SPECIAL Part 2

COVID-19 Response ECHO for Oregon Clinicians

Session 7  September 10, 2020
Housekeeping

• We have added sessions to this ECHO.
  • Originally scheduled to wrap-up on September 24, the ECHO program will now end on December 10. The remaining sessions in 2020 will occur on:
    • September 24
    • October 8
    • October 22
    • November 12
    • December 10

• For the most up-to-date information on CME and Maintenance of Certification credits, please go to the ECHO connect portal at www.oregonechonetwork.org.
Housekeeping

- Everyone is muted
- Use the Chat Box to submit questions/comments/share links & resources
  - We will strive to select questions directly relevant to the presentations for asking during the session, but will not be able to address all questions
  - Questions not directly answered will be collated and used in the planning of future sessions
- All sessions will be recorded and available for viewing after the session within 24 hours
- Resources and transcript of today’s chat box, PowerPoint slides, and video recording will be posted on our ECHO Network website at www.connect.oregonechonetwork.org (where you registered)
- PLEASE fill out the post-session survey that you’ll receive by email today
Part 2 COVID-19 ECHO Series Goals

1) Share the latest information on COVID-19 impact in Oregon and amplify the public health response;
2) Provide guidance on evidence-based management of COVID-19 and its clinical, behavioral & care delivery consequences;
3) Create a forum to share clinical, community, and system cases to improve quality and inform ‘best practice’
Today’s Agenda

• COVID-19 Update:
  • Oregon Health Authority
  • Metro Public Health

• Expert presentation: “Coronavirus Vaccination Update” - Mark Slifka, PhD, OHSU

• Q & A
Oregon Wildfires: another state of emergency

As of 9/9/20 @ 11 pm:
• 37 active fires in Oregon
• >672,000 acres burned
• Broad evacuations
• Many road closures
• Hospital impacts
  • Silverton Hospital
  • North Lincoln Hospital
  • Others ready for evacuation
• Emergency coordination activated
• Fires and hotspots dashboard:
Air Quality Index
As of September 9:

- 28,471 Total Cases
- 2,215 Hospitalized Cases
- 494 Deaths
The COVID-19 Pandemic Update in Oregon

For the week of **August 30 – September 5***:

- 1163 new cases
- 4.3% test positivity

*Numbers will change as additional test results from specimens collected during the time period are reported*

<table>
<thead>
<tr>
<th>MMWR Week</th>
<th>Positive</th>
<th>Negative</th>
<th>Total Results</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/1</td>
<td>2012</td>
<td>30348</td>
<td>32360</td>
<td>6.2</td>
</tr>
<tr>
<td>8/8</td>
<td>1821</td>
<td>32813</td>
<td>34634</td>
<td>5.3</td>
</tr>
<tr>
<td>8/15</td>
<td>1775</td>
<td>31735</td>
<td>33510</td>
<td>5.3</td>
</tr>
<tr>
<td>8/22</td>
<td>1593</td>
<td>29954</td>
<td>31547</td>
<td>5.0</td>
</tr>
<tr>
<td>8/29</td>
<td>1441</td>
<td>31020</td>
<td>32461</td>
<td>4.4</td>
</tr>
<tr>
<td>9/5</td>
<td>1163</td>
<td>25692</td>
<td>26855</td>
<td>4.3</td>
</tr>
<tr>
<td>Total to date</td>
<td>26930</td>
<td>561784</td>
<td>588714</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Figure 2: Model projections for the next 4 weeks, assuming that after August 27: 1) transmission does not change (red line), 2) transmission decreases by 5 percentage points (blue line), and 3) transmission increases by 5 percentage points (green line). The lighter shaded areas correspond to 80% forecast intervals (i.e., 10th and 90th percentiles of the projection).
Figure 3: Projected effective reproduction number (Re) through September 24, assuming that starting August 28: 1) transmission does not change (red line), 2) transmission decreases by 5 percentage points (blue line), and 3) transmission increases by 5 percentage points (green line). The lighter shaded areas correspond to 80% forecast intervals (i.e., 10th and 90th percentiles of the projection). Re is the expected number of secondary cases that a single case generates.
School Readiness Metrics

Required for return to in-person instruction, or a hybrid model of onsite and online learning:

**State level**
COVID-19 test positivity $\leq 5\%$ in the preceding 7 days for 3 weeks in a row

**County level**
$\leq 10$ COVID-19 cases per 100,000 population in the preceding 7 days
COVID-19 test positivity $\leq 5\%$ in the preceding 7 days for 3 weeks in a row
Oregon COVID-19 County Case Rates and Test Positivity by MMWR Week: July 5th - September 5th

This table is based on data pulled at 12:01 AM on September 8th, 2020. For county case rates, cases are assigned to a week based on their true case date, which is the date when public health first identified them as a confirmed or presumptive COVID-19 case. For percent positivity in testing, persons tested are assigned to a week based on their specimen collection date. All data are provisional and subject to change.

