COVID-19 Efficacy Trial Design Considerations & Early Learnings from Ongoing Studies

September 24, 2020
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<td>Jakob Cramer</td>
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<td>Amol Chaudhari, Joan Capdevila Pujol</td>
</tr>
<tr>
<td>17:10 – 17:50</td>
<td>Panel Discussion: Operational Considerations</td>
<td>Moderated by Peter Dull</td>
</tr>
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<td>17:50 – 18:00</td>
<td>Wrap-up and next steps</td>
<td>Peter Dull</td>
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Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the “Chat” function or hold your questions for the discussion sessions.

- In the “Chat” function, you can send your comments and questions to “Panelists only” or “All Panelists and Attendees.”

- 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.

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

Melanie Saville, MD
Director of Vaccine Development (CEPI)
Access to COVID-19 tools (ACT) accelerator

ACCESS TO COVID-19 TOOLS (ACT) ACCELERATOR
A Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines

Key players

DIAGNOSTICS

THERAPEUTICS

VACCINES (COVAX)

CEPI
Development & Manufacturing
Led by CEPI, with industry

Gavi
Procurement and delivery at scale
Led by Gavi

WHO
Policy and allocation
Led by WHO

SOURCE: (ACT) ACCELERATOR Commitment and Call to Action 24th April 2020
COVAX SWAT teams are being set up as a joint platform to accelerate COVID-19 Vaccine development and manufacturing by addressing common challenges together.

**Timely and targeted**
Addresses specific cross-developer technical challenges as they are raised and/or identified on an ongoing basis.

**Multilateral**
Establishes a dialogue and global joint effort across different COVID-19 vaccines organizations (incl. industry and other global networks).

**Knowledge-based**
Identifies and collates most relevant materials and insights across the broader COVID-19 ecosystem to accelerate vaccine development and manufacturing.

**Resource-efficient**
Coordinates between different organizations/initiatives to limit duplications and ensure expertise is efficiently leveraged.

<table>
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<tr>
<th>SWAT teams</th>
<th>Enabling sciences</th>
<th>Clinical Development &amp; Operations</th>
<th>Manufacturing</th>
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</thead>
</table>

*Regulatory Advisory Group*
Meeting Objectives

To support COVID-19 vaccine developers with the rapid planning and implementation of pivotal phase 3 vaccine efficacy trials, the aim is to provide developers with

• product-agnostic supportive information and considerations on the assessment of vaccine efficacy
• a forum to communicate and address individual challenges developers may face

In this workshop, we will
• review the regulators positions
• address scientific aspects including but not limited to case definitions and endpoints as well as statistical considerations related to vaccine efficacy
• focus on operational aspects related to the conduct of vaccine efficacy trials
• discuss lessons learnt from the field
Introduction

Jakob Cramer, MD

Head of Clinical Development (CEPI)
Efficacy Trial Design Considerations & Early Learnings from Ongoing Trials

• SARS-CoV-2 (and COVID-19) is approx. 10 months old
• Vaccines are expected to become available at large scale within the next ~6 months
• Limited (no) time for ‘trial and error’
• Phase 3 efficacy studies are complex in “normal times” – these are not normal times
• Yet, no shortcuts allowed to establish vaccine efficacy, safety and trust

Part 1: Vaccine efficacy: scientific considerations for Phase 3 trials

Part 2: Vaccine efficacy: operational considerations for Phase 3 trials
Vaccine Efficacy: The Regulators’ Perspective

Debra Yeskey, Pharm.D.
*Head of Regulatory Affairs – North America (CEPI)*

Svein Rune Andersen, Dr. Sci.
*Head of Regulatory Affairs – Europe (CEPI)*
Vaccine efficacy: Current regulatory guidance

A brief overview
FDA – guidance published June 2020

Vaccine Efficacy - recommendations

**Randomised, double-blinded, placebo controlled:**

Randomisation : 1:1 – preferred

Observation time – as long as feasible – ideally 1-2 years to assess duration of protection and potential VMED

**Efficacy considerations:**

Primary end-point:

- Either lab confirmed COVID-19 or SARS-CoV-2
  - Acute COVID-19 cases virologically confirmed
  - SARS-CoV-2 infection, including asymptomatic infection – monitored/confirmed by virological or serological method.

**Primary endpoint or a secondary endpoint** (with or without formal hypothesis testing) defined as virologically confirmed SARS-CoV-2 infection + one or more symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea
Severe COVID-19:

- **Consider** powering efficacy trials for formal hypothesis testing
- If not evaluated as primary, should be evaluated as secondary end-point (with or without hypothesis testing)
- Defined as virologically confirmed SARS-CoV-2 infection with any of the following:
  - At rest: **respiratory rate** ≥ 30 per minute, **heart rate** ≥ 125 per minute, **SpO2** ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
  - **Respiratory failure** (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO)
- **Evidence of shock** (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
- **Significant acute renal, hepatic, or neurologic dysfunction**
- **Admission to an ICU**
- **Death**

*SARS-CoV-2 infection*

- Infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.
Statistical considerations

- Vaccine efficacy – primary end-point: $\geq 50\%$, CI LL $>30\%$
  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.
  - A lower bound $\leq 30\%$ but $>0\%$ may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.
• Phase 3 clinical trials
  • **Enrollment of many thousands of participants**, including those with medical comorbidities, to generate relevant data for the **key target populations**.
  • Powered to assess the overall vaccine efficacy across subgroups enrolled
  • Include diverse populations, e.g. race and ethnicity,
  • **Randomized, double-blind and controlled either using placebo or active comparator**. Other Phase 3 clinical trials should be discussed with the respective NRA.
  • **Stringent success criteria to ensure** that SARS-CoV-2 vaccines have **adequate efficacy** should be specified in initial clinical efficacy trials:
    • Should include **efficacy point estimates** that reflect the **desired vaccine efficacy** and **specification of the lower bound** of appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate.
    • However, a **specific numeric value to be used for the lower bound and vaccine efficacy point estimate was not agreed** upon at this stage
    • It was also reflected that **efficacy estimates crossing a certain pre-specified lower bound for efficacy, due to factors such as epidemiological evolution** of the pandemic, would **not preclude the possibility of a positive benefit risk conclusion** if there also were other data supportive of efficacy.
Vaccine Efficacy: Statistical Considerations

