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Workshop Report

COVAX Clinical Development & Operations SWAT Team Workshop on “*Connecting COVID-19 primary and booster vaccination goals: historical precedents, immunological considerations, and approaches to meeting regulatory and policy requirements*”

August 5th, 2021

Meeting report prepared by
Dr Julia Granerod

Executive summary

On 5th August 2021, the COVAX Clinical Development & Operations SWAT Team hosted a workshop on “Connecting COVID-19 primary and booster vaccination goals: historical precedents, immunological considerations, and approaches to meeting regulatory and policy requirements.” The main aim was to review immunological principles and historical precedents for booster vaccination and recent immunological durability data and ongoing/planned booster studies, to summarise available regulatory guidance for booster vaccine registration, and to explore alternative approaches for new or existing vaccines with heterologous and/or reduced dose boost vaccination.

Key points included:

- Large global vaccine disparity exists, with the lowest proportion of vaccinated individuals in low- and middle-income countries (LMICs). Thus, the World Health Organisation (WHO) called a moratorium on booster vaccination through September and believes there is not enough information available at present to provide a booster recommendation. It remains however, important to discuss booster vaccinations as the COVAX Clinical SWAT aims to provide developers guidance to generate the right data to inform both regulatory and policymaker goals.
- The experience of introduction of the *Haemophilus influenzae* type b (Hib) and meningococcal booster vaccines in the UK is relevant to COVID-19 vaccines, in terms of understanding the balance between circulating antibody and immune memory and the value of post-introduction effectiveness data to guide policy decisions.
- It is better to establish policy and regulation based on prospectively designed studies than to revise policy and regulation based on limited retrospective data as was the case for yellow fever vaccines (YFV).
- Preliminary analyses of SARS-CoV-2 variant mRNA Moderna vaccine boosters in adults show safety and tolerability profiles comparable to those observed after priming and induction of antibody responses not only against the wildtype strain, but also against variants of concern (VoC).
- Despite declining antibody titres, vaccine efficacy against severe COVID-19 appears to be maintained to date, despite circulating VoC. Several booster studies are planned/underway to generate relevant data to inform decisions.
- For a variant that is more infectious or has a shorter incubation time (e.g., delta), higher levels of pre-existing antibody may be required as there is less time for activation of memory. If additional effectiveness study bear that out, this may be the rationale for administering a third dose even if suitable priming is achieved after two.
- For mRNA vaccines, there is evidence that immune maturation occurs as additional doses are administered.
- Studies underway have shown very comparable reactogenicity following dose two and three of Moderna vaccine, but sample sizes remain small and larger real-world evidence studies will be important to monitor safety should booster vaccines be implemented.
- A pragmatic approach on fractional doses is currently being discussed within the Coalition of Epidemic Preparedness Innovations (CEPI) and at COVAX level. The concept is to conduct a prospective randomised trial to assess the immunogenicity of fractional versus full doses given as a single booster vaccination in previously primed populations. Workshop participants are encouraged to send comments, suggestions, feedback, or expressions of interest to amol.chaudhari@cepi.net.
- Guidance from some regulators is available for data requirements for boost, including for heterologous (prototype or variant) boost, but it remains unclear what the regulatory pathway may be for vaccines intending to pursue a “boost-only” indication.
- The importance of generating high-quality data to enable regulatory and policy-maker decisions was emphasised. The data need to reflect the real-world booster situation,

address the appropriate gap between the primary series and boost, and the patient population reflected in the boost needs to be informative for the real world.

- A further question is whether a boost might be needed for all or selected sub-populations. This could have major implications for vaccination programs that need consideration.
- Some participants emphasized an interest that any potential booster should be with a vaccine that matches circulating variants.
- All vaccine manufacturers and other groups conducting immunogenicity studies are strongly encouraged to use the international standard in reporting the results of antibody assays.
- Some debate was raised around whether to characterise the six-month vaccination as the final dose in a three-dose primary series (or two-dose, as appropriate), or as a boost dose, depending upon what the indication sought for the vaccine might be. In this case, the dosing interval needs to be determined and clarification is required on when a boost is a boost and when is it part of a primary series.
- With worldwide vaccine shortages and if there is a requirement to frequently boost in the future, fractional dosing may be very important. Fractional dose studies should be compared with the full dose.
- The biggest risk at present is not waning immunity and the need to boost, but low vaccine coverage. Thus, the priority from a policy perspective is to increase global vaccine coverage however, it is also important to conduct academic studies to generate data on potential boosters.

