Statistical Methods for Infectious Diseases
Correlates and Surrogates of Protection
Lecture 14

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Vaccine efficacy for susceptibility

$$\begin{aligned} VE_S &= 1 - RR \\ RR &= \text{relative risk in vaccinated} \\ &\quad \text{compared to unvaccinated} \end{aligned}$$

- incidence rates, hazard rates, incidence proportion, transmission probability
- outcomes usually clinical disease, sometimes infection

Motivation

- Replace Phase III trials, or reduce sample size and shorten duration of study
- With already licensed vaccines, placebo-controlled phase III trials not possible (second and further tier candidates)
- Future vaccines for possibly emerging pathogens where studies not possible

General Issues

- Biological
  - $\longrightarrow$ finding the right marker(s)
  - $\longrightarrow$ time of assay after vaccination,
  - $\longrightarrow$ short-term protection, long-term immunological memory
  - $\longrightarrow$ antibody concentration, avidity, functional antibodies
  - $\longrightarrow$ choice of assay
- Statistical association versus causal
  - $\longrightarrow$ correlation versus surrogate
  - $\longrightarrow$ may be based on individual or population

The problems

- To identify immunological markers predictive of protection
- To identify immunological markers predictive of **vaccine-induced** protection

Accounting for exposure to infection

- Problem: not everyone in the group under observation is exposed to infection.
- Thus, a person might not develop disease because of not being exposed, not necessarily because of being protected.
- A simple general approach assumes the probability of disease is the product of the probability of disease if not protected and the probability of not being protected:

  $$\Pr[\text{disease}] = \Pr[\text{disease}|\text{not protected}] \times \Pr[\text{not protected}].$$

- In a study, the probability of disease can be estimated by the attack rate.

Removing exposure term

$$\begin{aligned} VE_{S,CI} &= 1 - \frac{\Pr[\text{disease (vac)}]}{\Pr[\text{disease (controls)}]} \\ &= 1 - \frac{\Pr[\text{disease}|\text{not protected (vac)}]\Pr[\text{not protected (vac)}]}{\Pr[\text{disease}|\text{not protected (control}]\Pr[\text{not protected (control)}]} \end{aligned}$$

- The terms for the probability of disease if not protected cancel assuming
  1. exposure to infection is equal in vaccinated and control groups,
  2. the probability of disease is equal in both groups if exposed and not protected:

$$VE_{S,CI} = 1 - \frac{\Pr[\text{not protected (vac)}]}{\Pr[\text{not protected (control)}]}.$$

Threshold and Continuous Models

- The probability of not being protected can be based on a threshold level of antibody above which everyone is protected.

- $\longrightarrow$ then probability of being protected is estimated by proportion of people with immune response above threshold.

- Alternatively, one can estimate the probability of protection as a continuous function of the level of antibody.

- $\longrightarrow$ then probability of not being protected is replaced by average probability of being protected over the predicted probabilities of protection at the individual antibody titers.

Special case: everyone is exposed

- Challenge studies.
- Household exposure to infection has been used as a natural challenge.
- The probability of developing disease was modeled directly as a continuous function of the antibody titers (Storsaeter et al 1998).
- $\longrightarrow$ the probability of disease in the vaccinated and unvaccinated groups of another vaccine study predicted (Kohberger et al 2008).

All-or-none model assumption

- All of these models are based on an all-or-none model of vaccine protection, whether the threshold or continuous model is assumed.
- In the continuous model, at a given antibody titer, a person is either protected or not with an antibody-specific probability.
- The model also generally assume that the protection conferred by titers produced by natural exposure or vaccination are equivalent.

Threshold models for protection

- Assume AB(protective) is level of antibody that is protective.

$$\begin{aligned} VE_{S,CI} &= 1 - \frac{\Pr[\text{disease}|\text{vaccinated}]}{\Pr[\text{disease}|\text{control}]} \\ &= 1 - \frac{\Pr[\text{not protected (vac)}]}{\Pr[\text{not protected (control)}]} \\ &= 1 - \frac{\%\text{ of vaccinated with [Ab]} < \text{AB(protective)}}{\%\text{ of controls with [Ab]} < \text{AB(protective)}} \end{aligned}$$

- If VE_S based on the clinical outcome is known and the antibody level is measured in everyone, then solve for AB(protective)
- If licensed on immunogenicity, can use post-license surveillance to check relation of observed VE_S compared to observed antibody levels.

