Immune Correlates Analysis of the mRNA-1273 Vaccine Efficacy Trial

Peter Gilbert (for the Moderna / USG COVID-19 Response Team Partnership)
Fred Hutchinson Cancer Research Center
University of Washington

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USG Vaccines Team and Working Groups of the USG Vaccines Development Team (R&D)

- **USG Vaccines Team**
  - Lead: Matt Hepburn

- **USG Vaccines Development Team (R&D)**
  - Chair: John Mascola

**Working group core members**
- Chris Houchens (BARDA)
- Karen Martins (BARDA)
- Lakshmi Jayashankar (BARDA)
- Flora Castellino (BARDA)
- Evan Sturtevant (BARDA)

**Immune assays working group**
- Chairs: Ruben Donis (BARDA), Rick Koup (NIH)

**Pre-clinical working group**
- Chairs: Cristina Cassetti, April Brys

**Clinical working group**
- Chairs: Merlin Robb, Mary Marovich

**USG laboratory leads**
- Adrian McDermott (NIH VRC)
- David Montefiori (Duke)
- Janet Lathey (NIH / Battelle)
- Ralph Baric (UNC)
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- Moderna COVE study team
- CoVPN colleagues (biostatistics, laboratory, clinical, community)
  - Biostatistics: Weiping Deng, Honghong Zhou, Shu Han (Moderna), David Benkeser (Emory), Youyi Fong (Fred Hutch), et al.
  - Immunology labs: Adrian McDermott et al. (VRC-NIAID-NIH), David Montefiori et al. (Duke)
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mRNA-1273 Vaccine Efficacy

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

N=30,415 participants enrolled July 27, 2020 to October 23, 2020

- Primary endpoint is COVID-19:
  - First occurrence of symptomatic COVID-19 with virologically-confirmed SARS-CoV-2 infection in participants with no evidence of previous SARS-CoV-2 infection

- Per-protocol cohort analysis
  - VE = 94.1% (95% CI 89.3 to 96.8%)

MITT cohort analysis

- Incidence Rate (95% CI) per 1000 person-yr:
  - Placebo: 79.7 (70.5–89.9)
  - mRNA-1273: 5.6 (3.4–8.8)

Cumulative Covid-19 Incidence (%)

Days since Randomization

100 μg of mRNA-1273

2X

28 days apart

Placebo

2X
COVE Trial Blood Storage for Immunogenicity and Immune Correlates Analyses

Article assessed D29 and D57 Ab markers as correlates of COVID-19 through 4 months post D29

Injection

Timeline

Serum samples

D0  D1  D29  D57

Stage 1 – for peak Ab correlates analysis

D209  D394  D759

Stage 2 – for durability study / more correlates analysis

• Data cut for immune correlates analyses: March 26, 2021
• COVID-19 endpoint cases diagnosed from September 2020 to March 2021
Two-Phase Case-Cohort Sampling Design for Assessing Antibody Marker Correlates Against the COVID-19 Primary Endpoint

- Sampling stratified by baseline covariates (Vaccine, Placebo) x (SARS-CoV-2 Neg, Pos) x (Baseline demographics)

- Immune correlates analyses in per-protocol baseline negative cohort
  - Per-protocol = received both doses without major protocol violations
Four Antibody Markers Assessed as Immune Correlates

1. bAb to Spike
2. bAb to RBD

Readout BAU/ml (= IU/ml) based on NISBC standard*

3. PsV nAb ID50 titer
4. PsV nAb ID80 titer

Readout calibrated titers to the WHO International Standard (cID50, cID80)*

- Binding antibody (bAb) measured from MSD VRC assay
  - VRC-NIAID-NIH (Adrian McDermott)

- Neutralizing antibody (nAb) lentivirus-based spike-pseudotyped virus assay in 293T cells
  - Duke University (David Montefiori)

*Enables comparison of results to those from other studies, e.g. vs. UK phase 3 trial of the ChAdOx1 nCoV-19 Vaccine (Merryn Voysey’s talk)
Immune Correlates Objectives Addressed in the Article

• To assess Day 29 and Day 57 Ab markers as immune correlates:

