

COVAX



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

Workshop Report

Workshop on “*Pre- and Post-Licensure Assessments of COVID-19 Vaccine Efficacy/Effectiveness Against Infection & Transmission*” co-organised by the COVAX Clinical Development & Operations SWAT Team and the COVAX Post Introduction Evaluations Workstream

December 17th, 2020

Meeting report prepared by
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Executive summary

On 17th December 2020, the COVAX Clinical Development & Operations SWAT Team and Post-introduction Evaluations Workstream hosted a workshop on “*Pre- and Post-Licensure Assessments of COVID-19 Vaccine Efficacy Against Infection & Transmission.*” The main aim was to discuss available evidence concerning infection and transmission from ongoing Phase 3 efficacy trials, highlight remaining gaps in the understanding of COVID-19 infection and transmission following vaccination, and identify optimal study designs to collect effectiveness data once an emergency use authorisation (EUA)/licensure is achieved.

The first part of the workshop provided an update on correlates of protection following the workshop held on November 19th.

Key points included:

- The design approach to COVID-19 Phase 3 efficacy trials will need to shift as vaccines receive EUA/licensure and become increasingly available.
- Evidence of high efficacy from several vaccines suggests the modest neutralization titres demonstrated in phase 1/2 clinical studies may be sufficient for short-term protection regardless of the vaccine platform.
- The onset of efficacy following the first dose of mRNA vaccines suggests the threshold, if neutralizing antibodies are the primary driver, may be near the assay lower limit of quantification.
- Non-human primate (NPH) models and natural infection studies also suggest that the threshold of protection is low for neutralizing antibody titres.
- Three new WHO International reference preparations have been established, and developers are strongly encouraged to use these standards and to express neutralizing titres and binding antibody titres in international units to better interpret clinical trial results and to facilitate establishment of correlates of protection.

The second part of the workshop focused on lessons learnt related to prevention of asymptomatic virus infection and transmission from pre-licensure trials.

Key points included:

- Transmission risk is highest on the day of symptom onset and the duration of infectiousness is about one week in most patients.
- Cell culture provides ~20% residual virus isolation success, which translates into about 10^6 - 10^7 copies of RNA per mL of swab suspension. This same limit of detection is the limit of detection of most antigen point of care tests (Ag-POCT).
- Sensitivity of Ag-POCT is determined by viral load. Therefore, Ag-POCT may be a good indicator for infectivity in clinical trials (less complex and less costly compared to quantitative PCR).
- Spike glycoprotein (GP) antibody levels elicited upon natural SARS-CoV2 infection correlate with virus neutralization and remain stable over months.
- Antibodies against N-protein circulate for less time and may be more cross-reactive with other coronaviruses compared to Spike GP antibodies.
- The infectious dose appears to be low in some animal models.
- Transmission has been demonstrated by direct contact in several animal models and by indirect contact/airborne transmission in ferrets. Transmission from vaccinated animals has not been directly assessed.
- Most Phase 2/3 trials include seroconversion against N-protein as a secondary endpoint, but seroconversion definitions and time points differ. There are limited data available on vaccine efficacy against infection and results so far are inconclusive.

The third part of the workshop focused on additional approaches to evaluating vaccine effectiveness against infection/transmission, including post-licensure studies.

Key points included:

- A vaccine which gives 90% efficacy against disease can still result in high population mortality in the absence of efficacy against transmission or non-pharmaceutical interventions (NPIs).
- Even if vaccines offer high efficacy against infection/transmission, high coverage in the general population will be necessary to stop transmission.
- Vaccinating older individuals first to reduce mortality is optimal when vaccine supplies are low, or high coverage of the wider population will take many months.
- Mass immunization programs leave epidemiological signatures in surveillance data in terms of the impact of vaccines on interrupting transmission, and modelling is an essential tool for interpreting the signature.
- Household studies, longitudinal prospective community-based cohort studies and outbreak investigations can yield important insights on impact of vaccines on transmission.
- Surveillance, microbiological and immunological data are essential for understanding why and how vaccines succeed or fail to prevent transmission, and appropriate specimen collection is needed to understand the model of success or failure.
- Studies to measure the impact of vaccination on transmission can be in the form of randomised trials or observational studies at the individual level or utilize larger-scale population level studies.
- There may be sufficient power to conduct family transmission studies in the context of ongoing Phase 3 studies which enrol ~30,000 individuals.
- Infection and infectiousness can also be studied pre-licensure in a Phase 2b (including endpoints like asymptomatic infection, seroconversion against antigens not included in the vaccine, and/or viral shedding, secondary transmission) trial rather than deferring to post-licensure transmission studies in Phase 4.

