# 2

# Overview of Vaccine Effects and Study Designs

## 2.1 Introduction

In this chapter, we present a systematic framework about the relation among many of the different types of vaccination effects and the parameters and study designs used to estimate them. This framework helps to structure thinking about the different vaccine effects of interest. We present different versions of vaccine efficacy and effectiveness as one minus some measure of relative risk, $RR$:

$$VE = 1 - RR \; . \tag{2.1}$$

We focus on the relation between the vaccine effects of interest and their relation to the choice of comparison groups, the unit of observation, the choice of parameter, and the amount of information about the transmission system required for estimation. Although it is not exhaustive, many designs not considered explicitly in this overview are special cases of these general designs aimed at evaluating the vaccine effects presented here. Our primary concern in this chapter is conceptual. More complex methods of estimation and inference are left to following chapters.

## 2.2 Vaccine effects of interest

Table 2.1 lists several different vaccine effects of interest. The primary effect of interest of vaccination has historically been how well it protects the vaccinated individual. $\text{VE}_S$, the vaccine efficacy for susceptibility, is a measure of how protective vaccination is against infection. With many infectious agents, particularly those with short incubation periods, such as influenza or pertussis, ascertainment is often by observing diseased individuals, who then might have a biological test done to confirm the infection of interest. In this case, asymptomatic infections would not be ascertained. $\text{VE}_{SD}$ denotes vaccine efficacy against disease. However, many times, both in this book and the

**Table 2.1.** Vaccine Effects of Interest

| Symbol | Definition |
|---|---|
| $VE_S$ | vaccine efficacy for susceptibility |
| $VE_{SP}$ | vaccine efficacy for susceptibility to disease |
| $VE_{col}$ | vaccine efficacy for colonization |
| $VE_P$ | vaccine efficacy for progression, pathogenicity |
| $VE_I$ | vaccine efficacy for infectiousness |
| $VE_T$ | total vaccine efficacy |
| $VE_{IIa}$ | indirect effects of vaccination in those not vaccinated |
| $VE_{IIb}$ | total effects of vaccination in those vaccinated |
| $VE_{III}$ | overall population-level effects |

literature in general, the distinction between the two is made clear simply by the case definition used in the study and the ascertainment method. The general representation is $VE_S$. Whether infection or disease is the outcome of interest, nonlinearities on the pathway from infection to manifest disease could mean that the efficacy as measured by the observed outcome would be quite different from the biologic efficacy if it could be measured along the pathway (Struchiner et al 1994).

$VE_{col}$ measures the efficacy against colonization (Auranen et al 2000). Many infectious agents, such as pneumococcal and meningococcal bacteria, colonize the nose and throat passages without causing overt disease. Colonized individuals may themselves not be ill, but can, however, play an important role in transmission. They can transmit to other susceptible individuals who in their turn develop severe disease (Auranen et al 2000). Recent interest is growing in evaluating the effect of vaccination on colonization. It is an aim of one of the Gates' Grand Challenge Grants (See www.pneumocarr.org in Finland.) Pneumococcal carriages acquisition rates can also be estimated conditional on exposure to infection or unconditionally.

$VE_P$, vaccine efficacy for progression or pathogenicity, measures the efficacy of vaccination in preventing a post-infection outcome. Depending on the situation, the measure of interest can be the effect of prophylactic vaccination on the rate or probability of progressing to disease, conditional on being infected. If ascertainment is on disease, $VE_P$ could be a measure of the effect of vaccination on the probability of severe disease. $VE_P$ could also measure the reduction in duration of being infected, such as in pneumococcal colonization. Although $VE_S$, $VE_{SD}$, and $VE_P$ are all measures of the direct protective effects of vaccination, there is an important difference. The main distinction between $VE_S$ or $VE_{SD}$ and $VE_P$ is that studies to estimate $VE_S$ evaluate susceptibles and the exposure to infection needs to be taken into account. Studies to estimate $VE_P$ are conditional on the participants already being infected, so the progression within infected individuals is important.

A vaccinated person who nonetheless becomes infected may also be less infectious to other susceptibles or be infectious for a shorter period of time. The vaccine efficacy for infectiousness, $VE_I$, measures the reduction in the ability of a vaccinated infected person compared to an unvaccinated infected person to transmit the infectious agent to others. The combined effect of having both individuals in a contact being vaccinated compared to neither being vaccinated is denoted by $VE_T$. Both $VE_I$ and $VE_T$ are of interest because a vaccine that reduces infectiousness could have important public health consequences (Halloran et al 1994; Farrington 2003).

Widespread vaccination can have indirect effects for unvaccinated people as well as for vaccinated people. The indirect effects are due to the change in collective level of immunity in the population, or *herd immunity*, due to vaccination. Differentiation of the population-level effects in the unvaccinated and vaccinated groups is important because they might not be the same. The former is called indirect effectiveness, the latter total effectiveness (Table 2.2, middle, columns 4 and 5). The overall effectiveness of a vaccination strategy or allocation within a particular population is the weighted average of the outcomes in the vaccinated and the unvaccinated people (Table 2.2, middle, column 6).

To evaluate the direct protective effects of vaccination, $VE_S$ and $VE_P$, usually the individual is the unit of observation. To evaluate $VE_I$, generally small transmission units, such as households or partnerships in which contacts can be defined, are needed (Fine et al 1988, Preziosi and Halloran 2003, Halloran et al 2003). This type of study in small transmission units can also be used to evaluate $VE_S$. To evaluate the population level effects, the unit of observation becomes the population, so that several populations need to be included in the study. Table 2.2 provides an overview of several different types of effects and the parameters used to estimate the effects.

## 2.3 Vaccine efficacy for susceptibility, $VE_S$ ($VE_{SP}$)

We first consider study designs for estimating the protective effects of vaccination, $VE_S$ ($VE_{SD}$). In Table 2.2, these are represented in the column labeled "susceptibility". The estimates of $VE_S$ are obtained from the relative risk of infection or disease in the vaccinated individuals compared with the unvaccinated individuals:

$$VE_S = 1 - \frac{\text{R(vaccinated people)}}{\text{R(unvaccinated people)}},$$

where $R$ denotes one of the measures of risk. The measure of risk can be a form of the transmission probability, which conditions on exposure to infection, or the incidence rate, hazard rate, or cumulative incidence (attack rate), which do not condition on exposure to infection.

### 2.3.1 $VE_S$ conditional on knowledge of exposure to infection

The top row of Table 2.2 contains measures of VE that rely on information about exposure to infection and contacts between infectious individuals and susceptible individuals. The first is a measure of $VE_S$ based on the transmission probability, $VE_{S,p}$. Let the *transmission probability*, denoted $p_{ij}$, be the probability that, conditional upon a contact between an infective source with covariate status $i$ and a susceptible host with covariate status $j$, successful transfer and establishment of the infectious agent will occur. A related concept is the *secondary attack rate*, ($SAR_{ij}$), defined as the proportion of susceptibles with covariate status $j$ making contact with an infectious person of covariate status $i$ who become infected.

Let 0 and 1 denote being unvaccinated and vaccinated. Then, for example, $p_{01}$ denotes the transmission probability per contact from an unvaccinated infective person to a vaccinated uninfected person. Let $p_{.0}$ and $p_{.1}$ denote the transmission probability to unvaccinated and vaccinated susceptibles, where the dot in the subscript can denote any vaccine status or an average across the population.

Then $VE_{S,p}$ based on the transmission probability or secondary attack rate (Table 2.2, top row) is estimated from

$$VE_{S,p} = 1 - \frac{p_{.1}}{p_{.0}} = 1 - \frac{SAR_{.1}}{SAR_{.0}} = 1 - \frac{\frac{\text{vaccinated infections}}{\text{vaccinated contacts}}}{\frac{\text{unvaccinated infections}}{\text{unvaccinated contacts}}}.$$

Estimating vaccine efficacy from the transmission probability ratios requires information on who is infectious and when, and whom they contact and how. The concept of a *contact* is very broad and must be defined in each particular study. Often it is defined within a small transmission unit such as a household or sexual partnership.

There are two main ways to design a study to estimate the relative transmission probabilities. The first method, called the secondary attack rate (Fox et al 1970; Fine et al 1988), or case-contact rate method, has been used since the pertussis vaccine trials in 1930's (Kendrick and Eldering 1939) to estimate vaccine efficacy. Another method of estimating the transmission probability is based on the Bernoulli model. In this case, we observe susceptible people, count the number of contacts they make with infectives, and count the number of these susceptible people who become infected, and use a transmission model to estimate the transmission probability and related covariate effects. These approaches are presented in more detail in Chapters 10 through Chapters 12.

