COVID-19 UPDATE: COVID-19 VACCINES

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Disclosures: Consultant - PDI, Germitec, Pfizer; Merck, UV Innovators
GREATEST PUBLIC HEALTH ACHIEVEMENTS IN THE US

1900-1998
- Vaccination
- Motor vehicle safety
- Safer workplaces
- Control of infectious diseases
- Decline in deaths from coronary artery disease and stroke
- Safer and healthier foods
- Healthier mothers and babies
- Family planning
- Fluoridation of drinking water
- Recognition of tobacco use as a health hazard

2001-2010
- Vaccination
- Prevention and control of communicable diseases
- Tobacco control
- Maternal and infant health
- Motor vehicle safety
- Cardiovascular disease prevention
- Occupational safety
- Cancer prevention
- Childhood lead poisoning prevention
- Public health preparedness and response

CDC. MMWR 1999;48:241-243
CDC. MMWR 2011;60:619-623
### IMPACT OF VACCINES, US

<table>
<thead>
<tr>
<th>Disease</th>
<th>Max. Cases (Year)</th>
<th># 2018</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>206,939 (1921)</td>
<td>1</td>
<td>99.99%</td>
</tr>
<tr>
<td>Invasive Hib (&lt;5 yrs)</td>
<td>20,000 (1984)</td>
<td>38</td>
<td>99.81%</td>
</tr>
<tr>
<td>Measles^</td>
<td>894,135 (1941)</td>
<td>375</td>
<td>98.34%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209 (1968)</td>
<td>2,515</td>
<td>99.13%</td>
</tr>
<tr>
<td>Meningococcal ACWY*</td>
<td>330 (2008)</td>
<td>100</td>
<td>69.70%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>265,269 (1934)</td>
<td>15,609</td>
<td>94.12%</td>
</tr>
<tr>
<td>Polio</td>
<td>21,269 (1952)</td>
<td>0</td>
<td>100.00%</td>
</tr>
<tr>
<td>Rubella</td>
<td>57,686 (1969)</td>
<td>4</td>
<td>99.99%</td>
</tr>
<tr>
<td>Rubella (congenital)</td>
<td>20,000 (1964-65)</td>
<td>0</td>
<td>100.00%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>601 (1948)</td>
<td>23</td>
<td>96.17%</td>
</tr>
</tbody>
</table>

^indigenous 296, imported 79; CDC, https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp
COVID-19, US

Worldwide >67,900,000 cases (>1,551,000 deaths)
US >15,000,000 cases (>20% of world’s total), >284,000 deaths):
- deaths undercounted; the leading cause of death in the US
NC >404,000 cases (>5,600 deaths); hospitalized 2,373

https://coronavirus.jhu.edu/
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

K. Dooling, ACIP 6/24/2020
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 6-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.

4. A typical 15-month process is accelerated by:
   - Planning for infrastructure and distribution before the vaccines are approved or authorized.
   - CDC leading distribution planning with DoD augmentation.

5. 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.

R&D + Preclinical Trials Vaccine Candidate/s Identified
Phase I Clinical Trials
Phase II Clinical Trials
Phase III Clinical Trials
Manufacturing
Distribution

https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed
FDA APPROVAL

Licensure: Process must address statutory & regulatory requirements for approval
- Review of complex clinical, non-clinical & manufacturing data
- Information requests, meetings w/ appl.
- Facilities and trial site inspections
- Safety update with longer-term safety data
- Pharmacovigilance plan
- Plans to satisfy pediatric study reqmts.
- External scientific advisory committee input (VRBPAC), as needed

Emergency use authorization (EUA): Qualifying Criteria:
- Declaration by HHS secretary of emergency situation
- Evidence of effectiveness
  - EUA standard: “May be effective”
- No adequate, approved, & available alternative
- Known/potential benefits outweigh known & potential risks
  - Intended use (i.e., # of individuals treated) & risk uncertainties inform level of effectiveness needed

D. Fink, ACIP 7/29/2020
## 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>Schedule</th>
<th>Age</th>
<th>Size</th>
<th>Trial #</th>
<th>Recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273</td>
<td>Moderna</td>
<td>mRNA</td>
<td>III</td>
<td>2 doses (0, 28d)</td>
<td>≥18 years</td>
<td>30,000 participants</td>
<td>NCT04470427</td>
<td>Enrollment complete</td>
</tr>
<tr>
<td>mRNA-BNT162</td>
<td>Pfizer, Inc./BioNTech</td>
<td>mRNA</td>
<td>III</td>
<td>2 doses (0, 21d)</td>
<td>12-85 years</td>
<td>44,000 participants</td>
<td>NCT04368728</td>
<td>✓</td>
</tr>
<tr>
<td>AZD1222</td>
<td>U of Oxford/AstraZeneca</td>
<td>Viral vector (Non-replicating)</td>
<td>III</td>
<td>2 doses (0, 28d)</td>
<td>≥18 years</td>
<td>40,000 participants</td>
<td>NCT04516746</td>
<td>✓</td>
</tr>
<tr>
<td>Ad26COV-S1</td>
<td>Janssen</td>
<td>Viral vector (Non-replicating)</td>
<td>III</td>
<td>1 dose</td>
<td>≥18 years</td>
<td>30,000 participants</td>
<td>NCT04614948</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>18-84 years</td>
<td>1400 participants</td>
<td>NCT04368988</td>
<td>Enrollment complete</td>
</tr>
<tr>
<td>--</td>
<td>Sanofi/GSK</td>
<td>Protein Subunit</td>
<td>I/II</td>
<td>1 dose or 2 doses (0, 21d)</td>
<td>≥18 years</td>
<td>440 participants</td>
<td>NCT04537208</td>
<td>✓</td>
</tr>
</tbody>
</table>

