Immune Correlates, SARS-CoV-2 variants and ‘mix and match’: How vaccine developer approaches might be impacted by emerging data
## Workshop Agenda

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00 – 15:15</td>
<td>Welcome, meeting objectives, and immune correlates introduction</td>
<td>Peter Dull Donna Ambrosino</td>
</tr>
</tbody>
</table>

### Part 1: Progress toward immune correlates for COVID-19 to enable accelerated vaccine development

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:15 – 15:30</td>
<td>Overview: Establishing a correlate from imperfect evidence – a historical perspective</td>
<td>David Goldblatt</td>
</tr>
<tr>
<td>15:30 – 15:40</td>
<td>Evidence for a serological correlate of protection from animal models and planned future studies</td>
<td>Cristina Cassetti</td>
</tr>
<tr>
<td>15:40 – 15:55</td>
<td>Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains</td>
<td>Florian Krammer</td>
</tr>
<tr>
<td>15:55 – 16:15</td>
<td>Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies</td>
<td>Stephen Lockhart Daniel Stieh</td>
</tr>
<tr>
<td>16:15 – 16:30</td>
<td>Evidence of contribution of cell-mediated immunity to vaccine efficacy, and utility of T cell assays to correlates analyses</td>
<td>Julie McElrath</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:30 – 17:05</td>
<td>Panel Discussion</td>
<td>Moderated by: Peter Dull</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17:05 – 17:10</td>
<td>Break</td>
<td></td>
</tr>
</tbody>
</table>

### Part 2: Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17:10 – 17:20</td>
<td>International standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants</td>
<td>Paul Kristiansen</td>
</tr>
<tr>
<td>17:20 – 17:30</td>
<td>Neutralizing antibody assays against new variants: Overview of current activities</td>
<td>William Dowling</td>
</tr>
<tr>
<td>17:30 – 17:40</td>
<td>‘Mix &amp; Match’: Heterologous primary vaccination and heterologous boosting regimens</td>
<td>Jakob Cramer</td>
</tr>
<tr>
<td>17:40 – 18:25</td>
<td>Panel Discussion</td>
<td>Moderated by: Jakob Cramer</td>
</tr>
<tr>
<td>18:25 – 18:30</td>
<td>Wrap Up &amp; Next Steps</td>
<td>Jakob Cramer</td>
</tr>
</tbody>
</table>
Welcome & Meeting Objectives

Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
Context for today’s workshop

Overall objectives:

PART 1: HOW CAN WE MAKE ADDITIONAL APPROPRIATE AND IMPACTUFL VACCINES AVAILABLE?

- Review the accumulating evidence that a neutralizing antibody response provides the primary contribution to protection against COVID-19 and discuss alternative supportive mechanisms.
- Discuss past approaches to advancing vaccine development despite imperfect evidence and lessons to mitigating the risks through confirmatory studies.

PART 2: HOW CAN WE USE THE AVAILABLE VACCINES IN A BETTER WAY?

- Review the available international standard in the context of new variants.
- Provide an overview on the development of neutralising antibody assays against new variants.
- Introduce and discuss a practical approach for the assessment of vaccine ‘mix & match’ strategies:
  - Heterologous primary vaccination
  - Heterologous boosting regimens
Part 1:

Progress toward immune correlates for COVID-19 to enable accelerated vaccine development

Peter Dull, MD
Deputy Director, Integrated Clinical Vaccine Development, Bill & Melinda Gates Foundation (BMGF)
Early evidence from multiple study types suggests a serological correlate of protection exists

**COVID-19 Correlate Data Package**

- **Vaccine-induced Immunity**
  - Phase III efficacy studies
    - Neutralizing and binding titers at baseline, post-1\textsuperscript{st} dose, and post-2\textsuperscript{nd} dose in random subcohort and breakthrough cases

- **Natural History**
  - Longitudinal re-infection studies
    - Comparison of neutralizing titers in re-infected individuals and control subcohort

- **Passive Immunization**
  - Protective dose of mAbs or convalescent sera in animal challenge models

**Other potential sources:**
- CHIMs studies
- PrEP studies

**Early evidence in support of CoP:**
1. Positive correlation between interval, nAbs, and efficacy
2. Cross-platform relationship between nAbs and efficacy
3. Case study: nAbs protect against infection in outbreak
4. Adoptive IgG transfer protects macaques from challenge
Neutralizing titers correlate with increased efficacy against symptomatic COVID-19 in the ChAdOx/AZ Phase III trial

Effect of interval between doses on immunogenicity and efficacy

As interval between doses increases:
- Neutralizing titers increase
- Efficacy point estimates increase

Preliminary data suggest this relationship persists across platforms

Elevated neutralization titers in Ph I/II correlate with efficacy against ancestral SARS-CoV-2 strains

<table>
<thead>
<tr>
<th>Neuts vs. HCS:</th>
<th>Novavax</th>
<th>BioNTech / Pfizer</th>
<th>Moderna</th>
<th>Sinopharm</th>
<th>Oxford / AZ</th>
<th>Janssen</th>
<th>Sinovac</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0-fold higher¹</td>
<td>3.4-fold higher³</td>
<td>3.8-fold higher²</td>
<td>Comparable⁴</td>
<td>Comparable⁵</td>
<td>2.3-fold lower⁶</td>
<td>6-fold lower⁷</td>
<td></td>
</tr>
</tbody>
</table>

### Efficacy:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novavax</td>
<td>95.6%⁸</td>
</tr>
<tr>
<td>BioNTech/ Pfizer</td>
<td>95%⁹</td>
</tr>
<tr>
<td>Moderna</td>
<td>94.1%⁹</td>
</tr>
<tr>
<td>Sinopharm</td>
<td>79.3%¹⁰</td>
</tr>
<tr>
<td>Oxford / AZ</td>
<td>62.1%¹⁰</td>
</tr>
<tr>
<td>Janssen</td>
<td>66-72%⁹</td>
</tr>
<tr>
<td>Sinovac</td>
<td>50.4%⁹</td>
</tr>
</tbody>
</table>

---

¹ wt MN titers in subjects aged 18-59, 14 days after 2nd 5µg dose; HCS: full range of disease severity. ² wt VNA titers (NT₅₀) in subjects aged 18-55, 7 days following 2nd 30µg dose; HCS: n=38, across full range of disease severity. ³ Lentivirus PsVNA titers (ID₅₀) in subjects aged 18-55, 14 days after 2nd 100µg dose; HCS: n=42, across full range of disease severity. ⁴ wt VNA titers (50% CPE) in subjects aged 18-59, 28 days after 2nd 4µg dose; HCS range cited in supplement is plotted here for comparison, severity not specified. ⁵ Monogram lentivirus PsVNA titers in subjects aged 18-55, 14 days after 2nd 5x10¹⁰vp dose; HCS: n=146 hospitalized patients and 24 asymptomatic HCWs. ⁶ wt MN titers in subjects aged 18-55, 28 days following a single 5x10¹⁰ vp dose; HCS: n=32, mostly severe patients. ⁷ wt VNA titers in subjects aged 18-59, 28 days following 2nd 3µg dose; HCS: n=117 symptomatic patients across full range of disease severity. ⁸ Post hoc analysis. ⁹ Primary analysis. ¹⁰ Interim analysis.
Analysis: Phase III efficacy highly correlated with Phase I/II neuts expressed relative to HCS panels

**Strong correlation** between Ph III efficacy and vaccinee / HCS GMT ratio ($\rho = 0.83$)

79.9% of variance in efficacy is explained by neut Abs

**Methods / key:**
- Includes all 7 vaccines for which Phase III efficacy and nAbs GMTs (run alongside HCS panels) are reported
- X-axis: Ratio of geometric mean neutralization titer (GMT, $ND_{50}$) at peak immunogenicity timepoint post-vaccination
- Error bars: 95% confidence interval, based on available data
- Marker size indicates number of cases underlying VE estimate
- Dashed line: non-parametric LOESS fit

Source: Analysis conducted by Donna Ambrosino, George Siber, Peter Gilbert and Andrew Fiore-Gartland
Analysis: Phase III efficacy highly correlated with Phase I/II ELISA GMEPTs expressed relative to HCS panels

Strong correlation between Ph III efficacy and vaccinee / HCS GMEPT ratio ($\rho = 0.94$)

92.8% of variance in efficacy is explained by binding Abs

Methods / key:
- Includes 6 vaccines for which Phase III efficacy and binding Ab GMEPTs (run alongside HCS panels) are reported
- X-axis: Ratio of geometric mean endpoint titer (GMEPT, ID$_{50}$) at peak immunogenicity timepoint post-vaccination
- Error bars: 95% confidence interval, based on available data
- Marker size indicates number of cases underlying VE estimate
- Dashed line: non-parametric LOESS fit

Source: Analysis conducted by Donna Ambrosino, George Siber, Peter Gilbert and Andrew Fiore-Gartland
Conclusions

Strong correlation between both neutralizing ($\rho = 0.83$) and binding ($\rho = 0.94$) antibody responses and efficacy

In absence of International Units to compare across studies, calibration to a human convalescent sera panel is necessary

- Relationship between efficacy and reported neutralizing / binding titers is weak ($r^2 = 0.24$, 0.21 respectively)

Calibration to WHO International Standard may improve correlation

Nearly all variance is explained by antibody responses, leaving little room for impact of T cells on correlation

Determination of a threshold value for a protective correlate will require individual antibody distributions (i.e., reverse cumulative distribution function curves)
We believe that there is adequate evidence to support a non-inferior immunogenicity approach for Wave 2 EUAs

Rationale for this approach:

Is there an accepted threshold for a correlate of protection?

- Yes
- No

Seroconversion to CoP
Placebo-controlled or non-inferiority vs. comparator

Is there sufficient data that a serological biomarker correlates with efficacy to base approval on immunogenicity?

- Yes
- No

Would some efficacy data be required for EUA/EUL?

