DC CTSA Spring Regulatory Update & Hot Topics in Clinical and Translational Research

Moving Swiftly to Combat the COVID-19 Global Health Crisis

Keynote Address

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George Washington University School of Medicine & Health Sciences

Moderator: Rebecca Eberle, MSHS, CIP
Interim Director, Office of Human Research
George Washington University

9:45 - 10:30 AM EST
COVID-19 Vaccine Development:  
*The GW Experience*

David Diemert, MD  
*Professor of Medicine & Microbiology, Immunology and Tropical Medicine*  
*GW SMHS*  

23 Apr 2021
Disclosures

- Exhausted, but...
- Relieved & hopeful
In US, 3 EUA vaccines:
- Pfizer
- Moderna
- Janssen/J&J

Number of people who received at least one dose of COVID-19 vaccine

Total number of people who received at least one vaccine dose. This may not equal the number of people that are fully vaccinated if the vaccine requires two doses.

Source: Official data collated by Our World in Data

CC BY
COVID-19 Vaccines in Clinical Trials

Summary Information on Vaccine Products in Clinical Development

1. Number of vaccines in clinical development: 91
2. Number of vaccines in pre-clinical development: 184

3. Candidates in clinical phase

Filter: All
Select phase of development (default is all)

<table>
<thead>
<tr>
<th>Platform</th>
<th>Candidate vaccines (no., and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>29 (32%)</td>
</tr>
<tr>
<td>VVr</td>
<td>14 (15%)</td>
</tr>
<tr>
<td>DNA</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>IV</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>RNA</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>VVr</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>VLP</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>VW + APC</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>VVr + APC</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>LAV</td>
<td></td>
</tr>
<tr>
<td>VVr + APC</td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO, 20APR2021
Mechanism of target cell entry

- Spike protein binds to ACE2 receptor via receptor binding domain (RBD)
- Endocytosis into vesicle
- Spike cleaved by endosomal proteases
- Fuses with endosomal membrane

US Gov’t-Supported COVID-19 Vaccine Candidates

- Moderna: mRNA
- AstraZeneca: Replication Incompetent Adenovirus (ChAdOx1)
- Janssen: Replication Incompetent Adenovirus (Ad26)
- Sanofi: Adjuvanted protein subunit
- Merck & IAVI: Replication-competent Vesicular Stomatitis Vector (VSV)
- Novavax: Adjuvanted protein subunit
- Pfizer: mRNA
Speed Requires a Paradigm Shift

**Traditional paradigm**
- 5 - 10+ years
- Target ID, development partner selection, and pre-clinical: 6-36 months

**Outbreak paradigm**
- 12 - 18 months
- Target ID, development partner selection, and pre-clinical: 4 - 8 months

**Clinical development**
- Early stage: 3 - 4 months
  - First in human (Ph I)
- Late stage: 6 - 8 months
  - Late Stage (Ph II) development: n=10s to n=100s
  - Advanced development: n=100s to n=1000s
  - Final stage production / (Emergency authorization)

**Licensure**
- 3 - 18 months

Source: CEPI
mRNA Vaccine Approach

NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins

Study Enrolling Seattle-Based Healthy Adult Volunteers

Trial of vaccine candidate mRNA-1273 will enroll 45 healthy adult volunteers ages 18 to 55 years over approximately 6 weeks
COVID-19 mRNA Vaccine Design

SARS-CoV-2 virus

mRNA packaged in lipid nanoparticles

Vaccine delivered as injection

mRNA released into cell

Host cell

mRNA used to make viral proteins

Spike protein

mRNA is made with instructions to make viral proteins

Immune response

CBC NEWS

mRNA-1273 program timeline

**mRNA-1273 timeline:** Research and development of SARS-CoV-2 vaccine

**January 13, 2020**
Sequence for mRNA-1273 against the novel coronavirus finalized

**March 16, 2020**
First participant in NIH-led Phase 1 study was dosed

**April 16, 2020**
Award from U.S. government agency BARDA for up to $483 million to accelerate development

**April 27, 2020**
IND submitted to US FDA for Phase 2 study

**May 1, 2020**
Collaboration announced with Lonza Ltd to manufacture mRNA-1273 (goal of up to one billion doses per year)

