Early Efficacy from Covid-19 Phase 3 Vaccine Studies: Ethical, Operational, & Scientific Considerations

With time to address follow-up questions from the prior COVAX workshop on Sep 24

Clinical Development & Operations SWAT Team | Wednesday October 28, 2020
Meeting Norms and Recording Disclaimer

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

• During the discussion sessions, please “Raise Your Hand” if you want to say something. If called on by the moderator, you will have the ability to unmute yourself.

• Please use the “Chat” function for any technology or logistical issues.

• This workshop will be recorded. Please be mindful of the diverse audience attending the meeting when participating in open discussions.
## Workshop Agenda

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Lead Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00 – 14:05</td>
<td>Welcome &amp; Meeting Objectives</td>
<td>Jakob Cramer</td>
</tr>
<tr>
<td><strong>Part 1: Follow-Up from Previous Workshop on Vaccine Efficacy (Sep 24, 2020)</strong></td>
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<tr>
<td>14:05 – 14:20</td>
<td>Primary Efficacy Endpoints</td>
<td>Edde Loeliger</td>
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<tr>
<td>14:20 – 14:30</td>
<td>Set of Symptoms that Triggers Diagnostic Work-Up of Suspected COVID-19 Cases</td>
<td>Joan Capdevila Pujol</td>
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<td><strong>Part 2: Placebo Group Vaccination in Phase 3 Trials</strong></td>
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<tr>
<td>14:30 – 14:35</td>
<td>Introduction – Global Phase 3 Studies and Emergency Use Overviews</td>
<td>Peter Dull</td>
</tr>
<tr>
<td>14:35 – 14:50</td>
<td>Recent Experience with Novel Vaccines in Placebo-Controlled Trials</td>
<td>Peter Smith</td>
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<tr>
<td>14:50 – 15:00</td>
<td>Introduce Early Efficacy Scenarios for Discussion</td>
<td>Peter Dull</td>
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<td>15:00 – 15:10</td>
<td>Perspectives from an Indian Context</td>
<td>Gagandeep Kang</td>
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<tr>
<td>15:10 – 15:20</td>
<td>Perspectives from a Brazilian Context</td>
<td>Gustavo Santos</td>
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<tr>
<td>15:20 – 15:55</td>
<td>Panel Discussion: Scenario-based Discussion of Efficacy Results and Implications in Different Trial Settings</td>
<td>Moderated by Peter Dull</td>
</tr>
<tr>
<td>15:55 – 16:05</td>
<td>Impact of an Efficacious Vaccine on COVID-19 Vaccine Trials</td>
<td>Dean Follmann</td>
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<td>16:05 – 16:15</td>
<td>Non-Inferiority Trial Design Considerations</td>
<td>Martha Nason</td>
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<td>16:15 – 16:25</td>
<td>Evaluating VAED in Phase III Beyond: Setting Realistic Expectations</td>
<td>Steven Black</td>
</tr>
<tr>
<td>16:55 – 17:00</td>
<td>Wrap Up and Next Steps</td>
<td>Jakob Cramer</td>
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</tbody>
</table>
Welcome & Meeting Objectives

Jakob Cramer, MD
Head of Clinical Development (CEPI)
Context for today’s workshop

• Numerous developers are currently conducting Phase 3 trials for COVID-19 vaccines, with more developers preparing to start Phase 3 trials soon

• After the September 24 COVAX workshop on vaccine efficacy, there are a few follow-up questions to address on de-risking primary endpoints and clinical case workup

• Also, the first EUA for a COVID-19 vaccine could be issued in the United States by the end of the year
  • After early efficacy results are released, developers may experience pressure to offer the active vaccine to the placebo group in ongoing Phase 3 trials
  • It’s also unclear what approach developers should take for Phase 3 studies that have not started yet, in particular for countries where there are no national guidelines

• This topic is already being discussed in the media and developers have asked for guidance
Primary Efficacy Endpoints

Edde Loeliger, MD, MSc
Clinical Development
(CEPI)
Primary efficacy endpoints

COVID-19 Burden of Disease Endpoint & Vaccine-Attenuated Disease

A. Edde Loeliger MD, MSc
Measuring Vaccine Efficacy

• Vaccine efficacy can be assessed in individually-randomized efficacy trials by measuring
  1. The efficacy to prevent disease
  2. The efficacy to prevent infection
  3. The efficacy to reduce disease severity in individuals with breakthrough disease
  4. The efficacy to reduce infectiousness in individuals with breakthrough infection

• Endpoints in COVID-19 efficacy trials the above objectives include
  1. The incidence of COVID-19; can be measured as COVID-19 irrespective of disease severity; as moderate to severe COVID-19; as severe COVID-19; as hospitalizations; ICU admissions; death etc.
  2. Symptomatic and asymptomatic SARS-CoV-2 infection as measured indirectly by seroconversion of antibodies against antigens not included in the vaccine; directly by PCR or other NAAT
  4. Viral shedding by measuring SARS-CoV-2 viral load in bodily fluids
The COVID-19 Vaccine Efficacy Conundrum

• “Ideally COVID-19 vaccines should prevent infection and therefore interrupt disease transmission; should that fail, they should reduce the likelihood of severe disease and hospital admission” (adapted from BMJ Editorial: “Will COVID-19 vaccines save lives? Current trials aren’t designed to tell us” 1)
  • COVID-19 vaccines, like other respiratory and mucosal virus vaccines, may not prevent infection per se
  • NHP challenge data for most vaccines in Phase 3 trials show only partial protection against infection 2

