COVID-19: Immunity and Vaccines

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Delaware Communicable Diseases Health Summit
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Disclosures

• No financial or other conflicts of interest.

• *Full disclosure:* Data presented are accurate as of 11.8.2020...
Agenda

- Immunology 101
- Natural COVID-19 infection & immunity
- COVID-19 vaccine development process
- COVID-19 candidate vaccines
- Vaccine safety monitoring
- Implementing a COVID-19 vaccination program
IMMUNOLOGY 101
Innate vs. Active Immunity

**Innate immunity** (quick, non-specific)
- Infection
- Recognition of pathogens by sensors
- Activation of cells and inflammation
- Removal of infectious agent

**Adaptive immunity** (long-term, specific)
- Infection
- Stimulation of T and B cells in lymphoid organs
- Expansion and training of effector T and B cells
- Migration to infection site
- Removal of infectious agent

Figure courtesy of Akiko Iwasaki, PhD (https://app.biorender.com/biorender-templates)
Innate Immunity

Figures courtesy of Akiko Iwasaki, PhD
(https://app.biorender.com/biorender-templates)
Adaptive Immunity

- **CD8+** = cytotoxic
- **Th2**
- **Th1**
- Humoral response
- Cell-mediated response
- Killer T cells =CD8+ = cytotoxic
- APC
- Antigen

LibreTexts, https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/...Types_of_Adaptive_Immunity
Neutralizing vs. Non-neutralizing Ab

Figures courtesy of Akiko Iwasaki, PhD (https://app.biorender.com/biorender-templates)
Adaptive Immune Response to SARS-CoV-2

Immune System Components Important For Vaccine Response:
- Antibody response (seropositivity)
- Neutralizing antibody response
- CD8+ T cell response
- CD4+ T cell – Th1 vs. Th2 response (Th2 may increase risk of Vaccine-mediated enhanced disease (VMED))
COVID-19

NATURAL INFECTION & IMMUNITY
Coronavirus Immune Response

- Transient protection from common CoV infections
  - Waning serum antibody levels contribute to susceptibility
  - Repeat infections may be less severe (or asymptomatic) & associated with lower viral titers

- SARS-CoV-1
  - 36-mo study of convalescent SARS patients (n=56)
    - SARS-specific IgG and neutralizing Ab peaked at month 4 and diminished thereafter
    - IgG/neutralizing Ab detectable in 70%/20% by month 36

- Middle East Respiratory Syndrome (MERS)
  - Antibodies (including neutralizing) persisted in 6 (86%) of 7 persons after 34 months

- Human coronaviruses
  - 229E
  - NL63
  - OC43
  - HKU1

- Zoonotic coronaviruses
  - SARS-CoV-1
  - MERS
  - SARS-CoV-2

Callow et al, Epidemiol Infect, 1990
Kiyuka et al, J Infect Dis, 2018
S.K. Lal (ed.), Molecular Biology of the SARS-Coronavirus, 2010
Payne DC et al. Emerg Inf Dis 2010
Serum antibodies decline between acute phase and 2 months post discharge (expected).
Neutralizing Antibody Titers

- 15 hospitalized persons with SARS-CoV-2 neutralizing antibody
  - 88 samples collected between 0-75 days post-symptoms
- Titers demonstrated little to no decrease over 75 days since symptom onset

Iyer et al. Science immunology. October 8, 2020
M. Wallace, ACIP 10/30/2020
COVID-19 Cellular Immune Response

• In symptomatic COVID-19 patients, memory B cells did not wane at the same rate as serum antibodies

• Recovered COVID-19 patients have SARS-CoV-2-specific CD4+ T cells and CD8+ T cells