<table>
<thead>
<tr>
<th>County</th>
<th>Week Start Date</th>
<th>Case Count</th>
<th>Case rate per 100,000</th>
<th>Test Positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oregon, statewide</td>
<td>7/5/2020</td>
<td>1,934</td>
<td>46</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>7/12/2020</td>
<td>2,398</td>
<td>57</td>
<td>5.4%</td>
</tr>
<tr>
<td></td>
<td>7/19/2020</td>
<td>2,173</td>
<td>51</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>7/26/2020</td>
<td>2,321</td>
<td>55</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td>8/2/2020</td>
<td>2,174</td>
<td>51</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>8/9/2020</td>
<td>1,991</td>
<td>47</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>8/16/2020</td>
<td>1,683</td>
<td>40</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>8/23/2020</td>
<td>1,684</td>
<td>40</td>
<td>4.4%</td>
</tr>
<tr>
<td></td>
<td>8/30/2020</td>
<td>1,506</td>
<td>36</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
Testing Recommendations for Contacts

On August 24th, CDC updated their testing guidance, prioritizing testing for individuals with symptoms and suggesting that those who have been exposed but do not have symptoms may not need to be tested.

Public health approach to contacts in Oregon (unchanged):

• **Active monitoring** is required for all close contacts: daily symptom and temp checks.
• LPHAs work with any **contacts who develop symptoms** to determine a plan to seek care safely and access COVID-19 testing.
• Routine testing of asymptomatic contacts is not recommended.

**14-day quarantine is the key intervention to prevent transmission.**

OHA's clinician testing guidance states that **asymptomatic contacts** may be tested, at the provider's discretion.
Portland Metro Regional Update
Questions
Recent updates on COVID-19 vaccines

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Twitter @MarkSlifka

Disclosure: Mark Slifka is the President and CSO of Najít Technologies, Inc. (NTI), a small clinical-stage vaccine development company based in Beaverton, OR. NTI is developing peroxide-inactivated whole virus vaccines against West Nile virus, yellow fever, chikungunya, dengue, zika, and influenza. The company has no plans to develop a vaccine against SARS-CoV-2. Dr. Slifka has no financial interests in the vaccines, technologies, or companies discussed in this presentation.
Overview

• COVID-19 Vaccine update
  • 321 vaccine candidates (Nat Rev Drug Disc https://www.nature.com/articles/d41573-020-00151-8)
  • 32 vaccine candidates in clinical trials. Phase III trials complicated by evolving epidemiology/interventions
  • COVID-19 case definition and Clinical Endpoint is “complicated”
  • Concerns over durability of protection and estimated vaccine efficacy after short observation period
  • Focus on Operation Warp Speed candidates and data from recent ACIP meeting held 8/26/20
  • Discuss recent Clinical Hold placed on AstraZeneca vaccine candidate and implications
COVID-19 Vaccine update
Types of COVID-19 vaccines

• COVID-19 Vaccine technologies
  • mRNA
  • DNA
  • Recombinant live virus (e.g., recombinant adenovirus vector)
  • Subunit protein vaccine (e.g., purified Spike protein + adjuvant)
  • Purified-inactivated virus (PIV)
  • Virus-like particle (VLP)
  • Attenuated live virus
Concerns regarding durability of vaccine-mediated protection and early (?) approval of a vaccine within the first few months after initiating Phase III trials.