• Primary efficacy endpoints in ongoing COVID-19 Phase 3 efficacy trials
  • Moderate-or-severe COVID-19: Janssen Vaccines/J&J (protocol-defined moderate and severe disease)
  • Both symptomatic COVID-19 irrespective-of-disease-severity, and moderate-or-severe COVID-19: Novavax

• The balancing act behind COVID-19 primary efficacy is larger trials versus the need for more COVID-19 cases
  • The low incidence of severe COVID-19 → need larger trials
  • Lower vaccine efficacy in preventing mild disease than severe disease → need more cases to reject H0

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1 Doshi P. Will covid-19 vaccines save lives? Current trials aren’t designed to tell us BMJ 2020;371:m4037 doi: https://doi.org/10.1136/bmj.m4037 (Published 21 October 2020)
Vaccine-Attenuated Disease & Vaccine Efficacy

• STATEMENT: “Vaccines are often more successful in preventing severe disease than mild disease”

• MISCONCEPTION: “vaccines have a greater biological activity against severe disease than mild disease”

• FACT: Vaccine efficacy is almost always greater against severe disease than mild disease for vaccines associated with attenuated disease severity, in people with breakthrough disease
  → Vaccines almost always have lower efficacy in preventing mild disease than severe disease

• When vaccines cannot prevent infection per se, typically, VE against critical disease > severe disease > moderate disease > mild disease.

• The gradual lowering of VE estimated is caused by the accumulation of clinically-symptomatic breakthrough disease in vaccinated persons
  → lower efficacy against mild disease is driven by vaccine-attenuated disease (VAD) cases
Distribution of COVID-19 by disease severity

PLACEBO ARM

VACCINE ARM
Hypothetical ‘black-box’ visualization of impact of VAD on C-19 vaccine efficacy

<table>
<thead>
<tr>
<th>C-19 disease severity</th>
<th>Placebo arm</th>
<th>Vaccine arm</th>
<th>VE</th>
<th>C-19 cases averted</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>BOD score</td>
<td>BOD score</td>
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<tr>
<td>Endpoint</td>
<td></td>
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<td>Critical C-19</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Severe C-19</td>
<td>3</td>
<td>20</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Moderate C-19</td>
<td>2</td>
<td>40</td>
<td>10</td>
<td>20</td>
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<td>Mild C-19</td>
<td>1</td>
<td>60</td>
<td>30</td>
<td>30</td>
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<tr>
<td>Asymptomatic SARS-CoV-2 +</td>
<td>0</td>
<td>70</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Burden of Disease (BOD)</td>
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<td></td>
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<tr>
<td>Severe/critical</td>
<td>30</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe/critical</td>
<td>70</td>
<td>14</td>
<td></td>
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<tr>
<td>Mild/moderate/severe/critical</td>
<td>130</td>
<td>44</td>
<td></td>
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<tr>
<td>All SARS-CoV-2 Infections</td>
<td>200</td>
<td>200</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine arm “black-box” outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
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<tr>
<td>Critical</td>
</tr>
<tr>
<td>Severe (=VAD)</td>
</tr>
<tr>
<td>Moderate (=VAD)</td>
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<tr>
<td>Mild (=VAD)</td>
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<td>Asymptomatic</td>
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<tr>
<td>Severe</td>
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<td>Moderate (=VAD)</td>
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<td>Severe</td>
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<td>Moderate (=VAD)</td>
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<td>Mild (=VAD)</td>
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<td>Asymptomatic</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Moderate (=VAD)</td>
</tr>
<tr>
<td>Mild (=VAD)</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>
Efficacy estimates – hypothetical example

- Asymptomatic
- Mild
- Moderate
- Severe
- Critical
- All severity
- BOD

30%  50%
Developed in 1994 by Chang, Guess and Heyse as a new efficacy measure for prophylactic interventions that may affect both disease incidence and disease severity\(^1\)

→ for vaccines associated with VAD

Proposed by Devan Mehrotra et.al. as a composite endpoint incorporating COVID-19 incidence and severity for use in efficacy trails\(^2\)

Accepted as a primary endpoint in the Shingles prevention study\(^4\)

Used to support the label claim that Zostavax is indicated “for prevention of zoster and zoster-related post-herpetic neuralgia” to regulatory agencies\(^5\)

Could be used as an outcome measure for the prevention of COVID-19 and COVID-19-related pneumonia

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COVID-19 BOD Endpoint & Pneumonia

• COVID-19 disease severity categorization (WHO)\(^1\)
  • Mild COVID-19: symptomatic disease meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
  • Moderate COVID-19: **clinical signs of pneumonia** (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia

• Why include moderate disease in a BOD endpoint score?
  • The low incidence of severe COVID-19 limits the number of VAD cases that are of essence for BOD, making it too similar to an all-severity COVID-19
  • Moderate disease if WHO-defined as clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia and occurs in up to 40% of symptomatic individuals
  • Allows for a more granular assessment of severity reduction
  • Prevention of COVID-19 related pneumonia is a clinically relevant outcome

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COVID-19 BOD Endpoint – Wrap Up

• The BOD endpoint to de-risk the primary efficacy endpoint
  • Insufficient cases of severe COVID-19
  • Insufficient cases of COVID-19 cases if as a result of accumulation of VAD cases

• Consider the BOD endpoint for a multiple primary endpoint approach
  • Differs from both a composite primary endpoint approach and a co-primary endpoint approach\(^1\)
  • Useful when demonstration of an effect on at least one of several primary endpoints is sufficient
  • As a dual primary endpoint, with the COVID-19 ‘irrespective-of-disease-severity’ endpoint
  • As a triple primary endpoint that includes, in addition, a ‘moderate-to-severe/critical’ COVID-19 endpoint
  • The statistical penalty for closely related multiple endpoints for COVID-19 is relatively small