## COVID-19 Re-infections

### Review of 5 reports of suspected cases of SARS CoV-2 Reinfection

<table>
<thead>
<tr>
<th>Report</th>
<th>Days from 1st course onset</th>
<th>Features of 2nd clinical course</th>
<th>Evidence for reinfection/Contribution to literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>To et al. – Healthy 33M from Hong Kong (Aug 25)</td>
<td>145 days</td>
<td>Asymptomatic</td>
<td>Strongest evidence published case – demonstrated evidence for acute, substantial infection (high viral load, serological conversion after) as well as substantial genome differences (23 nucleotides, different clades/lineages).</td>
</tr>
<tr>
<td>Van Eslande et al – 52F on inhaled corticosteroids from Belgium (Sep 05)</td>
<td>83 days</td>
<td>Symptomatic w/ similar but milder URI symptoms</td>
<td>Intermediate evidence - demonstrated RT-PCR positive (Ct value = 33 on reinfection) and genomic difference &gt; expected molecular clock (11 nucleotides).</td>
</tr>
<tr>
<td>Tillet et al. – 25M from Reno, Nevada (Aug 31)</td>
<td>43 days</td>
<td>Atypical pneumonia w/ hypoxemia, 2nd course worse than 1st</td>
<td>Lesser degree of evidence – demonstrated distinct viral genomes from 2 episodes (7 nucleotides) but did not demonstrate significant viral burden (Ct =35).</td>
</tr>
<tr>
<td>Raddad. et al – migrant workers in Qatar (Aug 26)</td>
<td>Median of 65 days</td>
<td>Unknown clinical course, uses location of swab (health facility vs survey) as proxy</td>
<td>First attempt at quantifying reinfection – searched for repeat positive RT-PCR &gt;45 days among 133K cases. 35 (0.03%) of which had Ct values &lt;30 on the 2nd specimen</td>
</tr>
<tr>
<td>CDC Reinfection Investigation</td>
<td>Initial 3 months after primary infection</td>
<td>Recurrent COVID-19 like symptoms with positive SARS-CoV-2 RT-PCR, but no alternate etiology identified for their symptoms.</td>
<td>26 cases with specimens available for both illness episodes. All specimens from the second episode of infection had Ct values &gt;30 and no replication-competent virus isolated.</td>
</tr>
</tbody>
</table>
Summary: COVID-19 Immune Response

- Repeat exposure to SARS-CoV-2 may boost immune response
- Several studies demonstrated waning of serum antibodies in COVID-19 patients after few months
  - Implications for protection unknown
- Neutralizing antibody titers demonstrated little or no decrease at 75 days post-symptom onset
- SARS-CoV-2 specific cellular B and T cell responses detected in COVID-19 patients
  - Memory B cells did not wane as fast as serum antibody titers
- Re-infection with SARS-CoV-2 possible, but unlikely within 3 months
SARS-CoV-2 Viral Vaccine Targets

Single-stranded positive-sense RNA virus
4 major structural proteins:
• Spike protein (S) → contains receptor binding domain (RBD)
• M protein
• Envelope (E) protein
• Nucleocapsid (N) protein
Viral Vaccine Antigens

A

RBD = receptor binding domain →

B

Antigens used to detect SARS-CoV-2:
Spike:
- RBD
- S1
- S2P
- Ab to all 3 may contribute to neutralization

Nucleocapsid:
- unlikely a target for neutralizing Ab

Wrapp et al, Science 2020
N. Thornburg, ACIP 6/24/2020
COVID-19
VACCINE DEVELOPMENT PROCESS
How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

**PHASE 1**

- 20-100 healthy volunteers

- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

**PHASE 2**

- Several hundred volunteers

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

**PHASE 3**

- Hundreds or thousands of volunteers

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

**FDA licenses the vaccine only if:**

- It's safe and effective
- Benefits outweigh risks

[https://www.cdc.gov/vaccines/hcp/conversations/ensuring-safe-vaccines.html](https://www.cdc.gov/vaccines/hcp/conversations/ensuring-safe-vaccines.html)
Path from clinical development to recommendation

Clinical Development
- Generates safety, immunogenicity, and efficacy data
- Close coordination within OWS (DHHS [CDC, NIH, ASPR], DoD)
- Manufacturing of vaccine - could save months of time post-approval

FDA
- Licensure
- Emergency Use Authorization (AVA Anthrax for PEP)
- Expanded Access IND (MenB vaccine during college outbreaks)

ACIP
- Review Evidence, utilize Evidence to Recommendation Framework
- Make recommendations regarding the use of vaccines to the CDC Director

CDC Recommendation
Post-approval monitoring
ACIP Structure & Function

Membership
- 15 voting members
  - Represent various expertise: Int Med, pediatrics, ID, OB/gyn, Fam Med, public health, etc.
  - Independent of CDC - voting members not CDC employees
- 8 Ex Officio members representing other federal agencies
  - FDA, NIH, DOD, CMS, etc.
- 30 Liaison representatives - non-voting
  - SHEA, IDSA, NFID, AAP, ACP, AMA, etc.

Schedule
- Public ACIP meetings (virtual since 6/20)
  - Feb, June, Oct
  - “Stand-up” meetings July, Aug, Sept devoted to COVID-19
  - Must have time for public comment
- COVID-19 vaccine work group (WG)
  - Weekly meetings since April
  - Confidential
  - Review epidemiology, modeling, ethical principles, specific vaccine candidate data, etc.
Evidence to Recommendation

**Evidence**
- Published
- Gray literature

**Evidence to Recommendation Framework**
- Problem
- Benefits & Harms
- Values
- Acceptability
- Feasibility
- Resource use
- Equity

**ACIP Recommendation**
1) Recommend
2) Recommend for individuals based on shared clinical decision making
3) Do not Recommend

