COVID-19 Vaccine Development in an Increasingly Seropositive World

Clinical Development & Operations SWAT Team | Wednesday October 27, 2021
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>October 27, 2021 -Topics</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00-15:10</td>
<td>Part I - Welcome, meeting objectives and updates</td>
<td>Peter Dull, BMGF</td>
</tr>
<tr>
<td>15:20-15:30</td>
<td>Vaccination among the previously infected: Immunology and effectiveness</td>
<td>Florian Krammer, Icahn School of Medicine at Mount Sinai</td>
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<tr>
<td>15:30-15:40</td>
<td>Vaccination among the previously infected - Lessons from Clover’s phase 3 efficacy study</td>
<td>Htay Htay Han, Clover</td>
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<tr>
<td>15:40-15:50</td>
<td>Covid-19 vaccine delivery update</td>
<td>Emily Nickels, BMGF</td>
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<tr>
<td>15:50-16:05</td>
<td>Heterologous COVID-19 Booster Vaccine studies</td>
<td>Paul Oloo, CEPI</td>
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<tr>
<td>15:50-16:05</td>
<td>Fractional doses – research gaps</td>
<td>Christof Vinnemeier, CEPI</td>
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<tr>
<td>16:05-16:15</td>
<td>Heterologous vaccination: what can we anticipate in terms of breadth and durability?</td>
<td>Robbert van der Most, CEPI</td>
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<tr>
<td>16:15-16:25</td>
<td>Q&amp;A Session for Part I</td>
<td>Moderated by Peter Dull</td>
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<tr>
<td>16:25-16:35</td>
<td>Part II - Regulatory Considerations for Booster Vaccinations</td>
<td>Jakob Cramer, CEPI</td>
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<tr>
<td>16:35-16:45</td>
<td>How the USA Increased Its Access to Seasonal Influenza Vaccines 15 Years Ago</td>
<td>Bruce Innis, PATH</td>
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<td>16:45-17:00</td>
<td>Surrogate markers and correlates of protection: immuno-bridging in an increasingly primed population</td>
<td>Edde Loeliger, CEPI</td>
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<td>17:00-17:10</td>
<td>Success criteria for phase 3 immunologic non-inferiority trial for COVID-19 vaccines</td>
<td>Christian Taucher, Valneva</td>
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<td>17:10-17:55</td>
<td>Panel Discussion: Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines</td>
<td>Moderated by Peter Dull, BMGF</td>
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<tr>
<td>17:55-18:00</td>
<td>Wrap Up &amp; Next Steps</td>
<td>Jakob Cramer</td>
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Meeting Objectives

• Review global epidemiology of past natural infection with SARS-CoV-2
• Provide update on global vaccine delivery and uptake by vaccine type
• Review vaccine immune responses and efficacy among those with prior COVID-19 infections
• Discuss current and future approaches to generating supportive efficacy data for vaccine licensure
## COVID-19 vaccine development landscape

As of 14 October 2021, a total **332 candidate vaccines** of which **113** in clinical trials, **22 in large scale use**

[https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines](https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)

### Table: COVID-19 Vaccine Development Landscape

<table>
<thead>
<tr>
<th>Technology Type</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
<th>In Use</th>
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<td>RNA</td>
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<td>3</td>
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<td>Vector (replicating)</td>
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<td>3</td>
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<td>7</td>
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<td>Other/Unknown</td>
<td>32</td>
<td>3</td>
<td>2</td>
<td>1</td>
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</tr>
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</table>

[https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/](https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/)
Covid-19 Vaccine development – new challenges

- Diversity of vaccines available with increasing volume but remain imperfectly distributed
- Impressive performance across several vaccine platforms but…still gaps remain
  - Durability of protection across different clinical endpoints, variable impact on variants, relatively high COGs / price, volume insufficient, deliverability (cold chain), safety evaluations continue to evolve
- Environment for new vaccine development continues to shift
  - Placebo controlled studies challenging but ongoing (e.g., WHO Solidarity Trial Vaccines)
  - Seropositivity, “natural” or vaccine induced, is increasing
  - Booster or “additional” dose as a new development target (heterologous successes)
- Each product may have different challenges
  - Antibody not putative driver of efficacy, NRA setting without immuno pathway, product better aligned for use among sero-positive / exposed persons
- Never too early to look forward ---- challenges ourselves with an “influenza pathway”
Global COVID-19 seroprevalence studies in unvaccinated populations, 2020-2021

Workshop “COVID-19 Vaccine Development in an Increasingly Seropositive World”

27th of October 2021
Emmanuelle Espié
Seroprevalence data from observational real-life studies
Geographic patterns and temporal trends
Cumulative number of serosurveys published over time
(source: SeroTracker)

2550 seroprevalence studies
in 119 countries including 26 million participants
Geographical distribution of national seroprevalence studies reporting population-wide estimates, 2020

- Sub-Saharan Africa: 19.5% [9.0-26.0%]
- North Africa, Middle East: 8.2% [0.1-17.7%]
- South Asia: 17.1% [8.7-25.0%]
- Latin America: 10.6% [3.0-46.5%]
- US-EU: 4.1% [2.4-6.9%]
- Central & Eastern Europe: 12.2% [4.5-25.4%]
- East Asia, Oceania: 0.6% [0.3-1.4%]

Median seroprevalence [IQ]): 4.5% [2.4–8.4%]

Seroprevalence data in Europe, 2020-2021

- EU/EEA: Among non-vaccinated adult population, ~20% had detectable antibodies against SARS-CoV-2, with a higher proportion in 11-19 years old compared to 20-64 years old.

- Sweden: March 2021 (prior to vaccination), seroprevalence among blood donors of 22% [95%CI 20.3-24.5]

- UK: August 2021 (Week 34), seroprevalence among unvaccinated blood donors aged 17 years and older of 18.9% [95%CI 17.9-20.0]


Folkhälsomyndigheten. [https://www.folkhalsomyndigheten.se/contentassets/376f021a4c84da08de18ac597284f0c/pavisningantikroppar-mot-sars-cov-2-blodgivare.pdf](https://www.folkhalsomyndigheten.se/contentassets/376f021a4c84da08de18ac597284f0c/pavisningantikroppar-mot-sars-cov-2-blodgivare.pdf)
SARS-Cov2 antibody seroprevalence (% seropositive) in blood donors in England, 2020-2021
In repeated studies of blood donors, seroprevalence increased from 3.5% in July 2020 to 20.2% in May 2021.
Seroprevalence data in LMIC

- **Brazil**: Among the Sao Paulo population aged 18 years, seroprevalence increased from 13.6% in September 2020 to 25% [95%CI 21.7-28.7] in February 2021.

- **Kenya**: Among blood donors (aged 16-64 years), the seroprevalence increased from 9.1% in September 2020 to 44.2% [95%CI 42.4-46.0] by March 2021.

- **South Africa**: Among blood donors (aged 15-69 years) over the 1st quarter of 2021, the seroprevalence was estimated 47.4% [95%CI 46.2-48.6].

- **India**: In January 2021, the third national survey showed a seroprevalence of 24.3% [95%CI 23.1-25.6] in the population aged >10 years, with higher rates in urban (Delhi, Hyderabad 54-56%) versus rural areas.

July 2021: Seroprevalence in children 57.2% and 61.6% respectively in 6-9 yoa and 10-17 yoa.