The slideset from the meeting can be found here:

https://media.tghn.org/medialibrary/2021/08/20210805_Workshop_MASTER_DECK_FINAL.pdf

Agenda

| Time (CET) | August 5, 2021 -Topics | Speaker(s) |
|-------------|--|-------------------------------|
| 15:00-15:20 | Part I - Welcome, meeting objectives and updates <ul style="list-style-type: none"> Key updates from last workshop (correlates analyses and regulatory implications, clinical trial operational updates, recent efficacy readouts) Context setting for discussion on booster vaccinations | Peter Dull, BMGF |
| 15:20-15:35 | Historical perspective on booster vaccinations – Bacterial conjugate vaccines | David Goldblatt, UCL |
| 15:35-15:50 | Historical perspective on booster vaccinations and dose-sparing strategies – Yellow fever vaccine | Erin Staples, CDC |
| 15:50-16:05 | Overview of Latest Clinical Data – Moderna COVID-19 Vaccine program | Jackie Miller, Moderna |
| 16:05-16:20 | Update on ongoing and completed homologous/heterologous booster vaccine studies & overview of core protocol elements | Paul Oloo, CEPI |
| 16:20-16:35 | Q&A Session | Peter Dull, BMGF |
| 16:35-16:40 | Break | |
| 16:40-16:55 | Part II - Regulatory Considerations for Booster Vaccinations <ul style="list-style-type: none"> Key data informing use case for boosting including recent persistence and boostability data Dose sparing / fractional dose strategies | Jakob Cramer, CEPI |
| 16:55-17:05 | Summary of regulatory guidance/challenges for various boosting scenarios <ul style="list-style-type: none"> Homologous platform primary vaccination/homologous platform (variant or original virus) boost Homologous platform/heterologous (variant or original virus) boost Summary of US, EU, ACCESS, and WHO guidance on strain change including application to booster vaccination | Ian Hudson, BMGF |
| 17:05-17:55 | Panel discussion: Example scenarios of boosting regimens with homologous and heterologous vaccines including variant and fractional dosing <p>Data requirements for example scenarios:</p> <ul style="list-style-type: none"> Vaccine A primary vaccination series followed by Vaccine B boost Vaccine A primary vaccination series followed by variant Vaccine B boost Vaccine A primary series followed by fractional Vaccine B boost How does licensure only as boost affect requirements? Implications for regulators vs. policy makers <p>Panelists:</p> <ul style="list-style-type: none"> Marie-Christine Bielsky, Expert Medical Assessor, MHRA Mimi Darko, Chief Executive, Ghana FDA Helen Rees, Executive Director, WRHI Phil Krause, Deputy Director, Office of Vaccines Research and Review, FDA/CBER Adam Hacker, Head of Global Regulatory Affairs, CEPI | Moderated by Ian Hudson, BMGF |
| 17:55-18:00 | Wrap Up & Next Steps | Jakob Cramer, CEPI |

Part I - Welcome, meeting objectives, and updates

Dr Peter Dull, Bill and Melinda Gates Foundation (BMGF), welcomed participants to the workshop. The aim of the workshop was to review immunological principles and historical precedents for booster vaccination and recent immunological durability data and ongoing/planned booster studies, to summarise available regulatory guidance for booster vaccine registration, and to explore alternative approaches for new or existing vaccines with heterologous and/or reduced dose boost vaccination.

Dr Dull set the context for the workshop with the following key points:

- Large global vaccine disparity exists, with the lowest proportion of vaccinated individuals in LMICs. Thus, the WHO called a moratorium on booster vaccination through September and believes there is not enough information available at present to provide a booster recommendation. Boosters remain however, important to discuss as the COVAX Clinical SWAT aims to provide developers guidance to generate the right data to inform both regulatory and policymaker goals.
- The current status of COVID-19 vaccination and vaccines is as follows:
 - The WHO aims to vaccinate $\geq 10\%$ of the population of every country by September 2021, $\geq 30\%$ by the end of 2021, and 70% globally by the middle of 2022.
 - At present, 75% of all vaccine doses have been administered in just 10 countries and three countries have not rolled out any COVID-19 vaccines. Inequity is decreasing, but high-income countries (HICs) have administered 61 times more doses per inhabitant than low-income countries (LICs).
 - 22 vaccines have been approved by at least one National Regulatory Agency (NRA), with seven vaccines achieving WHO Emergency Use Listing (EUL) status.
 - 4.6 billion doses have been delivered to 207 countries globally, and 174 million doses have been shipped to 138 countries through COVAX. Distribution through COVAX should improve dramatically in 2022 but challenges (e.g., raw material shortage, cold freezer accessibility) remain.
- Placebo-controlled Phase 3 efficacy trials are becoming more difficult to conduct due to factors such as increased local vaccine availability, variable enrolment rates across countries, increasing requests for subject unblinding, increasing baseline seropositivity rates, and difficulty in interpreting efficacy results with shifting VoC contributions (e.g., recent data from Curevac).

Historical perspective on booster vaccinations – Bacterial conjugate vaccines in childhood

Prof David Goldblatt, University College London, provided a historical perspective on booster vaccinations, particularly with regards to bacterial conjugate vaccines in childhood.

Key points included:

- The Hib experience:
 - The Hib conjugate vaccine was introduced in 1992 into the UK accelerated infant immunisation schedule (at 2, 3, and 4 months) with no routine booster dose but with a catch-up campaign in Year 1 for all children aged < 5 years and enhanced surveillance to monitor disease trends.
 - An increase in disease was observed from 1999 onwards, particularly in those aged between one and three years and > 15 years. A corresponding marked reduction in vaccine effectiveness was demonstrated two years after vaccination in those vaccinated at 2, 3, and 4 months who did not receive a booster dose.

- A catch-up campaign in six-month to four-year olds and a routine booster introduced at 12 months of age has resulted in Hib being under control in the UK ever since.
- A combination of enhanced surveillance to demonstrate an increase in disease and an understanding of the importance of antibody as a correlate of protection enabled the formulation of rational decisions to prevent disease resurgence in the future.
- The meningococcal experience:
 - The UK licensed the meningococcal group C conjugate vaccine in 1999 based purely on correlates of protection and subsequently (as a global first) introduced this vaccine into the population.
 - Three doses were recommended for those under six months of age, with no routine booster but with enhanced surveillance. Two doses were recommended for toddlers or six to 11 months old, with a single dose given to those aged between one and 18 years. Vaccine efficacy was shown to wane after the first year in individuals vaccinated routinely at 2, 3, and 4 months.
 - A routine booster was introduced in 2006, at the same time Hib boosters were routinely introduced.
- Relevance for COVID-19 vaccines:
 - The issue of balance between circulating antibody and immune memory is highly relevant. Memory may be insufficient for pathogens that have short incubation times. It has been suggested that the delta variant might have a slightly shorter incubation period and perhaps this might help explain why the delta variant is still a problem in individuals of pre-existing immunity and vaccinated individuals.
 - Disease modifying immunity (i.e., prevention of disease/hospitalization/death) may remain robust in the face of waning antibody. However, the role of T cells in the context of sterilising immunity is not well understood.
 - It is unclear whether a boost with original strain vaccination will provide robust immunity to variants or whether a bespoke variant vaccine will be required.

Historical perspective on booster vaccinations and dose-sparing strategies – Yellow fever vaccine

Dr Erin Staples, Centers for Disease Control and Prevention, provided an overview of booster vaccinations and dose-sparing strategies for YF vaccine.

Summary points included:

- YF vaccine has been around since 1937, but critical knowledge gaps remain.
- Huge milestones of YF vaccination include preventing disease cases and curbing outbreaks. Retrospective reviews have addressed periodic questions or issues, but these are imperfect.
- There is continued need to generate immunogenicity and safety data, including data on dose optimisation, correlate of protection, duration of immunity, and differences in immunogenicity and safety among vaccines, vaccine recipients, and against variants, for COVID-19 vaccines to inform policy.
- It is easier to establish policy and regulation based on prospectively collected, robust data than to revise policy and regulation based on limited retrospective data as was the case for YF.

Overview of latest clinical data – Moderna COVID-19 vaccine program

Dr Jackie Miller, Moderna, presented preliminary analyses of safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in adults.