The slideset from the meeting can be found here:

https://media.tghn.org/medialibrary/2020/12/20201217_COVAX_Covid19_Transmission_Workshop_Presentation_Materials_FINAL.for.distribution.pdf

Agenda

Time (CET)	December 17, 2020	Speaker(s)
15:00 – 15:10	Welcome & Meeting Objectives	Jakob Cramer, CEPI
	Part 1: correlates of protection update	
15:10 – 15:15	<i>Moderator: Peter Dull</i>	
15:15 – 15:40	Correlates of Protection Update <i>Recent study results of relevance including new efficacy results</i> <i>Update on International Standard from WHO ECBS meeting and guidance for use</i>	Peter Dull, BMGF Ivana Knezevic, WHO
	Part 2: What can we learn from pre-licensure trials?	
15:40 – 15:45	<i>Moderator: Jakob Cramer</i>	
15:45 – 16:00	SARS-CoV-2 natural course of infection, viral shedding, virus detection and quantification using PCR and rapid diagnostic tests: Current knowledge and gaps <i>Summarize current knowledge on SARS-CoV-2 natural infection; review transmission parameters like viral shedding, risk factors and age groups; discuss infection versus transmission; sensitivity / specificity for diagnostic tests, correlation of viral RNA on a test with infectivity</i>	Christian Drosten, Charité, Berlin
16:00 – 16:15	Assessment of non-vaccine antibodies post natural infection as tool to evaluate asymptomatic infection <i>Review candidate antigens targeted by immunoassays for SARS-CoV-2 and seasonal coronaviruses</i>	Viviana Simon, Icahn School of Medicine, NY
16:15 – 16:30	Pre-clinical animal studies: evidence from different vaccine platform technologies on infection / duration of viral shedding <i>Review of animal models for infection and respective read-outs, overview on evidence from different vaccine platform technologies including re-infection and passive transfer studies</i>	William Dowling, CEPI
16:30 – 16:40	Planned assessments of infection in Phase 2/3 trials <i>Overview of available information from ongoing and planned efficacy studies</i>	Amol Chaudhari, CEPI
16:40 – 16:50	Experience from using weekly PCRs to detect asymptomatic infections <i>Lessons learnt from the Oxford ChAdOx1 Ph2/3 trial in the UK</i>	Andrew Pollard, University of Oxford Merryn Voysey, University of Oxford

Part 3: Additional approaches, evidence / post-licensure studies		
16:50 – 16:55	<i>Moderator: Daniel Feikin</i>	
16:55 – 17:10	Modelling: impact of vaccine efficacy against disease versus transmission on public health and pandemic curves	Neil Ferguson, Imperial College, London
17:10 – 17:25	Observational studies: what can we learn from other vaccines? <i>Post-licensure trial designs assessing infection, seroconversion, infectiousness, transmission; e.g., pertussis and measles</i>	Natasha Crowcroft, WHO
17:25 – 17:35	Statistical approaches to studying transmission <i>Design and analysis of studies to measure the impact of vaccination on transmission on both the individual and population level</i>	Ira Longini, University of Florida / WHO
17:35 – 17:45	Household transmission studies <i>Approach to studying household transmissions within a Phase 3 efficacy study</i>	Adam Finn, University of Bristol
17:45 – 17:55	Phase 2b trial design to assess vaccine efficacy against infection, viral load, and secondary transmission <i>A study to evaluate individual-level vaccine effects on infectiousness</i>	Holly Janes, Operation Warp Speed
17:55 – 18:25	Panel Discussion <i>Workshop speakers and invited guests</i>	Moderated by Daniel Feikin, WHO
18:25 – 18:30	Wrap Up & Next Steps	Jakob Cramer, CEPI

Welcome and meeting objectives

Dr Jakob Cramer, Head of Clinical Development at the Coalition for Epidemic Preparedness Innovations (CEPI), welcomed participants and set the context for the workshop.