References:
Seroprevalence data from clinical trials setting
<table>
<thead>
<tr>
<th>Country</th>
<th>Seropositivity % *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>1.10%</td>
</tr>
<tr>
<td>Spain</td>
<td>4.05%</td>
</tr>
<tr>
<td>Belgium</td>
<td>4.22%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>4.56%</td>
</tr>
<tr>
<td>Argentina</td>
<td>4.94%</td>
</tr>
<tr>
<td>Colombia</td>
<td>10.7%</td>
</tr>
<tr>
<td>Panama</td>
<td>14.6%</td>
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<tr>
<td>Peru</td>
<td>18.7%</td>
</tr>
<tr>
<td>Mexico</td>
<td>12.4%</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>56.3%</td>
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* Presence of antibodies binding against SARS-Cov2 Nucleoprotein

**HERALD Phase IIB/III clinical trial
Recruitment: from December 2020 to April 2021**

<table>
<thead>
<tr>
<th>Country</th>
<th>Seropositivity**</th>
</tr>
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<tbody>
<tr>
<td>Belgium</td>
<td>13%</td>
</tr>
<tr>
<td>Brazil</td>
<td>30%</td>
</tr>
<tr>
<td>Colombia</td>
<td>46%</td>
</tr>
<tr>
<td>South Africa</td>
<td>46%</td>
</tr>
<tr>
<td>Philippines</td>
<td>65%</td>
</tr>
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</table>

**SPECTRA Phase II/III clinical trial
Recruitment: from May 2021 to August 2021**

** Presence of antibodies binding against SARS-Cov2 Spike protein
Seroprevalence in unvaccinated populations, 2021

Take home messages
Summary and discussions

• **Wide variations of seropositivity in unvaccinated populations up to mid-2021**
  - HIC: seropositivity ~ 20% with high vaccination coverage (≥ 60%)
  - LMIC: seropositivity up to 50-60% with low vaccination coverage (< 20%)

• **Methodological limitations**
  - Study design and population (specific population subgroups vs. general population )
  - Sampling size and selection (small convenient sample vs. large representative sample)
  - Sensitivity and specificity of immunoassays

• **Impact of the increasing seropositivity rate in unvaccinated populations**
  - Public health perspective:
    • Major risk of disease transmission from infected unvaccinated individuals
    • Recommendations for vaccination of previously infected individuals
    • Vaccine effectiveness and safety in previously infected individuals
  - Future vaccine development:
    • Control / Placebo seronegative group
    • Dose ranging and dose finding

• Given pandemic progression and vaccination rollout → need for updates (especially in LMIC)
Vaccination among the previously infected:
Immunology and effectiveness

Florian Krammer
Mount Sinai Professor in Vaccinology
Icahn School of Medicine at Mount Sinai

COVAX Workshop COVID-19 Vaccine Development in an Increasingly Seropositive World
October 27th, 2020
How do we find out who was previously infected?
Infection induces long-lived anti-spike responses in individuals with mild COVID-19

approximately 5% of antibody positive participants sero-reverted

John Kubale, Aubree Gordon, Florian Krammer, Viviana Simon plus the PARIS study team
Assay sensitivity and/or persistence of immunity is influencing NP seroprevalence

Carreño et al., iScience, 2021
This has also been observed by other laboratories – but it is unclear if it is caused by biology or technology.

Grandjean et al., CID, 2021

Muecksch et al., JID, 2021
Sero-prevalence study in New York City
(data until beginning of May 2021)

First and worst wave
in New York

2020/21 winter
wave starts

Vaccination becomes available for people with underlying conditions

Vaccination becomes available for HCWs

Juan Manuel Carreño and Krammer lab serology core
Spike-binding IgG antibodies mounted upon natural infection provide significant protection from re-infection

**PARIS NYC** data included in this analysis:
- 154 seropositive
- 246 seronegative

Follow up every 2-4 weeks:
Median: 102.5 days

**11 documented new SARS-CoV-2 infections**
- 10 in naïve participants
- 1 in a participant with COVID-19 history but no detectable antibodies (sero-reversion) at the time of re-infection
- p=0.01
Pre-Delta studies showing that natural infection affords protection from reinfection (similar to vaccines)


Post-Delta studies showing that natural infection affords protection from reinfection (similar to vaccines)

- https://www.nature.com/articles/s41591-021-01548-7
What happens if you vaccinate previously infected individuals?
What happens if you vaccinate previously infected individuals?

Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine

Pfizer and Moderna mRNA vaccinees
Antibody titers after mRNA vaccination in naïve individuals and individuals previously infected with SARS-CoV-2

14 breakthrough infections so far in fully vaccinated individuals, all in the naïve vaccinated group

PARIS cohort with Viviana Simon
A large number of studies show that vaccinating individuals previously infected with SARS-CoV-2 leads to very robust immune responses.
What to expect when vaccinating previously infected (or vaccinated) individuals?

• Typically a quick and robust anamnestic antibody response after one vaccination
  • This is also seen in sero-reverters
  • A second dose may not further increase the immune response
• Even after one dose peak titers are often higher in pre-exposed individuals than in naïve individuals
• Timing between infection and vaccination may matter
• Not every vaccine may boost pre-existing immunity in the same way
• Boosting vaccine-induced pre-existing immunity may be different than boosting infection-induced pre-existing immunity
• Placebo controlled trials with partially immune control groups would need to be very large
Vaccination among the previously infected - Lessons from Clover’s phase 3 efficacy study

Htay Htay Han
October 27, 2021
Clover’s COVID-19 Vaccine Candidate: SCB-2019 (CpG 1018/Alum)

- **Adjuvanted Protein-Based COVID-19 Vaccine Candidate**: SCB-2019 antigen (30 µg/dose) in combination with CpG 1018 adjuvant and aluminum hydroxide (alum)
  - **Two-dose** vaccine candidate (administered 21 days apart)
  - **Intramuscular (IM) injection** (0.5 mL/dose)
  - **Standard refrigeration** (2-8°C) storage & transportation conditions

**SCB-2019 Antigen**

- SCB-2019 is a recombinant SARS-CoV-2 Spike (S) protein, preserved in the *native trimeric prefusion conformation* form utilizing Trimer-Tag™

**Global Collaborations**

- Up to $360.5 million grant funding by CEP
- Clinical & commercial supply agreements with Dynavax for CpG 1018 adjuvant supply
- Advanced Purchase Agreement (APA) signed with Gavi to supply up to over 400 million doses to the Covax facility for global distribution

SCB-2019 Antigen Structure

- **S1** Prefusion Spike (S) Protein of SARS-CoV-2 Original Strain
- **S2** Trimer-Tag™
Phase 2/3 Efficacy Trial Initiated on 24 MARCH 2021

➢ Over 30,000 participants aged 18 years or older enrolled in SPECTRA in 5 Countries across 4 Continents (South America, Asia, Europe and Africa)
Global Phase 2/3 Pivotal Trial Design

Double-Blind, Randomized, Controlled Trial Evaluating Efficacy, Immunogenicity & Safety

30,128 Adults & Elderly Participants (1) (≥18 Years of Age)

R 1:1

SCB-2019 (CpG 1018/Alum)
2 Injections, 21 Days Apart
N= 15,064

Placebo (Saline)
2 Injections, 21 Days Apart
N= 15,064

➢ Primary Efficacy Endpoint:
  ▪ Prevention of PCR-confirmed COVID-19 of Any Severity ≥14 Days After Second Dose (in baseline seronegative participants)

➢ Secondary Efficacy Endpoints(2):
  ▪ Prevention of moderate-to-severe COVID-19, severe COVID-19, hospitalization due to COVID-19
  ▪ SARS-CoV-2 strain-specific prevention of any, moderate-to-severe, and severe COVID-19
  ▪ Efficacy in baseline seropositive (previously-infected) participants
  ▪ Immunogenicity (including neutralizing antibodies)

