Vaccines for the Prevention of COVID-19:  
An Unprecedented Need  
An Unprecedented Response  
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Disclosures

None
Outline

• Vaccine and Trial Design
• mRNA Vaccines (Pfizer & Moderna)
• Adenoviral Vector Vaccines (Janssen & AstraZeneca)
• Protein Subunit Vaccines (Novavax)
• Unanswered Questions
• Vaccine Hesitancy & Roll-Out
Vaccine and Trial Design
Potential SARS-CoV-2 Vaccine Platforms

Current stage: Development of vaccine candidates and pre-clinical testing

- RNA vaccines
- DNA vaccines
- Recombinant protein vaccines
- Vectored vaccines
- Inactivated vaccines
- Live attenuated vaccines

Spike protein (S)
Envelope protein (E)
Matrix protein (M)
Nucleoprotein (N) and viral RNA
Receptor binding domain

not to scale
SARS-CoV-2 Spike: Two distinct conformations

Vaccine Design:
- S proteins – stabilized in the prefusion “up” position.
  - Binds ACE2 with higher affinity than SARS-CoV-2

## US Phase 3 COVID Vaccine Pipeline

<table>
<thead>
<tr>
<th>Phase 3 Studies</th>
<th>Study N</th>
<th>Platform</th>
<th>Start Date</th>
<th>First Data Readout</th>
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<tbody>
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<td>Moderna</td>
<td>30,000</td>
<td>RNA</td>
<td>July 2020</td>
<td>November 2020</td>
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<td>44,000</td>
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<td>AstraZeneca</td>
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<td>Janssen</td>
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<td>Sanofi</td>
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<td>Protein subunit</td>
<td>Delayed</td>
<td>Delayed</td>
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</table>

*Not a COVID-19 Prevention Network (CoVPN) study
The Vaccine Production Process

1. Research
   Normal: 2–4 years
   Accelerated: 6 months

2. Preclinical preparation
   Normal: 2 years
   Accelerated: 6 months

3. Clinical trials
   Normal: Up to 5 years
   Accelerated: 1.5 years

4. Approval
   Normal: 1 year
   Accelerated: 6 months

5. Manufacturing
   Normal: 2 years
   Accelerated: 3–6 months

6. Distribution
   Normal: 3–6 months
   Accelerated: 1 month

Normal vaccine production timeline: 8–15 years
Vaccine development target under Warp Speed: 12-18 months
Pfizer/BioNTech SE Vaccine
Pfizer Vaccine Mode of Action

1. mRNA formulated in LNP enters cell
2. mRNA is released
3. Spike protein is made and processed
4. APCs present S protein fragments

CD4+ Helper T Cell

B Cell

Virus Neutralizing Antibodies
Bind Spike proteins and prevent virus infection of human cells

Pfizer Vaccine Mode of Action

1. mRNA is formulated in LNP and enters the cell.
2. mRNA is released.
3. Spike protein is made and processed.
4. APCs present S protein fragments.

- Activates T and B cells
- CD4+ Helper T Cell
- CD8+ Cytotoxic T Cell
- Eliminates virus infected cells; potentially increases length of protection
- B Cell
- Memory T and B cells
- Virus Neutralizing Antibodies
  - Bind Spike proteins and prevent virus infection of human cells

**Pfizer mRNA Vaccine: Phase 2/3**

- BNT162b2 encodes full-length SARS-CoV-2 spike, stabilized in the prefusion conformation
- Trial locations: approximately 150 clinical trial sites in 6 countries, including 39 US States
- Eligibility: Age ≥12 years (stratified 12-15, 16-55, or >55)

**Randomization 1:1 Vaccine to Placebo (N=44,000)**


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Pfizer: Local and Systemic Reactions within 7 days of Vaccine or Placebo

Efficacy of Pfizer mRNA vaccine

VE 95% ≥7 days after 2\textsuperscript{nd} dose
Moderna Vaccine
**Moderna Phase III / Cove Study – Study Overview**

- Phase III study assessing the safety, efficacy and immunogenicity of **mRNA-1273**
- mRNA-1273 encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in a lipid nanoparticle.

