

# Estimating vaccine efficacy in a population stratified into households

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# Abstract

Most literatures on estimation of vaccine efficacy assume random mixing throughout the population. In practice population is somehow stratified into different groups or obviously into households. In such stratified population within group mixing is usually be higher than between groups and thus overall mixing is non-random. The present project aims to estimate vaccine efficacy in a population partitioned into households for a particular outbreak of acute, directly transmitted infectious disease.

Following Smith *et al.* (1984) and then Haber *et al.* (1991a) we define two models for vaccine efficacy in terms of transmission rates that can be estimated from final attack rates. Model 1, called *leaky* vaccine model, assumes that everyone is equally affected by the vaccine while Model 2, called *all-or-nothing* vaccine model, assumes that some are completely protected while others have no protection. Again, following Halloran *et al.* (1992) we also define a general model, called *summary* vaccine model, in terms of transmission rates for such stratified population on the basis of heterogeneity of vaccine action across the vaccinated strata. For all models mentioned above we describe estimation procedures of transmission rates from usual attack rate data is given through a deterministic epidemic approach proposed by Haber *et al.* (1991a). When vaccinated strata are not identifiable, a bound is derived for *summary* vaccine efficacy parameter where estimates of vaccine efficacy defined by Model 2 and Model 1 represent lower and upper bound respectively. We also discussed estimation of fraction of population has to be vaccinated to stop epidemic. An application of all vaccine models is provided by simulation study as well as numerical analysis.

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# Chapter 1

## Introduction to measures of vaccine efficacy

### 1.1 Introduction

Prevention for the control of infectious diseases through vaccination is the key to public health. Thus, for designing and implementing vaccination programs, it is important to have consistent estimates of vaccine efficacy (Davis, *et al.* 2006; Orenstein, *et al.* 1988). Estimation of vaccine efficacy has received much more attention in the literatures. But estimation procedures in such literatures are different based on assumptions they used and thus those estimates have different interpretations. Literatures showed that measures of vaccine efficacy depends on several assumptions including demographic characteristics of population, population mixing pattern, nature of the disease, length of infectious period, vaccine response, vaccination coverage, community structure, approach of formulation of epidemic models are applied etc. Most of the literatures mainly discussed the estimation of vaccine efficacy in a homogeneous and randomly mixing population. Estimation of vaccine efficacy based on these assumptions has received much more attention in those literatures (Smith *et al.* 1984; Orenstein *et al.* 1985; Halloran *et al.* 1991; Haber *et al.*

1991a; Haber *et al.* 1991b; Haber *et al.* 1995; Halloran *et al.* 1996; Davis *et al.* 2006; Longini *et al.* 1996; Longini *et al.* 1999; Becker *et al.* 2002).

Now let us consider an example of epidemic in a general population resided in a large community. It is more practical that population of the community may be partitioned into either several groups or households of different sizes. Thus, it can be assumed that there is a homogeneous mixing within each household and also a homogeneous mixing between the households, but allow for higher frequencies of contacts within household than between households. So, the overall mixing pattern is non-homogeneous. Estimation of vaccine efficacy in the population of such type of community divided into households is often ignored in the literatures. Becker and Utev (1997) estimated immunity coverage in a large community, which may be effective in controlling the disease transmission, considering more complex community structures that include households and localities. Haber *et al.* (1991b) estimated vaccine efficacy in a stratified population, where population was classified into households and then neighborhoods. They provided estimation of vaccine efficacy from simulation study considering all households of equal size and thus transmission rate in all households was also considered equal. They assumed greater transmission rate within households or neighborhoods than between households or neighborhoods. Haber *et al.* (1995) again estimated vaccine efficacy in a non-randomly mixing population where they considered only two strata with equal size. However, a few studies on epidemic modeling in a population stratified into households showed that mixing distribution between households depends on size of households (Watson 1972; Billard 1976).

Morover, modelling epidemics in a population partitioned into households have a long history, including the classical Greenwood and Reed-Frost (see Bailey 1975). Most recently in much more literatures, different epidemic models either stochastic or deterministic have been formulated for such stratified population considering higher infection rate

within group than between groups (Watson 1972; Daley and Gani 1994; Daley and Gani 1999; Ball *et al.* 1997; Ball 1999; Ball *et al.* 2001). They also discussed on vaccination strategy and estimation of fraction of population to be vaccinated to control epidemic.

With this contextual background, the present project aims to estimate vaccine efficacy in such type of population partitioned into households and also discuss estimation of fraction of population need to be vaccinated to control epidemic. An application of such methods will be provided by simulation study as well as numerical analysis.