➢ Primary Safety Endpoints:
  ▪ Solicited AE – Systemic & Local (within 7 days after each dose)
  ▪ Unsolicited AEs (up to day 43)
  ▪ SAE, MAAE, AESI (all participants)

Abbreviations: AE (adverse event), SAE (serious adverse event), MAAE (medically-attended adverse event), AESI (adverse event of special interest).
(1) Number of participants randomized and dosed in trial.
(2) Prespecified secondary efficacy endpoints in protocol for which data are available at time of topline results.
Key Takeaways from SPECTRA Global Phase 2/3 Trial

- SPECTRA successfully enrolled over 30,000 adult & elderly participants in 5 countries across 4 continents
- 100% of SARS-CoV-2 strains observed in the efficacy analysis were variants (Delta was predominant strain)

✓ Primary and secondary efficacy endpoints were successfully met
✓ 100% efficacy against severe COVID-19 & hospitalization, 83.7% efficacy against moderate-to-severe COVID-19, 67.2% efficacy against COVID-19 of any severity caused by any strain of SARS-CoV-2 in SPECTRA
✓ Delta: 78.7% efficacy against COVID-19 of any severity caused by the globally-dominant Delta strain
✓ Favorable safety profile: No significant differences in systemic adverse events or severe/serious adverse events compared to placebo
✓ First COVID-19 vaccine to demonstrate significantly reduced risk of COVID-19 disease in previously-infected individuals, a growing & increasingly important population as SARS-CoV-2 continues to spread globally

Note: Abbreviations of “SCB-2019(CpG 1018/Alum)” are used in the following slides, including “SCB-2019”. SARS-CoV-2 variants are identified in the following slides by their WHO assigned labels based on the letters of the Greek alphabet (e.g., Delta for Delta Variant).
Significant Overall Efficacy Against COVID-19 (Including Globally-Dominant Delta Strain)

✓ Vaccine efficacy appears to be persistent through 112 days after second dose in environment dominated by Delta and other concerning variants

Notes: Figure shows data for PCR-confirmed COVID-19 of any severity (against any strain) at ≥14 days after second dose in participants without evidence of prior SARS-CoV-2 infection (baseline seronegative). Primary endpoint in protocol.
Enables Clover to Evaluate Efficacy Against Delta in a Randomized Clinical Trial

- Delta was the predominantly circulating strain globally during SPECTRA enrollment
- SPECTRA evaluated SCB-2019 (CpG 1018/Alum) against concerning variants including Delta

Source: Strain distribution data from Nextstrain.org (GISAID data) as of 06-SEP-2021


Novavax case collection window for primary efficacy endpoint from 25-JAN-2021 to 30-APR-2021 (PREVENT-19 Final Data Announcement Presentation; 14-JUNE-2021).

Clover case collection window for primary efficacy endpoint in SPECTRA from 28-APR-2021 to 10-AUG-2021.

Global SARS-CoV-2 Strain Distribution (GISAID Database)

Delta is now responsible for >90% of COVID-19 cases globally
Delta was the Dominant SARS-CoV-2 Strain in SPECTRA

- 100% of identified SARS-CoV-2 strains observed in the efficacy analysis were variants
- Globally dominant Delta was the strain most observed in SPECTRA (38% of all sequenced cases)
- >85% of strains in SPECTRA were VOCs/VOIs with suspected escape mutations (Delta, Mu, Gamma, Beta, Theta, Lambda)

COVID-19 Cases included in primary efficacy analysis:\(^1\):

- Total Adjudicated Cases:\(^2\): 207 cases

Strain sequencing provides basis for strain-specific efficacy analysis in SPECTRA:

- Adjudicated + Sequenced Cases: 179 cases
- Adjudicated + Sequenced/Identified: 146 cases
- 100% of these strains were variants
- Top 3 Variants (Delta, Mu, Gamma) represented 73% of strains
- No cases were caused by Original Strain of SARS-CoV-2

Note: VOC (Variant of Concern), VOI (Variant of Interest).

\(^1\) Counting of cases for primary efficacy analyses begins at ≥14 days after second dose. Cutoff date for primary efficacy analyses was 10 AUG 2021 in all countries in SPECTRA.

\(^2\) 207 cases included in primary efficacy analyses in baseline seronegative participants were adjudicated by an independent endpoint adjudication committee (EAC). 41 additional cases in baseline seropositive participants were adjudicated and included for secondary efficacy analyses.

\(^3\) Samples processed for sequencing, but strains were not identified (e.g., lack of sufficient nasopharyngeal swab sample collected, unsuccessful RNA-sample extraction, etc.).
Significant Efficacy Also Observed Against Gamma (VOC) and Mu (VOI)

✓ First COVID-19 vaccine to demonstrate significant efficacy against **Delta, Gamma & Mu variants** (Top 3 strains in SPECTRA, comprising 73% of all strains identified)

- Differences in vaccine efficacy likely driven by unique mutation profiles of each variant strain

- **Gamma**: 91.8% efficacy against Gamma (any severity)
  - Gamma (P.1) harbors E484K escape mutation in RBD, and demonstrated high transmissibility in Brazil and other Latin American countries[^1]

- **Mu**: 58.6% efficacy against Mu (any severity)
  - Mu (B.1.621) is predominant strain in Colombia[^1], and believed to be ‘Beta-like’ based on spike protein mutation profile and cross-neutralization studies[^2]
  - A Phase 2b/3 clinical trial of an mRNA COVID-19 vaccine candidate demonstrated lowest efficacy against Mu (41.5% vaccine efficacy) among all variant strains evaluated[^3]

- **Other**: Against all other sequenced strains (including Alpha, B.1.623, Beta, Lambda, Theta, Other & Not Identified), efficacy against moderate-to-severe COVID-19 was 90.2% (95% CI: 31.2, 99.8), and efficacy against COVID-19 of any severity was 55.0% (95% CI: 24.9%, 73.8%)
  - No hospitalizations or severe COVID-19 cases in vaccine group (2 severe COVID-19 cases in placebo group)
  - Insufficient number of cases of each individual variant strain to enable statistical analyses of vaccine efficacy

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Notes: VOC (variant of concern); VOI (variant of interest). RBD (receptor binding domain of spike protein). Figures show data for PCR-confirmed COVID-19 at ≥14 days after second dose in participants without evidence of prior SARS-CoV-2 infection (baseline seronegative).

[^1]: NextStrain.org (GISAID database) as of 06-SEP-2021.
[^2]: DOI: 10.1101/2021.09.06.459005
[^3]: DOI: 10.2139/ssrn.3911826
Enrollment of Previously-Infected Individuals in SPECTRA

- Previous COVID-19 vaccine clinical trials evaluated efficacy & safety primarily in SARS-CoV-2 naïve individuals ('baseline seronegatives')
- As SARS-CoV-2 continues to spread globally, evaluation of vaccine efficacy & safety in previously-infected individuals ('baseline seropositives') is becoming increasingly important
- ~49% of all participants enrolled in SPECTRA were baseline seropositive, providing basis for landmark analysis of vaccine efficacy in this population
- Analysis for vaccine efficacy in SPECTRA were stratified by baseline seropositivity status

Data shown for all participants with available seropositivity testing results.

