Presenter Reminders

• Please **turn on your video** during your assigned session. As a presenter / panelist, your video will be shown to the audience unless you turn it off.

• As a presenter, **you can mute / unmute yourself to speak**. Note that general attendees cannot do this – they can only speak if Peyton identifies an individual to take themselves off mute. If you would like to call on an attendee to speak, please state their first and last name.

• Please **say “next slide”** to advance the slides. Peyton will be sharing her screen with everyone’s presentations already loaded.

• If you do not see the correct slide on your screen, it may be due to internet connectivity issues. Please **say the name of the slide header** that you’d like to see on the screen. As a backup, please open your slides separately in PowerPoint to reference the materials in the event internet issues arise.

• Peter or Jakob will chime in if you are over time. Otherwise, it is up to you to stay within your allocated time.

• During the discussion sessions, Peter or Jakob will serve as moderator, and the other will be sifting through the Q&A and feeding questions to the main moderator. However, if you see a question that was submitted by an audience member in the Q&A that pertains to your presentation, please write back to answer it.

• Q&A Chat: Please DO NOT click “answer live” and kindly only type in responses to the questions asked by attendees.
Connecting COVID-19 primary and booster vaccination goals: historical precedents, immunologic considerations and approaches to meeting regulatory and policy requirements
Meeting Norms and Recording Disclaimer

• Throughout the workshop, please ask any questions in the “Q&A” function. If you see that your question is already asked, you can “like” the question in the “Q&A” function.

• This workshop will be recorded. Please be mindful of the diverse audience attending the meeting when participating in open discussions.
Welcome & Meeting Objectives

Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>August 05, 2021 -Topics</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00 -15:20</td>
<td>Part I - Welcome, meeting objectives and updates</td>
<td>Peter Dull, BMGF</td>
</tr>
<tr>
<td>15:20-15:35</td>
<td>Historical perspective on booster vaccinations – Bacterial conjugate vaccines in childhood</td>
<td>David Goldblatt, UCL</td>
</tr>
<tr>
<td>15:35-15:50</td>
<td>Historical perspective on booster vaccinations and dose-sparing strategies – Yellow fever vaccine</td>
<td>Erin Staples, CDC</td>
</tr>
<tr>
<td>15:50-16:05</td>
<td>Overview of latest clinical data – Moderna COVID-19 vaccine program</td>
<td>Jackie Miller, Moderna</td>
</tr>
<tr>
<td>16:05-16:20</td>
<td>COVID-19 Vaccine Booster Studies: An Overview</td>
<td>Paul Oloo, CEPI</td>
</tr>
<tr>
<td>16:20-16:35</td>
<td>Q&amp;A Session</td>
<td>Moderated by Peter Dull</td>
</tr>
<tr>
<td>16:35-16:40</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>16:40-16:55</td>
<td>Part II - Regulatory Considerations for Booster Vaccinations</td>
<td>Jakob Cramer, CEPI</td>
</tr>
<tr>
<td>16:55-17:05</td>
<td>Summary of regulatory guidance/challenges for various boosting scenarios</td>
<td>Ian Hudson, BMGF</td>
</tr>
<tr>
<td>17:05-17:55</td>
<td>Panel discussion: Example scenarios of boosting regimens with homologous and heterologous vaccines including variant and fractional dosing</td>
<td>Moderated by Ian Hudson, BMGF</td>
</tr>
<tr>
<td>17:55-18:00</td>
<td>Wrap Up &amp; Next Steps</td>
<td>Jakob Cramer</td>
</tr>
</tbody>
</table>
Meeting Objectives

- Review immunological principles and historical precedents for booster vaccination
- Review recent immunological durability data and ongoing / planned booster studies
- Summarize available regulatory guidance for booster vaccine registration, including study design, endpoints and success criteria
- Explore alternative approaches for new or existing vaccines with heterologous and/or reduced dose boost vaccination
BOOSTERS? WHY ARE WE TALKING ABOUT BOOSTERS?

COVID-19 GLOBAL VACCINE TRACKER
SHARE OF PEOPLE WHO HAVE RECEIVED AT LEAST ONE DOSE OF COVID-19 VACCINE

N/A 0% 5% 10% 20% 30% 40% 50% 60% >70%

CANADA 70%
U.S. 55%
U.K. 68%
FRANCE 53%
MEXICO 26%
BRAZIL 42%
CHILE 69%
ISRAEL 66%
KENYA 2%
S. AFRICA 7%
JAPAN 31%
S. KOREA 31%
RUSSIA 20%
INDIA 23%
AUSTRALIA 27%

SOURCES: OFFICIAL DATA;
OUR WORLD IN DATA
LATEST DATA AVAILABLE, AS OF JULY 13, 2021
FORTUNE
**BOOSTERS? WHY ARE WE TALKING ABOUT BOOSTERS?**

"...there's not enough information to provide a recommendation at this point," Kate O'Brien, WHO IVB Director

**WHO calls for moratorium on booster vaccine shots through September, citing global disparity**

The World Health Organization doesn’t recommend Covid-19 booster shots "at this time," the group’s top vaccine doctor said Wednesday, citing a lack of data on their effectiveness.

Dr. Kate O’Brien, the WHO’s director of immunization, vaccines and biologicals, said the organization is still researching whether a booster shot is needed to increase protection against highly contagious mutations of the coronavirus.

**COVAX Clinical SWAT goals: Provide developers guidance to generate the right data to inform both regulatory and policymaker goals**
Vaccine Access in LMICs Lagging and Uncertainties Remain

**WHO Target:** Vaccinate at least 10% of the population of every country by September, at least 30% by the end of the year, and 70% globally by the middle of 2022.

**Current Status:** 75% of all vaccine doses have been administered in just 10 countries. 3 Countries have not rolled out any COVID-19 vaccines. Inequity is decreasing, but HICs have administered 61x more doses per inhabitant than LICs.

**Vaccine Supply to Date:** 22 vaccines have been approved by at least one NRA with 7 vaccines achieving WHO EUL status (AstraZeneca/Oxford + SII, Janssen, Moderna, Pfizer/BioNTech, Sinopharm BBIP, and Sinovac)
- Global: 4.6B doses delivered to 207 countries (3.6B H1 2021)
- COVAX: 174M doses shipped to 138 countries

**Outlook for H2 2021 and 2022:**
- Global  
  H2 2021 = 5.7B as base case for currently approved vaccines (9.4B for all of 2021)  
  16.9B for all of 2022  
- COVAX*
  Q3 = 410M, Q4 = 1.2B  
  2022 anticipated supply = 3.5B

*COVAX volumes are not risk-adjusted: e.g., time to market for Novavax, SII export restrictions, raw material shortages, ultra cold freezer availability, expanded age targets, potential booster vaccination, safety issues for authorized vaccines, funding, etc.