**Table 2.2.** Parameters used for measuring various effects of vaccination. The levels form a hierarchy, with higher levels requiring less information about the transmission system, with only level I requiring actual contact information.∗

| | | Comparison groups and effect | | | |
|---|---|---|---|---|---|
| Level | Parameter choice | Susceptibility | Infectiousness | Combined change in susceptibility and infectiousness | |
| | Conditional on exposure to infection: | | | | |
| I | Transmission probability, $p$<br>Secondary attack rate, SAR | $\mathrm{VE}_{S,p}$† $= 1 - \frac{p_{\cdot 1}}{p_{\cdot 1}}$ | $\mathrm{VE}_{I,p} = 1 - \frac{p_{1\cdot}}{p_{0\cdot}}$ | $\mathrm{VE}_{T,p} = 1 - \frac{p_{11}}{p_{00}}$ | |
| | | Study design | | | |
| | | I<br>direct | IIA<br>indirect | IIB<br>total | III<br>overall |
| | Unconditional: | | | | |
| II | Incidence rate, IR | $\mathrm{VE}_{S,IR} = 1 - \frac{\mathrm{IR}_{A1}}{\mathrm{IR}_{A0}}$ | $\mathrm{VE}_{IIA,IR} = 1 - \frac{\mathrm{IR}_{A0}}{\mathrm{IR}_{B0}}$ | $\mathrm{VE}_{IIB,IR} = 1 - \frac{\mathrm{IR}_{A1}}{\mathrm{IR}_{B0}}$ | $\mathrm{VE}_{III,IR} = 1 - \frac{\mathrm{IR}_{A\cdot}}{\mathrm{IR}_{B\cdot}}$ |
| | Hazard rate, $\lambda$ | $\mathrm{VE}_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$ | $\mathrm{VE}_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$ | $\mathrm{VE}_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$ | $\mathrm{VE}_{III,\lambda} = 1 - \frac{\lambda_{A\cdot}}{\lambda_{B\cdot}}$ |
| III | Proportional hazards, PH | $\mathrm{VE}_{S,PH} = 1 - e^{\beta_1}$ | NA | NA | NA |
| IV | Cumulative incidence, CI<br>Attack rates, AR | $\mathrm{VE}_{S,CI} = 1 - \frac{\mathrm{CI}_{A1}}{\mathrm{CI}_{A0}}$ | $\mathrm{VE}_{IIA,CI} = 1 - \frac{\mathrm{CI}_{A0}}{\mathrm{CI}_{B0}}$ | $\mathrm{VE}_{IIB,CI} = 1 - \frac{\mathrm{CI}_{A1}}{\mathrm{CI}_{B0}}$ | $\mathrm{VE}_{III,CI} = 1 - \frac{\mathrm{CI}_{A\cdot}}{\mathrm{CI}_{B\cdot}}$ |

∗ From Halloran et al., Am. J. Epidemiol 1997; 146;789–803. Reproduced with permission. The subscripts 0 and 1 denote unvaccinated and vaccinated people, respectively. Population A contains both vaccinated and unvaccinated people. All people in population B are unvaccinated (see figure 2.3). The subscripts $S$, $I$, and $T$ denote susceptibility, infectiousness, and combined effects. The Cox proportional hazards estimator is denoted by $e^{\beta_1}$. Time has been omitted from the table for notational clarity.
† Vaccine efficacy/effectiveness; NA, not applicable

### 2.3.2 $VE_S$ not conditional on knowledge of exposure to infection

Information on exposure to infection is often difficult or impossible to collect. More commonly, studies are designed to estimate $VE_S$ from events per person-time of potential rather than actual exposure or simply from the proportion of people who become infected in the vaccinated compared to the unvaccinated groups. Standard parameters for estimating $VE_S$ that do not require exposure to infection information are incidence rates, hazard rates, or cumulative incidence (attack rate).

Greenwood and Yule (1915) gave three conditions necessary for valid inference:

1. The persons must be, *in all material respects,* alike.
2. The effective exposure to the disease must be identical in the case of inoculated and uninoculated persons.
3. The criteria of the fact of inoculation and of the fact of the disease having occurred must be independent.

If the vaccinated and unvaccinated groups are equally exposed to infection, any differences in the risk in the two groups is likely due to the biological effects of the vaccine. These days, these criteria would be considered conditions to prevent confounding. Double-masked randomized trials are designed to ensure that these criteria are met.

Primary vaccine efficacy studies often report $VE_{S,IR}$ based on relative events per person time, or level II information,

$$VE_{S,IR} = 1 - \frac{\text{vaccinated events/person-time}}{\text{unvaccinated events/person-time}}. \tag{2.2}$$

The usual assumption is that the numbers of events follow a Poisson distribution. Similarly, investigators may estimate the hazard rates in the vaccinated and unvaccinated, $\lambda_1(t)$ and $\lambda_0(t)$, using survival analysis methods. Then the $VE_S$ is based on the hazard rate ratio

$$VE_{S,\lambda}(t) = 1 - \frac{\lambda_1(t)}{\lambda_0(t)}. \tag{2.3}$$

When covariates such as age and gender are added, the analyses are stratified by the covariates or Poisson regression can be used. Under the assumption that the effect of the vaccine is multiplicative, constant, and homogeneous, the Cox proportional hazards model can be used to estimate $VE_{S,PH}$. In this case, it is not necessary to estimate the hazard rate in the unvaccinated group, but only the relative hazard rate. This requires only the ordering of the infection times. Covariates, including time-dependent covariates, can easily be incorporated using standard software.

An early example of estimating $VE_{S,IR}$, the study by Kendrick and Eldering (1939) of pertussis vaccine reported the number of cases per person-time

(Figure 1.2). The vaccinated and control groups had 1,815 and 2,397 children, respectively, who contributed 2,268 and 2,307 person-years at risk. There were 52 cases in the vaccinated and 348 cases in the control group, so

$$\widehat{\mathrm{VE}}_{S,IR} = 1 - \frac{\frac{52 \text{ cases}}{2268 \text{ person-years}}}{\frac{348 \text{ cases}}{2307 \text{ person-years}}} = 0.85 \tag{2.4}$$

More recently, Urdaneta et al. (1998) present estimates of $\mathrm{VE}_{S,IR}$ as the result of a randomized, placebo controlled field trial of Spf66 malaria vaccine in Costa Marques, Rondonia, Brazil. A total of 572 participants completed the 3 dose vaccine schedule and were followed up for 18 months. The 287 vaccinated individuals contributed a total of 12,178 person-weeks at risk, and 76 first *P. falciparum* malaria episodes were observed among them. In the placebo group, 285 individuals contributed 11,698 person-weeks at risk and 85 cases leading to an estimate of $\widehat{\mathrm{VE}}_{S,IR} = 0.14$.

In some studies, it is possible to compute both a conditional and an unconditional estimate of vaccine efficacy from a single study. The Kendrick and Eldering (1939) study on pertussis vaccine also had information on children who had been exposed to pertussis within their own households (Figure 1.3). In the vaccinated group, 29 of 83 exposed children developed pertussis, while 143 of 160 exposed children in the unvaccinated group developed pertussis. Thus, the estimate of $\mathrm{VE}_{S,p}$ is

$$\widehat{\mathrm{VE}}_{S,p} = 1 - \frac{29 \text{ cases}/83 \text{ vac exposed}}{143 \text{ cases}/160 \text{ unvac exposed}} = 0.61 \ . \tag{2.5}$$

While everyone is included in the estimate of $\mathrm{VE}_{S,IR}$, only the children with (presumed) exposure to infection are included in the $\mathrm{VE}_{S,p}$ estimate. The interpretations of the two estimates are also different, since one measures the protection conferred as measured by infections per person time and the other by the probability of an infection per potentially infectious contact. (See Section 10.2.2.)

