Development of SARS-CoV-2 Vaccines

Sharon Riddler, MD
Update in Internal Medicine Oct 2020
Overview

• Introduction – SARS-CoV-2
• Vaccine development process
• Operation Warp Speed
• Candidate vaccines
• Preliminary data
• Pittsburgh’s role
Coronaviruses and SARS-CoV-2

- Single-stranded, enveloped RNA viruses
- With spiked glycoprotein embedded in envelope
- Inter- and intra-species transmission plus genetic recombination contribute to emergence of new coronavirus strains

Table 1. Human coronaviruses.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Genus</th>
<th>Disease</th>
<th>Discovered</th>
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</thead>
<tbody>
<tr>
<td>CoV-229E</td>
<td>Alpha</td>
<td>Mild respiratory tract infection</td>
<td>1967</td>
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<tr>
<td>CoV-NL-63</td>
<td>Alpha</td>
<td>Mild respiratory tract infection</td>
<td>1965</td>
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<tr>
<td>CoV-HKU-1</td>
<td>Beta</td>
<td>Mild respiratory tract infection; pneumonia</td>
<td>2005</td>
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<tr>
<td>CoV-OC43</td>
<td>Beta</td>
<td>Mild respiratory tract infection</td>
<td>2004</td>
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<tr>
<td>SARS-CoV</td>
<td>Beta</td>
<td>Human severe acute respiratory syndrome, 10% mortality rate</td>
<td>2003</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Beta</td>
<td>Human severe acute respiratory syndrome, 37% mortality rate</td>
<td>2012</td>
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<tr>
<td>SARS-CoV-2</td>
<td>Beta</td>
<td>Severe acute respiratory infections, &lt;2% mortality rate</td>
<td>2019</td>
</tr>
</tbody>
</table>

Loeffelholz and Tang 2020
Emerg Microbes Infect.

Shereen et al. 2020
J Adv Res.
SARS-CoV-2

Antibody Target

Antibody Target
Infection and Immune Response

1. Virus enters the body

Coronavirus
- Spike protein
- M protein
- RNA

Coronavirus infection*
The virus uses its surface spike protein to lock onto ACE2 receptors on the surface of human cells. Once inside, these cells translate the virus's RNA to produce more viruses.

2. Virus enters a cell

ACE2 receptor

3. Virus fuses with vesicle and its RNA is released

4. Virus assembly

Viral RNA translated into proteins

5. Virus release

Immune response*
Specialized 'antigen presenting cells' (APCs) engulf the virus and display portions of it to activate T-helper cells.

T-helper cells enable other immune responses:
- B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction.
- Cytotoxic T cells identify and destroy virus-infected cells.

Viral peptide

B cell

Anti-coronavirus antibody

Prevents virus from binding, or tags it for destruction

Cytotoxic T cell

Destroys infected cells

Long-lived 'memory' B and T cells that recognize the virus can patrol the body for months or years, providing immunity

*Simplified
Antibody responses in COVID-19

- 100% for IgG within 19d of onset of symptoms
- Seroconversion of IgM and IgG occurred simultaneously or sequentially
- Titers plateaued within 6d of seroconversion
SARS-CoV-2 and Ab response

Azkur et al. 2020
Allergy
Vaccine Development Process
Traditional Vaccine Development Pathway

Discovery and Target Validation
- Preclinical Stage
  - Translational medicine entry
  - Initial bioprocess, formulation, and analytics

Manufacturing Development
- Clinical Assay Optimization (antibody)
- Dose Regimen Selection

Phase I
- Safety
- 10+ people

Phase II
- Safety and immunogenicity
- 100+ people

Phase III
- Safety, efficacy, and regulatory approval
- 1000+ people

Innovative Clinical Trials
- Large sample size needed for safety and efficacy evaluation
- 3-8 Yr

2-10 Yr

1-2 Yr

Regulatory Review

Average Time to New Vaccine Approval = 10.7 Years!
Operation Warp Speed

• “Operation Warp Speed (OWS) aims to deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021, as part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics (collectively known as countermeasures)”
OWS: Accelerating the Timeline