Different potential immune profiles after vaccination:

A. % Vaccine Efficacy
   - Stop trial here and find >50% VE

B. % Vaccine Efficacy
   - Stop trial here and find <50% VE

Hypothetical time points after completing primary vaccination series:

1M 3M 6M
Notes:
- mRNA vaccine against surface protein (HA, hemagglutinin) of a respiratory virus (flu)
- Weak HAI (hemagglutinin inhibition) immunity after first dose
- Reasonable HAI immunity after second dose
- HAI levels are mRNA dose-dependent (400 ug dose discontinued after Clinical Hold due to AEs)
- Rapid loss of immunity within 6 months
- However, COVID-19 vaccine may be different or may just require annual boosters - TBD

R.A. Feldman et al., Vaccine 37 (2019) 3326–3334
COVID-19 vaccines: Work Group interpretations

Sara Oliver MD, MSPH

ACIP Meeting
August 26, 2020

https://www.cdc.gov/vaccines/acip/meetings/live-mtg-2020-08.html
https://www.cdc.gov/vaccines/acip/meetings/slides-2020-08.html
<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Phase</th>
<th>Trial characteristics</th>
<th>Trial #s</th>
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</thead>
<tbody>
<tr>
<td>mRNA-1273</td>
<td>Moderna TX, Inc.</td>
<td>mRNA</td>
<td>III</td>
<td>• 2 doses (0, 28d)</td>
<td>NCT04283461 (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IM administration</td>
<td>NCT04405076 (II)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-55, 56+ years</td>
<td>NCT04470427 (III)</td>
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<tr>
<td>mRNA-BNT162</td>
<td>Pfizer, Inc./BioNTech</td>
<td>mRNA</td>
<td>I/II/III</td>
<td>• Single or 2 doses</td>
<td>NCT04368728</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IM administration</td>
<td>EudraCT 2020-001038-36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-85 years</td>
<td>ChiCTR2000034825</td>
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<tr>
<td>INO-4800</td>
<td>Inovio Pharmaceuticals, Inc.</td>
<td>DNA plasmid</td>
<td>I/II</td>
<td>• 2 doses (0, 4w)</td>
<td>NCT04336410 (I)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• SC administration/electroporation</td>
<td>NCT04447781</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ≥18 years</td>
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<tr>
<td>Ad26COVS1</td>
<td>Janssen Pharmaceutical Companies</td>
<td>Non-Replcating Viral Vector</td>
<td>I/II</td>
<td>• 2 doses (0,56d)</td>
<td>NCT04436276</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IM administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-55, 65+</td>
<td></td>
</tr>
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</table>

NCTxxx…. Are clinical trial identification numbers that can be found at ClinicalTrials.gov
# COVID-19 vaccines in human clinical trials – outside United States* mRNA/DNA vaccines

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Trial Location</th>
<th>Phase</th>
<th>Trial #</th>
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</thead>
<tbody>
<tr>
<td>CVnCoV</td>
<td>CureVac</td>
<td>mRNA</td>
<td>Belgium, Germany</td>
<td>I/II</td>
<td>NCT04449276, NCT04515147</td>
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<tr>
<td>--</td>
<td>People’s Liberation Army Acad. Med.</td>
<td>mRNA</td>
<td>China</td>
<td>I</td>
<td>ChiCTR2000034112</td>
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<tr>
<td>--</td>
<td>Sciences</td>
<td></td>
<td></td>
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<tr>
<td>--</td>
<td>Arcturus/Duke-NUS</td>
<td>mRNA</td>
<td>Singapore</td>
<td>I/II</td>
<td>NCT04480957</td>
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<tr>
<td>LNP-nCoVsRNA</td>
<td>Imperial College London</td>
<td>saRNA</td>
<td>U.K.</td>
<td>I</td>
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<tr>
<td>GX-19</td>
<td>Genexine Consortium</td>
<td>DNA</td>
<td>South Korea</td>
<td>I/II</td>
<td>NCT04445389</td>
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<tr>
<td>--</td>
<td>Osaka University/AnGes</td>
<td>DNA</td>
<td>Japan</td>
<td>I/II</td>
<td>NCT04463472</td>
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<td>--</td>
<td>Cadila Healthcare Limited</td>
<td>DNA plasmid</td>
<td>India</td>
<td>I/II</td>
<td>CTRI/2020/07/026352</td>
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## COVID-19 vaccines in human clinical trials – outside United States*  
Protein subunit vaccines

