An Overview of COVID-19 Vaccine Efficacy Trials

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VACCINE BASICS
WHO R&D Blueprint

Prioritized pathogens
- Crimean Congo Hemorrhagic Fever (CCHF)
- Ebola and Marburg virus disease
- Lassa fever
- MERS-CoV and SARS
- Nipah and henipaviral diseases
- Rift Valley Fever (RVF)
- Zika
- Disease X
Expectations for COVID-19 vaccines

- "The principal goal of a vaccine efficacy trial is to obtain efficacy and effectiveness data that can support broader use of a vaccine under a defined regulatory framework."

- Intended use for COVID-19: billions vaccinated

Dean et al. 2019 [https://stm.scientificmag.org/content/11/499/eaat0360.abstract]
Regulatory pathway for vaccines

**Preclinical data**
- Evidence of safety and anti-disease activity in animals
  - Requires a validated animal model

**Phase 1 trials**
- Smallest trials
- First-in-human
- Focus on safety
- Establish dosing
- Some immune response data

**Phase 2 trials**
- Larger trials
- More safety data
- More immune response data
- Explore subgroups

**Phase 3 trials**
- Largest trials
- Field trials
- Disease-related primary outcome (e.g. prevent COVID-19)
- More safety data
Accelerating this pathway during a pandemic

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**Conduct animal studies in parallel where safe to start in-human trials**

**Start planning subsequent steps before the prior step is completed**

**Shorter duration of follow-up than in a traditional trial**

**Start scaling up manufacturing before receiving regulatory approval**

**Accelerated review process**
- Emergency Use Authorization instead of full licensure

**REGULATORY APPROVAL**
COVID-19 vaccine platforms

Over 100 vaccine candidates currently in development, utilizing a range of vaccine platforms

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Single dose</th>
<th>Licensed platform</th>
<th>Fast to develop</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA</td>
<td>✔</td>
<td>✔</td>
<td>☑</td>
<td>BioNTech/Pfizer, Moderna</td>
</tr>
<tr>
<td>DNA</td>
<td>✔</td>
<td>✔</td>
<td>☑</td>
<td>Inovio</td>
</tr>
<tr>
<td>Non replicating vector</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Gamaleya, Oxfords/AZ, Janssen</td>
</tr>
<tr>
<td>Inactivated</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>Sinopharm, Bharat Biotech</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Codagenix</td>
</tr>
<tr>
<td>Replicating viral vector</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Merck</td>
</tr>
<tr>
<td>Protein subunit</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>Novavax</td>
</tr>
</tbody>
</table>

Table: Summary of general attributes

Modified from Lurie et al. (2020) *NEJM*  [https://covid19.trackvaccines.org/vaccines/](https://covid19.trackvaccines.org/vaccines/)
Tracking vaccines in the pipeline

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee  Updated Jan. 12, 2021

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>43</td>
</tr>
<tr>
<td>Phase 2</td>
<td>21</td>
</tr>
<tr>
<td>Phase 3</td>
<td>20</td>
</tr>
<tr>
<td>Limited</td>
<td>8</td>
</tr>
<tr>
<td>Approved</td>
<td>2</td>
</tr>
<tr>
<td>Abandoned</td>
<td>1</td>
</tr>
</tbody>
</table>

- Phase 1: Vaccines testing safety and dosage
- Phase 2: Vaccines in expanded safety trials
- Phase 3: Vaccines in large-scale efficacy tests
- Limited: Vaccines in early or limited use
- Approved: Vaccines approved for full use
- Abandoned: Vaccines abandoned after trials

COVID-19 VACCINES

Key features of COVID-19 trials

- Adult participants (16+ or 18+)
  - Including high-risk groups (elderly adults, people with comorbidities)

- Individual randomization
  - Active vaccine vs. placebo

- Large trials
  - Tens of thousands of participants across many locations, countries

- Trials are EVENT-DRIVEN
  - The amount of efficacy data we need depends upon the number of cases we observe
What is a successful vaccine?

- Efficacy = 1 – [“risk” in vaccine]/[“risk” in placebo]
- 50% efficacy against disease or infection
- Rule out a lower confidence bound of 30%
  - e.g. 95% CI (0.35, 0.85) successful
  - e.g. 95% CI (0.25, 0.75) not successful
- Prevent the approval of weakly effective vaccines
  - Divert resources
  - Lead to riskier behavior
  - Jeopardize evaluation of future vaccines
  - Erode public confidence in the process

Krause et al. Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31821-3
Selecting the primary endpoint

- **SARS-CoV-2 infection**
  (+) Relevant to stemming spread. Many infections will be observed.
  (-) Clinical relevance unclear. Measured coarsely in time. Many false positives.