Thresholds: meningococcal C conjugate

- meningococcal C conjugate vaccine in England licensed based on immunogenicity alone (Serum bactericidal assay, SBA).
- Serologic correlate of protection validated using postlicensure surveillance (Andrews et al 2003).
- Used screening method (proportion of cases vaccinated, proportion of population vaccinated) to estimate effectiveness.

- Issue with change of assay; re-evaluated cutoffs based on observed data.
- Population-based approach, measured immunogenicity in a representative and statistically adequate sample of vaccinated and unvaccinated population in whom efficacy is measured.

Thresholds: meningococcal C conjugate

- Cases of confirmed meningitis C infection that occurred in vaccinated and unvaccinated individuals in England from January 2000 to the end of 2001 and coverage levels of vaccination were used for the computation.

- In preschool children, 27 cases occurred, all in unvaccinated children for an efficacy estimate of 100% (95% CI, 93.3–100%).

Table: Predicted vaccine efficacy and 95% CIs estimated for unvaccinated and vaccinated preschool children with titers below the different serum bactericidal assay (SBA) cutoffs one month after vaccination with the meningococcal conjugate vaccine measured by SBA (from Andrews et al 2003).

	% Individual with titers below cutoff		
Cutoff	Vaccinated	Unvaccinated	Predicted % vaccine efficacy (95% CI)
1:4	0.0	90.4	100 (95–100)
1:8	0.0	93.3	100 (95–100)
1:16	2.5	94.3	97 (92–99)
1:32	4.1	95.2	96 (90-98)
1:64	4.9	97.1	95 (89–98)
1:128	9.8	97.6	90 (83–94)

Thresholds: meningococcal C conjugate

- Coverage levels were not given in the paper.
- From Table 1, the predicted efficacy from titers one month after vaccination is consistent with the observed efficacy at all of the cutoffs except 1:128.
- However, using titers 7 and 9 months postvaccination, the predicted vaccine efficacy significantly underestimated the observed efficacy in infants and toddlers (preschool children were not included).
- This suggests that when the postvaccination titers have declined
  $\longrightarrow$ immunologic memory and a rapid booster response may be responsible for efficacy, which would better be measured by antibody avidity.

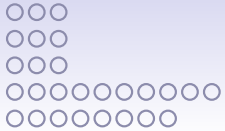
Thresholds: pneumococcal vaccines

- Jódar et al (2003): multivalent pneumococcal vaccines. Report of consultation in Anchorage, 2002.

- Assumed IgG after 3 doses of vaccine predicts protection.
- Assumed that relation of risk of disease and antibody is step-wise function, although knew it is continuous.
- Use aggregate antibody titers
  - Absences of precise efficacy data makes type-specific thresholds difficult to define.
  - Unlikely that type-specific thresholds could be defined for additional serotypes that had not undergone efficacy trials.

Issues of thresholds

- Does threshold discriminate immune response in vaccinees and controls?
- Small changes in point estimate of efficacy may significantly change threshold antibody concentrations that predict efficacy.
- Relation between protection and antibody level likely continuous, not discrete.



Taking other factors into account

- At low assay values, whether a person develops disease could be associated with whether the person as exposed or not.
- The probability of disease in individuals with low assay values could depend on the prevalence of the disease or other factors not associated with the immunological measures.
- Dunning (2006) proposed a model that separates effect of assay values from such factors as level of exposure and disease prevalence.
- This model estimates the parameter in contrast to the previous model where it is assumed to cancel out.

Setup

- Assume data from n participants, $i = 1, \ldots, n$.
- Outcome $y_i = 1$ if person i develops disease, and $y_i = 0$ if not.
- x_i is the assay value for subject i, x is log transformed so that it can have negative values.