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Trial Location</th>
<th>Phase</th>
<th>Trial #</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVX-CoV2373</td>
<td>Novavax</td>
<td>Protein subunit</td>
<td>Australia</td>
<td>I/II</td>
<td>NCT04368988</td>
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<tr>
<td>--</td>
<td>Anhui Zhifei Longcom/Chinese Academy of Science</td>
<td>Protein subunit</td>
<td>China</td>
<td>II</td>
<td>NCT04445194, NCT04466085</td>
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<td>SCB-2019</td>
<td>Clover/GSK/Dynavax</td>
<td>Protein subunit</td>
<td>Australia</td>
<td>I</td>
<td>NCT04405908</td>
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<td>Covax-19</td>
<td>Vaxine</td>
<td>Protein subunit</td>
<td>Australia</td>
<td>I</td>
<td>NCT04453852</td>
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<td>--</td>
<td>University of Queensland/CSL/Seqirus</td>
<td>Protein subunit</td>
<td>Australia</td>
<td>I</td>
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<td>--</td>
<td>Instituto Finlay de Vacunas</td>
<td>Protein subunit</td>
<td>Cuba</td>
<td>I/II</td>
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### COVID-19 vaccines in human clinical trials – outside United States*  
**Viral Vector vaccines**

<table>
<thead>
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<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Trial Location</th>
<th>Phase</th>
<th>Trial #</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>Medicago</td>
<td>VLP</td>
<td>Canada</td>
<td>I</td>
<td>NCT04450004</td>
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<tr>
<td>ad5-nCov</td>
<td>CanSino Biologics, Inc.</td>
<td>Viral vector (NR)</td>
<td>China</td>
<td>II*</td>
<td>NCT04313127, NCT04398147, NCT043431389</td>
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<tr>
<td>AZD1222</td>
<td>University of Oxford/AstraZeneca consortium</td>
<td>Viral vector (NR)</td>
<td>UK, South Africa, Brazil</td>
<td>II/III</td>
<td>NCT04324606, NCT04400833, EudraCT 2020-001072-15, EudraCT 2020-001228-32</td>
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<tr>
<td>aAPC</td>
<td>Shenzhen Geno-Immune Medical Institute</td>
<td>Viral vector</td>
<td>China</td>
<td>I</td>
<td>NCT04299724</td>
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<tr>
<td>LV-SMENF-DC</td>
<td>Shenzhen Geno-Immune Medical Institute</td>
<td>Viral vector</td>
<td>China</td>
<td>I</td>
<td>NCT04276896</td>
</tr>
<tr>
<td>Ad26Cov1</td>
<td>Janssen</td>
<td>Viral Vector (NR)</td>
<td>Belgium</td>
<td>I/II</td>
<td>NCT04436276, NCT04505722</td>
</tr>
<tr>
<td>Gam-COVID-Vac</td>
<td>Gamaleya Research Institute</td>
<td>Viral vector (NR)</td>
<td>Russia</td>
<td>I</td>
<td>NCT04437875, NCT04436471</td>
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<td>--</td>
<td>Institut Pasteur/Themis/University of Pittsburgh CVR/ Merck Sharp &amp; Dohme</td>
<td>Viral vector</td>
<td>France, Belgium</td>
<td>I</td>
<td>NCT04497298</td>
</tr>
</tbody>
</table>

The ChAdOx1 nCoV-19 vaccine, also known as the “Oxford vaccine” is also performing Phase III trials in the U.S.
- Interesting because it uses a Chimpanzee adenovirus instead of a human adenovirus
- Is the only vaccine in Operation Warp Speed that does not use a genetically stabilized version of the Spike protein
## COVID-19 vaccines in human clinical trials – outside United States*

### Inactivated vaccines

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Trial Location</th>
<th>Phase</th>
<th>Trial #</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBIBP-CorV</td>
<td>Beijing Institute of Biological Products/Sinopharm</td>
<td>Inactivated</td>
<td>China</td>
<td>III</td>
<td>ChiCTR2000032459, ChiCTR2000034780</td>
</tr>
<tr>
<td>--</td>
<td>Wuhan Institute of Biological Products/Sinopharm</td>
<td>Inactivated</td>
<td>China, UAE</td>
<td>III</td>
<td>ChiCTR2000031809, ChiCTR2000034780</td>
</tr>
<tr>
<td>CoronaVac</td>
<td>Sinovac/Instituto Butantan</td>
<td>Inactivated</td>
<td>China, Brazil</td>
<td>III</td>
<td>NCT04352608, NCT04383574, NCT04456595</td>
</tr>
<tr>
<td>BBV152</td>
<td>Bharat Biotech</td>
<td>Inactivated</td>
<td>India</td>
<td>I/II</td>
<td>CTRI/2020/07/026300, NCT04471519</td>
</tr>
</tbody>
</table>
Immunogenicity and Safety Information Reviewed by Work Group
mRNA1273 (Moderna)  N=130