[Randomization 1:1 Vaccine to Placebo N=30,000](https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf)
Solicited Local Adverse Events

Baden LR, et al. NEJM, DOI: 10.1056/NEJMoa2035389

Delayed injection site reactions ≥day 8 (0.8% 1st & 0.2% 2nd dose)
Solicited Systemic Adverse Events

Baden LR, et al. NEJM, DOI: 10.1056/NEJMoa2035389
Vaccine Efficacy of mRNA-1273

A Per-Protocol Analysis

<table>
<thead>
<tr>
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<th>Vaccine Efficacy (95% CI)</th>
<th>Incidence Rate (95% CI)</th>
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<tr>
<td></td>
<td>%</td>
<td>per 1000 person-yr</td>
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<tr>
<td>mRNA-1273</td>
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<td>3.3 (1.7–6.0)</td>
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No. at Risk

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<th>mRNA-1273</th>
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</table>

Baden LR, et al. NEJM, DOI: 10.1056/NEJMoa2035389
mRNA Activity Against Circulating Variants

- Susceptibility of B.1.1.7, B.1.351, and WT viruses to neutralization by vaccinee sera (N=22)
  - 12 Moderna (2 doses – day 43)
  - 10 Pfizer (2 doses – day 28 or later)

- No loss of NAb activity against B.1.1.7
- Every sample had decreased activity against B.1.351
  - 12.4-fold for Moderna / 10.3-fold for Pfizer
- P.1/501Y.V3 (Brazilian variant) contains 3 mutations at same RBD residues as B.1.351 – findings likely similar for this variant.

Johnson and Johnson (J&J) and Janssen Pharmaceutical research teams
Janssen Phase III – Study Overview

- Phase III study assessing the safety, efficacy and immunogenicity of Ad26.COV2.S
- Ad26.COV2.S is a replication-incompetent adenovirus type 26 (Ad26) vector encoding SARS-CoV-2 spike (S) protein.
- Earlier studies: side effects generally mild/moderate and resolved within 1-7 days

Randomization 1:1 Vaccine to Placebo
N=40,000

Countries Participating

<table>
<thead>
<tr>
<th>US</th>
<th>South Africa</th>
<th>Brazil</th>
<th>Chile</th>
<th>Colombia</th>
<th>Peru</th>
<th>Mexico</th>
<th>Argentina</th>
<th>Philippines*</th>
<th>Ukraine*</th>
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</table>
Janssen Phase III Enrollment (N=43,783)

- Enrolled 44% in U.S., 41% in Central/South America and 15% in South Africa
  - 45% Female
  - 34% > age 60

- Race/Ethnicity
  - **Global**: 59% White; 45% Hispanic; 19% Black/African American; 9% Native American; 3% Asian
  - **US**: 74% White; 15% Hispanic; 13% Black/African American; 1% Native American; 6% Asian

- 41% with comorbidities: Obesity (28.5%), DM (7.3%), HTN (10.3%), HIV (2.8%), and other immunocompromised conditions
Janssen Phase III Interim Analysis (1/29/2021)

28 Days after vaccination:

• **VE 85%** in preventing severe COVID disease in all geographies.
  • 100% protection against COVID-related hospitalization and death
  • Protection generally consistent across race and age groups (34% >60 yrs), and across all variants and regions studied.

• In US, **VE 72%** in preventing moderate and severe disease (66% avg globally).

• **VE 89%** against severe disease caused by the South African B.1.351 Variant.
  • VE 57% against any symptomatic COVID-19 caused by B.1.351

• Vaccine well tolerated with no notable safety signals
  • Lower reactogenicity in older (age ≥ 65) vs. younger (18-64) adults
  • Most frequent AEs were HA, chills, fatigue, and myalgias (all 1.5-2.1%)
Janssen (J&J) Timeline

• Phase 3 Interim Analysis: Jan 29, 2021
• FDA submission for EUA: Feb 4, 2021
• FDA’s Vaccines and Related Biologics Product Advisory Committee (VRBPAC): Feb 26, 2021
• Anticipate EUA approval early March
AstraZeneca Vaccine
AstraZeneca Phase III / CoVPN 3002 – Study Overview

- Phase III study assessing the safety, efficacy and immunogenicity of **AZD1222**.
- AZD1222 is a replication-deficient simian adenovirus vaccine vector encoding full-length SARS-CoV-2 Spike protein.
- Earlier studies: side effects were generally mild or moderate and resolved within 1-7 days.