Bell, B, ACIP, 23 November
## COMPARISON OF mRNA VACCINES

<table>
<thead>
<tr>
<th></th>
<th>Pfizer &amp; BioNTech</th>
<th>Moderna</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>mRNA (virus genetic code)</td>
<td>mRNA (virus genetic code)</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Spike protein, 30 µg</td>
<td>Spike protein, 100 µg</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>Two injections, 21 days apart</td>
<td>Two injections, 28 days apart</td>
</tr>
<tr>
<td><strong>Study participants</strong></td>
<td>~44,000</td>
<td>~30,000</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&gt;16 years</td>
<td>&gt;18 years</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>~95%</td>
<td>~95%</td>
</tr>
<tr>
<td><strong>Long-term storage</strong></td>
<td>-75 °C</td>
<td>-20 °C (up to 6 months)</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Intramuscular (IM)</td>
<td>Intramuscular (IM)</td>
</tr>
<tr>
<td><strong>Stability when mixed</strong></td>
<td>6 hours</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
### CDC REVIEW OF CURRENT COVID-19 VACCINES

# Reactogenicity

<table>
<thead>
<tr>
<th></th>
<th>Moderna¹</th>
<th>Pfizer²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100µg</td>
<td>30µg</td>
</tr>
<tr>
<td>N=15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>—</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (27%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (7%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (25%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Data from published Phase I/II trials

Adults 18–55 years of age

## Systemic symptoms more common after second dose

SUMMARY OF COVID-19 VACCINES LIKELY TO BE AVAILABLE VIA EUA IN DECEMBER

- Pfizer vaccine (mRNA): BNT162b2 – ~43,000 participants – Likely will be reviewed by FDA on Dec. 10
  - Efficacy: 95% against COVID-19 infection beginning 28 days after 1st dose (7 days after 2nd dose), 170 cases of COVID-19 (162 in placebo group, 8 vaccine group); efficacy was consistent across age, gender, race and ethnicity demographics (efficacy in adults over 65 years of age was over 94%); severe COVID-10 reported in 10 subjects (9 placebo, 1 vaccine)
  - Safety: Grade 3 AEs >2% = Fatigue 3.8%, headache 2.0% {following dose 2}

- Moderna vaccine (mRNA): ~30,000 participants – Likely will be reviewed by FDA on Dec. 17
  - Efficacy: 94.1% against COVID-19 infection beginning 14 days after 2nd dose (2nd dose 28 days after 1st dose), 196 cases of COVID-19 (185 in placebo group, 11 vaccine group); efficacy was consistent across age, race and ethnicity, and gender demographics; severe COVID-10 reported in 30 subjects (30 placebo, 0 vaccine)
  - Safety: Grade 3 AEs >2% in frequency after 1st dose included injection site pain 2.7%, and after 2nd dose included fatigue 9.7%, myalgia 8.9%, arthralgia 5.2%, headache 4.5%, pain 4.1% and erythema/redness at the injection site 2.0%. These solicited adverse events were generally short-lived.

Phase II/III randomized clinical trial

Study participants
- Occupation with high risk of SARS-CoV-2 exposure (e.g., healthcare, emergency response)
- Resident in a long-term facility
- Chronic condition (e.g., hypertension; diabetes; asthma; pulmonary, liver, or kidney disease)
- Autoimmune disease requiring therapeutic intervention (or history of)
- Chronic HIV, HCV, or HBV infection that is stable and controlled
- Vaping or smoking (or history of smoking within the prior year)

Post-vaccine safety follow-up = 24 months

1\textsuperscript{st} Primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed $\geq 7$ days after Dose 2

2\textsuperscript{nd} primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed $\geq 7$ days after Dose 2.

https://www.fda.gov/media/144246/download
BNT162b2-INDUCED VIRUS NEUTRALIZATION TITERS

Arrowheads indicate days of vaccination. SARS-CoV-2 50% neutralization titers (VNT50) in immunized participants and HCS. Each serum was tested in duplicate and geometric mean titer plotted. For values below the lower limit of quantification (LLOQ) = 20, LLOQ/2 values were plotted. Group geometric mean titers (values above bars) with 95% confidence interval.

https://www.fda.gov/media/144246/download
BNT162b2-INDUCED VIRUS NEUTRALIZATION TITERS

Figure 8. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Evaluable Immunogenicity Population – Phase 2

Abbreviation: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Note: Data present individual antibody levels.
Note: Numbers within each box denote geometric mean.