Holly Janes, PhD

Professor, Vaccine and Infectious Disease Division (Fred Hutchinson Cancer Research Center)
COVID Prevention Network (CoVPN)

Focal point for USG-sponsored COVID-19 vaccine and mAb trials

Vaccine Trial Leadership: Larry Corey (FHCRC) and Kathleen Neuzil (U Maryland)

Candidate COVID-19 vaccines

<table>
<thead>
<tr>
<th>Platform 1</th>
<th>Platform 2</th>
<th>Platform 3</th>
<th>Platform 4</th>
<th>Platform 5</th>
</tr>
</thead>
</table>

Proposed government-supported infrastructure

<table>
<thead>
<tr>
<th>Harmonized efficacy trials</th>
<th>Collaborating clinical trials networks</th>
<th>Collaborating labs</th>
<th>Data and Safety Monitoring Board</th>
<th>Between-trial statistical groups for correlates of protection</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>• Defining COVID-19 infections from vaccination</td>
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<td>• Quantitative immune responses to spike and spike epitopes</td>
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<td>• T cell responses</td>
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Laboratory Leadership
Julie McElrath  Rafi Ahmed
David Montefiori  Georgia Tomaras  Ralph Baric
Mark Dennison  Tim Sheahan

Statistical Leadership
Dean Follmann  Peter Gilbert
Mike Fay  Yunda Huang
Holly Janes  Martha Nason

WHO Solidarity III Vaccine Efficacy Trial

• Key statistical approaches shared between CoVPN and Solidarity III trial designs
• Primary difference is ‘platform’ trial vs. parallel harmonized trials

An international randomised trial of candidate vaccines against COVID-19. World Health Organization. 09 April 2020
‘Prototypical’ CoVPN Vaccine Efficacy Trial

**Population:** ~30,000 adults age 18 and over, at risk of SARS-CoV-2 infection and COVID-19 disease (no screening for prior infection)

- Enriched for high risk based on age, co-morbidities, race/ethnicity
- For U.S., underrepresented minorities enrolled at or above U.S. demographic frequencies

**Randomized** to 2:1 (or 1:1) to Vaccine or Placebo, potentially within risk strata

**Follow-up** for 2 years post-last vaccination

**Primary endpoint:** virologically-confirmed symptomatic disease
Follow-up and Sampling Schedule

- **Enrollment**: Day 1, Dose 1, Dose 2*
- **Screening visit**: Day 29
- **Collection of nasopharyngeal swab, anterior nasal swab, or saliva cup**
- **Centralized testing via NAAT or antigen test for COV-DIS**
- **Specified symptoms triggering specimen testing**
- **Weekly participant contacts for symptom-triggered nasopharyngeal swabs, anterior nasal swabs, or saliva cups**
- **Collection of**: Sera, Nasopharyngeal swabs, anterior nasal swabs, or saliva cups. All COV-DIS endpoints

Blood storage* for retrospective virus detection and antibody detection (seroconversion)

*Also for immunogenicity & immune correlates analyses
Follow-up and Sampling Schedule

Blood collected at active study visits to assess seroconversion
Post-COVID-Diagnosis Follow-Up

To assess vaccine effect on severity and duration of symptoms and viral shedding ($2^0$ endpoints)

**All Cases**

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
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<th>6</th>
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<tbody>
<tr>
<td>Self-assessed symptoms/signs</td>
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<tr>
<td>Nasal swab</td>
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<td>Blood draw</td>
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</table>

- **If SARS-CoV-2 positive on Day 21**
  - Collection of data on disease severity (signs, symptoms) via diary card/mobile app
  - Obtain sample (self-collected from nasal swabs) for SARS-CoV-2 detection by PCR (Central lab)
  - Blood draw

- **If SARS-CoV-2 negative on Day 21**
  - Collection of data on disease severity (signs, symptoms) via diary card/mobile app
  - Obtain sample (self-collected from nasal swabs) for SARS-CoV-2 detection by PCR (Central lab)
  - Blood draw

- **Day 22** to **35** (or until resolution of symptoms)

**All Cases:**

Continue clinical monitoring and safety f/u through study completion
Randomization Ratio

Factors mildly in favor of 2:1 vs. 1:1 Vaccine:Placebo

- Fewer primary endpoints required
  - E.g., 150 vs. 170 events to reject H0: VE ≤30% in FAS, Day 57+
- Similar time to primary analysis (primary endpoints accrue more slowly)
- Similar performance for evaluating VE (90% power, slightly narrower 95% CI)
- Similar performance for evaluating safety

Major argument in favor of 2:1 vs. 1:1 is increased power for discovering immunological correlates/surrogate endpoints

- 33% increase in breakthrough cases with 2:1 vs. 1:1
Endpoints

**Common primary endpoint**
Protocol-specified list of COVID-19 symptoms with virological confirmation of SARS-CoV-2 infection (symptom-triggered)

Mehrotra, Gilbert et al. submitted
Endpoints

**Key Secondary Endpoints**
Positive SARS-CoV-2 PCR or seroconversion

COVID endpoint plus one protocol-specified severe disease event
Study Duration and Timing of Primary Analysis

- **Event-driven primary analysis**
  - When target number of primary endpoints have accrued:
    - 150 events if 2:1
    - 170 events if 1:1

- **Continued blinded f/u** if positive result at primary analysis

- Trials sized so that under conservative assumptions around COVID-19 incidence, primary analysis likely to occur within ~7 months of trial start
- Continued blinded f/u necessary to evaluate durability of VE (2° objective) and to adequately power VE against severe COVID

* Rationale for target event totals next slides
Primary Analysis and Success Criteria

Vaccine efficacy, $VE = [1 – \text{Endpoint hazard ratio (vaccine/placebo)}] \times 100\%$

