Vaccines and the Virus Omicron

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We have developed highly effective biomedical interventions; COVID-19 has been an unprecedented scientific success story

- Highly effective vaccines
- Highly effective monoclonal antibodies both for outpatient therapy and longer-term prevention
- Increasingly effective outpatient antiviral therapy to prevent hospitalization
  - PAXLOVID
  - IV Remdesivir 3-day regimen
  - Oral Molnupiravir
State of the COVID-19 Pandemic in January 2022 (month 24)

- Yet the Delta variant wave has become an Omicron tsunami of cases with public fatigue and discontent

- COVID-19 lifestyle restrictions are still operant for most of us in the US and globally

- It’s clear the virus is firmly established in the human population
  - New variants likely to emerge
  - Even the less lethal variants, such as Omicron, can produce significant morbidity and mortality
The Winter of Our Discontent

• Why are we living John Steinbeck’s book or perhaps, more correctly, Shakespeare had it right; as always!

• Has science not led us out of this wilderness as well as we need?
  • Are our tools not good enough?

• It is clear the virus is ‘quite skilled’ at antigenic variation, altering itself, and spreading quicker than any other human pathogen.
  o We must build and sustain an implementation science, basic and translational research infrastructure that matches these viral alterations and continue to improve our countermeasures.
My Role as Panelist

• Quick review of USG vaccine program

• How has the unanticipated variant change affected vaccination efficacy and strategy?

• What’s next?
From Discovery to Public Vaccination in 11 Months: Remarkable

- Virus isolated 1/7
- Sequence posted 1/10
- 2 SP spike protein sequence sent to Moderna 1/13
- Operation Warp Speed (OWS) announced 4/29
- Moncef Slaoui named OWS Chair 5/15
- RNA vaccine shipped for bottling for phase I clinical trials 2/24
- Initiated discussion on structure of phase 3 program 3/15
- Phase 1 clinical trial started [MODERNA] 3/16
- Phase 3 trial planning initiated 3/20
- Clinical site expansion initiated [MODERNA] MID-APRIL
- CoVPN officially announced
- ACTIV initiated
- First phase 3 trial initiated [COVE] 7/27
- [PFIZER TRIAL] 7/28
- Presidential election 11/3
- 1st interim efficacy data [PFIZER] 11/9
- 1st interim efficacy data [MODERNA] 11/16
- EUA [PFIZER] 12/11
- EUA [MODERNA] 12/18

2020

JAN  FEB  MAR  APR  MAY  JUN  JUL  AUG  SEP  OCT  NOV  DEC

SARS-CoV-2 ISOLATED & SEQUENCED

PHASE 1 TO PHASE 3 START

PHASE 3 ENROLLMENT TO 150 ENDPOINT FINISH EUA APPROVAL
Efficacy Results - starting Nov 2020

Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine
FP Polack et al. for the C4591001 Clinical Trial Group

- 2-dose regimen of BNT162b2
- 43,548 participants randomized
- 95% $Ve$ (95% CI 90.3; 97.6)
- EUA issued December 11, 2020
- FDA approval August 23, 2021

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine
LR Baden et al. for the COVE Study Group

- 2-dose regimen of mRNA-1273
- 30,420 participants randomized
- 94.1% $Ve$ (95% CI 89.3; 96.8)
- EUA issued Dec 18, 2020

J Sadoff et al. for the ENSEMBLE Study Group

- 1-dose regimen of Ad26.COV2.S
- 44,325 participants randomized
- 66.1% $Ve$ (95% CI 55.0; 74.8) overall
- US: 72% $Ve$ (95% CI 58.2; 81.7)
- EUA issued Feb 27, 2021
Science’s Breakthrough of the Year 2020: COVID-19 Vaccines
The full development pathway for an effective vaccine for SARS-CoV2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths. . . . We further discuss a collaborative platform for conducting harmonized, randomized controlled vaccine efficacy trials. This mechanism aims to generate essential safety and efficacy data for several candidate vaccines in parallel, so as to accelerate the licensure and distribution of multiple vaccine platforms and vaccines to protect against COVID-19.
Organizational Structure of OWS Clinical Trials Program

Harmonized Efficacy Trials

- RNA Platform 1
- ChAdOx1 Platform 2
- Ad26 Platform 3
- Nanoparticle Platform 4
- Pre-fusion Spike Recombinant Protein Platform 5

Collaborating clinical trial networks (CoVPN)

Harmonized endpoint data collection

Common Labs
1. Defining infection from disease
2. Quantitative immune responses to spike and spike epitopes
3. T-cell responses

Correlates of protection analyses within and cross protocols

Common DSMB
WHAT’S THE CHALLENGE?