Source Data: Table 8. Table Generation: 12MAR2020 (09:22) Source Data: adra Table Generation: 12MAR2020 (09:22)

https://www.fda.gov/media/144246/download
Figure 9. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years

Figure 10. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: >55 Years

Note: Numbers above each bar denote percentage of subjects reporting the reactions with any severity.

Figure 13  Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (19:49) Source Data: aed19efb Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ../data_unblinded/C4591001_Efficacy_FA_164/aed19efb_f001_len41_msd

https://www.fda.gov/media/144246/download
<table>
<thead>
<tr>
<th>Efficacy Endpoint Subgroup</th>
<th>Vaccine Group (as Randomized)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BNT162b2 (30 μg) (N=21669)</td>
<td>n1 b</td>
<td>Surveillance Time c (n2 c)</td>
<td>n1 b</td>
<td>Surveillance Time c (n2 c)</td>
</tr>
<tr>
<td>First severe COVID-19 occurrence after Dose 1</td>
<td></td>
<td>1</td>
<td>4.021 (21314)</td>
<td>9</td>
<td>4.006 (21259)</td>
</tr>
<tr>
<td>After Dose 1 to before Dose 2</td>
<td></td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dose 2 to 7 days after Dose 2</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥7 Days after Dose 2</td>
<td></td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** VE = vaccine efficacy.

- N = number of subjects in the specified group.
- n1 = Number of subjects meeting the endpoint definition.
- Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- n2 = Number of subjects at risk for the endpoint.
- Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

**PFIZER CONFIDENTIAL SDTM Creation:** 17NOV2020 (09:48) **Source Data:** adc19ef Table Generation: 18NOV2020 (17:43)

(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
/nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_pdl1_aai
Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were:

- fatigue: younger group (47.4% vs 59.4%) compared to older group (34.1% vs 50.5%)
- headache: younger group (41.9% vs 51.7%) compared to older group (25.2% vs 39.0%)
- muscle pain: younger group (21.3% vs 37.3%) compared to older group (13.9% vs 28.7%)
- chills: younger group (14.0% vs 35.1%) compared to older group (6.3% vs 22.7%)
- joint pain: younger group (11.0% vs 21.9%) compared to older group (8.6% vs 18.9%)
- fever: younger group (3.7% vs 15.8%) compared to older group (1.4% vs 10.9%)
- vomiting: reported less frequently in the older group and was similar after either dose
- diarrhea: reported less frequently in the older group and was similar after each dose.

https://www.fda.gov/media/144246/download
Figure 11. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years

Note: Number above each bar denotes percentage of subjects reporting the event with any severity.

Pfizer Confidential. SDTM Creation: 17NOV2020 (09:54). Source Data: adf_lighted. Table Generation: 17NOV2020 (16:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: "\public torchvision\visont\Project\Files\3122_3011\3011_culp_max_age_p3"

https://www.fda.gov/media/144246/download
Figure 12  Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: >55 Years

<table>
<thead>
<tr>
<th>Fever</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Chills</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Muscle pain</th>
<th>Joint pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>34</td>
<td>33</td>
<td>29</td>
<td>18</td>
<td>5</td>
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</tr>
<tr>
<td>11</td>
<td>0</td>
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<td>50</td>
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<td>8</td>
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<td>8</td>
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<tr>
<td>8</td>
<td>0</td>
<td>20</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Number above each bar denotes percentage of subjects reporting the event with that severity.

Severity: Green = Mild, Yellow = Moderate, Red = Severe, Purple = Grade 4

Fever: Green = ≥38.0°C to 38.4°C, Yellow = >38.4°C to 38.9°C, Red = >38.9°C to 40.0°C, Purple = >40.0°C

Source Data: adhoc. Table Generation: 17NOV2020 (16:40)
(CutOffDate: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_1A_P3_2MPD2/adce_001_se_max_age_p3

[https://www.fda.gov/media/144246/download](https://www.fda.gov/media/144246/download)
Figure 1. Safety Evaluation Follow-Up Periods in Study C4591001

- Vaccination period
  - 21 days apart
  - X
  - X
- Follow-up period
  - 2 years

- Active surveillance
  - for potential COVID-19 symptoms – telehealth or in-person visit and nasal swab

- Reactogenicity: at least 6000 subjects, at least 500 in each country
- 7 days post dose
- 7 days post dose
- 1 month post dose 2
- 6 months post dose 2
- 2 years post dose 2