- **Immunogenicity**
  - Neutralizing antibodies (pseudovirus neutralization assay titers) and binding antibodies (ELISA) measured 7 days post-dose 2
  - Responses similar to or exceeded convalescent sera comparison
  - Th1-biased CD4+ T-cell response
  - **100µg** dose selected for Phase III clinical trials

- **Safety**
  - Local and systemic symptoms followed for 7 days post-vaccination
    - Pain, myalgia, fatigue most common symptoms reported
  - Reactogenicity symptoms higher after second dose
  - No vaccine-related serious adverse events (SAEs) reported
Immunogenicity and Safety Information Reviewed by Work Group
BNT162b2 (Pfizer/BioNTech) N=195

▪ **Immunogenicity**
  - Neutralizing antibodies (50% neutralization titers) measured 7 days post-dose 2
  - Responses similar to or exceeded human convalescent panel
  - CD4+ and CD8+ T cell response demonstrated
  - Th1-biased CD4+ T-cell response
  - **30µg** dose of BNT162b2 selected for Phase III clinical trials

▪ **Safety**
  - Local and systemic symptoms followed after administration
    - Fatigue, headache and muscle pain most common
  - Reactogenicity symptoms lower in older population (65-85 years)
Plans for Phase III

- Both vaccine candidates currently enrolling large (~30,000 people) Phase III efficacy trials

- Primary endpoints: symptomatic, virologically confirmed COVID-19 disease

- Attempting to enroll diverse populations:
  - Race and ethnicity
  - Age (<65 years and ≥65 years of age)
  - Underlying medical conditions
Work Group Interpretation

- Phase I data from both mRNA vaccines show induction of neutralizing antibodies at 7 days post-dose 2 that exceed levels in convalescent sera.

- Data from both mRNA vaccines support advancing to large scale Phase III clinical trials to assess safety and efficacy.

- Diverse cold-chain or ultra-low temperature requirements can substantially affect implementation efforts.
COVID-19 vaccine prioritization: Work Group considerations

Kathleen Dooling, MD MPH
August 26, 2020
Administration of COVID-19 vaccine will require a phased approach

**Limited Doses Available**
- Constrained supply
- Cold chain & handling may require specialized equipment and high throughput
- Highly targeted administration

**Large Number of Doses Available**
- Likely sufficient supply to meet demand
- Additional vaccine products allow a *wider range of administration locations*
- Broad administration network required (pharmacies, doctors offices, public health clinics, mobile clinics, FQHcs)
- Focus on increasing *access for critical populations*

**Continued Vaccination**
- Sufficient supply to meet demand
- Harness vaccine provider networks with proven ability to *reach critical populations*
- Enhance series completion
Work Group Interpretation: Implementation challenges & implications for distribution of initial vaccine

- A COVID-19 vaccine that requires distribution and storage at -20°C, followed by 7 days (max) at 2-8°C, will require diligent vaccine management to minimize waste.

- The storage, distribution and handling requirements of a -70°C vaccine will make it very difficult for community clinics and local pharmacies to store and administer.
  
  ➢ will necessitate most vaccine be administered at centralized sites with adequate equipment and high throughput

  ➢ vaccinating healthcare personnel at centralized sites with high throughput is the best allocation of initial supply
Summary: Groups for early phase vaccination

- Overlapping
- Significant heterogeneity
- Accounts for > half of U.S. adults
- Need for additional sub-grouping
An mRNA Vaccine against SARS-CoV-2 — Preliminary Report


ABSTRACT

BACKGROUND
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and spread globally, prompting an international effort to accelerate development of a vaccine. The candidate vaccine mRNA-1273 encodes the stabilized prefusion SARS-CoV-2 spike protein.

METHODS
We conducted a phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 μg, 100 μg, or 250 μg. There were 15 participants in each dose group.

RESULTS
After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti–SARS-CoV-2 antibody geometric mean titer (GMT), 46,277 in the 25-μg group, 199,209 in the 100-μg group, and 243,526 in the 250-μg group). After the second vaccination, the titer increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively). After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-μg dose group reported one or more severe adverse events.