• Including moderate disease may be critical to its added value when used as a dual or triple primary endpoint
  • Moderate disease as defined by WHO by signs and symptoms of pneumonia is present in up to 40% of individuals\(^2\)
  • Prevention of COVID-19 and COVID-19 related pneumonia is a clinically-relevant primary objective

\(^1\) FDA 2017: Multiple endpoints for clinical trials; draft guidance for industry; available from https://www.fda.gov/media/102657/download (accessed 26 October 2020)
Set of Symptoms that Triggers Diagnostic Work-Up of Suspected COVID-19 Cases

Joan Capdevila Pujol, PhD
Data Scientist
(ZOE)
Set of symptoms that triggers diagnostic work-up of suspected COVID-19 cases

Interim analysis by a joint team from CEPI & ZOE & KCL
Rationale

- In subjects enrolled in vaccine efficacy trials, ideally, all COVID-19 (C-19) symptoms should trigger case work-up, including PCR testing for C-19.
  - Indiscriminate PCR testing may **overwhelm laboratory capacity**.
- This study aims:
  - to quantify how individual and combinations of C-19 symptoms contribute to case finding in a community-based, prospective, observational cohort study.
  - to obtain sets of symptoms through a **multi-objective optimisation** on two conflicting objectives: recall and number of tests needed.
- Laboratory capacity can be taken into account when deciding which symptoms should trigger a case work-up.
Recap - methods

**Data selection** from the COVID Symptom Study App:

- 105,123 *newly symptomatic* users have entered valid PCR results - *positive or negative*
  - 55% aged 18 - 49, 34% aged 50 - 65 and 11% aged 65+
  - 75% female and 25% male

**Terminology:**

- **Recall or Sensitivity:** % of C-19 positive users who are correctly identified by a symptom or a combination of symptoms.
- **Precision or PPV:** % of users identified by a symptom or a combination of symptoms who are C-19 positive.
Recap - previous results

<table>
<thead>
<tr>
<th>Symptom combinations</th>
<th>3-day analysis</th>
<th>7-day analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recall</td>
<td>Precision</td>
</tr>
<tr>
<td>Respiratory symptoms1</td>
<td>516/1154 (44.7%)</td>
<td>516/22390 (2.3%)</td>
</tr>
<tr>
<td>WHO defined pneumonia2</td>
<td>679/1154 (58.8%)</td>
<td>679/34726 (1.9%)</td>
</tr>
<tr>
<td>C-19-specific symptoms3</td>
<td>778/1154 (67.4%)</td>
<td>778/37259 (2.1%)</td>
</tr>
<tr>
<td>Extended symptoms4</td>
<td>1047/1154 (90.7%)</td>
<td>1047/90547 (1.2%)</td>
</tr>
</tbody>
</table>

1Cough, dyspnoea; 2Cough, dyspnoea, fever; 3Fever, cough, dyspnoea, and anosmia/ageusia; 4Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache; 5The numbers of PCR tests needed to identify one PCR+ C-19 case
Outline

- Rationale
- Recap previous results
- Result consistency across
  - Age groups
  - UK and US cohorts
- Multi-objective optimisation: learn triggering symptoms from the data
  - Generalisation
  - Most frequently selected symptoms
- Conclusions
### Results by age group (18-54, 55+)

<table>
<thead>
<tr>
<th>Symptom combinations</th>
<th>Age group</th>
<th>3-day analysis</th>
<th>7-day analysis</th>
<th>Tests per C-19 case&lt;sup&gt;5&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Recall</td>
<td>Precision</td>
<td>Recall</td>
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<tr>
<td><strong>C-19-specific symptoms&lt;sup&gt;3&lt;/sup&gt;</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>18 - 54</td>
<td></td>
<td>614/902 (68.1%)</td>
<td>614/25873 (2.4%)</td>
<td>42</td>
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<tr>
<td>55+</td>
<td></td>
<td>164/252 (65.1%)</td>
<td>164/11386 (1.4%)</td>
<td>69</td>
</tr>
<tr>
<td><strong>Extended symptoms&lt;sup&gt;4&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18 - 54</td>
<td></td>
<td>823/902 (91.2%)</td>
<td>823/61972 (1.3%)</td>
<td>75</td>
</tr>
<tr>
<td>55+</td>
<td></td>
<td>224/252 (88.9%)</td>
<td>224/28575 (0.8%)</td>
<td>128</td>
</tr>
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</table>

<sup>3</sup>Fever, cough, dyspnoea, and anosmia/ageusia;  
<sup>4</sup>Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache;  
<sup>5</sup>The numbers of PCR tests needed to identify one PCR+ C-19 case
Result by cohort (UK/US)

The UK cohort has been regularly invited for testing thanks to the DHSC testing programme, while the US cohort has not.