- Yes
- No

To be confirmed by NRA / PQ meetings:
- Need for efficacy data
- Choice of comparator
- Non-inferiority margins

NI Immunogenicity + clinical efficacy data
Large comparative study with prolonged follow up time

NI Immunogenicity
With post-authorization effectiveness trial

Clinical efficacy
Placebo-controlled or non-inferiority vs. comparator
- Very large study to enable primary analysis in short time
Overview: Establishing a correlate from imperfect evidence – a historical perspective

David Goldblatt, PhD
Professor of Vaccinology and Immunology
University College London
Overview: Taking action on a correlates despite imperfect evidence-a historical perspective

David Goldblatt
Professor of Vaccinology and Immunology

February 2021
How to Define the Level of an immune marker that Is Protective?

- Seroepidemiology linked to disease epidemiology
- Passive infusion of antibody in animals or humans
- Observations from efficacy trials
- Observations from effectiveness studies nested in roll out/Phase IV
*H. influenzae* type b

*S. pneumoniae*

*N. meningitidis*

*N. meningitidis*

*S. aureus*

*E. Coli*

*Salmonella Typhi*

*Group B Strep*

*Shigella*
Capsule = Virulence Factor

Target for Protective Antibody

Anti-complementary

C' Receptor

Phagocytic Cell

Fc Receptor

SBA (Mening)

ELISA

Opsonophagocytic Assay

Protein
A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection


Per Protocol VE: 90%

Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children

STEVEN BLACK, MD, ... INFECT DIS J, 2000;19:187–95 Vol. 19, No. 3
Copyright © 2000 by Lippincott Williams & Wilkins, Inc. Printed in U.S.A.

A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection


Per Protocol VE: 90%

Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children

STEVEN BLACK, MD, ... INFECT DIS J, 2000;19:187–95 Vol. 19, No. 3
Copyright © 2000 by Lippincott Williams & Wilkins, Inc. Printed in U.S.A.

Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial

Katharine L. Bruckner, Lauren A. Winkler, Noelle H. J. Roberts, Sheryl Young, and Dukki Lee Brown, Simone M. Nave, Anne P. Freedman, Shari U. Mehta, N. Chang, Robert Robertson, Shangtun Wu, and Christien Wessels

The Lancet • Vol 362 • August 2, 2003

Per Protocol VE: 76.8%

Serologic Correlate of Protection

Vaccine efficacy for Invasive Pneumococcal Disease (% protected)

Distribution of serum antibody concentrations in vaccinated population

Serum Antibody Protective Threshold

Vaccine efficacy for Invasive Pneumococcal Disease (% protected)
Reverse Cumulative Distribution Curves of Antibody Concentration: NCKP Trial

No. of Cases | Per Protocol $V_E$ (95% CI)
--- | ---
Contr | PCV
All types (PP) | 39 | 1 | 97.4% (82.7, 99.9)

Geometric Mean Concentration

Post Primary Concentrations

Reverse Cumulative Distributions of Post-Dose 3 ELISA Antibody Concentrations in NCKP Population: 7 Serotype Aggregates

Per protocol VE: 97.4%

Predicted VE with 0.2μg/mL cut off: 97.3%

RCD’s of IgG anti-pneumococcal capsular polysaccharide antibody concentrations aggregated for the 7 vaccine types in three controlled PnC efficacy studies and the pooled studies weighted for no. of study subjects.

Siber et al. Vaccine 2007
Post-Dose 3 OPA Response: Type 4
(Types 6B, 9V, 14, 18C and 23F Are Similar)

R=0.92
(p<0.0001)

N=79

ELISA titer of 0.20 ≈ OPA titer of 1/8

Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants

Luis Jódar\textsuperscript{a,1}, Jay Butler\textsuperscript{b}, George Carlone\textsuperscript{c}, Ron Dagan\textsuperscript{d}, David Goldblatt\textsuperscript{e}, Helena Käyhä\textsuperscript{f}, Keith Klugman\textsuperscript{g}, Brian Plikaytis\textsuperscript{c}, George Siber\textsuperscript{h}, Robert Kohberger\textsuperscript{h}, Ih Chang\textsuperscript{h}, Thomas Cherian\textsuperscript{a,*}

© World Health Organization
WHO Technical Report Series, No. 927, 2005

Annex 2

Recommendations for the production and control of pneumococcal conjugate vaccines

Non-inferiority at the serological correlate of protection 0.35µg/ml
WHO Standards, QC Panels, Assay Standardisation

SINGLE SOURCE OF ANTIGENS

20 Valent

10A
12F
11A
8
15B

1
6A
33F
22F

15 Valent

Heart Poly saccharide vaccine (Adsorbed) I.P.

2020

Prevnar13™
Licensed 2010

Synflorix™
10 Valent
Licensed 2009

Licensed in 2000
Are correlates developed with invasive disease endpoints relevant to mucosal carriage?
Serum Serotype-Specific Pneumococcal Anticapsular Immunoglobulin G Concentrations after Immunization with a 9-Valent Conjugate Pneumococcal Vaccine Correlate with Nasopharyngeal Acquisition of Pneumococcus

Risk of acquiring nasopharyngeal carriage

Israel: 14, 19F, 6A (not 9V, 23F)
American Indian: 23F (not 19F)

5 μg/ml protects from acquisition
“circulating IgG at time of pneumococcal exposure did not protect against carriage”
Is a single aggregate correlate (0.35) valid for all serotypes?
Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study

Nick J Andrew, Pauline A Waigh, Polly Burbidge, Emma Pearce, Lucy Royle, Marita Zancoli, Mary Slack, Shamer N Ladhani, Elizabeth Miller, David Goldstein

Summary
Background Efficacy of the 13-valent pneumococcal conjugate vaccine (PCV13) was inferred before licensure from an aggregate correlate of protection established for the seven-valent vaccine (PCV7). We did a postlicensure assessment of serotype-specific vaccine effectiveness and immunogenicity in England, Wales, and Northern Ireland to derive the correlates of protection for individual serotypes.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>Predicted vaccine effectiveness at 0.35 μg/ml ELISA control*</th>
<th>Calculated correlate of protection in μg/ml for ELISA* (95% CI)</th>
<th>Calculated correlate of protection in titres for opsonophagocytic antibody* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>84% (54 to 95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>26% (-49 to 68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6A1</td>
<td>98% (64 to 99.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7F</td>
<td>91% (70 to 98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>67% (33 to 84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra serotypes in PCV13 (plus 6C)</td>
<td>73% (55 to 84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra serotypes in PCV13 (plus 6C), excluding 3</td>
<td>80% (65 to 89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PCV7 serotypes</td>
<td>90% (34 to 98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PCV13 serotypes (plus 6C)</td>
<td>75% (58 to 84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PCV13 serotypes (plus 6C), excluding 3</td>
<td>82% (68 to 89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>97% (65 to 99.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6B</td>
<td>58% (3 to 82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9V</td>
<td>70% (-25 to 93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>98% (88 to 99.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18C</td>
<td>96% (81 to 99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F</td>
<td>75% (37 to 90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>78% (23 to 94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PCV7 serotypes</td>
<td>82% (22 to 89)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing predicted efficacy and correlates of protection](image)

Predicted Efficacy @ 0.35 μg/ml for each serotype?
Correlate of Protection @ Observed UK Vaccine Efficacy?
Observed Vaccine Effectiveness
Predicted Vaccine Effectiveness (based on % >0.35)

PCV13-7
PCV7 (Post 7)
PCV7 (post 13)

VE higher than predicted by existing CoP
VE lower than predicted by existing CoP

Perfect Agreement at 0.35 µg/µl

Lancet Infectious Diseases 2014
Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study

Nick J Andrews, Pauline A Woigt, Polly Burbidge, Emma Pearce, Lucy Roelfe, Marta Zancolli, Mary Shack, Shumez N Ladhani, Elizabeth Miller, David Goldblatt

Corr of Protection

3 = 2.83
19F = 1.17
19A = 1.0
7F = 0.87
1 = 0.78
9V = 0.62
14 = 0.46
4 = 0.35
23F = 0.20
6B = 0.16
6A = 0.16
18C = 0.14
Prior Serum Bactericidal Activity (hSBA) against Meningococcal C ≥ 1 in 4

- Cases 3/54 (5.6%) hSBA ≥ 1 in 4
- Non-cases 444/540 (82.2%) hSBA ≥ 1 in 4
An rSBA titre $\geq 8$ or 16 correlates closely with efficacy data.
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

Prime with Conjugate Vaccine
Boost with Polysaccharide Vaccine

Response to Polysaccharide Booster in primed infants

1 10 100 1000 10000
2 3 4 5 15 16 48 49
Age in Months
SBA

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

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

J Infect Dis 2002
Effective meningococcal serogroup C conjugate vaccine 4 years after introduction

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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age at vaccination</th>
<th>Doses scheduled*</th>
<th>Period of observation, by quarter year</th>
<th>Overall</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>Within 1 year of scheduled vaccination†</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>More than 1 year after scheduled vaccination†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Vaccine effectiveness (95% CI)</td>
<td>Cases</td>
<td>Vaccine effectiveness (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td>Routine</td>
<td>2–4 months</td>
<td>3</td>
<td>Q1 2000–Q1 2004</td>
<td>28 (21)</td>
<td>66% (6 to 86)</td>
<td>9 (3)</td>
<td>93% (67 to 99)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Infant catch-up</td>
<td>5–11 months</td>
<td>2</td>
<td>Q3 2000–Q1 2004</td>
<td>13 (5)</td>
<td>85% (46 to 96)</td>
<td>6 (2)</td>
<td>87% (11 to 99)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Toddlers catch-up</td>
<td>1–2 years</td>
<td>1</td>
<td>Q3 2000–Q1 2004</td>
<td>25 (10)</td>
<td>83% (60 to 93)</td>
<td>19 (6)</td>
<td>88% (65 to 96)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Pre-school catch-up</td>
<td>3–4 years</td>
<td>1</td>
<td>Q3 2000–Q1 2004</td>
<td>37 (2)</td>
<td>98% (91 to 100)</td>
<td>45 (1)</td>
<td>98% (90 to 100)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Infant school catch-up</td>
<td>4–6 years</td>
<td>1</td>
<td>Q3 2000–Q1 2004</td>
<td>19 (0)</td>
<td>100% (71 to 100)</td>
<td>45 (1)</td>
<td>96% (89 to 99)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Junior school catch-up</td>
<td>7–10 years</td>
<td>1</td>
<td>Q3 2000–Q1 2004</td>
<td>8 (3)</td>
<td>88% (38 to 98)</td>
<td>45 (1)</td>
<td>96% (89 to 99)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Secondary school catch-up</td>
<td>11–16 years</td>
<td>1</td>
<td>Q2 2000–Q1 2004</td>
<td>40 (8)</td>
<td>96% (90 to 98)</td>
<td>45 (4)</td>
<td>96% (89 to 99)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Sixth form catch-up</td>
<td>17–18 years</td>
<td>1</td>
<td>Q1 2000–Q1 2004</td>
<td>44 (4)</td>
<td>93% (82 to 98)</td>
<td>124 (16)</td>
<td>93% (82 to 98)</td>
<td>90 (37)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>214 (53)</td>
<td></td>
<td>124 (16)</td>
<td></td>
<td>90 (37)</td>
</tr>
</tbody>
</table>

Q=quarter. *Vaccine effectiveness compares children eligible for complete vaccination who had received all scheduled doses versus no doses. Partly vaccinated children were excluded. †For the time change analysis, pre-school, infant, and junior cohorts were combined, as were the secondary school and sixth form cohorts.

