Correlates of Immunity in Vaccinology

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Correlates of Immunity in Vaccinology

1) Vaccine development
2) Vaccine evaluation
Vaccine evaluation

Pre-licensing (phase I-III)

Vaccine efficacy:
- % reduction in disease incidence (vaccinated Vs unvaccinated) groups

- under optimal conditions (eg RCT)

Post-licensing (phase IV)

Vaccine effectiveness:
- Protective ability of a vaccine towards the target disease/outcomes of interest in real life situations
Vaccine efficacy = \( \frac{ARU - ARV}{ARU} \times 100 \)

Vaccinated

\[
\begin{array}{c}
\text{\rotatebox{90}{\Large\text{Vaccinated}}} \\
\begin{array}{cccccc}
& & & & & \\
\text{\textcolor{green}{\large\text{\textbullet}}} & \text{\textcolor{green}{\large\textbullet}} & \text{\textcolor{green}{\large\textbullet}} & \text{\textcolor{green}{\large\textbullet}} & \text{\textcolor{green}{\large\textbullet}} & \text{\textcolor{green}{\large\textbullet}} \\
\end{array}
\end{array}
\]

\[ARV = \frac{2}{10} = 0.2\]

Unvaccinated

\[
\begin{array}{c}
\begin{array}{cccccccc}
\text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} \\
\text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} & \text{\textcolor{red}{\large\textbullet}} \\
\end{array}
\end{array}
\]

\[ARU = \frac{9}{10} = 0.9\]

Efficacy = \( \frac{0.9 - 0.2}{0.9} = 78\% \)
Vaccine effectiveness

-Many study designs can be used to calculate this measure:
  -Case-control study
  -Screening method
  -Cohort study
  -Household contact study

-If:

PCV = vaccination coverage in cases
PPV = Population vaccination coverage

\[
\text{Effectiveness} = 1 - \frac{\text{PCV} \times (1-\text{PPV})}{(1-\text{PCV}) \times \text{PPV}} = (1-\text{OR}) \times 100
\]
Correlates of Immunity in Vaccinology

1) How well does a candidate vaccine prevent the targeted disease?

2) Is there a threshold in vaccine prevention to the target disease that constitutes a public health benefit?
Seroconversion

- Seroconversion is the development of detectable and specific antibodies to a pathogen in the blood serum.

- Seroconversion can result due to infection or immunization.

- Serology (the testing for antibodies) is used to determine antibody positivity.
Seroconversion

• Prior to seroconversion, the blood test is seronegative for the antibodies; after seroconversion, the blood test is seropositive for the antibody

• Seroconversion - you may have developed immunity to the specific infection

• Seroconversion- may indicate current infection—eg, HIV seroconversion to p24 and/or p41 antibody production or HBV—seroconversion to surface antibody-HBsAb.
**Sero**protection

• The level of antibody titers equal or above which you are regarded as being protected from disease.

• Sero**protection** rates refer to the % of host with antibody titers equal or above the assay cut-off were set such that subjects who had titers above *the cut off* could be considered protected from disease.
Factors that may influence seroprotection rates following vaccination

• Age – elderly and very young / premature infants
• Immune deficiency
• Genetic factors
• Dose of vaccine
• Nutritional status – malnourished / vitamin A deficient
• Route of administration – id vs im
Serosurveillance

- Useful to measure immunity in a population, complements traditional disease surveillance methods

- Immunity to antigens such as: measles, mumps, rubella, varicella, hepatitis A, hepatitis B, hepatitis C, diphtheria, tetanus, polio and pertussis, rubella, etc

- Bloods from biobanks can be used for the serosurveillance
Correlate/s (Surrogate) of protection

• A measurable sign/s that a person is immune, i.e protected against becoming infected and/or developing disease.
# Nomenclature for Immune Correlates of Protection After Vaccination

**Stanley A. Plotkin**¹ and **Peter B. Gilbert**²,³

¹University of Pennsylvania and Vaxconsult, Doylestown; ²University of Washington, and ³Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle

<table>
<thead>
<tr>
<th>Term</th>
<th>Synonyms</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoP (correlate of protection)</td>
<td>Predictor of protection</td>
<td>An immune marker statistically correlated with vaccine efficacy (equivalently predictive of vaccine efficacy) that may or may not be a mechanistic causal agent of protection⁴</td>
</tr>
<tr>
<td>mCoP (mechanistic correlate of protection)</td>
<td>Causal agent of protection; protective immune function</td>
<td>A CoP that is mechanistically and causally responsible for protection</td>
</tr>
<tr>
<td>nCoP (nonmechanistic correlate of protection)</td>
<td>Correlate of protection not causal; predictor of protection not causal</td>
<td>A CoP that is not a mechanistic causal agent of protection</td>
</tr>
</tbody>
</table>

⁴ A correlate of protection can be used to accurately predict the level of vaccine efficacy conferred to vaccine recipients (individuals or subgroups defined by the immune marker level).
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Correlate/s (Surrogates) of protection

