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## Workshop Report

# **COVAX Clinical Development & Operations SWAT Team Workshop on “*Booster and Mix & Match COVID-19 Vaccine Strategies - Planning Ahead in an Environment of Increasing Complexity*”**

**June 3<sup>rd</sup>, 2021**

Meeting report prepared by  
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## Executive summary

On 3<sup>rd</sup> June 2021, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on “Booster and Mix & Match COVID-19 Vaccine Strategies – Planning Ahead in an Environment of Increasing Complexity.” The main aim was to support COVID-19 vaccine developers to deliver on safe, effective, and appropriate vaccines with a focus on booster vaccination strategies and heterologous vaccine schedules to maximize impact on the ongoing pandemic.

Key points included:

- An absolute threshold (i.e., titre above which the risk of disease is zero) may not exist, but there is general alignment to use a population-based correlate to support an immuno-bridge registration pathway for variant-adapted prototype vaccines.
- Immuno-bridging across platforms has been accepted by some National Regulatory Authorities (NRAs) as a pathway to licensure for new vaccines.
- Tracking the evolution and geographical spread of SARS-CoV-2 variants and evaluating their impact on vaccines, therapeutics, and diagnostics is crucial; however, capacity to detect and monitor variants in many countries is incomplete and requires urgent investment.
- Despite waning over time, anti-SARS-CoV-2 antibodies are reported to persist for up to six to 12 months following natural infection. If post-vaccination immune responses follow similar kinetics, persistence of similar duration might be expected; however, data are currently limited and interpretation with respect to relevance for protection is unknown.
- Post-introduction COVID-19 vaccine effectiveness data suggest minimal waning of vaccine effectiveness against symptomatic COVID-19 for three to four months after vaccination; however, this is restricted to three vaccines (i.e., Pfizer-BioNTech, Moderna, ChAdOx-1 [AstraZeneca]). Data on post single dose vaccine effectiveness as well as effectiveness against severe disease are still incomplete.
- Where data are available, short-term vaccine effectiveness against variants of concern (VoC) remains high against clinically relevant (hospitalisation/severe) disease.
- Evidence suggests that in individuals primed by natural infection, a single dose acts as an efficacious booster, enhancing humoral and cellular immune responses including against VoC. Single dose reduces reinfections and lowers viral load after breakthrough infection, with potential impact on transmission. A single dose in individuals primed by vaccination may have a similar effect as a single dose in individuals primed by prior SARS-CoV-2 infection.
- Heterologous priming: There are potential implementation challenges for heterologous vaccination but as demonstrated for Ebola these obstacles can be overcome even under challenging conditions.
- It is a challenge to determine which vaccines to mix & match and which are more suitable as the first versus the second vaccine in a heterologous priming regimen.
- Increased reactogenicity has been documented with ChAdOx-1 and Pfizer-BioNTech mixed schedules as compared to homologous priming with either vaccine.
- There is emerging evidence from ‘real-world’ observational studies indicating heterologous priming regimen being non-inferior to homologous priming in terms of immunogenicity (involving ChAdOx-1 followed by Pfizer-BioNTech). However, different vaccination intervals likely contribute to observed effects and data from controlled, prospective trials are still lacking.

- Developers, public health, and academia are encouraged to incorporate the anti-SARS-CoV-2 immunoglobulin WHO International Standard in testing to allow comparability across ‘mix and match’ studies.
- The importance of keeping immunisation registries for all age groups was emphasised, as was the importance of documenting the target group an individual belongs to at the time of vaccination.
- While in many low- and middle-income countries (LMICs) considerations related to a heterologous priming may be relevant for special populations and for practical reasons, the primary focus currently is on vaccination coverage with a first dose.

The slideset from the meeting can be found here:

[https://media.tghn.org/medialibrary/2021/06/20210603\\_Workshop\\_MASTER\\_DECK\\_FINAL\\_UPDATED\\_Bm5iywZ.pdf](https://media.tghn.org/medialibrary/2021/06/20210603_Workshop_MASTER_DECK_FINAL_UPDATED_Bm5iywZ.pdf)