- Non-serious AE: all subjects
- Serious AE: all subjects
- Deaths and related SAEs: all subjects

https://www.fda.gov/media/144246/download
Pfizer COVID-19 Vaccine
Distribution and Storage Considerations
Modern COVID-19 Vaccine Distribution and Storage Considerations

Vaccine B

Vaccine Storage
- Vaccine is shipped and stored at freezer temperatures (-25°C to -15°C) until ready for use.
- 6 Months
- 30 Days
- 2°-8°C
- Administration Site(s)
- Refrigerator

Vaccine Thawing
- Vaccine Packaging: 10 doses per vial (10 doses), 10 vials per carton (100 doses), 12 cartons per case (1200 doses)
- 6 Hours
- Room temperature: 1 hour stay
- Freezer: 2 hour freeze
- Refrigerator: 1 hour cool
- 15 minute warm
- Unopened vials can be stored at room temperature for 12 hours
- Once vial is punctured, remaining doses must be discarded after 6 hours.

CHALLENGES IN ASSESSING COVID-19 VACCINES

- Large sample size required (~30,000-40,000 per trial)
- At the time of release the following will NOT be known
  - Duration of protection
  - Long term safety will not available
  - Efficacy and safety in: pregnant women, children and immunocompromised persons
- Correlates of immunity is unknown
- Multiple doses required to achieve protection
- Compatibility with other vaccines (e.g., influenza) is not being assessed
- Potential inability to recruit needed sample size for studies further behind in the pipeline
HOW RNA VACCINES WORK?

Nature 2020;580:576-577
HOW RNA VACCINES WORK?

How an RNA vaccine would work

Scientists take part of the virus genetic code that tells cells what to build and coat it in a lipid so it can enter the body's cells.

This is injected into the patient.

The vaccine enters the cells and tells them to produce the coronavirus spike protein.

This prompts the immune system to produce antibodies and activate T-cells to destroy infected cells.

If the patient encounters coronavirus, the antibodies and T-cells are triggered to fight the virus.

Source: Nature

Authors address the following issues study endpoints in COVID-19 vaccine efficacy trials.

- First, we propose a general set of clinical endpoints to facilitate a harmonized evaluation and comparison of the efficacy of vaccine candidates, overall and across relevant subgroups.
- Second, we consider the pros and cons of various endpoints for use as primary endpoints.
- Third, we recommend adequate follow-up of all participants to enable enhanced sensitivity regarding effects on severe COVID-19 as well as assessment of the longer-term vaccine effect on the set of endpoints, including an assessment of durability of protection.
- Fourth, we recommend including asymptomatic infection as a study endpoint, given that vaccine protection against COVID-19 could be accompanied by a shift toward more asymptomatic SARS-CoV-2 infections, a plausible outcome if the vaccine does not confer sterilizing immunity.

The nesting of endpoints and their partitioning into mutually exclusive and exhaustive categories aid in the interpretation of results (Figure 1, top). Accordingly, for each of the core endpoints described in Figure 1, we advocate reporting point estimates and 95% CIs for vaccine efficacy for prespecified subgroups defined by factors that include sex assigned at birth; age; geographic location; race/ethnicity; and presence or absence of preexisting health problems, such as heart or lung conditions, severe obesity, or diabetes.
Pros and cons of different endpoints for use as the primary COVID-19 vaccine endpoints

- From both a public health perspective and an individual perspective, prevention of severe COVID-19 is perhaps the most important clinical benefit expected from an effective vaccine. There is precedent (for example, dengue, influenza, pertussis, pneumococcal bacteremia, rotavirus, and varicella) that many vaccines confer greater efficacy against severe disease than milder disease. However, severe COVID-19 constitutes a relatively small portion of COVID-19 cases, and incidence varies widely by age, underlying risk, and ethnicity, implying that statistical power to demonstrate adequate vaccine efficacy against the severe COVID-19 endpoint may be lower than that for an endpoint that includes reduction in non-severe COVID-19. For that reason, the broader-encompassing endpoint of COVID-19 symptomatic disease is deemed an appropriate primary endpoint and has been selected as such for all 6 ongoing phase 3 trials and for the Solidarity Vaccines Trial. Moreover, there is consensus to assess severe COVID-19 as a key secondary endpoint.

- Given that detection of safety problems with vaccines is critically important, the statistical analysis plans of the trials use 2-sided 95% CIs for vaccine efficacy for each study endpoint, so the data analyses can detect evidence for a higher rate of any endpoint in the vaccine versus the placebo group.

Figure 2. Hypothetical example of results of a COVID-19 vaccine efficacy trial with 2:1 (vaccine-placebo ratio) randomization, with the analysis done for 147 total COVID-19 cases.