Estimation of $\mathrm{VE}_{S,CI}(T)$ based on the cumulative incidence requires only information about whether persons are infected or not by the end of the study at time $T$, that is, final value data:

$$\begin{aligned} VE_{S,CI}(T) &= 1 - \frac{\text{vaccinated infection events/persons–at–risk}}{\text{unvaccinated infection events/persons–at–risk}} \\ &= 1 - \frac{CI_1(T)}{CI_0(T)} \ . \end{aligned} \tag{2.6}$$

As an example, Greenwood and Yule (1915) used the cumulative incidence in studying the efficacy of anti-typhoid inoculation in the troops in the early part of the twentieth century (Figure 1.1). In one analysis, Greenwood and Yule assumed that the denominators were based on the vaccinated and unvaccinated groups at the beginning of the study. They had 56 cases of typhoid in

10,378 vaccinated soldiers, and 272 cases in 8,936 unvaccinated soldiers. The estimated efficacy based on these numbers is

$$\widehat{\mathrm{VE}}_{S,CI}(T) = 1 - \frac{56 \text{ cases}/10,378 \text{ at-risk}}{272 \text{ cases}/8,936 \text{ at-risk}} = 0.82 \ . \tag{2.7}$$

A more recent example is from a double-blinded randomized trial of live-attenuated influenza vaccine compared with inactivated influenza vaccine in children (Belshe et al 2007). In this trial, of the 3,936 children who received inactivated vaccine, 338 developed culture-confirmed cases of influenza. Of the 3,912 children who received live-attenuated vaccine, 153 cases developed. Based on these numbers, $\widehat{\mathrm{VE}}_{S,CI}(T) = 1 - \frac{153/3,912}{338/3,936} = 0.54$ This is called the relative efficacy of two vaccines, rather than the absolute efficacy.

Which parameter to use to estimate $\mathrm{VE}_S$ in a particular study depends on the type and duration of the study, the infectious agent and its transmission mode, the resources available, and the assumptions of the distribution of protection within the vaccinated group. Chapter 6 considers estimation of $\mathrm{VE}_S$ from the unconditional parameters in detail.

## 2.4 Hierarchy of $\mathrm{VE}_S$ measures

Estimation of the different $\mathrm{VE}_S$ parameters requires differing levels of information and makes different demands on study design and data collection (Rhodes et al 1996). Incidence rates or hazard rates require the time to event and the period of potential exposure of each person under study. The hazard rate in infectious diseases is often called the *force of infection*. A Cox proportional hazards model requires only the ordering of the event times. An estimate of cumulative incidence requires only final value data, that is, whether an infection occurred by the end of the study or not. Correspondingly, in Table 2.2, $\mathrm{VE}_{S,IR}$ based on incidence rates and $\mathrm{VE}_{S,\lambda}$ are level II parameters, $\mathrm{VE}_{S,PH}$ based on Cox proportional hazards is level III, and $\mathrm{VE}_{S,CI}$ based on cumulative incidence or final value data is level IV. The levels form a hierarchy, with higher levels requiring less information about the transmission system, with only level I requiring actual contact information. Since $\mathrm{VE}_{S,p}$ based on the transmission probability is defined conditional on exposure to infection, it is called a conditional parameter, while the other measures are called unconditional parameters.

Because of the dependent happening structure of events in infectious diseases, there is an intrinsic relation among the different parameters on which the $\mathrm{VE}_S$ estimators are based. Understanding this relation helps to see the relation of the different estimators of $\mathrm{VE}_S$ to one another. Figure 2.1 (to be redone) illustrates the dependent happening relation of the hierarchy of parameters to one another. Section 2.9 develops the relation formally.

Let $p_{ij}$ be the transmission probability as defined above. Let $c$ denote the contact rate in a population assuming that people are randomly mixing, and

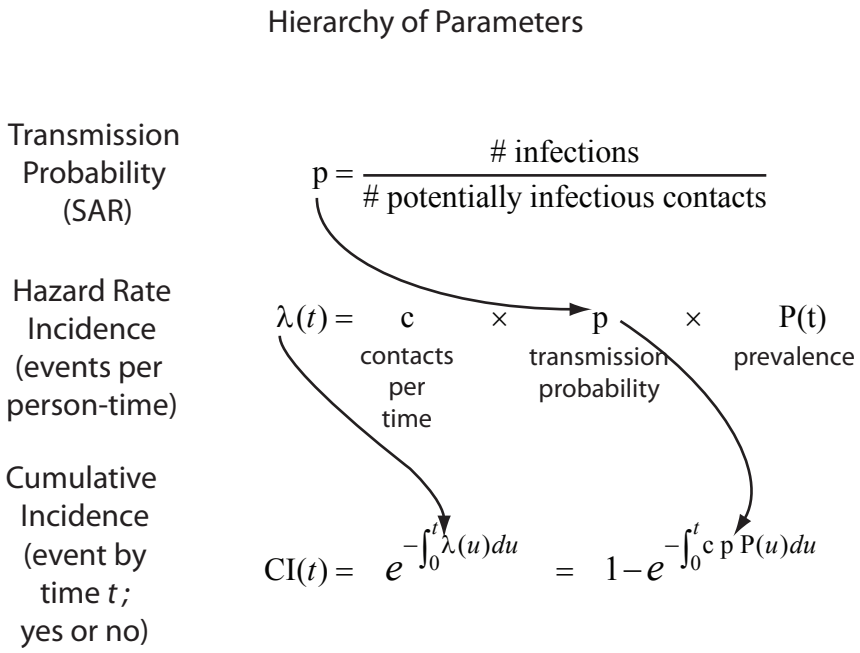


**Fig. 2.1.** Hierarchy of $VE_S$ parameters showing the dependent happening relation among them.

let $P(t)$ denote the prevalence of infectives at time $t$. Then the hazard rate $\lambda(t)$ (or incidence rate or force of infection) at time $t$ can be expressed as the product of the contact rate, the transmission probability, and the probability that a contact is infectious:

$$\lambda(t) = cp_{ij}P(t). \tag{2.8}$$

So even if the different components of the hazard rate are not measured, we can consider the underlying process that is producing the infections we observe. Similarly, the cumulative incidence, $CI(T)$, at some time $T$ is a function of the hazard rate during the follow-up period, and thus also a function of the transmission probability, contact rate, and prevalence of infection in the contacts. Even though the cumulative incidence estimate is a sort of black-box estimator, it is useful in vaccine studies to think about the underlying transmission system that would produce the observed final values.

The following quote from Joseph Heller's *Catch-22* (page 8) gives a flavor of how the information about the transmission system disappears as we move from level I to level IV through the hierarchy.

> All the officer patients in the ward were forced to censor letters written by all the enlisted-men patients, who were kept in residence in wards of

> their own. It was a monotonous job, and Yossarian was disappointed to learn that the lives of enlisted men were only slightly more interesting than the lives of officers. After the first day he had no curiosity at all. To break the monotony he invented games. Death to all modifiers, he declared one day, and out of every letter that passed through his hands went every adverb and every adjective. The next day he made war on articles. He reached a much higher plane of creativity the following day when he blacked out everything in the letters but *a, an* and *the*. That erected more dynamic intralinear tensions, he felt, and in just about every case left a message far more universal. Soon he was proscribing parts of salutations and signatures and leaving the text untouched. One time he blacked out all but the salutation "Dear Mary" from a letter, and at the bottom he wrote, "I yearn for you tragically. A. T. Tappman, Chaplain, U.S. Army." A. T. Tappman was the group chaplain's name.

## 2.5 Vaccine efficacy for infectiousness, $VE_I$

The efficacy of a vaccine in reducing infectiousness, $VE_I$, can be estimated epidemiologically by comparing the per-contact transmission probability from vaccinated people who become infected with the transmission probability from unvaccinated people who become infected. The relative risk comparison groups are defined according to the vaccination status of the infectious person contacting the susceptible person (Halloran and Struchiner 1995). In Table 2.2, the $VE_I$ estimator is shown in the second column of the top row of conditional parameters. The third column contains the estimate of combined effect of the vaccine in reducing the transmission probability if both the infectious person and the susceptible person in the contact are vaccinated, ($VE_T$). In contrast to $VE_S$, which can be estimated using either conditional or unconditional parameters, the $VE_I$ and $VE_T$ can generally be estimated using only conditional measures such as the transmission probability or secondary attack rate (Koopman and Little 1995; Longini et al 1996; Préziosi and Halloran 2003; Halloran et al 2003).

Studies for estimating $VE_I$ can be incorporated into those for estimating $VE_{S,p}$ based on the transmission probability, if the vaccination status of the infectious person in a contact is known. The analysis can then simply stratify on the vaccination status of both the infectious and susceptible persons in the contact to get estimates of $VE_S$, $VE_I$, and $VE_T$. In the case of the binomial model, the likelihood can simply be constructed from the different contributions of each contact, where the parameters for relative susceptibility and for relative infectiousness are built directly into the likelihood (Longini et al 1996; Hudgens et al 2001).