Setup

- The model has two main components.
  1. $\alpha(x)$ = probability a person with titer x is protected.
  2. ω = probability a susceptible person develops disease (attack rate in susceptibles)

- The probability $\alpha(x)$ is essentially an all-or-none model of protection where the probability of being completely protected is a function of the immunological assay value.

- Protected individuals are assumed completely immune from disease.

- The $(1 - \alpha(x))$ susceptible individuals are assumed to be homogeneously susceptible.

The model

- The probability that an individual develops disease is the product of the probability that the individual is susceptible and the probability that a susceptible individual will develop disease:

$$\Pr(Y_i = 1 | X_i = x) = \omega(1 - \alpha(x_i)). \tag{1}$$

- If an inverse logit function is used to model a relation of X, $f(X)$, to $\alpha(X)$, then the probability of being protected is modeled

$$\alpha(X) = \frac{1}{1 + \exp(-f(X))}. \tag{2}$$

- For small assay values, $\alpha(x) \to 0$, for large assay values, $\alpha(x) \to 1$.

The complete model

- Combining (1) and (2) gives a model for the probability that an individual with assay value X develops disease:

$$\Pr(Y_i = 1 | X_i = x) = \frac{\omega}{1 + \exp(f(X))}. \quad (3)$$

- Example: model $f(X) = a + bx$ (Dunning 2006).

- The parameters ω, a, and b can be estimated by standard likelihood methods.

A new vaccine formulation

- Given estimates of $\hat{a}$ and $\hat{b}$, suppose that in a trial of a new vaccine candidate in a similar setting, the immunological assays are performed but no clinical outcomes were measured.
- Let ω' be the unknown probability of developing disease in the susceptible individuals in the trial.
- From (3), the number of individuals expected to develop disease in the vaccinated group is

$$\sum_{i \in V} \Pr(\text{disease}) = \sum_{i \in V} \frac{\omega'}{1 + \exp(\hat{a} + \hat{b} x_i)}. \tag{4}$$

- A similar computation yields the expected number of cases in the unvaccinated group.

Efficacy of a new vaccine formulation

- In the computation of vaccine efficacy, the value of ω' would cancel in the ratio of expected number of vaccinated and unvaccinated cases.
- The efficacy of the new vaccine formulation would be predicted by (Dunning 2006)

$$\mathrm{VE}_{new} = 1 - \frac{1/n_v \sum_{i \in V} 1/(1 + \exp(\hat{a} + \hat{b} x_i))}{1/n_c \sum_{i \in C} 1/(1 + \exp(\hat{a} + \hat{b} x_i))}. \tag{5}$$

- This model assumes that the protective effect is the same in the vaccinated and the unvaccinated group.

Household exposure as natural challenge

- Storsaeter et al (1998): household study nested in placebo-controlled efficacy trial of acellular pertussis vaccines (DTaP), a whole cell vaccine (DTwP) compared to DT. The objectives were
  1. to evaluate possible serological correlates of protection by relating clinical outcome after household exposure to antibody levels against PT, PRN, FHA, and FIM;
  2. to explore possible use of post-vaccination anti-pertussis antibody levels as surrogate markers to predict protective efficacy of the whole cell or multicomponent pertussis vaccines.

Household exposure as natural challenge

- A problem in evaluating correlates of protection is that possibly many participants are not even exposed to infection.
- Examining children with household exposure to pertussis proposed as natural challenge experiment.
- Antibody titers after exposure were measured. Either earlier sample from trial or post-exposure sample was used in regression model.
- Requires a relatively high secondary attack to be efficient.