## Agenda

Time (CET)	June 03, 2021 -Topics	Speaker(s)
15:00 -15:15 (15 mins)	<b>Welcome, meeting objectives and updates</b> <ul style="list-style-type: none"> <li>• <b>Correlates of protection and immuno-bridging</b></li> <li>• <b>Survey of developer efforts toward new placebo-controlled Phase 3 efficacy studies</b></li> <li>• <b>Context setting for booster vaccination</b></li> </ul>	<b>Peter Dull, BMGF</b>
15:15-15:25 (10 min)	COVID-19 Global Epidemiology and Immunity Update <ul style="list-style-type: none"> <li>• How additional or new vaccines may be used should reflect where they are most needed. This overview serves to guide developer thinking of which vaccines (primary series or boost doses, variant vaccines) should be directed where</li> </ul>	<b>Boris Pavlin, WHO</b>
15:25-15:35 (10 in)	Durability of immune responses following natural SARS-CoV-2 infection & vaccination: overview of evidence <ul style="list-style-type: none"> <li>• Data on durability (6 months or longer) of antibodies following natural infection &amp; vaccination</li> <li>• Summary of B &amp; T cell persistence data following natural infection &amp; vaccination</li> </ul>	<b>Amol Chaudhari, CEPI</b>
15:35-15:50 (15 in)	Updates on post-introduction vaccine effectiveness to guide approach to booster vaccination <ul style="list-style-type: none"> <li>• Recent UK data, Chile data, others as available</li> <li>• Trajectory of new effectiveness studies</li> </ul>	<b>Daniel Feikin, WHO</b>
15:50-16:05 (15 min)	Overview of single-dose strategies and scenarios <ul style="list-style-type: none"> <li>• Single dose boosts immunity in primed individuals</li> <li>• High single dose efficacy &amp; effectiveness in unprimed individuals</li> <li>• Protective immune mechanisms relevant for single dose</li> </ul>	<b>Edde Loeliger, CEPI</b>
16:05-16:35 (30 min)	Discussion of regulatory pathway for product as boost-only vaccination <ul style="list-style-type: none"> <li>• Historical precedence for boost only regimen</li> <li>• Regulatory considerations for boost-only vaccines</li> <li>• Confirmed panelists:               <ul style="list-style-type: none"> <li>○ Niranjan Kanesa-thasan, Icosavax</li> <li>○ Daniel Basseur, Former EMA Expert</li> <li>○ Marco Cavaleri, EMA</li> <li>○ Michel De Wilde, Independent Consultant</li> </ul> </li> </ul>	<b>Moderated by Peter Dull, BMGF</b>
16:35-16:40 (5 min)	<b>Overview of Heterologous COVID-19 Vaccine Strategies</b>	<b>Jakob Cramer, CEPI</b>
16:40-16:50 (10 min)	Registration of Zabdeno®, Mvabea® Vaccination for Ebola	<b>Jerry Sadoff, Janssen</b>
16:50-16:55 (5 min)	COVID-19 vaccine Mix & Match – Current clinical research landscape	<b>Paul Oloo, CEPI</b>
16:55-17:05 (10 min)	Update on ongoing and planned studies – Com-COV1, Com-COV2, and Cov-Boost	<b>Matthew Snape, Oxford Vaccine Group, UK</b>
17:05-17:20 (15 min)	Further evidence from heterologous studies <ul style="list-style-type: none"> <li>• Spanish Combi-VacS study</li> <li>• Berlin/Charite study</li> </ul>	<b>Alberto Borobia &amp; Jesus Frias, Spain</b> <b>Leif Erik Sander, Germany</b>
17:20-17:55 (35 min)	Panel Discussion - Vaccine policy implications	<b>Moderated by Jakob Cramer, CEPI</b>

	<p>Confirmed Regulators / NITAGs / SAGE:</p> <ul style="list-style-type: none"> <li>• Willis Akhwale, Chair of the COVID-19 Taskforce in Kenya</li> <li>• Rudzani Muloiwa, University of Cape Town</li> <li>• Thomas Mertens, Ulm University Institute of Virology</li> <li>• Kari Johansen, SAGE</li> </ul>	
<b>17:55-18:00 (5 mins)</b>	<b>Wrap Up &amp; Next Steps</b>	<b>Jakob Cramer, CEPI</b>

## **Welcome, meeting objectives, and updates**

Dr Peter Dull, Deputy Director of Integrated Clinical Vaccine Development at the Gates Foundation, welcomed participants to the workshop. The aim of the workshop was to support COVID-19 vaccine developers to deliver on safe, effective, and appropriate vaccines with a focus on booster vaccination strategies and heterologous vaccine schedules to maximise impact on the ongoing pandemic. Specific objectives were:

- To support product-agnostic developers and enable regulators and policymakers to make informed decisions based on the best possible evidence.
- To facilitate/emphasize need for guidance to reflect current and anticipated region-specific COVID-19 disease epidemiology including seropositivity rates and vaccine coverage.
- To provide the latest information from pre-clinical and clinical studies to guide “best-practice” study designs and drive efficiency in supporting conduct of appropriate studies and the right product being authorised for use.