- Assess by proportional hazards model with separate placebo arm baseline hazard function for each study site x randomization stratum (anticipate heterogeneity in epidemics across sites)

Primary analysis cohort: participants baseline negative for SARS-CoV-2 (PCR/serology) in ‘full analysis set’ (FAS) [enrolled ppts receiving 1+ dose], counting events 15+ days after last dose*

Success criteria: estimated $VE \geq 50\%$, and lower bound on 95% confidence interval $\geq 30\%$
- Per FDA guidance and satisfies WHO Target Product Profile

* Some trials perform primary analysis among ‘per-protocol’ participants
Sample Size and Target Endpoint Total

Success Criteria:
Estimated VE ≥ 50% and LB of 95% CI ≥ 30%

150 primary endpoints needed for 90% power for VE=60% (2:1 Vaccine:Placebo Allocation)

- Work backwards to identify sample size
  - Specify proportion enrolled baseline SARS-CoV-2 negative
  - Specify 6-month placebo-arm incidence in baseline SARS-CoV-2 negative group
- E.g., 90% baseline SARS-CoV-2 negative and 1% 6-month placebo incidence implies total N = 30,000
## Interim Monitoring

<table>
<thead>
<tr>
<th>Type</th>
<th>Purpose</th>
<th>Methodology and Frequency</th>
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</table>
| **Potential harm/enhancement** | Stop vaccinations as early as possible if evidence of increased risk associated with the vaccine | Nominal 1-sided 0.05-level exact binomial tests of fraction of endpoints in vaccine arm, *continuously* from 8th primary endpoint to time of primary analysis  
  • COVID and severe COVID |
| **Non-efficacy**            | Early detection of absent or weak vaccine efficacy, to deliver result to field in a timely manner | Two interim analyses at 35% and 70% of primary endpoint total. Nominal 95% CI monitoring (Friedlin et al.)                                                                                                                     |
| **Efficacy**                | Early detection of vaccine efficacy, to permit rapid licensure          | Two interim analyses at 35% and 70% of primary endpoint total. O’Brien-Fleming monitoring                                                                                                                                       |

Freidlin, Gray, and Korn (2010, *Clin Trials*)
Potential Outcomes of Interim and Primary Analysis

**Interim or Primary Efficacy Analysis**

**Efficacy Criteria Met**
- Randomization Ceases
- Blinded Follow-Up Continues, to Evaluate VE Durability
- Result is Reported Publicly
- Select Group of Investigators Provided Unblinded Data to Produce Reports

**No Criteria Met**
- Randomization and Follow-Up Continue as Planned

**Non-Efficacy or Increased-Risk Criteria Met**
- Randomization Ceases
- Oversight Group Determines Whether and How Long to Continue Blinded Follow-Up
- If Demonstrated Vaccine-Harm or Major Concern, Participants Unblinded/Notified to Enable Follow-Up, Treatment, as Required
- Result is Reported Publicly
Leadership and Operations
Larry Corey and Kathy Neuzil
Jim Kublin

Laboratory
Julie McElrath
John Hural

Statistics and Data Management
Dean Follmann
Jessica Andriesen
Lindsay Carpp
Youyi Fong
Ollivier Hurien
Alex Luedtke
Ying Huang
April Randhawa

Management
Peter Gilbert
David Benkeser
Mike Fay
Doug Grove
Michal Juraska
Martha Nason
Yunda Huang
THANK YOU
Vaccine Efficacy: Statistical Considerations – Novel Endpoint Approach

Devan Mehrotra, PhD
VP, Biostatistics (Merck)
COVID-19 Vaccine Efficacy Evaluation

*Focus: Burden of Disease Endpoint and Asymptomatic SARS-CoV-2 Infections*

Devan V. Mehrotra, PhD*
Peter B. Gilbert, PhD

(on behalf of a team of biostatisticians, clinicians and infectious disease specialists from academic centers, industry and US government)

COVAX Clinical SWAT Team Workshop
Sep 24, 2020

*devan_mehrotra@merck.com*
Two Goals of Today’s Presentation

[1] Propose a burden of disease (BOD) endpoint as part of a harmonized evaluation and comparison of the efficacy of candidate COVID-19 vaccines

[2] Draw attention to a potential shift towards more SARS-CoV-2 infections that are asymptomatic if the vaccine prevents COVID (below) but not infection
## Endpoints and Vaccine Efficacy (VE) Definitions

### Binary Efficacy Endpoint Scores

<table>
<thead>
<tr>
<th>Participant-level Clinical Outcome</th>
<th>SARS-CoV-2 infection? no=0, yes=1</th>
<th>COVID disease? no=0, yes=1</th>
<th>Severe COVID disease? no=0, yes=1</th>
<th>BOD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not infected (negative SARS-CoV-2 tests)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infected, no COVID (asymptomatic)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infected, non-severe COVID</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infected, severe COVID</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**VE\text sub{COVID} (%) = 100 × (1 − \frac{\text{mean COVID score for Vaccine}}{\text{mean COVID score for Placebo}})**

**VE\text sub{BOD} (%) = 100 × (1 − \frac{\text{mean BOD score for Vaccine}}{\text{mean BOD score for Placebo}})**

Burden of disease (BOD) endpoint scores severe COVID as a worse clinical outcome than non-severe COVID.