Table: MCC vaccine effectiveness in immunised cohorts to end of March, 2004

Lancet 2004
Summary

• An aggregate threshold derived from aggregated efficacy data defined a CoP which led to the successful licensure of extended valency pneumococcal conjugate vaccines (n=3, soon n=5)

• All models are wrong but some are more useful than others

• Standardization of assays and reagents allowed multiple manufacturers to license using CoP and head to head non-inferiority trials

• There are lessons here for establishing correlates for the next generation of SARS CoV 2 vaccines
Evidence for serological correlate of protection from animal models and planned future studies

Cristina Cassetti, PhD
Deputy Director of NIAID’s Division of Microbiology and Infectious Diseases
NIAID at NIH
Immune correlates and SARS-CoV-2 variants: Mounting evidence for a serological CoP from animal models

Cristina Cassetti, Ph.D.
Deputy Director
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases, NIH
ccassetti@niaid.nih.gov
Advantage of animal models to elucidate CoPs

- Dose down the vaccine (or serum from vaccinated animals/humans) to allow for breakthrough infections
- Intensive sample collection (esp. PBMCs for T-cell analysis)
- Select challenge timing and strain
- Compare different vaccines in the same study
- Use validated assays from Phase 3 trials- compare data from clinical trials
Outline

- Existing data in NHPs and hamsters
  - IgG passive transfer in NHPs/Dan Barouch
  - Novavax vaccine in NHPs/Galit Alter
  - Clover vaccine passive transfer in hamsters
  - Rockefeller U. mAbs in NHPs/ Michele Nussenzweig

- Ongoing study
  - BARDA/NIAID/Battelle 4 vaccine study
Purified IgG protects macaques against SARS-CoV-2 in a dose-dependent fashion

N = 12
Naïve

Pooled, NAb = 1,581

Day -3

Dan Barouch- https://www.nature.com/articles/s41586-020-03041-6
Logistical regression analysis defines Nab threshold titer of $\sim 50$ for protection.
Novavax / Galit Alter-NHP and human CoP study

- System serology study of NHPs immunized with NVX-CoV2373
- Both neutralizing and Fc-effector functions contribute to protection, potentially through different mechanisms in the upper and lower respiratory tract
- Both macaque and human vaccine-induced antibodies exhibit altered Fc-receptor binding to emerging mutants.

M.J. Gorman at al. - https://www.biorxiv.org/content/10.1101/2021.02.05.429759v1
**Key Question**: Are neutralizing antibodies induced in humans by Clover’s COVID-19 vaccine protective against exposure to SARS-CoV-2 virus?

- Are higher levels of neutralizing antibodies more protective?
- What level of neutralizing antibodies confers protection (correlate of protection)?

**Study Concept**: Human subjects were vaccinated with Clover’s SCB-2019 vaccine in Ph 1 Study (CLO-SCB-2019-001). Serum containing neutralizing antibodies collected from vaccinated subjects is injected into hamsters ("passive transfer"). Hamsters are exposed to SARS-CoV-2 virus ("challenge"). Will the passively-transferred neutralizing antibodies protect hamsters from SARS-CoV-2 challenge? Observe: body weight loss, viral loads in lungs/throat swabs, etc.

Note: dpi (days post-inoculation)
Correlation Analyses: Immune Protection vs. Baseline Circulating VNTs

Change in Body Weight (5 dpi/Baseline)

Relative Lung Weight\(^{(1)}\) (5 dpi; at necropsy)

Higher Circulating Neutralizing Antibodies (Day 1) Correlated with Better Protection from SARS-COV-2 Challenge

(Pending results for viral loads in throat swabs and lung tissue)

Note: Dpi (days post-inoculation). VNT (viral neutralization titer). Dots represent data for individual animals.

Represents data in 48 animals (body weight @ 5dpi) and 25 animals (relative lung weight @5dpi) passively transferred with pooled human sera from Phase 1 vaccinees (n=20) across three dilutions. VNTs in negative control groups (NaCl and Naïve Human Sera) groups were all BLQ (below limit of quantification). Boxplot bars represent IQR, and whiskers represent min:max range.

\(^{(1)}\) % of lung weight (g) in relation to body weight (g) upon necropsy.
Passive Transfer of mAbs C144-LS + C135-LS into NHPs to Assess CoPs

- Antibody titers
- viral RNA
- Pathology
- Clinical

-3  0  1  2  3  5  7
N=14

IN + IT
1 x 10^6 TCID_{50}
SARS-CoV-2 WA1

- Necropsy

N=4: 20 mg/kg
N=4: 6 mg/kg
N=4: 2 mg/kg
N=2: control

- In vitro IC_{50} of ~5ng/ml
- Neut epitopes on RBD
- long half life
- Ph I trial started Jan 21 (BMS)

Michel Nussenzweig, Rockefeller Univ, Chad Roy, TNPRC
High mAb levels post challenge (pseudovirus neut. assay)

Day - 3

Mean serum conc/NT90 titers

20mg/kg 550ug/ml ; 1:9000
6 mg/kg 140ug/ml ; 1:2300
2 mg/kg 50ug/ml ; 1:700

Ab half life = 47 days!

Prophylactic administration of 2 mAbs reduces viral shedding in URT and LRT

Unpublished results: Michel Nussenzweig, Rockefeller Univ, Chad Roy, TNPRC
One large, combined CoP NHP study sponsored by BARDA/NIAID

Vaccine products
- Janssen, Moderna, Novavax, Sanofi

USG provider
- Battelle

Study timeline
- Study initiated in February 8 (1 large study)

Protocol harmonization
- Study protocol and Statistical Analysis plan agreed upon by product developers

Funding
- Provided by USG
Test System: Rhesus macaque, Chinese origin, Naïve and specific pathogen free

Challenge Material: SARS-CoV-2, USA-WA1/2020, Lot TVP 23180, 1.6x10^4 PFU/mL, passed characterization criteria

This timeline is days relative to challenge, it does not reflect the actual chronology of the study activities as products are distributed across the 8 challenge days; Vx1 dates are staggered accordingly.

Control animals (n=16) are vaccinated on days -56 and -28 relative to challenge

BAL, PBMC, and NW also collection prior to Vx1 for each candidate

Body Weights collected at least every 2 weeks
Several pre-clinical studies suggest that neutralizing antibodies are sufficient to confer protection against SARS-CoV-2 infection. Other immune responses (Fc-effector functions, CD8+) may contribute to protection, but their relative importance is still under investigation. Ongoing study will compare CoPs in different vaccine platforms.
Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains

Florian Krammer, PhD
Professor of Microbiology
Icahn School of Medicine at Mt. Sinai
Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains

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

COVAX Workshop
February 25th, 2020
A glimpse of evidence for protection by neutralizing antibodies from a fishing vessel

- 122 individuals on the ship
- 3 had neutralizing antibodies before going to sea
- Outbreak with 82.5% attack rate occurred

Individuals with neutralizing antibodies were not infected
Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers


• 12,541 health care worker in the UK
  • 11,346 serologically negative
  • 1,265 serologically positive
  • Observation period 6 months
  • NAAT every two weeks

• 223 of the negatives had a positive NAAT in observation period
  • 1.09 per 10,000 days at risk
• 2 of the spike serologically positives had a positive NAAT in observation period (asymptomatic)
  • 0.13 per 10,000 days at risk, adjusted 0.11 per 10,000 days at risk
Health care workers in the UK
- 14,173 serologically negative
- 6,614 serologically positive
- Observation period June to November 2020
- NAAT every 2 to 4 weeks

318 of the negatives had a positive NAAT or in observation period (94 additional ones seroconverted)
44 of the serologically positives had a positive NAAT or in observation period

Interpretation: A prior history of SARS-CoV-2 infection was associated with an 83% lower risk of infection, with median protective effect observed five months following primary infection. This is the minimum likely effect as seroconversions were not included.
• 3.2 million individuals tested for antibodies
• 2,876,773 were negative
• 378,606 were positive
• PCR positives 90+ days after antibody test
  • 3% of negatives
  • 0.3% of positives
• 3,249 eighteen to twenty year old marine recruits
• 2 week quarantine
• RBD/spike titers assessed
• Tested 3x biweekly by PCRs post quarantine in training
• Among 189 seropositive participants, 19 (10.1%) had at least one positive PCR test
• 1,079 (48.0%) of the 2,247 seronegative participants tested positive
• 3,249 eighteen to twenty year old marine recruits
• 2 week quarantine
• RBD/spike titers assessed

- Tested 3x biweekly by PCRs post quarantine in training
- Among 189 seropositive participants, 19 (10.1%) had at least one positive PCR test
- 1,079 (48.0%) of the 2,247 seronegative participants tested positive
PARIS (SEM CIVIC)/SPARTA (CIVR)

Commonalities between all sites:

• Samples take every 2 months (most sites have shorter intervals)
  • Serum
  • Saliva
  • PBMCs (selected sites, but for several thousand subjects)
• Common serology (Mount Sinai ELISA)
• Nasal swap/nasopharyngeal sample take if somebody becomes symptomatic
  • SARS-CoV-2 PCR
  • Most sites also run a respiratory panel/Biofire
• Primary analysis at sites
• Secondary analysis: Sarah Cobey and Marc Lipsitch
PARIS
(Protection Associated with Rapid Immunity to SARS-CoV-2)