<table>
<thead>
<tr>
<th>Symptom combinations</th>
<th>Cohort</th>
<th>Recall</th>
<th>Precision</th>
<th>Tests per C-19 case</th>
<th>Recall</th>
<th>Precision</th>
<th>Tests per C-19 case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3-day analysis</td>
<td>7-day analysis</td>
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<td>3-day analysis</td>
<td>7-day analysis</td>
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<tr>
<td><strong>C-19-specific symptoms</strong>³</td>
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<td></td>
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<td></td>
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<tr>
<td>UK</td>
<td></td>
<td>778/1154 (67.4%)</td>
<td>778/37259 (2.1%)</td>
<td>47</td>
<td>974/1202 (81.0%)</td>
<td>974/41658 (2.3%)</td>
<td>42</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td>63/79 (79.7%)</td>
<td>63/1142 (4.4%)</td>
<td>23</td>
<td>73/79 (92.4%)</td>
<td>73/1614 (4.5%)</td>
<td>22</td>
</tr>
<tr>
<td><strong>Extended symptoms</strong>⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td>1047/1154 (90.7%)</td>
<td>1047/90547 (1.2%)</td>
<td>86</td>
<td>1148/1202 (95.5%)</td>
<td>1148/94447 (1.2%)</td>
<td>83</td>
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<tr>
<td>US</td>
<td></td>
<td>76/79 (96.2%)</td>
<td>76/2640 (2.9%)</td>
<td>35</td>
<td>78/79 (98.7%)</td>
<td>78/2745 (2.8%)</td>
<td>35</td>
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</tbody>
</table>

³Fever, cough, dyspnoea, and anosmia/ageusia; ⁴Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache; ⁵The numbers of PCR tests needed to identify one PCR+ C-19 case
Multi-objective optimization

Recall ~ 97.5%
# test ~ 89.0%

Recall ~ 94.6%
# test ~ 77.5%

3 days symptoms

Each point has a different trade-off between recall and % tested population

7 days symptoms
Most frequently selected symptoms for solutions >90% recall

- 3 days scenario
  - Fatigue, loss of smell, persistent cough, diarrhea, headache and sore throat

- 7 days scenario
  - Fatigue, loss of smell, persistent cough, sore throat, fever and unusual muscle pains
## Overall results

<table>
<thead>
<tr>
<th>Symptom combinations</th>
<th>3-day analysis</th>
<th>7-day analysis</th>
<th>Tests per C-19 case&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Tests per C-19 case&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recall</strong></td>
<td><strong>Precision</strong></td>
<td><strong>Recall</strong></td>
<td><strong>Precision</strong></td>
<td><strong>Recall</strong></td>
</tr>
<tr>
<td>Respiratory symptoms&lt;sup&gt;1&lt;/sup&gt;</td>
<td>516/1154 (44.7%)</td>
<td>516/22390 (2.3%)</td>
<td>43</td>
<td>693/1202 (57.7%)</td>
</tr>
<tr>
<td>WHO defined pneumonia&lt;sup&gt;2&lt;/sup&gt;</td>
<td>679/1154 (58.8%)</td>
<td>679/34726 (1.9%)</td>
<td>51</td>
<td>845/1202 (70.3%)</td>
</tr>
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<td>86</td>
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</tr>
<tr>
<td>Most frequently selected symptoms</td>
<td>1097/1154 (95.1%)</td>
<td>1097/107748 (1.0%)</td>
<td>98</td>
<td>1161/1202 (96.6%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Cough, dyspnoea; <sup>2</sup>Cough, dyspnoea, fever; <sup>3</sup>Fever, cough, dyspnoea, and anosmia/ageusia; <sup>4</sup>Fever, cough, dyspnoea, anosmia/ageusia, fatigue, and headache; <sup>5</sup>The numbers of PCR tests needed to identify one PCR+ C-19 case: (3-day) fatigue, loss of smell, persistent cough, diarrhea, headache and sore throat; (7-day) fatigue, loss of smell, persistent cough, sore throat, fever and unusual muscle pains
Conclusions (I)

- Pneumonia symptoms are overall not very predictive of positive PCR result by themself and they do better when combined with anosmia/ageusia - *classic symptoms*.
- 32.6% of the positive cases do not show *classic symptoms* during the first three days of symptoms and 19%, not even during the first week.
- An *extended* list of *symptoms*, which includes the *classic symptoms* plus *fatigue* and *headache*, increases recall above 90% despite doubling the number of test required.
- These findings were shown to be consistent across two age groups (18 - 54, 55+) and across the UK and US cohorts.
Conclusions (II)

- We also presented an optimisation method to learn sets of triggering symptoms from the data which takes into account the trade-off between recall and number of required tests.
- We showed that solutions with a high recall tend to include most of the extended symptoms, but we noticed the following differences:
  - Headache is more likely to be selected during the first 3 days but Fever tends to be more selected during the 7 days scenario
  - Shortness of breath tends to never be selected, suggesting it might occur later in the disease or co-occur with other selected symptoms
Introduction: Global Phase 3 Studies and Emergency Use Overviews

Peter Dull, MD
Deputy Director, Integrated Clinical Vaccine Development (BMGF)
Key objectives for Part 2 of the workshop

• Review **key historical examples** of placebo-controlled vaccine studies and relevance for COVID-19

• Discuss **country- and vaccine-specific scenarios** with early efficacy results
  o Hear perspectives from countries facing important decisions about managing early efficacy results in the regional context (India and Brazil)
  o Hear perspectives on scientific, regulatory, and operational considerations if the placebo groups can no longer be enrolled or require vaccination
Additional context – Why does this matter?

- Multiple phase 3 efficacy placebo-controlled studies for "Wave 1" Covid-19 vaccines have initiated, many of which are multi-country studies.

- Further vaccines are in development and these "Wave 2" vaccines may have product characteristics which are critical for global impact (e.g., higher efficacy, better tolerability profiles, scalability, impact on shedding, population sub-groups).

- Immune correlates recognized as clearly critical but information very limited at present.
  - If correlate identifiable, likely will occur only after initial efficacy studies completed and may be platform-specific.