• Development
  • Selection of promising candidate vaccines; provide support for development
  • Align safety and efficacy protocols; overseen at federal level

• Manufacturing
  • Invest USG funds into manufacturing and distribution early
  • Scale up manufacturing during clinical testing

• Distribution
  • Build distribution infrastructure prior to approval(s)
  • Expand supplies of materials and resources (cold-chain storage, vials, etc)
  • Utilize government resources such as DoD to enable rapid distribution
Operation Warp Speed Vaccines

- Knowledge of the role of the spike protein in coronavirus pathogenesis
- Evidence that neutralizing antibody against the spike protein is important for immunity
- Evolution of nucleic acid vaccine technology
Accelerating the Timeline

SARS-CoV-2 Vaccine Pipeline

By Aaron Steckelberg, Carolyn Y. Johnson, Gabriel Florit and Chris Alcantara

Updated Sept. 24 at 5:28 p.m.

170+ vaccines are being tested in animals and lab experiments

10 vaccines are being tested in a small number of healthy, young people to assess safety and correct dose

14 vaccines are broadened to a larger group of people, including people at higher risk of illness

10 vaccines are being tested in thousands of people to check their effectiveness and safety

0 vaccines have been determined to provide benefits that outweigh known and potential risks

Rational, rapid vaccine development

Vaccines come in many flavors

Vaccines in development are targeting the Spike protein

Modified from Paul Duprex, Pitt Center for Vaccine Research
Vaccine Candidates in Development for SARS-CoV-2

**Vaccine Platforms**
- DNA
- RNA (+ LNPs)
- Protein based (eg, spike)
- Viral vector (nonreplicating)
- Viral vector (replicating)
- Virus (inactivated)
- Virus (attenuated)
- Coronavirus spike gene
- Virus genes (some inactive)

**Vaccine Candidates**
- DNA
- RNA
- SARS-CoV-2 live attenuated
- SARS-CoV-2 inactivated
- Protein based

Funk. Frontiers in Pharmacology. 2020;[Epub].
Slide credit: clinicaloptions.com
SARS-CoV-2 Vaccines in Phase 3 Trials

• Nucleic acid
  • Moderna – mRNA
  • Pfizer/BioNTech – mRNA

• Vector vaccines
  • CanSinoBIO – Ad5
  • AstraZeneca/University of Oxford – ChAdOx1
  • Gameleya Research Institute (Russia) – Ad5 and Ad26
  • Johnson & Johnson/Janssen – Ad26

• Subunit vaccines
  • Novavax – Protein subunit

• Inactivated virus
  • Sinovac Biotech – inactivated virus
  • Wuhan Institute/Sinopharm – inactivated virus
  • Sinopharm/Beijing Institute – inactivated virus

Red=Phase 3 in US
As of 9/26/2020
Preclinical Evaluation
Animal Models in Preclinical testing

- Proof of concept testing
  - Immunogenicity
    - Level of antibody, Ab class/subclass
    - Cell-mediated immunity
    - Duration of immune response
  - Challenge Studies

- Safety Testing
  - Toxicity testing (inactivated vaccines)
  - Viral safety testing (live-attenuated vaccines)
  - Batch-release testing

- Quality testing
  - Adventitious agents
Study Design mRNA-1273 in Rhesus Macaques

**Immunizations W0/W4:**
- PBS
- 10 µg mRNA-1273
- 100 µg mRNA-1273

**Post-challenge sampling:**
- Blood: Days 0, 7 and 14
- Nasal swabs: Days 1, 2, 4 and 7
- Bronchoalveolar lavage: Days 2, 4 and 7

Antibody Responses after mRNA-1273 Vaccination in NHP
Efficacy of mRNA-1273 against Upper and Lower Respiratory Viral Replication

