Session 5: Vaccines

May 14th, 2021
12:45 PM to 1:45 PM (Pacific Time)
Rapid Federal Response to Development of Vaccines against COVID-19 (SARS-CoV-2)

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Vaccine Research Program, DAIDS, NIAID/NIH
Friday, May 14, 2021

* This presentation represents a summary as compiled from various sources by the presenter and does not reflect official NIAID/DAIDS policy.
Vaccine Development: A Lengthy, Risky and Expensive Process

Rapid Response in Developing COVID Vaccine

- Late Dec – early Jan 2020: Cases of pneumonia-like virus reported in China
- Jan 2020 – First genome sequence reported to GenBank by YZ Zhang et al/Fudan U
  - 68 days from sequence selection to 1st human injection of mRNA-1273
- Advance concepts/technology characterize a wide range of immune responses
- Evaluate safety, immunogenicity, efficacy, correlates of risk and protection
- Actively coordinate clinical research with basic/preclinical and translational research partners as well as clinical site operations, regulatory affairs, and other key issues
- Integrating NIH-supported networks to form CoVPN
- Building on existing research and infrastructure
# COVID-19 Vaccines based on Earlier Approaches

<table>
<thead>
<tr>
<th>Platform</th>
<th>Type</th>
<th>Developer</th>
<th>Phase</th>
<th>Same Platform</th>
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<tbody>
<tr>
<td>Non-replicating viral vector</td>
<td>ChAdOx1-S</td>
<td>Oxford/AZ</td>
<td>1/2</td>
<td>MERS, influenza, TB, Zika, HIV</td>
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<tr>
<td>Non-replicating viral vector</td>
<td>Ad Type 5</td>
<td>CanSino Biol Inc</td>
<td>2</td>
<td>Ebola, HIV</td>
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<td>RNA</td>
<td>LNP-mRNA</td>
<td>Moderna/NIAID</td>
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<td>Influenza, Zika, Chik</td>
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<td>Inactivated</td>
<td>Inactivated +/- alum</td>
<td>Multiple Chinese developers</td>
<td>1/2</td>
<td>Multiple</td>
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<td>Protein subunit</td>
<td>Recombinant GP nanoparticle/matrix M</td>
<td>Novavax</td>
<td>1/2</td>
<td>RSV; CCHF, HPV, VZV, Ebola, HIV</td>
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<td>RNA</td>
<td>3 LNP-mRNAs</td>
<td>Pfizer/BioNTech</td>
<td>1/2</td>
<td>HIV</td>
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<td>DNA</td>
<td>DNA plasmid/electroporation</td>
<td>Inovio Pharm.</td>
<td>1</td>
<td>Multiple</td>
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<td>Company</td>
<td>Phase 1 Milestones</td>
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<tr>
<td>Moderna</td>
<td>• Phase 1 manuscript published in NEJM 7/14/20</td>
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<td></td>
<td>• Phase 2 enrollment completed as of 7/8/20</td>
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<td></td>
<td>• Phase 3 started 7/27/20</td>
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<td>• As of 8/18/20: 10,393 enrolled; 73 sites enrolling</td>
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<td>AstraZeneca</td>
<td>• Oxford Phase 1/2 started 4/23/20 in UK</td>
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<td>• Oxford Phase 2/3 started early June 2020 in UK</td>
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<td>• IND submitted 7/15/20 and FDA Safe to Proceed received 8/14/20</td>
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<td>• Phase 3 started 8/28/20</td>
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<td>Sanofi</td>
<td>• Phase 1/2 scheduled to start 9/3/20</td>
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<td>• Protocol changes and manufacturing delays</td>
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<td>Janssen</td>
<td>• Phase 1/2 scheduled to start in July 2020</td>
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<td>• IND submitted on 7/2/20</td>
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<td>• Phase 3 started 9/21/20</td>
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<td>Novavax</td>
<td>• Phase 1 in Australia 18-59 years (n=131) published</td>
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<td>• Phase 2 US and Australia started 8/21/20</td>
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<td>• Phase 3 started 12/28/20</td>
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Vaccines against COVID-19: Summary/Future Challenges

• Importance of pivoting with existing and established resources and research infrastructure to address the COVID-19 pandemic
• NIH-funded research infrastructure and clinical trial networks to conduct efficacy trials with close communication with federal, industry, and other partners
• Robust pipeline of promising candidates in clinical development
  • Multiple and simultaneous approaches were necessary
  • Many challenges – New disease, incompletely understood immunity, uncertain trajectory of outbreak, political debates
  • Vaccine safety was be meticulously assessed
• Future challenges – variants, new pathogens
• Expanding research and public health capacity
SARS-CoV-2 variants and impact on antibodies and vaccines

Linqi Zhang, Tsinghua University
A cryo-electron tomography image of SARS-CoV-2 viruses, in gray, with a computer reconstruction of one virus. Sai Li, School of Life Sciences, Tsinghua University.

Yao and Li Cell 2020
Antibody blocks ACE2 and RBD interaction

Ju and Zhang Nature 2020
Key mutations in the spike of SARS-CoV-2 variants

Side view

Top view

with mAb P2C-1F11

Wang and Zhang Immunity 2021
Convalescent sera

Reciprocal serum ID$_{50}$ titre

B.1.1.7  WA1  B.1.351

1.4×  P = 0.522  P < 0.0001

10$^5$
10$^4$
10$^3$
10$^2$

Immune sera

Reciprocal serum ID$_{50}$ titre in authentic virus assay

B.1.1.7  WA1  B.1.351

Modern

1.6×  P = 0.064  P = 0.0005

Pfizer

1.3×  P = 0.322  P = 0.002

Wang and Ho Nature 2021
Conclusions

Our results clearly demonstrate major antigenic shifts and potentially broadening the host range of SARS-CoV-2 variants (B.1.351 and P1), which pose serious challenges to our current antibody therapies and vaccine protection.