Note: Baseline seropositivity status determined by presence of antibodies binding to SARS-CoV-2 Spike (S) protein in Day 1 serum samples (Roche Elecsys® anti-S test) or known history of COVID-19 disease.
Unprecedented Analysis of Efficacy in Previously-Infected Population

- Previous SARS-CoV-2 natural infection provides significant protection against symptomatic re-infection; however,
- SCB-2019 vaccination can significantly boost protection in previously-infected subjects
- SCB-2019 is the first COVID-19 vaccine globally to demonstrate vaccine efficacy & safety in previously-infected individuals

![Diagram showing COVID-19 Incidence Per Person-Year by participant baseline seropositivity status and vaccine group.](#)

**COVID-19 of Any Severity**

- **Incidence of COVID-19 in SPECTRA Caused by:**
  - **Delta**
    - Placebo: 0.091 (71.4% Reduction), SCB-2019: 0.026 (94.5% Reduction)
    - 95% CI: SCB-2019 81.4–99.8
  - **Any Strain**
    - Placebo: 0.31 (81.8% Reduction), SCB-2019: 0.06 (93.5% Reduction)
    - 95% CI: SCB-2019 88.0–96.8

**Participant Baseline Seropositivity Status:**
- **SARS-CoV-2 Naïve (Baseline Seronegative)**
- **Previously-Infected (Baseline Seropositive)**

**Trial Group:**
- Placebo
- SCB-2019

**# at Risk:**
- Placebo: 5,806, 6,147, 6,195
- SCB-2019: 155, 30, 11

**# of Cases:**
- Placebo: 46, 14, 3
- SCB-2019: 155, 30, 11

Source: Adapted from Clover Public Presentation for SPECTRA Ph 2/3 Trial Data (22 SEP 2021).
Notes: Figures show data for PCR-confirmed COVID-19 at ≥14 days after second dose. Preliminary efficacy in baseline seropositives relative to baseline seronegative placebo group is exploratory post-hoc analysis. "Reduction" refers to reduction in risk of COVID-19 compared to placebo group in SARS-CoV-2 naïve (baseline seronegative subjects).
Neutralizing Antibodies (Wildtype SARS-CoV-2 Neutralization Assay)

- High neutralizing antibodies induced in SARS-CoV-2 naive participants after 2 doses of SCB-2019 (CpG 1018/alum); results are in-line with Clover’s Phase 1 clinical trial.

- Rapid & strong boosting effect induced in previously-infected participants after 1 dose, supporting further evaluation of SCB-2019 (CpG 1018/alum) as a booster vaccine.

Notes: Bars represent Geometric Mean Concentrations (GMC) ± 95% confidence intervals (95% CI). Validated Wildtype neutralization assay against the original strain of SARS-CoV-2 (VisMederi). Titers expressed was international units/mL (IU/mL) based on WHO international standard sera (WHO IS 20/136). Samples with titers below LLOQ were assigned a value of 12.5.

Baseline Seronegatives (1)

Baseline Seropositives (1)

---

Notes: Bars represent Geometric Mean Concentrations (GMC) ± 95% confidence intervals (95% CI). Validated Wildtype neutralization assay against the original strain of SARS-CoV-2 (VisMederi). Titers expressed was international units/mL (IU/mL) based on WHO international standard sera (WHO IS 20/136). Samples with titers below LLOQ were assigned a value of 12.5.

Baseline Seronegatives (S-)

Baseline Seropositives (S+)

---

Notes: Bars represent Geometric Mean Concentrations (GMC) ± 95% confidence intervals (95% CI). Validated Wildtype neutralization assay against the original strain of SARS-CoV-2 (VisMederi). Titers expressed was international units/mL (IU/mL) based on WHO international standard sera (WHO IS 20/136). Samples with titers below LLOQ were assigned a value of 12.5.

Baseline Seronegatives (S-)

Baseline Seropositives (S+)
Key Takeaways from SPECTRA Global Phase 2/3 Trial

- SPECTRA successfully enrolled over 30,000 adult & elderly participants in 5 countries across 4 continents
- 100% of SARS-CoV-2 strains observed in the efficacy analysis were variants (Delta was predominant strain)

- ✓ Primary and secondary efficacy endpoints were successfully met
- ✓ 100% efficacy against severe COVID-19 & hospitalization, 83.7% efficacy against moderate-to-severe COVID-19, 67.2% efficacy against COVID-19 of any severity caused by any strain of SARS-CoV-2 in SPECTRA
- ✓ Delta: 78.7% efficacy against COVID-19 of any severity caused by the globally-dominant Delta strain
- ✓ Favorable safety profile: No significant differences in systemic adverse events or severe/serious adverse events compared to placebo
- ✓ First COVID-19 vaccine to demonstrate significantly reduced risk of COVID-19 disease in previously-infected individuals, a growing & increasingly important population as SARS-CoV-2 continues to spread globally
Thank You
COVID-19 VACCINE DELIVERY UPDATE

COVAX Clinical Dev & Ops Workshop, Oct 27, 2021

Emily Nickels
Program Officer
Bill & Melinda Gates Foundation
COVERAGE INEQUITY: HIC 66%, UMIC 60%, LMIC 26%, LIC 2%
At least 56 countries have confirmed COVID-19 vaccine boosters/additional doses

**PLEASE NOTE: WHO DOES NOT RECOMMEND BOOSTER DOSES, AND HAS CALLED FOR A VACCINE BOOSTER MORATORIUM UNTIL END OF 2021**

### Key takeaways

- 50 countries (70% are HICs) started administering boosters/additional doses as of Oct 5th:
  - 6 HICs confirmed a booster program but yet to start
  - At least 12 other countries are considering a booster program

At least 3x as many booster doses are administered daily as there are primary doses in LICs

---

**Data as of Oct 05, 2021**

**Status of COVID-19 booster administration, # of countries**

<table>
<thead>
<tr>
<th>Category</th>
<th>LIC</th>
<th>LMIC</th>
<th>UMIC</th>
<th>HIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries providing boosters/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>additional doses</td>
<td>12</td>
<td>35</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Countries with boosters</td>
<td>50</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>confirmed but not yet started</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total confirmed</td>
<td>56</td>
<td>56</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Government statements, press search
MOST COUNTRIES HAVE RECEIVED 4+ PRODUCTS

PROPORTION OF TOTAL DOSES RECEIVED BY PRODUCT ACROSS AMC92 PARTICIPANTS

EXAMPLE: PRODUCT INFLUX IN KENYA

**Summary of vaccination program**

- 4.9M doses administered
- 9.2 doses administered / 100 population
- 6.4% first dose coverage
- 2.6% fully vaccinated

**Key challenges**

- Microplanning with limited supply visibility
- Managing different product profiles:
  - Cold chain requirements
  - Immunization schedules
  - Training and administration
  - 2nd dose follow-up
- Prioritization based on expiration
- Availability of ancillary products (notably 0.3ml syringes)

COVAX FACILITY GLOBAL SUPPLY FORECAST

COVAX Forecasted Supply under Most Likely Scenario,
Cumulative, M doses, 2021 and 2022

1 Forecasts are based on best available information from manufacturers and analysis from Gavi and UNICEF. Timing of available supply is based on anticipated date of release by manufacturer, at which point doses become available for delivery, as such, timing of delivery to countries will be lagged. Volumes for expected single-dose regimen candidates doubled to ensure comparability across vaccines. Volumes have been rounded to nearest 5M, except those less than 10M, and so totals may not equal sum of segments.