CoR

1. Correlates of risk in vaccine recipients (prediction of COVID-19)

2. Mediation causal methods
   a. Controlled VE (Robins/Greenland/Pearl causal effects)
      • Compare COVID-19 risk under assignment to (vaccine, Ab marker
       value) vs. under assignment to placebo
   b. Mediation of VE (Natural direct and indirect effects)
      • Estimate proportion of overall VE mediated by the Ab marker
Numbers of Per-protocol Baseline Negative Vaccine Recipients with Antibody Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity subcohort</td>
<td>1010</td>
</tr>
<tr>
<td>COVID-19 cases for Day 29 marker correlates</td>
<td>46</td>
</tr>
<tr>
<td>COVID-19 cases for Day 57 marker correlates</td>
<td>36</td>
</tr>
</tbody>
</table>

- Day 29 marker analyses: include all cases starting 7 days post Day 29
- Day 57 marker analyses: include all cases starting 7 days post Day 57
Context: The Article Assessed Correlates Against COVID-19 Caused by Viruses Close to the Vaccine Strain

Nextstrain data September to March in U.S.

- 20A/B/C/G: clades of the Wuhan ancestral strain (All identical in Spike, w/ G614)
- 20I: Alpha (UK variant B.1.1.7)
- 21F: Iota (New York variant B.1.526)
- 21C: Epsilon (California variants B.1.427/B.1.429)

Spike Sequence Hamming Distances to the Vaccine Strain (# Mismatches)

*Distribution based on 1122 randomly sampled sequences from GISAID to represent sequences circulating during the COVE trial (Craig Magaret)
Correlations of Day 57 Ab Markers in Per-Protocol Baseline Negative Vaccine Recipients

- High correlation of bAb Spike and bAb RBD responses ($r=0.969$)
- High correlation of PsV nAb cID50 and cID80 responses ($r=0.961$)
- Article focused on reporting results for bAb Spike and cID50
- Moderate-to-high correlation of bAb markers with nAb markers (0.734-0.800)
Antibody Levels Lower in Vaccine Breakthrough Cases than Vaccine Non-Cases for All 4 Markers and Both Time Points

<table>
<thead>
<tr>
<th>Marker</th>
<th>GMC or GMT (95% CI)</th>
<th>Ratio</th>
<th>Cases/Non-Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Cases</td>
<td>Cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>bAb Spike</strong></td>
<td>318 (292, 347)</td>
<td>183 (126, 266)</td>
<td>0.57 (0.39, 0.84)</td>
</tr>
<tr>
<td><strong>bAb RBD</strong></td>
<td>327 (302, 354)</td>
<td>207 (147, 293)</td>
<td>0.63 (0.44, 0.90)</td>
</tr>
<tr>
<td><strong>nAb cID50</strong></td>
<td>13.0 (11.9, 14.1)</td>
<td>7.6 (5.4, 10.8)</td>
<td>0.59 (0.41, 0.84)</td>
</tr>
<tr>
<td><strong>nAb cID80</strong></td>
<td>29.0 (27.1, 31.0)</td>
<td>18.0 (13.3, 24.2)</td>
<td>0.62 (0.46, 0.84)</td>
</tr>
</tbody>
</table>

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<tr>
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<td>Cases</td>
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<tr>
<td><strong>bAb Spike</strong></td>
<td>2652 (2457, 2863)</td>
<td>1890 (1449, 2465)</td>
<td>0.71 (0.54, 0.94)</td>
</tr>
<tr>
<td><strong>bAb RBD</strong></td>
<td>3937 (3668, 4227)</td>
<td>2744 (2056, 3664)</td>
<td>0.70 (0.52, 0.94)</td>
</tr>
<tr>
<td><strong>nAb cID50</strong></td>
<td>247 (231, 265)</td>
<td>160 (117, 220)</td>
<td>0.65 (0.47, 0.90)</td>
</tr>
<tr>
<td><strong>nAb cID80</strong></td>
<td>478 (450, 508)</td>
<td>332 (248, 444)</td>
<td>0.69 (0.52, 0.93)</td>
</tr>
</tbody>
</table>
Antibody Levels Lower in Vaccine Breakthrough Cases than Vaccine Non-Cases