Vaccines are needed to control and eventually end this pandemic. Vaccines have demonstrated high efficacy against COVID-19 (any severity) illness based on primary endpoints, but it remains unknown if vaccines will be effective against infection and transmission.

This workshop was divided into three parts. The first part aimed to provide an update on correlates of protection following the workshop held on November 19th. The second and third parts of the workshop focused on infection and transmission and aimed to address the following questions:

- Will vaccines be effective against infection and transmission?
- Will a vaccine effective against infection also be effective against transmission?
- Will a vaccine without clear efficacy against infection still be effective against transmission?
- What do we know about sudden acute respiratory coronavirus 2 (SARS-CoV-2) infection and transmission?

Part 1: Correlates of protection update

Correlates of protection update

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, provided an update on correlates of protection following the workshop held on November 19th.

Key points included:

- The structure of Phase 3 trials will necessarily shift as vaccines receive emergency use authorisation (EUA)/licensure and become more broadly recommended and available.
 - *Early Wave 1 vaccines*: trial recruitment started before November 2020. Placebo-controlled efficacy studies conducted with positive or pending results across a number of candidate vaccines and EUA across various geographies.
 - *Late Wave 1 vaccines*: recruitment to start before the second quarter of 2021. Efficacy studies can still be conducted but enrolment should target adults in settings with no EUA or licensed vaccines or populations not recommended as priority with available vaccines.
 - *Wave 2 vaccines*: recruitment to start after the second quarter of 2021. These next-generation vaccines may be more deliverable, scalable, and cost less. Question of how to get these next-generation vaccines approved if there is no longer an option to conduct a placebo-controlled trial or if non-inferiority studies on a clinical endpoint are deemed infeasible. Correlates may become the only pathway for primary licensure.
- Correlates analyses are expected approximately two months after primary analyses in Phase 3 efficacy trials. It would be of benefit to accelerate this time frame, and the wider community are encouraged to engage in discussions of possible correlates results as soon possible after primary analyses. A statistical analysis plan has been made available on how these analyses may be conducted (https://figshare.com/articles/online_resource/CoVPN_OWS_COVID-19_Vaccine_Efficacy_Trial_Immune_Correlates_SAP/13198595).
- Multiple vaccines (Pfizer/BioNTech, Moderna, Gamaleya, Sinopharm, Oxford/ Astra Zeneca) have demonstrated efficacy against disease. Neutralization titres from the Phase

1/2 studies of these vaccines suggest the threshold of protection may be modest across platforms. The relative neutralizing titres demonstrated in Phase 1/2 studies in adults do show some reasonable relationship back to the eventual efficacy results of the Phase 3 trial.

- The onset of efficacy following the first dose of mRNA vaccines suggests the threshold, if neutralizing antibodies are the primary driver of protection, may be near the assay lower limit of quantification. Efficacy data compiled for the Food and Drugs Administration review of both Pfizer/BioNTech and Moderna vaccines suggest both products effectively protect subjects between first and second doses, when neutralization titres are still very modest.
- Non-human primate (NPH) models and natural infection studies support evidence that the threshold of protection is low for neutralizing titres.

Dr Ivana Knezevic, Group Lead of Norms and Standards for Biologicals at the World Health Organization (WHO), and Dr Giada Mattiuzzo, Senior Scientist at the National Institute for Biological Standards and Control, updated on WHO standards for COVID-19.

Summary points included:

- The main outcomes of the 71st and 72nd Expert Committee on Biological Standardization (ECBS) meetings can be found at <https://www.who.int/groups/expert-committee-on-biological-standardization>. Updated guidance for assuring quality, safety, and efficacy of plasmid DNA vaccines may be important for developers using a nucleic acid platform for vaccine development.
- At the 73rd ECBS meeting, three new WHO International reference preparations were established, including SARS-CoV-2 RNA for nucleic acid amplification (NAT)-based assay, anti-SARS-CoV-2 immunoglobulin, and anti-SARS-CoV-2 immunoglobulin panel.
- These measurement standards for COVID-19 aim to facilitate the development, validation, and assessment of molecular and antibody assays. This will facilitate the comparability of results from different assays/labs and help harmonize the evaluation of diagnostics, vaccines, and other products.
- Workshop attendees are encouraged to use these WHO International Standards and to express neutralizing titres in international units. This would help interpretation of clinical trial results and facilitate establishment of correlates of protection.
- The WHO International Standards will be available for distribution by beginning of January 2021 at www.nibsc.org.