- On October 22 at the VRBPAC meeting, US FDA stated that “availability of a licensed vaccine does not automatically preclude continuation of blinded, placebo-controlled trials”.
  - Also stated that “continuation of placebo-controlled follow-up after EUA will be critical to ensure that additional safety and effectiveness data are accrued to support submission of a licensure application as soon as possible following an EUA.”
Recent Experience with Novel Vaccines in Placebo-Controlled Trials

Peter Smith
Professor of Tropical Epidemiology
(London School of Hygiene & Tropical Medicine)
Recent experience with novel vaccines in placebo-controlled trials

Peter Smith
Participation is a vaccine trial should be driven by altruism

• Vaccine trials are not conducted for the benefit of those in the trial.

• Participants may benefit from better care, and have a chance of receiving the vaccine, which might be beneficial, ineffective or cause harm.

• Participants should not be disadvantaged compared to those in the same community not included in the trial.

• Nor should they be unduly advantaged.
Key questions in a pivotal vaccine trial

• Is the vaccine safe?
• Is the vaccine efficacious?
• How long does protection last (and, if necessary, can it be prolonged by booster doses)?

Addressing these questions generally requires a comparator group who have not been vaccinated.

• Do the results justify “licensure”?  
• Will the results convince public health authorities to deploy the vaccine (and potential recipients to be take it up)
Early examples of different approaches to unvaccinated group

**MRC trial of BCG vaccine (1950-52)**
- Participants randomised at age 14-15y
- Unvaccinated group never vaccinated
- Enabled efficacy to be evaluated over 20+ years
- Short-term results (VE >80%) provided basis for policy for BCG vaccination in schools at age ~13y.

**MRC trial of live measles vaccine (1964)**
- Participants aged 10mo-2y
- Efficacy shown to be 85% in first 9 months
- All unvaccinated offered vaccine at 9 months, as originally promised
- About 20% declined vaccination (had similar measles incidence as those ineligible for the trial)
- Follow-up for further 2 years showed continuing high efficacy
Recent examples of placebo group preserved beyond demonstration of efficacy

**Rotavirus vaccines**
- Protection against severe rotavirus gastroenteritis demonstrated in first year of follow-up
- Placebo group maintained to measure protection in second year.

**Dengvaxia dengue vaccine**
- Primary analysis showed protection against dengue in 1st year after last dose
- Follow-up, with placebo group, continued for 5 years
- Evidence of vaccine enhanced disease in a sub-group found only from 2nd year after last dose.

**RTS,S/AS01 malaria vaccine**
- Vaccine efficacy against primary endpoint after one-year of follow-up
- Placebo groups maintained to access decline of protection with time and impact of a booster dose. Apparent rebound effect of severe malaria found with extended follow-up, indicating importance of booster dose.
Situations in which use of a placebo in vaccine trials may be justifiable when there is already an efficacious vaccine

1. Developing a locally affordable vaccine (e.g. Rotavac in India)
2. Evaluating the local safety and efficacy of an existing vaccine (e.g. Rotarix and Rotateq in Africa)
3. Testing a new vaccine when an existing vaccine is not yet in local use (e.g. Rotasil in Niger) – likely to be relevant for COVID-19 vaccines
4. Determining the local burden of disease (e.g. vaccine-probe studies – Hib)
Head-to-head vaccine comparisons with clinical outcome

Such comparison are rarely done, mainly because of the large study sizes required to establish non-inferiority or superiority. However, some exceptions:

**Relative efficacy of 1 or 2 dose AS03-Adjuvanted A(H1N1) reduced dose vaccine vs. 2-dose Non-Adjuvanted A(H1N1) influenza vaccine (2010-11)**
- 6000 children (6mo-10y) randomised between 3 arms followed for 1y for H1N1
- Fewer cases observed (total 23) than expected in 3rd pandemic wave
- Relative efficacy 2 dose adjuvanted vs non-adjuvanted = 77% (95%CI 18%-93%)

Relative Efficacy of AS03-Adjuvanted Pandemic Influenza A(H1N1) Vaccine in Children: Results of a Controlled, Randomized Efficacy Trial

Terry Nolan,1,2∗ Sumita Roy-Ghanta,3∗ May Montelaro,4 Lily Weckx,4 Rolando Ulloa-Gutiérrez,5 Eduardo Laccano-Ponce,6 Angkooi Kerdjunch,6 Marco Aurelio Palazzi Salado,6,7 Aurelio Cruz-Valdez,7 Sandra Línea,7 Fang Song Lim,7 Abhilash Madequzari de los Santos,7 Miguel Ángel Rodríguez-Webb,6 Juan Carlos Tinoco,7 Marcela Hernandez de Muzerolle,11 Kip Fanningricht,11 Penrose Koszewski,11 Pio Lopez,11 Charissa Borja-Yabono,11 Ping Li,11 Sérgio Dervieux,24 Louis Fries,4 Gary Dubin,4 Thomas Breuer,16 Bruce L. Innis,∗ and David W. Vaughn∗
Early Efficacy Scenarios for Discussion

Peter Dull, MD
Deputy Director, Integrated Clinical Vaccine Development (BMGF)
What is the impact on i) ongoing or ii) planned new Ph3 placebo-controlled vaccine efficacy trials in case ...

**Trial site country: levels evidence / action**

- … a vaccine’s efficacy has been demonstrated per interim analysis?
- … a vaccine has been *approved*, supply not yet available?
- … a vaccine has been *approved* and some supply available (however, no formal recommendations for selected risk populations in place yet)?
- … a vaccine has been *approved*, some supply available only to cover official recommendation for high-risk populations?
- … a vaccine has been *approved*, recommended for high-risk populations, and sufficient supply available for routine use in the full adult population?