CONCLUSIONS
The mRNA-1273 vaccine induced anti–SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified. These findings support further development of this vaccine. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 ClinicalTrials.gov number, NCT04283461).
Figure 1. Systemic and Local Adverse Events.
The severity of solicited adverse events was graded as mild, moderate, or severe (see Table S1).
Red arrows added to indicate modest decay rates from day 43 to day 57
Red circle added to emphasize that neutralizing assays (PRNT) were performed with just 3 convalescent samples
RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study

Edward E. Walsh, MD1*, Robert Frenck, MD2*, Ann R. Falsey, MD1, Nicholas Kitchin, MD3a, Judith Absalon, MD3b, Alejandra Gurtman, MD3b, Stephen Lockhart, DM3a, Kathleen Neuzil, MD4, Mark J. Mulligan, MD5, Ruth Bailey, BSc3a, Kena A. Swanson, PhD7b, Ping Li, PhD3c, Kenneth Koury, PhD3b, Warren Kalina, PhD3b, David Cooper, PhD3b, Camila Fontes-Garfias, BSc6, Pei-Yong Shi, PhD6, Ḱezlem Türeci, MD7, Kristin R. Tompkins, BSc3b, Kirsten E. Lyke, MD4, Vanessa Raabe, MD5, Philip R. Dormitzer, MD3b, Kathrin U. Jansen, PhD3b, Uğur Şahin, MD7 and William C. Gruber, MD3b

*Drs. Walsh and Frenck contributed equally to this article.

1University of Rochester and Rochester General Hospital, Rochester, NY; 2Cincinnati Children’s Hospital, Cincinnati, OH; 3Vaccine Research and Development, Pfizer Inc, 4Hurley, UK, 5Pearl River, NY, 6Collegeville, PA; 7University of Maryland School of Medicine, Center for Vaccine Development and Global Health, Baltimore, MD; 8New York University Langone Vaccine Center and New York University Grossman School of Medicine, New York, NY; 9University of Texas Medical Branch, Galveston, TX; 10BioNTech, Mainz, Germany.
B1 encodes SARS-CoV-2 RBD trimerized by addition of T4 fibrin foldon domain for multivalent display
B2 encodes SARS-CoV-2 full-length spike, modified by 2 proline mutations to lock in prefusion conformation
B1 encodes SARS-CoV-2 RBD trimerized by addition of T4 fibritin foldon domain for multivalent display

B2 encodes SARS-CoV-2 full-length spike, modified by 2 proline mutations to lock in prefusion conformation
Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

Pietro M Fulgeri1, Kate J Ivor2, Pennderer T Kay5, Brian Angus, Stephan Becker, Sandra Bely-Rammeister, Duncan Bellamy, Sagda Bihl, Montsephina Bittepe, Elisabeth A Clutterbuck, Christina Dool, Soh M Feast, Adam Finn, Amy J Flemson, Basram Hill, Paul Heath, Daniel Jenkins, Rijkjeke Janssen, Rebecca Makinen, Angelo M Minassian, Estelle M Proctor, Midrakli Ramassamy, Harshil Ramose, Matthew Snape, Richard Tenner, Meryn Vynny, Catherine Green, Alexandre D Douglas6, Adrian V M Harris7, Teresa Lamba8, Sarah C Gillett, Andrew J Pollard9, on behalf of the Oxford COVID Vaccine Trial Group

Summary

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed by vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vector vaccine that expresses the spike protein of SARS-CoV-2.

Methods

We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5 x 10^9 viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to receive vaccine, ranked from first to 10th, were randomly assigned, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, a multiplexed immunoassay, three low SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation test (PRNT), a microneutralisation assay (MNA), and MNA), and Maberry VN, and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex vivo interferon-gamma–linked immunospot assay. As measured by cases of symptomatic virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events, Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after vaccination. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. The study is ongoing, and was registered at ISRCTN, ISRCTN15281137, and ClinicalTrials.gov: NCT04314666.

