‘Correlates’ of vaccine-induced protection: methodological issues

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Outline

- Causal diagrams
- Brief review of statistical methods
- ‘All-none’ and ‘partial’ models

A quick word about definitions

- The terms 'correlate' and 'surrogate' are used differently in the literature
- In this presentation we will use:

Correlate:

- a factor that is statistically associated with clinical protection

Substitute endpoint or *surrogate:*

- a correlate that lies on the causal pathway between vaccination and clinical protection

Understanding mechanisms

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(Leandro et al, Braz J Med Biol Res 2009)

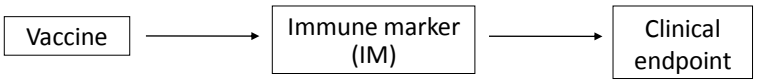
Causal diagrams may help to:

- summarise knowledge about interrelationships between vaccination, immune markers & clinical endpoints
- guide statistical analysis and interpretation of findings

Causal diagrams (1)

Some simplified scenarios:

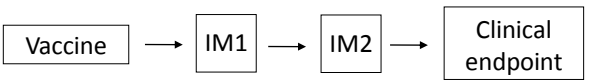
A) Single pathway: all the protective effect of the vaccine is mediated through one immune marker



Immune marker is *necessary* and *sufficient* for protection

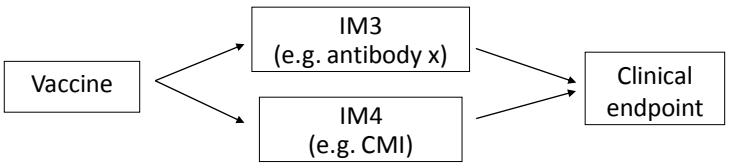
Causal diagrams (2)

B) Single pathway: more than one immune marker (IM)



Example: cytokine cascade?

C) Two independent pathways to protection:



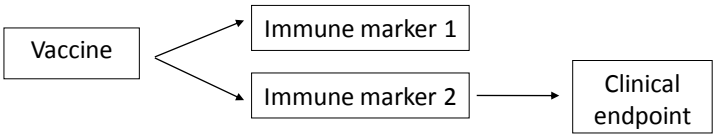
Example: pertussis PT, FIM, PRN antibodies?

Some markers/pathways may be more important than others

Causal diagrams (3)

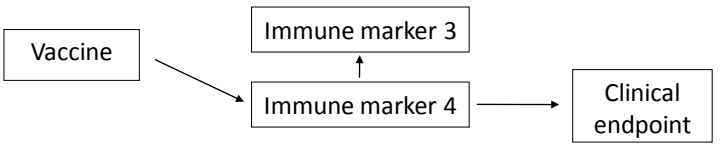
C) One or more immune marker has no role in protection:

(i)



IM1: 'correlated' with protection?

(ii)



IM3: could be 'correlated' with protection, if IM3 is a necessary (quantitative) product of IM4

Statistical Methods

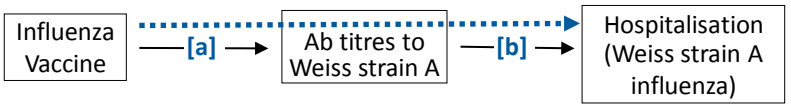
Is the immune marker a valid substitute endpoint?

A) Prentice criteria (1989): hypothesis-testing approach used to validate substitute endpoints

1) Vaccine has a significant effect on the clinical endpoint ⋯➔
2) Vaccine is significantly related to substitute endpoint **[a]**
3) Substitute endpoint is significantly related to clinical endpoint **[b]**
4) Full effect of vaccine on clinical endpoint is explained by the substitute endpoint (sole causal pathway)

Prentice criteria - Example

Qin et al (2007): 1943 trial of trivalent influenza vaccine



VE = 73%

Antibody titres: significantly higher in vaccinated **[a]**

: inversely associated with hospitalisation **[b]**

After controlling for ab titres:

- risk of infection (vaccinated) = risk of infection (unvaccinated)
- ab titres still inversely associated with protection

Statistical methods: 'Proportion explained'

- Prentice criteria: full effect of vaccine is not explained by the immune marker if >1 causal pathway
- Alternative - proportion of treatment effect explained:

$$PTE=(b1-b2)/b1$$

(b1=unadjusted effect of vaccine; b2 = effect adjusted for IM)

Example: Kohberger et al - pertussis household contact study
- IgG abs to PT, FIM, PRN antigens (combined effect)

PTE by combined ab response = 93% (95% CI: 51%-184%)

- BUT: concerns raised about use of the PTE method.....