A World Health Organisation (WHO) meeting on correlates of protection was held on 26<sup>th</sup> May 2021. Key points included:

- Neutralising and binding antibody show a strong association with short-term efficacy.
- An absolute threshold (i.e., titre above which the risk of disease is zero) may not exist, but evidence of a population-based correlate is becoming stronger with new analyses (e.g., ChAdOx-1 Phase 3 efficacy).
- Some regulators have expressed comfort with immuno-bridging new products to authorised products, especially within the same platform, and demonstrating superiority to comparator.
- The need for standardisation across laboratories/immunoassays (e.g., using the WHO International Standard) was emphasised.

A survey of 10 companies/non-governmental organisations (NGOs) executing or anticipating Phase 3 placebo-controlled efficacy trials found:

- Phase 3 placebo-controlled efficacy trials were possible in May 2021, but negative trends are emerging (i.e., some trial site countries rejected placebo-controlled trials).
- A significant proportion of companies reported slow recruitment, especially for those with comorbidities and those aged over 65 years, a higher rate of screen failures (i.e., due to seropositivity) than anticipated, and a high drop-out rate.

## **COVID-19 global epidemiology and immunity update**

Dr Boris Pavlin, WHO, provided an update on COVID-19 global epidemiology and vaccination.

Key points included:

- Epidemiological situation:
  - It is likely mortality due to COVID-19 will be higher in 2021 than 2020 with more cases of COVID-19 reported globally in the first two weeks of May 2021 than during the first six months of the pandemic.
  - The increase in incidence globally has slowed in recent weeks; however, marked variations exist between countries.
  - Numerous countries are experiencing acute crises due to premature relaxation of public health and social measures combined with low vaccination rates and a high proportion of population susceptible to infection.

- Variants of interest and concern:
  - Tracking the evolution and geographical spread of SARS-CoV-2 variants and evaluating their impact on vaccines, therapeutics, and diagnostics is crucial; however, capacity to detect and monitor variants in many countries is underpowered and requires urgent investment.
- Risk and vulnerability:
  - Evidence from serological studies suggests that most countries remain susceptible to large-scale outbreaks. A reduction in prevalence remains the most effective way to reduce mortality and risk of emergence of significant variants.
- Vaccine inequity:
  - The rapid development of COVID-19 vaccines promises to facilitate control of and minimise the impact of the pandemic. In countries with access to large quantities of vaccine, age groups with high vaccination coverage have experienced commensurate declines in death, severe disease, and transmission. Only 0.4% of global vaccine supply is available in low-income countries. Limited supplies and limited capacities to roll out vaccines rapidly risks prolonging the pandemic and requires urgent action to redress the balance.

### **Durability of immune responses following natural SARS-CoV-2 infection & vaccination: overview of evidence**

Dr Amol Chaudhari, Coalition for Epidemic Preparedness Innovations (CEPI), provided an overview of the evidence regarding the durability of immune responses following natural SARS-CoV-2 infection and vaccination.

Summary points included:

- Despite waning over time, anti-SARS-CoV-2 antibodies are reported to persist for up to six to 12 months following natural infection. Antibody titres correlate directly with disease severity.
- If post-vaccination immune responses follow similar kinetics to natural infection, persistence of similar duration might be expected; however, data are currently limited and interpretation with respect to relevance for protection is unknown.
- It has been shown that memory B cells persist for months; these may contribute to long-term protection, particularly against severe COVID-19 and death.
- The emergence of VoC may pose challenges in terms of the potential to evade immune responses elicited by natural infection or vaccination. This needs to be further assessed and closely monitored, especially for any impact on reduced protection or reinfection, especially with regards to sequelae such as severe and critical disease, hospitalization, or death.
- Thus far, data on six-month follow up has only been published for the Moderna vaccine with neutralising antibody titres decreasing but remaining well above the detection limit over time. Developers are encouraged to generate these data using the International Standard and share when possible.

