WHO COVID-19 Vaccines Research

Can booster doses contribute to control this pandemic: what research is needed?

13 August 2021, virtual consultation
Geneva, Switzerland

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Executive Summary

COVID-19 vaccines are highly effective at preventing severe disease. However, with supply of vaccines constrained, many low- and middle-income countries have been unable to achieve initial global coverage targets set by WHO’s Director General to vaccinate 10% of the population of each country by the end of September 20211.

Some countries have recently introduced (or are considering introducing) booster doses of COVID-19 vaccine. This could further exacerbate global vaccine inequities, with vaccine doses that could have been used for primary vaccination in low-resource settings instead being allocated for booster vaccination in high-income countries. Furthermore, continuing viral circulation in mostly unvaccinated populations will increase the risk that new variants will emerge, including those potentially more transmissible or able to evade vaccine-induced immunity.

It is therefore essential that booster doses are used only when there is a compelling public health reason. Currently, limited evidence is available to inform this decision.

Recent evidence suggests neutralizing antibodies decrease over time for some vaccines, but it is unclear how or if this translates to decreased clinical protection, especially against severe disease against the Delta variant. Other antibody-based responses, T-cell-mediated immunity and memory responses appear to also play important roles in protection. Randomized clinical data is not available to understand the efficacy of most vaccines against Delta, though some observational studies report decreased vaccine effectiveness. However, unmeasured bias in observational studies may impact results. Clinical trials of booster vaccinations show significantly higher levels of cross-reactive neutralizing antibodies compared to the primary series. RCTs to assess the safety and impact of booster doses on neutralizing responses are ongoing, although studies are not large enough to detect rare but serious events, including potentially increased frequencies of immune-mediated events that have been detected with some vaccines.

In addition to studies that would confirm the benefit of boosting strategies, strong post-marking surveillance and pharmacovigilance with global sharing will be required to inform optimal decision-making.

Outside of boosters and mass vaccination, complementary strategies such as adjusted doses and targeted immunization programs should be considered and evaluated as they are rolled out. Using novel technologies and modelling approaches can help identify where to target and which strategies would impact transmission and prevent disease. The global COVID-19 crisis remains, and innovative strategies are needed to save lives and reduce disease.

Data sharing and open, transparent decision-making will be an essential component of these decisions.

1 https://www.who.int/director-general/speeches/detail/director-general-s-opening-remarks-at-the-world-health-assembly---24-may-2021
Introduction
The global consultation aimed to answer the fundamental question: Are booster doses needed, if so when, for which vaccines, and in whom? Additional doses may be needed if primary vaccination does not induce enough immunity (such as in immunocompromised persons), vaccine induced immunity wanes over time, or new variants escape vaccine-induced immunity. In all situations there needs to be a clear benefit of boosting to outweigh any risks (safety, public health outcomes, long-term consequences). This risk-benefit assessment should be made with respect to the relative priority and importance of the different outcomes assessed (immunogenicity, infection, mild or severe disease, transmission). Any decisions on booster dosing needs to be based on the science and the relevant moral framework.

Overview of current COVID-19 epidemiological situation
In recent weeks there has been a global increase in COVID-19 cases and deaths, despite the availability of tools to prevent new waves. Likely an underestimate, last week 4.2 million new cases and ~65,000 new deaths were reported. These new waves of transmission are likely due to 1) evolution of the virus, 2) inconsistent use of public health and social measures, 3) increases in social mixing and 4) uneven and inequitable vaccine distribution. With four variants of concern (VOC) currently in circulation, studies are tracked online to understand how VOCs impact transmissibility, disease severity, reinfection, diagnostics, therapeutics, and vaccines. Among all variants, Delta has the highest transmissibility with a ~75% increase in the effective R relative to the ancestral strain. This may be due to higher viral load for a potentially earlier/longer period, shorter serial interval, and decreased latent period. Despite the vaccines available, there remains a worldwide crisis.

