Evidence on vaccine benefit based on Correlates of Protection: insights and considerations

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Outbreaks provide a unique opportunity to evaluate candidate vaccines by assessing their clinical efficacy, safety among populations at risk…

Valuable information can be obtained from randomized trials among high-risk people , if the goal of the trial is to determine if the vaccine has high true efficacy (as per TPPs):

Differences can be observed after relatively few cases: 15-20 events are plenty.

- After 20 cases, a 20% lower bound on efficacy is met with a point estimate of 70%
- With 20 cases, a vaccine with true efficacy of 85% has ~80% power to meet a 20% lower bound.
- For outbreak settings, this may be feasible even in a Phase 2b trial

If needed, to accumulate cases, trials can even continue across outbreaks

For example, for filovirus vaccines, Ervebo tells us that 90+% efficacy is feasible and that is a reasonable expectation for vaccine efficacy

Licensure through clinical endpoint efficacy trials, when feasible, yields clearest results

R&DBlueprint
Powering research to prevent epidemics

… what if the outbreak is rapidly controlled….?

We can not predict –a priori- what the size of an outbreak would be therefore there is value in planning for and attempt to conduct RCTs.

The sooner we start the trial, the sooner we would get the needed efficacy data

In parallel to any preparation for trials during outbreaks, a clinical development plan should aim to generate evidence to support market authorization using various regulatory pathways

If the animal rule is an option, then let's get the best animal data we can.

Regulators should be calling the shots and evaluating the animal data to decide if it is reasonable or ethical to approve (and deploy) the vaccine.

Unapproved candidate vaccines should not be distributed for "political" reasons.

CoP- a few observations

If ~20 events are needed in vaccine recipients to establish a CoP, with 1% attack rate, a vaccine with 85% efficacy requires 13,333 people in vaccinated group

Also need immunogenicity samples for all these participants

15-20 events (3,000-4,000 participants with 1% AR in 1:1 vaccine and placebo group combined) are usually enough to directly demonstrate **efficacy** of high efficacy vaccines

Perverse incentive: Finding a correlate works better if vaccines aren't highly immunogenic and don't work well

- More variability in response
- Ability to immunobridge from weak vaccine to better vaccine

Even then, it is generally much harder to find CoP than to study vaccine efficacy

Uses of surrogate markers

Scientific principles to support surrogate marker

"Correlate of protection"

Immunobridging

Uses

- Different age or demographic groups not included in the original efficacy trial.
- Different dose levels or dosing regimens that previously studied.
- Modified vaccine formulations.
- Changes in manufacturing processes.
- Approval of new vaccine candidates.

When could immunobridging support approval of new vaccines?

If two vaccines induce similar levels of immune responses that are needed to protect, immunobridging can be considered.

If CMI is important for protection, could antibody/neutralizing responses induced by an effective vaccine be used to establish a level needed for a second vaccine?

For example, immune responses to VSV-vectored and Ad-vectored Ebola vaccines were considered different enough that efficacy of Ad-vectored vaccine even against Ebola Zaire could not be established by immunobridging. But could VSV-induced immune responses to Ebola Zaire be used to infer reasonable likelihood of protection against other filoviruses?

For COVID, cellular responses may have been responsible for long-term protection and resilience of protection against severe disease to viral mutagenesis. Neutralizing responses were less durable. Could neutralizing responses from mRNA and vectored vaccines predict efficacy of newer vaccines, e.g., RBD only, adjuvanted inactivated, etc.?

Regulatory framework for immune markers of protection

Traditional approval based on substantial evidence of efficacy

“Accelerated” or “Conditional” approvals:

- endpoint reasonably likely to predict clinical benefit

Role in animal rule approvals

- product is reasonably likely to produce clinical benefit
- need to bridge animal and human studies
- no alternatives

EUA/EUL (“authorization”)

- may be effective and known and potential benefits outweigh known and potential risks
- no alternatives

No shortcuts for safety

Biomarker Identification/CoP

Key Approach

- In general, *vaccine-induced* immune response identified by analysis of results from a successful clinical disease endpoint efficacy trial
- Ideally, in a vaccine trial, evaluate correlation of clinical protection with post-vaccination immune response at selected time points

Alternative Sources for Biomarker Identification

- Population-based vaccine studies.
- Trials using specific immune globulins.
- Antibody levels associated with post-infection immunity.
- Protection thought to be conferred to infants by maternal antibody.
- Controlled human infection studies.
- Animal challenge/protection studies.

