved conditionally based on immunogenicity, post-introduction confirmation of effectiveness is needed.
- COVID-19 post-introduction studies are challenging due to the rapidly changing epidemiology, rapid rollout of vaccines in target populations, timely results required for policy and regulatory processes, and inherent biases associated with observational studies.
- Methods for post-introduction studies include cohort studies (either prospectively over time or retrospectively via a large electronic database), case-control studies, screening method, regression discontinuity design, and "randomised" introductions.
- Each type of post-introduction study has its advantages and disadvantages.
- A best practice guidance document on evaluating COVID-19 vaccine effectiveness is being prepared by WHO and will be available on their website next month.
- WHO is assessing the current landscape of post-introduction studies to help policymakers understand where evidence is lacking and to enable developers to collaborate with groups already conducting these types of studies. Developers planning a vaccine effectiveness study are encouraged to contact WHO (patelm@who.int; feikind@who.int).

Panel Discussion: Practical paths to approval of vaccines still in development

A panel discussion included the following key points:

- Dr Ralf Clemens, Principal and Founder GRID Consulting –
  - o Time is of utmost importance in the clinical development of second or third wave COVID-19 vaccines.
  - o Three critical elements to consider in the development of these second or third wave vaccines include ethics, science, and clinical operations.
  - o Ethical considerations include:
    - ▪ The rights of a participant override societal rights or societal benefits.
    - ▪ It is only ethical to perform controlled trials in groups without access to a licensed vaccine and who will likely not get access soon.
    - ▪ Individuals who get access to a licensed vaccine during the trial (i.e., a vaccine is rolled out in their risk group) will need to be informed and thus have a right to exit the trial. This is true for both vaccine candidate and control recipients. Loss of a large number of individuals may introduce bias, and thus trial data will need to be censored at that point in time.
  - o Scientific considerations include:
    - ▪ A comparative trial could perhaps be executed and accepted by regulators if the trial is calibrated to a margin which results in a 50% efficacy for the new vaccine (just as the original threshold for a placebo-controlled study was justified). WHO and various National Regulatory Authorities (NRAs) have set as limits for vaccine licensure a point estimate of 50% and a lower bound of 30%. If a comparative trial against a licensed and available vaccine would be required, can that second wave vaccine be licensed if inferior to the comparator but exceeding the WHO and NRA criteria?
  - o Clinical operations considerations include:
    - ▪ Comparative trials are possible but access to a comparator may be challenging, including liability aspects

- - Performing studies in countries with vaccination rollout programs will become increasingly difficult. Different studies may need to be considered for the future, but site capability, experience, and other operational factors need to be assessed.
    - A stepped-wedge trial pre-licensure may be considered in a country with a small population if the company has data on protection in non-human primates, ideally passive transfer, and Phase 1 data which show high neutralising antibodies .

- Dr Adam Hacker, Head of Global Regulatory Affairs CEPI –
  - The increasing complexity of conducting placebo-controlled trials was acknowledged (i.e., heterogeneous mix of population who could be eligible for vaccine, different vaccines with varying efficacies received by different people within the population) and this will be even more complex later this year when some developers are planning to initiate their pivotal study.
  - Developers may favour conducting a comparative study; however, the selection of comparator will be challenging.
  - In the absence of a firm correlate of protection the validity of comparisons is still questionable; however, this will be important to assess.
  - Developers are encouraged to evaluate breakthrough cases and use standardised assays going forward.
  - The lack of standardisation is problematic for developers particularly with the introduction of variant strains.
  - Standardised assays will enable more robust cross comparisons particularly as the patient population will be very heterogeneous going forward.