UNICEF COVID-19 Vaccine Market Dashboard
Clinical trials were complex to conduct before ---- and have only become more difficult

- Vaccines have become available and recommended in more countries and in a broader target population
  - Elderly and HCWs are highest risk and already excluded
- Country approval requirements shifting and multi-country studies require nimble protocol adaptation to address changes
  - e.g., Ethics committee approves protocol; Expert committees declines to endorse
- Enrollment rates mixed and increasing frequency of subject request for unblinding
- Increasing baseline seropositivity rates (next slide) decrease available efficacy population
- Interpretation of efficacy results with shifting VoC contributions complicated (e.g., Curevac)
COVID-19 PHASE 3 CLINICAL TRIAL OPERATIONAL UPDATES

- High and increasing rates of seropositivity observed among target population in efficacy studies --- limiting available per protocol population

<table>
<thead>
<tr>
<th>Region</th>
<th>Seropositivity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>European country 1</td>
<td>12.1%</td>
</tr>
<tr>
<td>European countries 2-4</td>
<td>1.1% – 4.6%</td>
</tr>
<tr>
<td>Latin American country 1</td>
<td>10.7%</td>
</tr>
<tr>
<td>Latin American country 2</td>
<td>29.5%</td>
</tr>
<tr>
<td>Latin American countries 3-7</td>
<td>4.9% – 56.3%</td>
</tr>
<tr>
<td>East Asian country</td>
<td>66.0%</td>
</tr>
<tr>
<td>African country</td>
<td>45.8%</td>
</tr>
<tr>
<td>Overall</td>
<td>Not available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Efficacy study A</th>
<th>Efficacy study B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment start</td>
<td>December 2020</td>
<td>March 2021</td>
</tr>
</tbody>
</table>

- Overall seropositivity rate: 48.2%
Among candidate with recent efficacy readouts, interpretation complicated by VoCs, other factors

CureVac Final Data from Phase 2b/3 Trial of First-Generation COVID-19 Vaccine Candidate, CVnCoV, Demonstrates Protection in Age Group of 18 to 60

- 40K subjects aged 18-80 years enrolled across 10 countries in Europe and Latin America
- Efficacy against COVID-19 of any severity 48% (83 vaccine vs. 145 placebo); Efficacy against moderate to severe disease 77% (9 vaccine vs. 36 placebo)
- 86% of cases with sequence data were VoCs (51%) or VoIs (35%), including Lambda (21%) and B.1.621 (14%)

Early efficacy studies ‘fortunate’ to operate is less confusing background; additional vaccine efficacy study readouts are forthcoming
Connecting COVID-19 primary and booster vaccination goals: historical precedents, immunologic considerations and approaches to regulatory and policy requirements

Historical perspective on booster vaccinations:
Bacterial Conjugate Vaccines in Childhood

David Goldblatt, Professor of Vaccinology and Immunology
University College London, UK
Epidemiology of invasive infection due to *H. influenzae* type b, *N. meningitidis* and *S. pneumoniae*.
• Hib conjugate vaccine licensed in 1987 for infants as a 4 dose course (3 dose priming and 1 dose booster) and first introduced widely in the USA 1989 (2/4/6 + 12-18m)
• Immunological memory demonstrated and thought likely to provide the basis for long term protection
• Hib Conjugate introduced into the UK accelerated infant immunization schedule (2/3/4 months) in 1992
  BUT
  - with no routine booster dose
  - a catch up campaign in Year 1
    for all < 5 years of age
- Hib Conjugate Vaccine introduced in 1992
- Given at 2/3/4 months
- No routine booster dose
- Catch up campaign (0-5yrs)
Reports of invasive Hib disease to HPA, England and Wales 1990-1997

Data courtesy of M Ramsay, HPA
Reduction in Hib disease in the UK
(8 year follow up following Hib conjugate introduction in 1992)
Invasive Hib infections by age group, 1992/3-2009/10
England and Wales, HPA Centre for Infections

Hib Conjugate Introduction 1992
Hib vaccine effectiveness (screening method) in cohorts born between 1996-99 and eligible for vaccination with DTwP/Hib-TT vaccine at the 2/3/4 month schedule*  

- Estimated using screening method
  \[ VE = 1 - \frac{[PCV(1-PPV)]}{[PPV(1-PCV)]} \]

- PPV is the proportion of the popn vaccinated (coverage)
- PCV is the proportion of the cases vaccinated

<table>
<thead>
<tr>
<th>Within 1 year of scheduled vaccination</th>
<th>1-2 yrs after scheduled vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases (# vaccinated)</td>
<td>Number of cases (# vaccinated)</td>
</tr>
<tr>
<td>Vaccine effectiveness (95% CI)</td>
<td>Vaccine effectiveness (95% CI)</td>
</tr>
<tr>
<td>24 (15)</td>
<td>98 (92)</td>
</tr>
<tr>
<td>87.3 (67.1 to 94.8)</td>
<td>19.2 (-125.9 to 64.3)</td>
</tr>
</tbody>
</table>

Ramsay et al JID 2003
Seroepidemiology of Hib IgG titres (England and Wales) by age: 9 years post introduction

Trotter et al Lancet 2003; 361:1523-4
Fig 1. Number of Hib reports in adults (15 years or older) and median Hib antibody titres in people aged 30-39 years, by year.
Invasive Hib infections by age group, 1992/3-2009/10
England and Wales,
HPA Centre for Infections

Cases (n)

Hib Conjugate Introduction 1992

6m-4yr catch up

Routine Booster 12m introduced

Epidemiological Year
Reports of isolates from the CSF: England and Wales 1982-2005

- Other named
- N meningitidis
- H influenzae
- S pneumoniae

Hib vaccine introduced in the UK

Enhanced surveillance from 1990 for Hi, 1993 for NM and 1996 for St pn
E Coli, Listeria, Group B Streptococcus, Mycobacterium TB, Staph aureus
Antibody Persistence and Immunological Memory at Age 4 Years after Meningococcal Group C Conjugate Vaccination in Children in the United Kingdom

Ray Borrow, David Goldblatt, Nick Andrews, Jo Southern, Lindsey Ashton, Sarah Deane, Rhonwen Morris, Keith Cartwright, and Elizabeth Miller