### **Updates on post-introduction vaccine effectiveness to guide approach to booster vaccination**

Dr Daniel Feikin, WHO, discussed post-introduction COVID-19 vaccine effectiveness and the potential need for booster vaccines.

Summary points included:

- The need for booster vaccines might become apparent in post-implementation vaccine effectiveness studies if effectiveness wanes over time since vaccination and through assessment of vaccine effectiveness against VoC.
- Vaccine effectiveness evidence on duration of protection suggests:
  - Evidence thus far suggests minimal waning of vaccine effectiveness for three to four months after vaccination.
  - However, most of the data available is for one dose and any discussion of boosters would be most appropriate after two doses for the two-dose vaccines. In addition, data are only available for three vaccines (i.e., Pfizer-BioNTech, Moderna, ChAdOx-1 [AstraZeneca]); further data for other vaccines will be important.
  - It is important to continue to monitor sequential vaccine effectiveness data over time with discreet time intervals assessed.
- VoC data suggests:
  - Reduced neutralisation might be reflected in slightly lower vaccine effectiveness, particularly with one dose but less so with two, and particularly against mild/moderate but not severe disease.
  - The vaccine effectiveness for VoCs is still high enough to prevent clinically relevant disease.
  - The question over whether variants will have increased waning of protection over time is being closely monitored.
- The WHO policy decision on need for booster doses will be made on an individual case basis (i.e., vaccine by vaccine) by Strategic Advisory Group of Experts in Immunisation (SAGE), with input from numerous other working groups.

### **Overview of single-dose strategies and scenarios**

Dr Edde Loeliger, CEPI, summarised evidence for single vaccine dose strategies for vaccines where the 50% vaccine efficacy threshold is achieved after a single dose.

Summary points included:

- Single-dose effectiveness modelling studies suggest that single dose saves lives and represents optimum vaccine allocation. If single-dose effectiveness exceeds 50%, mortality can be reduced by up to 48% compared to two-dose vaccine efficacy exceeding 90%.
- Evidence suggests that in individuals primed by natural infection, a single dose acts as an efficacious booster, enhancing humoral and cellular immune responses including against VoC. Single dose reduces reinfections and lowers viral load after breakthrough infection, with potential impact on transmission.
- A single dose in individuals primed by vaccination may have a similar effect as a single dose in individuals primed by prior SARS-CoV-2 infection, at least in terms of peak antibody responses.
- The immunity provided by the late second dose (i.e., 12 weeks) is significantly better and may behave similarly to single-dose vaccination in individuals with a history of SARS-CoV-2 infection.
- Single-dose vaccination of unprimed individuals with vaccines exceeding the single-dose efficacy threshold of 50% provides high efficacy and effectiveness in preventing severe disease and hospitalisation.
- There are as yet no data available on the boostability of single-dose immune responses by SARS breakthrough infection.

### **Panel: Discussion of regulatory pathway for product as boost-only vaccination**



A panel discussion included the following key points:

- *Dr Niranjan Kanesa-thasan, Icosavax –*
  - Icosavax plans to focus on development of a single-dose booster vaccine (i.e., IVX-411) able to broadly protect against emerging variant strains in SARS-CoV-2 primed adults, and not intended for primary vaccination of SARS-CoV-2 naïve individuals.
  - At present, there is no clear regulatory guidance for licensure of booster “second wave” vaccines which lack placebo-controlled efficacy studies. Icosavax intends to use immuno-bridging to support heterologous (cross-platform) boosting with IVX-411 in SARS-CoV-2 primed (previously infected or vaccinated) individuals.
  - IVX-411 utilises the Icosavax platform 2-component virus-like particles (VLP) technology to display receptor binding domain (RBD) antigens. The RBD antigen appears to have both manufacturing and immunogenicity advantages over the spike antigen; advantages that should be further enhanced by expression on a VLP.
  - Nonclinical data supports IVX-411, formulated with and without the Seqirus, Inc. proprietary MF59® oil-in-water adjuvant, as a vaccine against SARS-Cov-2 B.1 and VoC B.1.351.
  - The Icosavax IVX-411 booster clinical program aims to demonstrate that heterologous boosting with IVX-411 is tolerable and immunogenic against B.1 and VoC in subjects previously immunised with licensed SARS-CoV-2 vaccines or previously infected with SARS-CoV-2, and to identify the best IVX-411 candidate vaccine (aqueous or MF59-adjuvanted; dose) to advance to pivotal Phase 3 studies.
  - There are plans to develop and refine the regulatory strategy for heterologous boosting indication with early feedback from NRAs including support for immuno-bridging data from boosted individuals.
  