**Spike IgG**

<table>
<thead>
<tr>
<th>Cohort Event</th>
<th>Day 29</th>
<th>Day 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>Rate</td>
<td>67.5%</td>
<td>100%</td>
</tr>
</tbody>
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<th>Day 57</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>1005</td>
</tr>
<tr>
<td>Rate</td>
<td>62.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**PsV nAb cID50**

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<th>Day 57</th>
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<td>n</td>
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<td>38</td>
</tr>
<tr>
<td>Rate</td>
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<td>65.7%</td>
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<tr>
<td>Rate</td>
<td>100%</td>
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</table>
Each Antibody Marker is an Inverse Correlate of Risk in Vaccine Recipients

<table>
<thead>
<tr>
<th>Antibody Marker</th>
<th>Estimated Hazard Ratio per 10-fold Increase in the Marker (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 29</td>
</tr>
<tr>
<td>bAb Spike</td>
<td>0.54 (0.40, 0.74)</td>
</tr>
<tr>
<td>bAb RBD</td>
<td>0.45 (0.30, 0.69)</td>
</tr>
<tr>
<td>PsV nAb cID50</td>
<td>0.33 (0.17, 0.64)</td>
</tr>
<tr>
<td>PsV nAb cID80</td>
<td>0.19 (0.07, 0.56)</td>
</tr>
</tbody>
</table>

*Cox model adjusted for communities of color indicator, at-risk status, and baseline risk score
Day 57 Markers: Cumulative Incidence of COVID-19 Decreases with Ab Level (Cox Modeling)

Risk by clD50: Varies from 0.030 at undetectable to 0.0009 at titer 10,000 (33x)
• This nonparametric analysis supports a ‘continuum’ model that the higher the antibody level the greater the vaccine protection

*Van der Laan Lars, Zhang, Gilbert (2021, arXiv)*
Day 57 Markers Impact VE*

Estimated VE at < LOD = 50%

Estimated VE at < LOD = 61%

*Sawicki, Fong, Carone (2021, arXiv)
Causal Mediation Analysis of Day 29 Neutralizing Ab Markers*

<table>
<thead>
<tr>
<th>Point Estimates (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Day 29 cID50 Titer</strong></td>
</tr>
<tr>
<td><strong>Day 29 cID80 Titer</strong></td>
</tr>
</tbody>
</table>

Direct VE: VE comparing vaccine vs. placebo with marker set to undetectable
Indirect VE: VE in vaccinated at observed marker vs. at marker deactivated to be undetectable
Prop. Mediated: Fraction of total risk reduction from vaccine attributed to the marker

- Interpretation of cID50 titer result: If circulating neutralizing antibodies at Day 29 could be removed but the other consequences of vaccination remained, overall VE would be expected to reduce by 68.5% from 92.3% to 56.0% (on the log scale)

*Benkeser, Diaz, Ran (2021, arXiv)
Discussion
Summary of Correlates of Risk Results in Vaccine Recipients

- The 4 antibody markers at Day 29 and Day 57 are inverse correlates of risk of COVID-19, passing pre-specified family-wise error rate multiplicity adjustment

<table>
<thead>
<tr>
<th>Cumulative Incidence of COVID-19 Through 4 Months Post Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Point estimate</strong></td>
</tr>
<tr>
<td><strong>Day 29 cID50 Titer</strong></td>
</tr>
<tr>
<td>Undetectable</td>
</tr>
<tr>
<td>6,350 (Max)</td>
</tr>
<tr>
<td>0.0135</td>
</tr>
<tr>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Day 57 cID50 Titer</strong></td>
</tr>
<tr>
<td>Undetectable</td>
</tr>
<tr>
<td>10,000 (Max)</td>
</tr>
<tr>
<td>0.030</td>
</tr>
<tr>
<td>0.0009</td>
</tr>
</tbody>
</table>
Vaccine efficacy against COVID-19 increases with Day 29 and Day 57 antibody level for each of the 4 antibody markers.