Similar VE definitions for other efficacy endpoints.
Power based on choice of primary efficacy endpoint(s)
Simulated design with $V:P=2:1$, $n=147$ disease cases (fixed), $\alpha=2.50\%$ (1-tailed)

<table>
<thead>
<tr>
<th>Assumed VE (%)</th>
<th>Implied VE (%)</th>
<th>Power (%) with chosen primary or dual primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID</td>
<td>Severe COVID</td>
<td>Non-Severe COVID</td>
</tr>
<tr>
<td>55</td>
<td>60</td>
<td>54</td>
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<tr>
<td>55</td>
<td>70</td>
<td>51</td>
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<td>60</td>
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<td>57</td>
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<td>60</td>
<td>80</td>
<td>55</td>
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<tr>
<td>60</td>
<td>90</td>
<td>52</td>
</tr>
</tbody>
</table>

VE = vaccine efficacy; assuming 20% of disease cases in placebo arm will be severe (Clark et al 2020 Lancet Global Health), $VE(\text{COVID})=0.8 \times VE(\text{non-severe COVID}) + 0.2 \times VE(\text{severe COVID})$; power based on statistical success defined as point estimate of VE at least 50% with lower bound of corresponding 95% CI greater than 30% (2020 FDA guidance); COVID scoring is 0=no disease, 1=disease and BOD scoring is 0=no disease, 1=non-severe disease, 2=severe disease; * dual primary endpoints analysis uses novel multiplicity adjustment that leverages the strong correlation between the COVID and BOD endpoints (success = win on at least one after multiplicity adjustment).
The latest CDC estimate is that **40% of SARS-CoV-2 infections are asymptomatic.** Given that, the following table is instructive:

<table>
<thead>
<tr>
<th>Assumed Vaccine Efficacy (VE)</th>
<th>Implied VE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SARS-CoV-2 Infection</strong></td>
<td><strong>Symptomatic Infection (COVID)</strong></td>
</tr>
<tr>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>10%</td>
<td>70%</td>
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<tr>
<td>20%</td>
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</tr>
<tr>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>40%</td>
<td>70%</td>
</tr>
</tbody>
</table>

VE(infection)=0.4xVE(asymptomatic infection) + 0.6xVE(disease)

A vaccine with strong efficacy for reducing symptomatic COVID but weak efficacy for reducing SARS-CoV-2 infections has the potential to prolong the pandemic if the increased asymptomatic carriers transmit infective virus (unknown).
**Hypothetical Example**

2:1 (V:P) randomization, analysis at 147 COVID cases

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>SARS-CoV-2 Infected</th>
<th>Among participants that become infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asymptomatic No COVID</td>
</tr>
<tr>
<td>Placebo</td>
<td>10,000</td>
<td>121 (1.21%)</td>
<td>45 (37.2%)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>20,000</td>
<td>199 (1.00%)</td>
<td>128 (64.3%)</td>
</tr>
</tbody>
</table>

**FDA success criteria:**

1) Estimated vaccine efficacy (VE) > 50%
2) 95% CI lower bound (LB) for VE > 30%

![Endpoint Vaccine Efficacy (%) [95% CI]](image)

- Infection: 17.8 (-4.0, 34.7)
- Asymptomatic Infection: -42.2 (-104.5, -0.5)
- COVID: 53.3 (34.6, 66.7)
- Non-Severe COVID: 44.7 (19.5, 62.0)
- Severe COVID: 78.9 (49.6, 92.0)
- Burden of Disease (BOD): 58.4 (41.2, 70.2)
**Summary**

• **Burden of Disease (BOD) Endpoint**
  - The proposed burden of disease (BOD) endpoint explicitly recognizes severe COVID as being a worse clinical outcome than non-severe COVID; it modifies the 2-level disease score endpoint (0=no COVID, 1=COVID) to a 3-level disease score endpoint (0=no COVID, 1=non-severe COVID, 2=severe COVID)
  - COVID-19 vaccines in development are expected to reduce the incidence of COVID, particularly severe COVID; this (in support with simulation results) makes BOD a promising primary, dual primary or key secondary endpoint

• **Asymptomatic SARS-CoV-2 Infections**
  - If vaccines under development do not materially reduce the risk of SARS-CoV-2 infection, a reduction in the incidence of symptomatic COVID-19 disease may be accompanied by a shift towards more infections that are asymptomatic
  - A thoughtful consideration of this issue and design implications is warranted
Vaccine Efficacy: Solidarity III Trial

Phil Krause, MD
Chairperson (WHO Vaccines Expert Group / US FDA)
Statistical and endpoint considerations for COVID-19 vaccines, in the context of WHO’s Solidarity Vaccines Trial

Phil Krause
Chair WHO COVID vaccines Expert Group
What is the most appropriate endpoint?

Vaccines are almost always more successful in preventing severe disease than mild disease.

If the endpoint is tilted towards mild disease, there may be a risk of study failure if vaccine only is effective against severe disease; however, a 50% point estimate gives a lot of room for success. On long term follow-up, a vaccine that is effective against severe but not mild disease will still become apparent.

If the endpoint is tilted towards rarer severe disease, it may be difficult to adequately power the study. Also, if a vaccine prevents severe but not mild disease, it is less likely to be useful in controlling transmission.

If the endpoint misses some cases, as long as this does not bias the results, the consequences only influence study power. Thus, there is no requirement to capture every single case of disease.
Key principles for endpoint selection

Should not be so rare as to render the trial infeasible

Simplicity of endpoints is valued, otherwise an adjudication committee may be required which complicates interpretation of interim results

In most trial locations, clinicians will follow WHO evaluation and testing recommendations whether participants are in trials or are not

WHO Solidarity Vaccines Trial assumes that trial participants are likely to be referred for testing based on WHO case definition criteria but considers anyone with a positive test as a case for purposes of evaluating trial endpoints (as also WHO criteria states). WHO Clinical criteria are used to define severity

This avoids the complexity of having substantially different trial criteria vs. surveillance clinical criteria used in most communities.
Disadvantages of COVID-19 burden of illness endpoints

Not validated or standardized
• Definition of severe disease puts a lot at stake, and outcome may be influenced by antivirals, steroids, etc.
• Chance differences in incidence of the less common severe disease endpoint would have amplified effects

Difficult to explain what BOI endpoints mean

May have minimal advantages, given relatively low incidence of severe disease
There is general agreement on appropriate success criteria

>50% point estimate with >30% LB
(on alpha-adjusted confidence interval) endorsed by WHO, USFDA, India, China, HC

This assures that weakly effective vaccines will not meet criteria for wide distribution, potentially doing more harm than good

This also assures studies of sufficient size to evaluate safety and other important endpoints

Interim analyses

Interim analyses may be performed using the same criteria as used for the primary endpoint.