## **1.2 The conceptual framework on measures of vaccine efficacy**

### **1.2.1 General concept of measures of vaccine efficacy**

The conceptual framework of vaccine efficacy has been discussed in literatures. The first concept of vaccine efficacy was introduced by Greenwood and Yule (1915) which is measured by  $VE = 1 - AR_v/AR_u$ , where  $AR_u$  and  $AR_v$  are the observed attack rates among vaccinated peoples and non-vaccinated peoples, respectively. The measure of vaccine efficacy has typically focused on relative reduction in susceptibility to infection of vaccinated compared to unvaccinated or relative reduction in infectiousness of a vaccinated person who became infected (Longini *et al.* 1996, Davis and Haber 2006). The susceptibility of an uninfected person is defined as the probability that the infectious agent is transmitted to that person via a contact with an infected person, while the infectiousness defined as the state or quality of being infectious. Estimation based on susceptibility is called vaccine efficacy for susceptibility ( $VE_S$ ) while estimation based on infectivity is referred as vaccine efficacy for infectiousness ( $VE_I$ ) (Datta *et al.* 1999). Both  $VE_S$  and  $VE_I$  are measures of the true biological effects of a vaccine (Davis and Haber 2006). Estimation of  $VE_S$  requires different levels of information depending on what type of

parameterizations is used (Halloran *et al.* 1997). On the other hand, estimation of  $VE_I$  requires information on exposure to infection which is very expensive even impossible in collecting and thus challenging to estimate it (Longini *et al.* 1996; Longini *et al.* 1999). Thus,  $VE_I$  cannot be estimated from a sample of unrelated individuals. But household data are commonly used to provide more information about exposure to infectious individuals (Davis, and Haber 2006). In the present project we estimate the vaccine efficacy in terms of relative reduction in susceptibility to infection of vaccinated compared to unvaccinated.

### 1.2.2 Vaccine efficacy vs. effectiveness of vaccination programme

More recently some researchers argued that vaccine efficacy and effectiveness of vaccination programme are not similar. Halloran *et al.* (1991) and Haber *et al.*(1991a) first distinguished between the effects of a vaccine and those of a vaccination programme. They defined *efficacy* of a vaccine in terms of the relative reduction in susceptibility. They also argued that the quantity, defined by Greenwood and Yule (1915), can be considered as a measure of the *effectiveness* of the vaccination programme, as it depends on the proportion of vaccinated, the length of the infectious period and other factors that are not related to the action of the vaccine. On the other hand, Greenland and Frerichs (1988) defined *efficacy* as the ability of the vaccine to produce effects (i.e, the biological potency of the vaccine) when administered under ideal conditions, and *effectiveness* is then defined as the actual field performance of a vaccination programme. Halloran *et al.* (1991) distinguished between the term *efficacy* and *effectiveness*. They defined *efficacy* as it can be applied to estimates of efficacy parameters obtained from controlled prospective trials, while *effectiveness* can be used for estimates of efficacy obtained from observational studies.

In this present report we measure vaccine efficacy assuming whether vaccine reduce

susceptibility of infection or vaccine may give complete protection to a proportion of individuals while remaining proportion has same level of susceptibility with unvaccinated individuals or vaccine has heterogeneous actions across the vaccinated strata.

### **1.3 Conclusion**

In this chapter we discussed rationale of estimating vaccine efficacy in a population stratified into households. We also discussed conceptual framework on measures of vaccine efficacy. Discussion on epidemic modelling for spread of infectious disease is essential when one is interested to estimate vaccine efficacy. In the next chapter we will discuss background of epidemic modelling as well as a basic formulation of stochastic and deterministic approach of epidemic modelling, particularly, in stratified population. We will also discuss some models of estimating vaccine efficacy.

# Chapter 2

## Review of modelling epidemics and methods of estimating vaccine efficacy

### 2.1 Introduction

It is essential to know the historical background and basic formulation of epidemic modelling for spread of infectious disease when one is interested to estimate vaccine efficacy and effectiveness of vaccination while these are applied to control epidemic. Section 2.2 discusses the background of modelling epidemics of both stochastic and deterministic approaches followed by foundation of those models in general case. Basic formulation of both deterministic and stochastic version of modelling epidemics in stratified population is discussed in Section 2.3. Section 2.4 demonstrates the review of some vaccine models, especially the models under heterogeneity of vaccine actions. Finally Section 2.5 concludes the chapter.

## 2.2 Epidemic modelling for spread of infectious disease

The development of mathematical models for the spread of infectious disease and their dissemination is at most over three centuries old. For a more detailed historical overview interested readers have been referred to the books by Bailey (1975) and Anderson and May (1991). There are two main features that make a difference between modelling infectious diseases and that of other type of disease (Anderson and Britton, 2000). The most important reasons is that there exist a strong natural dependency that whether an individual becomes infected or not depends on other individual in its locality. The second features is that most often the epidemic process is only partly observed, which may sometimes affects the statistical analysis. However, there are two approaches of modelling infectious diseases: stochastic and deterministic. Several reasons suggest that stochastic models are to be preferred when their analysis is possible. Conversely, deterministic models are simple. Sometimes it can be more complex, yet still possible to analyze, at least when numerical solutions are adequate. Anyway, both types of model play an important role in better understanding the mechanism of disease spread. Kermack and McKendrick (1927) proposed the first complete mathematical model for the spread of an infectious disease which was a deterministic model. On the other hand, the first stochastic model, which received more attention at that time even though it was never published, was the chain binomial model of Reed-Frost, 1928.

