Immunological Correlates of Protection: Statistical Perspectives and Methods

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Correlate of Protection

- Immunological assay whose values correlate with protection from disease

- Become ‘established’, i.e. generally accepted, by
  - references in standard texts (e.g. Plotkin/Vaccines; WHO Immunological Basis for Immunization Series)
  - regulatory guidance (e.g. FDA/diphtheria, tetanus; FDA/influenza; WHO/pneumococcal)
  - statements in vaccine package inserts/summary of product characteristics (regulatory approval)
Correlate of Protection – Questions

- Is a correlate of protection a level at which ...
  - all individuals are protected? or
  - 90% are protected? or
  - a ‘population average’ (50% protected)?

- Is it level to be achieved ...
  - post-vaccination, when immune response is at its highest
    - (possibly more relevant in vaccines research)
  - or pre-exposure
    - (possibly more relevant in general scientific terms)?

- If an individual achieves a protective level, are they protected ...
  - at the time the sample is taken
  - for 1 year, 2 years, 5 years, 10 years
  - for life
Correlate of Protection - Questions

• Is the threshold required for protection the same for infants, children, adolescents, adults, elderly?

• Does protective level depend on etiology of immune response being measured?
  – natural infection
  – killed vaccine
  – live attenuated vaccine
  – asymptomatic carriage

• How may these questions be answered in a quantitative sense?
Björkholm/diphtheria (1986)

Ppn. Developing Disease

0.01 IU/mL
0.1 IU/mL
1.0 IU/mL

Diphtheria antitoxin IU/mL

<=0.0025
0.01
0.16
0.64
2.56
0.0
0.2
0.4
0.6
0.8
1.0

7/10
Titer-Specific Rates of Disease

• Similar methods – inspection of titer-specific rates of disease:
  – Ipsen/diphtheria 1946
  – Goulon/tetanus 1972
  – Neumann/measles 1985
  – Chen/measles 1990
  – White/varicella 1992

• See discussion in Siber 1997

• Selected level not necessarily predictive of vaccine efficacy
Logistic regression: e.g. White/varicella

Ppn. Developing Disease

Six-week gpELISA Titer

- <0.3
- 0.3-0.64
- 0.65-1.3
- 1.4-2.5
- 2.6-4.9
- 5.0-9.9
- 10-19.9
- >=20

13/113
5/55
16/186
16/239
13/370
8/617
5/891
3/988
Logistic regression - limitations

• Conclusion depends on length of surveillance and prevalence of disease
• Limited interpretability
  – “for every increase of 1 in \( \log_e (\text{gp ELISA}) \) the risk of disease decreased by 51.7%”
• Models rate of disease, but interest is in protection

• Examples:
  – see also Chan (2002)
7-valent Pneumococcal Conjugate

- 7-valent pneumococcal conjugate vaccine efficacy trial (Black 2000)
  - 38,000 infant subjects, randomized 1:1 to 7-valent pneumococcal conjugate vaccine or placebo
  - subsets of 75 vaccinees and placebo recipients provided samples for assay
  - 40 cases of invasive pneumococcal disease (none among assay subset)

- Titer-specific rates of disease cannot be used
  - titers of cases not known

- Logistic regression cannot be used
  - no cases in immunogenicity subset
7v-PVC: Method of Chang & Kohberger

• Protective threshold is assay value at which relative risk of being below the value equals relative risk of disease (Jódar 2003)

• i.e. find $t_p$ such that:

$$t_p : \frac{P(t < t_p \mid \text{vaccinated})}{P(t < t_p \mid \text{not vaccinated})} = \frac{P(\text{disease} \mid \text{vaccinated})}{P(\text{disease} \mid \text{not vaccinated})}$$

where $t =$ assay value (titer)

$t_p =$ protective threshold
7v-PVC: Method of Chang & Kohberger

**Cases = 39**

**Cases = 1**

**Protective threshold = 0.18**

**Susceptible**

**Protected**

VE = 97.4%
RR = 0.026

Cases = 1

23

87.1 = 0.026

Distribution

Pneumococcal IgG ELISA

Non-vaccines

Vaccines
7v-PVC: Method of Chang & Kohberger

- Lead to adoption by WHO of 0.35 µg/mL IgG reference level after pneumococcal conjugate vaccination (WHO 2005)

- Method also used for 1:8 SBA titer following meningococcal C conjugate vaccination (see Andrews 2003)

- Samples from subset of subjects sufficient

- Predictive of vaccine efficacy

- Population average measure

- Assumes same threshold for vaccinees and non-vaccinees
Scaled logit model

- Bridges from disease to protection
- Incorporates exposure into logistic regression
- Useful paradigm: “Both exposure and susceptibility (i.e. lack of protection) are necessary for disease to occur, and together they are sufficient”

\[ P(\text{Disease}) = P(\text{Exposure}) \times (1 - P(\text{Protected})) \]

- (same paradigm applied in previous method)

- Refs./examples:
Scaled Logit Model (varicella data)

exposure parameter = 0.118

logistic regression
scaled logit model

Ppn. Developing Disease

Six-week gpELISA Titer

<0.3
0.3-0.64
0.65-1.3
1.4-2.5
2.6-4.9
5.0-9.9
10-19.9
>=20
Scaled Logit Protection Curve

