Immunological Correlates of Vaccine-Derived Protection
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Immunological ‘correlates’ of protection: Epidemiological perspective & methods

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Outline

• A simple causal diagram
• Epidemiological approaches to identifying possible vaccine-induced substitute endpoints
• Methodological considerations
Causal diagrams

(Leandro et al, 2009)
Causal diagrams

• Start with very simple relationship between vaccine, substitute endpoint and clinical endpoint:

Vaccine \(\rightarrow [a] \rightarrow\) Immune marker (IM) \(\rightarrow [b] \rightarrow\) (Protection against) Clinical endpoint

\(\rightarrow\) : effect of vaccination on the clinical endpoint

[a] : Association between vaccination & substitute endpoint

[b] : Association between substitute endpoint & clinical endpoint

(Clinical endpoint: infection, disease, severe disease, infectiousness, etc)
Yesterday: “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
Epidemiological approaches

**STUDY DESIGNS**

**OBSERVATIONAL**
- Cohort studies
- Case-control studies
- Ecological studies
  - Natural history studies
  - Maternal-newborn studies

**EXPERIMENTAL**
- Randomised controlled trials
  - RCTs: clinical endpoints
  - RCTs: immunogenicity
- Other studies
  - Challenge studies
  - Passive immunisation studies

*(Gold standard)*
Experimental designs (1)
RCTs: immunogenicity & clinical protection

Example: RCT of 9-valent pneumococcal conjugate vaccine (PCV-9) in The Gambia
Cutts FT et al, Lancet Infect Dis 2005; 365: 1139-41
Saaka M et al, Vaccine 2008; 26: 3719-26

Main trial: VE against serotype-specific pneumococcal disease = 77%

Sub-study: blood taken from 212 / 17,437 children 4-6 weeks after 3rd dose of PCV-9 or placebo
Example: RCT measuring immunogenicity

- Saaka et al: type-specific antibody GMTs in vaccinated (B) & placebo () groups.

![Graph showing antibody GMTs for different vaccines and control groups.](image-url)
Experimental designs (2): Challenge studies & passive immunisation studies

• Challenge studies:
  - use animals or human volunteers with known levels of immune marker
  - challenge with different doses of pathogen
  - relate responses to pre-challenge immune status

• Passive immunisation studies:
  - administer immune globulins
  - follow up → rate of natural infection at various antibody titres
**Example: Challenge study**


Children vaccinated with 3 doses of E-IPV or OPV:

1) pre-challenge immune markers measured (total s-IgA, type 1 specific sIgA, neutralizing abs)

2) challenged with high- or low-dose type 1 OPV vaccine

3) outcome: shedding of type 1 OPV in pharynx & stool

<table>
<thead>
<tr>
<th>Vaccinees</th>
<th>Pre-challenge GMT type 1 polio-specific sIgA</th>
<th>Shed virus</th>
<th>Did not shed virus</th>
<th>p=0.005</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPV (n = 25)</td>
<td>5.0</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-IPV (n = 28)</td>
<td>7.0</td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Specific sIgA associated with protection against poliovirus shedding among OPV-vaccinated children?
  (No association with other immune markers)
Observational studies

STUDY DESIGNS

OBSERVATIONAL
- Cohort studies
  - Natural history studies
- Case-control studies
  - Maternal-newborn studies
- Ecological studies

EXPERIMENTAL
- Randomised controlled trials
  - RCTs: clinical protection
  - RCTs: immune responses
- Other designs
  - Challenge studies
  - Passive immunisation studies

Vaccine not allocated randomly
- ↑ risk of confounding / bias
Observational designs (1): Cohort studies

1) Individuals classified by vaccination status and followed up to measure immune response
   - measures element [a]

   OR

2) Individuals classified by immune marker status and followed up to measure clinical endpoint
   - measures element [b]
**Example: Cohort study**


Outbreak of measles at Boston University shortly after a blood drive

- PRN antibody titres measured in stored blood samples

<table>
<thead>
<tr>
<th>Pre-exposure PRN ab titre</th>
<th>Attack rate (Clinical measles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 120</td>
<td>8/9 (89%)</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0/71 (0%)</td>
</tr>
</tbody>
</table>

PRN titre of 120 = ‘correlate’ of protection (clinical measles) (N.B. Some with titres >120 had ≥ 1 symptom)
Observational studies (2): Natural history studies

- Useful for diseases with long-lasting immunity (e.g. measles, mumps, chickenpox)
  - follow up individuals who develop and recover from infectious disease
  - measure their immune response
**Example: Natural history study**


VZV-specific ab levels and lymphocyte transformation (LT) tests after chickenpox: 6-8 weeks (1-10) & ≥5 years (11-23)