1Public Health Laboratory Service Meningococcal Reference Unit, Withington Hospital, Manchester, 2Immunobiology Unit, Institute of Child Health, and 3Immunisation Division, Public Health Laboratory Service Communicable Disease Surveillance Centre, London, and 4Public Health Laboratory, Gloucester Royal Hospital, Gloucester, United Kingdom

Functional Antibody (polysaccharide)

15m booster (polysaccharide)
4yr booster (polysaccharide)
15m MACP boost control

J Infect Dis 2002
1999

Within 1 calendar year:

- < 6 months:
  3 doses: 2/3/4 m
  (no boosters)**
- 6-11 months:
  2 doses
- 1-18 years:
  1 dose

**enhanced surveillance

Men C Conjugate
Licensed in the UK on Correlates of Protection
Global First Introduction

Join Femail’s campaign to save pashminas from the style snobs
Millions to be protected from killer MENINGITIS VACCINE FOR ALL CHILDREN

MILLIONS of children and teenagers are to be protected against meningitis C for the first time this winter.
Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction

Caroline L Trotter, Nick J Andrews, Edward B Kaczmarski, Elizabeth Miller, Mary E Ramsay

**Figure:** Cases of laboratory-confirmed meningococcal serogroup C disease by age group and quarter, 1995–2004
Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction

Caroline L Trotter, Nick J Andrews, Edward B Kaczmarski, Elizabeth Miller, Mary E Ramsay

Updated to 7 years post introduction
Men C functional antibody persistence after immunisation

SBA titres by time since MCC vaccination

- **Infants**
  - SBA titres
  - Time since vaccination (months)
  - Boostable

- **14-17 year olds**
  - SBA titres
  - Time since vaccination (years)
  - (Borrow et al Unpublished VEC data)
Laboratory Confirmed Cases of Meningococcal Disease, England & Wales, Five Weekly Moving Averages: 1997 - 2012 (11th Jan)

Slide courtesy of Ray Borrow
**Effect of vaccination status on SBA titre in convalescent sera**

<table>
<thead>
<tr>
<th>Vaccine status</th>
<th>No.</th>
<th>Adjusted* fold difference in SBA (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Failure</td>
<td>31</td>
<td>5.7 (1.2 – 27.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Unvaccinated Men C case</td>
<td>35</td>
<td>Referrent</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted by age at onset and interval to blood (days).
Clinical and Immunologic Risk Factors for Meningococcal C Conjugate Vaccine Failure in the United Kingdom

Cressida Auckland,1 Stephen Gray,4 Ray Borrow,4 Nick Andrews,3 David Goldblatt,3 Mary Ramsay,1 and Elizabeth Miller1

Antibody Avidity in cases and controls
Relevance for Covid 19 vaccines?

• Balance between circulating antibody and immune memory?
  – Short incubation times = memory may be insufficient (δ variant?)

• Role of T cells in preventing infection and/or disease
  – Disease modifying immunity (ie prevention of disease/hospitalization/death) may remain robust in the face of waning antibody

• Relevance of original strain vaccine immunity to protection against Variant strain
ACKNOWLEDGEMENTS

- Liz Miller
- Nick Andrews
- Ray Borrow
- Mary Ramsay
- David Salisbury
Historical perspective on booster vaccinations and dose-sparing strategies – Yellow fever vaccine

J. Erin Staples, MD, PhD
Arboviral Diseases Branch
Division of Vector-borne Diseases
Fort Collins, CO

COVAX Workshop – 6 August 2021
Background on yellow fever (YF)

- Caused by mosquito-borne virus (*Flavivirus*)
- Endemic in equatorial Africa and South America
- Varies from mild febrile illness to severe disease with jaundice and hemorrhagic manifestations
  - 30-60% case fatality rate for severe disease
- Preventable with live, attenuated viral vaccine developed in 1930s
  - Recommended for all persons aged ≥9 months residing in or traveling to endemic areas
  - Administered as one 0.5mL dose SC or IM
YF Vaccine Efficacy and Correlate of Protection

- No YF vaccine efficacy studies have been performed

- Several observations supported protective effect
  - Reduction in lab-acquired infection in vaccinated workers
  - Only unvaccinated persons developed disease following vaccine intro
  - Disappearance of cases in outbreaks when campaign conducted
  - Protection of monkeys against virulent virus challenge by passive transfer of neutralizing antibodies generated in response to vaccination

- Monkey studies have determined $\log_{10}$ neutralization index (LNI) of $\geq 0.7$ correlates with protection*
  - Correlates using more common plaque reduction neutralization test (PRNT) not established

YF Booster Doses
YF Vaccine Booster Dose

- Booster dose requirement established in 1965 for International Health Regulations (IHR)
- Interval of every 10 years based on 2 studies documenting ~80% recipients with neutralizing antibodies around 10 years post-vaccination
- In 2011, WHO SAGE Working Group formed to revisit need for booster doses
  - Accumulating evidence of long-standing immunity
  - Potential sparing of doses to improve vaccine coverage
Findings of Systematic Review Conducted for SAGE on YF Vaccine Booster Dose

- At 10-20 years post vaccination, high proportion (>90%) of ~1,000 vaccine recipient with neutralizing antibodies
- In ~150 persons vaccinated >20 years previously, ~80% have detected neutralizing antibodies
  - Antibodies detected as long as 60 years post vaccination
- From over 500 million doses delivered, 12 vaccine failures documented; all <5 years after initial vaccination
SAGE Working Group Considerations and Concerns with YF Vaccine Booster Dose Data

- Lack of understanding of protective immunity
  - Neutralizing antibodies associated with protective immune response
  - Significance of innate and cell-mediated immunity unknown

- Role natural boosting likely to occur in endemic areas
  - Travelers vs laboratory personnel vs endemic populations

- Limited data suggest certain populations might have lower seroconversion rates or more rapid antibody decay
Updated SAGE YF Vaccine Recommendations – 2013

- “A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary.”
Additional Booster Dose Considerations

- ACIP also discussed need for booster doses
- Reviewed similar data immunogenicity and safety data
- ACIP followed IHR so never recommended booster doses
  - Discussion was whether data supported need for booster doses rather than to remove booster doses
- ACIP: “A single primary dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers”
  - Additional populations noted for booster doses
Immune Response Following Use of Fractional Dose of YF Vaccine
Yellow fever (YF) outbreaks in Africa 2015-2016