Findings

Between April 23 and May 22, 2020, 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534). Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all p<0.05). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific IgG responses peaked on day 14 (median 856 spots-forming cells per million peripheral blood mononuclear cells, 1QR 493–1802; n=43) and on day 56 (median 1576 ELISA units (EU), 1QR 657–5157; n=42), and were boosted following a second dose (day 84 EU, 1QR 600–3012; n=40). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (59%) of 53 participants after a single dose when measured in MNA, and in 35 (98%) of 36 participants when measured in PRNT. After a booster dose, all participants had neutralising activity (titre of nine in MNA, at day 42 and ten in VN at day 54). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA (R² = 0.67 by VN, Maberry VN, p<0.001).

Interpretation

ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support large-scale evaluation of this candidate vaccine in an ongoing phase 3 programme.

Funding

UK Research and Innovation, Coalition for Epidemic Preparedness Innovations, National Institute for Health Research (NIHR), NIHR Oxford Biomedical Research Centre, Thames Valley and South Midlands NIHR Clinical Research Network, and the German Center for Infection Research (DZIF), Partner site Gießen-Marburg-Lahn.

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Methods:
“Use of saline as a placebo would risk unblinding participants as those who had notable reactions would know they were in the ChAdOx1 nCOV-19 vaccine group”
Figure 3: SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
Figure 5: PseudoNA results in trial participants and in convalescent plasma samples from 146 patients with PCR-confirmed COVID-19 and 24 asymptomatic health-care workers.

Solid lines connect samples from the same participant. Boxes show median (IQR). Results for days 35 and 42 are samples from participants who received a booster dose at day 28. IC=inhibitory concentration.

MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.
AstraZeneca Pauses Vaccine Trial for Safety Review

The company halted late-stage trials of its coronavirus vaccine because of a serious suspected adverse reaction in a participant.

“...a volunteer in the U.K. trial had received a diagnosis of transverse myelitis, an inflammatory syndrome that affects the spinal cord and is often sparked by viral infections. However, the timing of this diagnosis, and whether it was directly linked to AstraZeneca’s vaccine, is still unknown.” NYT, 9/8/20
Transverse myelitis can affect people of any age, gender, or race. It does not appear to be genetic or run in families. A peak in incidence rates (the number of new cases per year) appears to occur between 10 and 19 years and 30 and 39 years. It is estimated that about 1,400 new cases of transverse myelitis are diagnosed each year in the United States.

https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Transverse-Myelitis-Fact-Sheet

The annual incidence of transverse myelitis ranges from 1.34 to 4.60 cases per million.

https://www.nationalmssociety.org/What-is-MS/Related-Conditions/Transverse-Myelitis
Assessing the Safety of Adjuvanted Vaccines

S. Sohail Ahmed,1* Stanley A. Plotkin,2,3 Steven Black,4 Robert L. Coffman5

Despite the very low risk-to-benefit ratio of vaccines, fear of negative side effects has discouraged many people from getting vaccinated, resulting in reemergence of previously controlled diseases such as measles, pertussis, and diphtheria. Part of this fear stems from the lack of public awareness of the many preclinical and clinical safety evaluations that vaccines must undergo before they are available to the general public, as well as from misperceptions of what adjuvants are or why they are used in vaccines. The resultant “black box” leads to a preoccupation with rare side effects (such as autoimmune diseases) that are speculated, but not proven, to be linked to some vaccinations. The focus of this review article is to open this black box and provide a conceptual framework for how vaccine safety is traditionally assessed. We discuss the strengths and shortcomings of tools that can be and are used preclinically (in animal studies), translationally (in biomarker studies with human sera or cells), statistically (for disease epidemiology), and clinically (in the design of human trials) to help ascertain the risk of the infrequent and delayed adverse events that arise in relation to adjuvanted vaccine administration.

Transverse myelitis incidence: ~0.2/100,000 person-years, and 1,400 new diagnoses/year

Table 2. Estimated new cases in 2009 of autoimmune disease in the United States based on mean weighted incidence rates reported in a systematic meta-analysis (71). Expected new diagnoses were extrapolated using the 2009 U.S. Census data for population >18 years of age (73).