Logistic regression model

- The outcome Y is 1 if diseased and 0 if not diseased.
- X = values of immune assays, possibly vaccination status, other covariates
- $g(X)$ = function of X, say, a linear combination of X, and unknown parameters be estimated.
- The probability of disease as a function of X in the logistic model as

$$\Pr(\text{disease}|X) = \frac{1}{1+\exp(-g(X))} \tag{6}$$

Predicting efficacy from regression model

- Using the values $g(X)$ in the estimated regression model for the individuals in the vaccinated and unvaccinated, can estimate the probability of disease for a person with immune measure x_i, $P_i(x_i)$. So in a group of size N, predict

$$\text{probability of disease(vaccinated)} = \frac{\text{sum of } \ P_i(x_i)}{N}$$

- Similarly predict in the unvaccinated group.
- For a new vaccine, then

$$VE_{S,new} = 1 - \frac{\text{probability of disease(vaccinated)}}{\text{probability of disease(unvaccinated)}}$$

- Kohberger et al (2008) re-visited Storsaeter pertussis study and predicted efficacy from another pertussis study.

Comparison of two models

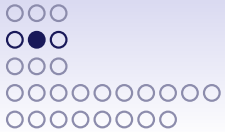
- Although the probability of protection model (2) looks similar to the probability of disease model (6), the interpretation is very different.
- Model (6) is an expression for the probability of developing disease at certain assay and other covariate values, but model (2) is an expression for the probability of being protected at a certain assay value.

Correlates and Surrogates

- The term correlate of protection has been used to describe several different aspects of the relation of a vaccine-induced response and the infection or disease outcome.
- In a series of papers, Qin et al (2007), Gilbert et al (2007), Gilbert and Hudgens (2008a), and Qin et al (2008), propose a framework for assessing immunological correlates of protection in vaccine trials.
- The framework is based on the methods of Prentice (1989) and Frangakis and Rubin (2002).
- The framework defines different levels of confidence in immunological markers.
- The first level is a correlate of risk (CoR).
- The next two levels are surrogates of protection (SoP)

Table: Definitions of three levels of an immunological correlate of protection (Gilbert, Qin, and Self 2007)

Term	Definition	Framework for assessment	Analytic method
CoR (Correlate of risk)	An immunological measurement S that correlates with the study endpoint Y measuring vaccine efficacy in a defined population	Vaccine trial (efficacy or proof of concept) or epidemiological study	Regression models
Specific SoP (Surrogate of protection for the same setting)	An immunological measurement that is a CoR within a defined population of vaccine recipients and satisfies either:		
SoP^S (Statistical surrogate of protection for the same setting)	Relation between immunological measurement S and endpoint Y is the same in the vaccine and placebo groups	Single large efficacy trial	Statistical surrogate framework
SoP^P (Principal surrogate of protection for the same setting)	The immune response S satisfies average causal necessity and average causal sufficiency	Single large efficacy trial	Principal surrogate framework
General SoP (Surrogate of protection for new	An immunologic measurement predictive of vaccine efficacy in different settings, such as human populations,	Multiple trials and/or post-licensure	Meta-analysis



Correlates of risk

- An immunological measurement that predicts a clinical end point in a particular population is a correlate of risk (CoR).
- Various statistical approaches such as fitting regression models can be used to fit the data for the clinical end point of interest to the immunological measurement.
- The immunological measurement must have a source of variability to be used in the regression models.

Correlates of risk

- If the individuals in the study population have no previous exposure to the infection, they would generally have zero or near zero immune measurements for the infectious agent of interest.
- Then the correlate of risk can be evaluated only in the vaccinated people.
- In some diseases in which repeated exposure occurs with the development of partial immunity, such as malaria, or repeated exposure with similar strains, such as influenza, an immunological measurement could be positive and have variability in the unvaccinated people as well as the vaccinated people.

Surrogates of Protection

- A surrogate of protection is a correlate of risk that reliably predicts a vaccine's level of protective efficacy on the basis of contrasts in the vaccinated and unvaccinated groups' immunological measurements.

- A specific surrogate of protection: The same setting would include a similar population, the same infectious agent, and the same vaccine product.

- A general surrogate of protection: A new setting could be a new population, different strains of the infectious agent, or different vaccine products.

Surrogates of Protection

- The specific surrogates of protection further classified:
  $\longrightarrow$ statistical surrogates of protection (SoP^S) and
  $\longrightarrow$ principal surrogates of protection (SoP^P).