- *Dr Daniel Brasseur, Independent Consultant (ex-chair CHMP-PDCO-VWP at European Medicines Agency [EMA]) –*
  - There is regulatory precedence for approval of booster-only vaccines (e.g., dTpa boost, monovalent polio, influenza vaccines [across season], Hib-PRP conjugate with diphtheria).
  - It is important to indicate intention for linkage to booster for specific vaccine or a universal Covid-19 vaccine booster.
  - The concept of immune cross-reaction can convincingly lead to the conclusion of clinical cross-protection and has been supported within product labelling.
  - Implying the use, the demonstration of the same mechanism of action (type of immune response elicited).
  - Not necessarily being achieved using the same platform (no matter the brand).
  - But a similar magnitude of response (bridging) compared to a clinically demonstrated effective vaccine.
  
- *Dr Marco Cavaleri, EMA –*
  - EMA is open to discuss a proposal for a boost-only vaccination such as that presented by Icosavax; however, detail regarding exactly what is planned and the hypothesis being tested for this kind of immuno-bridging is required.
  - Universal boosting (i.e., broad coverage) will increase flexibility in the vaccination campaigns and greatly assist public health authorities in the roll out of vaccines. However, regulators must also be reassured that any differences have been

- considered, i.e., boosting different types of vaccines in terms of platform technology or whether boosting natural immunity. The population is quite diverse in terms of immune response and regulators need to be reassured that the sample is representative of what can happen in the broader population.
- The choice of comparator is important, as is the primary analysis in the clinical trial (i.e., comparison of the booster effect of the homologous vaccine versus the new vaccine or versus the immune response after the primary series with the vaccine already approved).
  - Variants are the complicating factor, and any approved booster vaccine will need to have good coverage against circulating variants at that point in time.
- *Dr Michel De Wilde, Independent Consultant (ex- Vaccines Research & Development professional) –*
    - The following needs consideration in terms of vaccines that are boost only, not approved for primary immunisation, and would be used either as a boost to vaccination or true infection:
      - There are indications that current vaccines applied as “primary immunisation” in infected people are somewhat reactogenic. Thus, safety is an important consideration for developers of booster-only vaccines and dosage/adjuvants should be adapted accordingly.
      - A superiority (rather than non-inferiority) design should be considered for these vaccines; this would also facilitate the regulatory pathway.
  - *Is there a potential to compare the primary immunisation responses versus the booster responses?*
    - If a vaccine is approved as a booster vaccine, a head-to-head comparison and non-inferiority design would be appropriate. The choice of comparator would depend on the vaccine and the platform technology.
    - Regulators feel more comfortable bridging a strain composition change (i.e., minor changes to the composition of the strain in the vaccine but the vaccine is the same) than a completely different vaccine/platform that has not demonstrated prior efficacy.
    - However, regulators are open for discussion to find a way forward for evaluating the efficacy of any new vaccine.

## **Overview of heterologous COVID-19 vaccine strategies**

Dr Jakob Cramer, CEPI, provided an overview of heterologous COVID-19 vaccine strategies.

Key points included:

- Heterologous vaccination regimens can be used for both heterologous priming as well as using a different vaccination or vaccine platform for booster months after primary immunisation. Heterologous primary vaccination certainly only applies to two-dose regimen using two different vaccine types/vaccine platforms for primary immunisation.
- Reasons to consider a heterologous vaccination regimen include improving the immune response and addressing practical and operational aspects (i.e., ‘interchangeability’ of vaccines).
- Points for consideration with regards to research on heterologous priming include the time lag between the initiation of trials and data being available, dose intervals, and vaccine combinations.
- It remains unknown whether potential boosting will be aimed at the original SARS-CoV-2 variant or a new SARS-CoV-2 variant in future. The former would be considered

(heterologous) boosting while the latter might be considered priming against a new variant. Original antigenic sin is possible and should be investigated.