**May 4, 2020**
FDA clearance to proceed with Phase 2 study

**May 18, 2020**
Announcement of positive data from Phase 1

**May 29, 2020**
Announcement of first dosing in Phase 2

**June 11, 2020**
Announcement of completed enrollment in younger adults in Phase 2 and Phase 3 to start in July

**July 27, 2020**
Phase 3 initiated ~30,000 subjects

Total of 63 days from sequence selection to first human dosing
Moderna COVID-19 Vaccine: IgG Responses to S Protein

Binding Ab (ELISA) vs. Neutralizing Ab (Pseudovirus)

Phase 1 Trial (<55 years old)

Jackson L et al, NEJM, ePub 14Jul2020
Moderna mRNA-1273 IgG Durability

A Receptor-Binding Domain ELISA

B Pseudovirus Neutralization Assay

Phase 1 Trial

Doria-Rose et al, NEJM, 06pr2021

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

smhs.gwu.edu
Phase 3 COVID-19 Prevention Trial Network

• NIAID-led consortium

Goals:
• Enroll 5 Phase 3 trials by mid-2021
  – 30,000 participants/trial
• Harmonized protocol design
  – Similar definitions of primary and main secondary endpoints
• Central laboratories
• Common DSMB
Moderna mRNA vaccine Accelerated Clinical Development

- **May 18:** Preliminary Results
- **Phase 1**
  - **1st week of July:** Blinded safety post-Vax#1
  - **Mid-July:** Blinded safety post-Vax#2
- **Phase 2**
- **Phase 3**
  - **July 27th:** Initiation of vaccinations
Modern mRNA COVID-19 Phase 3 Trial Design

- Randomized, placebo-controlled, observer blind
- 100 µg mRNA-1273-P301 vs. saline placebo (1:1), IM

**Primary Efficacy Endpoint:**
- $\geq 2$ of fever, chills, myalgia, headache, sore throat, new olfactory/taste disorder, OR
- $\geq 1$ of cough, SOB/dyspnea, OR clinical/radiologic evidence of pneumonia, AND
- NP, nasal or saliva sample + for SARS-CoV-2 by RT-PCR
- Target VE against COVID-19: 60%
  - Lower 95% confidence limit >30%
  - Total target # of cases = 151
- Assumed incidence of 0.75%/6 months in placebo arm
- Power = 90%, 1-sided false positive error rate of 2.5%

Original estimate: July 2021
Actual: Nov 2020
Enrollment closed on Oct 23, 2020: n=30,420 (n=349 at GW)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N=15,170)</th>
<th>mRNA-1273 (N=15,181)</th>
<th>Total (N=30,351)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> — no. of participants (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8,062 (53.1)</td>
<td>7,923 (52.2)</td>
<td>15,985 (52.7)</td>
</tr>
<tr>
<td>Female</td>
<td>7,108 (46.9)</td>
<td>7,258 (47.8)</td>
<td>14,366 (47.3)</td>
</tr>
<tr>
<td><strong>Mean age (range) — yr</strong></td>
<td>51.3 (18–95)</td>
<td>51.4 (18–95)</td>
<td>51.4 (18–95)</td>
</tr>
<tr>
<td><strong>Age category and risk for severe Covid-19 — no. of participants (%)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;65 yr, not at risk</td>
<td>8,886 (58.6)</td>
<td>8,888 (58.5)</td>
<td>17,774 (58.6)</td>
</tr>
<tr>
<td>18 to &lt;65 yr, at risk</td>
<td>2,535 (16.7)</td>
<td>2,530 (16.7)</td>
<td>5,065 (16.7)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>3,749 (24.7)</td>
<td>3,763 (24.8)</td>
<td>7,512 (24.8)</td>
</tr>
<tr>
<td><strong>Hispanic or Latino ethnicity — no. of participants (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3,114 (20.5)</td>
<td>3,121 (20.6)</td>
<td>6,235 (20.5)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>11,917 (78.6)</td>
<td>11,918 (78.5)</td>
<td>23,835 (78.5)</td>
</tr>
<tr>
<td>Not reported and unknown</td>
<td>139 (0.9)</td>
<td>142 (0.9)</td>
<td>281 (0.9)</td>
</tr>
<tr>
<td><strong>Race or ethnic group — no. of participants (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11,995 (79.1)</td>
<td>12,029 (79.2)</td>
<td>24,024 (79.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1,527 (10.1)</td>
<td>1,543 (10.3)</td>
<td>3,090 (10.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>731 (4.8)</td>
<td>651 (4.3)</td>
<td>1,382 (4.6)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>121 (0.8)</td>
<td>112 (0.7)</td>
<td>233 (0.8)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>32 (0.2)</td>
<td>33 (0.2)</td>
<td>67 (0.2)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>321 (2.1)</td>
<td>315 (2.1)</td>
<td>636 (2.1)</td>
</tr>
<tr>
<td>Other</td>
<td>316 (2.1)</td>
<td>312 (2.1)</td>
<td>628 (2.1)</td>
</tr>
<tr>
<td>Not reported and unknown</td>
<td>127 (0.8)</td>
<td>155 (1.0)</td>
<td>282 (0.9)</td>
</tr>
</tbody>
</table>
Modernm mRNA COVID-19 Phase 3 Trial Results