K. Dooling, ACIP 7/29/2020
Three Entities with Distinct Roles in COVID-19 Response

Operation Warp Speed
USG body responsible for strategic approach, coordination and resource allocation

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)
NIH established Public-private partnership for coordinating COVID-19 response

COVID-19 Prevention Network
NIH Funded networks - Phase 3 trial execution

Semi-Independent Harmonized Trials

Candidate COVID-19 vaccines

Platform 1  Platform 2  Platform 3  Platform 4  Platform 5

Harmonized efficacy trials
Collaborating clinical trials networks
Collaborating labs
1) Defining COVID infections from vaccination
2) Quantitative immune responses to spike and spike epitopes
3) T-cell responses

Data and Safety Monitoring Board
Between-trial statistical group for correlates of protection

NIH/COVID Network-supported infrastructure

J. Ledgerwood, ACIP 7/29/2020
**OPERATION WARP SPEED**

**ACCELERATED VACCINE PROCESS**

**MISSION:** Deliver 300 million doses of safe and effective vaccine by 1 January 2021.

**TYPICAL PROCESS**
- 3 MONTHS
- 5 MONTHS
- 21 MONTHS
- 23 MONTHS
- 15 MONTHS
- 6 MONTHS
- 73 MONTHS TO COMPLETION

**ACCELERATED PROCESS**
- 5 MONTHS
- 6 MONTHS
- 3 MONTHS
- 14 MONTHS TO COMPLETION

1. A typical 8-month process is accelerated by:
   - Creating vaccine candidates immediately after viral genome sequence is available.
   - Using vaccine platforms developed for other diseases.

2. A typical 42-month process is accelerated by:
   - Large scale Phase III clinical trials of 30,000 volunteers allowing for rapid collection and earlier analysis of safety and efficacy data of demographically diverse populations by the FDA, reducing the typical 12 month approval process to three months.
   - Two promising candidates began Phase III clinical trials in July, with others to follow quickly in coming months. Before beginning Phase III, candidates must show safety data from animal and human studies.
   - The U.S. Government funding at-risk, large-scale manufacturing of the most promising vaccine candidates during Phase III clinical trials to ensure any vaccine proven to be safe and effective is available immediately upon FDA Emergency Use Authorization (EUA) approval or licensure.

3. A typical 15-month process is accelerated by:
   - A tiered approach based on CDC recommended allocation methodology used as part of pandemic flu planning and the COVID-19 response will be used to determine vaccine distribution.
   - Planning for infrastructure and distribution before the vaccines are approved or authorized.
   - CDC leading distribution planning with DoD augmentation.

4. A typical 12-month FDA review for EUA approval or licensure is accelerated by:
   - Providing continuous safety and efficacy data collected in large Phase III clinical trials.

**Key Agencies:**
- DOD
- DHHS
- CDC
- NIH
- FDA
- BARDA

[https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/]
What Do We Want a Vaccine to Do?

Hodgson SH, et al, *Lancet Inf Dis*, published online 10.27.2020
Herd Immunity

• AKA ‘population immunity’
  • Population can be protected if certain threshold of vaccination reached
  • Reduces overall amount of disease able to spread → not every single person needs to be vaccinated to be protected
• Threshold varies based on disease
  • Measles: 95%
  • Polio: 80%
  • COVID-19: 50-70%?
• Estimated current U.S. population immunity: <10%

WHO:
“Attempts to reach ‘herd immunity’ through exposing people to a virus are scientifically problematic and unethical. Letting COVID-19 spread through populations, of any age or health status will lead to unnecessary infections, suffering and death.”
OWS Phase III Efficacy Trial Principles

- Sample size: approximately 30,000 volunteers
- Study population: ≥ 18 years, enriched subset at higher risk of severe disease, diverse populations & elderly
- Primary endpoint: prevention of symptomatic COVID-19 (virologically-confirmed)
  - Primary efficacy endpoint point estimate ≥ 50%
  - Statistical success criterion: lower bound of CI ≥ 30%
  - Consistent with FDA guidance
- Harmonized immunogenicity assays and correlates analysis
- Common independent DSMB (managed by NIAID)
ACIP COVID-19 Vaccine Work Group: Proposed Guiding Principles

**Safety is paramount.** Vaccine safety standards will not be compromised in efforts to accelerate COVID-19 vaccine development.

**Inclusive clinical trials.** Study participants should reflect groups at risk for COVID-19 to ensure safety and efficacy data are generalizable.

**Efficient Distribution.** During a pandemic, efficient, expeditious and equitable distribution and administration of approved vaccine is critical.