2 "Dose donations" estimated based upon donor commitments to share new doses bilaterally with COVAX. The transfer of COVAX allocations from SFPs to AMC Participants are already included in "Supply from legally-binding agreements".
Heterologous COVID-19 Booster Vaccine Studies

COVAX Workshop on COVID-19 Vaccine Development in an Increasingly Seropositive World

27.10.2021

Paul Oloo
## Overview - Planned and Ongoing Heterologous Boost studies

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Dose interval (in months)</th>
<th>Location</th>
<th>Status</th>
<th>Preliminary data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Task Force, NIH, Uni Hosp of Southampton (COV Boost)</td>
<td>&gt;3 after 2\textsuperscript{nd} dose</td>
<td>UK</td>
<td>Ongoing</td>
<td>No</td>
</tr>
<tr>
<td>NIAID</td>
<td>3</td>
<td>USA</td>
<td>Ongoing</td>
<td>Yes (Preprint)</td>
</tr>
<tr>
<td>University of Birmingham (OCTAVE DUO)</td>
<td>At least 14 days after completing primary series</td>
<td>UK</td>
<td>Ongoing</td>
<td>No</td>
</tr>
<tr>
<td>Erasmus Medical Centre (SWITCH)</td>
<td>3</td>
<td>Netherlands</td>
<td>Ongoing</td>
<td>Yes (WHO consultation)</td>
</tr>
<tr>
<td>Christian Medical College (CMC) Vellore</td>
<td>6</td>
<td>India</td>
<td>Ongoing</td>
<td>No</td>
</tr>
<tr>
<td>Jiangsu CDC+Cansino</td>
<td>3–6</td>
<td>China</td>
<td>Active. not recruiting</td>
<td>No</td>
</tr>
<tr>
<td>Jiangsu CDC</td>
<td>3</td>
<td>China</td>
<td>Ongoing</td>
<td>No</td>
</tr>
<tr>
<td>Qihan Li</td>
<td>6</td>
<td>China</td>
<td>Not yet recruiting</td>
<td>No</td>
</tr>
<tr>
<td>Medical University Innsbruck, Austria</td>
<td>3</td>
<td>Austria</td>
<td>Ongoing</td>
<td>No</td>
</tr>
</tbody>
</table>
• Adults received Moderna, JnJ or Pfizer vaccines followed by booster after 12 weeks in 9 combinations
• mRNA peaks at D15, stable at D29
• JnJ incremental rise to D29
• Limitations:
  • Non-randomized
  • Study did not control for intervals between primary vaccines and boosts
  • Only antibody data available – cellular immune data pending
  • Data from early timepoints only

Erasmus Medical Centre Heterologous Boost study in Health Care Workers 18-65 years old (SWITCH Trial)

- Primary vaccine – Janssen vaccine single dose
- Booster dose after 12 weeks
- Primary outcome: IgG Ab titers 28 days after booster

- 389/434 Ad26.COV2.S HCW had binding antibodies at baseline (89.6%)
- Homologous and heterologous injections boosted binding antibodies
- Heterologous mRNA-boost most immunogenic, especially mRNA1273

Vries, R. Erasmus MC, Adopted from WHO consultation on COVID-19 Vaccine research, 25.10.2021, NCT04927936
Adverse events post-boost

- Only mild systemic and local adverse events reported
- Adverse events generally resolved within 48hrs
- mRNA1273 was most reactogenic
Key Learnings

• mRNA vaccines most reactogenic particularly mRNA-1273
• Use of mRNA-1273, Ad26.COV2.S and BNT162b2 as booster vaccines leads to anamnestic serologic responses after priming with Moderna or Pfizer or Janssen vaccines
• mRNA vaccines result in higher antibody titers in the first 28 days after boost compared to viral vectored vaccines
• No safety concerns identified so far
• Most trials focus on mRNA platform vaccines and Janssen vaccine. There is urgent need to close corresponding gaps for vaccines used in LMICs
Discussion

• More data on heterologous boost studies expected in coming weeks and months through Q1 2022
• Clinical trials ongoing: Which vaccine works best as a booster jab?
• The order of prime-boost administration may be important: may be antigen-dependent, influenced by the type(s) of immune responses to be achieved
• Benefits of booster doses should be clear in order to make a benefit:risk assessment
  • Primary vaccination may not induce adequate immunity in immunocompromised persons and recipients of vaccines with low efficacy
• More data on how long immunity lasts following the primary series of COVID-19 vaccines
• Risk of booster doses:
  • safety concerns (platform specific? Dose specific?);
  • unknown long-term consequences;
  • adverse public health outcomes
• Not all vaccines have controlled or systematic analyses of post-authorization safety data
• Data on administration of booster vaccine(s) together with flu vaccine(s) - studies ongoing
Fractional doses – research gaps

COVAX Clinical Development and Operations SWAT Team Workshop Oct 27, 2021

Christof Vinnemeier
Urgent need for data on fractional doses of COVID-19 vaccines

• Terminology

  *Booster dose:* To maintain immune response over time
  *Additional dose:* as part of / to complete primary immunisation (e.g. 2+1), 1 dose given months (>6 months) after priming (for vaccines with a rapid decline in Ab-levels, in special populations)

• Why fractional doses?  →  Supply shortages / safety considerations

• Fractional doses have been proven to be feasible with other vaccine platforms (e.g. live-attenuate YFV-17D (1/5 dose) or non-adjuvanted protein HBs Ag (1/4 dose)

• First data available (e.g. Moderna 50 µg, BNT/Pfizer 10 µg/3µg, Janssen 1.25x10^{10}), intradermal application of 10ug/20ug mRNA-1273, more data to be published soon (e.g. CoV-BOOST study)
Fractional doses – Questions and Challenges

- **Fractional doses in un-primed populations:** Primary immunisation?

- **Fractional in doses in primed populations:**
  - only for special populations (e.g. elderly, immunocompromised) given the recent SAGE recommendation and continuing supply shortages?
  - for individuals after natural infections (particular importance in LMICs)
    - Lancet data from Ethiopia indicates seroprevalence rates up to 73% in unvaccinated urban communities (as of April 2021)  
      - Gudina, EK et al. Lancet Glob Health 2021
Fractional doses – Questions and Challenges

• **Durability** of antibody responses when boosted (with fractional doses): all available data reflects short-time follow-up periods (up to 8 weeks)

• **Selection of vaccine**, dose selection (benefit/risk; dose dependent safety aspects), timing of booster

• **Practical challenges**: secure vaccine supply for trials, administration of small volumes of vaccines, shortages of syringes
A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations (FraCT-CoV)

Technical and administrative questions about this Call should be directed to cfp@cepi.net
Open call

Fractional dose platform trial: Core elements

1. **Full versus fractional single dose** of a selected vaccine. If the “booster“ vaccine differs from vaccine given for priming, a control group including the same vaccine (full dose) given for primary vaccination should be considered.

2. **4-week interval** between „booster“ dose and primary immunogenicity endpoint.

3. Immune response for primary endpoint assessed based on **binding antibodies** (IgG ELISA).

4. **Reactogenicity / safety** assessment (as co-primary objective).

5. Follow-up (safety) for at least **3 months**.
Heterologous vaccination: what can we anticipate in terms of breadth and durability?

25 October 2021

Robbert van der Most
• How to define heterologous boosting? *Platform and/or antigen*
• Consider **protection** as a function of antibody titer, durability, CMI and innate immunity
• Consider **boostability** as a function of memory B cells => numbers and specificities

**Situation**

1. Infection
2. Disease
3. Severe disease
4. Death
Example 1: it works

- **Hepatitis B fractional dose boosting**
- Subjects were immunized with different HBsAg vaccines => different memory levels
- Memory B cell numbers well maintained
- Boosted with 1/5 dose non-adjuvanted HBsAg => clear boost in responses
- However, this is not really heterologous

[Image of a and b graphs showing changes in antibodies and memory B cells over days post-vaccination.]