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Incidence (per 100,000 persons per year)</th>
<th>Expected new diagnoses (persons &gt;18 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult rheumatoid arthritis</td>
<td>23.7</td>
<td>55,092</td>
</tr>
<tr>
<td>Thyroiditis (hypothyroidism)</td>
<td>21.8</td>
<td>50,675</td>
</tr>
<tr>
<td>Graves disease (hyperthyroidism)</td>
<td>13.9</td>
<td>32,311</td>
</tr>
<tr>
<td>Type 1 diabetes (age &gt;20 years)*</td>
<td>8.1</td>
<td>18,829</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>7.3</td>
<td>16,969</td>
</tr>
<tr>
<td>Sjogren disease*</td>
<td>3.9</td>
<td>9,065</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3.2</td>
<td>7,438</td>
</tr>
<tr>
<td>Primary systemic vasculitis*</td>
<td>2.0</td>
<td>4,649</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>1.8</td>
<td>4,184</td>
</tr>
<tr>
<td>Systemic sclerosis*</td>
<td>1.4</td>
<td>3,254</td>
</tr>
<tr>
<td>Addison disease*</td>
<td>0.6</td>
<td>1,394</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>0.4</td>
<td>929</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>204,789</td>
</tr>
</tbody>
</table>

*Additional categories of autoimmune diseases with an age distribution older than 18 years for which missing or updated incidence data were available in a subsequent publication (72).
Table 3. Probability of observing autoimmune diseases owing to coincidental temporal association during clinical trials of various sizes (n). The probability of observing at least one subject with each of the listed autoimmune diseases was calculated using a Poisson probability distribution.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Study sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 200</td>
</tr>
<tr>
<td></td>
<td>Probability to observe at least one case</td>
</tr>
<tr>
<td>Adult rheumatoid arthritis</td>
<td>4.6%</td>
</tr>
<tr>
<td>Thyroiditis (hypothyroidism)</td>
<td>4.3%</td>
</tr>
<tr>
<td>Graves disease (hyperthyroidism)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Type 1 diabetes (age &gt;20 years)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1.4%</td>
</tr>
<tr>
<td>Sjogren disease</td>
<td>0.8%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.6%</td>
</tr>
<tr>
<td>Primary systemic vasculitis</td>
<td>0.4%</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>0.4%</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>0.3%</td>
</tr>
<tr>
<td>Addison disease</td>
<td>0.1%</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>0.1%</td>
</tr>
<tr>
<td>Total</td>
<td>15.0%</td>
</tr>
</tbody>
</table>
Updates from 12 hours ago...

- The case of transverse myelitis reported this week is not the first case to be identified in this trial
- The first potential case of transverse myelitis was identified in July, later diagnosed as multiple sclerosis
- Indicates that at least 2 cases of neurological disease have been identified to date
- Will require further review and comparison between the two cases and determine relatedness to the vaccine

According to Bloomberg; According to a participant information sheet dated July 12 that was posted on the ISRCTN clinical-trial registry, one volunteer in AstraZeneca’s U.K. trial had developed symptoms of transverse myelitis. The posting said the cause was being investigated.

An August update of the information sheet removed the reference to transverse myelitis and said the participant developed neurological symptoms that caused the study to be paused, and that the volunteer was later diagnosed with what was described as “an unrelated neurological illness.”

First-in-Human Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine

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Note that most adverse events are similar to placebo (Plc) – and unlike mRNA or ChAd vectors, almost no fever/chills
Neutralizing antibody titers appear to be nearly 10-fold higher than that obtained with the mRNA vaccines.
Summary

• COVID-19 Vaccine update
  • 321 vaccine candidates, 32 candidates in clinical trial, 1 on Clinical Hold (Astrazeneca)
  • Questions of durability and early estimates of vaccine efficacy need to be determined
  • Current frontrunners appear safe, tolerability may be an issue & need more information on Astrazeneca
  • First-to-Market mRNA, DNA, or recombinant adenovirus vaccines may be immediately successful or may function as Stop-Gap until other promising vaccines emerge with excellent candidates still in the pipeline
Questions
• Please complete the post-session survey in order to receive CME

• 1st and 3rd Thursdays, 12-1 p.m.: Oregon Health Authority COVID-19 Informational Session for All Providers: next OHA session is September 15

• 2nd and 4th Thursdays, June 11-December 10, 12-1:15 p.m.: Project ECHO COVID-19 Response for Oregon Clinicians - Part 2

• Next COVID ECHO session is Thursday, September 24
Welcome to the Oregon ECHO Network

Connect and Learn

ECHO is an interactive educational and community-building experience that allows healthcare professionals throughout the state of Oregon to create a case-based learning environment through the convenience of video connection.

Click for Oregon ECHO Network's current programs or scroll down to learn more.