

*WHO Initiative for Vaccine Research (IVR)*  
*Workshop on Correlates of Protection: Relevant*  
*to the African Context*

***Regulatory Perspective: Issues of***  
***Correlates Versus Surrogates and***  
***Implications for Licensure***

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# Presentation Outline

- Compare and contrast correlates of protection and surrogate endpoints
- Cite the associated regulatory implications
- Discuss examples of vaccines that have been licensed on either the basis of the identification of a correlate of protection or by a surrogate endpoint.

# Vaccine Licensure

- The gold standard for determining the effectiveness of a new vaccine is the clinical endpoint efficacy study.
  - Randomized, Double-blind, Well-Controlled Trial
- Optimal design of efficacy studies includes:
  - Careful selection of prospectively defined endpoints
  - Appropriate case definitions
  - Properly designed statistical plan.
  - Characterization of the immune response
- As part of an efficacy study, it is recommended that attempts be made to identify immune correlates of protection.
  - **Not a requirement for licensure**

# Clinical Efficacy Trial

- Necessary When:
  - Vaccine is novel, or contains novel components
  - First of its kind administered to a large target population
  - No accepted immune response correlate of protection
  - Comparative clinical endpoint efficacy trials of a new vaccine versus a licensed product may be acceptable.

# Regulatory Challenge

When is a clinical endpoint efficacy trial necessary and when can licensure be based on evaluation of immune responses?

# Clinical Endpoint Efficacy Studies

- Clinical trials demonstrating preventive efficacy for clinical endpoints provide the greatest scientific rigor for evaluating vaccines
- Prospective, controlled, randomized
- Primary endpoint: prevention of disease
- Necessary in situations when
  - Vaccine is novel
  - First of its kind administered to target population
  - No established immune response correlate of protection
- *Example:* NCKP efficacy trial of the heptavalent pneumococcal conjugate vaccine: ~ 38,000 infants
  - Prevention of invasive pneumococcal disease

# Regulatory Perspective: *Definitions*

## ■ Correlate of Protection

- Represents a frequent, but not unambiguous, marker of the protective immune response.
- A laboratory parameter shown to be *associated* with protection from clinical disease.
- Licensure may be based on immunity in lieu of field efficacy.



## ■ Surrogate

- Considered a consistent and reliable predictor of protection.
- A laboratory or physical sign that is used in clinical trials as a *substitute* for a clinically meaningful endpoint.
- Surrogate may be a predictor of protection when correlate is unknown

## Correlate of Protection

- Generally, a laboratory parameter that has been shown to be associated with protection from clinical disease.
  - Adequate and well-controlled trials
- An immunological correlate of protection is most useful if clear qualitative and quantitative relationships can be determined.

## Correlate of Protection (cont.)

May also be *suggested* by other sources:

- Population-based studies of vaccines
- Trials using
  - Specific immune globulins
  - Immune globulin with specific Ab
    - e.g. polio
- Animal challenge/protection studies
- Phase 2 clinical data
- Protection thought to be conferred to infants by maternal antibody

## Correlate of Protection (cont.)

- Identification of correlate of protection is not a requirement for licensure
- Examples of licensed vaccines *without* an identified immune correlate of protection:
  - Acellular pertussis, Typhoid, Tuberculosis (BCG)
- Immune correlate(s) useful for interpreting trials with immune response endpoints,
  - E.g., “bridging studies”