• Approximately 400 individuals enrolled
• Since April 2020
• Approximately half antibody positive, half antibody negative
• So far 5 symptomatic SARS-CoV-2 infections in sero-negative group
• 1 symptomatic infection in an individual that was sero-positive but sero-reverted
• Asymptomatic infections under investigation
Novavax Phase 2b in South Africa

Efficacy Endpoint Accrual: November 23 – December 30

- Placebo ITT population (7 days post-dose 1), symptomatic COVID
  - Seronegative: 3.9% (58/1494; 2.961; 4.990): 2.3% Mod/Severe (35/1494)
  - Seropositive: 3.9% (26/674; 2.535; 5.601): 2.4% Mod/Severe (16/674)

# Novavax Phase 2b in South Africa

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>NVX-CoV2373 % (n/N)</th>
<th>Placebo % (n/N)</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>1.1% (15/1357)</td>
<td>2.2% (29/1327)</td>
<td>49.4% (6.1, 72.8)</td>
</tr>
<tr>
<td>+</td>
<td>1.2% (6/500)</td>
<td>2.5% (13/514)</td>
<td>52.6% (-23.8, 81.8)</td>
</tr>
<tr>
<td>+/-</td>
<td>1.1% (21/1857)</td>
<td>2.3% (42/1841)</td>
<td>50.4% (16.6, 70.5)</td>
</tr>
</tbody>
</table>

## Impact of variants on neutralization of convalescent and vaccine serum

<table>
<thead>
<tr>
<th>Variant</th>
<th>Convalescent sera</th>
<th>Sera from vaccinated individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7</td>
<td>Little impact</td>
<td>Little impact (most studies) to up to 9-fold reduction after AZ vaccination</td>
</tr>
<tr>
<td>B.1.351</td>
<td>Strong reduction, loss in a proportion of individuals</td>
<td>Moderate impact (4 to 9-fold reduction), in some papers even higher</td>
</tr>
<tr>
<td>P.1</td>
<td>Likely similar to B.1.351</td>
<td>Likely similar to B.1.351</td>
</tr>
</tbody>
</table>
Impact of variants on neutralization of convalescent and vaccine serum

Figure 3

A

BNT162b2 (Pfizer)

<table>
<thead>
<tr>
<th>Country where variant first described</th>
<th>UK</th>
<th>DK</th>
<th>US</th>
<th>BR/JP</th>
<th>SA</th>
</tr>
</thead>
</table>

2 dose

Neutralization (NT50)

Tada et al., bioRxiv, 2021

Garcia-Beltran et al., medRxiv, 2021
Efficacy of AZD1222 against B.1.1.7 and B.1.351

Table 1 Vaccine efficacy against B.1.1.7 and non- B.1.1.7 strains. (SD/SD and LD/SD seronegative efficacy cohorts only)

<table>
<thead>
<tr>
<th>Variant</th>
<th>N (%)</th>
<th>ChAdOx1 nCoV-19</th>
<th>Control</th>
<th>VE 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Symptomatic COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.1.1.7</td>
<td>34 (14%)</td>
<td>7/4236</td>
<td>27/4236</td>
<td>74.6% (41.6%, 88.9%)</td>
</tr>
<tr>
<td>Other variants</td>
<td>86 (34%)</td>
<td>12/4236</td>
<td>74/4236</td>
<td>84.1% (70.7%, 91.4%)</td>
</tr>
<tr>
<td>No sequence result*</td>
<td>25 (10%)</td>
<td>5/4236</td>
<td>20/4236</td>
<td>72.4% (35.3%, 90.8%)</td>
</tr>
<tr>
<td>Not sequenced**</td>
<td>105 (42%)</td>
<td>28/4236</td>
<td>77/4236</td>
<td>64.3% (44.9%, 76.8%)</td>
</tr>
<tr>
<td>Total cases</td>
<td>250</td>
<td>52/4236</td>
<td>198/4236</td>
<td>74.2% (65.0%, 81.0%)</td>
</tr>
<tr>
<td><strong>Asymptomatic/Unknown infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.1.1.7</td>
<td>14 (7%)</td>
<td>6/4236</td>
<td>8/4236</td>
<td>26.5% (-112.0%, 74.5%)</td>
</tr>
<tr>
<td>Other variants</td>
<td>30 (14%)</td>
<td>6/4236</td>
<td>24/4236</td>
<td>75.4% (39.9%, 89.9%)</td>
</tr>
<tr>
<td>No sequence result</td>
<td>37 (18%)</td>
<td>21/4236</td>
<td>16/4236</td>
<td>-28.7% (-146.6%, 32.8%)</td>
</tr>
<tr>
<td>Not sequenced</td>
<td>127 (61%)</td>
<td>62/4236</td>
<td>64/4236</td>
<td>3.1% (-37.3%, 31.6%)</td>
</tr>
<tr>
<td>Total cases</td>
<td>208</td>
<td>96/4236</td>
<td>112/4236</td>
<td>15.7% (-10.7%, 35.8%)</td>
</tr>
<tr>
<td><strong>Any NAAT</strong>+ infection†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.1.1.7</td>
<td>51 (10%)</td>
<td>13/4236</td>
<td>38/4236</td>
<td>66.5% (37.1%, 82.1%)</td>
</tr>
<tr>
<td>Other variants</td>
<td>128 (26%)</td>
<td>21/4236</td>
<td>107/4236</td>
<td>80.7% (69.2%, 87.9%)</td>
</tr>
<tr>
<td>No sequence result†</td>
<td>69 (14%)</td>
<td>29/4236</td>
<td>40/4236</td>
<td>28.8% (-14.9%, 55.9%)</td>
</tr>
<tr>
<td>Not sequenced</td>
<td>251 (50%)</td>
<td>101/4236</td>
<td>150/4236</td>
<td>33.8% (14.7%, 48.6%)</td>
</tr>
</tbody>
</table>


Source: https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1.full.pdf
Impact of variants on neutralization of convalescent and vaccine serum

B.1.351

B.1.1.7

Figure 6. Live virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 (Victoria) strain

Madhi et al., medRxiv, 2021

Emary et al., SSRN, 2021
Conclusions

Protection after natural infection is robust and as good or even better than after vaccination

Protection is correlated with antibody responses to spike

We urgently need studies that determine the impact of variants on neutralizing activity of post-vaccination sera side by side!
Acknowledgements

Department of Microbiology/
Icahn School of Medicine at Mount Sinai
Peter Palese

Ania Wajnberg
(Mount Sinai Hospital)

Carlos Cordon-Cardo
Adolfo Firpo
(Mount Sinai Hospital)

Harm van Bakel
(ISMMS)

Mia Sordillo
David Rich
Judy Aberg
(Mount Sinai Hospital)

Adolfo García-Sastre
Lisa Miorin
Teresa Aydillo

Viviana Simon
Maria Bermudez-Gonzalez
Denise Jurczyszak
Matt Hernandez

Fatima Amanat
Daniel Stadlbauer

florian.krammer@mssm.edu
http://labs.icahn.mssm.edu/kramerlab/
Twitter: @florian_krammer

Kantaro

CIVICs

CEIRS
Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies (Part 1)

Stephen Lockhart, PhD
Vice President, Vaccine Clinical R&D Europe and Asia-Pacific Head
Pfizer
Thoughts on correlates

Stephen Lockhart

25 February 2021
Pilot work planned to assess cases in vaccine cohort

• 8 breakthrough cases without evidence of prior infection in November efficacy analysis for EUA¹
  • More cases likely to be identified following subsequent unblinding.

• Post dose 2 sera retained in all subjects²
  • In process of assessing post dose 2 neutralization titers

• PMBC not collected on subjects so T cell analysis cannot be performed²

¹ Polack et al 2020
Hypotheses to consider

• Neutralising antibody as mechanism or correlate of protection, pilot work can test this
  • Absence of neutralising activity post dose 2?
  • Lower neutralising activity post dose 2?
  • No relationship post dose 2?

• T-cell responses as mechanism or correlate of protection
  • Large scale pre-infection assessment of CMI challenging

• Host factors: comorbidities, health, race

• Viral factors: mutations in spike protein
Onset of protection while neutralizing titers are low

Cumulative Incidence of COVID-19 Occurrence

Days After Dose 1

BNT162b2 (30 μg)

Placebo


Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies (Part 2)

Daniel Stieh, PhD
Senior HIV Biomarker Lead
Janssen Pharmaceutical Companies of Johnson & Johnson
ENSEMBLE:
Immune Correlates Considerations & Planning

Daniel J Stieh, Sr. Biomarker Lead
25 February 2021
Janssen Investigational COVID-19 Vaccine Phase 3 Study: COV3001

- Locations: Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and United States
- Continuous, sequential monitoring for safety and efficacy
- Full protocol openly accessible at https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol

Healthy adults ≥18 years of age
(~20% aged 18 to 40 years, ~30% >60 years of age)
Total Enrollment >44,000

Single IM dose 5x10^{10} vp of Ad26.COV2.S OR Placebo

# of participants with first occurrence of molecularly confirmed moderate to severe/critical† COVID-19 w/seronegative status as of 14 days and 28 days after vaccination (planned follow up 2 years if feasible)

†Moderate defined as one sign and one symptom from a list of signs, such as heart rate >90 bpm and symptoms such as shortness of breath or cough or 2 symptoms from a list of symptoms or Severe COVID-19 defined in FDA guidance. *NLM Identifier: NCT04505722

The information provided herein, in connection with OTA No. HHSO100201700018C, is considered trade secrets, commercial or financial information that, JRD LLC, its Consortium Members, Affiliates, subcontractors and vendors customarily hold close and treat as confidential. The information is being provided under the assurance that the United States Government, including all its Departments, Agencies, Independent Establishments, Corporations, Organizations and Instrumentalities, including the U.S. Department of Health and Human Services and all of its agencies, including the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, will maintain the confidentiality of the information under the Trade Secrets Act, Procurement Integrity Act, other applicable statutes, regulations, rules, case law, contractual provisions, protective orders or otherwise and as such, the information provided herein is exempt from disclosure under Exemption 4 of the Freedom of Information Act (“FOIA”).
Variants assessed vary over time and by geography