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants, n</th>
<th>Uninfected, n (%)</th>
<th>Infected, n (%)</th>
<th>Among the Infected Trial Participants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asymptomatic (No COVID-19)</td>
</tr>
<tr>
<td>Placebo</td>
<td>10 000</td>
<td>9879</td>
<td>121 (1.21)</td>
<td>45 (37.2)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>20 000</td>
<td>19 801</td>
<td>199 (1.00)</td>
<td>128 (64.3)</td>
</tr>
</tbody>
</table>

Endpoint                  Vaccine Efficacy (95% CI), %
SARS-CoV-2 infection      17.8 (−4.0 to 34.7)
Asymptomatic infection    −42.2 (−104.5 to −0.5)
COVID-19 (symptomatic infection) 53.3 (34.6 to 66.7)
Nonsevere COVID-19         44.7 (19.5 to 62.0)
Severe COVID-19            78.9 (49.6 to 92.0)
BOD                       58.4 (41.2 to 70.2)

BOD = burden of disease; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. Top, Number of uninfected and infected participants in each group, along with breakdown by endpoint for infected trial participants. Bottom, Vaccine efficacy point estimates and 95% CIs against 6 clinical endpoints. The black, dashed vertical line in the forest plot marks the lower 95% confidence bound of 30% given in guidance from the U.S. Food and Drug Administration.
Ethical Principles are Critical When Allocation Needed

<table>
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<tr>
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<th>Mitigate health inequities</th>
<th>Promote transparency</th>
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<td>What groups are at highest risk for SARS-CoV-2 infection, COVID-19 disease, hospitalization, and death? What are the important characteristics of these groups (e.g., size or location) that might inform the magnitude of benefit based on the amount of vaccine available or its characteristics?</td>
<td>Does the allocation plan result in fair and equitable access of the vaccine for all groups? How do characteristics of the vaccine and logistical considerations affect fair access for all persons?</td>
<td>Does the plan identify groups who are disproportionately affected by COVID-19 or who face health inequities resulting from social determinants of health, such as income and health care access? What health inequities might inadvertently result from the allocation plan? Is there a mechanism for timely assessment of vaccination coverage among groups experiencing disadvantage and the possibility for course correction if inequities are identified?</td>
<td>How does development of the allocation plan include diverse input? Are the allocation plan and evidence-based methods publicly available? What is the process for revision of allocation plans based on new information? Is there a mechanism to report demographic data elements for vaccine recipients (e.g., age, race/ethnicity, and occupation) to support equitable vaccination coverage?</td>
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**ETHICAL PRINCIPLES ARE CRITICAL WHEN ALLOCATION NEEDED**

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McClung et al., MMWR Nov 2020
Administration of COVID-19 vaccine will require a phased approach

**Limited Doses Available**
- Projected short period of time for when doses are limited
  - Constrained supply, central distribution
  - Cold chain & handling may require specialized equipment and high throughput

**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

**Key Factors**
- Volume doses available (per month)
- Likely admin strategies

**Likely Admin Strategies**
- Phase 1a: Healthcare personnel
- Phase 1b may include: Essential Workers, High risk Medical Conditions, Adults 65+
Work Group Proposed Interim Phase 1 Sequence

Phase 1c
Adults with high-risk medical conditions
Adults 65+

Phase 1b
Essential workers
(examples: Education Sector, Food & Agriculture, Utilities, Police, Firefighters, Corrections Officers, Transportation)

Phase 1a
Health care personnel
LTCF residents

Time

Dooling K, ACIP, 1 December
# Proposed Groups of Phase 1a Vaccination, CDC

<table>
<thead>
<tr>
<th>Health care Personnel(^1,2) (HCP) (~21 million)</th>
<th>Long-Term Care Facility (LTCF) Residents(^3) (~3M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>Skilled nursing facilities (~1.3 M beds)</td>
</tr>
<tr>
<td>Long-term care facilities</td>
<td>Assisted living facilities (~0.8 M beds)</td>
</tr>
<tr>
<td>Outpatient clinics</td>
<td>Other residential care (~0.9 M beds)</td>
</tr>
<tr>
<td>Home health care</td>
<td></td>
</tr>
<tr>
<td>Pharmacies</td>
<td></td>
</tr>
<tr>
<td>Emergency medical services</td>
<td></td>
</tr>
<tr>
<td>Public health</td>
<td></td>
</tr>
</tbody>
</table>

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1. [https://www.cdc.gov/infectioncontrol/guidelines/healthcare](https://www.cdc.gov/infectioncontrol/guidelines/healthcare)
3. [https://www.cdc.gov/longtermcare/index.html](https://www.cdc.gov/longtermcare/index.html)

Dooling K, ACIP, 1 December
CONSIDERATIONS IN 1a GROUP VACCINATIONS, CDC

Rationale for vaccinating HCP
- As of Nov 30, at least 243,000 confirmed COVID-19 cases among HCP, with 858 deaths
- LTCF modeling demonstrates more cases and death averted at the facility by vaccinating staff compared to vaccinating residents
- COVID-19 exposure (inside and outside the healthcare setting) results in absenteeism due to quarantine, infection and illness. Vaccination has the potential to reduce HCP absenteeism