*Approved according to national requirements via emergency use procedure or full licensure*
Specific efficacy trial scenarios for discussion during today’s workshop

**Vaccine A Scenarios**

1. **NRA has not approved Vaccine A for emergency use or full licensure**

2. **NRA has approved Vaccine A for emergency use or full licensure but supply only sufficient for high-risk populations**

**Vaccine B Scenarios**

3a. **Vaccine B has ongoing Phase 3 trial in the same country as approved vaccine A**

3b. **Vaccine B has planned Phase 3 trial in the same country as approved vaccine A**

---

*For simplicity, presume efficacy supported in all age groups (adults and elderly); At any time, subjects may exit study without penalty and receive standard-of-care interventions. Sponsor is required to update informed consent form as vaccine risk-benefit is modified*
Perspectives from an Indian Context

Gagandeep Kang, MD, PhD
Professor of Microbiology
(CMC Vellore)

Vaccine A Scenarios

1. NRA has not approved Vaccine A for emergency use or full licensure

2. NRA has approved Vaccine A for emergency use or full licensure but supply only sufficient for high-risk populations

Vaccine B Scenarios

3a. Vaccine B has ongoing Phase 3 trial in the same country as approved vaccine A

3b. Vaccine B has planned Phase 3 trial in the same country as approved vaccine A

Vaccine A demonstrates efficacy at interim analysis and sponsor initiates application for emergency use, all within the same country*
Perspectives from a Brazilian Context

Gustavo Mendes Lima Santos
General Manager of Medicines and Biological Products (ANVISA)

Vaccine A Scenarios

1. NRA has not approved Vaccine A for emergency use or full licensure

2. NRA has approved Vaccine A for emergency use or full licensure but supply only sufficient for high-risk populations

Vaccine B Scenarios

3a. Vaccine B has ongoing Phase 3 trial in the same country as approved vaccine A

3b. Vaccine B has planned Phase 3 trial in the same country as approved vaccine A
Panel Discussion

Scenario-based Discussion of Efficacy Results and Implications in Different Trial Settings
## Discussion Panel Members and Example Questions

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Potential Discussion Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peter Smith, Professor of Tropical Epidemiology, LSHTM</td>
<td>1. Does it change the approach if approval is for emergency use, accelerated / conditional, or full licensure?</td>
</tr>
<tr>
<td>• Gagandeep Kang, Professor of Microbiology (CMC Vellore)</td>
<td>2. What is the effect of an approval by an NRA outside the country where the trial is being conducted of a multi-regional study? Of a separate study using the same vaccine?</td>
</tr>
<tr>
<td>• Gustavo Mendes Lima Santos, General Manager of Medicines and Biological Products, ANVISA</td>
<td>3. What if the trial vaccine is approved but supply is not yet available – should the trial vaccine be offered to the placebo group?</td>
</tr>
<tr>
<td>• Ross Upshur, Professor (University of Toronto) and Co-Chair (WHO COVID-19 Ethics Working Group)</td>
<td>4. What if a different (non-trial) vaccine is approved and supply is available with formal recommendation in high-risk populations – should vaccination be offered to respective participants in both the intervention and placebo groups?</td>
</tr>
</tbody>
</table>
Impact of an Efficacious Vaccine on COVID-19 Vaccine Trials

Dean Follmann, PhD
CoVPN Statistics Group
Chief, Biostatistics Research Branch
(NIH / NIAID)
Setup

• Trial of Vaccine A shows efficacy

• Try to maintain blinded follow-up to assess vaccine durability & vaccine associated enhanced disease (VAED)
  o US FDA guidance strongly encourages continued follow-up past EUA to support BLA

• At some point, vaccine may become widely available
  o Placebo volunteers may cross-over to receive vaccine A
  o Ideal to continue follow-up to assess immune correlates of protection and vaccine durability
Immune Correlates

• Assess whether antibody after last dose predicts disease acquisition

• Goal: Estimate an antibody level that gives very high VE

• Correlate allows licensure or bridging of same/similar platforms using small immunogenicity studies

*Illustration:* \( \text{Ab} \geq 10^3 \) supportive of licensure

Dengvaxia

[Graph showing BL seropositive and vaccine efficacy]
Measure Immune Response in the Placebo Crossovers

• When vaccine shows efficacy, may be relatively few disease cases on vaccine arm

• Correlates analysis at time of efficacy readout may be unconvincing/underpowered

• Can double the sample size for correlates by measuring antibody in the placebo crossovers

Blood draws to measure vaccine induced antibodies
### Randomized Trial of Vaccine vs Placebo

<table>
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<tr>
<th>Randomized to</th>
<th># cases August-November</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>125&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vaccine</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Vaccine Efficacy 80%</td>
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</table>

### Randomized Trial of Immediate vs. Delayed Vaccination

<table>
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<tr>
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<th># cases August-November</th>
<th># cases December-March</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Delayed</td>
<td>125&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vaccine Immediate</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vaccine Efficacy</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

(a) # cases on placebo  
(b) # cases on vaccine
Following placebo crossover, can collect data on durability

<table>
<thead>
<tr>
<th>Placebos Crossover to Vaccine</th>
<th># cases August-November</th>
<th># cases December-March</th>
<th># cases December-March</th>
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</thead>
<tbody>
<tr>
<td>Randomized to</td>
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</tr>
<tr>
<td>Placebo Delayed Vaccine</td>
<td>125&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vaccine Immediate Vaccine</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vaccine Efficacy 80%</td>
<td></td>
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</tbody>
</table>

**If more cases in original vaccine arm post crossover, vaccine efficacy is waning**

(a) # cases on placebo
(b) # cases on vaccine

0-4 months post vaccination

4-8 months post vaccination
Summary

• If a vaccine trial shows efficacy, continue blinded follow-up as long as possible to assess durability and VAED

• If placebo crossover to vaccine does occur *maintain follow-up*
  o Still have a randomized trial
  o Doubles sample size for immune correlates analysis
  o Can still assess vaccine durability, though less reliably than if no crossover
Non-Inferiority Trial Design Considerations

Martha Nason, PhD
Mathematical Statistician, Biostatistics Research Branch (NIH / NIAID)
When do we need a non-inferiority trial?