Alpha must be appropriately adjusted for interim analyses.
- The WHO Solidarity Vaccines Trial uses the conservative O’Brien-Fleming approach, which requires stronger evidence of efficacy at early interim analyses than others do.

Just because a trial meets success criteria at an interim analysis does not mean that it will meet criteria for EUA/EUL or licensure.
- These decisions will likely also depend on accumulation of safety data and data relevant to secondary endpoints, and sufficient follow-up to infer that vaccine efficacy is not extremely short-lived.

Even if interim success criteria are met, trials should continue in order to accumulate more data.
What does an EUA/EUL mean?

Any vaccine authorized/listed under EUA/EUL is still investigational.

Studies that have already begun should continue, yielding more data about efficacy against severe disease, more safety data, more data about duration of efficacy, and better assessments about potential for enhanced disease.

The Solidarity Vaccines trial contemplates formal statistical evaluation of duration of efficacy and efficacy against severe disease as secondary endpoints, which could happen after a vaccine is made available under EUA/EUL.

Additional safety studies may be initiated to accumulate sufficient safety data to support widespread confidence in the vaccine.
What if a vaccine is licensed?

This will make continuation of placebo in places where a vaccine is licensed and available infeasible.

The trial can then be switched to a non-inferiority design, where non-inferiority criteria may depend on the estimated efficacy of the licensed vaccine.

Continued use of clinical endpoint efficacy endpoints is preferable to other approaches, which are less reliable and may be biased.

The Solidarity Vaccines Trial contemplates this, and this is simpler in a multi-vaccine trial format.
Discussion: How to Establish Vaccine Efficacy

Moderated by Jakob Cramer
### Discussion Panel Members and Potential Questions

<table>
<thead>
<tr>
<th>Panel Members</th>
<th>Potential Discussion Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Holly Janes, PhD</strong>, Professor, Vaccine and Infectious Disease Division (Fred Hutchinson Cancer Research Center)</td>
<td>• What are strategies to de-risk the selection of an ‘inappropriate’ primary endpoint (e.g. dual / multiple primary endpoints; key secondary endpoint)?</td>
</tr>
<tr>
<td><strong>Devan Mehrotra, PhD</strong>, VP, Biostatistics (Merck)</td>
<td>• BOD endpoint to better reflect protection against disease severity: Consider as one of several primary endpoints or key secondary endpoint?</td>
</tr>
<tr>
<td><strong>Phil Krause, MD</strong>, Chairperson (WHO Vaccines Expert Group / US FDA)</td>
<td>• Dual / multiple primary endpoints as well as pre-defined IAs in case-driven trial design: How to address the multiplicity problem and spending alpha?</td>
</tr>
<tr>
<td></td>
<td>• Statistical approaches to assess vaccine efficacy for the primary objective: will different methods provide comparable results?</td>
</tr>
<tr>
<td></td>
<td>• Disease versus infection &amp; transmission: How should the latter objectives be addressed?</td>
</tr>
</tbody>
</table>
Break

5 minutes
Introduction: Operational Considerations

Peter Dull, MD
Deputy Director, Integrated Clinical Vaccine Development (BMGF)
# Introduction: Operational Considerations for Phase III Trials

## Context

- This unprecedented novel respiratory virus outbreak requires unprecedented vaccine development efforts
- We all have a common goal – a global supply of safe and effective vaccines
- Distrust of one vaccine will not be siloed; all developers will be negatively affected
- Multiple Phase III studies have initiated with tens of thousands enrolled

## Implications

- All developers will benefit if all studies are conducted with high quality and answer the right questions
- It is critical to continue collaborating and communicating across developers, especially as those already in Phase III trials have already learned critical operational lessons along the way
# Primary Objectives (Efficacy)

Developers – publicly available efficacy trial protocols

<table>
<thead>
<tr>
<th>Element</th>
<th>Moderna</th>
<th>BNT/Pfizer</th>
<th>AZ (US trial)</th>
<th>Janssen**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. At least 1 of: cough, SOB, or clinical/ radiographic pneumonia OR</td>
<td>b. At least 1 of: fever, cough, SOB, chills, muscle pain, sore throat, anosmia/ageusia, diarrhea &amp; vomiting</td>
<td>b. At least 1 of: Pneumonia (CXR/ CT); SPO2 ≤ 94% or need for O2; SOB OR</td>
<td>b. Any 1 of: RR ≥ 20 breaths/min, abnormal SpO2 but still &gt;93%, clinical/radiologic pneumonia, radiologic DVT, shortness of breath OR</td>
</tr>
<tr>
<td></td>
<td>c. At least 2 of: fever, chills, myalgia, headache, sore throat, effactory &amp; taste disorder</td>
<td>A 2nd definition with extra symptoms: fatigue, headache, congested/runny nose &amp; nausea</td>
<td>c. At least 2 of fever; cough; myalgia; fatigue; vomiting/diabetes*; anosmia/ageusia*</td>
<td>c. Any 2 of: fever, HR ≥ 90 BPM, shaking chills/rigors, sore throat, cough, malaise, headache, myalgia, GI symptoms, olfactory/ taste disorder, red/bruised feet/toes</td>
</tr>
<tr>
<td><strong>VE from</strong></td>
<td>14 days post dose 2 onwards</td>
<td>7 days post dose 2 onwards</td>
<td>15 days post dose 2 onwards</td>
<td>15 days post single dose onwards</td>
</tr>
<tr>
<td><strong>Stratification on baseline serostatus</strong></td>
<td>Only seronegatives in primary VE analysis; Separate analysis for seropositives</td>
<td>2 primary endpoints – a. without evidence of past infection &amp; b. with or without evidence of past infection</td>
<td>Only seronegatives in primary VE analysis; Separate analysis for seropositives</td>
<td>Only seronegatives in primary VE analysis; Secondary efficacy analyses include all regardless of serostatus</td>
</tr>
<tr>
<td><strong>Age range</strong></td>
<td>Age-based analysis: 18-64 &amp; ≥ 65; age-based stratification: (25-40% of enrollment either ≥ 65 or &lt;65 and at risk at screening)</td>
<td>Age-based stratification: 16-55 &amp; &gt;55 (~40% of total enrollment)</td>
<td>Stratified randomisation: 18-55; 56-69 &amp; ≥ 70; age-based analysis planned, no details</td>
<td>Age-based stratification: 18-60 &amp; &gt;60 (~30% of total enrollment ≥ 60, 20% between 18-40)</td>
</tr>
</tbody>
</table>