Qin framework (2007)

- Proposed hierarchical framework for assessing validity of immune markers as substitute endpoints:

Correlate of risk: IM correlates with clinical endpoint

Some correlates will be surrogates:

- Level I (*specific*) surrogate of protection:

a) Statistical surrogate: satisfies Prentice criteria

b) Principal surrogate: uses causal inference to compare potential outcomes ('what immune response would this vaccinated patient have had if s/he had not been vaccinated', etc)

- Level 2 (*general*) surrogate of protection: uses meta-analysis to predict protection across settings

Qin framework: Level 2 SOP

- Meta-analysis of data from individual trials:

- plot observed VE against measured differences in immune response between vaccinated & unvaccinated
- use relationship to predict VE in new setting, based on immune responses measured in that setting

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(Qin et al, J Infect Dis 2007)

- Problem: requires a lot of data (which we may not have)

Protection

What do we mean when we say a vaccine gives '75% protection' against infection?

- and how does this relate to levels of the immune marker?

Vaccine Efficacy

VE will depend on:

i) relationship between IM titres and clinical protection

ii) distribution of IM titres in the vaccinated population

- likely to vary by age, SES etc

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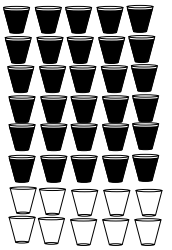
Relationship between clinical protection & log antibody titre (top line), & distribution of log antibody titres (bottom line)

Nauta et al, Biologicals 2009; 37: 216-21.

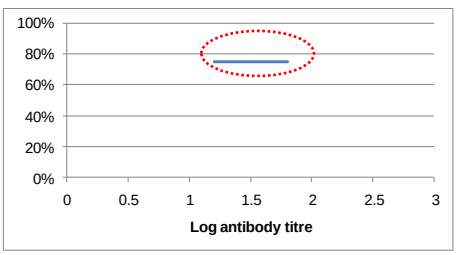
Mechanism of action: 'all/nothing'

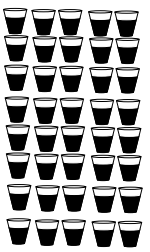


- 75% of individuals are above IM threshold and are fully protected ('all')
- 25% of individuals are below IM threshold and remain fully susceptible ('none')

Examples: pneumococcal conjugate vaccine, meningococcal C, measles, hepatitis A, etc.

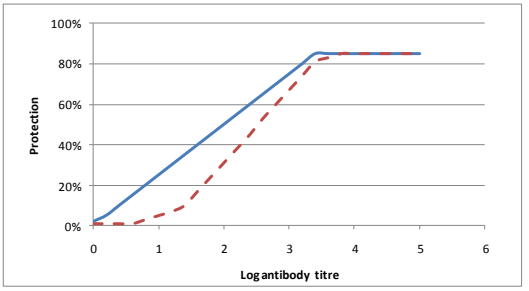
Mechanism of action: 'partial (1)'

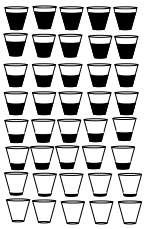




- vaccinated individuals reach an IM titre which confers 75% protection (all are at a reduced risk)

Mechanism of action: 'partial (2)'

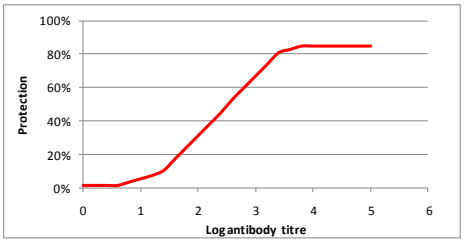


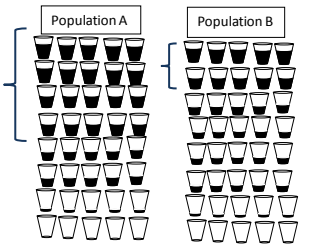


Level of protection varies continuously, depending on IM level. Shape of relationship could be linear, logistic, etc.

- VE will be <u>average</u> reduction in risk among vaccinated compared to unvaccinated

VE and host characteristics





- 2 populations given same vaccine:

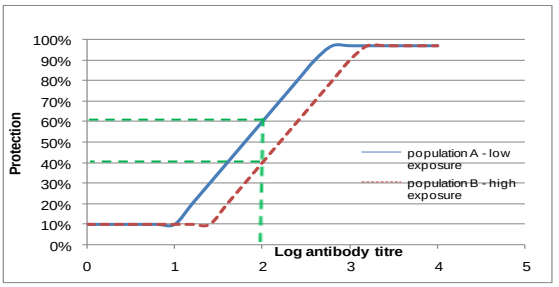
Population A: 50% of vaccinated develop 'good' protection

Population B: 25% of individuals develop 'good' protection

Challenge dose

Higher levels of immune marker may be needed to protect against higher/more frequent exposure:

- a specific IM titre may confer less protection in settings with high level of exposure to pathogen



Example: antibody titre of 2 is associated with 60% protection in population A, but only 40% protection in population B

Conclusions

- Use of immunological markers as substitute endpoints has huge potential advantages
- Identification & validation of markers is not straightforward
- This is a subject crying out for serious collaboration between immunologists, statisticians, epidemiologists & regulatory vaccinologists!

Thanks to.....

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