- Non-inferiority trial necessary when it is no longer considered ethical to randomize participants to Placebo.

- Once another vaccine has demonstrated efficacy and is available to the population being studied. This decision may be different in different locations, different subpopulations (priority groups).

- Strong scientific arguments to continue Placebo group as long as possible to collect data on safety, durability.
  
  (recent discussions with WHO, FDA's VRBPAC)
Non-inferiority trials: setup

Sometimes referred to as “equivalence trials”

Can’t ever prove two vaccines are the same. Instead show that:

- New vaccine is better than established vaccine (superiority)
  Or
- New vaccine is at least “not much worse” than established vaccine (non-inferiority)

Need to define how much worse is too much, and how much worse might be acceptable

- This is the non-inferiority margin
- "Typically" this is 10% and requires justification by the sponsor
Choice of margin

FDA initial guidance:

*For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is > -10 %.*

Assume vaccine A is established, vaccine B is new candidate:

\[
\frac{rate(Vacc \ B)}{rate(Vacc \ A)} < 1.10 = Margin
\]

- if \(VE(A)=50\%\) then must show \(VE(B)> 45\%\)
- if \(VE(A)=60\%\) then must show \(VE(B)> 56\%\)
- if \(VE(A)=70\%\) then must show \(VE(B)> 67\%\)
- if \(VE(A)=80\%\) then must show \(VE(B)> 78\%\)
- if \(VE(A)=90\%\) then must show \(VE(B)> 89\%\)
Sample Size calculations – Vaccine B comparable or better than Vaccine A

<table>
<thead>
<tr>
<th>VE in “successful” vaccine (A)</th>
<th>VE to rule out for new vaccine (B)</th>
<th>NI margin (RR scale)</th>
<th>True VE in new vaccine (B)</th>
<th># infections needed</th>
<th>Person-years assuming 1% incidence in unvaccinated</th>
<th>Approx # years Assuming n=30,000 enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>56%</td>
<td>10%</td>
<td>60%</td>
<td>4,660</td>
<td>1,160,000</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td></td>
<td></td>
<td>293</td>
<td>82,000</td>
<td>2.8</td>
</tr>
<tr>
<td>60%</td>
<td>50%</td>
<td>25%</td>
<td>60%</td>
<td>857</td>
<td>214,000</td>
<td>7.1</td>
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<td>70%</td>
<td></td>
<td></td>
<td>164</td>
<td>45,900</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Scenario Discussion –
Late arriving vaccine required to demonstrate non-inferiority:

Vaccine A *Observed* Efficacy: \( \text{VE}_A = 50\% \)
Want to show \( \text{RR}_{B:A} < 1.2 \) (i.e. \( \text{VE}_B > 40\% \))

Vaccine B *Hypothesized* Efficacy: \( \text{VE}_B = 60\% \)

Need 256 events under these assumptions, 90% power

*If 1% incidence without vaccine, n=30,000 people enrolled*

\( \rightarrow \) 2 years to 256 events
Scenario Discussion –
Late arriving vaccine required to demonstrate non-inferiority:

Suppose:
• Vaccine A shows efficacy with 50% Vaccine Efficacy, rules out VE<30%
• Vaccine B looks promising, high neutralizing titers and high scalability potential.

Potential Course of Action:
• Enroll n=30,000 people into a non-inferiority study of vaccine A vs B
• At 1 month post 2\textsuperscript{nd} dose, compare Neut titers between vaccines A and B in a small predefined subset.
  • If Neut titers to Vaccine B are shown to be non-inferior (or superior) to Neut titers to vaccine B, share data with regulators as confidence builds around correlates of protection
  • Request “accelerated/conditional” approval, depending on setting
• Continue to follow n=30,000 people for symptomatic disease, clinical non-inferiority for ~2 years
Conclusions

• Defining the margin is central to planning any non-inferiority trial
  • Suggest discussion among stakeholders now about the appropriate margin
  • Must think about margin on both VE and relative risk scale

• Non-inferiority takes very large sample size (or many years) if vaccines are truly equivalent

• If VE(A)=60% and VE(B)=70%, demonstration of non-inferiority would take 2-3 years*

*assuming n=30,000 and 1% incidence in unvaccinated
Acknowledgements

• Dean Follmann
• Michael Fay
• Yunda Huang
• David Benkasser
• And the rest of the OWS stats group
Backup: Sample Size calculations – Vaccine B comparable or better than Vaccine A
Additional scenarios ---- Fixed non-inferiority margin at 10%

<table>
<thead>
<tr>
<th>VE in “successful” vaccine (A)</th>
<th>VE to rule out for new vaccine (B)</th>
<th>Non-inferiority Margin On RR</th>
<th>True VE in new vaccine (B)</th>
<th># infections needed</th>
<th>Person-years assuming 1% incidence in unvaccinated</th>
<th>Approx # years follow-up on n=30,000</th>
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<tr>
<td>50%</td>
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Backup: Sample Size calculations – Vaccine B comparable or better than Vaccine A
Additional scenarios ---- Increasingly wide non-inferiority margin

<table>
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<td></td>
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<td>26</td>
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</table>
Evaluating VAED in Phase III Beyond: Setting Realistic Expectations

Steven Black, MD
Executive Board
SPEAC Project
(Safety Platform for Emergency vACcines)
Overview

• What is meant by enhanced disease and why would be worry about it?