In general, there are at least seven measures potentially of interest. Considering the estimates of VE based on the relative secondary attack rates,

there are three main unstratified vaccine effects:

$$VE_{S.1/.0} = 1 - \frac{SAR_{.1}}{SAR_{.0}} , \quad VE_{I1./0.} = 1 - \frac{SAR_{1.}}{SAR_{0.}} ,$$
$$VE_T = 1 - \frac{SAR_{11}}{SAR_{00}} . \tag{2.9}$$

If one stratifies on the vaccine status of the infective person or the susceptible person, then there are four further stratified measures of $\mathrm{VE}_S$ and $\mathrm{VE}_I$:

$$VE_{S01/00} = 1 - \frac{SAR_{01}}{SAR_{00}}, \quad VE_{S11/10} = 1 - \frac{SAR_{11}}{SAR_{10}},$$
$$VE_{I10/00} = 1 - \frac{SAR_{10}}{SAR_{00}}, \quad VE_{I11/01} = 1 - \frac{SAR_{11}}{SAR_{01}}. \tag{2.10}$$

Chapters 10 through 12 consider estimation of the conditional parameters based on transmission probabilities and SARs from studies in households and other small transmission units in detail.

### 2.5.1 Estimating multiple levels of parameters

Statistical models have been developed to express both the within household transmission probability and the unconditional probability of being infected from the community at large (Longini et al 1982; Hudgens et al 2001; O'Neill et al 2000; Becker et al 2003). In some vaccine studies, there may be information on contacts within transmission units such as households or sexual partnerships, but the individuals may also be exposed to infection outside of the transmission unit. It may also be that some individuals in a study are not members of clearly defined transmission units. These models are considered in detail in Chapters 10 through 12.

## 2.6 Vaccine efficacy for progression or pathogenesis, $\mathrm{VE}_P$

ADD HERE THE relation of $\mathrm{VE}_{SP}$, $\mathrm{VE}_S$ and $\mathrm{VE}_P$. Include the importance for distinguishing for natural history and for use in simulations.

Evaluation of the effect of prophylactic vaccination on an outcome that occurs after infection, $\mathrm{VE}_P$, requires comparison of morbidity or mortality in infected vaccinated people with that in infected unvaccinated people. The interest could be in the effect of vaccine on the probability of developing disease if infected, that is the pathogenesis. The interest could be on effect on the time from infection to develop of disease, that is, the rate of progression. The interest could be in the effect of vaccination on reducing the severity of disease or probability of death in symptomatic cases. If $\mathrm{VE}_P$ is based on relative morbidity, then appropriate definitions of morbidity levels would be

TABLE XLIII.

| Degree of effective vaccination | Strength to resist small-pox when incurred: Deaths | Recoveries | Total |
|---|---|---|---|
| Cicatrix absent | 94 | 383 | 477 |
| Cicatrix present | 42 | 1,562 | 1,604 |
| Total | 136 | 1,945 | 2,081 |

**Fig. 2.2.** $VE_P$: Death versus Recovery in Smallpox: Greenwood and Yule 1915

necessary. Similar to the $VE_S$ measures discussed above, $VE_P$ would be estimated by one minus the corresponding ratio in the vaccinated compared to the unvaccinated, including in the calculation only those people who had become infected.

Greenwood and Yule (1915) presented data from Pearson on the effect of smallpox vaccination to prevent death by comparing the number of cases recovering to those dying of smallpox (Figure 2.2).

$$\widehat{\text{VE}}_P = 1 - \frac{\frac{\text{no. severe vaccinated cases}}{\text{all vaccinated cases}}}{\frac{\text{no. severe unvaccinated cases}}{\text{all unvaccinated cases}}} \tag{2.11}$$

$$= 1 - \frac{\frac{42}{1{,}604}}{\frac{94}{477}} = 0.87$$

Considerable recent research has been devoted to estimating the effects of vaccination on post-infection outcomes (Préziosi and Halloran 2003), particularly on understanding potential selection bias (Gilbert et al 2003; Hudgens et al 2003; Hudgens and Halloran 2006, Jemiai et al 2007).

## 2.7 Contact Rates and Exposure Efficacy

Vaccinated people may alter their contact and exposure to infection patterns if they believe the vaccine is protective. *Exposure or behavior efficacy* is the relative increase or decrease in the relative risk of infection or disease due to the change in exposure to the infectious agent (Halloran et al 1994). For example, if we consider the components of the hazard rate as discussed above, changes in exposure to the infectious agent can occur in the rate of contacts, in the prevalence of infection in the contact groups, or in the transmission probability through changing the type of contact. In nonrandomized or observational studies, the vaccinated and unvaccinated groups often differ in their exposure to infection, resulting in biased estimates of $VE_S$. Although $VE_S$ estimates based on the transmission probability require more information than those based on the unconditional parameters, they are less sensitive to bias

from unequal exposure to infection in the two groups. The overall effect of biological protection and change in exposure to infection might be of interest for understanding the public health consequences of vaccination. Study designs need to be explicit about differentiating factors related to susceptibility, such as vaccination status, and factors related to exposure to infection.

## 2.8 Indirect, total, and overall effectiveness

Interest in evaluating the indirect and overall effects of vaccination strategies as part of Phase III as well as post-licensure is increasing (Fine 1993; Clemens et al 1996; Piedra et al 2007). Struchiner et al (1990) and Halloran and Struchiner (1991) define study designs for dependent happenings that allow evaluation of the indirect and overall effects of vaccination (Figure 2.3). Since the population-level effects of vaccination are defined within the context of a particular intervention program, or allocation of vaccination, the unit of inference is the population, and several populations or communities need to be included in the study. Exactly what the intervention program of interest is will depend on the vaccine and which subgroups suffer the greatest morbidity. The comparisons may be made between different levels of vaccination coverage, between allocation within different age groups or otherwise defined subgroups (Monto et al 1969; Moulton et al 2001).

In Table 2.2 and Figure 2.3, the different type of population level effects are considered on the simple example that no vaccination has taken place in population $B$, and a proportion of people are vaccinated in population $A$. The controls may be the same populations that receive the vaccination, but before the vaccination program started. The indirect effects of the vaccine given a particular allocation of vaccination is then the comparison of the incidence or other outcome of interest in the unvaccinated people in community $A$ compared to the unvaccinated people in the unvaccinated community $B$. These comparisons are called designs type IIA. The indirect effectiveness measures are denoted $\mathrm{VE}_{IIA}$. The total effects of the combination of being vaccinated and the allocation is the outcome in the vaccinated people in the communities $A$ compared to that of the unvaccinated people in the unvaccinated communities $B$. These comparisons are called designs type IIB, and the total effectiveness measures are denoted $\mathrm{VE}_{IIB}$. The overall effectiveness of the vaccine and allocation compare the average outcomes in the vaccinated communities with those of the unvaccinated communities. These comparisons are called designs type III, and the overall effectiveness measures are denoted $\mathrm{VE}_{III}$. Table 2.2 contains examples of the $\mathrm{VE}_{IIA}$, $\mathrm{VE}_{IIB}$, and $\mathrm{VE}_{III}$ based on the usual unconditional measures incidence rate, hazard rate, and cumulative incidence. Many other measures could be used, including average age of infection or the basic reproductive number, $\mathrm{R}_0$.

In choosing the communities or populations, it is important to ensure that they are separated as much as possible in every way that is relevant for

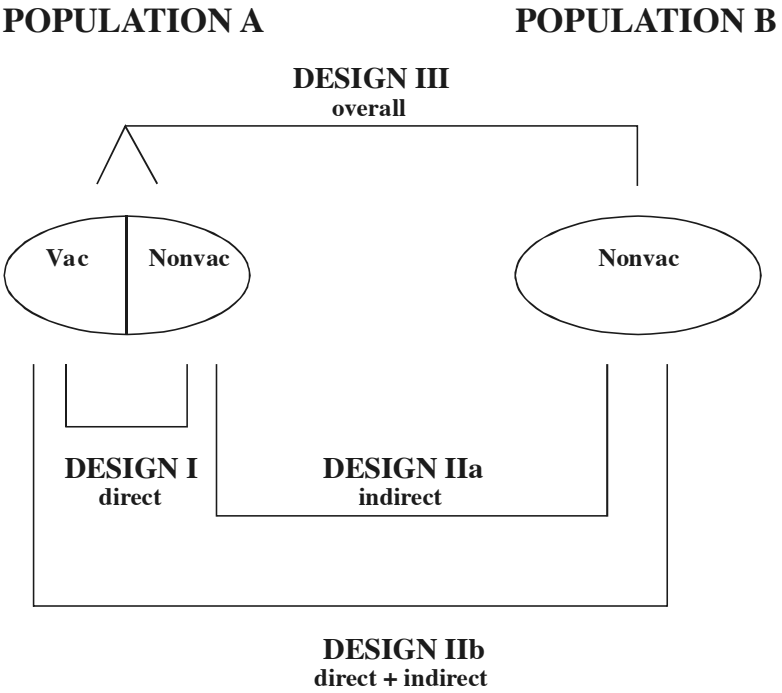


**Fig. 2.3.** Study designs for dependent happenings. Types of effects of vaccination programs and different study designs based on comparison populations for their evaluation. (Halloran and Struchiner 1991)

transmission. Transmission patterns can differ greatly among communities. It is necessary to give some thought to the likely transmission patterns and sources of exposure to infection in a population. These transmission patterns will greatly influence the magnitude of the indirect effects. Variability could swamp out the estimates of the effects of vaccination. Matching by transmission characteristics might be desirable (Hayes et al 1995). Interpretability and general applicability of quantitative results to other settings may be limited, although qualitative trends might hold (Halloran and Struchiner 1995).