- Dr Anh Wartel - Associate Director General, Epidemiology, Public Health, Impact, and Clinical Development at the International Vaccine Institute -
  - The achievement in COVID-19 vaccine development is remarkable; however, knowledge gaps still remain.
  - There are promising signs of an immunological correlate of protection; however, a cellular correlate of protection is more difficult to achieve.
  - It will be important to assess vaccine efficacy in other vulnerable populations such as pregnant women. This could be achieved by immuno-bridging if a correlate is demonstrated between neutralising activity and protection.
  - Developers may expect recommendations from the US FDA, EMA, or WHO on how to progress with second or third generation vaccines for COVID-19.
  - There are still opportunities to conduct placebo-controlled trials in low- and middle-income countries to generate additional data.

- *What efforts are ongoing to incorporate T cells into correlates of protection analyses?*
  - The incorporation of T cells into correlates analyses is a challenge in terms of logistics (i.e., how T cells might be assessed), whether peripheral blood is the correct sample to use, and what measurement could be critical to protection.
  - It has been important from a regulatory perspective to demonstrate a Th1 biased immune response, which more likely protects against enhanced disease. Thus, regulators request evidence on intracellular cytokine staining and developers have included T cell assays in their development programs. It remains unknown; however, how this relates to a correlate of protection and what T cell parameter in peripheral blood should be measured that relates to protection.
  - T cell responses, including gamma interferon ELISPOT, intracellular cytokine staining, or detailed analyses of the different subsets of T cells present, can be measured in COVID-19, and data from these are needed before a potential T cell correlate can be assessed.
  - T cell assays at scale (tens of thousands) are difficult to conduct and likely impossible in the midst of a pandemic, whereas collecting serum for antibody

studies is more straightforward. Studies using innovative methods, including adaptive technologies which use a DNA-based approach, are ongoing. These technologies can be applied to the blood clot when serum is taken or plasma can be stored for later DNA extraction, avoiding the complexities of storing cells.

- o CD4 and CD8 T cells likely play a critical role in controlling the virus early in infection, thus vaccines which induce these responses may protect against more severe disease. As demonstrated in animal studies, antibodies are likely required to prevent infection.
- o Further work is needed to assess T cell responses, particularly with the emergence of new variants.

- *What data package, in terms of characterising the immune response post-EUA approval, would provide adequate reassurance to regulators that a non-inferior immune response could be conducted within a platform and across platforms?*
  - o The strength of the immune data package submitted for the original EUA or conditional approval will determine the extent of post-marketing commitments to provide confirmation of that vaccine effectiveness.

- *A possible scenario was presented as follows: The AstraZeneca Serum Institute vaccine is granted EUA in India and subsequently achieves EUA in several other countries over the coming weeks and months. An immunological non-inferiority study is proposed and performed versus that product with commitment to enrol many thousands of subjects, such that clinical non-inferiority would eventually be generated to that product. Immunological support for an early EUA would be generated from that product, so the vaccine could be used with the commitment that a large clinical non-inferiority trial would run to its full fruition. If clinical non-inferiority is not achieved, the EUA would be withdrawn. In this setting, is this risk-based immunological non-inferiority study followed by a clinical non-inferiority study a reasonable middle ground?*
  - o This proposal is a reasonable middle ground as the non-inferiority immunogenicity study is embedded into the safety trial.
  - o EMA requires a minimum of 3,000 exposed to the vaccine. Thus, immunogenicity data can first be generated with the procedure unblinded by the Data Safety Monitoring Board rather than the company. Safety data can continue to be generated as can efficacy data.
  - o A three-arm trial could be conducted, with a placebo or control group for the efficacy comparison to the vaccine and a comparator for immuno-bridging for the vaccine to get an early license.
  - o This may be complicated by the emergence of new variants. Any association between protection and neutralising antibodies with the original strain would still be there with variant strains but the threshold might be higher if you wanted an absolute correlate for the variant. An immunological non-inferiority study could still be conducted if you're benchmarking against demonstrated efficacy that would still be maintained.

Part 2: Clinical development gaps - optimizing vaccination schedules of currently available COVID-19 vaccines to address delivery barriers, optimise durability of protection, and improve breadth of protection against new variants

Post-infection and vaccine-induced immune responses against SARS-CoV-2: summary of impact of new variants

Professor Shabir Madhi, University of Witwatersrand South Africa, summarised current knowledge on the impact of new variants.