Protection

Six-week gpELISA Titer

95% C.I

95% C.I

0.0
0.2
0.4
0.6
0.8
1.0

0.13
0.25
0.5
1.0
2.0
4.0
8.0
16.0
32.0
64.0

t_50

t_90
Scaled logit model

- Corresponds more closely to expectations in many cases
- Estimates protection rather than rate of disease
- Estimate of protection independent of length of surveillance or disease incidence
- Requires rich dataset; model fit not always achieved
- Protection curve conditional on exposure parameter; reliability of protection curve depends on small variance of estimated exposure parameter
Principal Surrogate method

• Experimental method

• Because a subject cannot be ‘assigned’ to an assay value, a designed experiment to test the relationship between assay value and disease cannot be devised

• Principal surrogate method applies causal inference methods

• Special study design or additional data needed

• Applied to ‘consistency’ question – see Gilbert 2007, Follmann 2006 (and next slide)
Classification scheme

- “Correlate of Risk” (weak) – high and low assay values associated with low and high risk of disease
- “Specific Surrogate of Protection” (medium) – reliably predicts vaccine efficacy from assay values in similar setting
  - relationship between assay value and protection consistent for vaccinees and placebo recipients
- “General Surrogate of Protection” (strong) – reliably predicts vaccine efficacy from assay values in different settings
  - consistent for any immunological history – e.g. different kinds of vaccine, immunity from natural infection, asymptomatic carriage, etc.
- see Qin 2007, Sadoff 2007
Challenges: Statistical Methods

• Method for finding threshold in homogenous subjects (i.e. no vaccinee/non-vaccinee distinction)
  • (see illustration next slide)

• Extension of exposure-based, continuous models (e.g. scaled logit)
  – test for consistency; case-cohort design (see Qin 2008); direct method for CI for $t_{50}$ and $t_{90}$; tractable form of ‘Nauta Integral’ (see Nauta 2009); more flexible/non-parametric models; goodness of fit
e.g. Swedish Pertussis Pertactin data
Challenges: Statistical Methods

- Two threshold method of Chang & Kohberger
  - without ‘same threshold’ assumption

- Principal surrogate methodology applied to homogenous subjects (i.e. no vaccinee/placebo recipient distinction)

- Link post-vaccination protection to pre-exposure protection
  - (see illustration in following slide)
Challenges: Post-vaccination/pre-exposure

- post-vaccination assay
- pre-exposure assay
- disease

Assay Value vs. Time
Challenges: Technical

• Protection is mediated through multiple immunological mechanisms of action, but assays only measure a single characteristic
  • (see illustration next slide)

• Kinetics of immune response poorly understood
  • (see illustration next slide)

• Despite efforts to standardize assays, differences in immune responses to same vaccine observed in different trials

• Lack of cases among vaccinees, and lack of immune response among placebo recipients renders demonstration of consistency problematic
Challenges: Mechanisms of action/kinetics
Challenges: Data

- Limited opportunities to collect data ...
  - Both immunogenicity and disease occurrence data needed

- Vaccine licensure efficacy trial
  - one chance only? – may be unethical to conduct placebo-controlled trial post-licensure
  - incentivize sponsor to look for correlate

- Observational study
  - cost
  - reliable surveillance

- Challenge study
  - ethical issues

- Acute-phase study
  - only certain diseases
  - timing problematic
Challenges: What’s possible?

• Sufficient assays cannot be conducted to fully describe immune response

• “Specific” correlates should be sought, specific to
  – assay timing ... (post-vaccination, pre-exposure)
  – stimulus ... (type of vaccine, etc.)
  – population ... (infants, adults, elderly, etc.)

• and
  – case definition
  – surveillance period (for post-vaccination assays)

• as well as the assay itself
Questions?
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• Jennifer Kensler, Laurent Coudeville, Amit Bhaumik and Fabrice Bailleux - Extensions to the Scaled Logit Model for Immunological Correlates of Protection Research Group
References


• World Health Organization, Department of Immunization, Vaccines and Biologicals. Immunological basis for immunization series; accessed at http://www.who.int/vaccines-documents/DoxTrng/h4tibi.htm


• U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. *Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*, May 2007

References

- Ipsen J. Circulating antitoxin at the onset of diphtheria in 425 patients. *Journal of Immunology* 1946; 54:325-347
References

- Siber GR. Methods for estimating serological correlates of protection. *Developments in Biological Standardization* 1997; 89:283-296
References

References


References

References

- Gilbert PB, Qin L, Self SG. Evaluating a surrogate endpoint at three levels, with application to vaccine development. *Statistics in Medicine* 2008; 27(23):4758-78.
Backup slides
Correlate of Protection – Uses

- Protective thresholds used for
  - assessment of individual protection
  - as alternative to vaccine efficacy trial
  - as means of quantifying response to new vaccine candidate
  - to compare immunogenicity of two vaccines – non-inferiority trial
  - vaccine non-interference trial
  - vaccine lot consistency trial
  - estimation of duration of protection
Other approaches

- Surrogate endpoint (Prentice criteria)
- Diagnostic testing (sensitivity and specificity)

### Surrogate Endpoint

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### Correlate of Protection

| Disease | | |
|---------|---------------|--|--|
| +       | ✓             | ✓ | |
| t < t_p | ✓             | ✓ | |
| t ≥ t_p | 0             | ✓ | |
31 Placebo-Controlled Trials of Cimetidine

Significant (Yates)
Not-significant
Upper control limit
Lower control limit
significance boundary

Interpretation: Stephen Senn