COVID-19 vaccines as an additional tool to control COVID-19 pandemic: a public health research perspective
The COVID-19 pandemic has continued to drive inequality across the world. Currently, 80% of vaccines have been distributed to high- and middle-income countries (HMICs) and 66% of all doses have gone to just five countries. Governments have funded pharmaceutical companies to rapidly develop vaccines, but governments have no share of the profit. Nonetheless, funding governments have leverage that could be used to help fill resource gaps for WHO Strategic Preparedness, RADAR, and COVAX. While Dr. Tedros called for a moratorium on booster doses until September 2021, there are financial incentives for pharmaceutical companies to promote booster doses, despite the current lack of evidence that they are needed. The moratorium should be extended until at least 2022.

A cry of inequity is unlikely to elicit global access to COVID-19 vaccines and therefore communication efforts should change to focus on the need for global vaccination to support slowing variants of concern, reducing the economic downturn, easing social and economic
disruption, reducing illegal immigration, and stabilizing global security. A reduction in access to routine immunization continues to further endanger public health. In addition to increasing coverage globally, we need to continue to overcome vaccine hesitancy, encourage the use of face masks and social distancing, improve testing and contact tracing, and develop comprehensive plans based on local needs. Surveillance and research programs need to be strengthened.

Key remaining research gaps include:
- Determine the duration of protection against COVID-19 or severe disease
- Understand and assesses VE and breakthrough infections
- Understand the role of neutralizing antibodies, immune memory, and cellular immunity to clinical protection
- Better understanding of how to induce protection from disease and prevention of infections/transmission
- Determine the level of protection provided by booster doses
- Assess vaccine/booster effectiveness among persons with impaired immunity who are highly susceptible to COVID-19
- Develop second-generation vaccines and understanding how they address inequity and improve protection

Session 1. What do we know and what additional evidence is needed to inform decisions on booster doses?

Current understanding of mechanisms of vaccine-induced protection
Infection-induced immunity provides a broader immune response with both systemic and mucosal immunity, while vaccine-induced immunity primarily targets the spike protein, often via neutralizing antibodies. Protection against SARS-CoV-2 has been shown in animal models to be based on neutralizing antibodies, though there may also be protection through non-neutralizing Fc dependent antibodies. There is evidence to support neutralizing antibodies as a correlate of protection in some settings and neutralizing antibodies have been linked to vaccine efficacy during clinical trials. A role for T-cell based immunity has also been observed, and some vaccines can induce strong CD4 and some CD8 T-cell responses, though we don’t fully understand the role or quantitative contribution to protection. Mucosal immunity also plays a role in upper respiratory infection.

Neutralizing antibody titers induced by some of the vaccines wane over time. Variants may negatively impact protection through partial escape from neutralizing antibodies and/or T cell responses, higher replication capacity, shorter incubation time, and exposure to higher viral loads. Waning of IgG on mucosal surfaces, and waning of immune response in general over time, together with these factors, may lead to further reduced protection against variants.
Key remaining research gaps include:
- Is there an absolute correlate of protection, and what is it? What is the level for protection from infection, illness, severe illness?
- How does the level of antibodies 6-12 months after vaccination correlate with long-term protection to know if a booster is needed?
- What is the role of anamnestic response (T cells, memory B cells) in protection and how is it influenced by shorter incubation times such as with Delta?
- What is the contribution of CD4 and CD8 responses to protection from infection, illness, and severe illness?
- How do these answers differ across vaccines and vaccine platforms?

Animal study evidence on SARS-CoV-2 Delta variant pathogenesis and host response
Ongoing work conducted in hamsters was presented. Infection with the Delta variant induced pathogenicity in hamsters with persistence of sub-genomic RNA in the upper respiratory tract with severe lung lesions and body weight loss. The hamster model is expected to be useful for predicting certain aspects of human pathogenesis of Delta.

Vaccines and variants: What randomized evidence is available?
The COVID-NMA (https://covid-nma.com) is an international research initiative supported by WHO and Cochrane to provide a live mapping of COVID-19 trials. Each week new studies are pulled from electronic databases that meet a set of criteria to assess the risk of bias and grade evidence. Results have been assessed according to each variant and only one randomized, placebo-controlled study is available for Delta (Bharat Biotech Ella R, 2021). Relevant methodological issues when assessing variant-specific efficacy or effectiveness studies include post-hoc analyses using sequenced samples which can result in a lack of power and imprecise results. When no sequencing is available studies can use the dominant circulating strain as a proxy. The interpretation and comparison of results can be difficult when there are multiple outcomes across different studies (time points after vaccination, direct/indirect evidence). Preliminary studies for booster doses focus on immunogenicity and RCTs or observational studies will be needed to evaluate the impact on clinical outcomes.