[Budroni et al., 2021: NPJ Vaccines DOI: 10.1038/s41541-021-00337-0]
Example 2: it may work or not

- **H5N1 influenza heterologous boosting**
- Same platform but different antigens (H5N1/Indonesia versus H5N1/Vietnam)
- H5N1/Vietnam-prime => H5N1/Indonesia boost => measure Indonesia-specific HAI-response
- Good news (1) & bad news (2): depending on the nature of immunological memory
- Hypothesis: difference between (1) and (2) explained by CD4 T helper cells
- *Continuous improvement*: with CD4 help, B memory cells can deal with antigenic differences: go from (2) to (1)

[Van der Most RG et al., 2014: Science Translational Medicine 6, 246  DOI: 10.1126/scitranslmed.3008409]
An immunological framework for heterologous boosting

- **A B-cell centric world view**
- Primary vaccination induces B cell responses that depend on CD4 help
- B cells differentiate into plasma cells and B memory cells

**CD4 help:** class switching, affinity, BCR hyper-mutation

- Memory B cells
  - *Their existence allows boosting*

- Plasma cells => homing to the bone marrow
  - *Their survival determines Ab durability*
An immunological framework for heterologous boosting

- Strain specificity is determined by the B cell receptor
- The memory pool has different specificities, including $\alpha/\beta/\gamma/\delta$ – specific or cross-reactive X

Boosting = pick & choose from the pool
Less need for CD4 help
Example 2 revisited

- **H5N1 influenza heterologous boosting after priming with or without adjuvant**
- The difference between success (1) and failure (2) is driven by memory
- (2) is an example of original antigen sin => *wrong-footing the system*
- Which B memory cells are being picked? OR:
- How to get Indonesia-antibodies with Vietnam-memory cells?

[Van der Most RG et al., 2014: Science Translational Medicine 6, 246 DOI: 10.1126/scitranslmed.3008409]
Translation to SARS-CoV-2 vaccines

- Longitudinal analysis of mRNA vaccine-induced responses:
  - Binding and neutralizing antibodies + memory B
  - B memory => what is the breadth and diversity?
  - Breadth => which variant sequences are recognized?

CEPI [Goel et al., 2021: Science Oct 14 DOI: 10.1126/science.abm0829]
Breadth of Spike-specific memory B cells

- At 6 months: memory B cells pool is diverse with many cells being cross-reactive
- This facilitates heterologous boosting because there are memory cells to choose from

[Goel et al., 2021: Science Oct 14 DOI: 10.1126/science.abm0829]
Real life: MixMatch data from ComCov

‘COM-COV 2’

Enrolled those
- immunized with a single dose of Pfizer or ChAdOx1 between 25th January and 20th March
- Randomisation at 2nd dose

Non-inferiority of immune response to ‘alternate’ vs ‘same’ boost

1070 > 50 year olds

<table>
<thead>
<tr>
<th>General and Immunology cohort</th>
<th>number</th>
<th>Enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>primed with Pfizer at 8 to 12 weeks previously</td>
<td>175</td>
</tr>
<tr>
<td>2</td>
<td>175</td>
<td>Moderna</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>Novavax</td>
</tr>
<tr>
<td>4</td>
<td>Primed with ChAdOx 8 to 12 weeks previously</td>
<td>175</td>
</tr>
<tr>
<td>5</td>
<td>175</td>
<td>Moderna</td>
</tr>
<tr>
<td>6</td>
<td>175</td>
<td>Novavax</td>
</tr>
<tr>
<td>Total</td>
<td>1050</td>
<td></td>
</tr>
</tbody>
</table>
Real life: MixMatch data from ComCov

28 days post boost dose-Immunogenicity plots: ELISA

Rank order at day 28 post boost

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Anti-spike IgG</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT/Moderna</td>
<td>22953</td>
<td>(20589-25590)</td>
</tr>
<tr>
<td>ChAd/Moderna</td>
<td>20116</td>
<td>(18150-22296)</td>
</tr>
<tr>
<td>BNT/BNT</td>
<td>16929</td>
<td>(15025-19075)</td>
</tr>
<tr>
<td>BNT/Novavax</td>
<td>8886</td>
<td>(7393-10680)</td>
</tr>
<tr>
<td>ChAd/Novavax</td>
<td>5597</td>
<td>(4756-6586)</td>
</tr>
<tr>
<td>ChAd/ChAd</td>
<td>1971</td>
<td>(1718-2262)</td>
</tr>
</tbody>
</table>

Data presented at D7 based on immunology cohort only (N=25 per group)
Question & Answer
Session for Part I

Moderated By:

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

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

Participants

- Emmanuelle Espie, CEPI
  “Global Covid19 seroprevalence studies in unvaccinated populations, 2020-2021”

- Florian Krammer, Icahn School of Medicine at Mount Sinai
  “Vaccination among the previously infected: Immunology and effectiveness”

- Htay Htay Han, Clover Pharmaceuticals
  “Vaccination among the previously infected - Lessons from Clover’s phase 3 efficacy study”

- Emily Nickels, BMGF
  “Covid-19 vaccine delivery update”

- Paul Oloo, CEPI
  “Heterologous COVID-19 Booster Vaccine studies”

- Christof Vinnemeier, CEPI
  “Fractional doses – research gaps”

- Robbert van der Most, CEPI
  “Heterologous vaccination: what can we anticipate in terms of breadth and durability?”

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

Jakob Cramer, MD
Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
How the USA Increased Its Access to Seasonal Influenza Vaccines 15 Years Ago

Bruce Innis, MD
October 27, 2021
Presentation Objective

• Impart a history lesson relevant to the present-day challenge of increasing access to next generation COVID-19 vaccines
History: Problem & Response

- US had a severe vaccine shortage for its influenza immunization campaign.
- GSK submitted an IND (Nov), did a phase 3 immuno/safety study vs placebo with HHS (Dec-May), filed a BLA (Jun), got a marketing authorization (Sep) with commitments to conduct an efficacy trial in adults, and to immunobridge via NI to Sanofi’s IIV3 for children and adults >49 YOA.
- Vaccine marketed in 2005/6 season.
Guidance for Industry

Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
MAY 2007

CBER clarified that the **Accelerated Approval Pathway** was available for new egg-, cell-, and recombinant HA-based IIVs
Accelerated Approval

• Granted for vaccines studied for safety and effectiveness in treating **serious or life-threatening illness** and for which there is **unmet need**

• Approval will be based on adequate and well-controlled clinical trials establishing that the vaccine has an effect on a **surrogate endpoint that is reasonably likely to predict clinical benefit**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence.

• CBER’s guidance proposed the **HI antibody response to vaccination** as an **acceptable surrogate endpoint for seasonal IIVs**
Serum hemagglutination inhibiting antibody titer is associated with a reduction in the risk of infection after experimental intranasal inoculation of the homologous influenza virus strain, types A and B.

Hobson et al, J Hyg, Camb. 1972

HI titers 1:18 to 1:36 reduced H3N2 and H2N2 infection rate by ~50%
Evidence Needed for Licensure

• BLA for a new seasonal IIV should include results from one or more well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory post-marketing studies of clinical effectiveness in preventing influenza in the next influenza season

  • The risk to CBER that an ineffective vaccine would be conditionally approved was mitigated by the sponsor’s post-marketing commitment

• A non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed seasonal IIV may support an accelerated approval. The study should assess co-primary endpoints for HI antibodies to each viral strain in the vaccine: GMT and seroconversion rates
The Outcome & Relevance to 2nd Gen COVID-19 Vaccines

- Numerous sponsors used the immunobridging pathway to license new IIVs in the US
- Post-marketing VE studies confirmed clinical benefit in preventing influenza
- The US has unmatched access to IIVs
- We can expect the same beneficial impact on the supply of 2nd gen COVID-19 vaccines, if immunobridging for authorization is adopted widely
- Evidence supporting the HI surrogate endpoint was no more robust than the current evidence supporting the correlation of SARS-CoV-2 spike antibody with VE in trials of diverse COVID-19 vaccines that elicit immunity to S protein
- Intra-pandemic, effectiveness may be confirmed in observational studies (e.g., test-neg case-control design)
Surrogate markers and correlates of protection: immuno-bridging in an increasingly primed population

27 October 2021

Edde Loeliger
Introduction

Objective: to discuss development of new of COVID-vaccine based on immuno-bridging (not including development of strain-adapted vaccines)

What is Immuno-bridging in a primed population?