Modelling epidemics is nothing but a mathematical representation of 'epidemic process'. The 'epidemic process' can be characterized as the evolution of some infectious disease phenomenon within a given population of individuals (Daley and Gani, 1999). The properties of the process include:

- (i) Assumptions about the population of individuals within which the disease first

manifests itself, and then spreads;

- (ii) Assumptions about the disease mechanism: how it is spread, and the mechanism of recovery or removal, if such occurs; and
- (iii) Mathematical modelling assumptions that allow the specification of the two preceding properties.

On the basis of such properties there are two basic epidemics: simple epidemic and general epidemic. The simple epidemic is one where infection spreads by contact between the members of a community, but there is no removal from the circulation by death or recovery or isolation. Ultimately, all susceptibles become infected. The basic parameter in simple epidemic model is infection-rate. On the other hand, the more realistic and generally applicable representation of an epidemic is called general epidemic where possibility of removal of infectives is considered. Anyway, both types of such model for the spread of an infectious disease have been described in literatures assuming that the population is closed, homogeneous and homogeneously mixing. The closed population is that there is no birth and immigration during the course of epidemic. The homogeneity of the population indicates that the individual belongs to the same group and there is equal degree of mixing among the individuals. Let us describe the more useful general stochastic epidemic model for the spread of an infectious disease in a closed, and homogeneously mixing population.

### **2.2.1 General stochastic epidemic model**

Let us consider an epidemic with initially  $m$  infectious individuals and  $n$  susceptible individuals. The infected individuals have close contacts with other people that results in infection. The infectious periods of different infectives are assumed to be independent and identically distributed according to the distribution of a random variable  $I$ , which can have any arbitrary but specified distribution. During infectious period an infective makes

contacts with a given individual at the time points of a time homogeneous Poisson process with intensity  $\lambda/n$ . If a contacted individual is still susceptible, then s/he becomes infectious and is immediately able to infect other peoples. The infectious individual is considered to be removed from the infection process once its infectious period has terminated. Thus the removed individual is immune to new infectious. The Poisson processes of different individuals are assumed to be independent. The epidemic model of such kind is called SIR (S-susceptible, I-infectious, R-removed) epidemic model. The special case where the infectious period follows an exponential distribution is known as the general stochastic epidemic. The general stochastic epidemic at the first time was initiated by Bartlett (1949) and has received remarkable attention in the literatures.

### Stochastic models in continues time

Let us consider an S-I-R model in which the total population  $N+I$  is subdivided into  $X(t)$  susceptibles,  $Y(t)$  infectives, and  $Z(t)$  immune or removals, with  $(X, Y, Z)(0) = (N, I, 0)$  and

$$X(t) + Y(t) + Z(t) = N + I \quad \forall t \geq 0 \quad (2.1)$$

We assume that  $\{(X, Y)(t) : t \geq 0\}$  is a bivariate Markov process; (2.1) ensures that  $Z(t) = N + I - X(t) - Y(t)$  is known when  $(X, Y)(t)$  is known. Let  $p_{ij}$  be the probability that at time  $t$  there are  $i$  susceptibles still uninfected and  $j$  infectives in circulation. We again assume that there is a homogeneous mixing so that the probability of one new infection in time  $\Delta t$  is taken to be  $\beta ij \Delta t$ , and the chance of one removal  $\gamma j \Delta t$ , where  $\beta$  and  $\gamma$  are infection rate and removal rate respectively. This yields infinitesimal transition probabilities

$$P\{(X, Y)(t + \Delta t) = (i - 1, j + 1) | (X, Y)(t) = (i, j)\} = \beta ij \Delta t + o(\Delta t)$$

$$\begin{aligned}
P\{(X, Y)(t + \Delta t) = (i, j - 1) | (X, Y)(t) = (i, j)\} &= \gamma ij \Delta t + o(\Delta t) \\
P\{(X, Y)(t + \Delta t) = (i, j) | (X, Y)(t) = (i, j)\} &= 1 - (\beta i + \gamma) j \Delta t - o(\Delta t)
\end{aligned}$$

