COVID Vaccines: Approaches to vaccine trial design

November 4, 2020
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These are my views, and do not represent those of the NIH, DHHS, or the US government.
Plan

- Vaccine research
- Ethical challenges in vaccine trials
- Approaches to testing a SARS CoV-2/COVID-19 vaccine
- Current status/ COVID-19 vaccine landscape
Vaccines

• “With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction...”

• Since 2000-
  – Deaths in children < 5yo reduced (Millennium Development Goals)
  – More children reached than ever before (>100 million in 2005-07)
  – More vaccines available and more lives saved in developing countries
  – More money available through innovative funding mechanisms
  – Most productive decade in history of vaccine development
  – Global vaccine market has tripled, vaccine industry one of fastest growing sectors of industry

Plotkin S. Vaccines we Need but Don’t Have. *Viral Immunology* 2018

One of the brightest chapters in the history of science is the impact of vaccines on human longevity and health.” (S Plotkin, 2014)
Vaccines

• Substantial contributions to global public health, but always controversial
  – Disturbing the natural order
  – Safety and untoward effects
  – Public good versus individual rights
  – Uneven access
  – ...
The paradox of vaccines

Vaccine risk
Vaccine success
Vaccines

• Many ethical challenges:
  – Development and testing of vaccines
  – Distribution/allocation of vaccines
  – Public health use of vaccines
  – Social acceptability of vaccines
  – Vaccine related injury and compensation
  – Anti-vax movement
  – Etc.
Vaccines

• Many ethical challenges:
  – Development and testing of vaccines
  – Distribution of vaccines
  – Public health use of vaccines
  – Untoward effects
  – Social acceptability of vaccines
  – Allocation
  – Etc.
Vaccine development and testing

- Basic research
- Preclinical testing
- Clinical Testing
  - Phase I - Safety/toxicity
  - Phase II - Safety/immunogenicity
  - Phase III - Safety/efficacy
  - Phase IV - Post-marketing
How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

**PHASE 1**
- 20-100 healthy volunteers
- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

**PHASE 2**
- Several hundred volunteers
- What are the most common short-term side effects?
- How are the volunteers’ immune systems responding to the vaccine?

**PHASE 3**
- Hundreds or thousands of volunteers
- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

**FDA licenses the vaccine only if:**
- It's safe and effective
- Benefits outweigh risks

FOR MORE INFORMATION, VISIT HTTPS://WWW.FDA.GOV/CBER

Vaccine Development Goals

• **SAFE** - Reasonably/acceptably safe in a wide range of possible users

• **EFFECTIVE** - in a large percentage of persons who are at risk
  - Relatively simple to deliver, store, and administer
  - Affordable & Widely available
  - Used
Ethical challenges in phase 3 vaccine research

- Healthy populations (at risk of infection or of disease)
- Large numbers of participants
- Some risk to individuals, conditional individual benefit
- Benefit to community or society
Vaccine benefits to community and society

- Reduced morbidity and mortality
- Herd immunity and protection
  - Herd immunity occurs when the % of persons immune to a disease (the herd) is large enough to reduce the likely spread from person to person. Others in the community, not just those who are immune, are protected.
  - Can protect those who can’t receive or sufficiently respond to a vaccine.
SARS CoV-2
SARS CoV-2
Prevention of COVID-19 with a Highly Effective Vaccine and Widespread Uptake

Combination Prevention for COVID-19

- Physical distancing
- Face coverings in public
- PPE for high-risk occupations
- Limit crowds/public gatherings
- School, venue and nonessential business closures
- Monoclonal antibodies and other drugs
- Hand hygiene
- Prompt testing and isolation
- Contact tracing
- Avoiding touching face

Vaccines

Courtesy of ASFAuci
COVID-19 Vaccine Development Goals

• SAFE - Reasonably/acceptably safe in a wide range of possible users

• EFFECTIVE in a large percentage of persons who are at risk
  • Relatively simple to deliver, store, and administer
  • Affordable & Widely available
  • Used

• FAST
Pre-Clinical Testing
- Test antigens
- Test adjuvants
- Use animal models
  - Mouse
  - Ferret
  - Rhesus macaque
- Use information from other related viruses