Subset of countries participating in ENSEMBLE

United States

Brazil

South Africa

Source: Nextstrain 20Feb2021
Overview of ENSEMBLE immune sampling plan

Based on ENSEMBLE protocol

Injection

Timeline

Serum samples

D0  D1  D29  D71  D168  D364  D546  D728

(D0  D1  D29  D71  D168  D364  D546  D728)

(D0  D1  D29  D71  D168  D364  D546  D728)

(D0  D1  D29  D71  D168  D364  D546  D728)

Stage 1 – for primary analysis

2 timepoints at D1 and D29 for both random subcohort and infected cases

1 Random subcohort
2 Infected cases are from vaccine group (baseline + and -) and placebo group (baseline + only)

Stage 2 – for durability study / more correlates analysis

5 additional timepoints through month ~24 for random subcohort; up to 7 timepoints total for additional infected cases

1 Same random subcohort
2 Additional infected cases from vaccine group (baseline + and -) and placebo group (baseline + only)
Randomly Sampled Sub-cohort:
Antibody Assessments of Immunogenicity and Immune Marker CoRss and CoPs

<p>| Numbers of Participants Sampled Into 64 Strata of Study Participants (Total N=1616) |
|-----------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Baseline SARS-CoV-2 Seronegative&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Baseline SARS-CoV-2 Seropositive&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Demographic Covariate Strata&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td><strong>Baseline SARS-CoV-2 Seronegative&lt;sup&gt;b&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vaccine</td>
<td>58</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup>The 16 baseline demographic covariate strata are as follows: 1 = underrepresented minority (URM) in U.S., age >= 60, presence of comorbidities; 2 = URM in U.S., age >= 60, absence of comorbidities; 3 = URM in U.S., age 18-59, presence of comorbidities; 4 = URM in U.S., age 18-59, absence of comorbidities; 5 = non-URM in U.S., age >= 60, presence of comorbidities; 6 = non-URM in U.S., age >= 60, absence of comorbidities; 7 = Latin America, age >= 60, presence of comorbidities; 8 = South Africa, age >= 60, presence of comorbidities; 9 = Latin America, age >= 60, absence of comorbidities; 10 = South Africa, age >= 60, absence of comorbidities; 11 = non-URM in U.S., age 18-59, presence of comorbidities; 12 = non-URM in U.S., age 18-59, absence of comorbidities; 13 = Latin America, age 18-59, presence of comorbidities; 14 = South Africa, age 18-59, presence of comorbidities; 15 = Latin America, age 18-59, absence of comorbidities; 16 = South Africa, age 18-59, absence of comorbidities.
Current Correlates SAP Focuses on bAb / nAb to the Vaccine Strain and the Endpoint COVID with Any Strain

- Plan to conduct the correlates analysis by each region separately (U.S., Central/South America, South Africa)

- Because the South African variant 501Y.V2 dominates the cases occurring in South Africa, the analysis assesses bAb / nAb to the vaccine strain as a CoR/CoP against the South African variant

- Combined study analyses evaluate bAb / nAb as CoR/CoP for COVID of different sets of circulating strains

- Comparing correlates results by region may give insights about whether the correlate may differ by viral lineage
  - E.g., does the nAb titer threshold for low risk differ depending on the circulating virus population?
Assessment of bAb / nAb to the Vaccine Strain as CoRs of AA Sequence-Specific COVID

- Assess whether bAb/nAb to the vaccine strain is a weaker correlate of risk of COVID when the acquired virus is farther from the vaccine strain*
  - Farther defined by larger: (1) IC50; (2) AA-predicted IC50; AA-Hamming distance to vaccine strain

### Precedents

- **(A) RV144:** IgG and IgG3 to V1V2 of the A244 vaccine strain were less correlated with HIV-1 acquisition for viruses with greater V1V2 Hamming distance to the A244 vaccine strain (Yang et al., 2017, *Stat Biosc*; Sun et al., 2018, *Biometrical Journal*). (B) CYD14 dengue VE trial for PRNT_{50} nAb titer and Hamming distance to vaccine insert.

\[
\beta_1(v) = \log \text{relative risk of endpoint with a distance } v \text{ virus per 10-fold increment in peak Ab immune response}
\]
Status report of correlates planning

- Sufficient vaccine breakthrough cases exist for correlates analyses, sample selection and distribution are in process
- Partnering with COVID-19 response team (formerly OWS) biostatistics for correlates analyses
- Binding Ab (Spike, RBD, N), wtVNA (MN50) are being considered for Day 1 and 29 samples
- Correlates analyses will be done as soon as the data set is available from one of the assays
  - E.g., may do correlates for bAb first: highest throughput assay
  - Accelerates time to some correlates results
Can NAb titer be a CoP for ENSEMBLE?

- NAb response rate at Day 29 can be greater or less than the estimate of VE

- Potential explanations:
  1. nAb is sufficient for protection but not **necessary** (may be another mechanism)
  2. nAb is a ‘perfect CoP’ (**necessary** and **sufficient** for protection) but the assay was not sufficiently sensitive at the lower end
  3. nAb is sufficient for protection from exposing strain while cross protection may require sufficient breadth of nAb induction

Note: If 1. were true, then the CoP could still be quite good – e.g., mediating 80% of vaccine efficacy, not 100%
Similar and Durable Humoral Immune Responses After Single Dose 5x10^{10} vp Ad26.COV2.S in Adults 18-55 and ≥ 65 Years

- Observed neutralizing antibody response: 96% of Ad26.COV2.S group (Day 29)
  - Response lasted ≥ 85 days in both age groups

**Observed Neutralizing Antibody Response**

<table>
<thead>
<tr>
<th>Group</th>
<th>18 – 55 year-old participants</th>
<th>≥ 65 year-old participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SARS-CoV-2</strong></td>
<td><strong>IC50 Log10 GMT (95% CI)</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>25 25 25 22 22</td>
<td>25 12 25 24 21</td>
</tr>
<tr>
<td><strong>Ad26.COV2.S</strong></td>
<td>29 57 71 85</td>
<td>15 29 184 258 165</td>
</tr>
</tbody>
</table>

**Adapted from Sadoff, Le Gars, et al NEJM, 2021**
Ad26.COV2.S Elicits CD4+ and CD8+ T Cell Responses

Th1:Th2 ratio well above 1 in all vaccine responders

% Positive responder defined by one-sided Fisher's exact test comparing non-stimulated versus S-peptide stimulated cells

The information provided herein, in connection with OTA No. HHSO100201700018C, is considered trade secrets, commercial or financial information that, JRD LLC, its Consortium Members, Affiliates, subcontractors and vendors customarily hold close and treat as confidential. The information is being provided under the assurance that the United States Government, including all its Departments, Agencies, Independent Establishments, Corporations, Organizations and Instrumentalities, including the U.S. Department of Health and Human Services and all of its agencies, including the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, will maintain the confidentiality of the information under the Trade Secrets Act, Procurement Integrity Act, other applicable statutes, regulations, rules, case law, contractual provisions, protective orders or otherwise and as such, the information provided herein is exempt from disclosure under Exemption 4 of the Freedom of Information Act ("FOIA").
Later Add ‘By Variant’ CoR and CoP Analysis

- Sequential correlates analyses will add data on bAb / nAb to panels of viral variants

- Assess bAb / nAb to a specific variant as a CoR / CoP against disease with the same variant
  - E.g., assess bAb / nAb against South African variant as CoR / CoP against South African variant COVID in the South Africa region

- May also study bAb / nAb against a specific variant as CoR/CoP against a vaccine-mismatched variant, to document weakening of the correlate
Challenge: Lack of the Same Set of Major Variants in the Same Region/Trial

- Currently, the B.1.351 variant can only be studied in the South Africa region (95% of South African cases with variant; few such cases outside of South Africa)
  - Thus, cannot infer whether different VE within South Africa is caused by the variant or by other regional factors
  - Baseline determinants of immunogenicity as well as mapping the presumed variant giving rise to baseline seropositivity on the observed efficacy may be able to disentangle these effects
Learning from NHP SARS-CoV-2 CoP analyses

- bAb and nAb are highly correlated, with both responses predicting protection in NHP for both Ad26.COVID2.S and a range of Ad26-based vaccines
  - Similar responses induced in humans

<table>
<thead>
<tr>
<th>SARS-CoV-2 neutralizing antibodies</th>
<th>S-protein binding antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph A" /></td>
<td><img src="image2.png" alt="Graph B" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Graph C" /></td>
<td><img src="image4.png" alt="Graph D" /></td>
</tr>
</tbody>
</table>

Lung Protection probability

- psVNA (IC$_{50r}$, log$_{10}$)
- Sensitivity
- Specificity
- Protection probability
- S-ELISA (EU/ml, log$_{10}$)
- Sensitivity
- Specificity

The information provided herein, in connection with OTA No. HHSO100201700018C, is considered trade secrets, commercial or financial information that, JRD LLC, its Consortium Members, Affiliates, subcontractors and vendors customarily hold close and treat as confidential. The information is being provided under the assurance that the United States Government, including all its Departments, Agencies, Independent Establishments, Corporations, Organizations and Instrumentalities, including the U.S. Department of Health and Human Services and all of its agencies, including the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, will maintain the confidentiality of the information under the Trade Secrets Act, Procurement Integrity Act, other applicable statutes, regulations, rules, case law, contractual provisions, protective orders or otherwise and as such, the information provided herein is exempt from disclosure under Exemption 4 of the Freedom of Information Act (“FOIA”).
Evidence of contribution of cell-mediated immunity to vaccine efficacy, and utility of T cell assays to correlates analyses

Julie McElrath, MD
Senior Vice President and Director
Vaccine and Infectious Disease Division
Fred Hutch Cancer Research
Contribution of cell-mediated immunity to vaccine efficacy