Summary points included:

- Different mRNA-based booster vaccines (mRNA-1273, investigational mRNA-1273.351, and mRNA-1273.211) were evaluated in 80 individuals (n=20 per group with two-dose groups for mRNA-1273.351) previously vaccinated with a two-dose primary series of mRNA-1273.
- Safety and tolerability profiles following a booster dose of each of these vaccines were comparable to those observed after dose two of mRNA-1273 in previously reported studies.
- Preliminary results indicate that investigational mRNA-1273.351 or mRNA-1273.211 can induce antibody responses not only against the wildtype D614G strain, but also against variants of concern.
- Further research is needed to determine the clinical significance of these preliminary results.
- A large confirmatory study is ongoing and includes variant-matched booster vaccines.

COVID-19 vaccine booster studies: an overview

Dr Paul Oloo, Coalition of Epidemic Preparedness Innovations (CEPI), provided an overview of vaccine booster studies.

Summary points included:

- A booster dose of Pfizer/BioNTech six months after dose two is well tolerated and elicits five times higher neutralisation titres against wild type virus and beta variant than after two primary doses. Strong neutralisation titres are also evident against the delta variant. Protection against COVID-19 is maintained six months post-dose two, especially against severe disease. It may be too soon for booster doses.
- There is limited persistence of neutralising antibody six months following two doses of Sinovac. An appropriate third dose boost response is evident, indicative of memory induction. The study was limited by lack of subjects aged >60 years and lack of assessment for cell-mediated immunity and VoC.
- A third dose of AstraZeneca given 38 weeks after dose two induces antibodies to a level correlating with high efficacy after the second dose and boosts T cell responses.
- Despite declining antibody titres, vaccine efficacy against severe COVID-19 appears to be maintained, despite circulating VoC.
- The question of whether booster doses might be important to maintain measurable antibody titres or to maintain protection against severe disease needs consideration.
- The need and optimal timing of booster doses should take into account immunogenicity, vaccine efficacy/effectiveness, local epidemiology, risk of infection, and vaccine supply.
- Follow-up to understand persistence of vaccine effectiveness over time is important, particularly with regards to VoC.
- CEPI will fund additional booster dose studies and also consider investigational fractional booster doses.

Q&A session

A Q&A session included the following key points:

- *Is a stronger immune response after dose three at six months in comparison to after dose two suggestive of induction of B and/or T cell memory and if so, why is the dose three booster needed? Would a similar robust immune response not be expected after natural infection?*
 - Higher antibody levels following a third dose suggests the presence of immune memory.
 - For a variant that is more infectious or has a shorter incubation time (e.g., delta), higher levels of pre-existing antibody are required as there is less time for activation of memory. That is the rationale for administering a third dose even if suitably primed after two.
 - Real-world observations from Moderna include:
 - Immunogenicity is important in understanding the immune response to vaccination however, the lack of a true threshold of protection complicates understanding of efficacy and effectiveness.
 - Updated Phase 3 efficacy data has been announced by Moderna and 93% vaccine efficacy is still observed four to six months after the second vaccine dose. It should be noted however, that the strains circulating during the conduct of the study were the ancestral strain, alpha strain, and some California variants.
 - Breakthrough cases are starting to occur in the US, emphasising the importance of continued follow-up of subjects from these efficacy trials.
 - Moderna has embarked on investigating boosters or third doses in the event of waning immunity and to provide authorities with evidence on which to base decisions.
- *Is there data to inform whether the decline in antibodies after a third dose compare will compare favourably to the more rapid decline evident after a two-dose series. What might happen to antibody kinetics at six to 12 months after a third dose boost?*
 - Following the first vaccine dose in the Moderna Phase 1 study, all participants developed binding antibody but only around half had neutralising antibody. Following the second dose, all participants had neutralising antibody. Peak titres 14 days after a third dose that were maintained at day 30 reflects maturation of the immune system and, while not a direct measure of memory B, implies maturation of those T cells into memory B cells through the course of the vaccination. Thus, there is evidence that immune maturation occurs as additional doses are administered.
 - Immunological readouts are complex to interpret, particularly in the absence of a threshold correlate of protection. Thus, effectiveness data will likely be used to guide the use of a booster and these data are eagerly awaited.
- *Is there any evidence of differences in age-stratified immunogenicity from paediatrics (i.e., pre- versus post-puberty)?*
 - The Moderna adolescent study, where subjects aged 12-17 years of age were compared to those aged 18-25 years of age (from the pivotal Phase 3 study), showed similar immunogenicity in these age groups.
 - Dose ranging studies are currently being conducted by Moderna in younger age groups (i.e., from six months of age) to determine the most appropriate dose for younger children.
 - In the YF fractional dose study, slower seroconversion was observed in older individuals compared to individuals 12 to 49 years of age. Also, slightly different kinetics in the immune response to a fractional dose was observed. This highlights the need to continue to consider age.
 - It is important to note that (in the US) a large proportion of exposures, particularly in the immunocompromised or other populations that may not be receiving the full benefit of the vaccination, is driven by children.