Clinical Testing
- Phase I: Dose tested, Small # of volunteers (~40), At-risk population
- Phase II: Larger # of volunteers (100s), At-risk population
- Phase III: Large # from general population (1000s)

Monitoring
- Phase IV: Mass vaccination

5-10 years
- 6-9 months, simultaneously

SARS-CoV-2
Accelerating SARS CoV-2 vaccines

• “Pandemic” Speed (Coalition for Epidemic Preparedness Innovation-CEPI)
• Operation Warp Speed- (US govt)
  – Produce and deliver 300 million doses of safe and effective vaccines as early as Jan 2021; part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.
  – Partnership among DHHS components, including CDC, NIH, BARDA, ASPR, DoD, and engagement with private firms and other federal agencies
  – Select promising candidates, investing in development and manufacturing.
  – Distribution strategy
Pace of vaccine development

- Vaccine research started within weeks of identifying and sequencing SARS CoV-2
- By October 2020, 200 vaccine candidates in the pipeline

“Shortcuts in vaccine development and testing might expedite the timeline of scientific progress, and could also result in compromising quality, acceptability, and ethics”

Grady C et al. So much at stake: Ethical tradeoffs in accelerating SARS CoV-2 vaccine. Vaccine Aug 2020
The Risks of Rushing a COVID-19 Vaccine

Telescoping testing time lines and approvals may expose all of us to unnecessary dangers

By William A. Haseltine on June 22, 2020
Adverse Consequences of Rushing a SARS-CoV-2 Vaccine
Implications for Public Trust

As the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic persists across the US and the world, the spotlight on vaccine science has never been more intense. Researchers across the globe are working rapidly to produce a potential vaccine, and 7 candidates are already in clinical trials. Operation Warp Speed, the vaccine development project announced by President Trump, has advocated for a vaccine to be made available in the US by the beginning of 2021. But for scientists and physicians, the term “warp speed” should trigger concern. Good science requires rigor, discipline, and deliberate caution. Any medical therapy approved for public use in the absence of extensive safeguards has the potential to cause harm, not only for COVID-19 prevention efforts and vaccine recipients, but also for public trust in vaccination efforts worldwide.

Long before coronavirus disease 2019 (COVID-19), vaccine hesitancy and refusal were increasing. In 2019, the World Health Organization listed vaccine refusal as one of the top 10 global health threats. Pediatricians, in particular, frequently encounter resistance to childhood vaccinations, and as a result, outbreaks of measles, mumps, and rubella are increasingly common. One recent outbreak in New York City affected 117 people, including 11 people who had to be quarantined. This is a serious problem that must be addressed.

What cannot and must not be allowed is for desperation to result in the suspension of scientific principles and ethical research values.
Lurie N et al. Developing COVID-19 vaccines at Pandemic Speed. NEJM May 2020
Various approaches for testing SARS CoV-2 vaccine

• Randomized controlled trials
• Combined phases
• Variations on RCT design
• Controlled human infection studies
• Approval via an emergency use authorization
Ethical framework: 8 principles

• Collaborative partnership
• Valuable scientific question
• Valid scientific methodology
• Fair subject selection
• Favorable risk-benefit
• Independent review
• Informed consent
• Respect for enrolled subjects

Table 1. Selected ethically relevant dimensions affecting social and scientific value in accelerated vaccine development approaches

<table>
<thead>
<tr>
<th>Approach</th>
<th>Speed</th>
<th>Total number of research participants</th>
<th>Risks to participants and vaccinees</th>
<th>Cost</th>
<th>Feasibility - research capacity</th>
<th>Feasibility - pandemic dynamics</th>
<th>Social risks: Distrust or Negative Public Perception</th>
</tr>
</thead>
<tbody>
<tr>
<td>STANDARD</td>
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<tr>
<td>Consecutive Phase I, II and III Trials</td>
<td>Years to trial completion</td>
<td>Thousands to tens of thousands</td>
<td>Low and carefully monitored</td>
<td>High</td>
<td>High: existing experience and infrastructure</td>
<td>Showing efficacy depends on sufficient incidence</td>
<td>Usually low; familiar trajectory</td>
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<tr>
<td>ACCELERATED</td>
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<tr>
<td>Individually randomized RCT Combining Phases II/III</td>
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<tr>
<td>Cluster randomized RCT in Phase III</td>
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<tr>
<td>EUA following Phase I</td>
<td></td>
<td>N/A</td>
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<tr>
<td>CHI study with or without field trial</td>
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Grady et al Vaccine 2020
Deming M et al. Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models. NEJM Sept 2020
Vaccine RCT considerations