**Randomization 2:1** Vaccine to Placebo (N=30,000)
VE of AZD1222 against Symptomatic COVID-19 (UK/Brazil)

- Based on interim analysis of pooled data from 2 ongoing trials in adults receiving 2 doses (vs. meningococcal vaccine)
  - COV002 – Phase 2/3, age 18+ in UK (total enrolled 10,673)
  - COV003 – Phase 3, age 18+ in Brazil (total enrolled 10,002)
- **VE 70.4%** - Combines SD/SD and LD/SD, variable dosing intervals
  - Only 6% ≥65 years old - too few cases to evaluate VE
  - VE = 73.43% in participants with ≥1 co-morbidity
  - No serious safety events
  - Longer dosing interval (9-12 wks) appeared to improve immunogenicity (small numbers, large CI)
- So African Study: VE may be negligible against B.1.351 variant

Voysey M, et al. Lancet 2020; DOI: [https://doi.org/10.1016/S0140-6736(20)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1)
WHO Grants Emergency Authorization for AstraZeneca (Feb 15, 2021)

- WHO’s Strategic Advisory Group of Experts on Immunization (SAGE):
  - Assessed the quality, safety and efficacy data, risk management plans and programmatic suitability, such as cold chain requirements
  - The newly approved vaccines are produced by AstraZeneca-SKBio in South Korea and the Serum Institute of India
  - Recommended dosing interval of 8-12 weeks
  - AZ currently approved in >50 countries, including Britain, India, Argentina, Australia, and Mexico.
    • Including use in countries where new variants prevalent (i.e., B.1.351)

Protein Subunit (Novavax)
Novavax: Protein Subunit Vaccine

• Modified spike gene inserted into a baculovirus – allowed to infect moth cells
• Infected cells produce spike proteins – assembled into nanoparticles
• Spike nanoparticles injected into people with honeycomb-like molecules, derived from plants (adjuvant) to attract immune cells to site of injection


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Novavax Phase III / PREVENT-19 – Study Overview

- Phase III study assessing the safety, efficacy and immunogenicity of NVX-CoV2373
- NVX-CoV2373 contains a full-length, prefusion stabilized rS protein and Matrix-M adjuvant
- Phase 1-2: reactogenicity absent or mild in majority, no serious AE

Novavax: UK Phase 3 Results

- Primary Endpoint: PCR confirmed, symptomatic COVID-19, ≥7 days after 2nd vaccination in participants seronegative (to SARS-CoV-2) at baseline
  - **VE 89.3%** (75.2-95.4) in preventing symptomatic COVID (61 of 62 cases were mild/mod)
  - **VE 95.6%** against the original Wuhan strain and **85.6%** against the UK variant strain (>50% of cases were 501Y.V1/ B.1.1.7)


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Novavax: South African Phase 2b Clinical Trial

- Enrolled >4,400 participants Aug 2020 – mid Jan 2021 (B.1.351 increased from <5% to ~80%)
- 44 COVID-19 events to date – 93% of those sequenced (25/27) are 501Y.V2/B.1.351
- **VE 60%** (19.9-80.1) for prevention of mild, mod and severe disease in participants without HIV, 49.4% (6.1-72.8) among participants with and without HIV

- Baseline seropositive for SARS-CoV-2: 30.2% (vaccine ≈ placebo, not included in primary analysis)
  - Attack rate was equal among seropositive and seronegative placebo recipients (dose 1 & 2)
  - No evidence of resistance from infection with previous recovered COVID infection

Unanswered Questions
Potential for Vaccine Associated Disease Enhancement

- No predictive *in vitro* or animal models of VADE in SARS-CoV-2
- Need phase 3 efficacy trials and post-licensure surveillance

COVID-19 Vaccines in Persons with HIV

- Pfizer, Moderna, Janssen and AstraZeneca all enrolled persons with HIV
  - Overall – relatively small numbers (200-300 per 30,000 to 40,000 study)
  - Participants were in general stable with CD4 >200-300 and durably suppressed
  - Pfizer analysis (NEJM) did not include the 196 people with HIV
  - AstraZeneca UK/Brazil analysis (Lancet) did not include the 160 people with HIV
  - Moderna enrolled 176 people with HIV – symptomatic COVID in 1 placebo/ 0 vaccine recipients. No unusual safety concerns.