The state  $(i, j)$  for  $\{(X, Y)(t) : t \geq 0\}$  have an hierarchical structure, with the value of  $X$  decreasing by single units, and the value of  $Y$  increasing or decreasing by single unit also. Now if we write the state probability as

$$p_{ij} = P\{(X, Y)(t) = (i, j) | (X, Y)(0) = (N, I)\}, \quad (2.2)$$

we can derive the Kolmogorov forward equations in the form

$$\frac{dp_{NI}(t)}{dt} = -I(\beta N + \gamma)p_{NI}, \quad (2.3)$$

$$\frac{dp_{ij}(t)}{dt} = \beta(i+1)(j-1)p_{i+1, j-1} - j(\beta i + \gamma)p_{ij} + \gamma(j+1)p_{i, j+1} \quad (2.4)$$

$$(0 \leq i + j \leq N + I, 0 \leq i \leq N, 0 \leq j \leq N + I),$$

subject to the initial conditions  $p_{NI}(0) = 1, p_{ij}(0) = 0$  otherwise.

The distribution of the number of initial susceptibles ultimately infected, i.e the distribution of ultimate size of epidemic, is given by

$$P_n = Pr\{\lim_{t \rightarrow \infty} (X, Y)(t) = (N - n, 0) | (X, Y)(0) = (N, I)\} = p_{N-n, 0}(\infty).$$

With the  $\rho = \frac{\gamma}{\beta}$  as the relative removal rate, equation (2.3) and (2.4) become

$$\frac{dp_{NI}(t)}{dt} = -I(N + \rho)p_{NI}, \quad (2.5)$$

$$\frac{dp_{ij}(t)}{dt} = (i+1)(j-1)p_{i+1, j-1} - j(i + \rho)p_{ij} + \rho(j+1)p_{i, j+1} \quad (2.6)$$

$$(0 \leq i + j \leq N + I, 0 \leq i \leq N, 0 \leq j \leq N + I),$$

subject to the same initial conditions  $p_{NI}(0) = 1$ . Solution of this equation can be found recursively, starting with  $p_{NI}(t) = e^{-(N+\rho)It}$ . Gani (1965, 1967) proposed a solution which based on the mixture of Laplace transformation and probability generating function(p.g.f). For details of such models see Daley and Gani (1999).

### **Stochastic models in discrete time: The Reed-Frost Model**

The Reed-Frost model is the discrete time model for an epidemic spreading in a homogeneously mixing closed population with one or more infectives. This model was initially proposed, but never published, by Reed and Frost in the 1920s, and was subsequently published with some extensions to the model by Abbey (1952) and then Bailey (1975) and O'Neill and Roberts (1999) for further explanation of the model. For this model, *latent* period can be defined as the period of time between infection and becoming infective while the *incubation* period as the time between infection and the first symptoms. This model assumes

- (i) Latent and incubation periods are constant.
- (ii) The period of infectiousness is reduced to a single point.
- (iii) A single attack of the epidemic gives immunity.
- (iv) The latent period is taken to be the unit of time.

If an epidemic started in a group of susceptible individuals with a single or multiple infective, the epidemic continues in a series of stages separated by time intervals, of length the latent period, until there are no infected individuals in the population.

Consider an initial population of  $N$  susceptible individuals and a infected individuals. For  $t = 0, 1, \dots$ , let  $S_t$  and  $I_t$  denote the number of susceptible and infected individuals in the population at time  $t$ . Let  $p = 1 - q$  is the chance of adequate contact and  $q$  is the chance of avoiding between any susceptible and infective at time  $t$ , then  $q^{I_t}$  is

the chance that any given susceptible will have adequate contact with none of the  $I_t$  infectives. Accordingly,  $1 - q^{I_t}$  is the probability of adequate contact with at least one, which is what we require for infection take place. The conditional probability of exactly  $I_{t+1}$  freshly infected persons, will in turn become infectious at time  $t + 1$ , is therefore

$$P\{I_{t+1}|S_t, I_t\} = \binom{S_t}{I_{t+1}} (1 - q^{I_t})^{I_{t+1}} q^{I_t S_{t+1}} \quad (2.7)$$

Thus, the conditional probability distribution for the number of new cases at each stage of epidemic is given by binomial expression with parameters  $S_t$  and  $(1 - q^{I_t})$ .

## 2.3 Epidemic models in a stratified population

It is more realistic that a population in a large community usually divided into classes or households such that the individuals of each class mix homogeneously amongst themselves, but mix to a lesser degree with individuals of other classes. So, the overall mixing pattern is heterogeneous. A class could be thought of either as a group of friends or associates, or households or as a collection of individuals in a certain region of the community. Thus, this assumption appears to be a quite realistic substitute for the homogeneous mixing assumption when one is interested to model infectious disease in a population stratified into different groups. Watson, (1972) argued that epidemics in large populations can often be broken down into smaller outbreaks which are in general not in phase, and which interact with each other to some extent, as envisaged in his model. The first simple deterministic epidemic models based on such assumption have been proposed by Rushton and Mautner (1955) in  $m$  equivalent classes. Haskey (1957) studied simple stochastic epidemic models in only two classes. Then Watson (1972) studied general epidemic model in  $m$  sub-populations. Immediately a few years later Billard (1976) discussed an alternative approach of Watson model. More recently, there

are so many different epidemic models in such stratified population have been found in the literatures (Daley and Gani 1994; Ball *et al.* 1997; Ball 1999; Ball *et al.* 2001).