# Quantitative Correlates of Protection

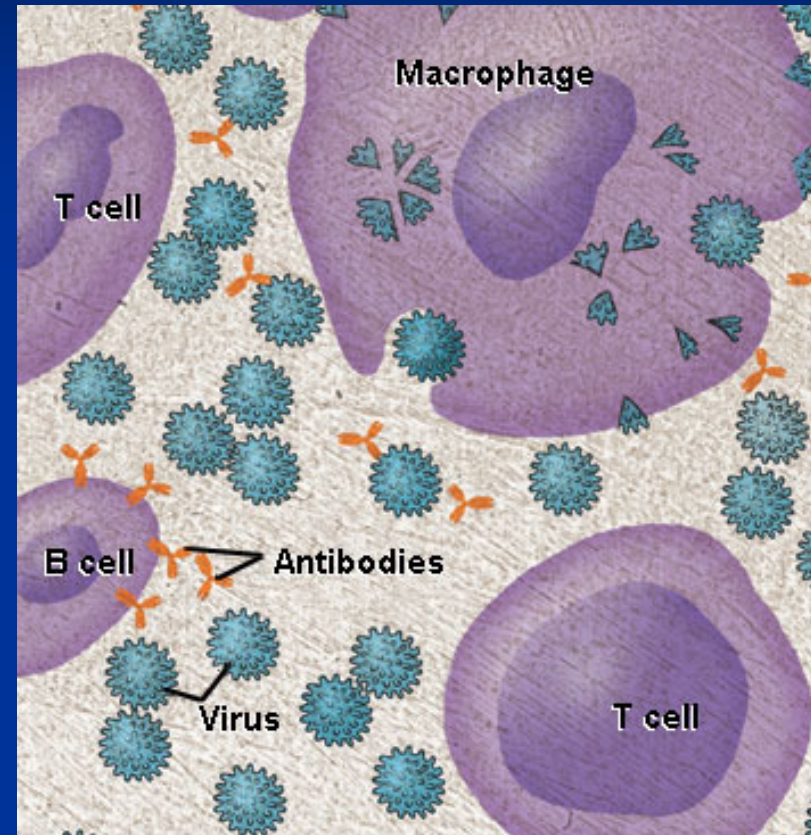
Vaccine	Test	Correlate of Protection
Diphtheria	Toxin Neutralization	0.01-0.1 IU/mL
Hepatitis A	ELISA	10 mIU/mL
Hepatitis B	ELISA	10 mIU/mL
Hib polysaccharides	ELISA	1 mcg/mL
Hib conjugate	ELISA	0.15 mcg/mL
Influenza	HAI	1/40 dilution
Lyme	ELISA	1100 EIA U/mL
Measles	Microneutralization	120 mIU/mL
Pneumococcus	ELISA; opsonophagocytosis	0.20 -0.35 mcg/mL (for children); 1/8 dilution
Polio	Serum neutralization	1/4 – 1/8 dilution
Rabies	Serum neutralization	0.5 IU/mL
Rubella	Immunoprecipitation	10-15 mIU/mL
Tetanus	Toxin neutralization	0.1 IU/mL
Varicella	Serum Neutralization; gbELISA	$\geq 1/64$ dilution $\geq 5$ IU/mL

# Immunogenicity Assessment

- **Assessment of immunogenicity may be sufficient for licensure under the following circumstances:**
  1. Once a component is licensed, and therefore accepted, effectiveness has been demonstrated;
  2. When there is an accepted immunologic correlate of protection;
  3. When components are fundamentally similar to licensed products ( non-inferiority studies adequate for licensure);
  4. When the incidence of disease is so low in a population that large-scale field efficacy trials are not feasible

# Immune Response Endpoints

- Fold-increase in titer
- Opsonophagocytic Titer (GMT)
- Antibody response (GMC)
- Others



## 21 CFR 601.40-46, Subpart E: Accelerated Approval of New Biologic Products for Serious or Life-Threatening Illnesses

- FDA may grant licensure on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a **surrogate endpoint** that is reasonably likely... to predict clinical benefits...
- Approval is subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

# ICH guidelines on Statistical Principles for Clinical Trials

*“In practice, the strength of the evidence for surrogacy depends upon*

- (1) the biological plausibility of the relationship;
- (2) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome; and
- (3) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome

# Example 1

- **Vaccine:** Hepatitis B
- **Correlate of Protection:** Antibody titer greater than or equal to 10 mIU/mL considered to be protective.
- **Demonstration of Efficacy for Licensure:** Clinical trials in healthy adults and adolescents showed that following a 3 dose course administered at months 0, 1, and 6, the seroprotection (antibody titers  $\geq 10$  mIU/mL) rate for all individuals was 96% at month.

# Example 2

- **Vaccine:** Tetanus Toxoid
- **Correlate of Protection:** Serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.
- **Demonstration of Efficacy for Licensure:** Efficacy was determined on the basis of an immunogenicity study with a comparison to a serological correlate of protection (0.01 antitoxin units/mL)
- Vaccine was administered to a previously unimmunized population with serologic evidence for no pre-existing immunity to tetanus, all had titers of 0.01 AU (antitoxin units) or more one month after the second and third immunizations.

## Example 3

- **Vaccine:** Japanese Encephalitis
- **Surrogate Endpoint:** PRNT titer of  $\geq 1:10$  as determined to be correlate threshold for protection
- **Demonstration of Efficacy for Licensure:**  
Primary endpoints in the Ixario JE trial were seroconversion rate (SCR), defined as PRNT titer of  $\geq 1:10$ , and geometric mean titers (GMT).