HVTN Laboratory Center
Fred Hutchinson Cancer Research Center

Julie McElrath, Kristen Cohen, Steve De Rosa
February 25, 2021
<table>
<thead>
<tr>
<th>Assay</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IFN-γ ELISpot</td>
<td>• High sensitivity for IFN-γ</td>
<td>• Limited ability to multiplex cytokines</td>
</tr>
<tr>
<td></td>
<td>• Relatively low cell requirements</td>
<td>• Unknown sensitivity for Th2-type cytokines (e.g., IL-4)</td>
</tr>
<tr>
<td></td>
<td>• Validated</td>
<td>• Validated assay does not distinguish CD4+ vs CD8+ T cells</td>
</tr>
<tr>
<td>2. Activation-induced marker (AIM)</td>
<td>• Multiplexed phenotypic, functional markers</td>
<td>• Inability to distinguish Th1/Th2</td>
</tr>
<tr>
<td></td>
<td>• High sensitivity</td>
<td>• Concern for lower specificity in comparison to other T cell assays</td>
</tr>
<tr>
<td>3. CyTOF</td>
<td>• Highly multiplexed for cytokines, tetramers,</td>
<td>• Low throughput</td>
</tr>
<tr>
<td></td>
<td>phenotyping</td>
<td>• Low cell recovery</td>
</tr>
<tr>
<td>4. Antigen-stimulated PBMC or whole blood</td>
<td>• High sensitivity (depending on cytokine)</td>
<td>• Bulk assay does not provide cell type (e.g., CD4 or CD8) and does not</td>
</tr>
<tr>
<td>cytokine secretion assay</td>
<td>• Multiplex capability</td>
<td>provide frequency of responding cells</td>
</tr>
<tr>
<td></td>
<td>• Qualified (PBMC)</td>
<td></td>
</tr>
<tr>
<td>5. Intracellular cytokine staining (ICS)</td>
<td>• Multiplexed phenotypic, functional markers</td>
<td>• Requires multiparameter flow cyrometer instruments</td>
</tr>
<tr>
<td></td>
<td>• High sensitivity for some key cytokines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Validated for Th1 CD4+ and CD8+ T cells,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>standardized for Th2</td>
<td></td>
</tr>
</tbody>
</table>
Minimal 12-color ICS panel for high-throughput and/or tech transfer

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viability</td>
<td>Live/Dead</td>
</tr>
<tr>
<td>CD14</td>
<td>Monocytes</td>
</tr>
<tr>
<td>CD19</td>
<td>B cells</td>
</tr>
<tr>
<td>CD16</td>
<td>NK cells (FcgR)</td>
</tr>
<tr>
<td>CD56</td>
<td>NK cells</td>
</tr>
<tr>
<td>CD3</td>
<td>T cells</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td></td>
</tr>
<tr>
<td>CD45RA</td>
<td>Memory T cells</td>
</tr>
<tr>
<td>CCR7</td>
<td></td>
</tr>
<tr>
<td>CD25</td>
<td>Tregs</td>
</tr>
<tr>
<td>FoxP3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>Th1</td>
</tr>
<tr>
<td>IL-2</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
</tr>
<tr>
<td>IL-17a</td>
<td>Th17</td>
</tr>
<tr>
<td>IL-4</td>
<td>Th2</td>
</tr>
<tr>
<td>IL-5/IL-13</td>
<td></td>
</tr>
<tr>
<td>CD154</td>
<td>CD4 response</td>
</tr>
<tr>
<td>CRTh2</td>
<td>Th2 (surface)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granzyne B</td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td>Perforin</td>
<td></td>
</tr>
<tr>
<td>CD32</td>
<td>FcgR</td>
</tr>
<tr>
<td>CD64</td>
<td></td>
</tr>
<tr>
<td>CXCR3</td>
<td>Th subsets</td>
</tr>
<tr>
<td>CCR6</td>
<td></td>
</tr>
<tr>
<td>Ki67</td>
<td>Activation</td>
</tr>
</tbody>
</table>
Design of consensus spike SARS-CoV-2 peptides

- Generated consensus sequence from alignment of available SARS-CoV-2 spike global sequences (n=17,811) from GISAID database in May 2020
- The consensus was a **perfect a.a. match** to the Wu-Han strain except for 614
- Designed variants to cover the diversity at position 614 (D/G variants) to bring overall coverage to >99%
Peptide pools for spike for variant regions

Consensus spike (2 pools, S1 and S2)

Mutations RSA B1.1.351

Mutations UK B1.1.7

Variant pool B1.1.351

Variant pool B1.1.7

Variant regions: Consensus

S1 Consensus without variant regions (S1-variant)

S2 Consensus without variant regions (S2-variant)

**Peptide pools to use for stimulation:**
1. S1 Consensus without variant regions
2. S2 Consensus without variant regions
3. Variant regions: Consensus
4. B1.1.351 variant pool
5. Optional: B.1.1.7 variant pool
Janssen Ad26.CVO2.S Phase 1/2a Study

Sadoff et al, NEJM Jan 2021
Janssen Ad26.CVO2.S Phase 1/2a Study

CD8 T cells (IFNg and/or IL-2)

% CD8 T cells expressing IFNg and/or IL-2 cytokines

- Day 1: 0.07, 0.09, 0.01
- Day 15: 0.07, 0.09, 0.01

N: 71, 72, 70, 72, 37, 37
- 5x10^{10} vp
- 1x10^{11} vp
- Placebo

Sadoff et al, NEJM Jan 2021
T cell responses in SARS-CoV-2 infection post-mRNA vaccination
T cell specificities: % of COVID-19 patients recognizing SARS-CoV-2 antigens

**CD4+ T Cells**

- S1
- S2
- N
- EM
- ORF3a6
- ORF7a7b8

No. of antigens: 1 2 3 4 5 6

% of participants with responses to each antigen combination:

n=114 (participants with data available for all 6 antigens)

**CD8+ T Cells**

- S1
- S2
- N
- EM
- ORF3a6
- ORF7a7b8

No. of antigens: 1 2 3 4 5 6

% of participants with responses to each antigen combination:

n=113 (participants with data available for all 6 antigens)
Conclusions

1. A wide array of T cell-based assays are being deployed in COVID-19 vaccine trials, which will illuminate differences in immune responses to various vaccine platforms.
2. IFNγ ELISpot and ICS are most widely used, but their correlation with efficacy is currently unknown.
3. Lack of validated SARS-CoV-2-specific assays across the trials, and difficult sample collection remain challenges for the utility of T cell assay-based biomarkers in large scale trials.
4. Requirement for T cell durability to be determined.
Panel Discussion

Moderated By:
Peter Dull, MD
Deputy Director,
Integrated Clinical Vaccine Development,
Bill & Melinda Gates Foundation (BMGF)
Discussion Panel Members and Example Questions

Panel Members

• **George Siber**, Co-founder and Member of Board at Affinivax, Inc., United States

• **Andy Pollard**, University of Oxford, United Kingdom

• **David Goldblatt**, University College London, United Kingdom

• **William Dowling**, CEPI, United States

• **Florian Krammer**, Icahn School of Medicine at Mt. Sinai, United States

• **Stephen Lockhart**, Pfizer, United Kingdom

• **Daniel Stieh**, J&J, Netherlands

• **Julie McElrath**, Fred Hutch Cancer Research Center, United States

Potential Discussion Questions

1. Where are we on the “road to a correlate” as we think about others that are currently licensed based on a biomarker? HPV? Polio? Pneumococcus? MenB?

2. Neutralizing antibody and binding antibody responses seem to correlate well across most vaccines studied. Why not focus on binding antibodies as a more robust and scalable assay readout?

3. What are the product development implications if there is a different biomarker associated with infection or with disease?

4. How can we support vaccine licensure where efficacy is no longer possible but the mechanism of protection is via mucosal antigen delivery with modest humoral immunity?

5. What is the status of the tools for reliably and consistently measuring T-cell biomarkers without the isolation of PBMCs
Break
Part 2:

Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines

Moderated By:
Jakob Cramer
Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants

Paul Kristiansen, PhD
Head of Standards and Assays, Preclinical and Immunology
CEPI
International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants

Paul Kristiansen

Enabling Sciences SWAT Team co-lead

CEPI - Head Biological Standards and Assays, Preclinical and Immunology

February 2021
SARS-CoV-2 WHO International Antibody Standard

- Development of SARS-CoV-2 antibody reference material:
  - Convalescent serum as Research Reagent and reference panel available from April 2020

To acquire the reference material:
https://www.nibsc.org/science_and_research/virology/centre_for_aids_reagents/covid-19_reagents.aspx
First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/136)

**Material:** Antibody, human, convalescent plasma, WHO IS

**Intended use:** Primary calibrant for serological assays

**Description:** Pool of convalescent plasma from recovered COVID-19 patients, containing high titre antibodies against SARS-CoV-2. Plasma has been solvent detergent treated to minimise the risk of presence of enveloped viruses.

**Enquiries:** standards@nibsc.org

---

First WHO International Reference Panel for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/268)

**Material:** Antibody, human, convalescent plasma, WHO reference panel

**Intended use:** Serological assay development and evaluation, Vaccine evaluation, Research,

**Description:** comprises of 5 panel members; four pools of convalescent plasma from recovered COVID-19 patients, containing high, medium, low anti-S but relatively high anti-N, low antibodies against SARS-CoV-2, and a negative control, pool of plasma from healthy donors collected before 2019.

**Enquiries:** standards@nibsc.org
Assay harmonization and tech transfer

Common SOPs, Critical reagents, Controls and panels

 nexelis
ELISA
PNA
ELISOT

Public Health
England

BSL-3
BSL-3
BSL-3
BSL-3

VNA

Sensitivity: CEPI Internal
CEPI Centralized Laboratory Network
2020 achievements in numbers

**Available assays**
- S, RBD, N ELISA assay
- Pseudo virus neutralization assay
- Wild type virus neutralization assay
- IFNy, IL-5 ELISPOT assay

**Covid-19 Vaccine developers engaged**
In 4 continents among CEPI-funded and non CEPI-funded developers

**Samples requested for analysis**
From Preclinical, Clinical Phase I and Clinical Phase II studies

**Laboratories worldwide**
- Nexelis (Canada), Q2 Solutions (US),
- PHE Porton Down (UK), NIBSC (UK),
- VisMederi Srl (Italy), Viroclinics (The Netherlands),
- icddr,b (Bangladesh), THSTI (India)

**USD invested**
Of the 16M USD total budget allocated to the program

**21,6K**
Samples requested for analysis

**4,7M**
USD invested

**6**
Available assays

**8**
Covid-19 Vaccine developers engaged

**41**
Laboratories worldwide
Concluding remarks

1. We have a tool for harmonizing the assessment of immunresponses to COVID-19 vaccine and to assess the impact of variants - use it!