### 2.3.1 Deterministic epidemic model in a stratified population

The deterministic epidemic model in stratified population was first described by Daley and Gani (1994). Now we describe the mathematical formulation of deterministic epidemic models in such populations. Let us consider a closed population of size  $N$  consists of  $m$  groups of sizes  $N_1, \dots, N_m$ , in each of which a general epidemic may break out. The population is considered to be non-homogeneous due to stratification. We don't need to specify here the basis of stratification: it may be geographical, behavioral, cultural or socioeconomic, for example. Let us define  $\beta_{ij}$  as the pairwise infectious contact rates for an infective in the  $i$ th group to infect a susceptible in the  $j$ th group, for  $i, j = 1, 2, \dots, m$ . We also define removal rates  $\gamma_j$  for the removal of infectives from the  $j$ th group. Now let  $X_j(t)$ ,  $Y_j(t)$ , and  $Z_j(t)$  be the number of susceptibles, infectives, and removed cases in  $j$ th group respectively at time  $t$  and  $X_j(0) = N_j$ ,  $Y_j(0) = a_j$ ,  $Z_j(0) = 0$ . Also  $X_j(t) + Y_j(t) + Z_j(t) = N_j + a_j$ , so the process is completely specified by  $\{X_j(t), Y_j(t), t \geq 0\}$ .

The deterministic system is derived from the assumption that during small time  $\Delta t$  there are  $X_j(t)\{\sum_{i=1}^m \beta_{ij}Y_i(t)\}\Delta t$  adequate contacts that made infections and  $\gamma_j Y_j(t)\Delta t$  of infectives will loose their infection. So, the number of susceptibles, infectives and removed cases at time  $(t + \Delta t)$  are:

$$\begin{aligned} X_j(t + \Delta t) &= X_j(t) - X_j(t)\left\{\sum_{i=1}^m \beta_{ij}Y_i(t)\right\}\Delta t + o(\Delta t) \\ Y_j(t + \Delta t) &= Y_j(t) + X_j(t)\left\{\sum_{i=1}^m \beta_{ij}Y_i(t)\right\}\Delta t - \gamma_j Y_j(t)\Delta t + o(\Delta t) \\ Z_j(t + \Delta t) &= Z_j(t) + \gamma_j Y_j(t)\Delta t + o(\Delta t). \end{aligned}$$

By definition, we can write  $\lim_{\Delta t \rightarrow 0} \frac{X_j(t+\Delta t) - X_j(t)}{\Delta t} = \frac{dX_j(t)}{dt}$  and thus the differential equations from above equations can be written as follows:

$$\frac{dX_j(t)}{dt} = -X_j(t) \sum_{i=1}^m \beta_{ij} Y_i(t) \quad (2.8)$$

$$\frac{dY_j(t)}{dt} = X_j(t) \sum_{i=1}^m \beta_{ij} Y_i(t) - \gamma_j Y_j(t) \quad (2.9)$$

$$\frac{dZ_j(t)}{dt} = \gamma_j Y_j(t) \quad (2.10)$$

for each  $j = 1, 2, \dots, m$ .

Dividing (2.8) by (2.9) and then taking integration from 0 to  $t$  yields

$$\ln[X_j(t)/X_j(0)] = -\sum_{i=1}^m \beta_{ij} Z_i(t)/\gamma_i \quad (2.11)$$

For  $t \rightarrow \infty$ , the eventual number of susceptibles are left in  $j$ th group is

$$X_j(\infty) = X_j(0) \exp\left\{-\sum_{i=1}^m \beta_{ij} Z_i(\infty)/\gamma_i\right\} \quad (2.12)$$

For more details see Daley and Gani (1999).

