Correlates of Vaccine-induced Immunity

by

Stanley A. Plotkin
References:


# Potential Protective Adaptive Immune Mechanisms Induced by Vaccination

<table>
<thead>
<tr>
<th>Serum Antibody</th>
<th>CD4+ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralizing</td>
<td>B cell help (Th2)</td>
</tr>
<tr>
<td>Non-neutralizing</td>
<td>T cell help (Th1)</td>
</tr>
<tr>
<td>Functionality (opsonsphagocytosis)</td>
<td>Help to inflammation (Th17)</td>
</tr>
<tr>
<td>Avidity (cytotoxicity, etc.)</td>
<td>Cytokines</td>
</tr>
<tr>
<td></td>
<td>Lysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucosal Antibody</th>
<th>CD8+ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA locally produced</td>
<td>Lysis</td>
</tr>
<tr>
<td>IgG diffused from serum</td>
<td>Avidity</td>
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</table>
My Definitions:

**Correlate**: An immune response that is responsible for and statistically interrelated with protection

**Absolute Correlate**: A specific level of response highly correlated with protection: a threshold

**Relative Correlate**: Level of response variably correlated with protection

**Co-Correlate**: One of two or more factors that correlate with protection in alternative, additive, or synergistic ways.

**Surrogate**: An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable
How Correlates Are Determined

1. Levels of passively administered or maternal antibody that protect

2. Analysis of immune responses in protected and unprotected subjects in efficacy trials

3. Observations made on vaccine failures, e.g. immunosuppressed individuals

4. Human challenge studies

5. Extrapolation from animal challenge studies
Principle 1

Must Define Protection

Against what?

Infection? (Local or Disseminated)

Disease? (Mild or severe)
Correlates of Protection Against Pneumococcal Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>ELISA Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>0.2 – 2.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.5</td>
</tr>
<tr>
<td>Otitis</td>
<td>2.0 – 3.5</td>
</tr>
<tr>
<td>NP Carriage</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Goldblatt D, WHO Banako meeting
The Mechanism of Protection by Vaccination is *NOT* Necessarily the Same Mechanism as Recovery From Infection
Antibodies produced by measles vaccination correlate with protection against infection and rash but CD8+ T cells are needed to control viremia if infection occurs.
Principle 3

A Large Challenge Dose Can Overcome Immunity
## “Challenge” of Poliovaccine by OPV

<table>
<thead>
<tr>
<th></th>
<th>Low dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV Vaccinees</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>IPV Vaccinees</td>
<td>30%</td>
<td>70%</td>
</tr>
</tbody>
</table>

% Infected 7 days after challenge
Principle 4

Most Current Vaccines

Protect Through Antibodies
Most vaccine preventable infections spread through the blood, produce toxemia, or replicate on mucosa.
Principle 5

Correlates may be relative
Protection Against Influenza and Anti-HA Antibodies

Coudeville, L Personal communication
Antibodies must be **FUNCTIONAL**
Opsonophagocytic Antibodies

Response to Pneumococcal Vaccine with Age

Romero-Steiner, CID, 1999

Opsonophagocytic GMT
Principle 7

Mucosal Antibodies Also Protect as Co-Correlates
Correlates of Immune Protection After Live Influenza Vaccine or Natural Infection (Artificial Challenge in Children)

<table>
<thead>
<tr>
<th>Serum HAI</th>
<th>Nasal IgA</th>
<th>Shedding</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>63%</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>19%</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>3%</td>
</tr>
</tbody>
</table>

Belshe, JID, 2000
Principle 8

Memory may be a Surrogate
Effector vs. Central Memory

Effector Memory important in short incubation infections like *H. influenzae* type b

Central Memory important for long incubation infections and long-term memory (long-lived plasma cells)
Memory B Cells are demonstrable by ELISPOT in Hepatitis B vaccinees and convalescents despite non-protective serum antibody levels.
Smallpox
Pathogenesis of Mousepox in Vaccinated Mice

CD8+ cell depletion = No CTL, No IFN
but still protection

CD4+ cell depletion = Poor CTL, low Ab
but still protection

B cell depletion = No protection

B cell depletion but passive antibody = protection
Persistence of Immunity after Vaccinia

Antibody: \( \geq 75 \text{ years} \)

CD8+ T-cell Memory: 20 years

CD4+ T-cell Memory: 50 years
**Immunity Against Poxviruses**

**Primary Infection and recovery from Vaccination:**
Both B cells and T cells necessary for survival

**Secondary Exposure to Infection in vaccinees:**
Only B cells necessary for protection, although T cells may give partial protection.