- In late 2015, outbreak started in Luanda, Angola
  - First YF disease cases reported since 1981
- By May 2016, local disease cases detected in Democratic Republic of Congo (DRC)
  - 4 confirmed cases in Kinshasa (pop’n ~10 million)
- Uganda also reported confirmed cases in locations that had not had activity since 1940s
- Reactive mass vaccination campaigns conducted in all areas with confirmed cases
YF vaccine supply limitations

- By July 2016, emergency stockpile of 6 million doses depleted twice with continued vaccine needs for outbreaks

- WHO conducted systematic review on use of fractional doses of YF vaccine
  - Reviewed data on vaccine potency
  - Assessed data from YF vaccine fractional dose studies

- WHO convened group of SME to review fractional dose data and develop considerations for SAGE
Batch records show variable but high potency among manufacturers

<table>
<thead>
<tr>
<th>Batch potency (IU)</th>
<th>Manufacturer 1</th>
<th>Manufacturer 2</th>
<th>Manufacturer 3**</th>
<th>Manufacturer 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>43651</td>
<td>25704</td>
<td>18977</td>
<td>12874</td>
</tr>
<tr>
<td>Maximum</td>
<td>114815</td>
<td>125896</td>
<td>177827</td>
<td>26284</td>
</tr>
<tr>
<td>Minimum</td>
<td>13490</td>
<td>3715</td>
<td>4169</td>
<td>7578</td>
</tr>
<tr>
<td>Average 1/5</td>
<td>8709</td>
<td>5129</td>
<td>4467</td>
<td>2569</td>
</tr>
</tbody>
</table>

*The WHO requirements do not specify a maximum potency; only a minimum potency of 1000 international units

**Reported in PFU; others reported in international units
Summary of data on fractional doses of YF vaccination considered by WHO

- Four studies describing three cohorts
  - 175 to 749 healthy adult participants per study
  - Two of three cohorts limited to males
  - One study involved intradermal delivery

- No safety concerns noted with limited numbers
  - Intradermal delivery with more local reactions

- All studies showed robust immune response with small as one-fifth to one-tenth standard dose

Interim position paper and GRADE tables available at:
http://www.who.int/immunization/position_papers/position_paper_process.pdf
SAGE/WHO interim statement on use of fractional doses

Based on limited evidence, SAGE/WHO issued the following statement regarding fractional doses:

*Fractional dose of YF vaccine “should be considered in response to an emergency situation in which current vaccine supply is insufficient. Fractional dose vaccination should be used for vaccination campaigns in response to an outbreak or in settings where the extension of the outbreak is imminent and should not be used for routine immunization.”*
Preemptive campaign launched in Kinshasa, DRC to prevent continued cases and further spread of disease

- Needed 7,586,400 doses but only 2,500,000 doses available
- To ensure rapid vaccination of entire target population in Kinshasa, fractional dose strategy was considered:
  - Fractional dose: 1/5th (0.1 mL) of full dose administered subcutaneously (SC) using BCG syringe and needle
  - Everyone aged ≥2 years would receive fractional dose (“minimal dose”) of Bio-Manguinhos 17DD YF vaccine
- Children aged 9-23 months and pregnant women received full dose due to lack of data and immunogenicity concerns
Evaluation methods for immune response to fractional doses of YF vaccine

- In August 2016, WHO and other international partners provided assistance to DRC MoH with campaign planning
  - Campaign implemented at 2,404 immunization posts throughout city with >14,000 vaccinators
  - Over 10 days, delivered 7.9 million doses of vaccine, including 7.5 million fractional doses

- Public health investigation launched to assess viability
  - Sample obtained from ~750 individuals prior to vaccination, 28 (+7) days post vaccination, and 1 year (+1 month) post vaccination
  - YF virus-specific neutralizing antibodies determined by plaque reduction neutralization test (PRNT)
Initial and long-term immunologic response assessment

- 98% (705/716) of recipients seropositive for YF neutralizing antibodies on 28 day sample
- At 1 year, 97% (666/684) participants in DRC fractional dose campaign were seropositive

Final recommendations on use of fractional doses – July 2017*

- Fractional doses can be used as part of emergency response if shortage of full dose
- Use full dose once supply limitations improve
- Fractional doses should not be used in routine program or as longer-term strategy
- Fractional dose does not meet requirements under International Health Regulations (IHR)
  - Need to re-administer full dose for travel requirements

Next steps for fractional dose YF vaccination

- Obtain additional long-term immunogenicity data
  - Determine if antibody decay rates vary by dose

- Assess safety and effectiveness
  - Serious adverse events following immunization (AEFI) monitoring
  - Programmatic errors (accuracy of 0.1mL delivery)

- Determine desire of manufacturer and regulatory agencies to revisit current regulations and approval packages
Summary of YF Vaccine Applied to COVID-19 Vaccines

▪ YF vaccine around since 1937; however, critical knowledge gaps remain
  – Preventing disease cases and curbing outbreaks huge milestones
  – Retrospective reviews have addressed periodic questions or issues but imperfect

▪ Need to continue generating immunogenicity and safety data for COVID-19 vaccines to inform policy
  – Dose optimization; correlate of protection (both antibody and cell-mediated); duration of immunity; differences in immunogenicity and safety among vaccines, vaccine recipients, and against variants

▪ Easier to establish policy and regulation on prospectively collected, robust data than to revise based on limited retrospective data
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Preliminary Analysis of Safety and Immunogenicity of SARS-CoV-2 Variant mRNA Vaccine Boosters in Adults (P201)

Jacqueline Miller, MD

5 August 2021 – COVAX
P201 Clinical Study Evaluates Boosting with mRNA-1273, a Vaccine Against the B1.351 (Beta) Variant, or a Multivalent Vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Dose 1 and 2 of mRNA-1273</th>
<th>Dose 3</th>
<th>Interval between Doses 2 &amp; 3</th>
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</thead>
<tbody>
<tr>
<td>201B</td>
<td>20</td>
<td>100 µg</td>
<td>mRNA-1273 50 µg</td>
<td>≥ 6 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA-1273</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 µg</td>
<td></td>
</tr>
<tr>
<td>201C</td>
<td>20</td>
<td>100 µg</td>
<td>mRNA-1273.351 20 µg (data not shown)</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA-1273.351 50 µg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>100 µg</td>
<td>mRNA-1273.211 50 µg</td>
<td></td>
</tr>
</tbody>
</table>

- Assess safety & immunogenicity
- Data used to inform large, pivotal booster study
- Primary analysis based on day 15 and day 29 post-dose 3

