SARS-CoV-2 Vaccines

Florian Krammer
Mount Sinai Professor in Vaccinology
Icahn School of Medicine at Mount Sinai

Workshop on Vaccine Efficacy & Safety
DHS UNIVERSITY CENTERS OF EXCELLENCE VIRTUAL WORKSHOPS
January 7, 2021
Immunity?

- Antibody responses target the spike protein including the receptor binding domain as well as the nucleoprotein and other targets
  - Anti-spike (and RBD) antibodies are neutralizing and correlate with protection
  - NP antibodies are not neutralizing (we do not know if they are helpful)
- T-cell responses target several proteins
  - Strong CD4+ response
  - Relatively weak CD8+ response
Vaccine development usually happens at a glacial pace

Design and exploratory preclinical

Process development, preclinical, toxicology studies

IND submitted

Clinical trials

Phase I

Phases II

Phase III

Regulatory review

BLA submitted

FDA, EMA etc.

Large scale production and distribution

Years

2-4 years

1-2 years

2 years

2-3 years

1-2 years

15 years
COVID-19 vaccine development

- **Design and exploratory preclinical**
  - Pre-existing from SARS-CoV-1 and MERS CoV
  - Partially pre-existing and parallel development

- **Process development, preclinical, toxicology studies**

- **Clinical trials**
  - Phase I/II
  - Phase III
  - Overlapping clinical phases
  - Production at risk

- **Regulatory review**
  - FDA, EMA etc.
  - Review on a rolling basis?
  - EUA?

- **Timeline**
  - Months
  - 10 months to 1.5 years
C. Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated.

D. Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture.

E. Recombinant spike protein based vaccines.

F. Recombinant RBD protein based vaccines.

A. SARS-CoV-2

B. Receptor binding domain (RBD)

G. Virus-like particles (VLPs) carry no genome but display the spike on their surface.

J. Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated.

H. Replication competent vector vaccines can propagate to some extend in the vaccinee’s cells and express the spike protein there.

I. Non-replication competent vector vaccines cannot propagate in the vaccinee’s cells but express the spike protein there.

K. DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promoter.

L. RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs).
Current vaccine development pipeline for SARS-CoV-2
<table>
<thead>
<tr>
<th>Company (ref.)</th>
<th>Vaccine candidate (type)</th>
<th>Dose range (route)</th>
<th>Neut. titre after prime</th>
<th>Neut. titre after boost</th>
<th>T cell response</th>
<th>Challenge dose (route)</th>
<th>URT protection</th>
<th>LRT protection</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinovac(^3^)</td>
<td>PiCoVacc (inactivated virion + aluminium hydroxide)</td>
<td>3–6 µg (i.m.)</td>
<td>None(^a)</td>
<td>1:10 range(^a) (1:15 range(^a) after 2nd boost)</td>
<td>ND</td>
<td>10^6 TCID(_{50}) (i.t.)</td>
<td>Partial(^b)</td>
<td>Incomplete (low dose)(^b) Yes (high dose)</td>
<td>Rhesus macaques</td>
</tr>
<tr>
<td>Beijing Institute of Biological Products(^3^)</td>
<td>BBIBP-CorV (inactivated virion + aluminium hydroxide)</td>
<td>4–8 µg (i.m.)</td>
<td>1:100 range(^a)</td>
<td>1:200 range(^a)</td>
<td>ND</td>
<td>10^6 TCID(_{50}) (i.t.)</td>
<td>Partial(^b)</td>
<td>Complete(^b)</td>
<td>Cynomolgus macaques</td>
</tr>
<tr>
<td>AstraZeneca(^4^)</td>
<td>ChAdOxnCoV-19 (non-replicating AdV)</td>
<td>2.4 x 10^{10} VP; 1x or 2x (i.m.)</td>
<td>1:5–1:40 range(^a)</td>
<td>1:10–1:160 range(^a)</td>
<td>Yes</td>
<td>2.6 x 10^{6} TCID(_{50}) (i.t., oral, i.n., ocular)</td>
<td>None (1x)(^c) None (2x)(^c)</td>
<td>Partial (1x)(^c) Complete (2x)(^c)</td>
<td>Rhesus macaques</td>
</tr>
<tr>
<td>Janssen(^4^)</td>
<td>Ad26COVS1 (non-replicating AdV)</td>
<td>1 x 10^{11} VP (i.m.)</td>
<td>1:100 range(^d)</td>
<td>—</td>
<td>Low</td>
<td>10^5 TCID(_{50}) (i.n., i.t.)</td>
<td>Complete in S.PP group(^c)</td>
<td>Complete in S.PP group(^c)</td>
<td>Rhesus macaques</td>
</tr>
<tr>
<td>Moderna(^5^)</td>
<td>mRNA-1273 (mRNA via LNPs)</td>
<td>2x 10–100 µg (i.m.)</td>
<td>ND(^e)</td>
<td>1:501–1:3,481 range(^d)</td>
<td>Yes, CD4, T(_{FH})</td>
<td>7.5 x 10^5 TCID(_{50}) (i.n., i.t.)</td>
<td>None (10 µg)(^c) Partial (100 µg)(^c)</td>
<td>Partial (10 µg)(^c) Complete (10 µg)(^c)</td>
<td>Rhesus macaques</td>
</tr>
<tr>
<td>Novavax(^8^)</td>
<td>NVX CoV2373 (spike protein + Matrix-M)</td>
<td>2x 2.5–25 µg</td>
<td>—</td>
<td>17,920–23,040 range(^a)</td>
<td>ND</td>
<td>10^4 (i.n., i.t.)(^f)</td>
<td>Partial (low dose)(^c) Complete (higher doses)(^c)</td>
<td>Complete(^c)</td>
<td>Cynomolgus macaques</td>
</tr>
<tr>
<td>Company (reference)</td>
<td>Vaccine (type)</td>
<td>Dose range (route)</td>
<td>Neut. titre after prime</td>
<td>Neut. titre after boost</td>
<td>T cell response</td>
<td>Trial registration number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinovac^55</td>
<td>CoronaVac (inactivated SARS-CoV-2 + aluminium hydroxide)</td>
<td>3–6 μg (i.m.) 2x</td>
<td>ND</td>
<td>1:30–1:60 range^a</td>
<td>ND</td>
<td>NCT04352608</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinopharm</td>
<td>Inactivated whole virus COVID-19 vaccine (inactivated SARS-CoV-2 + aluminium hydroxide)</td>
<td>2.5, 5 or 10 μg (i.m.) 3x (0/28/56 or 0/28) 5μg (i.m.) 2x (0/14 or 0/21)</td>
<td>Not reported in detail</td>
<td>1:316 (2.5 μg, 0/28/58)^c 1:206 (5 μg, 0/28/58)^c 1:297 (10 μg, 0/28/58)^c 1:121 (5 μg, 0/14)^c 1:247 (5 μg, 0/21)^c</td>
<td>ND</td>
<td>ChiCTR2000031809</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CanSino^46</td>
<td>Ad5 nCoV (non-replicating AdV5 expressing spike protein)</td>
<td>5 x 10^{10}, 10^{11} VP (i.m.)</td>
<td>1:18.3–1:19.5 range^b</td>
<td>—</td>
<td>Yes</td>
<td>NCT04341389</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca^47</td>
<td>ChAdOx1nCOV-19 (non-replicating chimpanzee AdV expressing spike protein)</td>
<td>5 x 10^{10} VP 1 x 2´ (i.m.)</td>
<td>Median 1:218^d  Median 1:51^d  Median 1:4–1:16^e</td>
<td>Median 1:136^d  Median 1:29^d</td>
<td>Yes</td>
<td>NCT04324606</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderna^59</td>
<td>mRNA-1273 (mRNA)</td>
<td>2x 25, 100, 250 μg (i.m.)</td>
<td>Low</td>
<td>1:112.3 (25 μg)^f 1:343.8 (100 μg)^f 1:332.2 (250 μg)^f 1:339.7 (25 μg)^f 1:654.3 (100 μg)^f</td>
<td>—</td>
<td>NCT04283461</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer^60</td>
<td>BNT162b1 (mRNA)</td>
<td>2x 10, 30, 100 μg (i.m.)</td>
<td>Low</td>
<td>1:180 (10 μg)^h 1:437 (30 μg)^h</td>
<td>ND</td>
<td>NCT04368728</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer^84</td>
<td>BNT162b1 (mRNA) and BNT162b2 (mRNA)</td>
<td>2x 10, 20, 30 μg</td>
<td>Low</td>
<td>Day 28^i  BNT126b1 (18–55 years): 1:168 (10 μg) 1:267 (30 μg) BNT126b1 (65–85 years): 1:37 (10 μg) 1:179 (20 μg) 1:101 (30 μg) BNT126b2 (18–55 years): 1:157 (10 μg) 1:363 (20 μg) 1:361 (30 μg) BNT126b2 (65–85 years): 1:94 (20 μg) 1:147 (30 μg)</td>
<td>—</td>
<td>NCT04368728</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novavax^90</td>
<td>NVX CoV2373 (Matrix-M) Spike protein ‘rosettes’</td>
<td>2 x 2.5–25 μg (i.m. ± Matrix-M) 1x 25 μg (i.m. + Matrix-M)</td>
<td>1:128 (25 μg + Matrix-M)^i</td>
<td>1:3,906 (5 μg + Matrix-M)^i 1:3,305 (25 μg + Matrix-M)^i 1:41 (25 μg unadjuvanted)^i</td>
<td>CD4^+</td>
<td>NCT04368988</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vaccines in Phase III

