WHO- Developing a Framework for Evaluating New Covid-19 Vaccines

Why selection of a comparator and assumptions on its efficacy are essential

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Designs for Evaluating New COVID-19 Vaccines

Experimental COVID-19 Vaccine (EXP) ↔ Placebo

1º Endpoint: *Virologically Confirmed Symptomatic COVID-19 Disease*

EXP, immediate vaccination ↔ EXP, vaccination within a few months

1º Endpoint: *Virologically Confirmed Severe COVID-19 Disease*

Experimental COVID-19 Vaccine (EXP) ↔ Active Comparator (AC) Vaccine

1º Endpoint: *Virologically Confirmed Symptomatic COVID-19 Disease*  
*or an Immunological Biomarker validated to be a Correlate of Protection*

- Efficient design
- Results that are: Interpretable & Reliable
- Randomized deployment...
- Potential ‘Follmann design’ for ↑ durability insights

World Health Organization  
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Powering research to prevent epidemics
Some Key Considerations in AC Trials of New Covid-19 Vaccines

✓ Active Comparator (AC) vaccine:
  - Should be reliably established to be safe and to have VE exceeding WHO/FDA criteria
  - Where the estimated VE of AC vaccine is valid in the setting of the EXP vs AC trial (i.e., the validity of the ‘Constancy Assumption’ has been properly addressed)
Non-inferiority Trials: Using Active Comparator vaccines*

Non-Inferiority (NI) Trials are designed to reliably assess whether it can be ruled out that the efficacy of the Experimental (EXP) vaccine is unacceptably worse than that of the Active Comparator (AC) vaccine.

The non-inferiority margin, $\delta$, defines the threshold for what would be unacceptably worse efficacy.

Two key considerations in formulating the NI margin, $\delta$:

— Adjustments are used to account for inherent unreliability about the effect of Active Comparator vaccine in the setting of the NI trial. …‘Constancy Assumption’…

— ‘Preservation of Effect’: An appropriate percentage of the effect of the Active Comparator vaccine should be preserved

* “COVID-19 vaccine trials: Use of active controls & non-inferiority studies,” Clinical Trials, Feb 2021
Cautionary Note: Influence of Viral Variants on VE for A.C. & Exp vaccines is integral to the integrity/interpretability of NI Trial results

- “Neutralization titers to Omicron are about 35-fold less than neutralization titers to the mRNA vaccine strain (Wuhan); immune correlates analyses suggest this is associated with reduced VE against Omicron vs. against Wuhan, from ~93% VE down to ~75% VE” (Peter Gilbert)

- Suppose, in the Non-inferiority Trial, EXP/AC HR is estimated to be 3

Since \( \text{EXP/PLA HR} = \text{EXP/AC HR} \times \text{AC/PLA HR} \)

- ✓ if AC/PLA HR = 0.07 (i.e., AC VE = 93%) (e.g., vs Wuhan variant) then EXP/PLA HR = 0.21 (i.e., EXP VE = 79%)

However,

- ✓ if AC/PLA HR = 0.25 (i.e., AC VE = 75%)  (e.g. vs Omicron variant) then EXP/PLA HR = 0.75 (i.e., EXP VE = 25%)

⇒ There is particular risk when the Constancy Assumption is meaningfully violated and when the non-inferiority margin, \( \delta \), is not rigorously justified
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✓ The non-inferiority margin, $\delta$, in the ‘EXP vs AC’ trial should be adequately rigorously justified
Assessing Influence of Viral Variants on Vaccine Efficacy

- Assessments of the influence of viral variants on vaccine efficacy:
  - Are of fundamental importance in placebo-controlled trials
  - Are key in assessing the validity of the ‘Constancy Assumption’ regarding the effect of the active comparator vaccine, in the setting of a non-inferiority trial
  - Are important in non-inferiority trials to understanding how viral variants impact the relative efficacy of the experimental and active comparator vaccine.
Using immunological correlates as the 1° endpoint in efficacy trials of new vaccines

- Would leave some uncertainty as to the true efficacy of a vaccine if the relationship between effects on an immunological endpoint and effects on clinical outcomes is still being assessed.

- Creates increased challenges in the evaluation of subsequent vaccines if a vaccine, established to be effective using an immunological correlate, were then the active comparator vaccine for a new vaccine.

Randomized, controlled efficacy trials with clinical endpoints provide the most reliable estimates of vaccine efficacy.
Immune Protective Mechanisms
- Neutralizing Antibody titre
- Binding Antibody titre
- IgG & IgA Mucosal Antibody
- CD4+ T-cells & CD8+ T-cells
- Memory B-cells

The vaccine’s effect on the **Immunologic Biomarker** could **underestimate** or **overestimate** the vaccine’s true clinical efficacy.
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✔ The non-inferiority margin, δ, in the ‘EXP vs AC’ trial should be adequately rigorously justified

✔ In an AC Trial, if the 1o endpoint is an immunological biomarker, it should be
  ▪ not only a ‘correlate of risk’,
  ▪ but also a rigorously established ‘correlate of protection’

✔ The Active Comparator Vaccine (AC)—while not necessarily being structurally similar to EXP—would have formulation justifying that establishing EXP effects on the correlate of protection, (e.g., neutralizing antibody titre), would indirectly confirm protective effects from other causal mechanisms, (e.g., durable cell-mediated immunity)