A Subgenomic RNA in BAL Fluid

B Subgenomic RNA in Nasal Swabs
Early Phase Clinical Trial Data
• Genetic
• mRNA1273
• First American company to put a vaccine into human trials
• Messenger RNA to produce viral proteins
• Published Phase 1 results in NEJM on July 14
• Phase 3 trial began July 27
mRNA 1273 (Moderna) Phase 1 – Preliminary Results

- Phase 1, open-label, dose escalation
- Healthy adults, aged 18-55 years
- 3 dose levels: 25, 100, 250 mcg per injection
- N=15 participants per group
- 2 IM injections, 4 weeks apart
- Additional arms ongoing (50 mcg dose; older age cohorts 56-70 years and 71+ years)
- NCT0428341

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report


NEJM 7/14/2020
mRNA 1273 (Moderna) Tolerability

- Mild to moderate systemic and local events were common
- Reactions were more frequent after the second dose
- Events occurring in more than 50% of participants included fatigue, chills, HA, myalgia, and injection site pain
- One participant (25 mcg) had urticaria 5 days after the first dose
- One participant (250 mcg) had fever (39.6) and other symptoms; possibly related to adenovirus infection

Jackson, NEJM 7/14/2020
mRNA1273 Vaccine Against SARS-CoV-2: Binding Ab

Binding Antibody IgG to S-P2

Binding Antibody IgG to Receptor Binding Domain

*Boxes denote IQR and horizontal bar denotes median AUC; whisker endpoints are maximum and minimum values below or above the median ± 1.5 times IQR. †Convalescent serum panel includes specimens from 41 participants; orange dots indicate the 3 specimens that were also tested in the PRNT assay.

Jackson. NEJM. 2020;[Epub].
mRNA 1273 Vaccine Against SARS-CoV-2: Neutralizing Ab

**Pseudovirion Neutralization Assay**

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* Boxes denote IQR and horizontal bar denotes median ID$_{50}$; whisker endpoints are maximum and minimum values below or above the median ± 1.5 times IQR. *Convalescent serum panel includes specimens from 41 participants; orange dots indicate the 3 specimens that were also tested in the PRNT assay.

**Plaque Reduction Neutralization Tests**

<table>
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<th>Study Day</th>
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<td>4</td>
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</table>

Jackson. NEJM. 2020;[Epub].

Slide credit: clinicaloptions.com
mRNA 1273 Ab Responses Similar for Older/Younger Adults

- N=10 per dose aged 56-70 and ≥71 years
- Binding and neutralizing Ab higher for 100µg dose
- Comparable immune responses to younger cohort
AZD1222 (ChAdOx1 nCoV-19)

• Non-replicating ChAdOx1 Vector Vaccine

• ChAdOx1 platform has been used in 14 previous clinical studies sponsored by the University of Oxford with immunogens from multiple pathogens such as influenza, tuberculosis, malaria, chikungunya, Zika, MERS-CoV, and Meningitis B.

• ChAdOx1 vaccines demonstrated robust immunogenicity and favorable safety profiles, with no vaccine-related SAEs.

• AZD1222 is composed of the ChAdOx1 expressing the SARS-CoV-2 Spike protein
ChAdOx1 nCoV-19 Phase 1

• N= 1077 participants: ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534)
  • Healthy adult participants aged 18–55
  • DOSE: 5 x10^{10} viral particles
    • 10 participants received 2 doses

• **Generally well tolerated:** Local and systemic reactions were more common with ChAdOx1 (reduced by prophylactic paracetamol)
  • Most common: pain, feeling feverish, chills, muscle ache, headache, and malaise
  • Reactogenicity was reduced after a second dose
  • No serious adverse events related to ChAdOx1 nCoV-19.
ChAdOx1 nCoV-19 Immunogenicity

• Spike-specific T-cell responses peaked on day 14

• Anti-spike IgG responses peaked by day 28
  • boosted following a second dose (639 EU, 360–792; n=10).

