

Statistical Methods for Estimating Vaccine Efficacy

Amelia Dale Horne, Dr.P.H.
Chief, Vaccine Evaluation Branch
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

WHO MALVAC Meeting
Geneva
3 June 2008

Outline

- Introduction
- Method that assumes equal follow-up
- Methods that account for differential follow-up
- Time-to-event analyses
- Summary

Introduction

- Vaccine efficacy estimated based on cases of disease/infection
- Large, randomized, double-blind, placebo-controlled clinical trials
- $VE = 1 - R$ where R is a ratio of risks, incidence rates, hazards, or (less often) odds of disease in vaccinated group relative to control group
- Different statistical methods for each type of R

Method that assumes equal follow-up

- **R is a ratio of risks (proportions)**

(1) $R = (\text{cases}_{\text{vaccine}}/n_{\text{vaccine}}) / (\text{cases}_{\text{placebo}}/n_{\text{placebo}})$

where n_{vaccine} and n_{placebo} are numbers of persons enrolled in vaccine and placebo groups, respectively.

- assumes all subjects followed for same amount of time (a person followed for 12 months is given as much weight as one followed for 18 months)
- for trials with staggered entry and a single closure date, this assumption not likely to hold
- does not allow covariate adjustment
- still used, but not as often as other models

Methods that account for differential follow-up

- **R is a ratio of incidence rates: Person-time approach**
 - a subject under study for 12 months has less time at risk of disease (while in the study) than one under study for 18 months
 - person-time method accounts for length of follow-up in the denominator by accumulating time until subjects are diagnosed with the disease or the trial ends, whichever comes first
 - model looks like (1) except the denominator is person-time instead of number of persons enrolled
 - assumes # cases in the study follows a Poisson distribution; conditional on total # cases, # cases in vaccinated group follows a binomial distribution
 - does not allow covariate adjustment
 - still frequently used method

Methods that account for differential follow-up

- **R is a ratio of incidence rates: Poisson Regression**
 - a sophisticated extension of the person-time approach
 - allows inclusion of covariates (age, region, other baseline prognostic information)
 - assumes observed # cases has a Poisson distribution, and models the mean # cases (expected value) as

$$(2) \quad \log(\mu) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \log(\text{follow-up time})$$

where μ is mean # cases, X_i variables are covariates (vaccine/control, age, etc.), and the β_i are coefficients estimated by the model; equivalent to modeling the incidence rate (rate= number cases/ follow-up time) by the equation involving the $\beta_i X_i$

Methods that account for differential follow-up

- **R is a ratio of hazards: Cox (Proportional Hazards) Regression**

- The “hazard” function $h(t)$ is the instantaneous *potential* of disease, i.e., at a specified moment in time, t , given that a subject has been disease free up to time t ; a conditional rate; similar in concept to velocity or speed¹
- Cox regression is a type of “survival” analysis model
- models the hazard rate, $h(t)$, as

$$(3) \quad h(t;x) = \lambda_0(t) \exp(X\beta)$$

where $X\beta = X_1\beta_1 + X_2\beta_2 + \dots + X_n\beta_n$. The function $\lambda_0(t)$ is called the baseline hazard rate and refers to the hazard when all X_i 's are 0.

- allows adjustment for covariates, the X 's in (3)

continued

Methods that account for differential follow-up

- **R is a ratio of hazards: Cox (Proportional Hazards) Regression** *continued*

- *To obtain an estimate of VE, an indicator variable X (one of the X 's in equation (3)), corresponding to the vaccine/control group, may be specified as*

$X = 1$ if vaccine received, or $= 0$ if placebo received.

- *The fitted model produces a regression coefficient for this variable, which, when exponentiated, gives the ratio of hazard rates of disease in the vaccinated relative to the control group.*
- *Confidence limits for VE can be constructed, using the coefficient and its variance.*
- *A popular model, especially in placebo-controlled trials where non-proportionality is often less likely to be a problem*

Time-to-event methods

- The methods presented, except for (1), all measure the time interval per person from some specified starting point until a specified ending point and incorporate that information into the analysis.
- Models such as Cox regression are called “time-to-event” models because of the way they were originally (and still are) used in trials of therapeutics:
 - Outcome measured is literally time to an event of interest, e.g.,
 - time in remission in cancer patients
 - time until death in heart transplant patients
 - Purpose of treatment is to extend remission, life, etc.
 - A major goal of analysis in therapeutic trials is to estimate/compare median time to remission, death, etc., based on survival functions, $S(t)$.
 - This information is generally not useful in preventive vaccine trials aimed at estimating VE as $1-R$, so we ignore that part of the output and use only the information on $h(t)$ described on the previous 2 slides.

Summary

- Well known statistical methods for estimating VE as $1-R$ include modeling R as a ratio of binomial risks, or incidence rates; Poisson regression; and Cox regression.
- There are also other sophisticated models, but less well known and not as often used.
- “Time-to-event” models, such as Cox regression, are often used to estimate VE by extracting the appropriate information from the analysis output.
- In all methods presented, the numerators of the proportions, incidence rates, or hazard rates are numbers of cases of disease. The models differ mainly in how the corresponding denominators are calculated.
- All statistical models have underlying assumptions, and the extent to which these assumptions are satisfied helps determine the appropriateness of the model for the study design and data to be analyzed.

Reference

- ¹ Kleinbaum, David G. (1996) *Survival Analysis: A Self-learning Text*. New York, Berlin: Springer-Verlag, Inc.