- It is possible that people with HIV may not respond as well to COVID vaccines – if the vaccine elicits a weaker immune response.
- However, people with HIV may also be at greater risk for severe COVID-19
- Safety and efficacy data specific to this group are not yet available

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Unanswered Questions

• What are the immune correlates of protection for SARS-CoV-2?
  • Can these serve as surrogate endpoints for future vaccine trials?
• Will less common AE or emerge in longer term follow-up?
• How likely is enhanced disease on exposure to the virus during follow-up?
• Does vaccination prevent asymptomatic infection? (and Transmission)
  • Post-vaccination - need for continued masks/social distancing
• Vaccine safety and efficacy in other populations?
• What is the durability of vaccine-induced immunity?
• Will circulating variants compromise COVID-19 vaccine efficacy?
Vaccine Hesitancy & Roll-Out
Vaccine Allergic Reactions

**Pfizer (first 10 days)**
- Approx. 1.9 million doses of vaccine administered
  - 21 cases of severe (life-threatening) allergic reaction: 11.1 cases/million doses

**Moderna (first 20 days)**
- Approx. 4.0 million doses of vaccine administered
  - 10 cases of severe (life-threatening) allergic reaction: 2.5 cases/million doses

People who have had an immediate allergic reaction (of any severity) to an mRNA COVID-19 vaccine or any of its components may be at increased risk

**Common, non-life threatening:** rash, itchy sensations in the mouth and throat, sensations of throat closure, and respiratory symptoms.

[https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html](https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html)

MMWR Dec 14-23. DOI: [http://dx.doi.org/10.15585/mmwr.mm7002e1](http://dx.doi.org/10.15585/mmwr.mm7002e1)

MMWR Jan 22, 2021. DOI: [http://dx.doi.org/10.15585/mmwr.mm7002e1](http://dx.doi.org/10.15585/mmwr.mm7002e1)
Clinical Considerations for COVID-19 Vaccination

- **No contraindications:**
  - Immunocompromised persons, autoimmune conditions, pregnant and lactating, h/o Guillain-Barré syndrome, persons with dermal fillers, anaphylaxis to non-injectables (i.e., food, bees)
  - Persons with current/prior SARS-CoV-2:
    - Defer until recovered from acute illness and criteria met to discontinue isolation. While vaccine supply limited, may temporarily delay vaccination.
  - Coadministration w/other vaccines:
    - Minimum interval of +/-14 days any other vaccine. Shorter period if benefits of other vaccine outweigh potential unknown risk of coadministration (i.e., measles or Hep A during outbreak)

- **Contraindications:**
  - Anaphylaxis or immediate allergic reaction (within 4 hrs) of any severity to previous mRNA vaccine or any of its components
  - Immediate allergic reaction of any severity to polysorbate or polyethylene glycol (PEG)

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html
Management of Reactogenicity

- Side effects of the vaccine typically start within 12 - 24 hours of administration and last 24-48 hrs
- Prophylactic administration of antipyretic or analgesic medications (e.g., acetaminophen, NSAIDS) to prevent post-vaccination symptoms is not recommended
  - Unclear if antipyretic analgesics may be associated with blunted vaccine immune responses*
- Antihistamines prior to vaccination to prevent allergic reactions are not recommended
  - These do not prevent anaphylaxis and may mask cutaneous symptoms – may delay diagnosis and management of anaphylaxis.
- Antipyretic or analgesic medications can be taken for the treatment of post-vaccination symptoms if medically appropriate.

Surveillance of Vaccine Safety

V-SAFE Vaccine Safety Monitoring App
• V-SAFE is patient-facing passive reporting system
• After vaccination, patients will receive a V-safe information sheet with instructions on how to register and use V-safe.

Vaccine Adverse Event Reporting System (VAERS)
• VAERS is provider-facing passive reporting system for adverse events (or errors) following vaccination
• Only clinically important adverse events are reported (info@VAERS.org)

VaxText™ COVID-19 Vaccination 2nd Dose Reminder
Overcoming Vaccine Hesitancy

• Misinformation and disinformation

• Lack of trust in healthcare system
  • History of mistreatment and unethical experimentation
  • For both Black and Latinx Americans, confidence in vaccine safety and effectiveness are greatest predictors of vaccine intention

• Concerned that the process moved too fast
  • Vast majority of AE occur within 42-60 days of immunization
  • Review process is transparent

• Religious Concerns
  No human fetal/stem cell tissue used in the mRNA vaccine development
Future Directions

• Vaccine development and widespread implementation - best hope for pandemic control

• To overcome vaccine hesitancy and build community trust, we must
  ➢ Engage in effective messaging that is open, honest, and comprehensive
  ➢ Directly address the deep historical traumas that have created high levels of distrust in the government, healthcare systems and COVID-19 vaccines
  ➢ Highlight how vaccination can save Black lives and strengthen Black communities
  ➢ Support rapid and equitable vaccine distribution

• Continue to adhere to non-pharmacologic interventions
Thank You for Your Attendance!

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