OVERVIEW OF VARIOUS GLOBAL EFFORTS TOWARDS THE IDENTIFICATION OF A PROTECTIVE LEVEL

Population- versus individual-level analytical approaches

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HOW TO USE “A CORRELATE” FOR COVID-19 VACCINES

• Support for authorization of new vaccines when efficacy trials are no longer feasible

• Support for immunobridging within existing vaccines (doses, target population, “additional dose”)

• Support for prediction of protection with available vaccines
  - Durability, new variants, severe disease/death, immunocompromised

• Informing/de-risking product development for pan-coronavirus vaccine candidates
TWO APPROACHES TO ANALYSES SUPPORT ANTIBODIES AS A CORRELATE OF PROTECTION

Highest quality analyses based on symptomatic disease due to original strain or Alpha and short duration

**Trial-level meta-analyses**

![Graph showing vaccine efficacy vs SARS-CoV-2 WT spike IgG binding](image)

**Breakthrough case analyses**

![Graph showing pseudovirus-nAb (IU/ml) vs LOD](image)

- e.g., Khoury et al, Earle et al, Goldblatt et al.
- e.g., Feng et al., Gilbert et al., Bergwerk et al.
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No absolute threshold

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Breakthrough case analyses: Objectives to Assess Delta Ab Correlates in USG Public-Private Partnership Phase 3 Trials

1. Assess post dose 2 Ab to Delta as a correlate against Delta COVID-19
   • Estimate the Blue Curve

2. Compare Delta vs. Original virus lineage VE curves for breakthrough cases 3-8 months post dose 2
   • Compare Blue to Black curve
   • Are higher titers to Delta needed for the same level of VE against Delta compared to original virus lineage?

Blue Curve hypothetical for illustration: to be estimated
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   • Use cross-over subjects encountering Delta later to compare to original subjects to review efficacy vs. ab

3. Similar approaches anticipated for JnJ, NVX, AZ

Slides courtesy of Peter Gilbert, Fred Hutch
TRIAL-LEVEL META-ANALYSIS - PREDICTING EFFICACY AGAINST SYMPTOMATIC INFECTION OR SEVERE DISEASE INCLUDING VARIANTS

Symptomatic infection

Severe disease

Cromer et al., Lancet Microbe, 2021
PREDICTION MODEL FOR EFFICACY FOR NEW VACCINES AND VARIANTS

A Predicting efficacy of new vaccine

B Predicting efficacy against new variant

Cromer et al., Lancet Microbe, 2021
INDIVIDUAL THRESHOLD LACKING, BUT POPULATION THRESHOLD HAS BEEN PROPOSED

- Similar approach used to arrive at regulatory approach for serotype-specific 0.35μg/ml level for new pneumococcal vaccines
- Proposed population-based model to calculate threshold for original variant of 60 BAU/ml (excluding 2-dose mRNA analyses)
- Similar analysis estimated 168 BAU/ml as threshold for alpha variant.
- Insufficient data for other variants at present
LOOKING BEYOND ANTIBODIES

• Moderna breakthrough analysis estimated 68.5% of vaccine efficacy mediated by neutralizing antibodies (Gilbert et al, 2021)
• What is responsible for the other 31.5%? CMI, other antibody functionalities, and/or innate?
• Are other arms of the immune response more/less important for protection against variants, infection vs. severe disease?
• T-cells have many putative values --- minimally impacted by spike mutations, higher durability, improvements in heterologous strategies ----- but reliable measurement is complex
• Immune response data from a representative sample of individuals that have received each vaccine integrated with vaccine efficacy/effectiveness estimates

• Multiple biomarkers can be analyzed together, though more difficult to resolve which biomarkers are causally related to protection when biomarkers themselves correlate

• Next steps: incorporate other immune markers beyond antibodies
  • CMI from a common lab/protocol
  • Systems serology/antibody effector functions
KEY QUESTIONS...CAN WE LEVERAGE OMICRON TO HELP ANSWER?

- How does protection against omicron differ by vaccine, vaccine regimen (including heterologous schedules), or natural infection?
- Can sufficient levels of (potentially) poorly neutralizing antibody still protect against severe disease and death?
- Will our current models allow us to predict protection against new variants based on neutralization alone (e.g. Cromer et al)?
- Role of non-neutralizing antibody, T cells, antibody effector functions in protecting against infection vs. clinical disease vs. severe disease?
  - Good problem: Need “white space” between vaccines for severe endpoints to allow less obvious contributors to protection to be quantified
- Approaches: Leverage existing cohorts for whom bloods collected serially (RCTs or HCW (or other) cohorts)) as new variants impact population. Critical use of available WHO International Standard in reporting. Where WHO IS not available, cross-vaccine studies in same lab much preferred