COVID-19 Vaccines: Progress and Priorities

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Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
December 10, 2020
NIH Research on Coronavirus Disease 2019 (COVID-19)

- Therapeutics
- Vaccines
- Diagnostics
- Research Resources
- Natural History
- Basic Research
NIH Research on Coronavirus Disease 2019 (COVID-19)

Therapeutics

Diagnostics

Natural History

Research Resources

Basic Research

Vaccines
Time to Develop a Vaccine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year of Discovery</th>
<th>Year of Vaccine Development</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid</td>
<td>1884</td>
<td>1989</td>
<td>105 years</td>
</tr>
<tr>
<td>Polio</td>
<td>1906</td>
<td>1948</td>
<td>42 years</td>
</tr>
<tr>
<td>Pertussis</td>
<td>1973</td>
<td>2006</td>
<td>33 years</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1984</td>
<td>2006</td>
<td>22 years</td>
</tr>
<tr>
<td>HPV</td>
<td>1965</td>
<td>1981</td>
<td>16 years</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1953</td>
<td>1963</td>
<td>10 years</td>
</tr>
<tr>
<td>Measles</td>
<td>1965</td>
<td>1981</td>
<td>10 years</td>
</tr>
<tr>
<td>COVID-19</td>
<td>2020</td>
<td>2021</td>
<td>11 months</td>
</tr>
</tbody>
</table>

Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine. Adapted from AVAC.
# Primary USG Vaccine Development Stakeholders

<table>
<thead>
<tr>
<th>Organization</th>
<th>Responsibilities</th>
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</thead>
<tbody>
<tr>
<td>NIH NIAID</td>
<td>Basic and clinical research on vaccine candidates.</td>
</tr>
<tr>
<td></td>
<td>Limited manufacturing and advanced development for warfighters.</td>
</tr>
<tr>
<td>ASPR</td>
<td>Advanced clinical development and manufacturing support via contracts.</td>
</tr>
<tr>
<td></td>
<td>ASPR oversees Strategic National Stockpile.</td>
</tr>
<tr>
<td>FDA</td>
<td>Advises on data requirements for each stage of vaccine development.</td>
</tr>
<tr>
<td></td>
<td>Reviews preclinical and clinical data packages for potential authorization or licensure.</td>
</tr>
<tr>
<td>CDC</td>
<td>Via Advisory Committee on Immunization Practices, recommends who is vaccinated, when and with what vaccine.</td>
</tr>
<tr>
<td></td>
<td>Shapes prioritization for immunization when quantities are scarce.</td>
</tr>
</tbody>
</table>
Pre-COVID-19 USG Vaccine Development Model

Early concept and product development
- NIH/DoD

Advanced development
- BARDA

Commercial manufacturing
- Industry

Regulatory review
- FDA

Industry

FDA consultation and interim review
Operation Warp Speed
Operation Warp Speed Organizational Structure

Overall lead (Moncef Slaoui)
COO (General Gustave Perna)

Diagnostics (Tromberg)

Therapeutics (Woodcock)

Vaccines (Hepburn)

Vaccine Development (Mascola)

Supply & Manufacturing (Angelastro)

Delivery & Admin. (Messonier)
Core Components of Vaccine Development and Delivery

- Developing vaccine construct – antigen and platform
- Manufacturing
- Clinical Trials
- Regulatory review and immunization policy
- Distribution and vaccinations
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Vaccine Construct

Vaccine Antigen

Vaccine Platform
History of the NIAID Vaccine Research Center
Meeting at the White House to Discuss AIDS Research, Dec. 3, 1996
"If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it... Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade."
VRC Research: From HIV to Zika

- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- Coronaviruses
- RSV
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika
VRC Research: From HIV to Zika

- HIV
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- RSV
- Tuberculosis
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Global Respiratory Syncytial Virus (RSV) Mortality and Morbidity

Global Annual Burden of Disease

- 33.8 Million Acute Lower Respiratory Infections
- 3.4 Million Hospitalizations
- 66,000-200,000 Deaths

- Causes 6.7 percent of deaths in children aged 1 month-1 year
- Nearly ¼ of children under age one hospitalized with RSV will develop asthma

F Protein Adopts Two Primary Conformations: Pre- and Post-Fusion

Pre-Fusion (Unstable)