Statistical Success Criteria for Immunobridging

Ensuring Vaccine Effectiveness

- Statistical criteria must be sufficiently stringent to avoid erroneous conclusions about vaccine effectiveness.

- **Commonly used statistical success criteria for regulatory decision-making:**
  - 1.5-fold non-inferiority margin for the ratio of geometric mean titers (GMTs).
  - 10% non-inferiority margin for the difference in sero-response rates.
  - Confidence intervals used to evaluate statistical significance around point estimates.

Some examples

Hepatitis B vaccine

Pneumococcal vaccines

SARS-CoV-2 vaccines

Cholera vaccine (age extension)

Meningococcal Group B vaccines

Chikungunya vaccines

HPV vaccines (non-immune and immune biomarkers)

Group B strep (not yet licensed)

Pneumococcal Vaccines

Each vaccine was approved based on comparison with previous vaccines

Pediatrics: proportion IgG>0.35 (10% margin) and GMC ratio > 0.5

Increasing number of antigens may reduce immunogenicity

Concern about immunogenicity creep

	Children	Adults
Prevnar 7	RCT IPD 97.4% RCT VT AOM 57%	
Prevnar 13	Met NI 10/13 serotypes	RCT VT-CAP 46% VT-IPD 75%
Prevnar 20	NI to P13 by GMC 20/20 after dose 3 BUT all ratios <1 for common serotypes 6 serotypes missed on predefined IgG after dose 3 Similar OPAs	OPA NI to P13 by GMC ratio (all ratios <1) OPA NI to PPSV23 by GMC ratio (all but 1) 50-64 immunobridged to 65+
Vaxneuvance 15	All but 1 GMC ratio <=1	NI to P13 for common serotypes
Capvaxive 21		NI to P20 for common serotypes

Licensure of 13 & 20 valent Pneumococcal Conjugate Vaccines (cont.)

Role of Opsonophagocytic Antibody (OPA) Response

- OPA response rates are considered important for protection against invasive disease.
  - Threshold of OPA titer that is associated with IPD protection remains undetermined.
- No observed differences in OPA response rates between higher- and lower-valency pneumococcal conjugate vaccines (PCVs).

Vaccine Licensure Considerations

- PCVs may be licensed even if some serotypes show "inferior" immunogenicity compared to a licensed comparator.
- Inferiority of certain serotypes may be justified by the benefit of licensing higher-valency PCVs.
- Totality of data should be considered when inferring vaccine effectiveness.

Challenges with Serial Immunobridging (IB) Trials

If active comparator was itself approved based on a NI trial (original comparator unavailable or no longer suitable), there is a risk of a significant drop in immunogenicity/efficacy compared to the original vaccine.

Future Considerations

- Revised approaches for evaluating the effectiveness of higher-valency PCVs.
- Strategies to mitigate the risk of "bio creep“

Pneumococcal vaccines solutions

Tighter boundaries

Different comparators

Post-licensure efficacy studies

Influenza

Historical FDA guidance for accelerated approval:

65: SC≥40%, SP (≥1:40 or 4x) ≥70%

≥65: SC≥30%, SP ≥60%

Concerns:

Difficulty with confirming benefit given changing strains

Recent concerns with mRNA vaccines inducing low titers against influenza B

Solutions:

RCTs

Develop mRNA vaccines with higher influenza B titers

Licensure of Group B Streptococcus (GBS) vaccines based on a surrogate endpoint

Intended Use & Challenges

- GBS vaccines in development for pregnant women to prevent GBS disease in newborns.
- Clinical disease endpoint efficacy trials are not feasible in the U.S. and other countries.