Vaccines and variants: what immunological data is available?
The immune response to Pfizer, Moderna, and J&J vaccines were evaluated across the variants of concern. All vaccines generally showed cross-reactive neutralizing antibody responses following the primary series, with some relative reduction in responses to Beta
compared to other variants. For the Moderna vaccine, binding and functional antibody responses persisted against all variants for 6 months, though the immune response was trending lower in the elderly. T-cell immunity was also examined for the J&J vaccine with comparability across strains and showed minimal decline over 8 months. Real world efficacy studies against Delta shows continued efficacy against severe disease and death, though some studies report reduced efficacy against infection and mild disease.

**Key remaining research gaps include:**
- The reduction in VE for some vaccines is not as great as the decline in antibody titers. We need to understand the relative role of declining immunity versus the infectiousness of the Delta variant in the reduction of VE. The need to investigate beyond the antibody response is critical.

**Vaccines and variants: Methodological issues in using non-randomized studies to estimate vaccine effectiveness**
To date there are 55 observational studies examining vaccine effectiveness against variants of concern, with 14 describing impact on Delta. Several methodological issues can arise during observational studies including: the definition of the comparison group and different types of confounding (baseline, time-varying, unmeasured). If not accounted for in the analysis or through appropriate comparison groups, time-varying confounders such as previous symptoms, results will be biased. Despite accounting for baseline and time-varying confounders, in the COVID-19 Longitudinal Health and Wellbeing National Core Study, effectiveness was still observed in the first week after vaccination indicating the possibility of some unmeasured confounding. It is difficult to know what magnitude of bias remains and for how long. Outside of this cohort study, several test-negative design studies have been implemented to assess vaccine effectiveness. While this design can reduce bias from varied healthcare seeking behaviors, researchers should be cautious of inferring an association when conditioning on a potential “collider” such as care-seeking, which may by itself be independently correlated with vaccination.

**Key remaining research gaps include:**
- Critical evaluation of design and analysis strategies to compare estimates from different approaches to improve understanding of unmeasured bias
- Explore the role of negative control outcomes, such as non-COVID mortality, to account for unmeasured bias
- What are the characteristics of the persistently unvaccinated?
Emerging evidence from ongoing studies: a zoom on the Delta variant

Updates on ongoing studies of VE against the Delta variant were presented. Across all studies presented, there was no observed decline in VE against severe disease over-time or against the Delta variant.

In Scotland, Pfizer VE against Delta and Alpha symptomatic disease were 79% and 92% respectively. AstraZeneca VE against Delta and Alpha symptomatic disease were 61% and 70%, respectively. In this study, most deaths were in the vaccinated population but tended to be older with comorbidities while deaths in the unvaccinated population were younger with few comorbidities.

In studies from England, VE against symptomatic disease starting 10 weeks after two doses of AstraZeneca the is about 80% for Alpha and 65% for Delta. After two doses of Pfizer, VE against symptomatic disease is over 90% for Alpha and about 80% for Delta. VE against hospitalization was over 90% for both vaccines against both variants after two doses. Further evaluation should be conducted to understand any remaining biases, such as collider bias.

In Ontario, Canada all three vaccines (Pfizer, Moderna, AstraZeneca) were evaluated using the test-negative design. The VE against symptomatic Delta infection was 85% two weeks after two doses of Pfizer. VE against symptomatic infection with full immunization could not reliably be estimated for Moderna and AstraZeneca. VE of full doses against hospitalization or death could not yet be estimated, but partial vaccination (21 days after dose 1) VE was 77%, 96%, and 88% for Pfizer, Moderna, and AstraZeneca, respectively.

In the South African Sisonke study ~477,000 health care workers were vaccinated with the J&J vaccine and compared to non-vaccinated health care workers and essential workers. During time periods of both Beta and Delta predominance, there was no difference in mild or moderate breakthrough infections and no difference in severe outcomes across time.