Part 2: What can we learn from pre-licensure trials?

SARS-CoV-2 natural course of infection, viral shedding, virus detection, and quantification using PCR and rapid diagnostic tests: current knowledge and gaps

Dr Christian Drosten, Professor of Virology at Charité, Berlin, summarized current knowledge on SARS-CoV-2 natural infection, reviewed transmission parameters including viral shedding, risk factors, and age groups, and discussed infection versus transmission, sensitivity/specificity for diagnostic tests, and correlation of viral RNA on a test with infectivity.

A summary of the main points includes:

- Transmission occurs on the day of symptom onset and lasts for one week in most patients.
- Cell culture provides ~20% residual virus isolation success, which translates into about 10⁶-10⁷ copies of RNA per mL of swab suspension. This same limit of detection is the limit of detection of most antigen point of care tests (Ag-POCT).

- Sensitivity of Ag-POCT is determined by viral load. Therefore, Ag-POCT may be a good indicator for infectivity in clinical trials (less complex and less costly compared to quantitative PCR).
- Quantitative reverse transcription polymerase chain reaction (RT-PCR) can provide an assessment of infectivity.
- Adapted Robert Koch Institute (RKI) recommendations have been in place since December 2nd, 2020. Individuals are no longer presumed infectious if the viral load is $<10^6$ copies per mL and information about the disease course is available with confirmation that the patient is beyond peak viral load (i.e., not a pre symptomatic case but rather a case that has been treated in hospital). This aids discharge decision making in hospitals and frees up hospital beds, particularly intensive care beds, for other patients.

Assessment of non-vaccine antibodies post natural infection as tool to evaluate asymptomatic infection

Professor Viviana Simon, from the Icahn School of Medicine New York, reviewed candidate antigens targeted by immunoassays for SARS-CoV-2 and seasonal coronaviruses.

Main points included:

- Spike antibody levels mounted upon natural SARS-CoV2 infection correlate with virus neutralization and remain stable over months.
- Seroprevalence data generated before, during, and after the first wave of the pandemic in New York City (NYC) suggests:
 - Seroprevalence in the ‘routine care’ group, which more closely resembles the general population (20%), falls significantly below the threshold for potential community-level herd protection.
 - Approximately 1.7 million New Yorkers have been infected with SARS-CoV2, based on a population of NYC of 8.4 million.
 - The infection fatality rate is 0.97% (compared to 0.01% and 0.001% in the 2009 H1N1 pandemic)
- This seroprevalence study will continue to cover the second wave in NYC as well as the introduction of vaccines.
- In terms of serology,
 - For vaccination:
 - Relatively homogenous response; spike only responses for most vaccines (except inactivated vaccines); no mucosal secretory IgA responses (IgG and monomeric IgA maybe found in saliva); unknown duration
 - Infection
 - Heterogeneous response in general; strong anti-spike and anti-nucleoprotein antibody responses; some responses to other proteins like ORF8; mucosal secretory IgA response; potentially long-lived duration
- Antibodies against N-protein circulate for less time and may be more cross-reactive to other coronaviruses compared to Spike GP antibodies

Pre-clinical animal studies: evidence from different vaccine platform technologies on infection/duration of viral shedding

Dr William Dowling from CEPI reviewed animal models for infection and evidence from different vaccine platform technologies including re-infection and passive transfer studies.

Key points are summarised as follows:

- Mice, hamsters, ferrets, and NHPs have been used to assess vaccine efficacy. The infectious dose appears to be low in some of these models and there is protection from reinfection.
- Transmission has been demonstrated by direct contact in several models and by indirect contact/airborne transmission in ferrets.
- Transmission from vaccinated animals has not been directly assessed; however, several vaccines protect against disease in animals but do not completely protect against viral shedding in the upper respiratory tract, allowing the possibility of transmission.

Planned assessments of infection in Phase 2/3 trials

Dr Amol Chaudhari, CEPI, provided an overview of available information from ongoing and planned efficacy studies.