**Flexibility.** Within national guidelines, state and local jurisdictions should have flexibility to administer vaccine based on local epidemiology and demand.
COVID-19

CANDIDATE VACCINES
COVID-19 Vaccines

• >200 candidates in development worldwide*
  • 47 in clinical development
  • 155 in pre-clinical development
• Within the U.S.:
  • Four vaccines in active Phase III clinical trials
  • Five vaccines in active Phase I/II clinical trials

Vaccine Strategies

• mRNA
• DNA
• Replication-defective viral vectors
• Replicating viral vectors
• Purified viral protein
• Whole, killed virus
• Live, attenuated virus

*As of 11/3/2020
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
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*As of 11/3/2020
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## Vaccine Platforms & Attributes

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<thead>
<tr>
<th>Platform</th>
<th>Single Dose</th>
<th>Licensed Platform</th>
<th>Speed</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>Medium</td>
</tr>
<tr>
<td>RNA</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>Low to medium</td>
</tr>
<tr>
<td>Nonreplicating vector</td>
<td>Possibly</td>
<td>No</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Replicating viral vector</td>
<td>Possibly</td>
<td>Yes</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Protein subunit</td>
<td>No</td>
<td>Yes</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Inactivated</td>
<td>No</td>
<td>Yes</td>
<td>Medium</td>
<td>Medium to high</td>
</tr>
<tr>
<td>Live attenuuated</td>
<td>Yes</td>
<td>Yes</td>
<td>Slow</td>
<td>High</td>
</tr>
</tbody>
</table>

K. Neuzil, ACIP 6/24/2020
# COVID-19 vaccines in human clinical trials – United States*

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Phase</th>
<th>Trial characteristics</th>
<th>Trial #</th>
<th>Recruiting</th>
</tr>
</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>NCT04470427</td>
<td>Enrollment complete</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>• IM administration</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-55, 56+ years</td>
<td></td>
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<tr>
<td>mRNA-BNT162</td>
<td>Pfizer, Inc./BioNTech</td>
<td>mRNA</td>
<td>II/III</td>
<td>• 2 doses (0, 21d)</td>
<td>NCT04368728</td>
<td>✓</td>
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<td></td>
<td></td>
<td></td>
<td>• 18-85 years</td>
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<tr>
<td>AZD1222</td>
<td>University of Oxford/AstraZeneca</td>
<td>Viral vector (NR)</td>
<td>III</td>
<td>• 2 doses (0, 28d)</td>
<td>NCT04516746</td>
<td>✓</td>
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<tr>
<td></td>
<td>consortium**</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• ≥18 years</td>
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<tr>
<td>Ad26COV-S1</td>
<td>Janssen Pharmaceutical Companies</td>
<td>Viral vector (NR)</td>
<td>III</td>
<td>• 1 dose</td>
<td>NCT04436276</td>
<td>✓</td>
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<td>• IM administration</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-55, 65+ years</td>
<td></td>
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<tr>
<td>--</td>
<td>Sanofi/GSK</td>
<td>Protein Subunit</td>
<td>I/II</td>
<td>• Single or 2 doses</td>
<td>NCT04537208</td>
<td>✓</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>• IM administration</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-49, 50+ years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVX-CoV2373</td>
<td>Novavax</td>
<td>Protein Subunit</td>
<td>I/II</td>
<td>• 2 doses (0, 21d)</td>
<td>NCT04368988</td>
<td>Enrollment complete</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>• IM administration</td>
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<td></td>
<td></td>
<td></td>
<td>• 18-84</td>
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<tr>
<td>V591</td>
<td>Merck</td>
<td>Viral Vector</td>
<td>I/II</td>
<td>• 2 doses (1, 57d)</td>
<td>NCT04498247</td>
<td>✓</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• 18-55</td>
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*As of October 27, 2020
**Currently on hold in US
## COVID-19 vaccines in human clinical trials – United States*

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<tbody>
<tr>
<td>AV-COVID-19</td>
<td>Aivita</td>
<td>AuDendritic cell</td>
<td>I/II</td>
<td>• 1 dose • 18+</td>
<td>NCT04386252</td>
<td>Not yet recruiting</td>
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<tr>
<td>VXA-CoV2-1</td>
<td>Vaxart</td>
<td>Viral vector (NR)</td>
<td>I</td>
<td>• 2 doses (1, 29d) • Oral tablet • 18-54</td>
<td>NCT04563702</td>
<td>✓</td>
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<tr>
<td>INO-4800</td>
<td>Inovio Pharmaceuticals, Inc.</td>
<td>DNA plasmid</td>
<td>I</td>
<td>• 2 doses (0, 4w) • SC administration/ electroporation • ≥18 years</td>
<td>NCT04336410</td>
<td>Active, not recruiting</td>
</tr>
</tbody>
</table>

*As of October 27, 2020
How Do RNA Vaccines Work?