<table>
<thead>
<tr>
<th>Day 57 cID50 Titer</th>
<th>Point Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable (&lt; 2.4)</td>
<td>51% (−51, 83%)</td>
</tr>
<tr>
<td>5</td>
<td>71% (30, 87%)</td>
</tr>
<tr>
<td>10</td>
<td>78% (54, 89%)</td>
</tr>
<tr>
<td>100</td>
<td>91% (87, 94%)</td>
</tr>
<tr>
<td>1000</td>
<td>96% (94, 98%)</td>
</tr>
</tbody>
</table>

~5-fold increase in VE from titer 5 to 1000
Summary of Correlates of Protection: Mediation Result

- Estimated proportion of mRNA-1273 VE against COVID-19 mediated by cID50 titer = 68%
  - Comparable to proportion VE mediated by HAI titer for inactivated flu vaccine

Estimated proportion of IIV VE mediated against B/Victoria influenza illness mediated by HAI = 57%

*Cowling BJ, Lim WW, Perera RA, Fang VJ, Leung GM, Peiris JM, Tchetgen Tchetgen EJ. Influenza hemagglutination-inhibition antibody titer as a mediator of vaccine-induced protection for influenza B. Clinical Infectious Diseases. 2018 Sep 8;68(10):1713-7
Do Neutralizing Antibodies Fully Mediate the Vaccine Efficacy of mRNA-1273 Against COVID-19?

- Perfect mediation through cID50 titer would be reflected by VE = 0% for vaccine recipients with undetectable cID50 titer
  - Point estimate of VE = 51% at undetectable Day 57 cID50 titer, implying imperfect mediation
  - Yet the wide confidence interval around 51% (−51% to 83%) leaves open the possibility that full mediation occurred
  - Alternatively, additional markers are needed to mediate 100% of the vaccine efficacy
Do Neutralizing Antibodies Fully Mediate the Vaccine Efficacy of mRNA-1273 Against COVID-19?

<table>
<thead>
<tr>
<th>Potential Additional Markers Mediating Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralization as a biological function could be a perfect mediator, but the cID50 titer marker was not sensitive to detect the lowest levels of neutralization activity that mediated partial efficacy. <strong>Design a more sensitive neutralization marker?</strong></td>
</tr>
<tr>
<td>Other immunological functions</td>
</tr>
<tr>
<td>Markers not fully measured in serum (e.g., mucosal markers)</td>
</tr>
<tr>
<td>Anamnestic responses not fully represented by a single time point measurement</td>
</tr>
</tbody>
</table>
Day 29 Markers May Be Advantageous as an Immune Marker Surrogate Endpoint

- The article assessed correlates for per-protocol recipients of both doses
- For this population, the data suggest that Day 29 markers are at least as strong as immune correlates as Day 57 markers
  - If confirmed, could lead to a more practical immune marker surrogate endpoint than a Day 57 marker
  - Hence speedier immunogenicity trials, as it would not be necessary to bring participants back for a Day 57 visit
Limitations / Caveats

- **Scope limits:** This study assessed early binding and neutralizing antibody markers as correlates for symptomatic infection (COVID-19) over 3-4 months, for viruses similar to the vaccine strain
  - Other markers of interest:
    - IgG subclasses, Fc effector functions, T cells, innate immunity, etc.
  - Other study endpoints of interest:
    - Asymptomatic infection, Infection, Severe COVID-19, Viral load in nasal swabs
  - Other SARS-CoV-2 strains of interest:
    - VoCs such as delta
  - Other periods of follow-up
    - Longer term for antibody markers and endpoint events
Epistemological limits

- Phase 3 trials can assess statistical CoPs but cannot prove mechanistic CoPs given limited experimental control and the reliance on causal assumptions that cannot be fully empirically verified.
- Yet if an immune marker is a mechanistic CoP, then a certain set of statistical results in Phase 3 trials is expected.
  - The COVE trial results are meeting this expectation.
- Evidence from other studies, especially vaccine challenge and passive antibody transfer challenge studies, may build a case for mechanism.
  - E.g., Corbett, Nason, Seder et al. (2021, Science)
What Types of Immunobridges are Ready?

New population same vaccine: Adults to children

Immunodeficient to Immunocompromised

New vaccine:

Change the dose
Add or change vaccine strain
Add a boost
De novo approval of a vaccine in the same class
De novo approval of a vaccine in a new class

New SARS-CoV-2 variants

Short bridges
Long bridges