Sera From Participants Immunized With mRNA-1273 in the Phase 1 Study Neutralizes Other SARS-CoV-2 Variants Of Concern, But To Different Degrees

- Sera from 8 phase 1 clinical trial participants collected 7 days after dose 2 showed:
  - Minimal effects on neutralization titers against B.1.1.7 (alpha)
  - Reductions in neutralization titers to other variants of concern ranged from 2.1- to 8.4-fold lower

Reference variant VOC VOI/Other

<table>
<thead>
<tr>
<th>GMT</th>
<th>Fold Change over D614G</th>
<th>Reciprocal ID 50 Titer (Log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1870</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>670</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>891</td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>273</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>222</td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>588</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>805</td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>567</td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>883</td>
<td></td>
<td>3.0</td>
</tr>
</tbody>
</table>

Horizontal dotted lines indicate the lower limit of quantification.
Solicited Local and Systemic Adverse Reactions within 7 days after administration of booster vaccine candidates

Safety and tolerability profiles following a booster of mRNA-1273, mRNA-1273.351, or mRNA-1273.211 were generally similar to those observed after dose 2 of mRNA-1273 in the previously reported Phase 2 and Phase 3 studies (data not shown)\(^1,2\).

Total N=80; n=20 per group. AE, adverse event.

P201 Part C
Comparison of booster strategies in validated assays at Day 1, 15, and 29 after vaccination

Validated clinical assays (NIH VRC)

D614G Neutralization

<table>
<thead>
<tr>
<th>Booster</th>
<th>Fold Increase</th>
<th>GMT 1</th>
<th>GMT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273</td>
<td>16.7</td>
<td>107</td>
<td>1786</td>
</tr>
<tr>
<td>mRNA-1273.351</td>
<td>11.1</td>
<td>156</td>
<td>1725</td>
</tr>
<tr>
<td>mRNA-1273.211</td>
<td>11.3</td>
<td>157</td>
<td>1757</td>
</tr>
</tbody>
</table>

B.1.351 (Beta) Neutralization

<table>
<thead>
<tr>
<th>Booster</th>
<th>Fold Increase</th>
<th>GMT 1</th>
<th>GMT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273</td>
<td>38.7</td>
<td>80</td>
<td>3083</td>
</tr>
<tr>
<td>mRNA-1273.351</td>
<td>46.4</td>
<td>3692</td>
<td></td>
</tr>
</tbody>
</table>

The geometric mean neutralizing antibody titers with 95% confidence intervals are denoted. The titers for individual participants are shown by the circles. The fold increase versus titers measured versus samples collected prior to the boost are shown. The horizontal dotted lines indicate the lower limit of quantification. N=20 participants per booster cohort. D, day; GMT, geometric mean titer; ID50, 50% inhibitory dilution; NAb, neutralizing antibody.

Strong boosting seen against D614G and Beta strains across all booster strategies (Day 15)

Updated booster candidates (including amounts of Beta antigen) did not materially increase GMT by Day 29
P201 Part C

Exploratory assay comparison against broader VOC 14 days post-dose 3

Dose 3 booster of 50 mcg of mRNA-1273 (prototype vaccine)

Exploratory assay (VSV-based) with strong correlation to validated assay for WT and Beta ($R^2$ of 0.92 and 0.94 respectively)

Neutralizing titers against ancestral strain remained above GMT against VOC waned substantially by 6 months post-dose 2

Dose 3 (50 mcg) booster increased GMT for Beta (32-fold), Gamma (43.6-fold) and Delta (42.3 fold) VOC
Limitations of this Preliminary Analysis of Booster Vaccine Candidates

- Results are based on non-randomized treatment groups
  - Cohort assignments were sequential based on availability of new vaccine formulations
- Sample size was small (N=20 per group) to facilitate rapid initiation of additional studies in support of licensure for a potential booster vaccine to address the evolving pandemic
- The research-grade used to evaluate some of the variants is not yet validated, but has been used consistently to assess the impact of variants on neutralization
- While the data are encouraging, the significant neutralization titers elicited from mRNA-1273.351 and mRNA-1273.211 are not definitive indicators of protection against B.1.351, P.1, or B.1.617.2
- Comparison of the results from mRNA-1273.211 and mRNA-1273.351 boosting with those from mRNA-1273 boosting should be interpreted with caution as participants were enrolled from two different clinical trials

PsVN, pseudovirus neutralization. VSV, vesicular stomatitis virus
Summary of the P201 Booster Study & Future Research

• 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 2 dose groups for mRNA-1273.351) previously vaccinated with a 2-dose primary series of mRNA-1273.1

• Safety and tolerability profiles following a booster dose of each of these vaccines were comparable to those observed after dose 2 of mRNA-1273 in previously reported studies1,2

• 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 concern1

Future Moderna clinical development

• 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

05 August 2021

Paul Oloo
“Mix & Match”

Concepts:
- Heterologous primary vaccination:
- Heterologous boosting:

Aim:
- **Address practical / operational aspects**
  - Can we do this? (‘interchangeability’ of vaccines $\rightarrow$ non-inferiority)
- **Improve immune response**
  - Can the immune response be improved? ($\rightarrow$ superiority)
- **Adjuvant- / antigen-saving strategy?**
- **Anti-vector immunity?**
- **Improve tolerability** (of the 2\textsuperscript{nd} dose) and safety?

$\rightarrow$ **Several trials** covering different regions / populations, vaccine combinations, circulating SARS-CoV-2 variants
Homologous Booster Studies: Overview

**Pfizer / BioNTech**

- Booster trial of a 3rd dose of BNT162b2 vaccine ongoing
- Booster dose 6 months after dose 2 well tolerated & elicits 5 x higher neutralization titers against wild type virus and Beta variant than after 2 primary doses
- Preclinical and clinical tests ongoing to confirm hypothesis that 3rd dose will boost Ab titers higher against Delta variant (B.1.617.2 lineage)(1)
- Plan to apply for EUA from US FDA to administer a 3rd dose

- **In the context of new SARS-CoV-2 variants:**
  - VE in preventing infection and symptomatic disease fell to 64%
  - VE in preventing hospitalization/critical disease remains high at 93% (2)
- Decline in VE is not the key message; instead, it should be –
  - Protection against COVID-19 is maintained six months post dose 2, especially against severe disease. It may be too soon for booster doses.

1. Liu, J. et al, BNT162b2-elicted neutralization of B.1.617 and other SARS-CoV-2 variants, [https://www.nature.com/articles/s41586-021-03693-y](https://www.nature.com/articles/s41586-021-03693-y)
Homologous Booster Studies: Overview [ctd.]

COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain¹,²

- Post dose 3 titers vs. the Delta variant are >5-fold post dose 2 titers in 18-55 y/o & >11-fold post dose 2 titers in 65-85 y/o
- Estimated potential for up to 100-fold increase in Delta neutralization post-dose three compared to pre-dose three

¹ Initial data; ² Samples were tested against each variant separately; PRNT: Plaque Reduction Neutralizing Test; WT: Wild Type; GMR: Geometric Mean Ratio

Second Quarter 2021 Earnings

Data submitted for publication

Source: https://investors.pfizer.com/investors-overview/default.aspx
Sinovac (CoronaVac) 6 month durability and 3rd dose boosting (Ph 2)*

- Limited neutralizing Ab persistence at 6 months
- Appropriate boost response among all subjects indicative of memory induction
- Limitations include lack of CMI, subjects > 60yo and VoC evaluations

*Pan, et al (2021), Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years
Immune response after 3rd dose of AstraZeneca vaccine

1. Antibody levels measured following 3rd dose of AZ vaccine*

2. IFNγ ELISpot responses in participants receiving a third dose of AZ vaccine*

- Primary series at 8-week interval
- 3rd dose at 38 weeks (~9 months) after second dose
- 3rd dose induces Abs to level correlating with high efficacy after second dose and boosts T-cell responses

*Flaxman, A. (2021) Tolerability and Immunogenicity After a Late Second Dose or a Third Dose of ChAdOx1 nCoV-19, Oxford Vaccine Group, https://www.ovg.ox.ac.uk/publications/1185667
Johnson & Johnson

• Single-shot generated strong, persistent activity against Delta variant
• Durability of the immune response lasted through 8 months (time evaluated to date)
• Humoral & cellular immune responses lasted through at least 8 months
• T-cell responses – including CD8+ T-cells persisted
• Average neutralizing titer at eight months > average at 29 days including against VoC
• Follow-up to assess persistence of vaccine effectiveness over time in context of new VoC (4)
## Core Elements in Heterologous Boosting Studies

<table>
<thead>
<tr>
<th>SPONSOR</th>
<th>Uni Hospital Southampton (COV Boost) - UK (1)</th>
<th>NIAID-US (2)</th>
<th>Qihan Li - China (3)</th>
<th>Jiangsu Province CDC - China (4)</th>
<th>Jiangsu Province CDC - China (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Phase</td>
<td>2</td>
<td>1 / 2</td>
<td>NA</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Sample size</td>
<td>2886</td>
<td>550</td>
<td>112</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Age</td>
<td>≥30</td>
<td>≥18 to 99</td>
<td>≥18</td>
<td>≥18 to 59</td>
<td>≥60</td>
</tr>
<tr>
<td>Screening test (PCR, N-protein)</td>
<td>None (online screening)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Interval to booster post last dose</td>
<td>≥3 months</td>
<td>≥3 months</td>
<td>6 months</td>
<td>3-6 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Assays</td>
<td>Binding Ab, Neutralising Ab, Neutralising Ab, ELISPOT, ICS</td>
<td>Binding Ab, Neutralising Ab</td>
<td>Binding Ab, Neutralising Ab, ELISPOT</td>
<td>Binding Ab, Neutralising Ab, ELISPOT</td>
<td>Binding Ab, Neutralising Ab, ELISPOT</td>
</tr>
<tr>
<td>CMI analysis (Y/N)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood draw timepoints</td>
<td>D0, 7, D14, D28, 84, 365</td>
<td>D14, D28; M3, M6, M12</td>
<td>D14, D28</td>
<td>D14, D28, M6</td>
<td>D14, D28, M6</td>
</tr>
<tr>
<td>Follow up duration after booster</td>
<td>12 months</td>
<td>12 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

3. Qihan Li, Ameliorating effect of mRNA vaccine in individuals immunized with inactivated vaccine, [https://clinicaltrials.gov/ct2/show/record/NCT04944381](https://clinicaltrials.gov/ct2/show/record/NCT04944381)
Discussion

- Despite declining Ab titres, VE against severe COVID-19 seems to be maintained – despite circulating VOCs
- Are booster doses important to maintain **measurable Ab titres vs clinically meaningful VE against severe disease**?
- 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 re. new VOCs
- Need for **booster doses in special populations** at risk for severe disease / with reduced or shortened immune protection (immunocompromised persons, the elderly etc)
- CEPI Planned Studies:
  - Through CfP, add booster doses to trials with M&M regimen (incl. AZ, Sinopharm)
  - Consider investigational fractional booster doses (to be discussed by Jakob in Part 2)
Question & Answer Session

Moderated By:

Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
Question & Answer Session

Moderated By:

Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)

Participants

• David Goldblatt, UCL
  “Historical perspective on booster vaccinations – bacterial conjugate vaccines in childhood”

• Erin Staples, CDC
  “Historical perspective on booster vaccinations and dose-sparing strategies – Yellow fever vaccine”

• Jackie Miller, Moderna
  “Overview of latest clinical data – Moderna COVID-19 vaccine program”

• Paul Oloo, CEPI
  “COVID-19 Vaccine Booster Studies: An Overview”

Please submit questions through the Q&A function on Zoom
Break
Regulatory Considerations for Booster Vaccinations

Jakob Cramer, MD

Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
Booster Vaccinations – Considerations Around Dose-Sparing Options / Fractional Doses

COVAX Clin. Dev. SWAT Workshop

Jakob Cramer

5th August 2021
Inverse figure for **seropositivity in unvaccinated persons**?

→ data e.g. from baseline samples in RCTs indicate

• 10-20% in HICs
• >50% to >80% in some (areas in) LMICs
Some Considerations ...

- The world needs more
  - **Vaccine** (= supply of those products already approved / authorized)
  - **Vaccines** (= products yet to be approved / authorized)

- There is a shift from **vaccinating immune-naïves** towards **vaccinating primed populations** (when will e.g. >50% of the world’s population be primed – with / without vaccination?):
  
  **2020 / 2021:**
  - Primary vaccination in unprimed (seronegatives)

  **2022 ff.:**
  - Primary vaccination in unprimed
  - Primary vaccination in primed (seropositives = post natural infection)
  - Booster vaccination in previously vaccinated

- Will we eventually need a (seasonal) VOC-adapted vaccine given irrespective of previous vaccination / infection (influenza)?

