

Trial designs for New SARS-CoV2 Vaccine

Placebo controlled & platform trials

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Today's topics

- Current situation on COVID-19 clinical trials
- Difficulty on placebo controlled trials and alternative approaches
- Correlates of prevention and immunogenicity
- Challenge to Platform design

Current situation on COVID-19 clinical trials

Current situation on COVID-19 clinical trials

- Vaccine approvals/EUA have been based on COVID-19 Vaccine Efficacy trials.
- Randomized placebo controlled trials are requested in guidance in worldwide.
- U.S.FDA/WHO Successful Criteria
 - Point estimate of $VE \geq 50\%$ with lower 95% confidence limit $>30\%$
- 16 COVID-19 vaccines are being distributed internationally.¹⁾

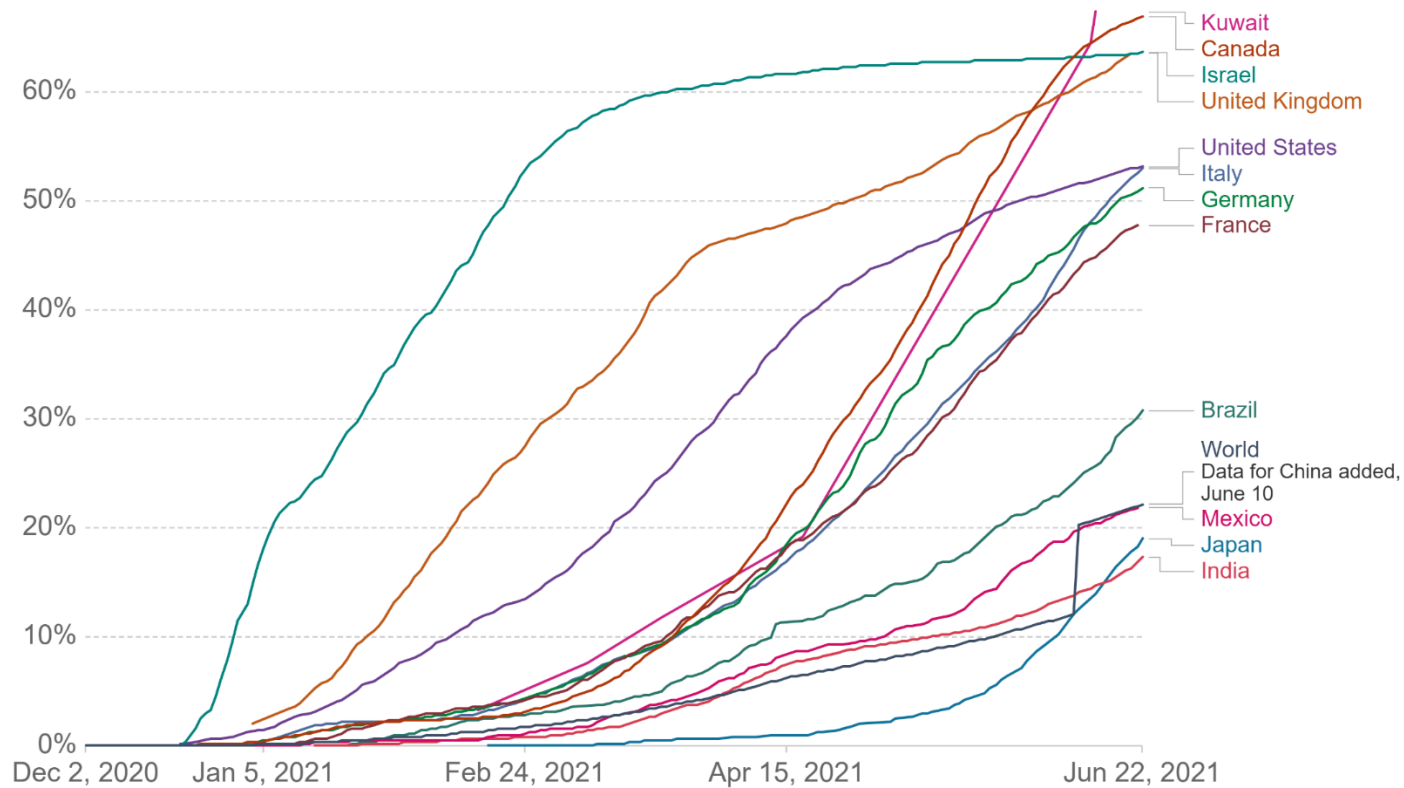
1) New York Times Coronavirus Vaccine Tracker, accessed June 23

Difficulty of placebo controlled trials and alternative approaches

Boosting vaccination in the world

Share of people who received at least one dose of COVID-19 vaccine

Share of the total population that received at least one vaccine dose. This may not equal the share that are fully vaccinated if the vaccine requires two doses.