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>ELISA</th>
<th>Subject no.</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;200</td>
<td>11</td>
<td>3,200</td>
</tr>
<tr>
<td>2</td>
<td>11,942</td>
<td>12</td>
<td>2,262</td>
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<tr>
<td>3</td>
<td>18,101</td>
<td>13</td>
<td>10,042</td>
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<td>4</td>
<td>21,526</td>
<td>14</td>
<td>1,492</td>
</tr>
<tr>
<td>5</td>
<td>&lt;200</td>
<td>15</td>
<td>&lt;400</td>
</tr>
<tr>
<td>6</td>
<td>2,262</td>
<td>16</td>
<td>9,370</td>
</tr>
<tr>
<td>7</td>
<td>8,444</td>
<td>17</td>
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</tr>
<tr>
<td>8</td>
<td>12,800</td>
<td>18</td>
<td>7,101</td>
</tr>
<tr>
<td>9</td>
<td>9,050</td>
<td>19</td>
<td>11,143</td>
</tr>
<tr>
<td>10</td>
<td>14,202</td>
<td>20</td>
<td>10,396</td>
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**LT tests**

<table>
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<th>SI</th>
<th>Subject</th>
<th>SI</th>
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<tbody>
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<td>1</td>
<td>4.3</td>
<td>11</td>
<td>24.2</td>
</tr>
<tr>
<td>2</td>
<td>14.1</td>
<td>12</td>
<td>10.8</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>13</td>
<td>8.6</td>
</tr>
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<td>6.0</td>
<td>14</td>
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<td>16</td>
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<td>6.1</td>
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<td>22</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>8.5</td>
</tr>
</tbody>
</table>
Observational studies (3): Maternal-newborn studies

- Measure level of maternal antibodies in neonates
- Relate maternal ab titre to incidence of clinical endpoint

**N.B.** Lacks contribution of elements of immune system not transferred across the placenta – antibody level needed for protection may be higher than that after natural infection.
Example: Maternal-newborn study


93 mothers exposed to cholera in the household
- breastmilk tested for IgA antibodies to cholera toxin & lipopolysaccharide
- infants followed up for cholera colonisation / disease

Results:
- no difference in IgA breastmilk titres between colonised & non-colonised children
- but colonised children: significantly higher IgA titres in breastmilk drunk by infants who did not develop diarrhoea

IgA abs protect against disease but not colonisation?
Observational studies (4): Case-control studies

Cases: those who developed clinical outcome
Controls: did not develop clinical outcome

- pre-exposure levels of immune marker compared
(N.B. need stored samples)
Example: Case-control studies

Taranger J et al, J Infect Dis 2000; 181: 1010-3

- RCT of pertussis toxoid vaccine in Sweden:
  - samples taken 21-77 days after 3rd dose & stored
  - nested case-control study of 126 children exposed to pertussis in the household
  - pre-exposure pertussis toxin (PT) IgG levels compared for cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Median (range) PT IgG level (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (severe disease)</td>
<td>n=27</td>
</tr>
<tr>
<td></td>
<td>79 (1 to &gt;400)</td>
</tr>
<tr>
<td>Cases (mild disease)</td>
<td>n=24</td>
</tr>
<tr>
<td></td>
<td>156 (12 to &gt;400)</td>
</tr>
<tr>
<td>Controls</td>
<td>n=75</td>
</tr>
<tr>
<td></td>
<td>246 (45 to &gt;400)</td>
</tr>
</tbody>
</table>

p<0.0001
Observational studies (5): Ecological studies

Associations are assessed only at the population level, not at the individual level → preliminary assessment of an association
**Example: Ecological studies**

- VE of BCG against pulmonary TB in Malawi < in the UK
- Studies of young people in Malawi (483) & the UK (180)
  
  Black GF et al *Lancet* 2002;359:1393-401

**Pre-vaccination:**
- IFN\(\gamma\) response to PPD-Mtb correlated to DTH to Mtb ags (both Malawi & UK)
- IFN\(\gamma\) positive responses higher in Malawi (61% vs 22%)

**Post-vaccination (12m):**
- *increase* in IFN\(\gamma\) response higher in UK

**Conclusion:** *increase* in IFN\(\gamma\) response post-BCG correlates better with BCG-associated protection (at the population level), rather than *absolute* IFN\(\gamma\) level
Methodological issues (1)

Clinical endpoint: different endpoints used
e.g. protection against infection, disease, severe disease, infectiousness, carriage, time to first endpoint / total number of episodes

→ major immunological implications: protection against different endpoints may require different titres and/or different markers

Immunological factors:
- type of antibody (functional antibody vs. total antibody)
- timing of measurement, kinetics of the immune response

Errors: need to consider
- confounding / other bias
- measurement error (can attenuate associations)
Methodological issues (2)

Antigen factors: relationship between IM and clinical protection may differ in vaccinated/unvaccinated:
- vaccine-derived vs natural immunity

Host factors:
e.g. Age - changes in immune system over lifecourse
  → quantitative/qualitative changes in components of protective immune response with age

Example: study of 90 nursing home residents:
  - antibody titres similar in those who did / did not develop influenza
  - CMI responses → possible better predictor of protection (McElhaney JE et al, J Immunol 1998; 176: 6333-9.)
Conclusion

Variety of approaches to identify immune markers as possible substitute endpoints for protection
- need to consider nature / strength of the evidence

BUT: **statistical correlation** between vaccination / immune marker / protection is not enough to identify a ‘correlate’

Questions to answer:

1) How do we **validate** an immune marker (IM) as a substitute endpoint for clinical protection?

2) If an IM is a valid substitute endpoint, what is the **relationship** between the distribution of the vaccine-induced titre of the IM and VE?
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