Additional evidence on booster doses: developers’ perspective

Representatives from several manufacturing companies outlined long-term VE results from Phase 3 trials and plans or results from Phase 1 or 2 studies on 6–8-month booster vaccines.

Most booster vaccines were the prototype vaccine (with antigens matching earlier circulating virus) and did not reveal safety concerns. In general, significantly increased neutralizing
antibody response compared to the priming regimen across multiple VoCs was observed. Some developers are working on Delta-specific or multivalent boosting vaccines.

**How much safety data is needed to support benefit-risk assessment of booster doses?**

Experts discussed the type and amount of safety data required for potential booster vaccines. The safety data required for approval or authorization may be different depending on if the booster is a vaccine already approved or authorized as a primary series, a vaccine developed from the start as a booster or a heterologous vs homologous booster. It was emphasized that the safety of a booster dose should not be assumed, especially considering immune-mediated adverse events such as myocarditis and Guillain Barre Syndrome, for which the risks may increase with additional dosing. Additional safety information may be needed for elderly and immunocompromised individuals which represent many different groups of patients. Obtaining data on safety of co-administration with influenza vaccines should also be considered. Generally, with booster doses for an approved primary series the focus will be on reactogenicity, especially as natural infection increases. For new vaccines developed as boosters with no primary vaccination programme, a larger safety database is needed along with a justification on timing.

RCTs demonstrate some information on safety and developers should make sure to discuss safety data during these meetings. Post-marketing surveillance is important to understand how the safety profile may change with booster doses. This will become increasingly complicated with different schedules and booster types. WHO has implementation plans for vaccine safety including sentinel hospital based and special studies to identify adverse events of special interest. Communication regarding safety is critical and should be evidence-based.

**Key remaining research gaps include:**

- Investigations for rare adverse reactions after homologous/heterologous boost
- Safety of boosters in naturally infected and vaccinated at different time points
- Safety of additional doses in immunocompromised population
- Co-administration of other vaccines, including influenza
- Exploration of fractional doses and timing of boosters, which might reduce the likelihood of adverse events
- Understand impact of vector-induced immunity
- What is the cumulative effect of lipid nanoparticles and biodegradable nanoparticles for mRNA vaccines?
- Need further data on special populations such as the elderly, children, and pregnant women

[Link to Slides]
What should a booster dose achieve from the public health perspective and what data is needed?
Some parts of the world are still waiting to protect their healthcare workers and the most vulnerable, which hinders worldwide control of the pandemic. The WHO called for at least 10% coverage of vaccine by the end of September and that does not look likely. We do not have a consensus if a booster is needed because of remaining questions on waning protection against severe disease or the Delta variant.

Key variables that might inform the use of booster vaccines include assessing immune parameters over time, which is problematic without a long-term correlate of protection, and vaccine effectiveness, which can have unmeasured bias and wide-ranging outcomes but is likely most reliably measured against severe disease. Both the need for and the performance of booster doses should be evaluated.

Important additional considerations include timing, homologous/heterologous, dose-sparing, impact of natural infection, focusing on high-risk populations, programmatic feasibility, and implementation of quality study designs to generate data on relevant outcomes for decision-making.

The specific data needs for police as outlined by SAGE/WHO are found here: [https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses](https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses).

Key remaining research gaps include:
- Epidemiology of breakthrough cases over time and by disease severity
- Subgroup analyses in high-risk groups: including immunocompromised, older frail adults, groups with high risk of exposure, type of vaccine, HIV+ with low CD4 counts, circulating variants of concern (VOCs)
- Vaccine-specific data against circulating variants
- The role of antibodies and cellular immunity
- Interpretation of correlates of protection/biomarkers for different outcomes (infection, disease, severe disease)
- Immunogenicity, safety, and effectiveness of booster doses

What additional research is needed to support informed regulatory decision-making about the benefits and risks of booster doses?
While most agreed that boosters should be ideally be considered in the context of a global plan to control COVID, policymakers have already started recommending and some are using boosters. Data gaps may differ between well-resourced countries and LMICs.
The first question that needs to be answered is whether or not a booster is needed, because that will influence considerations of benefit and risk. This decision will need to consider the projected epidemiology of the virus—if future waves, new variants, and continued spread of the virus are anticipated, the answers may be different than if they are not.