- For both heterologous priming and boosting, it is important to immunologically assess the best vaccines for priming versus boosting. In terms of the interchangeability, it is important to do landscape analysis and include the vaccines being rolled out widely.
- Operational aspects to consider with heterologous vaccination regimen include differences in shelf life, shipment/storage conditions, component-specific contraindications, and order of vaccination.
- CEPI and the Gates Foundation are funding mix & match studies (heterologous priming and boosting) with vaccine combinations relevant in LMICs.

### **Registration of Zabdeno®/Mvabea® vaccination for Ebola**

Dr Jerry Sadoff, Janssen, discussed the registration of Zabdeno®/Myabea® vaccination for Ebola, the first licensed heterologous multidose vaccine regimen.

Summary points included:

- Potential implementation challenges for heterologous multidose vaccination includes logistics, population acceptance and compliance, monitoring of regimen by tracking individuals, dates, and doses administered, and complex regulatory requirements. It has been demonstrated for Ebola that obstacles can be overcome under challenging conditions.
- The Ebola heterologous multidose vaccine regimen includes a first dose of the adeno vector Ad26 expressing the antigen and a second dose of the Modified Vaccinia Virus Ankara (MVA) given as a booster eight weeks later.
- An anamnestic response to Ad26.ZEBOV booster vaccination is seen in adults.
- There is no impact of pre-existing Ad26 immunity on vaccine humoral immunogenicity.
- Anti-Ad26 immunity does not hamper the response to a second dose of the same vaccine.
- It is evident that the sequence of different vaccines is important. An earlier onset of antibody response was seen when Ad26.ZEBOV was administered as the first dose. In addition, magnitudes of persisting antibody response are induced by regimens with different sequence and interval in the same range.
- A higher antibody response was evident following the heterologous Ebola regimen compared to both homologous regimens.
- Even in uniquely challenging circumstances, it is feasible to administer a two-dose vaccine regimen to adults in LMIC. Community engagement is critical to success.
- Two marketing authorisation applications were requested by EMA for licensure of the Ebola vaccine.

### **COVID-19 vaccine mix & match – current clinical research landscape**

Dr Paul Oloo, CEPI, presented an overview of pre-clinical and clinical mix & match activities.

Key points included:

- Pre-clinical mix & match studies provide important immunogenicity and safety data. Data for example from China have shown that the order of vaccines included in heterologous priming can be important. However, animal data do not always translate to humans. Similar trials in humans are needed for further evidence.
- Durability of immune responses may vary depending on the specific vaccine combination.

- It is a challenge to determine which vaccines to mix & match and which are more suitable as the prime versus the boost.
- Trials are underway to assess the mix & match of vaccines used in high-income countries.
- Relevant combinations for LMICs need to be assessed.

### **Update on ongoing and planned studies – Com-COV1, Com-COV2, and Cov-Boost**

Dr Matthew Snape, Oxford Vaccine Group, discussed emerging data and lessons being learnt from National Immunisation Schedule Evaluation Consortium heterologous prime/boost studies.

Summary points included:

- The COM-COV trial is designed as a non-inferiority trial. The ChAdOx-1 and Pfizer-BioNTech vaccines are being considered in different combinations and at different intervals (four and 12 weeks) to ensure the immune response to a mixed schedule is not inferior to the licensed schedule.
- Increased reactogenicity has been documented with ChAdOx-1 and Pfizer-BioNTech mixed schedules. Both mixed schedules were more reactogenic than homologous schedules in terms of systemic side effects, however, this was short lived.
- COM-COV-2 is a new study enrolling individuals immunised with a single dose of Pfizer-BioNTech or ChAdOx-1 between 25th January and 20th March who are then randomised at the second dose. The study assesses non-inferiority of immune response to 'alternate' versus 'same' boost.
- Lessons being learnt include:
  - Emerging data from the Spanish and German studies indicate a robust response in mixed schedules suggesting a possible need to switch to a superiority design.
  - The chosen intervals (four and 12 weeks) are a balance between matching United Kingdom local policy and providing data rapidly.
  - Randomisation at baseline (first dose) facilitates comparisons between whole schedules (prime and boost), without confounders of differences for populations receiving different prime. Randomisation at second dose still allows comparisons between homologous versus heterologous schedules and more rapid data but requires sufficient individuals who have had a first dose in the right age groups.
  - The single blind design has been important to ensure credibility of the reactogenicity results.
  - Targeting two different age groups, the elderly (>60 years) and those <40 years, rather than those >50 years would have given a combination of reactogenicity and immunogenicity across the full age range.
  - Increased systemic reactogenicity is evident in the adenovirus/mRNA schedule, leading to the addition of a questionnaire about impact on daily life and a further randomisation to assess whether tolerability can be improved through use of prophylactic paracetamol.
  - Given emerging evidence of increased immunogenicity for ChAdOx-1 followed by Pfizer-BioNTech compared with ChAdOx-1/ChAdOx-1, testing 'half dose' RNA boost arms should be considered to potentially spare doses.
  - Capacity issues have been experienced for virus neutralising antibody (VNA) assays; binding ELISA with confirmation of trend by live VNA on a subset appears to be practical solution.
  - In the COM-COV study, blood samples were taken at baseline to enable distinction between thrombocytopenia as a pre-existing condition or the occurrence as a result of the vaccine.
  - The COV-BOOST study is enrolling individuals primed with two doses of Pfizer-BioNTech or ChAdOx-1 to inform optimal use of third dose booster (i.e., of seven potentials) if required.