Comparisons across communities would also allow study of other biological questions. For example, vaccines might contain only particular serotypes or strains of an organism. Widespread vaccination could allow the expansion of non-vaccine serotypes that had been less important before vaccination (Lipsitch 2000) or put evolutionary pressure on the existing strains.

Conducting a trial to evaluate effectiveness across several different populations or communities does not preclude evaluating $VE_S$ or $VE_I$ of vaccination within the populations. A Phase III vaccine trial can be designed to answer several questions at the same time. Randomization within a population can

be used to answer efficacy questions, while comparison across populations can be used to evaluate the indirect and overall effects of vaccination. There is a tradeoff in designing studies to measure both direct and indirect effects of vaccination between vaccinating high numbers of people so that indirect effects are high, and vaccinating too many people so that the number of events in the vaccinated populations is too low to estimate $\mathrm{VE}_S$ or $\mathrm{VE}_I$ well.

Randomized community trials fall into the category of cluster or group randomized trials where whole social units, rather than independent individuals are randomly assigned to treatment groups (Hayes et al 1995; Koepsell et al 1992; Donner et al 1998; Prentice 1995; Klar et al 1995; Murray 1998). The analysis and sample size calculations need to take the clustering and possible group randomization into account. Community trials for estimating indirect, total, and or overall effects are discussed in more detail in Chapter 13.

### 2.8.1 Example

Figure 2.4 shows a simple example of estimating the direct, indirect, total, and overall effects using just two populations, each with a population $N = 1000$. We will assume that the populations are identical. We are going to base our estimates on the number of cases at the end of an epidemic, the attack rate or cumulative incidence, say, at the end of an influenza season. In population A, 700 people are randomly vaccinated and the other 300 are unvaccinated. In population B, we consider separately the 700 people who would have been vaccinated and the 300 who would not have been vaccinated, if population B had received vaccine. In population B, we observe 850 cases, so the attack rate is $\mathrm{AR}_B = 0.85$. Due to randomization, the attack rate is the same in those who would have received vaccine as those who would not have received vaccine, so 595 of the 850 cases are in the 700 people who would have received vaccine, and 255 of the cases are in the 300 people who would not have received vaccine. In population A, there are 70 cases in the 700 vaccinated people and 90 cases in the 300 unvaccinated people, for a total of 160 cases, and an attack $\mathrm{AR}_A = 0.16$. The $\mathrm{AR}_{A1} = 0.10$ in the vaccinated and $\mathrm{AR}_{A0} = 0.30$ in the unvaccinated. The VE estimates of interest are

$$\mathrm{VE}_{\mathrm{direct}} = 1 - \frac{0.10}{0.30} = 0.66, \qquad \mathrm{VE}_{IIa} = 1 - \frac{0.30}{0.85} = 0.65,$$

$$\mathrm{VE}_{IIb} = 1 - \frac{0.10}{0.85} = 0.88, \qquad \mathrm{VE}_{III} = 1 - \frac{0.16}{0.85} = 0.81.$$

The direct vaccine efficacy is a measure similar to the prevented fraction in the exposed, where the exposure is vaccination. If we used the usual prevented fraction in the exposed to compute the number of prevented cases in the vaccinated, we would compute the number of cases that we would have expected in the vaccinated people in population A by assuming that the attack rate in the vaccinated would have been the same as that in the unvaccinated population if no vaccination had occurred. Under this assumption, we would have

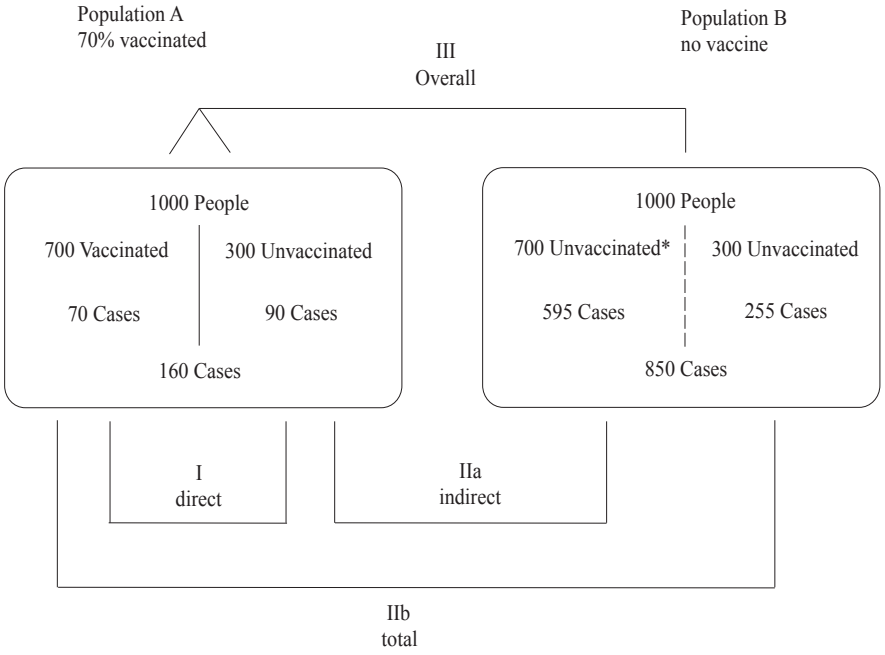


**Fig. 2.4.** An example of estimating direct, indirect, total, and overall effects of vaccination. The $*$ represents the people who would have been vaccinated if Population B had had a vaccination strategy.

expected $(90/300) \times 700 = 210$ cases. The number of prevented cases would have been $210 - 70 = 140$. However, this does not take into account that the number of cases in the unvaccinated group is also decreased by indirect effects. To compute the total number of cases prevented in the vaccinated by vaccination *and* the vaccination program, we need to use the 595 cases in the 700 people in population B who would have been vaccinated. Then the total number of prevented cases in the vaccinated people is $595 - 70 = 525$. The overall prevented cases by vaccination is $850 - 160 = 690$.

### 2.8.2 An influenza example

Monto, et al. (1969) estimated both the protective efficacy, $\text{VE}_S$, and the overall effect, $\text{VE}_{III}$, of an influenza vaccination program. They vaccinated 85 percent of the school-age children in Tecumseh, Michigan, against Hong Kong influenza just before the epidemic in 1968. The ten-week epidemic period was from November 17, 1968, to January 26, 1969. The weekly mean influenza illness rates in vaccinated and unvaccinated children were 0.072 and 0.090, respectively. This yields an approximate estimate of $\text{VE}_{S,IR} \approx 1 - \frac{0.072}{0.090} = 0.20$, which is rather low. The overall influenza illness cumulative incidence in

Tecumseh for the epidemic period was 0.14, while the adjusted overall influenza cumulative incidence in unvaccinated, neighboring Adrian, Michigan, was 0.42 for the same period. Using the methods of study design III, the overall effectiveness of vaccinating 85 percent of Tecumseh's school children is estimated to be $\mathrm{VE}_{III,CI} \approx 1 - 0.14/0.42 = 0.67$.

## 2.9 Counting Process Models for Hierarchy of Parameters

In this section, we present a part of the formal development of the hierarchy of parameters based on counting process models found in Rhodes, Halloran and Longini (1996). Before that, there had been little effort to relate the different measures of vaccine efficacy to one another formally, or their interpretation in terms of the underlying contact and infection processes. (This section is very technical and may be skipped.)