- Final analysis: reported on Nov 30, 2020
  - 196 cases: 185 in placebo arm, 11 in vaccine arm
    - VE = 94.1%, p<0.0001
    - 30 severe cases (1 death): all in placebo arm
    - Similar efficacy across age groups, racial/ethnic groups, co-morbidities
- EUA application filed with FDA on Nov 30, 2020
  - FDA external advisory committee meeting: Dec 17, 2020
  - EUA issued on Dec 18, 2020
mRNA-1273 Phase 3 Efficacy

A Per-Protocol Analysis

<table>
<thead>
<tr>
<th></th>
<th>Vaccine Efficacy (95% CI)</th>
<th>Incidence Rate (95% CI) per 1000 person-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.0 (1.7–6.0)</td>
<td>56.5 (48.7–65.3)</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>3.5 (3.3–3.7)</td>
<td>3.3 (1.7–6.0)</td>
</tr>
</tbody>
</table>

Cumulative Event Rate (%)

Days since Randomization

No. at Risk

| Placebo   | 14,073  | 14,073  | 14,073  | 14,072  | 13,416  | 12,992  | 12,361  | 11,147  | 9474   | 6563   | 3971   | 1172   | 0   |
| mRNA-1273 | 14,134  | 14,134  | 14,134  | 14,133  | 13,483  | 13,073  | 12,508  | 11,315  | 9684   | 6721   | 4094   | 1209   | 0   |

Baden et al, NEJM, 30Dec2020
mRNA-1273 Vaccine Efficacy by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo (N=14,073)</th>
<th>mRNA-1273 (N=14,134)</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events/tot. no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>185/14,073</td>
<td>11/14,134</td>
<td>94.1 (89.3–96.8)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18 to &lt;65 yr</td>
<td>156/10,521</td>
<td>7/10,551</td>
<td>95.6 (90.6–97.9)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>29/3552</td>
<td>4/3583</td>
<td>86.4 (61.4–95.2)</td>
</tr>
<tr>
<td>Age, risk for severe Covid-19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;65 yr, not at risk</td>
<td>121/8403</td>
<td>5/8396</td>
<td>95.9 (90.0–98.3)</td>
</tr>
<tr>
<td>18 to &lt;65 yr, at risk</td>
<td>35/2118</td>
<td>2/2155</td>
<td>94.4 (76.9–98.7)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>29/3552</td>
<td>4/3583</td>
<td>86.4 (61.4–95.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87/7462</td>
<td>4/7366</td>
<td>95.4 (87.4–98.3)</td>
</tr>
<tr>
<td>Female</td>
<td>98/6611</td>
<td>7/6768</td>
<td>93.1 (85.2–96.8)</td>
</tr>
<tr>
<td>At risk for severe Covid-19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43/3167</td>
<td>4/3206</td>
<td>90.9 (74.7–96.7)</td>
</tr>
<tr>
<td>No</td>
<td>142/10,906</td>
<td>7/10,928</td>
<td>95.1 (89.6–97.7)</td>
</tr>
<tr>
<td>Race and ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>144/8916</td>
<td>10/9023</td>
<td>93.2 (87.1–96.4)</td>
</tr>
<tr>
<td>Communities of color</td>
<td>41/5132</td>
<td>1/5088</td>
<td>97.5 (82.2–99.7)</td>
</tr>
</tbody>
</table>
mRNA-1273 Phase 3 Trial: Safety