Thank you for your attention and stay well.
COVID19, Vaccines and Diabetes: Perspective from India

Professor Anoop Misra
Chairman.
Fortis C-DOC Center for Diabetes, Obesity, Metabolic Diseases, and Endocrinology
New Delhi, India
Topic 1: The Second Wave, A Giant Tsunami!

- Consistently more than 300,000 cases per day for last 3 weeks.
- Number of active cases and deaths have been staggering.
- There is widespread collapse of healthcare; shortage of beds, oxygen, drugs, personnel
- Small hospitals are telling patients to come with their own oxygen and remdesivir!!
- Now COVID19 surging in rural villages.

Angry nurse: “You have got bed, oxygen and remdesivir….why didn’t you bring a doctor?”
Topic 2: What Caused it? (India Was Doing so Well!)

• Policymakers were totally blind sighted by this “Virus Blitzkrieg”.
• Decreased cases in Jan-Feb led to general belief that “India has defeated Corona”.
• A number of crowd gathering events were organised at the same time.

This is COVID19. Version 2 in India

• This virus appears different:
  • Very rapid spread (“one in family affected, others are 100% to be affected despite isolation”..).
  • Rapid rise of variants.
  • Airborne?
  • More virulence?
  • Affecting younger population? (because older people have been vaccinated?)

TIME, 10th May
Huge Gatherings Were Feasts for Unholy Virus!

Kumbh, a religious gathering which involves holy dip in The Ganges was attended by 3.5 million people. It was followed by rapid rise of COVID19 in attendees.

Elections in state of West Bengal and Rise of Virus

420-530% rise
Topic 3: World largest Vaccination Drive from World’s Largest Vaccine Manufacturer and Yet Not Enough Vaccines…..

• Vaccinations started well with two vaccines; Covaxin (Indian) and Covishield (AZ, manufactured in India).

• Initial planning was good, stepwise, HCW, then above 45 with morbidities, and then vaccinations opened to all adults from May 1. ▶

• Problems started when cases spiked; people avoided vaccinations/vaccination centres (“Covid hotspots”) ▶

• Then began shortage of vaccines….Additionally Sputnik vaccine was bought, and vaccine acquisition from other countries was made easy.
282 patients with new onset diabetes (NOD) occurring before pandemic were compared with NOD during COVID19 (NODCOVID). Patients with NODCOVID: Higher fasting, PP blood glucose and HbA1C than NOD.

Presently: Major spike in uncontrolled diabetes due to indiscriminate use of steroids; rising threat of rhinocerebral mucormycosis.

Durability of vaccine-induced antibody response in immunosuppressed uncontrolled glycemic state is unknown.
• Breakthrough infections are been recorded (9245/95 million vaccinated, CDC).

• In our center:
  • 123 employees, 113 vaccinated
  • 19 COVID19 infections, 15 breakthrough infections (13%).
  • All except one (moderate, hospitalised), mild and managed at home.

• Neutralization studies with Covaxin or Covishield sera against variant B.1.617:
  • Show positive results
  • Correlate with mild disease in patients with breakthrough infections.
• **B1.617** ("mutant of concern"):  
  - This variant carries 15 lineage defining mutations.
  - Two mutations, namely E484Q and L452R ("double mutant"), are in the area which is vital for antibody-based neutralization.
  - Third mutation, P681R, enables the virus to enter cells a little better.
  - More in western state of Maharashtra, now increasing in other areas.

• This mutant escapes inhibition by Bamlanivimab, and to some extent, against previous infection and vaccinations (Hoffman, 2021).
COVID-19 Vaccines in Immunocompromised Hosts

Aruna Subramanian, MD
Clinical Professor, Chief, Immunocompromised Host ID
Poor COVID-19 Outcomes in Immunosuppressed Patients: Urgent Need for Protection

- 318 HCT recipients
- 14% mechanical ventilation
- 30 day mortality: 33%
- Risk factors for death
  - Age >50
  - <12 months from allo HCT
  - Lymphoma in auto HCT

- 482 SOT recipients
- 27% mechanical ventilation
- 28 day mortality: 19%
- Risk factors for death
  - Age >50
  - Comorbidities

Antibody response after 2 dose mRNA vaccine in solid organ transplant recipients

658 participants:

- 15% Ab+ after 1st dose
- 39% Ab+ only after 2nd dose
- 46% Ab- despite 2 doses

Boyarsky B, et al. JAMA, May 2021
Effect of Immunosuppressive Agents on Response to Vaccines

FIGURE 2 Multivariate analysis for the risk of negative serology (odds ratio) in the transplant recipients’ group. Note: dashed line represents OR = 1

Kidney transplant and Hemodialysis Patients: Pfizer BNT162b2 - T cell responses

Sattler A, et al. medRxiv preprint doi: https://doi.org/10.1101/2021.04.06.21254963;
Recommendations from the American Transplant Society

1. Vaccinate all transplant recipients even with limited response to prevent or reduce severity of clinical disease
2. Priority vaccination of household members and caregivers
3. Continued masking/social distancing regardless of vaccination status
4. Vaccinate after recovery from COVID-19
5. Timing: preferably 2 weeks prior to transplant, or wait 1-3 months after transplant
6. No routine testing for antibody response
7. No routine immunosuppressant adjustment recommended

https://www.myast.org/covid-19-vaccine-faq-sheet