2. Upcoming events:
   • Workshop on the Centralized Laboratory Network: 12. March
   • WHO Assays Working group on how to implement the International Standard: by end of March
Neutralising Antibody assays against new variants: Overview of current activities

William Dowling, PhD
Non-Clinical Vaccine Development Leader
CEPI
Neutralizing Antibody assays against new variants: Overview of current activities

William Dowling, CEPI
Live virus neutralization Assays
<table>
<thead>
<tr>
<th>Assay</th>
<th>Virus</th>
<th>Institution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Madhi et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopathic effect (CPE) assay</td>
<td>B.1.351: GDPCC strain</td>
<td>Chinese Academy of Sciences (CAS)</td>
<td>Huang et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque reduction neutralization test (PRNT)</td>
<td>B.1.1.7: hCoV-19/India/20203522</td>
<td>National Institute of Virology, India (NIV)</td>
<td>Sapkal et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Fuse assay</td>
<td>B.1.1.7: Tours isolate B.1.351: CNR 202100078</td>
<td>Insitut Pasteur (IP)</td>
<td>Planas et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emary et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus Reduction Neutralization test (FRDT)</td>
<td>B.1.1.7: US CDC isolate Recombinant WA-1 with</td>
<td>University of Texas Medical Branch (UTMB)</td>
<td>Edara et al 2021</td>
</tr>
<tr>
<td>Plaque reduction neutralization test (PRNT)</td>
<td>69-70 del, E484K, N501Y or all B.1351 changes</td>
<td></td>
<td>Xie et al 2021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liu et al 2021</td>
</tr>
</tbody>
</table>
Neutralization of B.1.1.7 and B.1.351 by Convalescent and Pfizer vaccine sera

**Convalescent**

**Pre-boost (V1+28)**
Pfizer vaccine

**Post boost (V2+7)**
Pfizer vaccine

Skelly et al 2021
Neutralization of recombinant WA-1/B.1.351 Spike by Pfizer vaccine sera

P<0.001

PRNT_{90} (log2)

USA-WA1/2020  B.1.351-spike
Neutralization of B.1.1.7 by Convalescent and Moderna Vaccine sera

Convalescent

\[ p = 0.0001 \]
\[ 1.6x \]

mRNA-1273

\[ p = 0.04 \]
\[ 1.2x \]
Bharat Biotech vaccine sera efficiently neutralized B.1.17
BBIBP-CorV and RBD ZF2001 vaccine sera both neutralized B.1.351

Huang et al 2020
Oxford/AstraZeneca vaccine neutralization affected by both variants

Figure 6. Live virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 (Victoria) strain

Emary et al 2021  
Mahdi et al 2021
Oxford/AstraZeneca and Pfizer vaccine sera neutralization

Zhou et al 2021
Convalescent plasma from B.1.1.7 patients neutralizes B.1.351 more efficiently than pre-B.1.1.7 plasma

Zhou et al 2021
Pseudovirus neutralization
Neutralization with Variant B.1.1.7 pseudoviruses

Full set of B.1.1.7 Spike mutations – little effect on convalescent sera; some effects on mAbs

Rees-Spear et al 2021
Convalescent sera, Moderna and Novavax vaccine Phase I sera

- Pseudovirus neutralization from Montefiori lab
- B.1.1.7 – all mutations or individual
- Convalescent, Moderna and Novavax sera
- Modest effect on neutralization, 2 fold reduction

Shen et al 2021
Convalescent sera poorly neutralize Variant B1.351 pseudovirus

- Key mutation in RBD or all Spike mutations
- Significant decrease in neutralization by convalescent sera
- Neutralization escape for class 1 and class 2 mAbs

Wibmer et al 2021
Moderna vaccine Phase I sera

Neutralization with pseudoviruses: Wu et al 2021

• No significant reduction neut by B.1.1.7
• Reduction in neut by B.1.351 6 fold
Convalescent sera, Moderna and Pfizer vaccines

Wang et al 2021
Modern and Pfizer vaccine sera tested against a panel of pseudoviruses

A: BNT162b2 (Pfizer)
B: mRNA-1273 (Moderna)

Garcia-Beltran et al 2021
Summary

- Studies from different labs involving new variants have used distinct viral isolates or pseudoviruses and diverse assay formats, which makes direct comparison of the data difficult; use of the WHO International standard could be useful in this regard.

- In general, there is a slight reduction in neutralization of convalescent or vaccine sera observed with VOC B.1.1.7 and more significant reductions in neutralization observed with VOC B.1.351. This was seen in both live virus and pseudovirus assays.

- VOC P.1 and P.2 have recently been used in pseudovirus assays and neutralizing titers fell between B.1.1.7 and B.1.351.

- Neutralization of variants after a single dose is low versus post-second dose.

- Convalescent plasma from B.1.1.7 patients neutralizes B.1.351 more efficiently than pre-B.1.1.7 plasma.
Heterologous Prime:Boost SARS-Co-2 vaccines

Pre-clinical studies
• Heterologous prime: boost approaches:
  • Vaccinate with two different vectors or delivery system expressing the same antigen
  • Vaccinate with different antigens using the same delivery system (e.g. boost with a new variant)

• Example of licensed ERVEBO Ebola vaccine – Ad26 prime, MVA boost

• For COVID-19, the Gam-COVID-Vac vaccine, consists of an Ad26 prime with an Ad5 boost, both expressing the full Spike protein. This vaccine is approved for Emergency use in several countries. Pre-clinical data on this vaccine, however, are not available.
MVA prime and RBD protein boost produce higher ELISA and neutralizing Ab titers than a homologous boost.
MVA prime with RBD boost protects K18:hACE2 mice from SARS-CoV-2 challenge

Liu et al 2021
Heterologous prime:boost produces higher IgG titers than prime alone or ChAd homologous boost
saRNA and ChadOx1

- Heterologous prime:boost produces higher neutralizing titers than prime alone or ChAd homologous boost and higher T cell responses than prime alone, RNA prime:boost or rAd prime:boost
Spike and RBD proteins prime:boost

• In mice, Spike protein prime with RBD boost leads to high S titers, highest RBD titers and highest Neutralising titers, when compared to homologous prime boosts (S-S or R-R).

• However, in NHPs, there is no advantage to the heterologous prime:boost.

Tan et al 2021
Summary

- Heterologous prime:boost is an approach that has been successful in other contexts, including the Gamalaya Gam-COVID-Vac vaccine.
- Heterologous prime:boost approaches for COVID-19 vaccines may lead to strengthening and broadening of immune responses
  - Binding and neutralizing Ab responses in mice were highest for MVA vectors with RBD protein boosts rather than MVA boosts
  - Heterologous prime boost with saRNA and ChadOx1 led to stronger T cell responses than homologous boosts with either ChAd or RNA and higher antibody responses than ChAd prime:boost.
  - Heterologous prime:boost of S and RBD proteins led to higher neutralizing Ab titers in mice; however, there was no advantage over homologous boost in NHPs
‘Mix & Match’: Heterologous primary vaccination and heterologous boosting regimens

Jakob Cramer
Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
‘Mix & Match’: Heterologous Primary Vaccination and Heterologous Boosting Regimens

Jakob Cramer, MD

February 25th, 2021
COVID-19 Vaccines Against New Strains: Options

1. Address new variants with currently approved vaccines

2. Vaccine adaptation against new variants
   a) Based on approved ‘prototype’ vaccines (against original strain)
   b) Licensure of new vaccines against new strains without approved ‘prototype’ / without availability of evidence supporting vaccine efficacy of the ‘prototype’

3. Monovalent versus bi-/multivalent vaccines
COVID-19 Vaccines Against New Strains: Options

1. Address new variants with currently approved vaccines → ‘Mix & Match’

2. Vaccine adaptation against new variants
   a) Based on approved ‘prototype’ vaccines (against original strain)
   b) Licensure of new vaccines against new strains without approved ‘prototype’ / without availability of evidence supporting vaccine efficacy of the ‘prototype’

3. Monovalent versus bi-/multivalent vaccines
I. Available COVID-19 Vaccines: “Mix & Match”

Concepts:
- **Heterologous primary vaccination**: 
- **Heterologous boosting**: 

Aim:
- Improve immune response*
  - Breadth of IR
  - Duration
- **Address practical / operational aspects** (‘interchangeability’ of vaccines)
- **Adjuvant- / antigen-saving** strategy?
- **Anti-vector immunity**?
- Improve **tolerability** (of the 2nd dose)?

→ **Several trials** covering different regions / populations, vaccine combinations, circulating SARS-CoV-2 variants

*) dosing interval important as well: priming evolves over months
Current COVID-19 Vaccine Approval Status

Vaccinations per 100 people
- <0-10
- ≥10-20
- ≥20-30
- ≥30-40
- ≥40-50
- ≥50-60
- ≥60-70
- ≥70-80
- ≥80-90
- ≥90-100
- None

- Emergency approval
- Conditional marketing approval

WHO EUL/PQ

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Status</th>
<th>Anticip. decision date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cansino</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamaleya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZ / U. Oxford</td>
<td>EUL approved*</td>
<td>15 Feb 2021</td>
</tr>
<tr>
<td>Pfizer / BioNTech</td>
<td>EUL approved</td>
<td>31 Dec 2020</td>
</tr>
<tr>
<td>Moderna</td>
<td>In-progress</td>
<td>Feb 2021</td>
</tr>
<tr>
<td>FBRI SRC VB</td>
<td>In-progress</td>
<td>March 2021</td>
</tr>
<tr>
<td>VECTOR</td>
<td>In-progress</td>
<td>March 2021</td>
</tr>
<tr>
<td>CNBG (SinoPharm)</td>
<td>In-progress</td>
<td>March 2021</td>
</tr>
<tr>
<td>Sinovac Biotech</td>
<td>In-progress</td>
<td>March 2021</td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>In-progress</td>
<td>March 2021</td>
</tr>
</tbody>
</table>

*Data for COVAX expected in March 2021

Regulatory sources:
- Regulatory Affairs Professionals Society, Covid 19 Tracker
# Potential “M&M” Options – Heterologous Priming