# - nucleic acid amplification test
* - only one finding to be counted toward endpoint definition
** - moderate, not severe COVID-19 case endpoint listed; all moderate to severe/critical cases will be considered for primary objective
# Primary Objectives (Efficacy)

Developers – publicly available efficacy trial protocols

<table>
<thead>
<tr>
<th>Element</th>
<th>Moderna</th>
<th>BNT/Pfizer</th>
<th>AZ (US trial)</th>
<th>Janssen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target VE &amp; LB 95% CI</strong></td>
<td>≥ 50% &amp; &gt;30%</td>
<td>≥ 50% &amp; &gt;30%</td>
<td>≥ 50% &amp; &gt;30%</td>
<td>≥ 60% &amp; &gt; 30%</td>
</tr>
<tr>
<td><strong>Maximum n (V:P)</strong></td>
<td>30,000 (1:1)</td>
<td>43,998 (1:1)</td>
<td>30,000 (2:1)</td>
<td>60,000 (1:1)</td>
</tr>
<tr>
<td><strong>Analysis population for primary endpoint</strong></td>
<td>All doses received • No significant PDs • No evidence of infection or COVID-19 at baseline</td>
<td>All doses received • No significant PDs</td>
<td>At least one dose received • Not seropositive • Not withdrawn or no COVID-19 before Day 15 post dose 2</td>
<td>Receive study vaccine • Seronegative at time of vaccination • No other major PDs</td>
</tr>
<tr>
<td><strong>VE analysis method</strong></td>
<td>Cox-proportional hazard</td>
<td>Beta-binomial model</td>
<td>Poisson regression model</td>
<td>Sequential probability ratio test</td>
</tr>
<tr>
<td><strong>Cases needed for VE</strong></td>
<td>151</td>
<td>164</td>
<td>150</td>
<td>154</td>
</tr>
<tr>
<td><strong>No. of IAs planned</strong></td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1+</td>
</tr>
<tr>
<td><strong>IAs planned at no. of cases</strong></td>
<td>First: 53; Second: 106</td>
<td>First: 32; Third: 92; Fourth: 120</td>
<td>First: 75</td>
<td>First: 20; at least once a week after**</td>
</tr>
</tbody>
</table>

# - nucleic acid amplification test  
* - only one finding to be counted toward endpoint definition  
** - 4 conditions must be met: first 50% of planned participants had at least 2 months of follow-up after vaccination, ≥ 6 COVID-19 cases for ≥ 60 years age group, ≥20 cases meeting primary endpoint definition of moderate to severe/critical COVID-19, subset of ≥5 cases meeting primary endpoint definition of severe/critical COVID-19
## Triggers for COVID-19 case work up

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Moderna</th>
<th>BNT/Pfizer</th>
<th>AZ (US trial)</th>
<th>Janssen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cough</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dyspnorea</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anosmia/ageusia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chills</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes³</td>
<td>Yes</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Yes³</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes³</td>
<td>Yes</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Yes³</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nausea</td>
<td>Yes³</td>
<td>No</td>
<td>Yes³</td>
<td>Yes</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Yes³</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>Yes³</td>
<td>No</td>
<td>Yes³</td>
<td>Yes</td>
</tr>
<tr>
<td>Congested/runny nose</td>
<td>Yes³</td>
<td>No</td>
<td>Yes³</td>
<td>Yes</td>
</tr>
<tr>
<td>Diagnosis of COVID-19</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

1 – Fever, chills, cough, dyspnoea & difficulty breathing of any duration; other symptoms should be present for at least 48 hours;
2 – Fever, dyspnoea & difficulty breathing of any duration; other symptoms should be present for at least 48 hours
3 – These symptoms are only part of the secondary efficacy endpoint definition
4 – During first 7 days post vaccination, swab collection will be based on PI judgement for symptoms that overlap solicited reactions.
5 – Other symptoms to trigger work up for Janssen include: chest congestion, general malaise, wheezing, eye irritation/discharge, SpO2 ≤95%, HR ≥ 90 bpm, abdominal pain, neurologic symptoms, red/bruised looking toes, skin rash, symptoms of blood clots, confusion, bluish lips/face
Primary Objectives (Efficacy)
Developers – publicly available records on clinical trial registries for Phase 2b/3 efficacy trials

<table>
<thead>
<tr>
<th>Element</th>
<th>CanSino Bio./BIB</th>
<th>Oxford Univ. [UK only]</th>
<th>Gamaleya Research Institute</th>
<th>Butantan /Sinovac</th>
<th>CNBG/Wuhan IBP /Sinopharm</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE from</td>
<td>Day 28 after vaccine</td>
<td>Information unavailable</td>
<td>Information unavailable</td>
<td>14 days post dose 2 onwards</td>
<td>14 days post dose 2 onwards</td>
</tr>
<tr>
<td>Baseline serostatus</td>
<td>Information unavailable</td>
<td>Either</td>
<td>Only seronegatives</td>
<td>Only seronegatives</td>
<td>Unclear</td>
</tr>
<tr>
<td>Age range</td>
<td>≥ 18 YO</td>
<td>18-111 YO</td>
<td>≥ 18 YO</td>
<td>≥ 18 YO</td>
<td></td>
</tr>
<tr>
<td>Samples size</td>
<td>40,000</td>
<td>12,330</td>
<td>40,000</td>
<td>8,870</td>
<td>15,000</td>
</tr>
</tbody>
</table>
Lessons Learned from the Field

Mary Marovich, MD
Director, Vaccine Research Program (NIH, NIAID)

Merlin Robb, MD
Chief Medical Advisor (Henry M. Jackson Foundation for the Advancement of Military Medicine)
Lessons Learned: Phase 3 COVID-19 Vaccine Efficacy Trials