- *What is the safety profile of the boost thus far?*
 - It is important to balance the potential benefit with the safety profile.
 - Studies underway have shown very comparable reactogenicity following dose two and three of Moderna vaccine, but sample sizes remain small.
 - Larger real-world evidence studies are required to monitor safety should booster vaccines be implemented.
- *When might heterologous boost data from individuals who have received inactivated vaccines become available?*
 - Some heterologous booster studies that involve inactivated vaccines are yet to start. It is unlikely relevant data will be available before the end of 2021 or the first quarter of 2022.
 - Workshop participants were encouraged to share such data as soon they are available.

Part II - Regulatory considerations for booster vaccinations

Dr Jakob Cramer, CEPI, provided an overview of regulatory considerations for booster vaccinations.

Key points included:

- It is important to increase vaccine coverage in countries (i.e., LMICs) where coverage is currently low. However, data from baseline trial samples indicate 10-20% seropositivity in HICs and >50% to >80% seropositivity in some LMICs. This raises the question of whether to consider booster vaccination in terms of a third dose or first vaccination in subjects primed by natural infection.
- The following need consideration: shift from vaccinating immune-naïve individuals to vaccinating primed populations over time; possibility of a (seasonal) VoC-adapted vaccine given irrespective of previous vaccination/infection; possible dose-sparing options for approved/authorised vaccines to increase vaccine supply and improve reactogenicity; time taken to generate clinical evidence as it is increasingly difficult to recruit immune-naïve populations into trials; and data supporting label claims versus pragmatic National Immunisation Technical Advisory Groups (NITAG) recommendations in pandemic situation.
- Some issues regarding booster and fractional doses include: whether the public health focus is to prevent morbidity and mortality or to reduce incidence; whether fractional dose is suitable for boosting in the context of VoC; role of fractional dose in primed versus unprimed individuals; heterologous priming/boosting with fractional doses; which vaccine should be prioritised for fractional dose (i.e., highest immunogenicity or most widely used); what is the optimal dose; and currently licensed vaccine formulations may not be suitable for fractional dose administration.
- A pragmatic approach on fractional doses is currently being discussed within CEPI and at COVAX level. The concept is to conduct a prospective randomised trial to assess the immunogenicity of fractional versus full doses given as a single booster vaccination in previously primed subjects (i.e., those given at least one dose). It would be a single blind (or even unblinded) multi country approach. In areas with high seropositivity through natural infection, all comers would be given a full or fractional dose and offered full vaccination with locally registered or available vaccines where an insufficient immune response was mounted. This is a pragmatic way to generate data to answer the relevant questions. Workshop participants are encouraged to send comments, suggestions, feedback, or expressions of interest to Dr Amol Chaudhari at amol.chaudhari@cepi.net.

Summary of regulatory guidance/challenges for various boosting scenarios

Dr Ian Hudson, BMGF, discussed regulatory guidance and challenges for various boosting scenarios.