Two different vaccines given as 1<sup>st</sup> and 2<sup>nd</sup> dose for primary vaccination (e.g. 4-12 weeks apart)

<table>
<thead>
<tr>
<th>Platform</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; dose</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; dose</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>VV - mRNA</td>
<td>• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]</td>
<td>• Pfizer/BNT; • Moderna; • CureVac</td>
<td>• Enhance both CD4 and CD8 response, prolonged antigen presentation?</td>
</tr>
<tr>
<td>VV – VV</td>
<td>• JnJ [Ad26]; • CanSino [Ad5]; • AZ/Oxford [ChadOx-1]</td>
<td>• JnJ [Ad26]; • CanSino [Ad5]; • AZ/Oxford [ChadOx-1]</td>
<td>• Avoid anti-vector immunity?</td>
</tr>
<tr>
<td>VV – protein</td>
<td>• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]</td>
<td>• NVX (+ Matrix M); • Clover (+ Al/CpG)</td>
<td>• Tfh induction → more focused effect on B-cell differentiation and breadth of binding / neutralising antibody response?</td>
</tr>
<tr>
<td>WIV – protein</td>
<td>• Sinovac; • Sinopharm</td>
<td>• NVX (+ Matrix M); • Clover (+ Al/CpG)</td>
<td>• Tfh induction</td>
</tr>
<tr>
<td>mRNA – Protein</td>
<td>• Pfizer/BNT; • Moderna; • CureVac</td>
<td>• NVX (+ Matrix M); • Clover (+ Al/CpG)</td>
<td>• Strong Tfh priming?</td>
</tr>
<tr>
<td>Protein - VV</td>
<td>• NVX (+ Matrix M); • Clover (+ Al/CpG)</td>
<td>• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]</td>
<td>• Strong Tfh priming?</td>
</tr>
<tr>
<td>mRNA - VV</td>
<td>• Pfizer/BNT; • Moderna; • CureVac</td>
<td>• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]</td>
<td>• Strong Tfh priming?</td>
</tr>
</tbody>
</table>

VV = viral vector; WIV = whole inactivated virus; Tfh = T follicular helper cells

Incomplete list – for discussion
## Potential “M&M” Options – Heterologous Boosting

Different vaccine given e.g. 6-12 months after homologous primary vaccination

<table>
<thead>
<tr>
<th>Platform</th>
<th>Priming</th>
<th>Single booster dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>VV → mRNA</td>
<td>• AZ/Oxford [ChadOx-1];</td>
<td>• Pfizer/BNT;</td>
</tr>
<tr>
<td></td>
<td>• JnJ [Ad26] – single dose;</td>
<td>• Moderna;</td>
</tr>
<tr>
<td></td>
<td>• CanSino [Ad5] – single dose;</td>
<td>• CureVac</td>
</tr>
<tr>
<td></td>
<td>• Gamaleya [Ad26, Ad5]</td>
<td></td>
</tr>
<tr>
<td>VV → VV</td>
<td>• AZ/Oxford [ChadOx-1]</td>
<td>• JnJ [Ad26];</td>
</tr>
<tr>
<td></td>
<td>• JnJ [Ad26] – single dose;</td>
<td>• CanSino [Ad5];</td>
</tr>
<tr>
<td></td>
<td>• CanSino [Ad5] – single dose</td>
<td>• Gamaleya [Ad5]</td>
</tr>
<tr>
<td>VV → protein</td>
<td>• AZ/Oxford [ChadOx-1];</td>
<td>• NVX (+ Matrix M);</td>
</tr>
<tr>
<td></td>
<td>• JnJ [Ad26] – single dose;</td>
<td>• Clover (+ Al/CpG)</td>
</tr>
<tr>
<td></td>
<td>• CanSino [Ad5] – single dose;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Gamaleya [Ad5, Ad26]</td>
<td></td>
</tr>
<tr>
<td>WIV → protein</td>
<td>• Sinovac;</td>
<td>• NVX (+ Matrix M);</td>
</tr>
<tr>
<td></td>
<td>• Sinopharm</td>
<td>• Clover (+ Al/CpG)</td>
</tr>
<tr>
<td>mRNA → protein</td>
<td>• Pfizer/BNT;</td>
<td>• NVX (+ Matrix M);</td>
</tr>
<tr>
<td></td>
<td>• Moderna;</td>
<td>• Clover (+ Al/CpG)</td>
</tr>
<tr>
<td></td>
<td>• CureVac</td>
<td></td>
</tr>
</tbody>
</table>

... ... ...

**VV** = viral vector; **WIV** = whole inactivated virus

Incomplete list – for discussion
Potential Strategies to Investigate ‘M&M’

- **Plan** prospective clinical trials
  - Partnership between 2 different developers
  - Recruit subjects that have received a 1\textsuperscript{st} dose / full primary immunization and provide heterologous 2\textsuperscript{nd} dose (heterologous priming) or booster dose (heterologous boosting)

- **Speed**: Flexibility necessary to allow timely start of a series of trials and release of IA data

- **Core elements**:
  - Align on overall trial design aspects / endpoints to allow comparability: Uo Oxford COM-CoV (protocol available here: [https://comcovstudy.org.uk/study-protocol](https://comcovstudy.org.uk/study-protocol))
  - Use of WHO international reference standards in serologic assays ([www.nibsc.org](http://www.nibsc.org))
  - Consider plans to integrate immunological testing (of a comprehensive subset of samples) which would utilize CEPI’s available Centralised Laboratory network (email: centralizedlab@cepi.net)
  - **Site readiness initiative**: BMGF / CEPI preparing operational readiness of trial sites in LMICs ([https://epi.tghn.org/covax-overview/clinical-science/clinical/#ref1](https://epi.tghn.org/covax-overview/clinical-science/clinical/#ref1))
  - **DSMB support** offered as part of the Safety Platform for Emergency vACCines (SPEAC) project ([https://brightoncollaboration.us/speac/](https://brightoncollaboration.us/speac/))
COVID-19 Clinical Development Call for Proposals

- **CfP CCT** launched by CEPI on 28 January 2021
- **Aim:** Rapidly expand access to and confidence in COVID-19 vaccines by
  - i) generating clinical evidence in **special / sub-populations / age groups** or
  - ii) addressing **clinical development gaps**.
- Clinical trials which expand access and capacity in **LMICs are particularly encouraged**
- Call open through **28 May 2021**
- Applications will be reviewed on a **rolling basis** as received
- **US $140 million** funding available
- CEPI prepared to respond quickly

[https://cepi.net/get_involved/cfps/](https://cepi.net/get_involved/cfps/)
Panel Discussion

Moderated By:
Jakob Cramer
Head of Clinical Development
Coalition for Epidemic Preparedness Innovations (CEPI)
Discussion Panel Members and Example Questions (1 of 2)

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Potential Discussion Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helen Rees</strong>, University of the Witwatersrand, South Africa</td>
<td>1. If 2 developers decide to partner to establish evidence on ‘M&amp;M’, what data would likely be required for a <strong>label claim</strong>?</td>
</tr>
<tr>
<td><strong>Farah Qamar</strong>, The Aga Khan University, Pakistan</td>
<td>2. For most vaccines, it is unlikely that respective label claims will be sought. What would be a minimum data package that would allow NITAGs to allow a recommendation on <strong>vaccine ‘interchangeability’</strong>?</td>
</tr>
<tr>
<td><strong>Matthew Snape</strong>, Oxford Vaccine Group, United Kingdom</td>
<td>3. From a country perspective (rolling out vaccines), what are options and <strong>challenges to implement respective ‘M&amp;M’ trials</strong> (using deployed vaccines, respecting existing recommendations in populations at risk)?</td>
</tr>
<tr>
<td><strong>Arnaud Didierlaurent</strong>, University of Geneva, Switzerland</td>
<td>4. It has been observed that different vaccine (platforms) have been perceived differently in the population. Could this impact <strong>acceptability of heterologous vaccination regimens</strong> and what has to be taken into account?</td>
</tr>
<tr>
<td><strong>Adam Hacker</strong>, CEPI, United Kingdom</td>
<td>5. Different vaccines (platforms) are associated with different <strong>logistical challenges and contraindications</strong>. How will this increased complexity have to be balanced against potential benefits?</td>
</tr>
<tr>
<td><strong>William Dowling</strong>, CEPI, United States</td>
<td></td>
</tr>
<tr>
<td><strong>Paul Kristiansen</strong>, CEPI, Norway</td>
<td></td>
</tr>
</tbody>
</table>
### Potential Discussion Questions

6. Given the diversity of vaccine platforms being used, there is in theory numerous possible vaccine combinations. What are some key **immunologic considerations** that need to be taken into account re priming / boosting (strong priming effect, antigenic sin, Th1 bias re VMED, …)?

7. For heterologous primary vaccination, what additional aspects need to be considered for **selecting the appropriate 1st vaccine** (relevant vaccine efficacy post 1st (single) dose, improve reactogenicity of the 2nd dose, …)?

8. For heterologous boosting, **vaccines adapted to new SARS-CoV-2 strains** might be available in 6-9 months from now. For primed individuals, a single dose of an adapted vaccine may suffice. What are considerations re vaccines used for primary vaccinations as well as single booster?

### Discussion Panel Members

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Potential Discussion Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helen Rees</strong>, University of the Witwatersrand, South Africa</td>
<td></td>
</tr>
<tr>
<td><strong>Farah Qamar</strong>, The Aga Khan University, Pakistan</td>
<td></td>
</tr>
<tr>
<td><strong>Matthew Snape</strong>, Oxford Vaccine Group, United Kingdom</td>
<td></td>
</tr>
<tr>
<td><strong>Arnaud Didierlaurent</strong>, University of Geneva, Switzerland</td>
<td></td>
</tr>
<tr>
<td><strong>Adam Hacker</strong>, CEPI, United Kingdom</td>
<td></td>
</tr>
<tr>
<td><strong>William Dowling</strong>, CEPI, United States</td>
<td></td>
</tr>
<tr>
<td><strong>Paul Kristiansen</strong>, CEPI, Norway</td>
<td></td>
</tr>
</tbody>
</table>
Wrap Up & Next Steps

Jakob Cramer
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/

• 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