Regulatory Approach & Surrogate Endpoint

- Manufacturers requested FDA's Accelerated Approval pathway for GBS vaccine development.
- Effectiveness demonstrated using a surrogate endpoint (biomarker):
  - Anti-capsular GBS IgG antibody concentrations proposed as a basis to infer vaccine effectiveness.

Regulatory Review & FDA Decision

- May 17, 2018: VRBPAC met to discuss approaches for demonstrating effectiveness of GBS vaccines
- FDA agreed that anti-capsular GBS IgG antibody levels can serve as a surrogate endpoint reasonably likely to predict clinical benefit.
- This approach is not based on clinical immunogenicity bridging.

Group B strep

“Correlate of protection” taken from IgG titers in infants who are protected vs. not

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Concern: a titer against any individual bacterial antigen will likely correlate with titers for others (or with overall immunity), but given that immune responses to several bacterial antigens, together, confer protection, this may not yield a titer that is clearly protective

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Solutions: Also require overall OpKa as proposed correlate of protection

Licensure of Meningococcal Group B vaccines based on a surrogate endpoint

Disease Background

Endemic Group B meningococcal disease is caused by antigenically diverse strains.

Surrogate Endpoint for Vaccine Effectiveness

- Evidence that serum bactericidal antibodies against protein antigens are protective.
- hSBA (human serum bactericidal antibody) serves as a serologic marker for strain-specific protection.
- hSBA titer determination (≥4-fold rise) in sera from vaccinees, combined with:
  - Microbiologic bridging from hSBA assay strains to disease isolates, used to estimate effectiveness.

Regulatory Review & FDA Decision

- Trumenba & Bexsero approved based on hSBA biomarker, deemed reasonably likely to predict clinical benefit.
- Not an immunobridging approach.

Use of a non-immune biomarker to predict clinical benefit of a vaccine

Example: HPV Vaccine for Cervical Cancer Prevention

Challenges in Traditional Disease Endpoint Use

- Randomized, placebo-controlled trials with cervical cancer as the primary endpoint were deemed infeasible.
- Immune response markers were not a viable option due to:
  - Lack of sufficient evidence that they reliably predict protection.
  - Concern that serum IgG may not function as a protective mechanism against infections localized to the mucosa.

Non-Immune Biomarker as Alternative Endpoint

- Cervical Intraepithelial Neoplasia (CIN) was used as a histopathology endpoint, unrelated to immune response.
- CIN a scientifically well-established biomarker for predicting clinical benefit of HPV vaccines

Use of CoP/Biomarker to infer effectiveness – Caveats

Factors Affecting Biomarker Applicability

- Vaccine characteristics (e.g., antigen structure, mode of delivery).
- Vaccine platform may impact biomarker reliability.
- Validated assays required to accurately measure biomarkers (e.g., antibodies).

- Biomarker may vary depending on the outcome of interest, e.g.,
  - Prevention of infection at mucosal surfaces
  - Prevention of severe disease versus mild disease
  - Mechanisms providing initial protection after vaccination (or infection) may be different from those in effect after months or years

Clinical immunobridging studies – Caveats

Key Considerations

- Important tool for demonstrating vaccine effectiveness, but post-marketing effectiveness studies remain critical.
- Choice of licensed comparator vaccine is crucial:
  - Efficacy of the comparator vaccine impacts study validity.
  - Similarity of immune response induced by candidate vs comparator vaccine.
  - Statistical success criteria depends on comparator vaccine efficacy.

Potential Risks

Immunogenicity creep – Serial immunobridging may lead to a gradual decline in immunogenicity

Summary

Key Takeaways

- Immunobridging is an important tool to accelerate vaccine authorization.
  - Not a new regulatory approach.
  - Can eliminate the need for clinical disease endpoint efficacy studies, especially where ethical considerations make placebo controls impossible
  - May not be suitable in all cases.

Role of Biomarkers

- Vaccine-associated biomarkers typically measure immune responses.
- Preferably derived from clinical disease endpoint efficacy studies, but alternative sources may be considered.

Critical Considerations

- **Comparator vaccine selection is crucial**—use a vaccine with **demonstrated high efficacy** when possible.
- **Risk of 'bio creep'**—serial immunobridging could lead to reduced immunogenicity/effectiveness