Prefusion

Receptor

Post-Fusion (Stable)
Broadly Neutralizing Antibodies Bind More Readily to the Pre-Fusion Form

Pre-Fusion F Protein Stabilized Using Structure-Based Vaccine Design

Pre-Fusion F Protein

Vaccine immunogen

Stabilization

Structure-Based RSV Vaccine Shows Promise in Phase 1 Trial – “Precision Vaccinology”

- RSV fusion glycoprotein stabilized in prefusion conformation (DS-Cav1) used as immunogen

![Image of pre-fusion F protein stabilization]

- 1 dose of DS-Cav1 induced large increases in RSV-neutralizing antibodies that were sustained for several months

**A Proof of Concept for Structure-Based Vaccine Design Targeting RSV in Humans**

MC Crank, BS Graham et al., for the VRC 317 Study Team

*Science* August 2, 2019
VRC Research: From HIV to Zika

- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- **Coronaviruses**
- RSV
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika
Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen

Novel Human Virus? Pneumonia Cases Linked to Seafood Market in China Stir Concern

By Dennis Normile

Chinese Researchers Reveal Draft Genome of Virus Implicated in Wuhan Pneumonia Outbreak

Jon Cohen
Mutations

SARS-CoV-2 Spike protein
Pre-fusion form (Unstable) → SARS-CoV-2 Spike protein
Pre-fusion form (Stable)
Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation

D Wrapp, N Wang, KS Corbett, JA Goldsmith, C-L Hsieh, O Abiona, BS Graham, JS McLellan

Viral membrane

Atomic-level structure of SARS-CoV-2 spike protein. Receptor binding domain is colored green.
Using established immunogen design, the release of SARS-CoV-2 sequences triggered immediate rapid manufacturing of an mRNA vaccine expressing the prefusion-stabilized SARS-CoV-2 spike trimer.
Vaccine Platform Technologies

Genetic immunization (DNA and RNA vaccines)
- SARS, MERS, West Nile, Zika, RSV

Nanoparticles (viral protein on particle)
- Influenza, Malaria, RSV

Viral vector (e.g., VSV, adenovirus)
- Ebola, Marburg, Zika

Virus-like particle (VLP) (no RNA or DNA; non-infectious)
- Chikungunya, Zika, WEVEE

Recombinant protein
- Influenza, RSV

Adjuvants (e.g., AS01, MF59)

Selected Examples
## COVID-19 Vaccines in Operation Warp Speed Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Moderna</td>
<td>mRNA</td>
<td>mRNA: rapid manufacturing facilitating efficient move to clinic, highly immunogenic</td>
</tr>
<tr>
<td>BioNTech/Pfizer</td>
<td>mRNA</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Adenovirus vector</td>
<td>Adenovirus: rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe</td>
</tr>
<tr>
<td>Janssen</td>
<td>Adenovirus vector</td>
<td></td>
</tr>
<tr>
<td>Novavax</td>
<td>Recombinant protein + adjuvant</td>
<td>Adjuvanted recombinant protein: not as fast to manufacture but scalable, several approved vaccines use this approach</td>
</tr>
<tr>
<td>GSK/Sanofi</td>
<td>Recombinant protein + adjuvant</td>
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</tbody>
</table>
Core Components of Vaccine Development and Delivery

- Developing vaccine construct – antigen and platform
- Manufacturing
- **Clinical Trials**
- Regulatory review and immunization policy
- Distribution and vaccinations
SARS-CoV-2 Vaccine Development: mRNA-1273

- Jan 10: Virus sequence released
  - GMP production and preclinical evaluation initiated in parallel
- Mar 16: Phase I begins
- May 29: Phase II begins
- Jul 27: Phase III begins
- Nov 17: Interim analysis finds preliminary efficacy
- Nov 30: EUA submission

Days from sequence release:
- <5 days
- 65 days
- 139 days
- 198 days
- 311 days
- 325 days
## Selected COVID-19 Vaccine Candidates