### 2.9.1 Contact, infection, susceptibility and infectiousness processes

#### Overview

Rhodes et al (1996) extended counting process models for infection rates (Becker 1982, 1985, 1989) to incorporate contact rates between individuals, infectiousness of the infectives and variables affecting susceptibility to infection, such as vaccination, given that such a contact had occurred. Using these counting process models, they demonstrate that the commonly used relative risk parameters form a hierarchy requiring different amounts of information about the contact and infection processes. The emphasis is on the distinction between exposure opportunity and actual exposure, and the amoung of information that we have about these. Separation of the contact process and the infection process allows quantification of the different contributions of the contact process, infectiousness and susceptibility in the estimated relative risk of infection in the comparison groups. The hierarchy presented in Table 2.2 is a simplified version of the formal hierarcy, with the major difference in the interpretation of Level II.

Table 2.3 contains an overview of the hierarchy levels of information that could be known about a population of interacting hosts with an infectious agent circulating in it. At a minimum, we need to know those covariates that are relevant to susceptibility as well as who is actually susceptible. The hierarchy goes from level I to IV, or from (a) to (f), as information is either lost or ignored. In (a), we know all contacts between individuals, whereas in (b), we only know when infective individuals contact susceptibles. Level (b) is analogous to a vaccine efficacy study using the household secondary attack rate, studies in tuberculosis using contact tracing to estimate transmission probabilities, or discordant partner studies to estimate the transmission probability

of HIV. Levels IIA and IIB, or (c) and (d), have information only on contacts that lead to infection, or the times at which individuals are infectious, respectively. These levels have important differences, but share enough similarities that they are developed in tandem. The analysis of the former has the form of a Poisson regression. At level III, we know just the infection times, which under certain conditions leads to a stratified Cox regression analysis. Finally, at level IV, we only know that a person becomes infected sometime during the study period. This provides information for an analysis based on the cumulative incidence or distribution function, such as vaccine efficacy based on the attack rates.

**Table 2.3.** Level and amount of information for each history (Rhodes, Halloran, Longini (1996))

| Level | | Type of information for each history |
|---|---|---|
| I | (a) | All contacts between individuals and outcomes of those contacts (whether an infection is transmitted) |
| | (b) | Only those contacts between infective and susceptible individuals and infection outcome of those contacts |
| IIA | (c) | Only contacts leading to infections (who infects whom) |
| IIB | (d) | Infectious periods, i.e., the times at which individuals become and cease to be infectious |
| III | (e) | The times at which individuals become infected |
| IV | (f) | Whether or not an infection occurs to each individual in some time period $(0, T]$ |

### Notation and Definitions

All processes defined below occur in continuous time and are orderly, i.e., multiple points do not occur at any time $t$. Also, there are no tied jumps for pairs of processes of the same type involving different individuals, e.g., no two infections can occur at the same time. Some pairs of processes of different types may jump at the same time (e.g., see $C_{ij}$ and $N_{ij}$ below). Consider a closed population of $n$ individuals. Let $C_{ij}(t)$ be the counting process for person $j$ contacting person $i$ ($j \to i$), $i, j = 1, \ldots, n, i \neq j$. (Notation of the subscripts for the infectives and susceptibles is reversed in this section from the other sections in the book.) We set $C_{ij}(0) = 0$ for all $i, j$, i.e. we disregard all contacts that occur before the start of the study. For a study of length $T$, let $t_{ijk}$ represent times in $(0, T]$ at which $j \to i$, $k = 1, \ldots, C_{ij}(T) = c_{ij}$. For an epidemic, $T$ refers either to the end of the epidemic or to some preset ending time. For an endemic situation, $T$ is some selected time at which an analysis is to be performed.

Let $N_{ij}(t)$ be the counting process for the process $j$ infects $i$, i.e., $dN_{ij}(t) = 1$ if person $j$ infects person $i$ at time $t$. Let $\delta_{ijk}$ be an indicator variable for whether the contact at $t_{ijk}$ results in an infection (i.e. $\delta_{ijk} = dN_{ij}(t_{ijk})$). Let $N_{i.}(t) = \sum_j N_{ij}(t)$. Let $\delta_i = N_{i.}(T) - N_{i.}(0)$, i.e., $\delta_i = 1$ if person $i$ becomes infected in $(0, T]$ and 0 if not. It is possible that $N_{i.}(0) = 1$ which indicates that person $i$ was infected before the start of the current study. However, here we are interested only in counting infections that occur after time 0. We assume that the infection can occur at most once, i.e., $N_{i.}(t) \leq 1$.

Let $I_j(t) = 1$ if person $j$ is infectious at time $t$ and $I_j(t) = 0$ otherwise. A person is infectious immediately after becoming infected (no latent period). Let $S_i(t) = 1$ if person $i$ is susceptible at time $t$ and $S_i(t) = 0$ otherwise. We define both sets of these processes to be left continuous. Thus, $I_j$ and $S_i$ are predictable processes (Bremaud, 1981).

### Intensities for Contact Processes

Let the intensity of the contact process $C_{ij}$ be denoted by $\lambda_{ij}(t)$ ($\lambda_{ii}(t) = 0$), i.e.

$$\lambda_{ij}(t) = \lim_{\Delta \to 0} \frac{\Pr((C_{ij}(t+\Delta) - C_{ij}(t)) = 1 | \mathcal{H}_t)}{\Delta} , \tag{2.12}$$

where $\mathcal{H}_t$ is some history (Bremaud, 1981). Informally, by a history we mean some observed information arising from various processes on the time interval $(0, t]$. Technically, $\mathcal{H}_t$ is a $\sigma$-algebra generated by these processes on $(0, t]$. Several such histories may be of interest. We shall assume that the $\lambda_{ij}$ are constants that can be parametrized using covariates $\mathbf{G}_i$ and $\mathbf{G}_j$ and a set of parameters $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_R)$, where $R << n(n-1)$, the number of pairs of individuals.

More generally, the contact rates could vary over time, such as cyclically, or be history dependent. For example, the occurrence of an infection could cause a person $j$ to reduce his or her activity and thus lower the intensities $\lambda_{ij}$ for all $i$. We do not consider this aspect further, and drop the notation for $\mathbf{G}_j$.

### Intensities for Infection Processes

Consider any $C_{ij}$ contact process discussed earlier. The contact process plus the infection outcomes, $\delta_{ijk}$, constitute a marked counting process (Bremaud, 1981; Arjas, 1989). Consider the multivariate infection process $\mathbf{N}(t) = \{N_{1.}(t), \ldots, N_{n.}(t)\}$. The process $N_{..}(t) = \sum_{i=1}^{n} N_{i.}(t)$ plus the identity and covariate values of the person infected at each jump is also a marked counting process. Let the function $\rho(t)$ denote the probability that an event occurring at time $t$ in the original process will be retained by a thinned process. If $\lambda(t)$

is an intensity for the original process and $\rho(t)$ is predictable, the intensity for the thinned process is $\rho(t)\lambda(t)$ (Bremaud, 1981).

Each infection process $N_{ij}$ is a thinned version of the corresponding contact process $C_{ij}$. Let $p(t; \mathbf{z}_i, \mathbf{z}_j, \boldsymbol{\beta})$ represent the probability that a contact $j \to i$ at time $t$ results in an infection if person $j$ is infectious and person $i$ is susceptible. This is also called the transmission probability. The $\mathbf{z}_i$ are covariates associated with susceptible $i$, $\mathbf{z}_j$ are covariates associated with infective $j$, and $\boldsymbol{\beta}$ is a vector of unknown parameters. If either $I_j(t)$ or $S_i(t)$ is 0, a point from $C_{ij}$ has probability 0 of being accepted. If both $I_j(t)$ and $S_i(t)$ are 1, the point is accepted with probability $p(t; \mathbf{z}_i, \mathbf{z}_j, \boldsymbol{\beta})S_i(t)I_j(t)$. The time and history dependent probability $\rho_{ij}(t)$ that a point from $C_{ij}$ will be accepted for $N_{ij}$ is $p(t; \mathbf{z}_i, \mathbf{z}_j, \boldsymbol{\beta})$. A dependence on $\mathbf{z}_j$ implies that persons are differentially infectious. For simplicity, here we assume that all infectives are equally infectious, and drop the dependence on $\mathbf{z}_j$. An intensity for $N_{ij}(t)$ may then be written as

$$\alpha_{ij}(t) = \lambda_{ij}(t)p(t; \boldsymbol{z}_i, \boldsymbol{\beta})S_i(t)I_j(t) \ , \tag{2.13}$$

where the infection process is a thinned version of the contact process.