Arrows imply direct causal relationships
Correlate/s of protection

Arrows imply direct causal relationships

http://apps.who.int/iris/bitstream/10665/84288/1/WHO_IVB_13.01_eng.pdf
Table 4. Some quantitative correlates of protection after vaccination.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Test</th>
<th>Correlate of protection</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>Toxin neutralization</td>
<td>0.01–0.1 IU/mL</td>
<td>[14]</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>ELISA</td>
<td>10 mIU/mL</td>
<td>[15]</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>ELISA</td>
<td>10 mIU/mL</td>
<td>[16]</td>
</tr>
<tr>
<td>Hib polysaccharides</td>
<td>ELISA</td>
<td>1 mcg/mL</td>
<td>[17]</td>
</tr>
<tr>
<td>Hib conjugate</td>
<td>ELISA</td>
<td>0.15 mcg/mL</td>
<td>[18]</td>
</tr>
<tr>
<td>Influenza</td>
<td>HAI</td>
<td>1/40 dilution</td>
<td>[19]</td>
</tr>
<tr>
<td>Lyme</td>
<td>ELISA</td>
<td>1100 EIA U/mL</td>
<td>[20]</td>
</tr>
<tr>
<td>Measles</td>
<td>Microneutralization</td>
<td>120 mIU/mL</td>
<td>[7]</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>ELISA; opsonophagocytosis</td>
<td>0.20–0.35 mcg/mL (for children); 1/8 dilution</td>
<td>[21, 22]</td>
</tr>
<tr>
<td>Polio</td>
<td>SN</td>
<td>1/4–1/8 dilution</td>
<td>[23]</td>
</tr>
<tr>
<td>Rabies</td>
<td>SN</td>
<td>0.5 IU/mL</td>
<td>[24]</td>
</tr>
<tr>
<td>Rubella</td>
<td>Immunoprecipitation</td>
<td>10–15 mIU/mL</td>
<td>[25, 26]</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxin neutralization</td>
<td>0.1 IU/mL</td>
<td>[27]</td>
</tr>
<tr>
<td>Varicella</td>
<td>SN; gpELISA</td>
<td>≥1/64 dilution; ≥5 IU/mL</td>
<td>[28, 29]</td>
</tr>
</tbody>
</table>

**NOTE.** gp, glycoprotein; HAI, hemagglutination inhibition; Hib, *Haemophilus influenzae* type b; SN, serum neutralization.
# Programmatic application of correlate of protection

## 2013 vaccine schedules for South Africa

<table>
<thead>
<tr>
<th>Age of child</th>
<th>EPI schedule</th>
<th>Age of child</th>
<th>Private practice: Option 1</th>
<th>Private practice: Option 2</th>
<th>Age of child</th>
<th>Private practice: Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>OPV (0) BCG</td>
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<td>OPV (0) BCG</td>
<td>At birth</td>
<td>OPV (0) BCG</td>
</tr>
<tr>
<td>6 weeks</td>
<td>OPV (1) RV (1) DTaP-IPV//Hib (1) HBV (1) PCV (1)</td>
<td>6 weeks</td>
<td>OPV (1) RV (1) DTaP-IPV//Hib (1) HBV (1) PCV (1)</td>
<td>OPV (1) RV (1) DTaP-IPV//Hib//HBV (1) PCV (1)</td>
<td>2 months</td>
<td>OPV (1) RV (1) DTaP-IPV//Hib//HBV (1) PCV (1)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>DTaP-IPV//Hib (2) HBV (2)</td>
<td>10 weeks</td>
<td>RV (2)² DTaP-IPV//Hib (2) HBV (2) PCV (2)</td>
<td>RV (2)² DTaP-IPV//Hib//HBV (2) PCV (2)</td>
<td>3 or 4 months</td>
<td>RV (2)² DTaP-IPV//Hib//HBV (2) PCV (2)</td>
</tr>
<tr>
<td>14 weeks</td>
<td>RV (2) DTaP-IPV//Hib (3) HBV (3) PCV (2)</td>
<td>14 weeks</td>
<td>RV (2 or 3)² DTaP-IPV//Hib (3) HBV (3) PCV (3)</td>
<td>RV (2 or 3)² DTaP-IPV//Hib//HBV (3) PCV (3)</td>
<td>4 or 6 months</td>
<td>RV (2 or 3)² DTaP-IPV//Hib//HBV (3) PCV (3)</td>
</tr>
<tr>
<td>9 months</td>
<td>Measles vaccine (1) PCV (3)</td>
<td>9 months</td>
<td>Measles vaccine</td>
<td>Measles vaccine</td>
<td>9 months</td>
<td>Measles vaccine</td>
</tr>
</tbody>
</table>

Compiled by Amayezia Info Services’ Vaccine Helpline: 0860 160 160
How about correlate of risk (CoR)?