<table>
<thead>
<tr>
<th>Platform</th>
<th>Developer</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
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<tbody>
<tr>
<td>Nucleic acid</td>
<td>moderna</td>
<td>Enrolled</td>
<td>Enrolled</td>
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<td></td>
<td>BIONTECH</td>
<td>Enrolled</td>
<td>Enrolled</td>
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<tr>
<td></td>
<td>Pfizer</td>
<td></td>
<td></td>
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<tr>
<td>Viral vector</td>
<td>UNIVERSITY OF OXFORD</td>
<td>Enrolled</td>
<td>Ongoing</td>
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<td></td>
<td>AstraZeneca</td>
<td></td>
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<tr>
<td></td>
<td>Janssen</td>
<td>Enrolled</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>johnson-johnson</td>
<td></td>
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<tr>
<td>Protein subunit</td>
<td>NOVAVAX</td>
<td>Enrolled</td>
<td>Ongoing</td>
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<td>gsk</td>
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<tr>
<td></td>
<td>SANOFI</td>
<td>Enrolled</td>
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Unprecedented collaboration and resources will be required to research and develop safe and effective vaccines for COVID-19 that can be manufactured and delivered in the scale of billions of doses to people globally.
Elements of OWS Harmonized Protocols

- Harmonized endpoints
- Collaborating clinical trials networks
- Shared immune assays
- Common Data and Safety Monitoring Board
- Shared statistical plan for immune correlates of protection
OWS Phase 3 Design Overview

- Randomized, Placebo-Controlled Efficacy Trial: 1:1 or 2:1

- Sample size: 30,000 to 60,000 volunteers
  - A primary efficacy endpoint point estimate of $\geq 60\%$
  - The lower bound of the confidence interval $> 30\%$

- Study Population: age $\geq 18$ years, at risk of acquisition, targeting subset at higher risk of severe disease, diverse populations
  - The Pfizer trial, which is independently conducted, is now enrolling down to age 12

- Primary Endpoint: Prevention of symptomatic COVID-19 disease (PCR confirmed)
  - All identified cases are assessed for severity and followed to resolution
  - Unblinded clinical case data are submitted to shared biostatistical group
Modernna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization

Vaccine efficacy against COVID-19 was 94%; vaccine efficacy against severe COVID-19 was 100%
Pfizer and BioNTech to Submit Emergency Use Authorization Request Today to the U.S. FDA for COVID-19 Vaccine

- Vaccine efficacy rate of 95%, with no serious safety concerns observed to date
Core Components of Vaccine Development and Delivery

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- Distribution and vaccinations
In World First, UK Approves Pfizer-BioNTech COVID-19 Vaccine
<table>
<thead>
<tr>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
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<td>31</td>
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DECEMBER 2020

Fridays: Pfizer, Moderna
Vaccine distribution plan awaiting recommendations from CDC after consultation with the Advisory Committee on Immunization Practices (ACIP) and the National Academy of Medicine
Advisory Committee on Immunization Practices Proposed Vaccine Prioritization – Phase 1

**Phase 1a**
Healthcare Personnel
Long-term Care Facilities

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

**Phase 1c**
Adults with high-risk medical conditions
Adults 65+
Core Components of Vaccine Development and Delivery

- Developing vaccine construct – antigen and platform
- Manufacturing
- Clinical Trials
- Regulatory review and immunization policy
- Distribution and vaccinations
General: COVID-19 Vaccines Will Be Ready for Delivery 24 Hours After FDA Authorization

Operation Warp Speed has a delivery plan in place.
Vaccine Administration Sites

Walgreens

RITE AID

CVS pharmacy

Costco Wholesale
Efficacy

Versus

Effectiveness
Just 50% of Americans Plan to Get a COVID-19 Vaccine. Here’s How to Win Over the Rest

W Cornwall

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Not sure</th>
<th>No</th>
<th>Did not answer</th>
</tr>
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<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>49%</td>
<td>31%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td><strong>Under age 60</strong></td>
<td>40%</td>
<td>35%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td><strong>Age 60 and older</strong></td>
<td>67%</td>
<td>21%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>56%</td>
<td>27%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>25%</td>
<td>32%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>37%</td>
<td>37%</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>
Preventing the Spread of SARS-CoV-2 With Masks and Other “Low-tech” Interventions

AM Lerner, GK Folkers and AS Fauci

“While results of phase 3 trials for multiple candidate vaccines are on the near horizon, “low-tech” tools to prevent the spread of SARS-CoV-2 are essential, and it must be emphasized that these interventions will still be needed after a vaccine is initially available.”
Universal Coronavirus Vaccines: The Time to Start Is Now

LT Giurgea, A Han and MJ Memoli