RNA is often encased in a lipid coat so it can enter cells. DNA vaccine uses electroporation to create pores in membranes to increase uptake of DNA into a cell. RNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.

mRNA-1273: Moderna

Vaccine Characteristics

- mRNA vaccine
- No prior vaccine experience with this platform
- Encodes for the full-length spike protein in the pre-fusion conformation (S-2P)

Vaccine Logistics

- Two doses, 28 days apart
- Dose: 100µg
- Multidose vials (5 per vial)
  - Use within 6 hours
- No preservative or reconstitution
- Storage:
  - Long-term: -20° C
  - ~14 days at 2-8° C
mRNA-1273: Immunogenicity

- Phase I, dose-escalation, open-label
- 45 healthy adults (18-55 y)
- Trial expanded to include 40 older adults (56 to 70 years or ≥71 years)
- Binding & neutralizing Ab similar to those found in convalescent plasma
- Th1-biased CD4+ T-cell response across all age groups

J. Miller, ACIP, 8/26/2020
mRNA-1273: Safety

Phase 1: No Vaccine-Related SAEs Have Been Reported
Solicited Local and Systemic Symptoms Followed for 7 Days Post-vaccination
Majority of symptoms resolved within 2 days, some persisted as long as 5 days

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age group</th>
<th>Vaccination 1</th>
<th>Vaccination 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic symptom</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Fever</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Chills</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Headache</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
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</tbody>
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</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Nausea</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Any local symptom</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
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<tr>
<td>Erythema</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
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<tr>
<td>Induration</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
<tr>
<td>Pain</td>
<td>18-55</td>
<td>56-70</td>
<td>71+</td>
</tr>
</tbody>
</table>

1. Fever percentages reflect the number of subjects with at least one measurement available in the data system as the denominator. This denominator may differ from other systemic symptoms, which are solicited in-clinic at the post-dose assessment.

2. 18-55: N=15; 56-70: N=10; 71+: N=10; N = All subjects receiving Dose 1 with any solicited event data recorded in the database

J. Miller, ACIP, 8/26/2020
Clinical Trial Inclusivity

Race and ethnicity

- White: 63%
- Hispanic/Latino: 20%
- Black/AA: 10%
- Asian: 3%
- All others: 4%

22% healthcare personnel

Cove Study gender distribution

- Female: 53%
- Male: 47%

Age and gender

- 18 to 24: 2000
- 25 to 44: 6000
- 45 to 64: 10000
- 65 or above: 4000

27% of participants living with comorbidities: including diabetes, cardiac disease, lung disease, obesity

Sources: https://www.modernatx.com/sites/default/files/content_documents/2020-COVE-Study-Enrollment-Completion-10.22.20.pdf
Vaccine Characteristics
• mRNA vaccine
• No prior vaccine experience with this platform
• Encodes for the full-length spike protein in the pre-fusion conformation (S-2P)

Vaccine Logistics
• Two doses, 21 days apart
• Dose: 30 µg
• Multidose vials (10 per vial)
• Storage:
  • Long-term: -70º C
  • 10 days in storage container with dry ice (replenished)
  • 5 days at 2-8º C
• Reconstitution required
  • Use within 6 hours
• Phase I trial of safety and immunogenicity of varying doses of BNT162b1 and BNT162b2 vaccines among healthy adults aged 18–55 (left) or 65–85 years (right)
  • 90 participants received b2 vaccine candidate
  • 30 µg dose generated binding and neutralizing antibody levels similar or greater to convalescent plasma (green arrows) after 2\textsuperscript{nd} dose
  • Strong CD4+ and CD8+ T cell responses with TH1 dominance

BNT162b2 : Safety

Viral Vectored Vaccines

“Trojan horse”

Adapted from: https://www.ncbi.nlm.nih.gov/pubmed/27286566
https://thenativeantigencompany.com/repurposing-adenoviruses-as-vectors-for-vaccines/
AZD1222: Oxford /AstraZeneca

Vaccine Characteristics
- Based on existing simian recombinant adenovirus vaccine vector
  - ChAdOx1
  - Nonreplicating
  - Circumvents any pre-existing immunity to human adenoviruses
- Prior experience with ChAdOx1: influenza, Chikungunya, MERS, malaria, TB, Zika, meningitis B
- Contains genetic material of SARS-CoV-2 spike protein

Vaccine Logistics
- Two doses, 28 days apart
- Dose: $5 \times 10^{10}$ viral particles
- Multidose vials (10 per vial)
  - Use within 4 hours
- Storage at 2-8º C (do not freeze)
AZD1222: Immunogenicity

• Phase I/II, single-blind, randomized controlled trial
• Vs. MenACWY vaccine
• Single dose resulted in increase in S protein-specific Ab by Day 28
• 10 participants received 2nd dose → further increase in S protein-specific Ab observed
• Robust Th1-biased T cell response