# Bridging Studies

## Address:

- New population (foreign studies)
- Age group
- New product to standard of care
- New schedule
- Manufacturing changes
  
- If immune response/safety profile are similar, then efficacy can be inferred

# Considerations for Successful “Bridging”

- Validated immune response assays (vaccines)
- Foreign clinical data should meet standards of the new region
  - Study design, conduct & regulatory requirements (ICH E5)
  - Determine vaccine’s sensitivity to ethnic factors (ICH E5)
- Study should meet local and international standards
  - ICH E6: Good Clinical Practices
  - ICH E8: General Considerations for Clinical Trials
  - Other Documents (CFR, etc.)
- Generous banking of sera from efficacy trial
  - SOPP for storing sera

# Example 4 – Bridging Study

- **Vaccine: DTaP**
- **Correlate of Protection:** No well accepted serologic or laboratory correlate established for pertussis vaccines
- **Demonstration of Efficacy for Licensure:**
  - DTaP vaccines were licensed for use in infants and children following clinical endpoint efficacy studies
  - Demonstration of efficacy in infants served as the basis for efficacy when administered as a booster dose to adolescents and adults
    - Clinical endpoint pertussis efficacy study not required for licensure in adult or adolescent groups
    - Antibody data used to bridge the adult and pediatric groups and infer efficacy in the older population

# Example 4 – Bridging Study (continued)

- Non-inferiority of the immune response of adolescents/adults compared to the immune response of infants who received a primary series of the same antigens in a clinical endpoint efficacy study
- For each antigen:
  - UL 95% CI ratio  $\frac{\text{GMC infants}}{\text{GMC older individuals}} = <1.5$
  - OR
  - LL 95% CI ratio  $\frac{\text{GMC older individuals}}{\text{GMC infants}} = >0.67$

# Example 5

- **Vaccine:** Haemophilus b Conjugate Vaccine
- **Demonstration of Efficacy**
  - Initial licensure of two Hib conjugate vaccines was based on phase III clinical efficacy studies
  - Placebo controlled trials to assess efficacy of a third HIB no longer feasible
- **Immunologic Framework for Licensure**
  - Assessment of antibody response, as measured by ELISA
  - Persistence of antibody after the primary immunization series until the recommended booster dose is given.
  - Comparison of isotype and IgG subclass distribution to that reported for licensed vaccines.
  - Demonstration of functional capacity of conjugate-induced antibodies measured by either opsonic or bactericidal activity

# Example 6

- **Vaccine:** Pneumococcal Conjugate Vaccine
- **Licensure Pathway:**
  - Prevnar licensed via efficacy trial, 97% clinical efficacy
- **Correlate of Protection:** Few vaccine failures were observed so a minimum protective antibody level could not be derived directly from the efficacy data
- **Issue:** Difficult to determine efficacy for future pneumo vaccines

# Licensure Pathway for New Pneumococcal Conjugate Vaccines

- FDA's VRBPAC concurred that a non-inferiority comparison of candidate pneumococcal conjugate vaccine immune responses to Prevnar was an acceptable licensure approach for an Invasive Pneumococcal Disease (IPD) indication.
- A series of expert consultations, which included FDA, were convened by the WHO.
  - Objectives was to establish a pneumococcal IgG antibody reference value that related back to the demonstrated clinical efficacy outcome.
  - Comparison of immune responses thus pertained to licensure approaches for preventing vaccine serotype IPD in infants, but not to other pneumococcal disease manifestations or age groups.

# Licensure Pathway for New Pneumococcal Conjugate Vaccines

- The pneumococcal IgG antibody reference value for immunogenicity comparisons for all vaccine serotypes 1 month after three doses is, in part, based on the aggregate vaccine clinical efficacy estimate observed in the Prevnar NCKP trial.
  - The pneumococcal IgG antibody concentration was derived from pooled vaccine efficacy estimates from three clinical studies conducted in NCKP , American Indians, and South Africa.
  - A pooled efficacy estimate of 93% (95% CI: 81.0%, 98.2%) corresponded to an IgG antibody concentration of 0.35  $\mu\text{g}/\text{mL}$  (i.e., 93% of children in the clinical efficacy trials who provided blood samples after three doses achieved an antibody concentration of 0.35  $\mu\text{g}/\text{mL}$ ).