Figure 2. Solicited Local and Systemic Adverse Events.
mRNA-1273-P301 – Safety

- **Allergic Reactions**
  - 3 anaphylaxis cases, all unrelated (>10 days post-vax)

- **Bell’s Palsy**
  - 3 cases in mRNA-1273, 1 in placebo
  - All deemed unrelated to vaccine
  - FDA: not more than background rate

- **Dermal Filler Reactions**
  - 3 cases of facial/lip swelling in mRNA-1273 recipients
mRNA-1273: Unanswered Questions

- **Pregnancy**
  - 13 pregnancies through December 2, 2020 (6 vaccine, 7 placebo). Vaccination occurred:
    - 1 spontaneous abortion, 1 elective abortion, both in the placebo
    - Pregnancy outcomes are otherwise unknown at this time

- **Pediatrics**

- **Asymptomatic Transmission**

- **½ Dose?**
  - Phase 2 trial included 50µg arm: immunogenicity MAY be equivalent

- **Delayed 2\textsuperscript{nd} dose?**
Modernia Phase 3 Plans: Unblinding

- All participants invited for “Decision Visit” to unblind
  - Started at GW on Dec 30th, 2020
  - All Decision Visits completed at GW on Mar 15th, 2021

- Placebo recipients offered vaccine
• Phase 3 Trial: 40,277 participants
• VE = 95.0% (90.3 – 97.6)
• Similar safety profile to Moderna
• EUA – Dec 12th, 2020
  – Approved for ≥16 y/o
AZD1222 (ChAdOx1 nCoV-19) Candidate Vaccine

• University of Oxford/AstraZeneca
• Replication-deficient chimpanzee adenovirus vector expressing the full-length SARS-CoV-2 spike protein
• ChAdOx1 vector used to develop investigational vaccines against other pathogens:
  – Malaria, MERS, tuberculosis, influenza and chikungunya virus (Phase 1/2)

• Clinical development (Phase 1) initiated in April 2020
• Phase 2/3 in the UK
• Phase 3 in Brazil

• CoVPN Phase 3 fully enrolled (US & International)
SARS-CoV-2 Vaccine Development: Viral Vectored Vaccine Construct

**COVID-19 OXFORD VACCINE TRIAL**

- Chimpanzee adenovirus
  - Modified
  - Unable to cause disease
- ChAdOx1 viral vector
  - Cells express spike protein
  - Body produces antibodies against spike proteins
- ChAdOx1 nCov-19 vaccine
  - If infected, immune system attacks SARS-CoV-2
- Spike protein
  - Genes coding spike protein
- SARS-CoV-2
Table 2  COVID-19 Vaccine AstraZeneca efficacy against COVID-19

<table>
<thead>
<tr>
<th>Population</th>
<th>COVID-19 Vaccine AstraZeneca</th>
<th>Control</th>
<th>Vaccine efficacy % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Primary (see above)</td>
<td>5,807</td>
<td>5,829</td>
<td></td>
</tr>
<tr>
<td>COVID-19 cases</td>
<td>30 (0.52)</td>
<td>101 (1.73)</td>
<td>70.42 (58.84, 80.63)a</td>
</tr>
<tr>
<td>Hospitalisations(^b)</td>
<td>0</td>
<td>5 (0.09)</td>
<td>-</td>
</tr>
<tr>
<td>Severe disease(^e)</td>
<td>0</td>
<td>1 (0.02)</td>
<td>-</td>
</tr>
<tr>
<td>Any dose</td>
<td>10,014</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>COVID-19 cases after dose 1</td>
<td>108 (1.08)</td>
<td>227 (2.27)</td>
<td>52.69 (40.52, 62.37)d</td>
</tr>
<tr>
<td>Hospitalisations after dose 1(^b)</td>
<td>2 (0.02)c</td>
<td>16 (0.16)</td>
<td>-</td>
</tr>
<tr>
<td>Severe disease after dose 1(^c)</td>
<td>0</td>
<td>2 (0.02)</td>
<td>-</td>
</tr>
</tbody>
</table>