Key points included:

- Ongoing efficacy trials of COVID-19 vaccine candidates have included asymptomatic infection prevention as secondary or exploratory endpoints.
- Major approaches to identify asymptomatic infection include:
 - Serological - seroconversion to non-vaccine antigen (e.g., N-protein)
 - Virological – periodic RT-PCR (or other nucleic acid amplification test) samples from asymptomatic participants
 - Combination of serological and virological detection
- Definitions for N-protein seroconversion as well as scheduled assessments time points differ across COVID-19 vaccine efficacy trials.
- There are limited data available on vaccine efficacy against infection and results so far are inconclusive. More evidence is likely to be available in the coming months.
- Limited evidence on vaccine efficacy against transmission prevention may also become available from a few ongoing programs through surrogates like viral load and shedding.

Experience from using weekly PCRs to detect asymptomatic infections

Dr Merryn Voysey, University of Oxford, discussed experience from using weekly PCRs to detect asymptomatic infections and lessons learnt from the Oxford ChAdOx1 Phase 2/3 trial in the United Kingdom.

Summary points included:

- An estimated 40% of SARS-CoV-2 infections are asymptomatic.
- A vaccine with efficacy against asymptomatic infection has the potential to greatly reduce transmission and end the pandemic sooner.
- Two ways to assess asymptomatic infection include seroconversion to SARS-CoV-2 N protein and PCR positive asymptomatic infection; however, both methods have their limitations.
- The COV002 study is a single blind randomised trial of ChAdOx1 nCoV-19 versus MenACWY vaccine enrolling ~10,000 participants with asymptomatic PCR positive infection as a secondary endpoint.
- Participants are self-sampled on a weekly basis.
- To date, data from 186,604 swabs have been obtained with 744 (0.4%) positive results.
- There is some indication of efficacy against asymptomatic/unknown symptoms when the first vaccine dose was low dose and the second dose was standard dose (vaccine efficacy 59% [1.0%, 83%]) but confidence intervals are very wide. No protection against infection was observed in the standard dose/standard dose group (vaccine efficacy 4% [-72%, 46%]).
- Limitations include improvement in PCR testing for SARS-CoV-2 over time and possible importance of effect of false positives when there is low disease incidence.

- Next steps include correlation with seroconversion to N protein, detection/removal of false positives by N protein antibody response post PCR positive, analysis of shedding time, and analysis of cycle threshold values.

Part 3: Additional approaches, evidence / post-licensure studies

Modelling: impact of vaccine efficacy against disease versus transmission on public health and pandemic curves

Prof Neil Ferguson, Imperial College London, presented modelling data assessing the impact of vaccine efficacy against disease versus transmission on public health and pandemic curves.

Summary points included:

- Indirect protection or protection against infection is going to be critical to returning to normal long term.
- Even with 75-80% coverage with a vaccine which gives 90% efficacy against disease, ongoing transmission can result in very high mortality in the remaining 20% in the absence of efficacy against transmission or non-pharmaceutical interventions (NPIs).
- Even if vaccines offer high (e.g., 90%) efficacy against infection/transmission, high coverage in the general population will be necessary to stop transmission, given that the reproduction number of this virus in the absence of interventions is three or higher.
- Significant NPIs will therefore need to remain in place, even in high income countries, for at least the first two quarters of 2021.
- There are some circumstances (if efficacy against infection/transmission is high) where targeting vaccination at key transmitters (young adults) can in theory be optimal, particularly if there is evidence of immunosenescence leading to poor vaccine response among the elderly, but this has not been seen with mRNA vaccines so far.
- Vaccinating older individuals first is optimal when available vaccine supplies are low, or high coverage of the wider population will take many months.
- Global allocation by country size is not far from optimal (by population >65 a little more so).

Observational studies: what can we learn from other vaccines?

Dr Natasha Crowcroft, Senior Technical Adviser in the Measles and Rubella Control Program, from the WHO, used measles and pertussis as examples of lessons learnt when a vaccine is introduced into the population and how this might apply to COVID-19 vaccine effectiveness events transmission.

Summary points included:

- Mass immunization programs leave epidemiological signatures in surveillance data in terms of the impact of vaccines on interrupting transmission, and modelling is an essential tool for interpreting the signature. For example, pertussis epidemic cycles indicate ongoing transmission despite immunization, while widespread measles vaccination has led to disease elimination in the population, showing interrupted transmission.
- There are multiple ways to look at transmission in more detail. Each of these approaches have different strengths, weaknesses, and challenges. It is important to carry out as many of these studies as possible to provide different insights; however, community-based platforms might be required for some.
- Household studies, longitudinal prospective community-based cohort studies and outbreak investigations have yielded important insights on impact of vaccines on

transmission. Case definitions, secondary case definitions, ascertainment, and laboratory diagnostic methods are important considerations.