A summary of the main points included:
- In South Africa, early evolution has occurred of a variant with multiple mutations involving the immunodominant receptor binding domain and N-terminal domain. The emergence of this variant likely resulted from immunological pressure faced by the virus due to a high force of exposure and ongoing transmission of virus in South Africa.
- The UK variant (B1.1.7) was only modestly resistant to neutralisation by convalescent plasma (~3 fold) and mRNA vaccines (~2 fold).
- The South African variant (N501Y.V2) was >10-30 fold and ~6.5-8.6 fold more resistant to neutralisation by convalescent plasma and sera from mRNA vaccines, respectively.
- Differences in immunogenicity of vaccines designed based on the prototype virus may have differential effects on efficacy against the N501Y.V2 variant.
- Imminent vaccine efficacy readouts from South Africa for Novavax, AstraZeneca, and Janssen vaccines will provide efficacy estimates against the N501Y.V2 variant. Importantly, answers on whether past infection protects against repeat infection and COVID-19 will also be provided.

Heterologous prime-boost, prolonged dosing interval: immunologic considerations for improving the immune response

Dr Arnaud Didierlaurent, Associate Professor Translational Immunology University of Geneva, Switzerland, discussed immunological considerations in terms of heterologous prime-boost and prolonged dosing interval.

Main points included:
- Heterologous prime-boost regimen does not always improve the immune response and may decrease immunogenicity of an otherwise efficacious two dose vaccine. Thus, there is a potential risk of changing vaccine for the second dose that needs to be addressed.
- Priming is key as a good memory T follicular helper (Tfh) cell and B cell response leads to affinity maturation and results in mounting a better response at boost and a response that may be more cost neutralising. The importance of selecting the right vaccine for priming was highlighted.
- Factors associated with the quality of antibody response following the second vaccine dose include homology of sequence/conformation, antigen availability and presentation to memory B cells/Tfh, and ability to stimulate innate immunity (improved antigen presentation).
- Increasing the interval between first and second dose may favour a broader repertoire and increase affinity of antibodies but may require an interval of months rather than weeks.
- Boosting of T cells is likely to be less sensitive to mix & match although preferential T cell boosting (CD8 versus CD4 T cells for example) cannot be excluded.
- Further clinical data are needed including the quality of response after one dose across platforms which might indicate the preferred vaccine for priming, and memory response at one year with implications for revaccination. Additional data beyond the antibody level are required including affinity, breadth, B cell receptor repertoire, and Fc function with implications for response/efficacy against current and future variants.
- Variant adapted vaccines given after previous immunisation with original vaccines may broaden antibody repertoire further. Antigenic sin needs to be considered.
- The response in previously infected individuals due to pre-existing immunity also needs to be assessed (i.e., bridging studies in non-human primate animal models).

- Variant-adapted antigens may be required to further broaden antibody repertoire and cross-reactivity.

UK programme to assess a heterologous prime-boost regimen

Dr Matthew Snape, Associate Professor Paediatrics and Vaccinology University of Oxford, discussed comparing COVID-19 vaccine schedule combinations.

Key points are summarised as follows:
- The Com-COV study, funded by the UK Vaccine Task Force, is commencing in February 2021 and aims to assist flexibility in vaccine delivery.
- The two vaccines to be included in this single-blind non-inferiority randomized controlled trial include the AstraZeneca/Oxford ChAdOx1 nCOV-19 and Pfizer/BioNTech BNT162b2 vaccines. There is scope to add additional vaccines (e.g., protein/adjuvant, whole virus) as they are approved.
- The primary outcome is non-inferiority of immunogenicity of heterologous with homologous prime/boost schedules administered at four-week intervals (assessed by anti-spike IgG).
- The study population will include adults ≥50 years (as many individuals in the highest risk groups have already been vaccinated in the UK) and include ethnic minority groups and allow the inclusion of controlled mild-moderate co-morbidities.
- The immunogenicity assays to be used include the UK Vaccine Task Force preferred suppliers and will allow standardisation across multiple studies.
- Secondary outcomes include immunogenicity (for four and extended 12-week intervals), safety and reactogenicity, and further immunogenicity assays (i.e., neutralising and pseudo-neutralising antibodies). Immunogenicity, reactogenicity, and safety of COVID-19 vaccines in participants seropositive at baseline will also be assessed, and SARS-CoV2 infections (and immune response) will be characterised in participants who develop breakthrough infections during the course of the study.
- Serum and peripheral blood mononuclear cells will be stored for testing against newly emergent strains.