Rationale for vaccinating older adults in congregate settings
- Long-Term Care Facility (LTCF) residents and staff accounted for 6% of cases and 40% of deaths in the U.S. (Nov 24, 2020)
  - Skilled Nursing Facilities (~1.3M)
    - 496,000 confirmed + probable cases (as of Nov 15, 2020)
    - >69,000 deaths
  - Assisted Living Facilities (~0.8M)
    - 27,965 confirmed + suspected cases (as of Oct 15/2020, based on 23 states)
    - 5,469 deaths (as of Oct 15/2020, based on 20 states)

Dooling K, ACIP, 1 December - see presentation for references
RECOMMENDED MEMBERS OF COVID-19 VACCINE PLANNING GROUP

- Infection diseases
- Infection prevention
- Occupational health
- Pharmacy
- Local public health
- Physician leadership
- Nursing leadership
- Informatics

- Communications
- Diversity/community engagement experts
- Ethicist(s)
- Emergency preparedness
- Human relations/employee relations
- Legal
<table>
<thead>
<tr>
<th>Ethical Principle</th>
<th>Healthcare Personnel (~21 million)</th>
<th>Long-Term Care Facility Residents (~3 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximize benefits &amp; minimize harms</td>
<td>Multiplier effect – protection of HCP and preservation of healthcare capacity</td>
<td>LTCF residents are at high risk for infection, severe disease and death from COVID-19. Prevention may reduce hospital utilization</td>
</tr>
<tr>
<td>Promote justice</td>
<td>HCP provide care in high risk settings and will be essential for vaccine distribution</td>
<td>Federal Pharmacy Partnership Program will facilitate equal access to vaccine across most LTCFs</td>
</tr>
<tr>
<td>Mitigate health inequities</td>
<td>HCP includes broad range of occupations, inclusive of low wage earners, racial and minority groups</td>
<td>Federal Pharmacy Partnership Program will reach LTCF across socioeconomic spectrum</td>
</tr>
</tbody>
</table>
COVID-19 VACCINE SAFETY MONITORING, CDC
<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1a:</strong></td>
<td><strong>Phase 2</strong></td>
<td><strong>Phase 3</strong></td>
<td><strong>Phase 4</strong></td>
</tr>
<tr>
<td><strong>Health care workers at high risk</strong> for COVID-19 exposure based on work duties or vital to the initial COVID vaccine response</td>
<td><strong>Migrant Farm/fishery workers in congregate living without 2+ Chronic Conditions</strong></td>
<td><strong>Workers in industries critical to the functioning of society and at increased risk of exposure who are not included in Phase 1 or Phase 2</strong></td>
<td><strong>Remaining population</strong></td>
</tr>
<tr>
<td>• High risk of exposure is defined as those caring for COVID-19 patients, cleaning areas where COVID-19 patients are admitted, performing procedures at high risk of aerosolization (e.g., intubation, bronchoscopy, suctioning, invasive dental procedures, invasive specimen collection, CPR), handling decedents with COVID, administering vaccine in initial closed or targeted vaccination clinics.</td>
<td>• Incarcerated individuals without 2+ Chronic Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Population includes: nurses, physicians, respiratory techs, dentists, hygienists, nursing assistants, environmental services staff, EMT/paramedics, home health workers, personal care aids, community health workers, health care trainees (e.g., medical students, pharmacy students, nursing students, etc.), morticians/funeral home staff, pharmacists, public health nurses, public health and emergency preparedness workers who meet the above definition of &quot;high risk of exposure.&quot;</td>
<td>• Homeless shelter residents without 2+ Chronic Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long Term Care staff and Residents</strong> (e.g., Skilled Nursing Facilities, adult care homes, family care homes, and group homes; individuals with intellectual and developmental disabilities who receive home and community-based services and the workers directly providing those services)</td>
<td>• Frontline workers at high or moderate risk of exposure without 2+ Chronic Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 1b:</strong></td>
<td><strong>Phase 2</strong></td>
<td><strong>Phase 3</strong></td>
<td><strong>Phase 4</strong></td>
</tr>
<tr>
<td><strong>Adults with high risk of complications</strong> per CDC and staff of congregate living settings <strong>Operationally prioritize settings based on risk of exposure</strong></td>
<td><strong>Phase 1</strong></td>
<td><strong>Phase 2</strong></td>
<td><strong>Phase 3</strong></td>
</tr>
<tr>
<td>• Migrant farm and fisheries workers in congregate housing with 2+ Chronic Conditions* or ≥ age 65</td>
<td><strong>Incarcerated individuals with 2+ Chronic Conditions</strong> or ≥ age 65 and jail and prison staff</td>
<td><strong>Homeless shelter residents with 2+ Chronic Conditions</strong> &gt; 65 and homeless shelter staff</td>
<td><strong>Remaining population</strong></td>
</tr>
<tr>
<td>• Incarcerated individuals with 2+ Chronic Conditions* or ≥ age 65 and jail and prison staff</td>
<td></td>
<td></td>
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<tr>
<td>• Homeless shelter residents with 2+ Chronic Conditions* &gt; 65 and homeless shelter staff</td>
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<td></td>
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<tr>
<td>• Health care workers not included in Phase 1A with 2+ Chronic Conditions</td>
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</tr>
<tr>
<td>• Frontline workers with 2+ Chronic Conditions at high risk of exposure (e.g., firefighters, police, workers in meat packing plants, seafood and poultry not in congregate housing, food processing, preparation workers and servers, manufacturing, construction, funeral attendants and undertakers not included in Phase 1A, transportation workers, retail workers (including grocery store workers), membership associations/org staff (e.g., religious orgs), education staff (e.g., child care, K-12 or IHE) and workers in government, public health, emergency management and public safety whose functioning is imperative to the COVID-19 response)</td>
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<tr>
<td>• Other Adults with 2+ Chronic Conditions*:</td>
<td>• Other adults age 18-64 with one chronic condition*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Migrant Farm/fishery workers in congregate living without 2+ Chronic Conditions</td>
<td>• 65+ year olds with one or no chronic conditions*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Incarcerated individuals without 2+ Chronic Conditions</td>
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<td>• Homeless shelter residents without 2+ Chronic Conditions</td>
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<tr>
<td>• Frontline workers at high or moderate risk of exposure without 2+ Chronic Conditions</td>
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<td></td>
<td></td>
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<tr>
<td>• Other Adults without 2+ Chronic Conditions:</td>
<td>• K-12 students (if data from clinical trials), college students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Migrant Farm/fishery workers in congregate living without 2+ Chronic Conditions</td>
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<td>• Incarcerated individuals without 2+ Chronic Conditions</td>
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<td>• Other Adults without 2+ Chronic Conditions:</td>
<td></td>
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**VACCINE DISTRIBUTION PRIORITIZATION FRAMEWORK, NC**