### 2.9.2 Information Levels and Types of Statistical Analyses

In most of the development here, the covariates associated with the contact parameters are assumed to be the same for all individuals. $\mathbf{Z}_i$ and $\mathbf{G}_i$ denote covariates associated with the susceptibility and contact parameters.

#### Level I

In the first level of information, either all contacts between individuals and outcomes of those contacts are known, or contacts between infectives and the susceptibles whom they contact during their infectious period:

$$\mathcal{H}_t^I = \sigma\{C_{ij}(s),\ N_{ij}(t),\ I_j(s),\ S_i(s),\ \mathbf{Z}_i(s),\ \mathbf{G}_i(s),\ \ 0 \le s \le t\}$$

The analysis remains the same for evaluating covariates related to susceptibility since only contacts between infectives and susceptibles enter into the analysis. Estimation of the contact process will differ, however. The log-likelihood of observing contacts at the set of points $\{t_{ijk} : i, j = 1, \ldots, n, k = 1, \ldots, C_{ij}(T)\}$ (Fleming & Harrington, 1991) is given below in terms of stochastic integrals:

$$\log L(C) = \sum_{i=1}^{n}\sum_{j=1}^{n}\int_0^T \log(\lambda_{ij}(t))dC_{ij}(t) - \sum_{i=1}^{n}\sum_{j=1}^{n}\int_0^T \lambda_{ij}(t)dt. \tag{2.14}$$

The conditional likelihood for the infection outcome marks (the $N_{ij}$ processes) given the $C_{ij}$, $\mathbf{Z}_i$, $S_i$, and $I_j$ processes is

$$\prod_{i=1}^{n}\prod_{j=1}^{n}\prod_{k=1}^{c_{ij}}\{I_j(t_{ijk})S_i(t_{ijk})p(t_{ijk};\mathbf{z}_i,\boldsymbol{\beta})\}^{\delta_{ijk}}\times\{1-I_j(t_{ijk})S_i(t_{ijk})p(t_{ijk};\mathbf{z}_i,\boldsymbol{\beta})\}^{(1-\delta_{ijk})}.$$

We assume that the $\lambda_{ij}$ are parametrized by $\boldsymbol{\theta}=(\theta_1,\ldots,\theta_R)$ and that $p(t_{ijk};\mathbf{z}_i,\boldsymbol{\beta})=\exp(\boldsymbol{\beta}\mathbf{z}_i)$, where $\boldsymbol{\beta}$ has length $H$. $0^0$ is defined as 1. Since $p$ lies in the interval [0,1], in general we would want $\hat{\boldsymbol{\beta}}\leq 0$. Let $\gamma_{ijk}=I_j(t_{ijk})S_i(t_{ijk})$

$$IC_{i.}=\sum_{j=1}^{n}\sum_{k=1}^{c_{ij}}\gamma_{ijk},$$

i.e., the total contacts made on person $i$ by infectives while person $i$ was susceptible. Assuming sufficient regularity such that the interchange of the various integrals and derivatives is justified, and making a for can be written as, the $R+H$ score equations for Level I can be written as

$$\frac{\partial\log L(C,N)}{\partial\theta_r}=\sum_{i=1}^{n}\sum_{j=1}^{n}\int_0^T\frac{1}{\lambda_{ij}(t)}\frac{\partial\lambda_{ij}(t)}{\partial\theta_r}dC_{ij}(t)-\sum_{i=1}^{n}\sum_{j=1}^{n}\int_0^T\frac{\partial\lambda_{ij}(t)}{\partial\theta_r}dt$$

$$\frac{\partial\log L(C,N)}{\partial\beta_h}=\sum_{i=1}^{n}\delta_i z_{pi}-\sum_{i=1}^{n}(IC_{i.}-\delta_i)\frac{z_{pi}\exp(\boldsymbol{\beta}\mathbf{z}_i)}{1-\exp(\boldsymbol{\beta}\mathbf{z}_i)}. \tag{2.15}$$

These equations are formally equivalent to a log-linear binomial regression where each person $i$ with covariate $\mathbf{z}_i$ contributes $IC_{i.}$ trials with outcome $\delta_i$. The score equations for $\boldsymbol{\beta}$ and $\boldsymbol{\theta}$ can be solved separately. The information equations for this level and the score and information equations for all other levels are given in Rhodes et al (1994a).

**Level II**

In level IIA the source of each infection is known, that is, who infects whom, as well as how long each person is infectious. Level IIA is the last level with any direct contact information at all. On level IIB, it is known who is infectious and how long, but not who infects whom. The time that a person remains infectious plus contact rates with other individuals gives a measure of the exposure opportunity that this person provides to other individuals, after taking into account when each was susceptible: level IIA

$$\mathcal{H}_t^{IIA}=\sigma\{N_{ij}(s),I_j(s),S_i(s),\mathbf{Z}_i(s),\mathbf{G}_i(s),\ 0\leq s\leq t\};$$

level IIB,

$$\mathcal{H}_t^{IIB}=\sigma\{N_{i.}(s),I_j(s),S_i(s),\mathbf{Z}_i(s),\mathbf{G}_i(s),\ 0\leq s\leq t\}.$$

In most cases, information for pattern IIA will be difficult to obtain because of the necessity of observing who infects whom. When the $C_{ij}$ processes are

not directly observed, we treat the $N_{ij}$ processes as thinned versions of the $C_{ij}$. Using expression 2.13 for the intensity of $N_{ij}$, Rhodes et al (1996) give the log–likelihood for level IIA.

Without knowledge of the contact process, we cannot estimate both the set of parameters $\lambda_{ij}$ (or the $\boldsymbol{\theta}$) and the parameter $\beta_0$ corresponding to a constant term in $\mathbf{z}_i$. We must incorporate the value $\exp(\beta_0)$ into the $\lambda_{ij}$ functions and deal with a new set of parameters $\lambda^*_{ij} = \lambda_{ij} \exp(\beta_0)$. We shall also refer to the new set of parameters $\theta^*_1$ (note: $\theta^*_1 \neq \theta_1 \exp(\beta_0)$ except in special cases). In this instance, the $\boldsymbol{\beta}$ and $\boldsymbol{\theta}^*$ equations cannot be solved separately. However, the score equations for $\boldsymbol{\beta}$ have the form of a Poisson regression if the terms involving one portion of the log–likelihood, i.e.

$$\sum_{j=1}^{n} \lambda^*_{ij} \int_0^T I_j(t) S_i(t) dt \tag{2.16}$$

are known. Thus, estimation proceeds by alternating between solving the $\boldsymbol{\theta}^*$ equations and the $\boldsymbol{\beta}$ equations. Certain choices of the parametrization for the $\lambda^*_{ij}$ lead to both sets of equations conforming to a Poisson regression model.

The intensities for the $N_{i\cdot}$ processes are obtained by summing the intensities of the corresponding $N_{ij}$ processes (Bremaud, 1981). Level IIB has the same limitation in terms of not being able to estimate $\beta_0$ and $\lambda_{ij}$ separately. The log–likelihood is given in Rhodes et al (1996).

### Level III

We know the times at which infections occur and which individuals were susceptible as well as the values of all covariate processes. We do not observe how long each person remains infectious. Thus, for level III,

$$\mathcal{H}^{III}_t = \sigma\{N_{i\cdot}(s),\ S_i(s),\ \mathbf{Z}_i(s),\ \mathbf{G}_i(s), \quad 0 \leq s \leq t\}.$$

We proceed by writing a complete likelihood for the marked counting process $N_{\cdot\cdot}(t) = \sum_{i=1}^{n} N_{i\cdot}(t)$ and then decomposing it into components. The mark corresponds to the identity of the person infected when the combined process jumps. The contribution to the likelihood for the interval $(t_{d-1}, t_d)$ where $t_d$ is the time of the $d^{th}$ event in the process $N_{\cdot\cdot}$ is broken into two parts:

a) L (no event for $N_{\cdot\cdot}$ in $(t_{d-1}, t_d)$, event for $N_{\cdot\cdot}$ at $t_d | \mathcal{H}^{III}_t,\ t_{d-1} \leq t \leq t_d$),
b) L (identity of person infected at $t_d$ — event at $t_d$, set of individuals susceptible at time $t_d$, $\mathcal{H}^{III}_t$, $0 \leq t < t_d$).

The first term is obtained by treating $N_{\cdot\cdot}$ as the sum of thinned point processes and the second by considering the conditional probability of the identity of the infected individual given the set of individuals susceptible at time $t_d$. Level III has the same limitation in terms of not being able to estimate $\beta_0$ and $\lambda_{ij}$ separately. The expressions for the log-likelihoods are in Rhodes et al (1996).