Regardless of whether the major factor is new variants, waning immunity, or both, for the short term, the critical question is whether or not vaccine protection against severe disease is going down. If there is evidence that it is in certain subgroups, those groups could be considered for additional doses of vaccines. Data about waning protection may also help to define priority groups for additional doses of vaccine. While immunological studies may be helpful, by themselves these studies may not be sufficient to provide scientific support for policy changes.

Whether an additional dose of vaccine is considered to be part of a primary series vs. a booster might affect regulatory precedents regarding the amount of safety data needed. If an additional dose is considered part of the primary series, this may also have implications for heterologous boosting, whether using a different vaccine platform or a different antigen. Normally, an additional dose of vaccine would be considered a boost if the primary series induced protective immune responses and those responses started to wane, while an additional dose might be considered a part of the primary series in cases where the first dose or doses did not induce adequate protection.

The determination of the optimal primary vaccination series will have global implications and this question should be considered both globally and locally.

Safety is a major consideration in making decisions about boosting. The risk of immune-mediated adverse events such as myocarditis/pericarditis, which has been reported most frequently in young people who received mRNA vaccines, must be considered. Benefit/risk considerations for boosting may be different for people who have already been infected. Predicting effectiveness will also be complex.

Comparisons of immune responses among different vaccine regimens will be important for predicting effectiveness of boosting, but it may be difficult for investigators to access comparator vaccines. Use of the international standard in neutralizing assays may mitigate this concern. If additional doses are needed, an understanding of which vaccines need boosting and what boosts are appropriate to increase protection will be important. This includes boosting with the original vaccine, boosting with a variant-specific vaccine, and/or boosting with other vaccines. In addition, intervals between doses and the dose levels could be optimized to potentially increase the duration of protection and reduce the risk of adverse events. Randomized studies would provide the most definitive answers to some of these questions.

If boosting is implemented, the safety concerns suggest that a vigorous pharmacovigilance program should be implemented. Post-marketing surveillance will be complex, but clear protocols and guidelines should be established. These studies will need to be conducted in locations with strong pharmacovigilance systems where vaccine records enable
determination of who has received which doses at different times, also considering the possibility that some of the observational data will include heterologous boosting. Global coordination and reporting of safety monitoring will also be essential.

Key remaining research gaps include:
- Specific gaps in LMICs. Is there a two-tiered research agenda?
- Which vaccines will require additional doses?
- Do date support consideration of additional doses as part of a primary regimen, or as boosters?
- Which potential booster antigens, platforms, doses, and intervals are appropriate for each vaccine?
- If boosting is implemented, how can pharmacovigilance best address the need for rapid data on safety and real-world effectiveness of additional doses?
- What specific research agendas are appropriate for decision making in LMICs?
Session 2. How can research contribute to optimize the use of available doses of COVID-19 vaccines?

What research is needed to evaluate Adjusted/Fractional doses and regimens in the context of primary vaccination and booster doses?
Fractional dosing provides half-doses to twice the amount of people. Even if this led to reduced protection relative to full-dosing of individuals, modelling indicates that it would save many more lives on a population-level. Immunogenicity studies of Pfizer and Moderna vaccines with reduced antigen showed similar antibody responses as the approved dose, suggesting that the risk even to individual effectiveness of reduced dosing might not be high.

Booster doses increase neutralizing antibodies significantly, but we may not need antibodies this high, which provides an additional opportunity to consider dose-sparing strategies, possibly also with advantages for vaccine safety.

Fractionation would thus save antigen supply enabling more access to first doses in LMICs.

Key remaining research gaps include:
- What fractional doses would be optimal?
- How many lives could be saved if fractional doses were used?
- Conduct randomized evaluation of full vs fractional dose to confirm impact on clinical outcomes as either a primary dose or booster dose

What complementary vaccine delivery strategies should be considered (in which context?)
Vaccine sparing campaign ideas will be critical with Delta and an increasing R. Where supply is limited, vaccine could be used in a targeted way in the people/communities where vaccination will maximally reduce disease spread.

Learning from previous pandemics, we can use 21st century surveillance and containment strategies such as sewage sampling, exposure notification, digital syndromic surveillance, social media searches, and coordination of private sector systems.