Low titer antibodies (ca. 1/20- 1/32) are protective (5 proteins elicit SNAb)

However, susceptibility to nonfatal smallpox returns at about 20 years postvaccination

Liu, Nat Med, 2000
Meningococcal
Efficacy of Meningococcal Group C Vaccine Correlates with hSBA of 1/4 - 1/8

However, retrospective analysis of vaccine failures revealed T helper cell deficiency manifested by low T cell proliferation, low B cell activation in the presence of T cells.
Influenza
- HAI antibodies in serum and on mucosa correlate with protection

- However, in elderly antibody responses are poor. CD8+ responses, rather than CD4+ responses correlate with antibody rises, and CD8+ CTL independently correlates with protection

Granzyme B in CTL after Influenza Vaccination of Elderly

HPV
Mucosal Antibody Protects Against HPV

- Passive antibody protects in animal models
- Microtrauma allow access of virions to epidermal basement membrane
- IgG antibodies in serum transudate into cervical mucus and exudate at trauma site.
- Antibodies to L1 prevent binding to membrane cells and also form immune complexes with viral particles

Ebola
Assessment of antigen-specific Immunoglobulin G (IgG) in Ebola Vaccinated Monkeys

However, antibodies do not protect monkeys and the presence of antibodies may simply reflect CD4+ cell function, particularly as antibodies do not neutralize.

T cell depletion studies in monkeys show that T cells are necessary for protection.

Therefore, antibodies are a surrogate, not a correlate.
Zoster
Zoster Vaccine

• Vaccine contains large amounts of infectious and non-infectious varicella virus

• Inactivated virus also protects

• VZ antigen stimulates flagging cellular immunity in the elderly

• Correlate of protection is VZ-specific CD4+ lymphocyte proliferation stimulation index $\geq 5.0$, but VZ antibody response is used as surrogate

Hata et al. NEJM 2002
Plague
Yersinia pestis inactivates neutrophils

- Type 3 secretion system and LcrV protein translocates outer membrane proteins (Yops) into host cells, also reduces innate immunity

- LcrV antibodies protect against macrophage cytotoxicity

- F1 capsule antibodies and LcrV antibodies protect monkeys

- Antibody-deficient mice protected by T cells directed against other antigens

- Exact correlate remains elusive.

Williamson BD, Microbe. Path. 2007
Zanberman S. Vaccine, 2008
Tularemia
Synergy of Antibody and Cellular Immunity in Tularemia

Pertussis
Malaria
• Antibody to CSP definitely correlates with protection, but probably cellular immunity also important

• In challenge studies of individuals given adjuvanted RTS, S vaccine, genes that make immunoproteasomes are upregulated in protected subjects. They degrade proteins into peptides that bind to MHC Class I HLA for CTL stimulation

Kester K. JID 2009, Joos C, PLOS One, 2010
Mucosal Carriage
Is Cell-Mediated Immunity Responsible for Protection Against Mucosal Carriage?

- Pneumococcal conjugate vaccines reduce nasopharyngeal carriage of pneumonia
- In humans, antibodies to pneumococcal surface proteins A (PspA) correlate with prevention of carriage.
- Diffusion of serum antibody into the nasopharynx may play a role, but
- In mice prevention of pneumococcal carriage depends on a Th17 cellular response!
- Th17 cells also important in protection against TB

Casal J, Curr OP Inf Dis 2003; Zhang Z, JCI, 2009
Zyment J Immuni. 2009
Neutralizing antibodies are serotype-specific, directed against vp4(P) and vp 7(G) surface proteins.

Oral IgG can be protective.

Neutralizing antibodies protect against P and G serotypes.

Non-neutralizing antibodies can inactivate intracellular virus

B cells in intestine (IgA and IgG) are associated with protection.

Cellular immunity against VP6 gives partial heterotypic immunity, CD4 (IFNγ) mediated, and contributes to long-term immunity.

Protection is much stronger against disease than infection.

However, surrogate measurement of anti-rotavirus serum IgA gives good idea of protection.

HIV
• Recent data in NHP challenged with SHIV suggest that even low titers of neutralizing antibodies protect.

• RV 144 vaccine trial in Thailand suggested that antibodies, probably non-neutralizing, may be protective.

Hessell AJ. Nat. Med. 2009
Can cellular immunity confer sterile immunity?

Perhaps, if effector T cells present: experience of L. Picker lab with responses to Rhesus CMV carrying HIV gag; probable presence of mucosal CTL in uninfected sex workers; and data that cellular responses prevent fetal infection in monkeys.
Acquisition of HIV by Kenyan Sex Workers Prevented by Genital IgA and Systemic T Cell Proliferation

Correlates of Protection

<table>
<thead>
<tr>
<th>Anthrax</th>
<th>Zoster</th>
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<tbody>
<tr>
<td>Antibody Response</td>
<td>Cellular Response</td>
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