Summary points included:

- To date, licences have been based on homologous platform primary series only. A range of studies are planned/ongoing/completed looking at heterologous platform primary vaccination series, homologous platform prototype virus boost/homologous platform variant virus boost, and heterologous platform prototype virus boost/heterologous platform variant virus boost. Circumstances may also dictate heterologous platform primary vaccination then boost with prototype or variant virus using the first, second, or even a third-generation vaccine platform or fractional dose. This is a complex area with many permutations possible.
- Challenges include conducting clinical efficacy studies, identifying naïve subjects, uncertainty whether boost only would be acceptable for licensure, type of evidence needed for licensure versus policy considerations, and whether variant boost is more appropriate than original strain boost which may still offer sufficient protection.
- There is available guidance covering the variant boost scenario (i.e., strain change) from US Food and Drug Administration (FDA), European Medicines Agency, Access Consortium, and WHO, including guidance on study design and endpoints. However, it is not known whether this approach will be acceptable where vaccine licensure for primary vaccine is based on immuno-bridging rather than clinical data.
- There is no available guidance on appropriate studies and endpoints to enable licensure for homologous platform for primary vaccine series/heterologous (variant or original virus) boost scenario.
- An International Coalition of Medicines Regulatory Authorities (ICMRA) workshop was held on the 24th of June to exchange views on authorisation of second-generation vaccines and alternative approaches to demonstrate vaccine efficacy.
- Clarity is needed around data requirements for boost, especially data for heterologous (prototype or variant) boost, data for boost only approach to licensure, and data for licensure versus policy making.

Panel discussion: Example scenarios of boosting regimens with homologous and heterologous vaccines including variant and fractional dosing

A panel discussion included the following key points:

- *Adam Hacker, Head of Global Regulatory Affairs, CEPI -*
 - The strain change guidance was developed in response to the occurrence of variants and to enable changes in vaccines to be accelerated. There are important elements within the strain change guidance that may be applicable to the booster situation.
 - At the ICMRA meeting, regulators agreed that immuno-bridging could be accepted under certain circumstances and agreed the likely parameters. The requirements around immuno-bridging for primary series must be unravelled to tackle the critical questions around what those requirements might be for booster strategies.
 - A further complication is the lack of an immune correlate.
 - The importance of generating high-quality data to enable regulatory decisions was emphasised. The data need to reflect the real-world booster situation,

- address the appropriate gap between the primary series and boost, and the patient population reflected in the boost needs to be informative for the real world.
- Access to comparators has been challenging but is important to help generate heterologous data.
 - There may be opportunities for dose sparing.
 - The need to provide optionality was highlighted as supplies in different parts of the world are limited and it may not be possible to give homologous boosts.
- *Marie-Christine Bielsky, Expert Medical Assessor, Medicines and Healthcare Products Regulatory Agency -*
 - The Joint Committee on Vaccination and Immunisation in the UK has already issued interim advice on a potential booster program which could start in September 2021 in combination with flu vaccination and would occur in two stages. First, individuals most at risk would be vaccinated, followed by all adults aged ≥ 50 years. This remains a potential at present but may occur before a booster is licensed.
 - Data submitted for homologous booster indications should include the reactogenicity profile of the booster and a level of antibody response at least similar to that achieved after primary immunisation. In addition, data on the cellular immune response as well as antibody data against VoC are expected. If half doses are being tested, it would be preferable if there are comparative trials between the full and half doses.
 - For heterologous booster indications, a controlled trial would be expected where subjects immunised initially with a certain vaccine would be randomised to the same vaccine (i.e., homologous comparator arm) and the test booster vaccine (i.e., heterologous booster arm). The trials should demonstrate immune non-inferiority of the heterologous compared to homologous booster. There have however, been challenges to access comparator vaccine supplies. Academic trials may be able to generate data that could be used to support these applications. If such trials cannot be conducted, a pragmatic approach could be to accept comparisons with historical antibody level after primary immunisation with the test vaccine provided this vaccine has shown efficacy, at least similar to the priming vaccine, in placebo-controlled trials.
 - How broad a heterologous indication might be will likely depend on the robustness of the results. It is unlikely that a universal booster indication can be granted.
 - *Eric Karikari Boateng, Senior Clinical Reviewer, Ghana FDA -*
 - The margin and how this was set needs consideration in the marginal non-inferiority design if using a boost.
 - For the fractional boost, a Phase 2 proof of concept would be required before a Phase 3 study.
 - *Phil Krause, Deputy Director, Office of Vaccines Research and Review, FDA/Center for Biologics Evaluation and Research -*
 - Vaccines are still highly effective against severe disease and moderately effective against overall disease. A decline in total cases has been observed in the UK in the absence of boosting. Thus, there may be reason to question the need for a booster at this point in time.
 - A further question is whether a boost might be needed for all or just some of the vaccines. The latter could have major implications for vaccination programs that need consideration.