Multiple coordinated approaches can be used to quickly identify and act under one system. For the best overall public health outcomes, vaccine distribution should be guided by epidemiology and not availability.
What research is needed to evaluate complementary vaccine strategies?

The current vaccination strategy, mass vaccination, is too slow and is not slowing transmission. Alternative approaches include ring vaccination integrated into surveillance and containment, targeted vaccination with either expanded ring or geographic strategies, and reactive vaccination including fractionated doses. While the $R_0$ for Delta is between 5-8, modeling shows the effective reproductive ($R_e$) number to be $\sim$1.5, meaning it should be possible to limit transmission with targeted vaccination strategies. Simulations show that up to a $R_e$ of 1.5, both ring and spatial vaccination strategies are effective at containing outbreaks. As in Ebola, cluster randomized designs can be used to evaluate effectiveness of these strategies.

Key remaining research gaps include:
- How effective are the different vaccination strategies against different outcomes (preventing outbreak, reducing morbidity/mortality, reducing transmission)?
- How can we deliver limited quantities of COVID-19 vaccine to protect the vulnerable and stop transmission?

What research is needed to assess the potential impact of complementary vaccine delivery strategies?

Experts agreed that evaluating all complementary vaccination strategies would be important. Many of these vaccination strategies may be evaluated via operational research during vaccine deployment and administration, and we can study the impact while rolling out different strategies.

Such studies can be implemented quickly, and clinical trials aren’t necessarily needed. This could also potentially be done for fractional dosing though acceptance of reduced doses may be a problem as it was for Yellow Fever. Further research on the impact of fractional COVID-19 doses on clinical protection and lives saved may support communications related to fractional dosing.

Simultaneously, developers should continue to work on vaccines that can interrupt transmission and generally better understand the impact of vaccines against transmission.

Also, developers should continue to develop vaccines that don’t require refrigeration and use alternative routes of administration such as parenteral, nasal, oral, and intradermal. This may provide an easier way to roll out vaccines and quickly and increase uptake. Also, generally, we need a better understanding of the impact of vaccination on transmission.
Conclusions

Despite rapid development of effective vaccines, there is still a worldwide crisis with the highly transmissible Delta variant.

To date, there is no compelling evidence to suggest that vaccine effectiveness against severe hospitalization and death is waning. Key questions remain about the need for and assessment of booster doses related to the immune response, vaccine efficacy against Delta from randomized and non-randomized studies, and the safety of booster doses.

Decisions on booster doses should be based on scientific evidence and equity, and should be transparently made based on publicly available data.

The WHO plans to review and update shortly the Target Product Profile for COVID-19 vaccines and address the questions raised during this consultation.

Mass vaccination has not successfully prevented outbreaks worldwide and the need to evaluate different strategies is critical.

Implementation of a coordinated research agenda will allow us all, working together, to bring the world closer to ending the pandemic for everybody.

WHO R&D Blueprint Secretariat

Link to Slides
## Appendix I: Agenda

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<td>13:00 - 13:10</td>
<td>Welcome address</td>
<td>Dr Michael J Ryan</td>
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<tr>
<td></td>
<td>Objectives of the meeting</td>
<td>Philip Krause Center for Biologics Evaluation &amp; Research, FDA, USA</td>
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<td>Chairperson of the WHO COVID-19 vaccines research expert group</td>
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<tr>
<td>13:20 - 13:30</td>
<td>COVID-19 vaccines as an additional tool to control COVID-19 pandemic: a public health research perspective</td>
<td>Peter Figueroa University of the West Indies, Mona, Jamaica</td>
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<td>Chair of PAHO’s Technical Advisory Group (TAG) on Immunization</td>
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### Session 1. What do we know and what additional evidence is needed to inform decisions on booster doses?