- With a CoP
- Without a CoP

ICMRA Future steps workshop: https://www.icmra.info/drupal/en/covid-19/24june2021
Bridging studies - History

• ICH E5 (1998) “A bridging study is defined as a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region.

• ECH E5: An adequate a well-controlled trial: a design that permits a valid comparison with a control to provide a quantitative assessment of treatment effect to rule out a clinically significant difference (i.e. a NI trial)

• In the drug area, many generic drug approvals are based on the NI of an accepted surrogate – the blood level of the drug’s active ingredient.
Immuno-bridging studies - History

• In analogy with ICH E5 for drugs and biologicals, for vaccines, the original purpose was for supplemental studies performed in new populations.

• For vaccines, the surrogate for bridging is unique.

• Fritzell 1998: “The duplication of usually large-scale efficacy trials to generalise the clinical database of a new vaccine to other populations can be avoided by bridging studies”.
  • “Immunogenicity data can easily be used to extrapolate efficacy results when the immune response correlates with vaccine induced immunity”.
  • “In the absence of such a correlate of protection, the bridging process will be more controversial”.

Bridging and non-inferiority

• A NI trial seeks to determine whether a new intervention is no worse than a reference intervention

• Because proof of exact equality is impossible, a pre-stated margin of noninferiority (Δ; NI-margin; M2) for the treatment effect is defined.

• The pre-stated NI margin represents as the smallest value that would be a clinically important effect; this can be directly measured as a clinical outcome, or indirectly using a surrogate marker.

  • Non-inferiority of clinical outcomes (e.g. blood pressure; disease prevention)
  • Non-inferiority of surrogate endpoints (e.g. drug levels; antibodies)
COVID-19 and Seasonal Influenza vaccine immune bridging

• Similarities both for COVID-19 and Influenza: surrogate marker (endpoint)
  • Immune markers "that are reasonably likely to predict the clinical benefit of vaccines”
  • Influenza surrogate marker: anti-HA (HI) titres
  • COVID-19 surrogate marker: virus neutralizing antibodies; IgG binding antibodies
  • Both: protection from illness is increased for vaccines with higher antibody titres

• Key difference: between COVID-19 and Influenza: correlate of protection (CoP)
  • Influenza CoP: 4-fold increase in anti-HA titres provides 50% protection against illness
  • No CoP for COVID-19: no “established humoral and/or cellular immune parameters that correlate to clinical protection against disease” (ACCESS/ICMRA)
  • Ecological studies do not allow a quantitative assessment of treatment effect COVID-19
  • Threshold for neutralizing antibodies differ mRNA-1273 ChAdOx-1

FDA (2007) Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
Cross platform bridging

• With CoP: example: FDA seasonal influenza accelerated approval
  • HI titres: GMTs; SCR based on four-fold increase HI titres
  • US FDA: NI margin 0.67 for GMT ratios; 10% SCR
  • Recent example: Novavax novel nanoparticle platform against Fluzone

• Without CoP: COVID-19 ICMRA consensus
  • Immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible
  • Neutralising antibody titre as immune marker to predict vaccine effectiveness may be used in immunogenicity bridging studies for new vaccines
  • Study designs should be based on
    • NI immunogenicity if the comparator vaccine has high efficacy
    • Superiority trial if the comparator vaccine has modest efficacy

FDA (2007) Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
Novavax: Shinde et.al. Lancet Infect Dis 2021 Published Online September 23, 2021 https://doi.org/10.1016/S1473-3099(21)00192-4
COVID-19 cross platform bridging considerations

• The inclusion of SCR (in naives) or sero-response rates (SRR) as endpoints in primed population is not a measure of clinical benefit but to ensure non-inferior distribution of GMTs
  • Unlike Influenza, the surrogate marker for COVID-19 established in naïve population
  • Unlike Influenza, the clinical benefit a 4-fold increase in titres; it as yet unknown
  • No clinically substantiated SCR or SPR to guide SRR

• Additional considerations: NI on the GMT against a highly effective comparator because Ab titres are important, but not sufficient
  • The protection equation $P = f(\text{Ab, nAb, CD4, CD8, B, innate})$
  • Characterisation of comparative immunogenicity profiles, including CMI

• Recent examples COVID-19 cross platform bridging: Valneva; SK Biosciences

VLA2001 Cov-Compare Topline Results

October 27, 2021

Christian Taucher
Disclaimer

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INTRODUCTION
Valneva’s Response to the Global COVID-19 Crisis
Well-Known Inactivated Approach Based on Proven Technology

VLA2001:
• Inactivated, adjuvanted SARS-Cov 2 whole virus vaccine

• Intended for active immunization of at-risk populations to prevent carriage and symptomatic infection with COVID-19 during the ongoing pandemic and potentially later for routine vaccination, including addressing new variants
1. Program acceleration enabled through use of Valneva’s FDA-registered facility in Scotland, where commercial manufacturing commenced January 2021\(^1\)

2. Combines Valneva’s proven expertise with inactivated vaccines and Dynavax’s advanced CpG 1018 adjuvant\(^2\)

3. Phase 1/2 clinical trial results reported in April 2021\(^3\)

4. Rolling submission to MHRA commenced in Aug. 2021; Phase 3 “Cov-Compare” results intended to form the basis for potential regulatory approval in adults

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Note: Photo credit: CDC/Alissa Eckert, MSMI; Dan Higgins, MAM.\(^1\) Valneva commences manufacturing of its Inactivated, Adjuvanted COVID-19 vaccine, completes Phase 1/2 study recruitment.\(^2\) Valneva and Dynavax announce commercial supply agreement for Inactivated, Adjuvanted COVID-19 vaccine;\(^3\) Valneva Reports Positive Phase 1/2 Data for Its Inactivated, Adjuvanted COVID-19 Vaccine Candidate, VLA2001
COV-COMPARE TRIAL AND TOPLINE RESULTS
About Phase 3 Cov-Compare Trial (VLA2001-301)

- Randomized, observer-blind, controlled, immunogenicity trial comparing VLA2001 to AstraZeneca’s conditionally approved vaccine, AZD1222 (ChAdOx1-S)

- 2,972 participants 30 years of age and older randomized (2:1) received two doses of either VLA2001 (n=1977) or AZD1222 (ChAdOx1-S) (n=995) at the recommended dose level, 28 days apart

- Primary objective: Compare VLA2001 to AZD1222 (ChAdOx1-S) administered as above, to determine:
  1. Superiority in terms of Geometric Mean Titer ratio of SARS-CoV-2-specific neutralizing antibodies at two weeks after the second vaccination (Day 43) in adults aged 30 years and older; and
  2. Non-inferiority in terms of seroconversion rate and
  3. Frequency and severity of any Adverse Events

- Also evaluating the safety and tolerability of VLA2001 in additional adults 18-29 years of age (n=1040), two weeks after the second vaccination
SARS-CoV-2 Neutralizing Antibody Levels (ND50) - IMM – VLA2001 Higher Than AZD1222 at Day 43

**IMM** includes all randomized and vaccinated participants of the IMM subset for the primary endpoint evaluation, who were SARS-CoV-2 seronegative and have at least one evaluable post-baseline antibody titer measurement after vaccination. Participants who met the case definition of confirmed COVID-19 during the study are not included in the IMM.