### **Further evidence from heterologous studies**

Dr Cristóbal Belda-Iniesta, Spain, presented a Phase 2, randomised, multicentre, adaptive trial to evaluate the safety and immunogenicity of one dose of Pfizer-BioNTech mRNA vaccine in subjects that had received one dose of ChAdOx-1 vaccine.

Key points included:

- Pfizer-BioNTech mRNA vaccine given as a second dose in individuals prime vaccinated with ChAdOx-1 induced a robust immune response with an acceptable and manageable reactogenicity profile.
- In the absence of an experimental arm with ChAdOx-1 as the second dose, comparison with homologous schedules should be done with caution.
- However, the humoral and cellular immune response observed in this trial should be considered for future vaccination schedules.

Dr Leif Erik Sander, Germany, presented a prospective study in Germany on the safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx-1 and Pfizer-BioNTech vaccines.

Summary points included:

- Homologous Pfizer-BioNTech and heterologous ChAdOx-1/Pfizer-BioNTech prime-boost vaccination is well-tolerated with 10- to 12-week intervals between ChAdOx-1 and Pfizer-BioNTech.
- The reactogenicity of homologous Pfizer-BioNTech and heterologous ChAdOx-1/Pfizer-BioNTech is comparable.
- Homologous Pfizer-BioNTech and heterologous ChAdOx-1/Pfizer-BioNTech prime-boost vaccination is highly immunogenic.
- Heterologous ChAdOx-1/Pfizer-BioNTech vaccination slightly increases T cell reactivity and antibody avidity.
- This study provides real-world evidence that supports heterologous ChAdOx-1/Pfizer-BioNTech immunisation with 10- to 12-week intervals, as it is currently recommended in several countries.

### **Panel Discussion: Vaccine policy implications**

A panel discussion included the following key points:

- *Dr Willis Akhwale, Chair of the COVID-19 Taskforce in Kenya -*
  - Vaccine availability is a challenge faced by low-income countries. Thus, the potential to mix & match available vaccines is welcomed. Policymakers in Africa will however need to assess whether there are additional costs (e.g., training, transport) associated with a heterologous priming regimen.
  - Another consideration is the added advantage of mixing vaccines in terms of safety and efficacy. A critical question may be why add a second vaccine at an increased cost if for example the first vaccine is effective when used on its own.
- *Dr Rudzani Muloiwa, University of Cape Town -*
  - Vaccine efficacy against transmission would allow the concept of herd immunity.