Mary Marovich and Merlin Robb
24 September 2020
Operational Considerations and Impact on Design

• Enrollment strategies
• Case ascertainment and management
  • Monitoring frequency and process
  • Triggers for testing
  • Confirmatory testing process
  • Case management
• Need for space and personnel in view of COVID-19 generally and medical visits for COVID-19 cases
Enrollment strategy considerations

• Early community engagement
  • African American enrollment is notably less efficient than other ethnic and racial groups
  • It is possible that both media focus on moving vaccine discovery forward quickly and safety issue coverage may be impacting enrollment
  • Community engagement activities have built on tools and platforms used in HIV research for many years
Case ascertainment and management

• General consensus that there should be a medically attended initial visit early in entry into COVID-19 case evaluation
  • Allowing some clinical judgement probably helpful to exclude
    • Allergies with usual pattern and severity of symptoms
    • Expected reactogenicity following vaccination
    • Assess the ability of the participant to adhere to self monitoring activities
  • Permit use of a locally resourced but qualified assay for case ascertainment
    • Participants on quarantine pending central RNA test and TAT can take a week
    • Anxiety provoking for participants
    • Impacts the participant behavior, i.e. quarantine, inability to work, financial implications
    • Some have access to testing which excluded SARS CoV-2 diagnosis yet must continue the monitoring as if COVID-19 positive
Case ascertainment and management

• An emphasis on frequent monitoring
  • to advance severe cases quickly to higher levels of care
  • Ensure we capture COVID-19 cases comprehensively to
    • Assess severity
    • Identify enhanced or atypical disease

• Oximetry included routinely for case management
  • Variable oximeter platforms
    • Some with continuous monitoring and telemetry
  • Daily evaluation in AM, PM and before bed
  • Entered into an eDiary but ability to call for direction

• Technology challenged participants or participants with limitations for access
  • Retain a paper documentation system as a back-up
Personnel and Space Management

• Resource intensive trials in pandemic setting
• One site with about n=500 participants enrolled
  • N=90 staff required

• Incorporate COVID-19 case visits with regular COVID-19 care clinic

• Expand research clinic space to accommodate segregated follow-up for possible cases versus screening/enrollment etc
  • External semi-permanent trailers
  • Re-purpose office space
  • Dedicated rooms special air handling or open air
Clinical Case Workup in Efficacy Trials: Guidance from Community-Based Surveillance

Amol Chaudhari, MD
*Clinical Development Lead*

Joan Capedevila Pujol, PhD
*Data Scientist at ZOE*
Symptom analysis on a prospective, community-based cohort from the COVID Symptom Study

Interim analysis by a joint team from CEPI & ZOE
Rationale

- In subjects enrolled in vaccine efficacy trials, ideally, all C-19 symptoms should trigger case work-up, including PCR testing for SARS-CoV-2
  - Indiscriminate PCR testing all possible symptoms may overwhelm laboratory capacity
- The present study is conducted to quantify how individual COVID-19 (C-19) symptoms contribute to C-19 ‘case’ finding
Rationale

• The concept is to simulate C19-case-finding in a community-based, prospective, observational cohort study
  • The cohort must be a community-based to reflect the vaccine efficacy trial setting
  • The cohort must collect C-19 symptoms in a structured manner, and include PCR tests results in symptomatic people - both positive and negative
• It is assumed that PCR will *always* be triggered by the following ‘classic’ symptoms
  • New onset persistent cough, dyspnea, tachypnea, and fever: these symptoms point towards moderate or severe C-19 with lower respiratory tract involvement
  • Anosmia and/or ageusia should: these symptoms have been shown to have the highest specificity for predicting PCR positivity.
Background

- The COVID Symptom Study App was launched in the UK on the 24th of March, and in the US and Sweden on the following weeks together with KCL, MGH Harvard and Lund University
- Users can log up to 20 distinct symptoms on a daily basis and enter COVID test results
- 4+ million users have joined, 170+ millions health reports have been logged and 1+ million test results have been entered
- 800,000+ users have signed up to the vaccine registry allowing us to contact them about potential studies involving vaccines and other preventive treatments
Inclusion criteria

- UK 18+ users active from 24th of March to 15th of September 2020
  - Users who have regularly logged feeling healthy and then got sick (i.e. newly symptomatic) or kept feeling healthy (i.e. healthy).
- Included health reports that were logged any time after they got sick (i.e. symptoms onset) until 14 days after the onset - regular analysis - or until 3 days after the onset - 72 hours analysis.
- Included PCR test results that were logged any time from symptoms onset to 7 days after the onset.
- Included only first episode of PCR positive.
- Excluded users who signed up in the App and had already had COVID-19.
Data summary

- 1,404,740 users in the UK cohort meeting the inclusion criteria
- 468,263 users in the UK cohort have reported symptoms at some point - newly symptomatic
- 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
- 121,347 negative tests from newly symptomatic users
- 1,272 positive tests from newly symptomatic users
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.
14% of the positive cases showed no classic symptom during the two first weeks

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tested positive</th>
<th>Recall (or Sensitivity)</th>
<th>Tested negative</th>
<th>Precision (or PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>1068</td>
<td>84.0</td>
<td>63138</td>
<td>1.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1021</td>
<td>80.3</td>
<td>65038</td>
<td>1.5</td>
</tr>
<tr>
<td>Sore throat</td>
<td>744</td>
<td>58.5</td>
<td>55383</td>
<td>1.3</td>
</tr>
<tr>
<td>Loss of taste and smell *</td>
<td>730</td>
<td>57.4</td>
<td>5856</td>
<td>11.1</td>
</tr>
<tr>
<td>Persistent cough *</td>
<td>671</td>
<td>52.8</td>
<td>16648</td>
<td>3.9</td>
</tr>
<tr>
<td>Fever *</td>
<td>618</td>
<td>48.6</td>
<td>19576</td>
<td>3.1</td>
</tr>
<tr>
<td>Unusual muscle pains</td>
<td>592</td>
<td>46.5</td>
<td>20253</td>
<td>2.8</td>
</tr>
<tr>
<td>Shortness of breath *</td>
<td>527</td>
<td>41.4</td>
<td>15441</td>
<td>3.3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>522</td>
<td>41.0</td>
<td>16274</td>
<td>3.1</td>
</tr>
<tr>
<td>Skipped meals</td>
<td>513</td>
<td>40.3</td>
<td>16017</td>
<td>3.1</td>
</tr>
</tbody>
</table>

| Total num positive tests        | 1272            |
| Total num negative tests        | 121347          |