- Moderna
- Pfizer
- AstraZeneca
- Janssen
- Novavax
- Gamaleya
- Sinovac/Sinopharm (3x)
- Cansino
What do the Pfizer results mean?

• 43,538 individuals are in the study
• 170 COVID-19 cases were recorded
  • 162 in the placebo group (9 severe)
  • 8 in the vaccine group (1 severe)
• 95% efficacy (they start measuring this 7 days post dose 2)
• 94% efficacy in the 65-85 year old group
• No significant safety concerns

• The vaccine received different degrees of approval in Bahrain, the UK, Mexico, Canada, Saudi Arabia, the EU, the US etc.
Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1
All-Available Efficacy Population

No. with events/No. at risk

A: BNT162b2 (30 μg)  B: Placebo

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
Pfizer CONFIDENTIAL: SDTM Creation: 17NOV2020 (10:49) Source Data: ade19ef Table Generation: 17NOV2020 (11:41)
(Cutoff Date: 14NOV2020, SOAPplot Date: 14NOV2020) Output File: /klik_web/ldap/user/ade19ef/Efficacy_FA_104/ade19ef_E01_km_di.xlsx

https://www.fda.gov/media/144245/download accessed 8Dec20
What do the Moderna results mean?

• 30,000 individuals are in the study
• 196 COVID-19 cases were recorded (33 in older/65+ adults)
  • 185 in the placebo group (30 severe cases, one death)
  • 11 in the vaccinated group (no severe cases)
• 94.1% efficacy (they start measuring this 14 days post dose 2)
• No significant safety concerns
• Some indication of reduction of asymptomatic infections

• The vaccine received different degrees of approval in the EU, the US etc.
Other vaccine (interim) results

- **AstraZeneca**
  - Two studies (they start measuring this 14 days post dose 2)
    - 62% efficacy in Brazil (n=11,636)
    - 90% efficacy in the UK (n=2,741)
  - 131 COVID-19 cases
  - It turned out the UK group got only a half-dose as first shot due to an error.....
  - We don’t know how well this vaccine works, but it works

- **Sinovac**
  - Trial with 31,000 individuals
  - 86% efficacy (no data available)
  - Licensed in the UAE

- **Gamaleya**
  - Sputnik V
  - 95% efficacy (no data available)
Reactogenicity

- Injection site pain
- Headache
- Fatigue
- Elevated temperature
- Myalgia
- Mild flu-like symptoms

→ unpleasant, but not dangerous

AdV>mRNA>recombinant protein>inactivated vaccine

Moderna/VRC mRNA 1273 via LNPs
Some people have severe allergic reactions to vaccines
  • These people were excluded from the Pfizer trial
  • Regular ‘allergic’ individuals were not excluded

The rate is approximately 11 reactions per 1 million vaccinated individuals (CDC)
The vaccines seem to be working better in younger people.
Protection from disease versus protection from infection
Longevity of protection