Panel Discussion: Optimising vaccine impact

A panel discussion included the following key points:

- Dr Phil Krause, Deputy Director at the US FDA –
    - A critical aspect is the degree to which immune responses can be used to make clinical decisions.
    - Key data on vaccine efficacy is thus far based on clinical endpoint data. It is also important to obtain immune response information; however, the exact immune response assays carried out may or may not correlate to clinical outcome (i.e., lower immune responses with the heterologous boost may not mean lower vaccine-induced protection).
    - It is important to consider how immune response data can be used more widely. Using immune response data to compare results from a single vaccine is more robust that comparisons with other vaccines or with a heterologous boost.
    - It is essential that as much information as possible is obtained regarding vaccine breakthroughs from studies already conducted. A greater understanding of

vaccine breakthroughs will lead to more confidence in real use decisions based on these data.

- Dr Marco Cavaleri, Head of Biological Health Threats and Vaccines Strategy at the European Medicines Agency –
    - o It is critical to further our understanding of potential correlates of protection or immune responses which could be linked to protection in order to facilitate the interpretation of data.
    - o The proposed Com-COV study will provide important information, especially in terms of safety, regarding what happens when different vaccines and technologies are mixed. However, data interpretation may be challenging in the absence of a correlate of protection. Animal models may provide useful information, as could heterologous boosting schemes from other viruses.
    - o A heterologous approach with different vaccines is already being considered by some governments and public authorities due to supply issues; however, the safety of this approach is as yet unknown, and caution is urged until pilot data are available.

- Prof Andrew Pollard, University of Oxford -
    - o The mix and match regime is not anticipated to be a concern on immunological grounds. Current vaccines against COVID-19 (viral vectors, RNA vaccines, protein vaccines) are essentially all dressed up protein vaccines which result in expression of spike protein and subsequent immune responses generated against that protein. Thus, biologically it is expected that booster responses would be evident using a schedule where one vaccine type is boosted by a different vaccine type. Studies are required to ascertain the relative boost ability of different combinations.
    - o There is no anticipated safety issue with a mix and match regime given good safety data are independently available for all authorised vaccines and the vaccines all elicit a response to spike protein.
    - o Further studies and data are required to support a mix and match regime, especially from a regulatory perspective.

- *Will neutralising assays to pseudovirus or wild type virus as a readout also be included in the Com-COV study?*
    - o In the Com-COV study, neutralizing antibodies, antibodies based on pseudovirus, and T cell readouts will be available for every time point and for all vaccine combinations.
    - o The decision to use ELISA for the primary endpoint was pragmatic in order to generate data rapidly to inform the UK schedule and to account for any changes with new variants.

- *Will regulators require evidence on cross-neutralization against new variants?*
    - It may be too early to say exactly what regulators will require.
    - Although all current COVID-19 vaccines involve proteins on one level or another, the three vaccine types induce type 1 interferons in somewhat different ways and interact with the innate immune system very differently. Thus, they are likely to have different efficacies, and the dosing interval might affect vaccines differently.
    - It is important to gather data to address these issues and to ensure the data are as robust as can be. Samples that already exist could be used for these purposes.

- *Thousands of people have received licensed vaccines, many of them in clinical trials, with crossover occurring as individuals withdraw from efficacy studies and are*

vaccinated. Are there opportunities where some of these opportunistic immune readouts can be identified to assess these questions as new strains emerge?