- Surveillance, microbiological and immunological data are essential for understanding why and how vaccines succeed or fail to prevent transmission. Appropriate specimen collection is needed to understand the model of failure. It is important to understand why these vaccines fail to inform the development of vaccines more effective at interrupting transmission.
- From a public health perspective, the duration of protection and interruption of transmission are key to determine how far vaccines will go in tackling this pandemic.

Statistical approaches to studying transmission

Dr Ira Longini, University of Florida/ WHO, presented the design and analysis of studies to measure the impact of vaccination on transmission on both the individual and population level.

Summary points included:

- Studies to measure the impact of vaccination on transmission can be randomised or observational.
- Individual level studies provide direct evidence of vaccine efficacy against transmission and are carried out in transmission groups such as households or small mixing groups. This can also be done in contact studies or even ring vaccination studies where what happens to the contacts of vaccinated and unvaccinated index cases is studied.
- Larger-scale population level studies, including cluster randomised studies (and potentially stepped wedge vaccine introductions) and observational studies of clusters defined by variable vaccine coverage, provide estimates of vaccine impact on transmission.
- These studies could be done on an outbreak basis, as for example the Pfizer vaccine appears to provide some protection after about 10 days.

Household transmission studies

Dr Adam Finn, Professor of Paediatrics at University of Bristol, discussed household transmission studies and how this might be done in the setting of a clinical trial.

Key points included:

- Some ways to study impact on transmission include cluster randomised trials, staggered implementation studies either in time, location, or both, and studying onward transmission to close contacts of vaccine failures versus unvaccinated controls (e.g., families or households).
- Studies of onward transmission to close contacts of vaccine failures versus unvaccinated controls must consider:
 - *Surveillance* - need to ascertain not only symptomatic PCR positive blinded study subjects but also asymptomatic infections in real time
 - *Enrolment* – once a case is detected, it is important to be able to contact families/household immediately and obtain informed consent to commence sampling
 - *Samples* – saliva is the preferred sample as it is non-invasive to obtain, well tolerated, good volumes can be collected, and it is good for PCR and antibody detection
 - *Sampling* – at least twice weekly for three weeks
 - *Secondary cases* – defined as antibody negative on first sample or become PCR positive during sampling period or seroconvert

- *Readout* - proportion of susceptible family/household contacts of the index cases who become cases during the observation period comparing vaccine failures' contacts with those of unvaccinated controls
- *Power* – to assess whether these studies might be feasible, need to know number of infections in vaccinated and control groups, number of susceptible contacts, transmission rate from controls, and size of reduction in this rate from vaccinees want to be able to detect.
- Data from a planned Phase 3 study (Li and Smolenov et al.) show there may be sufficient power to conduct family transmission studies in the context of ongoing Phase 3 studies which enrol ~30,000 or more individuals.

Phase 2b trial design to assess vaccine efficacy against infection, viral load, and secondary transmission

Dr Holly Janes from the Fred Hutchinson Cancer Research Center presented a Phase 2b trial design to assess vaccine efficacy against infection, viral load, and secondary transmission.

Key points included:

- A Phase 2b trial design of an individually randomised trial to evaluate vaccine efficacy for a single or several different vaccines on SARS-CoV2 infection and infectivity was proposed.
- This Phase 2b trial design is proposed in university students, a population that has experienced a high burden of infection in the United States. Individuals (~7,000) will be randomised to one of three arms (i.e., vaccine 1, vaccine 2, or placebo), and randomisation will be stratified by key factors associated with transmission (i.e., university and residence at university). Small close contact groups of any individual who becomes infected will also be enrolled and surveyed for incident infection.
- The sampling schedule for main study participants includes four months self-collection of daily swabs for PCR diagnosis of SARS-CoV-2 infection.
- The sampling schedule for close contacts of study participants with positive SARS-CoV-2 PCR includes 14 days self-collection of nasal swabs for PCR diagnosis of infection and day 0 and 28 serology to capture past infection and missed incident infections.
- The study aims primarily to evaluate efficacy against SARS-CoV-2 infection (each vaccine versus placebo), to evaluate magnitude and duration of viral shedding among participants with incident SARS-CoV-2 infection, and to evaluate differences in safety parameters between vaccine and placebo recipients.
- Infectiousness should be studied in this Phase 2b study instead of deferring to Phase 4 as:
 - Policymakers and public need answers now to inform policy and individual actions;
 - Short window of opportunity for gold standard trial, before licensure and wide vaccine availability;
 - Most rigorous assessment of whether vaccines reduce infectiousness (versus observational and cluster-randomised stepped-wedge studies);
 - Aids bridging to new populations;
 - Provides data to validate viral load as surrogate of infectiousness;
 - Potentially identifies immune correlates of SARS-CoV-2 infection and shedding which may differ from disease, aiding licensure of future vaccines with effects on these endpoints;
 - Defines sensitivity of serology to detect all SARS-CoV-2 infections captured via daily PCR testing.

A panel discussion included the following key points:

- Professor Gagandeep Kang, Christian Medical College, Vellore, India –
 - The importance of understanding efficacy against infection and transmission for potential impact of these vaccines was highlighted.
 - From the perspective of countries included in the WHO Southeast Asian Region and low- and middle-income countries, it is important to understand what kind of studies are required to enable an assessment of vaccine effectiveness in terms of infection and transmission and how these countries should best be planning for that.
 - Effectiveness studies are very rarely conducted and will be more challenging than usual in the current situation. It will be critical to establish partnerships to enable these studies to be conducted.
 - Different vaccine types, settings, and phased vaccine roll out must be considered in the design and conduct of these studies.
 - It should be decided which geographical settings are most suitable for these studies.

- Dr Ole Wichmann, RKI, Germany –
 - The effect of vaccine on transmission is one of the most important questions that remains unanswered.
 - Evidence of vaccine efficacy against infection and/or transmission might affect vaccine policy recommendations.
 - Discussions are underway in Germany of which groups to target first with vaccination. A vaccine, independent of whether it is effective against transmission, should target the most vulnerable and older individuals first as supply is limited and a high enough coverage will not be achieved for any indirect effect from herd immunity.
 - There is a discussion on whether healthcare workers, and which, should be vaccinated first. It is clear those healthcare workers in very close contact with patients should receive vaccination; however, whether those caring for vulnerable patients should be vaccinated is a matter of debate. A vaccine with a known effect against transmission should be administered to healthcare workers and also those caring for vulnerable patients.
 - The question of other health measures on an individual level is being discussed, i.e., do vaccinated individuals still need to wear a mask and should they be treated differently in terms of quarantine upon contact with a case? It is difficult to have individual policies in place. It would be important to know about protection against transmission.

- Professor Peter Smith, London School of Hygiene and Tropical Medicine –
 - It is important to acquire as much data from randomised trials as possible.
 - In order to measure the efficacy or effectiveness of vaccines against asymptomatic disease through serological studies, it is important to understand what proportion of asymptomatic infection results in seroconversion and the duration of seroconversion. All trials are assessing asymptomatic infection to some extent.
 - There is some evidence of impact on asymptomatic infection for the Oxford-Astra Zeneca and Moderna vaccines.
 - To address transmission, it may be possible in some settings to identify household contacts of all vaccinated and placebo groups and use record linkage systems to measure what proportion acquire disease to assess vaccine effect on household transmission; however, there might be some difficulties in interpretation.
 - In areas where vaccine is in short supply, targeted groups at high risk of severe disease and healthcare workers may be the only groups to receive vaccination, and a marked impact on transmission is unlikely. In situations where it is

possible to expand vaccination more widely, choices may have to be made between focussing vaccination efforts on getting very high coverage of individuals at high disease risk and vaccinating those groups most likely to transmit the infection. It is common experience that vaccinating the first 50-80% of the target population will be relatively easy but it may be significantly more costly in resources and time to vaccinate the last 20%. In these circumstances, it may be worth also targeting those at high risk of transmitting.

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/>
- Workshops will continue in 2021. Potential topics include follow up on correlates of protection, vaccine safety/ pharmacovigilance, and follow up from previous workshops and more 'hot topics.' Attendees are encouraged to provide ideas and suggestions for future workshops.
- 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.