Folegatti PM, et al. Lancet 2020
AZD1222: Safety
Vaccine Characteristics
• Proprietary AdVac platform
  • Adenovirus 26
  • Ad 26 does not commonly circulate in humans
  • Nonreplicating
  • Extensive (>110K) experience with AdVac: Ebola, RSV, HIV, Filo, malaria, TB, Zika, HPV
    • Pregnant women, children
• Contains full length membrane-bound spike protein with stabilizing mutations

Vaccine Logistics
• One dose
• Dose: $5 \times 10^{10}$ viral particles
• Multidose vials (5 per vial)
  • Use within 6 hours
• Storage:
  • Long term storage: at $-20^\circ$ C
  • End-user storage after thawing: 2-8$^\circ$ C for 3 months
  • After first use: 6 hrs at 2-8$^\circ$ C
Ad26.COV2.S: Immunogenicity

- Phase 1/2a trial
  - Healthy adults 18-55y, adults ≥65y
  - 2 dose levels, 1 vs. 2 doses
  - 1045 participants
- Binding and neutralizing Ab response demonstrated at 28 d post vaccination
  - Responses similar to human convalescent sera
- CD4+ and CD8+ T cell response demonstrated
  - Th1-biased CD4+ T-cell response

Sadoff J, Janssen, ACIP 10.30.20
Ad26.COV2.S: Safety

Safety & Reactogenicity Assessment Post-Dose 1 (Blinded – Pooled Groups of $5 \times 10^{10}$ vp or $1 \times 10^{11}$ vp, Placebo)

Cohort 1: Healthy adults aged 18 – 55 (n=402)

Cohort 3: Healthy adults aged ≥65 years (n=403)

No grade 4 adverse events reported in any cohort
COVID-19 Vaccine Timeline

- mRNA-1273 vaccine (Moderna): *Enrollment Complete*
  - 30,000 participants enrolled as of 10/22/2020
  - 25,654 participants have received their second vaccination

- BNT162b2 vaccine (Pfizer/BioNTech)
  - 42,133 participants enrolled as of 10/26/2020
  - 35,771 participants have received their second vaccination

- AstraZeneca & Janssen on FDA hold/safety pause; lifted 10/23, allowing Phase III trials to continue

**Interim efficacy analyses:**
- Clinical efficacy outcome: VE=50% (95% CI LL=30%)
- Interim analysis @ 32 cases (Pfizer) & 53 cases (Moderna)

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jul</td>
<td>Aug</td>
</tr>
<tr>
<td>Moderna</td>
<td></td>
<td></td>
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<tr>
<td>Pfizer</td>
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<td>AstraZeneca</td>
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<td>Janssen</td>
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<tr>
<td>Novavax</td>
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</tbody>
</table>

B. Bell, ACIP 10.28.2020
K. Dooling, ACIP CVWG,
Used with permission
COVID-19

VACCINE SAFETY MONITORING
Clinical Trial Vaccine Safety Monitoring

- FDA guidance for Phase III trials: 2-month median follow-up (October 2020)
  - At least half of vaccine recipients with ≥2 months of follow-up after completion of full vaccination regimen

- Is this enough?
  - Adverse events plausibly linked to vaccination generally start within 6 weeks after vaccine receipt
  - FDA typically requires 6 mo. of follow-up for full licensure
  - New vaccine technologies require longer follow-up?

Shortened time frame justified?
- Extensive historical experience with adverse events after vaccination
- Need for vaccine to address pandemic
- Magnitude of vaccine effectiveness required to support favorable risk-benefit profile under EUA

Krause PR & Gruber MF (FDA), NEJM, 11/5/2020
U.S. Vaccine Safety Monitoring

- U.S. government responsible for public safety related to vaccines
- Monitoring independent from manufacturers; all vaccines covered
  - Manufacturers required to have safety monitoring plan
- USG maintains largest, most robust, and most sophisticated safety monitoring systems available
- USG agencies collaborate on monitoring
- ACIP established COVID-19 Vaccine Safety Technical Sub-Group

- Passive surveillance
  - Vaccine Adverse Event Reporting System (VAERS)
  - Clinical Immunization Safety Assessment (CISA) Project clinical consult service
- Active surveillance
  - FDA BEST
  - FDA-CMS partnership
  - Vaccine-safety datalink (VSD)
  - v-safe smartphone-based active surveillance
VAERS

• Nation’s frontline system for monitoring vaccine safety

• Strengths
  • National data
  • Accepts reports from anyone
  • Rapidly detects safety signals
  • Can detect rare adverse events
  • Data publicly available