- **COVID of any severity**
  (+) More clinically relevant. Reasonable number of cases expected.
  (-) Clinically relevant if symptoms are mild?

- **Severe COVID**
  (+) Most clinically relevant, a priori highest expected efficacy
  (-) Very few cases expected to be observed. Longer evaluation needed.
How long does it take to tell if the vaccine works?

- Target number of events is ~150 cases of PCR-confirmed, symptomatic COVID

- These events must occur more than 7 (or 14) days after the second dose to be counted
  - This excludes people who are infected before receiving the full vaccine

- How long it takes to accrue this data depends upon how transmission is ongoing…. 
How long does it take to tell if the vaccine works?
Follow up for safety

- "FDA guidance recommends that data from phase 3 studies to support an EUA … include a median follow-up duration of at least 2 months after completion of the full vaccination regimen” – Krause & Gruber

- EUA: “known and potential benefits of a product outweigh its known and potential risks”

- “Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt”

- Balances the need for long-term safety data with the need for a vaccine to address the current pandemic

Krause & Gruber (2020) NEJM, DOI: 10.1056/NEJMp2031373
STATUS UPDATE
COVID-19 VACCINES

Status update

BioNTech/Pfizer
BNT162b2

Approved in 48 countries
3 trials in 6 countries

Polack et al. (2020) NEJM
https://covid19.trackvaccines.org/

https://www.fda.gov/media/144245/download
COVID-19 VACCINES

Status update

**RNA**

**Moderna**

**mRNA-1273**

Approved in 34 countries

5 trials in 1 country

Baden et al. (2020) *NEJM*

https://covid19.trackvaccines.org/
COVID-19 VACCINES

Status update

Articles

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against COVID-19: an interim analysis of two randomised controlled trials

<table>
<thead>
<tr>
<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>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>
</tr>
<tr>
<td>COV002 (UK)</td>
<td>86</td>
<td>18/3744 (0.5%)</td>
<td>38.6 (170,369)</td>
</tr>
<tr>
<td>LD/SD recipients</td>
<td>33</td>
<td>3/1367 (0.2%)</td>
<td>14.9 (73,313)</td>
</tr>
<tr>
<td>SD/SD recipients</td>
<td>53</td>
<td>15/2377 (0.6%)</td>
<td>56.4 (97,056)</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>
</tr>
<tr>
<td>All SD/SD recipients</td>
<td>98</td>
<td>27/4440 (0.6%)</td>
<td>56.4 (174,986)</td>
</tr>
</tbody>
</table>

Non Replicating Viral Vector

COVID-19 VACCINES

Status update

Reports that the Phase 3 trial reached its final total of 78 cases

Estimated vaccine efficacy was 91.4%

20 of the 78 cases were severe, and all were in the placebo group

AstraZeneca is partnering with Gamaleya to see if combining their vaccines would increase the efficacy of the Oxford vaccine

https://covid19.trackvaccines.org/

Status update

South African Phase IIb trial likely to reveal results within the next two weeks

UK trial fully enrolled

US/Mexico trial launched

One dose vaccine

Results expected by the end of January

https://covid19.trackvaccines.org/
Status update

Almost a million people have been given an experimental Chinese coronavirus vaccine, pharmaceutical giant claims

https://covid19.trackvaccines.org/
What’s ahead in Phase 3 COVID-19 vaccine trials

- More Phase 3 trial results to come…
- What happens to ongoing/planned trials?
- Important that there is a clear pathway for generating evidence to support full licensure
- Do not discount the “tortoises”
Planning future trials amidst uncertain epidemiology

- Flexible trial design that uses a master or core protocol
- Modeling provides a data-driven approach for trial planning, site selection, feasibility assessment
- To come…
  - Correlates analysis
  - Observational studies

Key Open Questions

- Long-term efficacy/safety
- Subgroup specific effects
- Ability of the vaccines to prevent infection or otherwise reduce infectiousness

Science 2020, DOI: 10.1126/science.abe5938
CONCLUSION
Conclusion

- COVID-19 vaccine trials present a new paradigm for vaccine evaluation

- Because of widespread community transmission, these trials have been able to rapidly generate evidence

- It is critical that there remains a pathway for evaluating other vaccines, as we want diverse and widely available products to meet global need
THANK YOU!

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