WE NEED OVER 125,000 VOLUNTEERS READY TO ROLL UP THEIR SLEEVES BY THE END OF 2020

Sally Bock
The COVID 19 vaccine success was not quick!

It was based upon 20-years of hard scientific effort from basic science to translational vaccinology
The virus has fought back with rapid antigenic variation
Projected variant proportions in the US

- Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
- These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates.
- AY.1-AY.127 and their sublineages are aggregated with B.1.617.2. BA.1, BA.2 and BA.3 are aggregated with B.1.1.529.
Geometric mean of decrease in neutralization titers by variant

<table>
<thead>
<tr>
<th>Variant</th>
<th>Fold</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Alpha</td>
<td>1.6</td>
<td>1.5 - 1.7</td>
</tr>
<tr>
<td>Beta</td>
<td>8.8</td>
<td>8.0 - 9.7</td>
</tr>
<tr>
<td>Gamma</td>
<td>3.5</td>
<td>3.1 - 4.0</td>
</tr>
<tr>
<td>Delta</td>
<td>3.9</td>
<td>3.5 - 4.4</td>
</tr>
<tr>
<td>Omicron</td>
<td>30</td>
<td>20 - 38</td>
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</tbody>
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**Omicron Requires Boosting**  
Variants Influence Vaccine Effectiveness  
(MMWR – January 21, 2022)

<table>
<thead>
<tr>
<th></th>
<th>Delta (95% CI)</th>
<th>Omicron (95% CI)</th>
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<tbody>
<tr>
<td><strong>ER Visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mRNA vaccine</strong></td>
<td></td>
<td></td>
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<tr>
<td>2 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 14 – 179 days</td>
<td>86% (85 - 87)</td>
<td>52% (46 - 58)</td>
</tr>
<tr>
<td>• &gt;180 days</td>
<td>76% (75 - 77)</td>
<td>38% (32 - 43)</td>
</tr>
<tr>
<td>3 doses ⬤</td>
<td>94% (93 - 94)</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mRNA vaccine</strong></td>
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<tr>
<td>2 doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 14 – 179 days</td>
<td>90% (89 - 90)</td>
<td>81% (65 - 90)</td>
</tr>
<tr>
<td>• &gt;180 days</td>
<td>81% (80 - 82)</td>
<td>57% (39 - 70)</td>
</tr>
<tr>
<td>3 doses ⬤</td>
<td>94% (93 - 95)</td>
<td>90% (80 - 94)</td>
</tr>
</tbody>
</table>

* ⬤ median duration follow up post 3rd dose for Omicron period is only 44 days
Omicron and Beyond

• We will sweat through Omicron until we make more monoclonals and get the protease drugs into the field.
• Better treatment options will alter perception of risk.
• In the vaccine arena we have a durability issue. How to solve it? Platform versus insert or both?
• There are second generation vaccines in development; creating a research infrastructure to evaluate which ones add major benefit over current platforms is needed.
Living with SARS-CoV-2

• Endemicity of SARS-CoV-2 requires a sustained and thoughtful research program.
  - The structure we are working under had terrific alignment between big pharma and public health; less so now when greater innovation needed to solve the problem

• We need to fund a sustained research program for the continued development of better vaccines and therapies.

• We must take greater global responsibility than we now have. It’s not effective just to donate excess vaccines. Low- and middle-income countries need the ability to make their own vaccines and have vaccines be part of their culture and economy.

• We need to merge HIV and COVID-19 policies and practices (TB also).
  • Immune suppressed persons are where the multi-mutational variants have emerged; Alpha, Beta, and Omicron