• Limitations
  • Reporting bias
  • Inconsistent data quality and completeness
  • Lack of unvaccinated comparison group
  • Generally cannot assess causality

**Critical role of healthcare Providers**

Co-managed by CDC and FDA

http://vaers.hhs.gov

T. Shimabukuro, ACIP 10/30/2020
Clinical Immunization Safety Assessment (CISA) Project

- 7 participating medical research centers with vaccine safety expertise
  - Clinical consult services*
  - Clinical research
- Supports U.S. healthcare providers and health departments on complex clinical vaccine safety questions
  - Available by contacting CDC-INFO**
- Assists with evaluations of patients with adverse events, or in making clinical decisions about administering COVID-19 vaccine to person who may be at increased risk for adverse event

** https://www.cdc.gov/cdc-info/index.html
**FDA Biologics Effectiveness and Safety (BEST) System**

- Multiple partners
  - Acumen, IBM Watson, IQVIA, OHDSI, HealthCore, Humana, Optum, Healthagen, MedStar, OneFlorida, and academic organizations
- Represents variety of healthcare settings
  - Inpatient, emergency department, outpatient, etc.
- Emphasis on inclusion of EHR data, some claims data and linked claims-EHR data
- >250 million individuals covered
- Goal: to assess and confirm potential adverse events or safety concerns for COVID-19 vaccines
FDA-CMS Partnership

- Ongoing FDA-CMS partnership on vaccine safety since 2002
  - Very large population (~55 million beneficiaries ≥65 yrs of age)
  - Representative
    - >92% of those ≥65 yrs use Medicare (not a sample)
    - Variety of healthcare settings - inpatient, outpatient, etc.
  - Consists of claims data with access to medical charts
- “Near real-time surveillance” or rapid-cycle analyses (RCA)
  - Conducted for annual influenza vaccine and Guillain-Barre Syndrome since 2007
  - FDA plans on monitoring 10-20 safety outcomes of interest for COVID-19 vaccines
Vaccine Safety Datalink (VSD)

- 9 participating integrated healthcare organizations
- Data on over 12 million persons per year
- Near real-time sequential monitoring (Rapid Cycle Analysis [RCA])
- Monitoring for vaccine-mediated enhanced disease (VMED)
- Studies to evaluate COVID-19 vaccine safety during pregnancy, including fetal death and infant outcomes
v-safe

- **New** smart-phone based active surveillance program for COVID-19 vaccine safety
- Uses text messaging to initiate web-based survey monitoring
- Conducts electronic health checks on vaccine recipients
  - Daily for first week post-vaccination
  - Weekly thereafter for 6 weeks
  - Additional health checks at 3, 6, & 12 months post-vaccination
- Includes active telephone follow-up through VAERS

1. Text message check-in or email from CDC (daily 1st week post-vaccination and weekly thereafter until 6 weeks post-vaccination)
   - Vaccine recipient completes web survey

2. Clinically important event(s) reported
   - Missed work
   - Unable to do normal daily activities
   - Received medical care

3. A VAERS customer service representative conducts active telephone follow-up on a clinically important event and completes a VAERS report if appropriate

T. Shimabukuro, ACIP 10/30/2020
COVID-19

IMPLEMENTING A VACCINATION PROGRAM
ACIP COVID-19 Vaccination Program
Guiding Principles

- Maximize benefits and minimize harms
- Promote justice
- Mitigate health inequities
- Promote transparency

| Maximize benefits and minimize harms | Does the allocation plan address:
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- What populations are at highest risk of infection, hospitalization, and death from COVID-19?</td>
<td></td>
</tr>
<tr>
<td>- What populations are essential to the COVID-19 response?</td>
<td></td>
</tr>
<tr>
<td>- What populations are essential to maintaining critical functions of society?</td>
<td></td>
</tr>
<tr>
<td>- What are the key characteristics of these populations, e.g., size, density?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitigate health inequities</th>
<th>Does the plan identify and address any population that are disproportionately affected by COVID-19?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Does the allocation plan contribute to a reduction in disparities in COVID-19 disease and death?</td>
<td></td>
</tr>
<tr>
<td>- What health inequities may inadvertently result from allocation plan, and what interventions could remove them?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Promote justice</th>
<th>Does allocation planning include input from groups who are affected?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Promote transparency</th>
<th>How does the development of the allocation plan include diverse input, and if possible, public engagement?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Is the allocation plan and evidence-based method publicly available?</td>
<td></td>
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<tr>
<td>- Is the allocation plan clear about the knowns, unknowns, and certainty of evidence?</td>
<td></td>
</tr>
<tr>
<td>- What is the process for revision of allocation plans based on new information?</td>
<td></td>
</tr>
</tbody>
</table>
Phased Vaccination Approach