- Current vaccines are mainly used to protect at an individual (rather than population [herd immunity]) level. If vaccine efficacy against different severities of disease is impacted by circulating variants, National Immunisation Technical Advisory Group (NITAG)s from LMICs must decide whether to vaccinate the entire population or only susceptible individuals against severe disease.
  - NITAGs in LMICs will likely consider both the target population that needs to be vaccinated and if prevention against severe disease (rather than mild/moderate disease) can be achieved with a single dose. Thus, if it is not possible to vaccinate all individuals who qualify for vaccination, vaccination will be targeted for maximum impact. A single dose may be considered if a similar impact can be achieved (i.e., prevention of hospitalisation).
  - In the case of heterologous boosting - if booster vaccines do not result in long-lasting immunity, protect mainly against severe disease, and have minimal impact on transmission even if current variants are covered, a single dose may be sufficient as it does not matter whether they are boosting or revaccinating.
  - It is likely most LMICs will choose to use whichever vaccine is available.
- *Dr Thomas Mertens, Chairman of STIKO, Former director of the Institute of Virology, University of Ulm –*
    - Following the appearance of thrombosis with thrombocytopenia syndrome (TTS), vaccination of individuals under the age of 60 years with the ChAdOx-1 vaccine was not recommended in Germany. Thus, individuals in this age group who received a first dose of ChAdOx-1 were given an mRNA vaccine as the booster. Results show a good immune response in terms of antibodies and T-cell immunity.
    - Further immunological data are needed regarding different heterologous vaccination regimens. This will enable flexibility in vaccine delivery globally.
    - It is important to understand whether a sustained immunological response can be induced through a heterologous regimen in certain patient groups including immunosuppressed patients (e.g., organ transplant recipients). Several studies have shown that immune responses achieved through the standard vaccination protocol are not sufficient for protection.
    - The appropriate time point for administering a third vaccine dose (i.e., first booster dose after basic vaccination) is under discussion. It would be beneficial if overall efficacy of these vaccinations could be achieved by using a heterologous protocol.
    - Data are needed regarding administration of variant-adapted booster vaccines to fully vaccinated individuals.
    - Results on surrogate immunological markers are important but data are due on the protection from disease that can be achieved by heterologous boosting.
  - *Dr Kari Johanson, SAGE –*
    - NITAGs require immunological evidence as well as efficacy and effectiveness studies to recommend heterologous priming regimens without formal licensure. It is important that the WHO International Standard is used by developers, public health, and academia. Product-specific data are also required.
    - Sera are available and can be procured from National Institute for Biological Standards and Control. However, it is also important to consider cells and how the variants grow (i.e., variants grow differently). Increased knowledge around these assays is needed.
    - Evidence for homologous and heterologous vaccinations is still required for other special populations, including children and obese and malnourished individuals.

- It is important to keep track of vaccination status if/when further evidence accrues in support of heterologous boosting. Most countries in the European region document the vaccination status in immunisation registries; many other countries around the world are doing the same. The importance of keeping such registries for all age groups was emphasised, as was the importance of documenting the target group an individual belongs to at the time of vaccination.
  - Studies on dosing intervals are needed, particularly with regards to variants, to enable provision of optimal protection to populations.
  - Data are needed on long-term efficacy, long-term effectiveness, and long-term safety to provide the scientific evidence that NITAGs need to recommend the best and optimal vaccine schedules for the global population.
- *What is the status of vaccination records held in different countries, i.e., are data available regarding the specific vaccine administered for the first dose/primary immunisation and thus information to inform use of a different vaccine for a single booster months later?*
    - The vaccination of healthcare workers in South Africa began with the ChAdOx-1 vaccine. Following data suggesting that ChAdOx-1 was not as effective against the circulating beta variant, the Janssen vaccine was used but as a Phase 3B trial, meaning all individuals given that vaccine had to be registered under trial type conditions even though it was no longer controlled as an implementation trial. The same scheme is now being used to vaccinate the remaining population with registered Pfizer/BioNTech and now registered Janssen vaccine. This situation in South Africa resulted in creation of a database, and individuals are unable to get vaccinated unless they are registered on the system. Thus, a full record of which vaccine and when it was given is available.
    - Vaccination in Kenya began with the ChAdOx-1 vaccine. The Sputnik vaccine was also imported privately; however, it did not have WHO pre-qualification and was subsequently withdrawn for not meeting other regulatory requirements. The aim is to have multiple vaccines available, including also Pfizer/BioNTech and Janssen. The digital system will record the vaccine being issued.

## Wrap up and next steps

Dr Jakob Cramer, CEPI, thanked attendees for their participation in the workshop.

Closing remarks included:

- The Workshop report will be distributed following the meeting.
- Resources will continue to be shared at: <https://epi.tghn.org/covax-overview/clinical-science/>
- Attendees are encouraged to share their thoughts and suggestions on this and/or future workshops in the Discussion Forum: <https://epi.tghn.org/community/groups/group/cwsg/>
- The date of the next workshop is to be decided.
- 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.
- Attendees carrying out or planning heterologous studies are encouraged to contact Peter Dull/Jakob Cramer to ensure coordination and dialogue across studies.