The conditional probabilities may depend on the contact parameters and on the $I_j$ processes. In some instances, depending on the form of the $\mathbf{G_i}$ covariates, strata can be formed in which the conditional probability does not involve either the contact parameters or the $I_j$ processes. For example, if the $\lambda_{ij}(t)$ are all equal to a constant value $\lambda$, the conditional probability is free of both the above quantities. Also, consider the case where each individual belongs to one of $K$ mixing groups. In that circumstance we can work with $N_{k..}, k = 1, ..K$, the total infection processes in each of the $K$ groups. Part b is then the conditional distribution of the mark given the actual set of individuals who were susceptible at time $t_d$ in the group in which the infection occurred.

The Cox regression model has an advantage over analyses IIA and IIB in that no modification needs to be made for the situation where the study population constitutes only a portion of the entire population. For example, if one conducts a vaccine trial in a limited age group of the population and collects infection data only for that age group, the Poisson based methods could not be formulated correctly since one would not know the total exposure potential of the children in the trial.

**Level IV**

For level IV we know whether or not each individual has been infected in $(0, T]$ but not when the infection occurred:

$$\mathcal{H}_t^{IV} = \sigma\{N_{i.}(T), \mathbf{Z}_i(0), \mathbf{G}_i(0)\}$$

The analysis has the form of a binary regression, although the link is the complimentary log-log link (i.e. $\log(-\log(p))$). Censoring or late entry is not permitted, nor is it possible to incorporate time-dependent covariates. Thus, we restrict attention to the values of covariates at the start of study.

Consider the probability that an individual $i$ with covariates $\mathbf{z}$ would escape uninfected over the time period $(0, T]$ if we were given the full history of the infectiousness processes for all other individuals.

$$\Pr(N_{i.}(T) = 0 | I_j, \mathbf{Z}_i) = 1 - p_i(T) = \exp\left[ -\exp(\boldsymbol{\beta}\mathbf{z}_i) \int_0^T \sum_{j=1}^n \lambda_{ij}(t) I_j(t) dt \right] ,$$

or

$$\log(-\log(1 - p_i(T))) = \boldsymbol{\beta}\mathbf{z}_i + \log \int_0^T \sum_{j=1}^n \lambda_{ij}(t) I_j(t) dt = \boldsymbol{\beta}\mathbf{z}_i + \gamma_i \ . (2.17)$$

If the terms $\gamma_i$ are unique to each individual, estimation of the parameters of interest, $\boldsymbol{\beta}$, is not possible, since each individual adds a new parameter to

**Table 2.4.** Estimates of $\beta_1$ and estimated variances for $\beta_1$ assuming homogeneous mixing†(Rhodes, Halloran, Longini, 1996)

| Level | Estimator | Variance estimator |
|---|---|---|
| I | $\log\left(\frac{n_1 IC_0}{n_0 IC_1}\right)$ | $\frac{1-\hat{p}_0}{n_0} + \frac{1-\hat{p}_1}{n_1}$ |
| II | $\log\left(\frac{n_1 L_0}{n_0 L_1}\right)$ | $\frac{1}{n_0} + \frac{1}{n_1}$ |
| III | No closed form | No closed form |
| IV | $\log\left[\frac{\log\{-\log(1-\hat{p}_1)\}}{\log\{-\log(1-\hat{p}_0)\}}\right]$ | $\sum_{i=0}^{1} \frac{\hat{p}_1}{m_i(1-\hat{p}_i)\{(1-\hat{p}_i)\}^2}$ |

†$IC_i$ is the number of contacts made on individuals in group $i$ by infectives while those individuals in group $i$ were susceptible. $n_i$ is the number of infections in each group during the study. $L_i$ is the total time that susceptibles in group $i$ were exposed to infectives. $m_j$ is the initial number of susceptibles in group $i$, $\hat{p}_i = n_i/m_i$.

the analysis. However, if among the $n$ individuals there are a limited number of $\gamma$ parameters, estimation is possible. Thus, while the $I_j$ processes are not observable, under certain conditions, functions of these processes are estimable. However, these functions are not themselves of great interest. When there is a set of parameters $\boldsymbol{\gamma} = (\gamma_1, \ldots \gamma_K)$, where $K << n$, we then fit the complimentary log-log binomial regression model incorporating covariates for these parameters.

### 2.9.3 Homogeneous Mixing

We consider the case of homogeneous mixing, i.e. $\lambda_{ij}(t) = \lambda$ for $i \neq j$, with $p(t; \mathbf{z}_i, \boldsymbol{\beta}) = p_i = \exp(\beta_0 + \beta_1 z_i)$ for the case where $z_i$ is a single dichotomous covariate. When the contact processes are not observable, the parameters $\lambda$ and $\beta_0$ cannot both be estimated. The composite parameter $\lambda^* = \lambda \exp(\beta_0)$ is estimable and is interpretable as the average rate per unit of time at which one infective would tend to infect a susceptible with covariate equal to 0. The estimates for $e^{\beta_1}$ for the different information levels and the corresponding estimated variances are given in Table 2.4. The estimator for level I has the form of a log relative risk. Analyses IIA and IIB are the same since there are no contact covariates. The estimator for $\beta_1$ for level II is similar to that for level I except that a measure of exposure opportunity is substituted for a measure of actual exposure. The Cox regression estimator (Level III) does not have a closed form. The level IV estimator uses functions of the proportions infected in each group. If the probability of infection per contact is large, such as in measles or chickenpox, analysis I might be a better choice than analysis II (Figure 2.5). In this situation, knowledge of actual exposure, say a secondary attack rate study, provides a large improvement in the standard error

over the use of expected exposure or exposure opportunity, say a study using Poisson regression. Knowledge of the actual amount of exposure, measured by contacts with infectives, leads to a large gain in efficiency when the absolute probability of transmission per contact of an infective with a susceptible is high. Infectious diseases such as measles and chickenpox have transmission probabilities greater than 0.85, while the transmission probability for HIV is generally less than 0.01, except perhaps during certain periods of infectiousness.

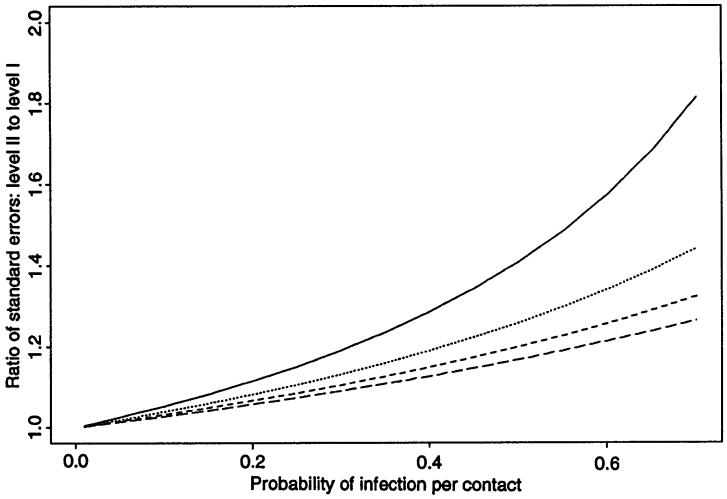


**Fig. 2.5.** Ratio of standard errors in the analysis at level II compared to level I by baseline transmission probability ($e^{\beta_0} = p_0$) and the covariate effect on the transmission probability, or transmission probability ratio ($TPR = e^{\beta_1}$) in group 1 compared to group 0. $TPR = e^{\beta_1} = 1$ (solid line), 0.5 (dotted line), 0.25 (short dashes), and 0.1 (long dashes). The ratios are based on the variances for $\beta_1$ at levels I and II given in Table 2. The number of infections is assumed to be the same in each group, and therefore, cancel out.

All of the models with the exception of level IV can be extended to accommodate individuals who are lost to follow-up or who enter the population after the study starts. A more complicated situation is introduced by the process letting $Y_j(t) = 1$ if person $j$ is *present* in the population at time $t$, and 0 otherwise. This differs from standard usage in survival analysis where $Y_j(t) = 1$ indicates that the person is *under observation* at time $t$ (Anderson & Gill, 1982). A person who is not under observation but remains present in the population may influence the infection outcomes of other population members. This type of dependence is not seen in noninfectious disease studies.

## Problems

**2.1. Problem Heading**
Problems for Chapter 2 will be added here.

**2.2. Problem Heading**
(a) The first part of the problem is described here.
(b) The second part of the problem is described here.