Design:
• Parallel individual randomization
• Cluster randomization
• Alternative design- e.g. ring vaccination, stepped-wedged

Comparator
Randomization
Double Blinded
Sample size
Primary endpoints
Coronavirus Vaccine Tracker

By Jonathan Corum, Sui-Lee Wee and Carl Zimmer  Updated October 26, 2020

Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing 48 vaccines in clinical trials on humans, and at least 88 preclinical vaccines are under active investigation in animals.
Platforms used by previous vaccines: inactivated, live attenuated, subunit
Newer Platforms: Nucleotide based, viral vector based
<table>
<thead>
<tr>
<th>Platform</th>
<th>Developer</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
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</thead>
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<tr>
<td>Nucleic acid</td>
<td>moderna</td>
<td>Enrolled</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>BIONTECH Pfizer</td>
<td>Enrolled</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Viral vector</td>
<td>UNIVERSITY OF OXFORD AstraZeneca</td>
<td>Enrolled</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Janssen</td>
<td>Enrolled</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>MERCK</td>
<td>Ongoing</td>
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<tr>
<td>Protein subunit</td>
<td>NOVAVAX</td>
<td>Ongoing</td>
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<td>gsk SANOFI</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Pfizer</td>
<td>Moderna</td>
<td>Astra-Zeneca</td>
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<tr>
<td>Sample size</td>
<td>30,000</td>
<td>30,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Participants getting vaccine</td>
<td>15,000</td>
<td>15,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Efficacy target</td>
<td>60%</td>
<td>60%</td>
<td>50%</td>
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<tr>
<td>Lower 95% CI efficacy</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Number of Events at Completion</td>
<td>164</td>
<td>151</td>
<td>150</td>
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<tr>
<td>Number of Interim Analyses</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Alpha-spending function at</td>
<td>Pocock-</td>
<td>O’Brien-</td>
<td>Lan-DeMets</td>
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<tr>
<td>Interim Analysis for Stopping</td>
<td>type</td>
<td>Fleming type</td>
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<td>Rule</td>
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<tr>
<td>Number of Events at 1st (or</td>
<td>32</td>
<td>53</td>
<td>75</td>
</tr>
<tr>
<td>only) Interim Analysis</td>
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</table>
FDA guidance


COVID-19 Vaccine development

- Scientific challenges
- Ethical challenges
- Practical challenges
- Societal challenges
Public trust

• Science literacy
• Trust in science
• Public Trust
Just 50% of Americans Plan to Get a COVID-19 Vaccine. Here’s How to Win Over the Rest

W Cornwall
A study of potential acceptance of a COVID-19 vaccine in 13,426 randomly selected individuals across 19 countries, most with a high COVID-19 burden.

- High heterogeneity in responses between countries.
- Furthermore, willingness to get vaccinated might not be necessarily a good predictor of acceptance.


<table>
<thead>
<tr>
<th>Willingness to take vaccine</th>
<th>Accept COVID Vaccine if available?</th>
<th>Accept vaccine if employer recommended?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely agree</td>
<td>46.8%</td>
<td>39.1</td>
</tr>
<tr>
<td>Somewhat agree</td>
<td>24.7%</td>
<td>29.5</td>
</tr>
<tr>
<td>Neutral</td>
<td>14.2%</td>
<td>20.6</td>
</tr>
<tr>
<td>Somewhat disagree</td>
<td>6.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Completely disagree</td>
<td>8.1</td>
<td>9.8</td>
</tr>
</tbody>
</table>
Scientists Warn Americans Are Expecting Too Much From a Vaccine
Ethical framework: 8 principles

• Collaborative partnership
• Valuable scientific question
• Valid scientific methodology
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• Independent review
• Informed consent
• Respect for enrolled subjects