Source: Official data collated by Our World in Data – Last updated 23 June, 10:00 (London time)

OurWorldInData.org/coronavirus • CC BY

Rapid vaccination makes difficult to keep placebo arms

The screenshot shows the top of a Washington Post article. The header includes the newspaper's name, a search icon, a 'Sections' menu, a subscription offer for \$29 per year, and a 'Sign in' button. Below the header is a navigation bar with links for 'Coronavirus', 'U.S. map', 'World map', 'Vaccine tracker', 'Vaccine FAQ', 'Variants FAQ', 'A pandemic year', and 'Coronavirus L'. The article is categorized under 'Business'. The main headline reads 'Elderly begin to drop out of Novavax vaccine trial to get Pfizer and Moderna shots'. A sub-headline states: 'States have responded to the slow rollout of coronavirus vaccine by expanding eligibility to people over 65. But that is making it more difficult to recruit subjects for clinical trials of other vaccines that have yet to win approval.' Below the text are two images: one of a syringe with 'NOVAVAX' in the background, and another showing an Aston Martin car with a Girard-Perregaux watch advertisement.

The Washington Post
Democracy Dies in Darkness


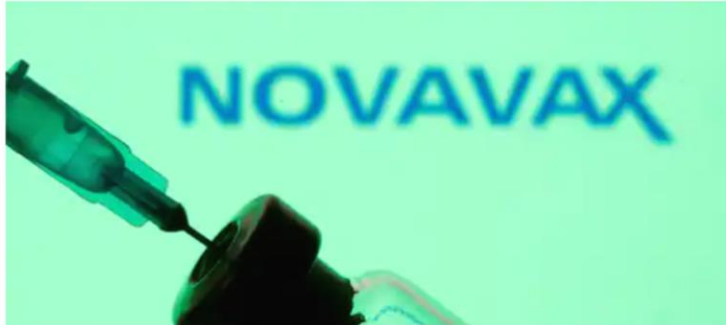
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Coronavirus U.S. map World map Vaccine tracker Vaccine FAQ Variants FAQ A pandemic year Coronavirus L

Business

Elderly begin to drop out of Novavax vaccine trial to get Pfizer and Moderna shots

States have responded to the slow rollout of coronavirus vaccine by expanding eligibility to people over 65. But that is making it more difficult to recruit subjects for clinical trials of other vaccines that have yet to win approval.



Challenge to evaluate “Next wave” vaccine candidates

- Randomized placebo controlled trials is still preferable design to evaluate vaccines.
- However, it becomes infeasible in many countries to set placebo arm.
- >100 additional candidate COVID-19 vaccines are in clinical phase.¹⁾
- It is still important to evaluate and approve “Next wave” COVID-19 vaccines to promote equitable access to vaccines in the world.

1) WHO COVID-19 vaccine tracker and landscape, accessed 23 June.

Alternative approaches?

Non-inferior design with clinical endpoints¹⁾

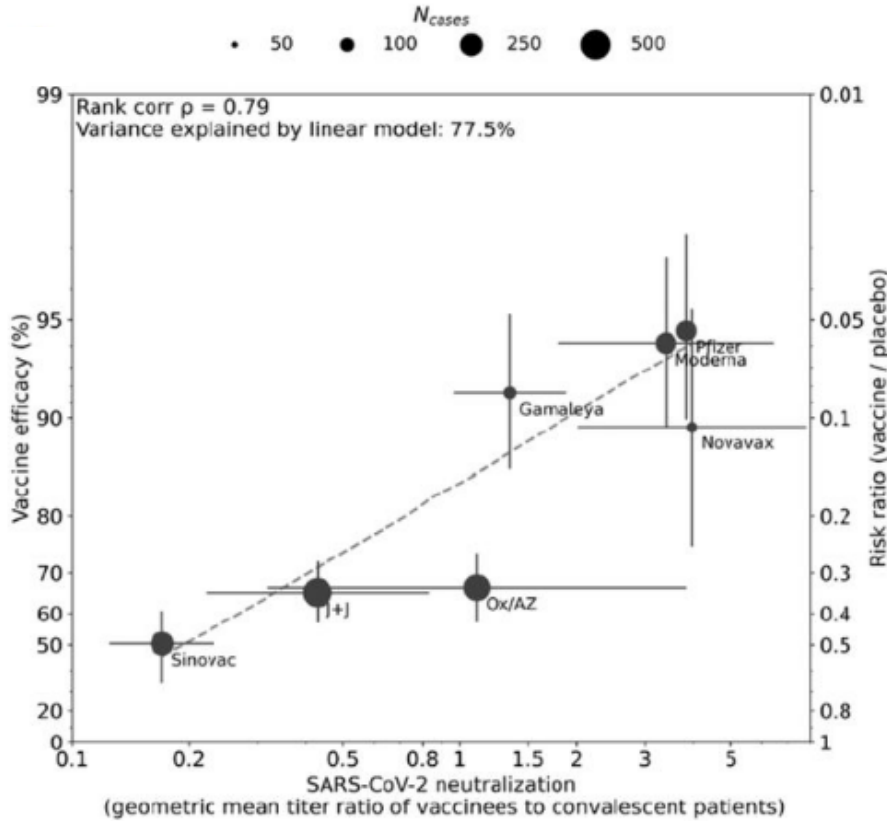
- “Such trials often require approximately two- to three-fold the person-years follow-up than a placebo-controlled trial.”
- Is it acceptable for peoples and developers?