### 2.3.2 Stochastic epidemic model in a stratified population

A stochastic analogue of the general deterministic epidemic of earlier section assumes that a finite population of a large community is stratified into  $m$  groups or households of sizes  $\mathbf{N} = (N_1, \dots, N_m)'$ . At time  $t \geq 0$  the  $j$ th group consists of  $X_j(t)$  susceptibles,  $Y_j(t)$  infectives, and  $Z_j(t)$  removed cases at time  $t$ . Let  $\beta_{ij}$  be the pairwise rate for an infective in the  $i$ th group to infect a susceptible in the  $j$ th group,  $\gamma_j$  for the removal of infetives from the  $j$ th group. At time  $t = 0$  suppose a single infective is added to stratum

*i.* In vector notation, the property of constant sizes of several strata is expressible as

$$\mathbf{X}(t) + \mathbf{Y}(t) + \mathbf{Z}(t) = \mathbf{N} + \mathbf{1}_i, \quad \forall t \geq 0 \quad (2.13)$$

and the initial condition is that  $(\mathbf{X}, \mathbf{Y}, \mathbf{Z})(0) = (\mathbf{N}, \mathbf{1}_i, \mathbf{0})$ , where the  $m$ -row vector  $\mathbf{1}_i$  has 1 as its  $i$ th component and all other elements zero.

Retaining the assumption of homogeneous mixing throughout the population, the probability of one new infection at  $j$ th stratum in time  $\Delta t$  is taken to be  $x_j(\sum_{i=1}^m \beta_{ij}y_i)\Delta t$ , and the chance of one removal at the same stratum is  $\gamma_j y_j \Delta t$ . We assume that for the strata  $i = 1, \dots, m$  with  $\mathbf{x}$  and  $\mathbf{y}$  denoting  $m$ -vectors of non-negative integer-valued components, then this yields infinitesimal probabilities

$$\begin{aligned} P\{(\mathbf{X}, \mathbf{Y})(t + \Delta t) = (\mathbf{x} - \mathbf{1}_j, \mathbf{y} + \mathbf{1}_j) | (\mathbf{X}, \mathbf{Y})(t) = (\mathbf{x}, \mathbf{y})\} \\ &= x_j \left( \sum_{i=1}^m \beta_{ij} y_i \right) \Delta t + o(\Delta t) = x_j (\mathbf{y}' \mathbf{B})_j \Delta t + o(\Delta t) \\ P\{(\mathbf{X}, \mathbf{Y})(t + \Delta t) = (\mathbf{x}, \mathbf{y} - \mathbf{1}_j) | (\mathbf{X}, \mathbf{Y})(t) = (\mathbf{x}, \mathbf{y})\} \\ &= \gamma_j y_j \Delta t + o(\Delta t) \\ P\{(\mathbf{X}, \mathbf{Y})(t + \Delta t) = (\mathbf{x}, \mathbf{y}) | (\mathbf{X}, \mathbf{Y})(t) = (\mathbf{x}, \mathbf{y})\} \\ &= 1 - \sum_{i=1}^m [x_j (\mathbf{y}' \mathbf{B})_j + \gamma_j y_j] \Delta t - o(\Delta t) \end{aligned}$$

where  $\mathbf{B} = (\beta_{ij})$ .

More specifically, the number among the  $X_j$  initial susceptibles in  $j$ th stratum contacted and therefore potentially infected is a binomial r.v.  $\text{Bin}(X_j, 1 - \exp(-(\sum_{i=1}^m \beta_{ij} y_i) \tau_j))$ , where  $\tau_j = 1/\gamma_j$  is the average length of infectious period at  $j$ th stratum. For more details see Daley and Gani (1999).

## 2.4 Measures of vaccine efficacy: A review of previous works

### 2.4.1 Vaccine efficacy under heterogeneity of vaccine action

Some literatures on vaccine efficacy often ignored the fact that immune response due to vaccine tends to vary among the hosts because of possible variation in immune systems of hosts and possible failure of vaccine for its imperfect use. Conversely, the concept of vaccine efficacy based on the level of protection against infection provided by a vaccine has received much attention in the literatures (Becker and Utev 2002).

Smith *et al.* (1984) argued that standard measures of vaccine efficacy should include the values that depend on the type of protection induced by the vaccine. They proposed two possible mechanisms of vaccine response. The first one is where a certain proportion of vaccinated people receive complete protection and the remaining proportion has no protection against infection. The other one is where every vaccinated person receives exactly the same partial protection. That is, vaccine reduces the susceptibility in every vaccinated individual. Halloran *et al.* (1991a) noted that in the case of first mechanism, there are actually two vaccinated strata, where the vaccine has a different effect in each of the two strata. Halloran *et al.* (1992) discussed the estimation of vaccine efficacy considering vaccine effect is heterogeneous across vaccinated strata. They considered different levels of susceptibility among the vaccinated strata and unvaccinated group and estimated a summary measure of vaccine efficacy. Becker and Utev (2002) allowed vaccine response to be random in a general way and their formulation of vaccine response includes two mechanisms considered by Smith *et al.* (1984) as particular cases. But their formulation didn't distinguish individuals with different vaccine responses. In the related work Halloran *et al.* (1996) and Longini *et al.* (1996) use a frailty mixing model to incorporate heterogeneous vaccine effect in the estimation of vaccine efficacy.