- The statistical surrogates of protection satisfy the Prentice criterion (1989) of a surrogate end point

- The principal surrogates of protection draw on the principal surrogate framework of causal inference (Frangakis and Rubin 2002)

- The specific principal surrogates of protection are defined by fixed values of the immune response if assigned vaccine. (!)

Prentice criteria

- In a groundbreaking paper, Prentice (1989) proposed four criteria for a biomarker to be a surrogate endpoint for the primary clinical outcome of interest.
- In the context of vaccines, the four can be stated as
  1. Protection is significantly related to the vaccine.
  2. The surrogate is significantly related to the vaccine
  3. The surrogate is significantly related to the clinical endpoint.
  4. The surrogate explains all of the clinical endpoints.

Prentice criteria

- The last criterion can be checked by a statistical regression model that has both the vaccine indicator and the value or model for the surrogate in the model.
- Different approaches available.
- If regression coefficient for the treatment indicator is not significantly different from 0, then the criterion is met.
- In another approach, one could require that the regression coefficient actually be 0, which will generally not happen.
- Kohberger et al (2008) take an alternative approach to the fourth criteria based on estimation of the proportion of the clinical endpoint explained (PE) by the surrogate (Burzykowski, et al 2005).

Causal inference

- Frangakis and Rubin (2002) criticized the Prentice approach because it is subject to post-randomization selection bias.
- In the vaccine context, under the Prentice approach, the risk of the clinical endpoints is compared in individuals with the observed values of the immunological markers.
- However, we observe only the immunological value and the clinical endpoint that the person has under the actual vaccine assignment. We do not observe the value of the immune marker value that the person would have had under the other vaccine assignment.

Introduction to Causal Inference

- (Rubin 1980, Holland 1986, Robins 1986)
- Causal inference is a framework for carefully defining causal estimands, that is the quantities that one wants to estimate, and then articulating the conditions and assumptions under which they can be estimated from the observed data.
- A potential outcome is the outcome that a person would have if a person received a particular treatment.
- Receiving the treatment does not necessarily occur.

What is an individual causal effect?

- The individual causal effect is defined as the difference in potential outcomes in individual i under one treatment compared to another treatment. Formally, for $i = 1, \ldots, n$,

$$Z_i = 0, 1 \qquad \text{treatment assignment/exposure}$$

$$Y_i(z) \qquad \text{outcome under assignment } z = 0, 1$$

$$Y_i(0) - Y_i(1) \qquad \text{individual causal effect}$$

- Fundamental Problem of Causal Inference (Holland 1986): generally only one of the potential outcomes of an individual can be observed.

Average Causal Effect

- Two usual assumptions:
  1. no interference between units (SUTVA)
  2. independence of treatment assignment from the potential outcomes, e.g. randomization.
- Need at least three elements in the model
  1. a population of units,
  2. at least two treatments (the causes),
  3. and the response variables, or potential outcomes of interest.

Average Causal Effect (ACE)

- Assume that we randomly assign $n_0 = n/2$ of the population to vaccine and to control.
- Under the assumptions of SUTVA and randomization (and compliance), the population average causal effect is

$$\begin{aligned} E\{Y(0) - Y(1)\} &= E\{Y(0)\} - E\{Y(1)\} \\ &= \\ &= E\{Y(0)|Z=0\} - E\{Y(1)|Z=1\} \\ &= \\ &= \frac{\sum_{i=0}^{n_0} Y_i(0)|Z=0}{n_0} - \frac{\sum_{i=0}^{n_0} Y_i(1)|Z=1}{n_0}. \end{aligned}$$

- which is identifiable from the observed data.

Table: Four kinds of people and the individual causal effects based on potential outcomes

Stratum	$Y(Z=1)$	$Y(Z=0)$	Causal effect
immune	0	0	0
harmed	1	0	-1
protected	0	1	1
doomed	1	1	0

Table: Four kinds of people based on immune response level (simple dichotomous case): 0 = low, 1 = high

Stratum	$S(Z=1)$	$S(Z=0)$
always low	0	0
increased	1	0
decreased	0	1
always high	1	1

- Imagine the response levels are continuous.