**GMT:** Geometric Mean Titre, **CI:** Confidence Interval

Note: [1] p-value and CI calculated using a two-sided t-test applied to log10 transformed data.

A final assay validation required by the MHRA to verify the integrity of the VLA2001-301 data remains ongoing and is a prerequisite for final submission of the clinical study report.

Valneva - VLA2001 Cov-Compare Results

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## Immunogenicity Results – Primary Endpoint Met

**SARS-CoV-2 Neutralizing Antibodies (ND50)- IMM – VLA2001 1.39 x AZD1222**

Co-Primary Endpoint: Ratio of geometric mean titer (IMM population) of SARS-CoV-2-specific neutralizing antibodies, at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>VLA2001 Age 30 and Above (N=492)</th>
<th>AZD1222 (ChAdOx1-S) (N=498)</th>
<th>Overall (N=990)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>492</td>
<td>498</td>
<td>990</td>
</tr>
<tr>
<td></td>
<td>GMT (95% CI)</td>
<td>31.0 (31.00, 31.00)</td>
<td>31.0 (31.00, 31.00)</td>
<td>31.0 (31.00, 31.00)</td>
</tr>
<tr>
<td></td>
<td>GMT Ratio (95% CI)</td>
<td>1.00 (1.00, 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value [1]</td>
<td></td>
<td></td>
<td></td>
<td>NE</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>492</td>
<td>493</td>
<td>985</td>
</tr>
<tr>
<td></td>
<td>GMT (95% CI)</td>
<td>803.5 (748.48, 862.59)</td>
<td>576.6 (543.59, 611.66)</td>
<td>680.6 (649.40, 713.22)</td>
</tr>
<tr>
<td></td>
<td>GMT Ratio (95% CI)</td>
<td>1.39 (1.25, 1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value [1]</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

IMM includes all randomized and vaccinated participants of the IMM subset for the primary endpoint evaluation, who were SARS-CoV-2 seronegative and have at least one evaluable post-baseline antibody titer measurement after vaccination. Participants who met the case definition of confirmed COVID-19 during the study are not included in the IMM.

**Note:** GMT: Geometric Mean Titre, CI: Confidence Interval; p-value and CI calculated using a two-sided t-test applied to log10 transformed data.

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Valneva - VLA2001 Cov-Compare Results
High Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies – PP

Co-primary Endpoint: Seroconversion (PP population) (defined as 4-fold increase from baseline) of SARS-CoV-2-specific neutralizing antibodies, at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

<table>
<thead>
<tr>
<th>Visit</th>
<th>VLA2001 (N=489) N(%)</th>
<th>AZD1222 (ChAdOx1-S) (N=498) N(%)</th>
<th>Overall (N=987) N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with eligible samples at visit</td>
<td>456</td>
<td>449</td>
<td>905</td>
</tr>
<tr>
<td>Participants with seroconversion (≥ 4-fold increase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(%)</td>
<td>444 (97.4)</td>
<td>444 (98.9)</td>
<td>888 (98.1)</td>
</tr>
<tr>
<td>95% CI [1]</td>
<td>(0.954,0.986)</td>
<td>(0.974,0.996)</td>
<td>(0.970,0.989)</td>
</tr>
<tr>
<td>p-value [2]</td>
<td></td>
<td></td>
<td>0.0911</td>
</tr>
</tbody>
</table>

The Per-Protocol population (PP) will consist of the IMM population subjects who have no major protocol violations that impact the immune response.

[1] Exact 95% Clopper-Pearson confidence interval for proportion.
[2] P value or Two-sided CI is for the difference in proportions (VLA2001-AZD122) of Participants with seroconversion at each particular visit.
The trial **met its co-primary immunogenicity endpoints** at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above

- VLA2001 demonstrated **superiority** against AZD1222 (ChAdOx1-S) in terms of geometric mean titer for neutralizing antibodies as measured by live virus microneutralization assay. (GMT ratio=1.39, p<0.0001) (VLA2001 GMT 803.5 (95% CI: 748.48, 862.59))
- VLA2001 demonstrated non-inferiority in terms of seroconversion rates (SCR above 95% in both treatment groups)

- At Day 43, 74.3% of a subset of study participants in the VLA2001 group had T-cells that were reactive against peptide pools spanning the full-length S-protein.

- In addition, in the VLA2001 group 45.9% had T-cells that were reactive against the N-protein and 20.3% against the M-protein.
Overall Clinical Data Conclusions
All Endpoints Achieved

- The trial met its co-primary endpoints. VLA2001 demonstrated:
  - **superiority** against AZD1222 (ChAdOx1-S), in terms of **geometric mean titer** for neutralization antibodies, as well as
  - **non-inferiority** in terms of **seroconversion rates** at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

- **VLA2001 was generally well tolerated**
  - The **tolerability profile** of VLA2001 was **significantly more favorable compared to the active comparator** vaccine.
  - Participants **30 years and above** reported **significantly fewer solicited adverse events** up to seven days after vaccination, **both** with regards to **injection site reactions**, and **systemic reactions**
  - Participants in the **younger age group** vaccinated with VLA2001 showed an **overall safety profile comparable to the older age group**.

- The occurrence of COVID-19 cases (exploratory endpoint) was **similar between treatment groups** in the participants **30 years and above**.

- The **complete absence** of any severe COVID-19 cases **may suggest** that **both vaccines** used in the study **prevented severe COVID-19 caused by the circulating variant(s) (predominantly Delta)**.

- **T-cell responses** analyzed in a **sub-set of participants** showed that **VLA2001 induced broad antigen-specific IFN-gamma producing T-cells reactive against the S, N and M proteins**.
Thank you
Merci
Danke
Tack
Panel Discussion:

Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines

Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
Panel: Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Sample Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam Hacker, CEPI</td>
<td>• Will the licensure pathway for future COVID-19 vaccines follow a similar pathway to that of influenza vaccine over the past few decades?</td>
</tr>
<tr>
<td>Dean Smith, Health Canada</td>
<td>• In pivotal phase 3 non-inferiority trials where the primary objective is to confirm a vaccine candidate’s acceptable immunogenicity in vaccine-naïve adults relative to an authorized comparator vaccine, what vaccine-homologous endpoints are most informative?</td>
</tr>
<tr>
<td>Rogerio Gaspar, WHO</td>
<td>• How should immunogenicity of a vaccine candidate be assessed in adults who have previously been vaccinated?</td>
</tr>
<tr>
<td>Gustavo Santos, ANVISA</td>
<td>• Is there a recommended threshold of response that could be considered clinically beneficial (either an absolute value or a fold-rise)?</td>
</tr>
<tr>
<td>Phil Krause, FDA</td>
<td>• Is there value in characterizing the induction of antibody responses to SARS-CoV-2 variants of concern by a vaccine candidate relative to an authorized comparator vaccine?</td>
</tr>
<tr>
<td>In-sook Park, MFDS</td>
<td></td>
</tr>
</tbody>
</table>
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/](https://epi.tghn.org/covax-overview/clinical-science/)

- 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

- COVAX Enabling Science SWAT Workshop on 'Interpreting SARS-CoV-2 immune assay data involving variants and the use of the WHO International Standard for anti-SARS-CoV-2 immunoglobulin' (28 Oct 2021, 15:00-19:00 CET)

- WHO BP team and COVAX Clin Dev SWAT team to co-organise a workshop on ‘fractional dosing’ – date TBC