Immunological approach to evaluate vaccines

1) Fleming TR *et al.*, Clinical Trials, 2021
DOI: 10.1177/1740774520988244

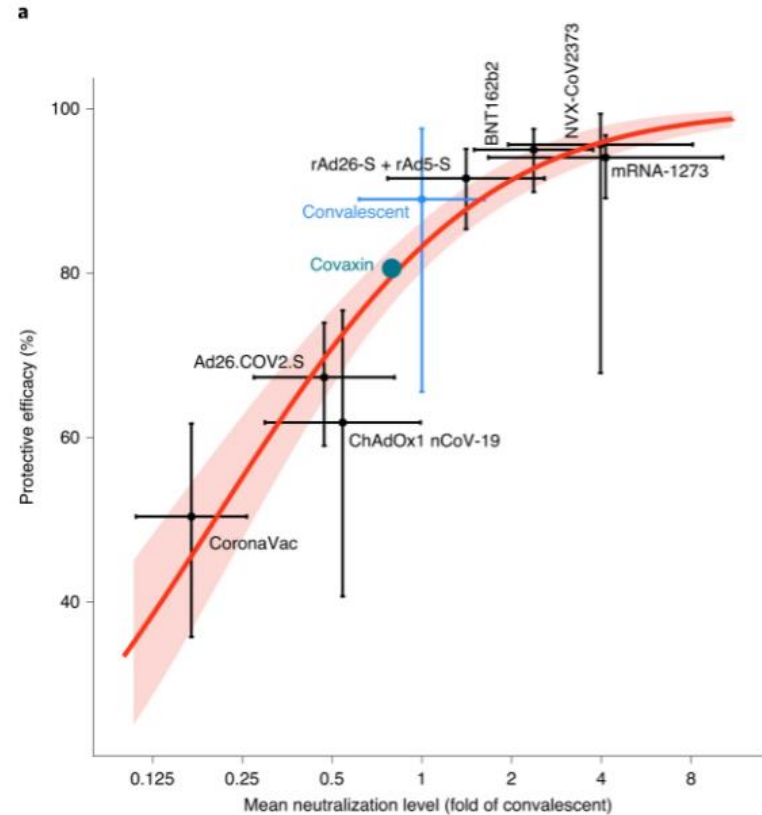
Correlates of protection and immunogenicity

Correlation between vaccine efficacy and immunogenicity



Neutralizing Assay

Earle KA, *et al.*, Vaccine, 2021



Khoury DS *et al.*, Nature Med, 2021

Neutralization Ab as a surrogate marker

- Recent researches suggest immune biomarkers (especially Neutralization Ab) can be work as a surrogate marker for bridging across vaccines.
- Immune biomarkers has already been used for bridging efficacy data to additional groups (e.g., pediatrics) and variant vaccines.
- Vaccines that can induce neutralizing antibodies to be expected VE exceeding the existing successful criteria ($VE \geq 50\%$) should be approved.

Need further consideration

How to choose active comparator?

- The same modality is preferable, but across modality can be acceptable in certain situations.

Cellular immune response

- Big difference on immune responses may make the evaluation difficult.

Follow up

- Vaccine effectiveness should be evaluated by hard endpoint and duration of efficacy is also important.

Challenge to Platform design

Challenge to platform design

- In order to evaluate multiple SARS-CoV-2 vaccines efficiently, it would be possible to evaluate their efficacy using **platform studies**.
- Platform study can be useful in particular when **the same active comparator is used**.
- Comparison with subjects in the active control group included at the same time is desirable when conducting the study.

Thank you very much!!