• Vaccine failures versus VAED

• Outline what data should be collected on all vaccine failures

• A possible approach to evaluation
What is VAED and Why are We Talking about it

• Simply, Vaccine Associated Enhanced Disease occurs when a vaccine recipient is exposed to the wild type virus and experiences more severe disease than they would have if they had not been vaccinated.

• Brighton Collaboration has developed a case definition with much more detail. [https://brightoncollaboration.us/vaed/](https://brightoncollaboration.us/vaed/)

• In some studies in animal models of other corona virus vaccines, vaccinated animals experienced more severe disease when exposed to the wild type virus

• This phenomenon has been observed for other vaccines including vaccines developed for measles, RSV and dengue.
Vaccine Failure versus Enhanced Disease

- No vaccine is 100% effective so that vaccine failures will occur.

- By definition, all cases of enhanced disease would occur in vaccinees and hence be a vaccine failure.

- Without a specific biomarker for enhanced disease, it is not currently possible to differentiate between
  - A vaccine failure with severe disease
  - A vaccine failure with more severe disease than they otherwise would have had without vaccine --- enhanced disease

- So what to do?
Evaluating VAED in phase 2-3 clinical trials

- This will require evaluating all vaccine failures and COVID disease patients in the control group in a blinded manner using a standard protocol which includes a standardized severity assessment score in all vaccine failures in the trial.

- One would then compare the average severity score in per protocol cases of COVID in the vaccine and placebo groups.

- Limiting factors include
  - VAED, if it exists for COVID vaccines, is likely to be uncommon.
  - Importantly, the risk of VAED may increase as the immune response wanes with time --- follow up may be too short in phase III trials.
Cross over designs and safety outcomes

Placebo

Cross Over

VACCINE

Safety outcomes here have a comparison group

Safety outcomes here have NO comparison group except initial control time period

Duration of comparative Safety follow up is short

If events occur here assessing causality is problematic

With blinded cross over, assessment of cases is blinded but one no longer has an unvaccinated group for comparison
• If a trial of 30,000 participants randomized 1:1 has accrued 100 cases of COVID and the vaccine’s true efficacy is 75%, one would expect 80 COVID cases in controls and 20 in the vaccine group.

• If VAED occurs in 10% of vaccine failures, one would only expect to see two such cases in vaccine recipients

• If VAED occurs in 5% of cases, one would only expect one such case

• Thus even in a large phase III trial, there is not sufficient power to detect VAED even it is relatively common.

• This situation is made worse if VAED risk occurs only after a long lag period in which case it could be occurring after the trial follow up is complete or in a cross over trial after the comparison group has been vaccinated.
Evaluating VAED after vaccine introduction.

• This will be very challenging unless
  • The rate of VAED is high
  • The severity and disease characteristics in VAED cases are different than routine COVID cases
  • A biomarker is identified

• Similar to the case in phase III trials, one would want to establish a registry of all vaccine failures with all the cases evaluated using a common protocol and standardized severity score.

• Since there would be no control group in this case, one would have to compare vaccinated and unvaccinated COVID cases adjusting for co-morbidities, therapies given, age, etc.
Summary

• There is a possibility that VAED may occur after some COVID vaccines

• Risk might be higher for unadjuvanted inactivated vaccines that develop a Th2 oriented response.

• There is no biomarker for VAED so that it is not currently possible to differentiate a vaccine failure from a vaccine failure with enhanced disease on an individual level.

• Assessment of all vaccine failures using a standardized protocol and severity score is critical.
Panel Discussion

Operational, Regulatory, and Scientific Considerations
## Discussion Panel Members and Potential Questions

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<tr>
<td><strong>Dean Follmann</strong>, Chief, Biostatistics Research Branch (NIH/NIAID)</td>
<td>1. How do we help additional vaccines move through licensure if we've lost the placebo arm and non-inferiority studies are not feasible?</td>
</tr>
<tr>
<td><strong>Martha Nason</strong>, Mathematical Statistician, Biostatistics Research Branch (NIH/NIAID)</td>
<td>2. What kind of arguments are required to define the non-inferiority margin for vaccine efficacy studies?</td>
</tr>
<tr>
<td><strong>Steven Black</strong>, Executive Board Member (SPEAC)</td>
<td>3. What have we learned so far about risk of vaccine-associated enhanced disease from either more recent animal studies or ongoing clinical trials?</td>
</tr>
<tr>
<td><strong>Marco Cavaleri</strong>, Head of Biological Health Threats and Vaccines Strategy (EMA)</td>
<td>4. From review of the publicly available study protocols, how are we doing at characterizing Covid-19 disease cases in ongoing and planned studies?</td>
</tr>
<tr>
<td><strong>Philip Krause</strong>, Deputy Director (US FDA / CBER / OVRR)</td>
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Wrap Up & Next Steps

Jakob Cramer
Head of Clinical Development
(CEPI)
• Thank you all for your participation and engagement today

• 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

• We will be holding a next workshop on advances toward identifying Immune Correlates of Protection (CoP), targeted for late November / early December

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

• We will distribute a workshop report to summarize today’s conversation and a post-workshop survey to collect feedback