# Example 7

- **Vaccine:** New Seasonal Inactivated Influenza Vaccine
- **Demonstration of Effectiveness to Support Licensure:**
  - Demonstration of effectiveness against influenza illness in an adequate and well-controlled clinical study
  - Effectiveness studies for at risk (e.g., individuals 6 to 59 months of age and those 65 years of age and older) populations can be based on appropriate immunogenicity endpoints.
  - Immunogenicity bridging studies can be conducted to compare the immune response observed in the clinical endpoint efficacy study to that elicited in other populations.

# Influenza Continued

- Appropriate endpoints may be the hemagglutination inhibition (HI) antibody responses to each viral strain included in the vaccine.
- Studies should be adequately powered to assess the following co-primary endpoints for each of these viral strains:
  - Geometric mean titer (GMT), and
  - Rates of seroconversion, defined as the percentage of subjects with either
    - A pre-vaccination HI titer  $< 1:10$  and a post-vaccination HI titer  $> 1:40$  or
    - a pre-vaccination HI titer  $> 1:10$  and a minimum four-fold rise in post-vaccination HI antibody titer.

# Summary

- Correlates are quantitative and qualitative laboratory parameters shown to be associated with protection from clinical disease.
- Surrogates are laboratory or physical signs that are used in clinical trials as a substitute for a clinically meaningful endpoint.
  - Surrogate may be a predictor of protection or meaningful clinical benefit when correlate is unknown
  - Accelerated approval based on use of a surrogate endpoint, with the requirement to confirm clinical benefit of the surrogate post-licensure
- Identification of a correlate of protection is not required by the US FDA for licensure.
- Identification of correlates of immunity may allow licensure without the demonstration of field efficacy.

# Extra Slides

# PCV

- Limitations of the statistical modeling
  - uncertain applicability across all serotypes, across different geographic regions, and among higher risk groups.
  - the 0.35  $\mu\text{g}/\text{mL}$  IgG antibody reference value applies only to
    - (1) comparisons among infants after receipt of three doses of a pneumococcal conjugate vaccine,
    - (2) the prevention of IPD, and
    - (3) populations rather than to individuals

# PCV

## Pneumococcal IgG antibody primary endpoints

- The proportion of subjects achieving a serum IgG antibody concentration  $\geq 0.35 \mu\text{g/mL}$  by ELISA one month after the third dose was chosen as a primary endpoint.
- This time point was chosen because the highest age-specific risk for IPD occurs at 6 to 12 months of age, which also corresponds to the interval between the third and fourth pneumococcal vaccine doses.
- IgG GMCs one month after the fourth dose were chosen as a co-primary endpoint.
- Since most children in the Prevnar NCKP efficacy trial received a fourth PCV7 dose and cases contributing to the efficacy evaluation accrued after the 4th dose, post-dose 4 antibody data provide information about antibody persistence and duration of protection beyond 1 year of age.

# PCV

## Pneumococcal IgG antibody primary endpoints

- Immunogenicity criteria to demonstrate non-inferior immune responses to the 6 additional serotypes in the 13vPnC vaccine were based on comparisons to the lowest immune response elicited by a PCV7 vaccine serotype in PCV7 recipients.
  - supported by IPD efficacy data from clinical trials for some PCV7 serotypes, and postmarketing effectiveness data from observational studies for the remaining serotypes.

# PCV: Pneumococcal opsonophagocytic antibody (OPA)

- Evaluation of functional antibodies, as measured in an OPA assay might be considered a preferable outcome measure because opsonophagocytosis is the main protective response in vivo. However, the OPA assay is more variable than the ELISA assay, and standardized OPA assay protocols are not yet available.
- OPA was included as an exploratory objective.
  - OPA geometric mean titers (GMTs) and the proportion of subjects achieving an OPA titer  $\geq 1:8$  were included as exploratory endpoints.
  - Data from the three efficacy trials used to establish the pneumococcal IgG antibody reference value showed that an ELISA antibody concentration in the range of 0.20 – 0.35  $\mu\text{g}/\text{mL}$  correlated with an OPA titer of 1:8.
  - Because the OPA assays are not controlled by an external standard, the 1:8 titer may not have equivalent biological meaning for all serotypes, particularly for the additional 6 serotypes for which there are no direct clinical efficacy data.

Correlate

Surrogate

- Associated with protection against infection
- Not necessarily protective
- Used as substitute for a clinical endpoint



# Correlate vs. Surrogate

The primary difference between a biomarker (correlate of protection) and a surrogate marker is that a correlate is a “candidate” surrogate marker, whereas a surrogate marker is a test used, and taken, as a measure of the effects of a specific treatment.