## 2.4.2 Review of some vaccine models

Measures of protective vaccine efficacy (VE) depend on the nature of host's response to the vaccine and it has been found in some investigations that host susceptibility and protection induced by vaccine follow certain probability distributions (Smith *et al.* 1984; Svensson 1991; Halloran *et al.* 1992). Greenwood and Yule (1915) first recognized the VE estimation problem and discussed the need to model the possible heterogeneity in host susceptibility in both vaccinated and unvaccinated people. Since then, some researchers have modeled unmeasured heterogeneity through stratification (Halloran *et al.* 1992; Longini *et al.* 1993a; Smith *et al.* 1984) while others have modeled by allowing the susceptibility to follow probability distributions (Brunet *et al.* 1993; Svensson 1991; Struchiner *et al.* 1995).

Smith *et al.* (1984) defined two models of vaccine action in a population. Model 1 defined depending on whether the vaccine reduced the probability of infection given exposure to infection in all of the vaccinated individuals equally. This model is called leaky vaccine model (Halloran *et al.* 1992; Struchiner *et al.* 1990). Model 2 defined assuming vaccines completely prevented infection in some, while having no effect in other and thus is called all-or-nothing vaccine model (Halloran *et al.* 1992). Halloran *et al.* (1991) noted that in the case of Model 2, there are actually two vaccinated strata, where the vaccine has a different effect in each of the two strata. The fundamental idea behind the Model 2 is that the vaccine may give complete protection to a fraction of the vaccinated,  $\alpha$ , while the remaining fraction,  $1 - \alpha$ , receive partial protection. Thus, the statistical problem is to estimate  $\alpha$  and the parameters of the distribution of partial protection from field data. Longini *et al.* (1996) and Halloran *et al.* (1996) demonstrated estimation and interpretation of such parameters from time to event data under unmeasured heterogeneity based on frailty mixing model using maximum likelihood approach.

### 2.4.3 Vaccine efficacy in terms of transmission probability

Haber *et al.* (1991a) derived expressions for the protective effects of the two vaccine mechanisms described by Smith *et al.* (1984) based on a dynamic epidemic model of an acute directly transmitted disease (Bailey, 1975) in which the number of new infections depends on the number already infected. In their model, the probability that a susceptible person becomes infected given that contact is made with a single infected person is assumed to remain constant over the course of an epidemic. Then they defined vaccine efficacy as the relative reduction in the transmission probability due to the vaccine, and demonstrate how it can be estimated from the usual attack rate data obtained in such vaccine efficacy studies.

Let us discuss the vaccine model in terms of transmission rates defined by Haber *et al.* (1991a). Let us define transmission rate  $\beta_u$  to an unvaccinated susceptible person as the probability that this person will become infected from a single infected person during one short time unit. The transmission rate can be written as  $\beta = \eta\theta$ , where  $\eta$  is the probability that any two people make adequate contact during a short time period, and  $\theta$  is the probability of transmission given contact between a susceptible and an infected person. Following Smith *et al.* (1984) there is two different models for the action of the vaccine. In Model 1, the probability of transmission from an infected person to a vaccinated susceptible person is reduced from  $\beta_u$  to  $\beta_v$ . Thus vaccine efficacy can be defined as  $VE = 1 - \beta_v/\beta_u$ . In model 2, a fraction  $\alpha$  of the vaccinated become totally immune while the remaining fraction  $1 - \alpha$  of vaccinated people are not affected by the vaccine. Thus the probability of a vaccinated person becoming infected from an infective person is zero with probability  $\alpha$  and  $\beta_u$  with probability  $1 - \alpha$ , i.e., the mean transmission rate to a vaccinated person is  $(1 - \alpha)\beta_u$ . Then vaccine efficacy under Model 2 can be defined as  $VE = 1 - (1 - \alpha)\beta_u/\beta_u = \alpha$ . Again, under the assumption of random mixing in a closed population Haber *et al.* (1991a) solved a deterministic epidemic model

for the transmission rates as a function of the final attack rates in the unvaccinated and vaccinated, denoted by  $AR_u$  and  $AR_v$ , respectively. Haber *et al.* (1991a) showed that the transmission rate to the unvaccinated,  $\beta_u$ , is related to the attack rates by:

$$\beta_u = -\frac{1}{\tau K} \ln(1 - AR_u) \quad (2.14)$$

where  $K = N[(1 - f)(AR_u) + f(AR_v)]$  is the total number of infected in the study population, and  $\tau$  is the average length of infectious period. Equation (2.14) holds for both models of vaccine mechanism. In Model 1,  $\beta_v$  is similarly given by

$$\beta_v = -\frac{1}{\tau K} \ln(1 - AR_v) \quad (2.15)$$

while in Model 2

$$\alpha = 1 - \frac{AR_v}{AR_u} \quad (2.16)$$

Therefore, an expression for vaccine field efficacy under Model 1 based on the relative transmission rates is given by:

$$VE = 1 - \frac{\beta_v}{\beta_u} = 1 - \frac{\ln(1 - AR_v)}{\ln(1 - AR_u)} \quad (2.17)$$