- For approved / authorized vaccines, are there dose-sparing options?
  - **Increase vaccine supply:** accelerate vaccination coverage (without compromising VE / public health impact)
  - **Improve reactogenicity (and safety?)** profile

- Generating clinical evidence takes **time**. It is increasingly difficult to recruit **immune-naïve populations** into RCTs

- Pandemic situation: data supporting **label claims** versus pragmatic **NITAG recommendations**
Booster / Fractional Doses: Increasing Complexity

- **PH objective**: Align on context re vaccine efficacy objective: end the pandemic by having an **impact on incidences** (VE against infection and transmission) or **prevent morbidity / mortality** (VE against severe disease, hospitalisation, death)?

- **VOC**: Fractional dose suitable for **boosting in the context of VOCs**?

- Fractional dose in **primed versus unprimed individuals**: role in a) primary immunisation, b) booster dose, c) both?

- **Interchangeability**: **Heterologous priming / boosting with fractional doses**

- **Vaccine**: **Which vaccine should be prioritised** for fractional dose?
  - vaccines with highest immunogenicity (vaccine efficacy)?
  - vaccines most widely used?

- **Optimal dose**: While **half dose** might be easiest from a practical perspective – is this the way forward (why not 1/3 or 3/4 or 1/10 dose)?

- **Formulation**: **Currently licensed vaccine formulations may not be suitable for fractional dose administration** – e.g. small dose volume, for other vaccines (formulated as multi-dose) impossible to double diluent volume

- **Alternative approaches**, e.g. ID application?
## Dose-Sparing: Options - TBD

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Objectives</th>
<th>Advantage</th>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Near-term (&lt;6 months)</strong></td>
<td>• Fractional dose for priming (general / risk population) - LMIC</td>
<td>➢ Increase vaccine supply quickly / significantly?</td>
<td>➢ Evidence will not become available short-term</td>
</tr>
<tr>
<td></td>
<td>• Fractional dose for 2&lt;sup&gt;nd&lt;/sup&gt; dose of a 2-dose priming regimen (general / risk population) – LMIC</td>
<td>➢ Increase vaccine supply quickly / significantly?</td>
<td>➢ Operational challenges: prospective randomization of unvaccinated (seronegative) population</td>
</tr>
<tr>
<td></td>
<td>• Fractional dose as 3&lt;sup&gt;rd&lt;/sup&gt; dose (increase IR post priming with moderately immunogenic vaccines – LMIC (MIC))</td>
<td>➢ Evidence can be generated fairly quickly (several countries interested in conducting respective trials)</td>
<td>➢ Evidence relevant only for those countries planning third dose for priming</td>
</tr>
<tr>
<td><strong>Mid-term (6-12 months)</strong></td>
<td>• Fractional dose for booster vaccination (general / risk population) - HIC</td>
<td>➢ Reduce pressure on vaccine supply mid-term in HIC → more vaccine for priming in LMIC?</td>
<td>➢ Limited immediate relevance for LMIC</td>
</tr>
<tr>
<td></td>
<td>• Fractional dose for priming in paediatric populations – HIC</td>
<td>➢ Less absorption of vaccine supply for paediatric vaccinations in HIC may have beneficial effect on vaccine supply in LMIC</td>
<td>➢ Evidence will not become available short-term</td>
</tr>
<tr>
<td><strong>Long(er)-term (&gt;12 months)</strong></td>
<td>• Fractional dose for booster vaccination (general / risk population) – LMIC</td>
<td>➢ Beneficial effect on vaccine supply in the long(er) term</td>
<td>➢ Low vaccination coverage for priming in LMIC: challenges in planning future booster vaccination strategies in LMIC</td>
</tr>
<tr>
<td></td>
<td>• Fractional dose for priming and boosting in paediatric populations – LMIC/HIC</td>
<td>➢ Increase vaccine supply long-term</td>
<td>➢ Evidence will not become available short-term</td>
</tr>
</tbody>
</table>
Platform Trial Concept [CONCEPT]: Prospective randomised trial to assess the immunogenicity of fractional *versus* full doses given as a single booster vaccination in previously primed subjects

- **Aim:** fractional doses for booster vaccination / ‘large simple trial’ (incl. secondary objective on vaccine effectiveness)
- **Primary objective:** Immune response (SRR) of ½ *versus* full dose (irrespective of number of doses received for priming)
- **Single blind (or even unblinded), multi-country**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Visit #1</th>
<th>Visit #2</th>
<th>... F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age groups 18-59 and 60+ with documented hx of …</strong></td>
<td>Day 1</td>
<td>Day 29 (week 4)</td>
<td>1, 2 years... ?</td>
</tr>
<tr>
<td><strong>Arm A</strong></td>
<td>• One dose (single dose regimen / incomplete 2-dose regimen) or 2 doses (any vaccine, different intervals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arm B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Alternatively** (in areas with high seropositivity through natural infection):
- All comers → assess single full / fractional dose post natural infection (=seropositive, no hx. of vaccination @ baseline)

→ Offer full vaccination with locally registered / available vaccine to those with insufficient immune response
Recruitment and Stratification Strategy [CONCEPT]

- **Country A**: 18-59 yo;
- **Country B**: ≥60 yo;
- **mRNA**: 2 priming doses: 3-<8 week interval;
- **VV**: 2 priming doses: ≥8 week interval;
- **WVI**: Incomplete 2 dose regimen (1st dose only);
- **Fractional single booster dose**: Booster <6 months post priming;
- **Full single booster dose**: Booster ≥6 months post priming;

**Immune response:**

**Primary comparison:** All Randomised

**Secondary comparisons** in subgroups, e.g.
- Age groups (18-59; 60+)
- Single / 2 dose for priming
- Vaccine received for priming
- Intervals
- ...
Platform Trial Approach: Organisational Structure [CONCEPT]

**COVAX / CEPI project team**
- Financial / scientific oversight

**Programme Coordination**
- Coordination
- Quality management
- Central data management, analysis

**Trial A**
(country / consortium A)

**Trial B**
(country / consortium B)

**Trial C**
(country / consortium C)

**Trial XY**
(country / consortium XY)

- **cTRG**
- **RDMIC**
- **EIC**

COVAX R&D&M Workstream: Overall strategic, scientific and budget approval

Develops core strategy / protocol, financial / strategic oversight

Expresses interest → application. Adopts protocol to local needs / sponsor role (CSA, trial execution, data entry etc.), owns trial data, ...