- Any potential booster should be with a vaccine that matches circulating variants. With the duration of response to a boost and the safety of multiple boosts unknown, there may be limitations to the total number of boosts individuals can receive. To keep this epidemic under control long term, individuals should not be given boosts prematurely with viruses that are much less likely to yield long-term protection.
 - Administering booster doses is a serious benefit risk calculation as side effects exist for all these vaccines. It is unknown if additional dosing will increase side effects.
 - Available vaccines will save more lives if they are delivered in countries with limited vaccine supply than if they are used for boosts. In addition, use of vaccines in countries with limited supply might reduce the likelihood that additional VoC will evolve.
 - Using vaccines for boosts that have already proved effective is easier than using vaccines that have not already proved effective. However, placebo-controlled trials are still feasible (e.g., WHO solidarity vaccines trial). In the event placebo-controlled trials become infeasible, the WHO will switch to non-inferiority comparisons by changing the comparator in the vaccine in the middle of the trial and use a hybrid statistical approach to acquire data which will be useful for evaluating vaccine efficacy with clinical endpoints.
 - Vaccine manufacturers are strongly encouraged to use the international standard in reporting the results of antibody assays.
- *Helen Rees, Board Chair of the SA Health Products Regulatory Authority (SAHPRA) -*
 - Some HICs are making booster recommendations before any regulatory indication that it will be acceptable. These recommendations are based on scant data and against a backdrop of not enough vaccine in the world.
 - Some ongoing issues include:
 - Mixing of vaccines will occur in the African region and data are needed to assess safety and effectiveness.
 - There is uncertainty on how to deal with travellers who have received one vaccine dose in a different country and that vaccine type is not available for the second dose in the country travelled to.
 - Due to reports of breakthrough infections in the media and subsequent lack of trust, healthcare workers are requesting specific vaccine types and booster doses.
 - There is a need for evidence to be generated, likely through immunobridging. The immunobridging will not only consider the immunogenicity but also the reactogenicity and safety.
 - Certain vaccines may need a three-dose rather than two-dose primary series. In this case, the dosing interval needs to be determined and clarification is required on when a boost is a boost and when is it part of a primary series.
 - With worldwide vaccine shortages and if there is a requirement to frequently boost in the future, fractional dosing may be very important. Fractional dose studies should be compared with the full dose.
 - As well as considering which types of vaccines might need a boost and what criteria would trigger this (e.g., waning immunity), the target population must also be considered when generating the data. Older age groups will be very important in certain countries while people living with HIV and other co-morbidities will be more important in others.
 - The biggest risk at present is not waning immunity and the need to boost, but low vaccine coverage (e.g., <2% of African population has access to vaccines). The latter will result in the continuous emergence of variants that may become more resistant to existing vaccines. Thus, the priority from a policy perspective is to

increase global vaccine coverage however, it is also important to conduct academic studies to generate data on potential boosters.

- *A boost only approach may be the only approach at some point in the future. Please comment on boost only as an approach.*
 - It is likely new vaccines in the future will have only booster indications. However, the challenge is to find a suitable design. Controls are important and access to available vaccines is needed.
 - Immunobridging will be the relevant endpoint for conditional approval for the boost only approach as efficacy data will not be available for these vaccines. However, post-approval effectiveness studies will be required for approval.
- *What types of studies should be conducted and what data collected by developers considering boost only vaccines?*
 - Clinical endpoint data should still be acquired through placebo-controlled trials where possible as there is still a substantial part of the global population that has not been vaccinated. When placebo-controlled trials are no longer feasible, non-inferiority trials or the WHO hybrid design can be used.
 - Immunogenicity plus another component, for example post authorisation studies or very strong immune response data, will be required to prove that boosters work.
 - Developers are encouraged to use the international standard to facilitate comparisons.
- *What are regulatory and policy perspectives on the way forward with fractional doses?*
 - Fractional dosing is a very important issue, particularly if boosting is required in the future. Early data on fractional doses of mRNA vaccines are promising.
 - Vaccine and antigen sparing strategies and cost need consideration in terms of the future.
 - Safety following fractional doses should not be assumed. Not all vaccine platforms lend themselves to this approach and it is the mRNA being considered for fractional dosing at present.
 - Fractional dosing is a research question at present and further data are required.

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/>
- 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.