Limited Doses Available
- Constrained supply
- Highly targeted administration required to achieve coverage in priority populations

Large Number of Doses Available
- Likely sufficient supply to meet demand
- Supply increases access
- Broad administration network required, including surge capacity

Continued Vaccination, Shift to Routine Strategy
- Likely excess supply
- Broad administration network for increased access

Example populations:
1a.
- HCPs
- First responders
- People with high-risk conditions
- Older adults, including those living in long-term care facilities

1b.
- Non-healthcare critical workers
- People in congregate settings
- All other older adults
- Young adults
- Other critical workers

Example population:
All others in the US who did not have access in previous phases

Illustrative example populations; final prioritization to be decided by ACIP
Vaccination Planning

- Many unknowns
- Assumptions:
  - mRNA vaccine will be first, with significant logistical constraints
    - Cold chain, multidose vials, reconstitution, need for high-volume throughput, two doses needed
  - Approval under FDA EUA process likely but not confirmed
    - Emergency FDA, then ACIP meetings
  - No recommendation to make vaccination mandatory
    - Recommend coverage of any AEs under workers’ compensation
  - Likely that HCP will be phase 1a

https://shea-online.org/images/resources/101420_VaccinePlanningConsiderations.pdf
Healthcare Personnel

• All paid/unpaid persons serving in healthcare settings with potential for exposure to patients or infectious materials
• Include those not performing direct patient care but who could still be exposed at work

Estimated Population
~17-20M

Examples:
- Hospitals
- Long term care facilities (assisted living facilities & skilled nursing facilities)
- Outpatient
- Home health care
- Pharmacies
- EMS
- Public health

K. Dooling, ACIP 8/26/2020
Prioritization Among HCP

- HCP who interact directly with patients (or family members of patients), and unable to work remotely
  - HCP who provide direct patient care to COVID-19+ patients or PUIs
  - HCP who provide direct patient care to patients not suspected of COVID-19
  - Other HCP providing essential services throughout healthcare delivery system

- Healthcare systems should ensure equity included in all stages of planning and implementation
  - Lower wage workers may have higher rates of COVID-19 due to inability to work remotely, need to take public transportation, and exposures in households, high-risk communities, and workplace

- Within above categories, if supply insufficient, consider prioritizing HCP at higher risk for severe disease

https://shea-online.org/images/resources/101420_VaccinePlanningConsiderations.pdf
Vaccine Hesitancy

What is getting in the way of vaccine confidence in the US?

There has been a considerable decline in COVID-19 vaccine acceptability in the past 4 months. Factors weighing on acceptance include:

- Concern about side effects
- Efficacy
- Risk perception/need for vaccine
- Associated costs

Perceived safety, cost, and accessibility can all affect COVID-19 vaccine acceptance...but attributes that made COVID-19 vaccine more acceptable included:

- If your healthcare provider said it was safe
- If there are no costs to the individual
- If it would help get back to school and work
- If they could get it easily, from a walk-in or drive-thru clinic, pharmacy or doctor’s office


Vaccine Demand Continuum

INCREASING CONFIDENCE IN VACCINE, VACCINATOR, AND HEALTH SYSTEM

May have questions, take “wait and see” approach, want more information

Refusal
Passive Acceptance
Demand

Adapted from source: SAGE Working Group on Vaccine Hesitancy 2017

A. Cohn, ACIP 10/30/2020
A National Strategy to Reinforce Confidence in COVID-19 Vaccines

**Reinforce Trust**
Objective: Regularly share clear and accurate COVID-19 vaccine information and take visible actions to build trust in the vaccine, the vaccinator, and the system.

**Empower Healthcare Providers**
Objective: Promote confidence among healthcare personnel in their decision to get vaccinated and to recommend vaccination to their patients.

**Engage Communities & Individuals**
Objective: Engage communities in a sustainable, equitable, and inclusive way—using two-way communication to listen, increase collaboration, and build trust in COVID-19 vaccine.
Coronavirus Disease 2019 (COVID-19)

YOUR HEALTH

Vaccines

Safety Is a Top Priority
The U.S. vaccine safety system ensures that all vaccines are as safe as possible. Learn more

Vaccine Information for You & Your Family
8 Things to Know about U.S. COVID-19 Vaccination Plans

How CDC is Making COVID-19 Vaccine Recommendations

Ensuring the Safety of COVID-19 Vaccines

Frequently Asked Questions about COVID-19 Vaccination

8 Things to Know about Vaccination Planning

What you need to know about COVID-19 vaccination planning in the United States.

Vaccination Plans

Questions

Thank you to SHEA, the members of the ACIP COVID-19 Workgroup, and all the CDC and FDA staff (and many others) who are devoting countless hours to the COVID-19 response.