Statistical Surrogate of Protection

- A statistical surrogate of protection (Frangakis and Rubin 2002) is evaluated by comparing the risk distributions

$$\begin{aligned} \text{risk}(s|Z=1) &\equiv \Pr(Y=1|Z=1,S=s) \\ \text{risk}(s|Z=0) &\equiv \Pr(Y=1|Z=0,S=s). \end{aligned}$$

- If for all values of S, $\text{risk}(s|Z=1) = \text{risk}(s|Z=0)$, then the immunological marker S is a statistical surrogate of protection for the clinical endpoint.

- The problem with this approach is that what is measured is a mixture of the causal vaccine effects and differences between participants who are infected in the vaccine and unvaccinated groups with values of $S = s$.

Principal Surrogate of Protection

- Assuming (Gilbert and Hudgens 2008)
  1. no interference between units (SUTVA)
  2. independence of treatment assignment from the potential outcomes, e.g. randomization.
- An immunological marker S is a principal surrogate endpoint if, for all $s_1 = s_0$, the following two risks are equal:

$$\begin{aligned} \text{risk}_{(1)}(s_1, s_0) &\equiv \Pr(Y(1) = 1 | S(1) = s_1, S(0) = s_0) \\ \text{risk}_{(0)}(s_1, s_0) &\equiv \Pr(Y(0) = 1 | S(1) = s_1, S(0) = s_0) \end{aligned}$$

- The contrast of the two risks measures a population-level causal vaccine effect on Y for participants with the potential immunological measures $\{S_i(1) = s_1, S_i(0) = s_0\}$.

- The contrast of the two risks measures a population-level causal vaccine effect on Y for participants with the potential immunological measures $\{S_i(1) = s_1, S_i(0) = s_0\}$.

Principal surrogates of protection

- Let $S(1)$ be the response that an unvaccinated subject would have if vaccinated.
- Let Y be the 0,1 outcome of being infected or not, Z be the 0,1 assignment to vaccine or control.
- For a specific principal surrogate of protection, one needs to estimate

$$\mathrm{VE}(s1) = 1 - \frac{\Pr[Y = 1 | Z = 1, S(1) = s1]}{\Pr[Y = 1 | Z = 0, S(1) = s1]}.$$

- Compare with what is generally estimated.

Principal surrogates of protection

- One needs to be able to predict the immune response that an unvaccinated subject would have had if vaccinated.
- Follmann (2006) introduced two approaches to predicting immune response in the controls.