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tested positive</th>
<th>Recall (or Sensitivity)</th>
<th>Tested negative</th>
<th>Precision (or PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Any classic symptom</td>
<td>1092</td>
<td>85.8</td>
<td>42292</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Total number of tests: 43,384
This percentage reduces to 3% if we include fatigue and headache into the triggering symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tested positive</th>
<th>Recall (or Sensitivity)</th>
<th>Tested negative</th>
<th>Precision (or PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>111</td>
<td>61.7</td>
<td>34243</td>
<td>0.32</td>
</tr>
<tr>
<td>Headache</td>
<td>106</td>
<td>58.9</td>
<td>39391</td>
<td>0.27</td>
</tr>
<tr>
<td>Sore throat</td>
<td>83</td>
<td>46.1</td>
<td>33685</td>
<td>0.25</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>44</td>
<td>24.4</td>
<td>15588</td>
<td>0.28</td>
</tr>
<tr>
<td>Unusual muscle pains</td>
<td>43</td>
<td>23.9</td>
<td>9483</td>
<td>0.45</td>
</tr>
<tr>
<td>Dizzy light headed</td>
<td>43</td>
<td>23.9</td>
<td>16695</td>
<td>0.26</td>
</tr>
<tr>
<td>Typical hayfever</td>
<td>43</td>
<td>23.9</td>
<td>18917</td>
<td>0.23</td>
</tr>
<tr>
<td>Nausea</td>
<td>42</td>
<td>23.3</td>
<td>16683</td>
<td>0.25</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>36</td>
<td>20.0</td>
<td>14371</td>
<td>0.25</td>
</tr>
<tr>
<td>Eye soreness</td>
<td>33</td>
<td>18.3</td>
<td>11732</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Extended symptoms = classic symptoms + fatigue + headache

<table>
<thead>
<tr>
<th>Total num positive tests</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total num negative tests</td>
<td>79055</td>
</tr>
<tr>
<td>Total number of tests</td>
<td>96,309</td>
</tr>
</tbody>
</table>
Classic symptoms are less likely to occur in the first 72 hours, but fatigue+headache might help case finding.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tested positive</th>
<th>Recall (or Sensitivity)</th>
<th>Tested negative</th>
<th>Precision (or PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>57798</td>
<td>68.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56176</td>
<td>6.1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>49526</td>
<td>4.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Persistent cough *</td>
<td>13411</td>
<td>3.9</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Fever *</td>
<td>16567</td>
<td>3.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Unusual muscle pains</td>
<td>16737</td>
<td>2.9</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>12126</td>
<td>2.4</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Skipped meals</td>
<td>13384</td>
<td>2.0</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>13248</td>
<td>2.0</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Loss of taste and smell</td>
<td>4673</td>
<td>2.2</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>

Total num positive tests: 1272
Total num negative tests: 121340

Extended symptoms = classic symptoms + fatigue + headache

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tested positive</th>
<th>Recall (or Sensitivity)</th>
<th>Tested negative</th>
<th>Precision (or PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any classic symptom *</td>
<td>36523</td>
<td>68.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Any extended symptom</td>
<td>89725</td>
<td>91.2</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

Total number of tests: 37,388
90,885
Summary

Based on data from the COVID Symptom Study App, we showed that:

<table>
<thead>
<tr>
<th></th>
<th>Recall</th>
<th>Tests per positive case</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>14 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic symptoms</td>
<td>85.8%</td>
<td>40</td>
</tr>
<tr>
<td>Extended symptoms</td>
<td>97.2%</td>
<td>77</td>
</tr>
<tr>
<td><strong>3 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic symptoms</td>
<td>68.2%</td>
<td>43</td>
</tr>
<tr>
<td>Extended symptoms</td>
<td>91.2%</td>
<td>78</td>
</tr>
</tbody>
</table>
Limitations

- This is work in progress - data analysis is not yet final
- This is based on self-reported data
- Setting is UK specific; i.e., no malaria, dengue, etc.
- Seasonality: study was conducted during the northern hemisphere summer; i.e., few concurrent respiratory pathogens, influenza, common cold etc.
- Study population biased towards people with smartphones and high socioeconomic status.
Conclusions

- The *COVID Symptom Study App* has created a large prospective community-based cohort to understand how symptoms that may trigger PCR contribute to case finding.

Based on data from the COVID Symptom Study App:

- 14% of the positive cases show no classic symptoms (Fever, cough, dyspnea, tachypnea, anosmia & ageusia) during the first two weeks of symptoms.
- By including fatigue and headache to the triggering symptoms, one would double the number of tests performed but 97.2% of the positive cases could be found.
- This is even more important during the first three days of symptoms, in which classic symptoms would only find 68.2% of the positive cases and the extended symptoms, 91.2%
Discussion: Operational Considerations

Moderated by Peter Dull
Discussion Panel Members

• **Ricardo Palacios, MD, PhD**, Clinical Research Medical Director (Instituto Butantan / Sinovac)

• **Jacqueline Miller, MD**, SVP Therapeutic Area Head, Infectious Diseases (Moderna)

• **Shabir Madhi, PhD**, Professor of Vaccinology, Director of the MRC Respiratory and Meningeal Pathogens Research Unit (ChAdOx-Novavax)
Wrap Up and Next Steps

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

• We will be sharing a post-workshop survey to capture any remaining questions or comments

• We will distribute a workshop report to summarize today’s conversation; for any outstanding questions, we will do our best to direct you to the appropriate resource