- Primary Analysis included 1367 LD/SD and 4440 SD/SD
- 94% < 65 years old
## AZ/Oxford Vaccine – Phase 3 Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Total number of cases</th>
<th>ChAdOx1 nCoV-19</th>
<th>Control</th>
<th>Vaccine efficacy (CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n/N (%)</td>
<td>Incidence rate per 1000 person-years (person-days of follow-up)</td>
<td>n/N (%)</td>
</tr>
<tr>
<td>All LD/SD and SD/SD recipients</td>
<td>131</td>
<td>30/5807 (0.5%)</td>
<td>44.1 (248 299)</td>
<td>101/5829 (1.7%)</td>
</tr>
<tr>
<td>COV002 (UK)</td>
<td>86</td>
<td>18/3744 (0.5%)</td>
<td>38.6 (170 369)</td>
<td>68/3804 (1.8%)</td>
</tr>
<tr>
<td>LD/SD recipients</td>
<td>33</td>
<td>3/1367 (0.2%)</td>
<td>14.9 (73 313)</td>
<td>30/1374 (2.2%)</td>
</tr>
<tr>
<td>SD/SD recipients</td>
<td>53</td>
<td>15/2377 (0.6%)</td>
<td>56.4 (97 056)</td>
<td>38/2430 (1.6%)</td>
</tr>
<tr>
<td>COV003 (Brazil; all SD/SD)</td>
<td>45</td>
<td>12/2063 (0.6%)</td>
<td>56.2 (77 930)</td>
<td>33/2025 (1.6%)</td>
</tr>
<tr>
<td>All SD/SD recipients</td>
<td>98</td>
<td>27/4440 (0.6%)</td>
<td>56.4 (174 986)</td>
<td>71/4455 (1.6%)</td>
</tr>
</tbody>
</table>

*Vaccine efficacy calculated as 1 - (observed cases in vaccinated group / expected cases in vaccinated group) - (observed cases in control group / expected cases in control group) / (1 - (expected cases in vaccinated group / total potential cases in vaccinated group)) (CI = Confidence Interval)

†Based on the total number of cases for all LD/SD and SD/SD recipients

‡Based on the total number of cases for COV002 (UK) and LD/SD recipients

§Based on the total number of cases for COV003 (Brazil; all SD/SD and All SD/SD recipients)
• Overall efficacy 79% at preventing symptomatic COVID-19
• 100% efficacy against severe or critical disease and hospitalisation

• Comparable efficacy result across ethnicity and age
  – 80% efficacy in participants aged ≥65 years
CoVPN: What’s Next?

- EUA late Feb 2021
- P2 Initiation Feb 2021
- Development abandoned
Janssen/J&J COVID-19 Vaccine

A Moderate to Severe–Critical Cases of Covid-19

VE:
• 66% (symptomatic COVID-19)
• 85% (severe-critical COVID-19)

Sadoff et al, NEJM, 22APR2021
COVID-19 Vaccine Trials at GW

FROM MODERNA TO SANOFI....
Sanofi-Pasteur Phase I/II VAT00001 Study

- Same technology used to produce recombinant influenza vaccine
- SARS-CoV-2 Spike protein + adjuvant
- Sept 2020, US, 440 ppts
- Good antibody response in younger people but lower levels in older individuals
  - Seroconversion 85% in >50 yo, 62.5% in > 60 yo

- Led Sanofi to optimize the vaccine dose & formulation
VAT00002 Study at GW

- US Phase II: US, 720 pts, ≥18 yo (50% ≥ 60 yo)
- Higher doses and greater purity of protein from VAT00001 study
- 3 different SARS-CoV-2 Spike protein doses (5, 10 and 15 mcg) with AS03 adjuvant (GSK)
- 2 injections (21 days apart), randomized 1:1:1
  - No placebo
- Participants randomized based on prior SARS-CoV-2 infection as naïve and non-naïve

- Enrollment 24FEB2021 – 09MAR2021
  - 44 enrolled at GW
  - Vaccinations completed on 26MAR2021
COVID-19 Vaccine Trials at GW
GW COVID-19 Vaccine Trials Team

GW Milken Institute School of Public Health

GW SMHS/MFA