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<tr>
<td>13:30 - 13:40</td>
<td>Current understanding of mechanisms of vaccine-induced protection</td>
<td>Florian Krammer Icahn School of Medicine and Mount Sinai, New York, USA</td>
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<tr>
<td>13:40 - 13:50</td>
<td>Animal studies evidence on SARS-CoV-2 Delta variant pathogenesis and host response</td>
<td>Pragya Yadav Indian Council of Medical Research-National Institute of Virology, Pune, India</td>
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<td>13:50 – 14:00</td>
<td>Vaccines and variants: What randomized evidence is available?</td>
<td>Anna Chaimani Institute of Health and Medical Research (Inserm), Paris, France</td>
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<tr>
<td>14:00 - 14:10</td>
<td>Vaccines and variants: what immunological data is available?</td>
<td>Dan Barouch Center for Virology and Vaccine Research, Harvard University, USA</td>
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<td>14:10 – 14:20</td>
<td>Vaccines and variants: Methodological issues in using non-randomized studies to estimate vaccine effectiveness</td>
<td>Jonathan Sterne Bristol Population Health Science Institute, University of Bristol, UK</td>
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<td>14:20 – 14:50</td>
<td>Emerging evidence from ongoing studies: a zoom on the Delta variant</td>
<td>Brief updates by: Aziz Sheikh Usher Institute, University of Edinburgh, UK &amp; Chris Robertson Public Health Scotland, UK Nick Andrews Public Health England, UK Sharifa Nasreen Dalla Lana School of Public Health, University of Toronto, Canada Linda-Gail Bekker Institute of Infectious Disease &amp; Molecular Medicine, Univ. of Cape Town, South Africa</td>
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### Session 1. How much safety data are needed to support benefit-risk assessment of booster doses?

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| 15:20 – 15:50 | How much safety data are needed to support benefit-risk assessment of booster doses? | **Panel Discussion**  
**Marco Cavaleri** (moderator); Biological Health Threats and Vaccines Strategy, EMA  
**Rita Helfand**: Centers for Disease Control and Prevention, USA; Chair of the WHO Global Advisory Committee on Vaccine Safety  
**Dror Mevorach**: Department of Internal Medicine, Jerusalem’s Hadassah Medical Center, Israel  
**Raina MacIntyre**: Biosecurity Program, Kirby Institute, University of New South Wales, Australia |

15:50 – 16:00 | What should a booster dose achieve from the public health perspective and what data is needed? | **Alejandro Cravioto**  
Faculty of Medicine of the Universidad Nacional Autónoma de México, Mexico  
Chairperson of the WHO Strategic Advisory Group of Experts on Immunization |

16:00 – 16:30 | What additional research is needed to support informed regulatory decision-making about the benefits and risks of booster doses? | **Panel Discussion**  
**Philip Krause** (moderator)  
**Marie-Christine Bielsky**: Medicines and Healthcare products, Regulatory Agency (MHRA), UK  
**Tumi (Boitumelo) Semete-Makokotlela**: South African Health Products Regulatory Authority, South Africa  
**Peter Marks**: Center for Biologics Evaluation and Research (CBER), FDA, USA  
**Helen Rees**: Wits RHI  
**Liu Bo**: NMPA, China |

### Session 2. How can research contribute to optimize the use of available doses of COVID-19 vaccines?

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<th>Time</th>
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| 16:30 – 16:40 | What research is needed to evaluate Adjusted/Fractional doses and regimens in the context of primary vaccination and booster doses? | **Benjamin Cowling**  
School of Public Health, The University of Hong Kong |

16:40 – 16:50 | What complementary vaccine delivery strategies should be considered (in which context?) | **Larry Brilliant**  
Pandefense Advisory and Advisory Board of the NGO Ending Pandemics, USA |

16:50 – 17:00 | What research is needed to evaluate complementary vaccine strategies? | **Ira Longini**  
Department of Biostatistics, College of Public Health, University of Florida, USA |

17:00 – 17:30 | What research is needed to assess the potential impact of complementary vaccine delivery strategies? | **Panel discussion**  
**Larry Brilliant** (moderator); Pandefense Advisory and Advisory Board of the NGO Ending Pandemics, USA  
**Benjamin Cowling**: School of Public Health, The University of Hong Kong  
**Ira Longini**: Department of Biostatistics, College of Public Health, University of Florida, USA  
**John Clemens**: International Vaccine Institute, Seoul, Korea  
**Nancy Messonnier**: Pandemic Preparedness & Health Systems, Skoll Foundation, USA |

17:30 – 18:00 | Conclusions and Next Steps | **Philip Krause and Ana Maria Henao-Restrepo** |

18:00 | END OF MEETING |