The immune response to the mRNA vaccines looks pretty normal
## Global rollout

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of doses administered ▼</th>
<th>Per 100 people</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global total</strong></td>
<td>15,905,118</td>
<td>–</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>U.S.</td>
<td>5,455,685</td>
<td>1.66</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>China</td>
<td>4,500,000</td>
<td>0.32</td>
<td>Dec. 31</td>
</tr>
<tr>
<td>Israel</td>
<td>1,490,000</td>
<td>16.46</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>U.K. +</td>
<td>1,300,000</td>
<td>1.95</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>U.A.E.</td>
<td>826,301</td>
<td>7.69</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Russia*</td>
<td>800,000</td>
<td>0.55</td>
<td>Jan. 02</td>
</tr>
<tr>
<td>Germany</td>
<td>367,331</td>
<td>0.44</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Italy</td>
<td>260,948</td>
<td>0.43</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Canada +</td>
<td>172,083</td>
<td>0.46</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Spain</td>
<td>139,339</td>
<td>0.30</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>100,000</td>
<td>0.29</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Poland</td>
<td>92,220</td>
<td>0.24</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Bahrain</td>
<td>63,893</td>
<td>4.31</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Denmark</td>
<td>63,312</td>
<td>1.09</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Mexico</td>
<td>48,236</td>
<td>0.04</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Portugal</td>
<td>42,035</td>
<td>0.41</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Argentina</td>
<td>32,013</td>
<td>0.07</td>
<td>Dec. 31</td>
</tr>
<tr>
<td>Romania</td>
<td>25,508</td>
<td>0.13</td>
<td>Jan. 04</td>
</tr>
<tr>
<td>Hungary</td>
<td>21,000</td>
<td>0.21</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>13,000</td>
<td>0.12</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Oman</td>
<td>10,728</td>
<td>0.26</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Slovenia</td>
<td>9,750</td>
<td>0.47</td>
<td>Dec. 29</td>
</tr>
<tr>
<td>Greece</td>
<td>9,528</td>
<td>0.09</td>
<td>Jan. 04</td>
</tr>
<tr>
<td>Chile</td>
<td>9,254</td>
<td>0.05</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Croatia</td>
<td>7,864</td>
<td>0.19</td>
<td>Dec. 30</td>
</tr>
<tr>
<td>Slovakia</td>
<td>7,201</td>
<td>0.13</td>
<td>Jan. 04</td>
</tr>
<tr>
<td>Austria</td>
<td>6,000</td>
<td>0.07</td>
<td>Dec. 30</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>5,448</td>
<td>0.08</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Finland</td>
<td>5,445</td>
<td>0.10</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Norway</td>
<td>4,036</td>
<td>0.08</td>
<td>Jan. 06</td>
</tr>
<tr>
<td>Ireland</td>
<td>4,000</td>
<td>0.08</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Estonia</td>
<td>2,535</td>
<td>0.19</td>
<td>Jan. 04</td>
</tr>
<tr>
<td>Kuwait</td>
<td>2,500</td>
<td>0.05</td>
<td>Dec. 29</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>2,455</td>
<td>0.05</td>
<td>Jan. 03</td>
</tr>
<tr>
<td>Lithuania</td>
<td>2,270</td>
<td>0.08</td>
<td>Dec. 28</td>
</tr>
<tr>
<td>France</td>
<td>2,000</td>
<td>0.00</td>
<td>Jan. 05</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>1,200</td>
<td>0.20</td>
<td>Dec. 30</td>
</tr>
</tbody>
</table>

Conclusions - Vaccines

• Several candidates induce strong neutralizing antibody responses in non-human primates and in humans

• Protection from lower respiratory tract infection (disease) in non-human primate models seems solid

• Protection from upper respiratory infection is often partial
  • None of the vaccines in clinical trials is designed to induce a mucosal immune response

• Pfizer and Moderna Phase III results look really good!

• The Pfizer and Moderna vaccines are already licensed in several countries, the AstraZeneca vaccine is licensed in the UK
Acknowledgements

Department of Microbiology/
Icahn School of Medicine at Mount Sinai
Peter Palese

Ania Wajnberg
(Mount Sinai Hospital)

Carlos Cordon-Cardo
Adolfo Firpo
(Mount Sinai Hospital)

Harm van Bakel
(ISMMS)

Mia Sordillo
David Rich
Judy Aberg
(Mount Sinai Hospital)

Adolfo García-Sastre
Lisa Miorin
Teresa Aydillo

florian.krammer@mssm.edu
http://labs.icahn.mssm.edu/krammerlab/
Twitter: @florian_krammer

Viviana Simon
Maria Bermudez-Gonzalez
Denise Jurczyszak
Matt Hernández

Fatima Amanat
Daniel Stadlbauer

Kantaro

CIVICs
Collaborative Influenza Vaccine Innovation Centers

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

Katherine Kedzierska (U Melbourne)
Jussi Hepojoki (U Helsinki)
Olli Vapalahti (U Helsinki)