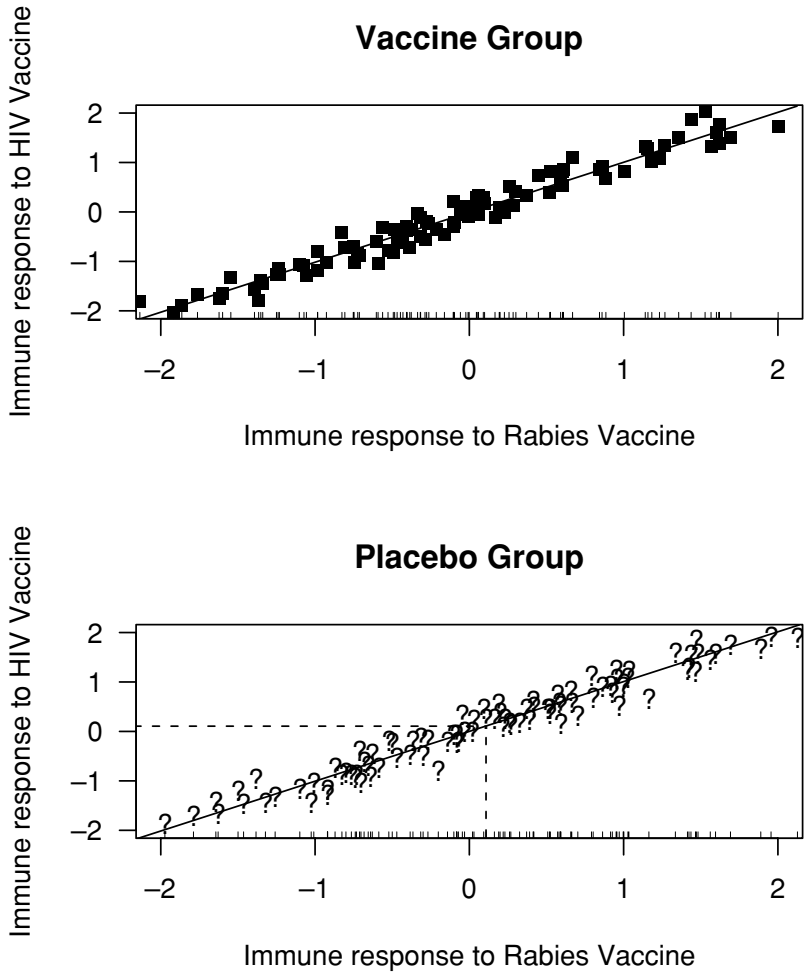


Figure: Imputing immune response to HIV vaccine. Bivariate distribution of X and W observed in vaccine group, then X imputed for placebo group. (Follmann 2006)

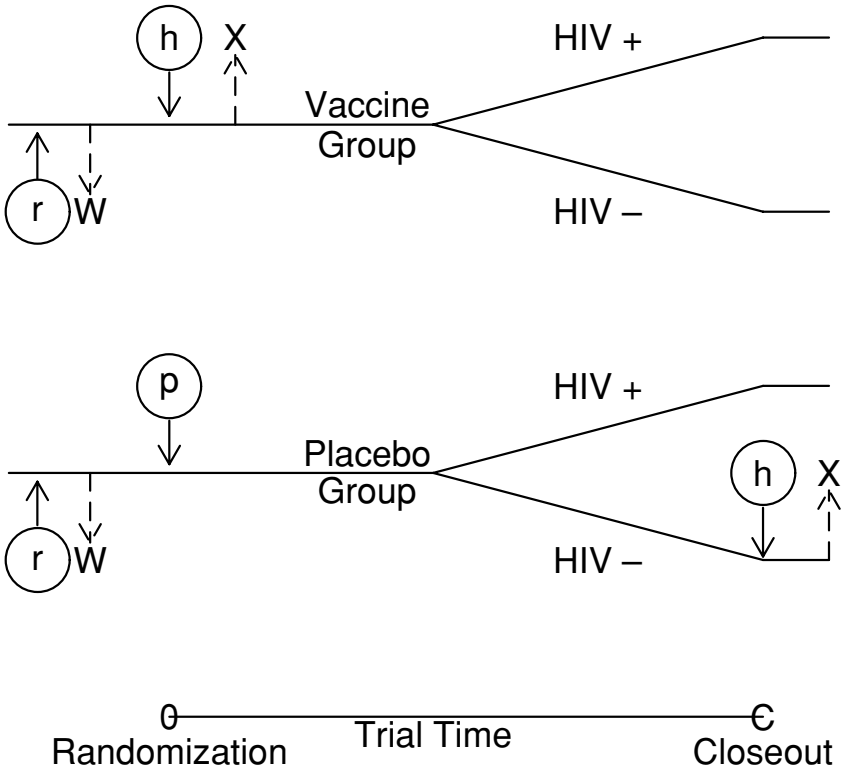


Figure: Close-out vaccination at end of study: Circles with letters h represent vaccination and p placebo. The uninfected people in the placebo arm are vaccinated at the end of the study and immune responses measured (Follmann 2006).

Two phase case-cohort sampling

- A two-phase outcome dependent case-cohort sampling design can be used. (Prentice 1986, Qin et al 2008).
- Commonly used in vaccine studies, in which samples are frozen on all participants, then the ones of interest are taken out for analysis later.

Summary

- Biological versus statistical issues
- Continuous protection curve versus thresholds
- Correlates versus surrogates of protection

Thank You!