- o In the UK, rollout of the Pfizer vaccine started in early December. Many participants in the Oxford/AstraZeneca trial were healthcare workers, the group targeted for vaccination at the start of the rollout. Thus, many trial participants were unblinded and received the Pfizer vaccine if they were found to be in the control group. A small proportion of trial participants who were unblinded had received a single dose of viral vector. In this instance, the UK Department of Health recommended another dose of the viral vector vaccine or a dose of the Pfizer vaccine as it was the only licensed product. This happened extremely rapidly as a result of being in a pandemic situation and outside the control of the trial team, hence appropriate baseline and follow-up samples may not have been collected. Thus, data are available; however, not be structured in a way that will provide absolute confidence in answering the question.

- *There is a difference between interchangeability of vaccines and a specific heterologous prime boost regimen. What additional data are required to establish a heterologous prime boost regimen? What would be necessary to back this up with the label from the regulator's perspective?*
  - o The proposed Com-COV study is important to assess immune responses across different platforms using a heterologous strategy; however, discussions will be required about whether this will suffice for a claim for use for any of the vaccines. Knowledge about correlates of protection will be important. Animal models could provide supporting data as could effectiveness studies in the field. As confidence in the use of immune markers increases, regulatory agencies may be more willing to consider granting approval on that basis, with the collection of effectiveness data post-approval.
  - o It is important to acquire extra samples to assess as broad an array of immune markers as possible, including cell-mediated responses, as it is not known what response is important for protection.
  - o Regulators encourage the collection of as robust data as possible to address these issues.

- *What has been the past experiences of regulators with heterologous schedules - have developers approached regulators or has it been driven by policymakers in governments?*
  - o Regulators have generally been approached by policymakers in government rather than developers with regards to heterologous schedules.
  - o There are some cases where it is clear heterologous boosting will not work due to differences in antigens (i.e., meningococcal B). There are enough similarities in COVID-19 vaccine antigens for heterologous boosting to be effective; however, robust data are required to support this.
  - o A heterologous boost vaccine was approved by EMA in 2020 for Ebola. This was an important experience for EMA, who is very open to discuss what data might be required to support such an approval.
  - o The importance of selecting the right vaccine for priming was highlighted.

Expanding access to vaccine / filling-in clinical development gaps: CEPI new Call for Proposals on clinical trials

Dr Jakob Cramer, Head of Clinical Development at CEPI, highlighted a new CEPI CfP to support clinical trials / trial amendments addressing significant gaps in clinical development and to expand access to COVID-19 vaccines.

The scope is to:
- Support new/separate trial(s) or amendment(s) (pre- or post-licensure)
- Vaccines must have entered the clinical development phase.
- A Clinical Development Plan (CDP) and pathway to EUA or similar must be available.
- Evidence generated with the funded trial(s) must generate new evidence/investigate new objectives considered relevant to expand access to vaccines or fill-in research gaps.
- This CfP is not intended to support clinical trials already included in the core CDP towards EUA or similar (e.g., dose selection, general vaccine efficacy).
- Funded clinical trials should commence within six months of contracting (latest).
- Applicants from, and conduct of trials in, low- and middle-income countries are particularly encouraged.

Applications are on a rolling call basis and are open from January 28th to May 28th. Further information can be obtained at https://cepi.net/get_involved/cfps/ or by contacting cfp@cepi.net.

Wrap-up and next steps

Dr Jakob Cramer thanked attendees for their participation in the workshop and outlined the next steps as follows:
- Resources will continue to be shared at the following website: https://epi.tghn.org/covax-overview/clinical/
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines.
- Workshop attendees are invited to join post-workshop discussions on the COVAX hub by:
    - Registering (signing up) on the hub
    - Joining the group 'COVAX Clinical Development SWAT TEAM Workshops'
There are several questions already in the forum. Please reply to those or create a new thread.