• Neutralizing Ab responses detected 91% - 100% participants after a single dose
  • Neutralizing antibody responses correlated strongly with antibody levels measured by ELISA
ChAdOx1 nCoV-19 IgG Response to Spike Protein

Folegatti, Lancet 7/20/20
General Phase 3 Trial Design

• Sample Size: 30,000+ participants
• Primary objectives:
  • Efficacy for prevention of symptomatic COVID-19
  • Safety and tolerability
• Study design:
  • Adults (age 18+) at increased risk of SARS-CoV-2 infection (by occupation or circumstances)
  • Randomization to active vaccine or placebo (1:1 or 2:1 typically)
  • Most are 2 doses; J&J evaluating 1 or 2 doses
  • Follow up for 2 years with weekly contact and multiple in person visits
AZ1222 Study design

a. Participants who present with qualifying symptoms will be tested for SARS-CoV-2 and if positive, will complete illness visits.

**Red bars:** Administration of study intervention.

**Gray bars:** Day 8 and Day 36 visits will be telephone contacts, not study site visits.

**Blue bars:** Day 15 and Day 43 visits will only be for participants in the sub-study. The first participants randomized in each age group, including 1,500 participants 18–55 years of age, 750 participants 56–69 years of age, and 750 participants ≥70 years of age will also participate in a sub-study assessing the reactogenicity and immunogenicity of AZD1222.

COVID-19, coronavirus disease 2019; IM, intramuscular; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; vp, viral particles.
Pittsburgh does vaccines ...
COVID-19 Prevention Network (CoVPN)

• Part of OWS
• Formed by the National Institute of Allergy and Infectious Diseases (NIAID)
• Utilizes the infectious disease expertise and research infrastructure of existing research networks
• To conduct Phase 3 efficacy trials for COVID-19 vaccines and monoclonal antibodies
CoVPN in Pittsburgh

• Pittsburgh Vaccine Treatment and Evaluation Unit (VTEU)
  • Recently funded in 2020 for clinical vaccine trials by DMID
  • Led by Judy Martin and Alejandro Hoberman

• University of Pittsburgh HIV/AIDS Clinical Research Site
  • Funded since 1998 by DAIDS
  • Co-PIs: Mellors and Riddler
  • Co-Is: Choudhary, Ho, Macatangay, McMahon
Community Vaccine Collaborative

- Clinical Translational Science Institute (CTSI) Clinical PARTners Core (Liz Miller, MD)
- Engaging community voices for vaccine trials and eventual roll-out of effective vaccines
- Urban League of Greater Pittsburgh
- UrbanKind Institute
- Casa San Jose
- Neighborhood Resilience Project
# Ongoing/Projected CoVPN Vaccine Trials

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Type</th>
<th>Product</th>
<th>Start date</th>
<th>Pittsburgh?</th>
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<tbody>
<tr>
<td>Moderna</td>
<td>mRNA</td>
<td>mRNA-1273</td>
<td>Late July</td>
<td>Yes</td>
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<tr>
<td>AstraZeneca/Oxford</td>
<td>Viral vector (ChAdOx1)</td>
<td>AZD1222</td>
<td>Late-Aug</td>
<td>Yes</td>
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<tr>
<td>Novavax</td>
<td>Recombinant Spike Protein Nanoparticle</td>
<td>NVX-CoV2373</td>
<td>Oct</td>
<td>No</td>
</tr>
<tr>
<td>Sanofi-GSK</td>
<td>Adjuvanted recombinant subunit vaccine</td>
<td></td>
<td>Dec</td>
<td>TBD</td>
</tr>
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</table>
More Information

• Local registry: Pittsburgh Vaccine Clinical Trial Unit Registry
  • PVTU.org
  • 412-692-7382
• CoVPN – national website
  • www.coronaviruspreventionnetwork.org
• COVID vaccine trackers
  • New York Times and Washington Post
Thanks

• For slides and other contributions
  • Paul Duprex – Center for Vaccine Research
  • Judy Martin – Department of Pediatrics; Pitt Vaccine Treatment Evaluation Unit
  • Beej Macatangay – Division of Infectious Diseases
  • Liz Miller – Department of Pediatrics and Pitt CTSI

• UPMC and Pitt for supporting rapid scale-up of our clinical trial capacity