Comments, suggestions, feedback, expression of interest:
Dr. Amol Chaudhari, CEPI: amol.chaudhari@cepi.net
Summary of Regulatory Guidance/Challenges for Various Boosting Scenarios

Ian Hudson
Senior Adviser,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
REGULATORY CONSIDERATIONS FOR BOOSTER VACCINATIONS

• To date, licences have been based on homologous platform (same company same platform), primary series only.

• Range of studies planned/ongoing/completed looking at:
  ▪ Heterologous platform primary vaccination series
  ▪ Homologous platform prototype virus boost/Homologous platform variant virus boost
  ▪ 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
  ▪ Fractional dose

It’s complicated with many permutations possible.
REGULATORY CONSIDERATIONS FOR BOOSTER VACCINATIONS

Challenges:

• Conducting clinical efficacy studies unlikely to be successful
• Increasing challenge of identifying naïve subjects
• Will boost only, without primary vaccination indication, be acceptable for licensure?
• No ICP established yet but growing confidence in using nAb to compare new vaccines to those with clinical efficacy data.
• What evidence is needed for licensure vs policy considerations; a licensure is a minimum but use may go beyond licensure.
• Is variant boost more appropriate than original strain boost which may still offer sufficient protection.
Guidance available covering variant boost scenario (as strain change).

Study design: primary series with homologous vaccine, followed by boost with variant, +/- randomization against homologous non-variant boost.

Endpoints: NI of seropositive rates and GMTs against the variant compared to primary series against the original virus.

What about the booster with non-variant vaccine? Increase in neutralizing antibodies commensurate with primary series?

Questions: Will this approach be acceptable where vaccine licensure for primary vaccine is based on immunobridging rather than clinical data?
SUMMARY OF US, EU, ACCESS, AND WHO GUIDANCE ON STRAIN CHANGE

- Four different guidance documents regarding strain change are available, including US FDA, EMA, Access Consortium, and WHO
- The scope for all guidance documents is similar with a requirement for the parent/prototype vaccine to be approved and the variant/adapted vaccine to use the same manufacturing process and sites, and with the assumption that there is no correlate of protection
- All allow immunobridging to prototype vaccine
- Different terminology is being used across the various guidance documents
- Similarities and differences exist between the various guidance documents in terms of chemistry, manufacturing and control, non-clinical considerations, clinical considerations, and safety data requirements.
HOMOLOGOUS PLATFORM FOR PRIMARY VACCINE SERIES/HETEROLOGOUS (VARIANT OR ORIGINAL VIRUS) BOOST

• No guidance available yet.
• For variant boost, will regulators accept NI of seropositive rates and GMTs against the variant compared to primary series against the original strain (in the absence of ICP)?
• For non-variant boost, will regulators accept increase in neutralizing antibodies at least equivalent to primary series with non variant virus vaccine?
• Is homologous boost required as comparator in study?
• Is licensure for primary series required for heterologous boost vaccine, as a pre-requisite for licensure as boost?
Stage 1

- A: 444 subjects 2 dose primary series with BNT162b2; 444 subjects 2 doses of ChAdOx1 nCov19; each group randomised to ChAdOx1 nCOV-19; Novavax; Novavax half dose+; Men ACWY (control) (111 participants each)

- B: 555 subjects primary series with BNT162b2; 555 subjects with ChAdOx1-nCov19; each group randomised to BNT162b2; VLA2001; VLA2001 half dose+; Ad26.COV2.S; MenACWY (111 participants each)

- C: 444 subjects 2 dose primary series with BNT162b2; 444 subjects 2 doses of ChAdOx1 nCov19; each group randomised to mRNA-1273 ;CVnCoV ; BNT162b2 half dose+; Men ACWY (111 participants each group)
COV-BOOST STUDY; ENDPOINTS

• Safety and reactogenicity

• To determine whether the immune response to booster immunisation with different COVID-19 vaccines is superior to control vaccination for participants who have received priming vaccination with either ChAdOx1-nCov19 or BNT162b2; The primary outcome assessed from stage 1 will be a geometric mean ratio in day 28 anti-spike protein IgG of 1.75 compared to the control group.
OTHER PERMUTATIONS

• Many other possible permutations in a real world setting, depending on availability etc:
  ▪ Unlikely that each will be licensed
  ▪ Likely scenario will be limited data supporting policy/use.
  ▪ Pre-requisite will be licensure for the vaccine to have it available
• Exchange of views on authorisation of second-generation vaccines and alternative approaches to demonstrate vaccine efficacy

• Comment that data to support the authorization of 2nd generation vaccines may depend on whether the vaccine will be used for primary series vaccination or for booster vaccination based on primary series vaccination with a different vaccine.

• Approaches to authorization of 2nd generation vaccines may include placebo controlled clinical disease endpoint trials provided they can still be ethically performed. Alternative approaches may include relative clinical disease endpoint efficacy studies and possibly human challenge trials.

• There was consensus that immunogenicity bridging studies may be needed if an assessment of effectiveness of 2nd generation COVID-19 vaccines in clinical endpoint efficacy studies are no longer feasible

• Other challenges for regulators included defining approaches to demonstrate effectiveness for 2nd generation vaccines that will be solely developed as booster vaccines e.g. administered as heterologous boost following a primary series with another vaccine
CONCLUSIONS

• Many scenarios are possible. If we need a booster:
  ▪ Focus on clarity around data requirements for boost, especially heterologous (prototype or variant).
  ▪ Data for licensure vs policy making.
  ▪ What data would be required for boost only approach to licensure?
Panel: Example Scenarios of Boosting Regimens with Homologous and Heterologous Vaccines Including Variant and Fractional Dosing

Moderated By:
Ian Hudson
Senior Adviser,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
### Panel Members

- Marie-Christine Bielsky, Expert Medical Assessor, MHRA
- Eric Karikari Boateng, Senior Clinical Reviewer, Ghana FDA
- Adam Hacker, Head of Global Regulatory Affairs, CEPI
- Phil Krause, Deputy Director, Office of Vaccines Research and Review, FDA/CBER
- Helen Rees, Board Chair of the SA Health Products Regulatory Authority (SAHPRA)

### Potential Scenarios for Discussion

- *Vaccine A primary series followed by Vaccine B boost*
- *Vaccine A primary 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*
Wrap Up & Next Steps

Jakob Cramer, MD
Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
Closing remarks

• Thank you all for your participation and engagement today

• Workshop report distributed shortly to summarize today’s conversation

• We will continue to share resources at the website here: https://epi.tghn.org/covax-overview/clinical-science/

• Next workshops: TBD

• 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
Clinical Development & Operations SWAT Team