Risk-based prioritization based on National Academy of Medicine Framework for Equitable Allocation of COVID-19 and CDC Advisory Committee Immunization Practice. Refined by input by North Carolina Institute of Medicine Vaccine Advisory Committee. May be revised based on Phase III clinical trial safety and efficacy data and further federal guidance.
COVID-19 VACCINE: KEY PLANNING CONSIDERATIONS

- **Timeline**
  - Approval of first COVID-19 vaccine anticipated December 10/11
  - Target go-live date: December 14, 2020

- **Distribution**
  - Distribution initially limited to only hospitals and local health departments

- **Vaccine storage, handling and preparation complexities**
  - Ultra-low cold freezers (-70°C), short stability and multi-dose vial packaging
  - Retain vaccine near site of administration

- **Limited initial supply**
  - Anticipated to fall short of initial eligibility

- **Phased eligibility to receive the vaccine**
  - Phase 1a – health care personnel and LTCF

- **Documentation requirements**
  - Double documentation – Epic and state vaccine management system – due to inability to integrate systems
  - 22 data reporting elements required for each individual vaccinated

- **Possible need for observation post vaccination**

- **Security concerns**
  - Theft
  - Irate/violent individuals – limited supply and eligibility

- **UNC-MC designation as “open” vaccination site**
PLANNING PROGRESSING RAPIDLY DESPITE UNKNOWN VARIABLES

- Unknown recipient volume
  - Healthcare personnel (HCP): Unknown how many will want the vaccine
  - Non-employee (HCP): Unknown volume who will utilize UNCMC for vaccination

- Unknown vaccine volume UNCMC will receive
  - Pfizer: expected to receive as bulk supply (minimum quantity: 975)

- Unknown date of vaccine availability

- Documentation (CVMS)
  - State system is not yet live (go-live: December 10)
  - Limited functionality at launch (no Spanish language instructions/forms available till at least mid-January)

- Observation of persons post-immunization
  - Specific requirements unknown until EUA is released (likely 15 min, possibly 30 min)
Current and Anticipated Future Requests

Current Requests
- Advocacy and broad communication regarding receiving the vaccine
- Necessity to continue with Universal Pandemic Precautions
- Translator services (newly identified need)

Anticipated Requests for Scale-up
- Space: already exploring additional options for increased capacity
- Labor: compiling campus support availability and needs for future phases
UNC HEALTH COVID-19 VACCINE IMPLEMENTATION

- UNC Shared Service Center Pharmacy has purchased a low temperature freezer capable of storing >30,000 doses
- UNC will adhere to EUA and DHHS priority algorithm (as required by law)
  - If vaccine supply is limited, UNC will provide vaccine per DHHS algorithm using a UNC-CH developed priority list until supply exhausted; once UNC receives a resupply immunization of designated groups will be reinitiated
  - The EUA vaccine information sheet will need to be provide to each vaccinated person*
  - For non-UNC HCP or patients, we can except a self-report of meeting the priority requirements*
  - Receipt of vaccine will be voluntary for UNC-CH healthcare personnel (i.e., not mandatory)
- Each UNC Health affiliate will receive its own vaccine supply from the State, and be responsible for administration and documentation*
  - Likely will need limited locations for vaccine administration (due to temperature requirements)
  - Ancillary vaccine administration kits will also be provided (needles, syringes, masks and face shields)
- Vaccine will be provided free. Ability to charge an administration fee is under consideration*
- DHHS has developed a vaccine “portal” – All HCP providing a COVID vaccine will be required to enter the portal and provide specific data on the person vaccinated (exact information required to be entered to be provided)*
- Vaccine administration to nursing homes (NHs) will be accomplished via retail pharmacies (NHs can sign up via CDC NHSN)*; does not include UNC Health pharmacies

*Per discussion with NC DHHS
PROBLEMS AND PROPOSED SOLUTIONS FOR VACCINE STORAGE AND ADMINISTRATION

Pharmacy issues
- Storage (-80 °C to -60 °C) = Purchase ultra-low storage freezer
- Transport = Assure ability to purchase dry ice
- Track storage temperature

Administration issues
- Strictly adhere to FDA EUA = Training of pharmacy and nursing staff in administration
- Multi-dose vial (5 doses, 6 hour half life when reconstituted) = Assure ability to use all doses prior expiration
- Multi-dose vial has NO preservatives: Aseptic management, training on new needle PLUS new syringe for each dose, ideally have vaccine drawn up by pharmacy technicians
- Multi-dose vial once reconstituted must be stored between 2 °C and 25 °C = Assure availability of temperature control
- Stagger vaccine receipt for persons working in same location/specialty so as to maintain workforce if side effects develop
- Pfizer and Moderna vaccines CANNOT be intermixed = Use only 1 vaccine per clinic or at minimum have separate vaccine lines/rooms for each vaccine

https://www.fda.gov/media/144246/download
IMPROVING VACCINE COVERAGE:
BARRIERS AND SOLUTIONS

- Access to vaccine, inconvenience
  - Off-hours clinics
  - Provision of adequate staff and resources including availability of Spanish speaking vaccinators

- Cost
  - Vaccine will be provided free under the EUA
  - Eliminate administration charges

- Concerns for vaccine adverse events, opposition to vaccines
  - Targeted education, including specific information to dispel vaccine myths
  - Coverage of adverse events under Worker’s Compensation
  - Evaluation of side-effects in occupational health (no charge to HCP)

- Other
  - Strong and visible administrative leadership
  - Visible vaccination of key leaders (within EUA criteria)
  - Individual counseling by trusted healthcare provider

Adapted from Talbot TR, et al. ICHE 2005;26:882-890
IMPROVING VACCINE COVERAGE: BARRIERS AND SOLUTIONS

- Notifications and education
  - Education and messaging directed at HCP who would receive the vaccine including in the person's native language
  - Education directed at vaccinators regarding effectiveness and safety of the vaccine
  - Wide spread communications to HCP regarding vaccine availability
  - Automatic reminders via text, email, phone, etc. to HCP reminders about 2nd dose
  - Automatic reminders to healthcare facility if HCP miss the 2nd dose
  - Provision of vaccine wallet sized “card” indicating date of 2nd dose

- Others
  - Use of a standing order to speed vaccine delivery
  - Continuous monitoring of HCP coverage

Adapted from: CDC/ACIP. MMWR 2011;60(RR-2)
PROPOSED ALGORITHM FOR EVALUATION OF HCP WHO DEVELOP SYMPTOMS POST-VACCINE

- Post-Immunization symptoms that are unlikely to be due to vaccine receipt – COVID-19 test recommended (onset of new or worsening symptoms/signs as follows):
  - Loss of sense of smell and/or taste, Sore throat, Congestion or rhinorrhea, cough, shortness of breath, nausea or vomiting, and/or diarrhea

- Post-Immunization symptoms that may be due to vaccine receipt or COVID-19 – COVID-19 test; use clinical judgement:
  - Isolated fever (i.e., no other symptoms/signs), headache, fatigue, arthralgia, myalgia

- Post-Immunization symptoms that are most likely to be due to vaccine receipt – COVID-19 test not recommended:
  - Immediate hypersensitive reaction following vaccine receipt including anaphylaxis; and, signs/symptoms at immunization site such as erythema, swelling, pain
THANK YOU FOR ALL YOU DO TO SUPPORT UNC HEALTH DURING THIS PANDEMIC