Vaccine efficacy under Model 2 is given by

$$VE = \alpha = 1 - \frac{AR_v}{AR_u} \quad (2.18)$$

Halloran *et al.*(1992) extended the method of Haber *et al.* (1991a) to develop a summary vaccine model ,that based on the relative susceptibilities in the vaccinated strata, for evaluating vaccine efficacy in an outbreak of a directly transmitted, acute infectious

disease. They proved that the upper and lower bounds on the summary vaccine efficacy at the beginning of the epidemic are the values obtained when assuming that Model 1 and Model 2 are operating, respectively.

All vaccine models discussed above were proposed for a homogeneously mixing closed population. However, they ignored estimation of vaccine efficacy in a population partitioned into households with different sizes where there is homogeneous mixing within household, but to a lesser frequency of mixing with individuals of other households and thus overall mixing are non-homogeneous. Haber *et al.*(1991b) and Haber *et al.*(1995) though estimated vaccine efficacy in such stratified population but they considered all households or strata of equal size. The present study aims to estimate vaccine field efficacy in such a population stratified into households of different sizes. We will also discuss the estimation of the threshold value of the fraction of the population that has to be vaccinated to stop epidemic.

## **2.5 Conclusion**

This chapter discussed the review of epidemic modelling, particularly in stratified populations and also discussed some vaccine models. In the next chapter we will discuss method of estimating vaccine efficacy in a stratified population.

# Chapter 3

## Measures of vaccine efficacy in a population stratified into households

### 3.1 Introduction

In this chapter, following Smith *et al.* (1984) and then Haber *et al.* (1991a) we define two models of estimating vaccine efficacy in terms of transmission rates estimated from final attack rates in a population partitioned into households of different sizes for a particular outbreak of acute, directly transmitted infectious disease. In Section 3.2 we define infection rates for modeling an epidemic process in a stratified population given by Watson (1972). In Section 3.3, we define our model for stratified population as well as describe estimation procedures of transmission rate from final attack rate via the deterministic approach proposed by Haber *et al.* (1991a). In Section 3.4 we discuss measures of summery vaccine efficacy under heterogeneity of vaccine action for stratified population. Section 3.5 demonstrates with discussion on the estimation of the threshold value of the fraction of the population that has to be vaccinated to stop epidemic. Finally, Section 3.6 concludes the chapter.

## 3.2 Infection rates for an epidemic process in stratified population

Let us consider an example of epidemic of directly transmitted infectious disease which is started in a large community of households. We assume homogeneous mixing among the individuals themselves within each household and also a homogeneous mixing between the members of others households, but allow for higher frequencies of contacts within household than between households. So the overall mixing pattern is non-homogeneous.

Let us consider a population of size  $N$  divided into  $m$  distinct households  $C_r$ , of size  $N_r$  ( $r = 1, 2, \dots, m$ ). Assume that initially the epidemic is started in a particular household and all other households are considered to be susceptible. It is also assumed that all individuals of any household are the same type, i.e the same level of susceptibility. Let us define  $\beta_{rs}$  as the infection rate in a particular type of households  $C_r$ , due to infective in other household  $C_s$ . Then  $\beta_{rs}$  can be expressed in terms of more meaningful parameters as follows:

$$\beta_{rs} = \beta_r p_{rs} N_r / N_s \quad (3.1)$$

where,  $\beta_r$  = infection rate within household  $C_r$ , and

$p_{rs}$  = proportion of mixing between members of household  $C_r$  those of  $C_s$ .

There are certain constraints on  $p_{rs}$  inherent in their meaning:

$$p_{rs} = p_{sr}, p_{rr} = 1, \text{ and } 0 \leq p_{rs} \leq 1.$$

It should be noted that  $p_{rs} = 1$  gives homogeneous mixing, while  $p_{rs} = 0$  gives  $m$  completely separate population. Thus, the process under consideration is bounded by these two known extremes.

Now if  $r = s$  then (3.1) yields the infection rate within household  $C_r$  is as follows:

$$\beta_{rr} = \beta_r p_{rr} N_r / N_r = \beta_r \quad (3.2)$$

To justify our assumption that members of a household mix homogeneously amongst themselves but to a lesser degree with members of other household, it can be shown using (3.1) and (3.2) that  $\beta_{rr} > \beta_{rs}$  since  $0 < p_{rs} < 1$ , and  $p_{rr} = 1$ .

### Example

It has been observed that the infection rate defined in (3.1) depends on size of the household. Thus, if all other assumptions remained the same then it can be shown that the infection rate defined in (3.1) among all households with equal sizes will be the same. Letting  $N_r = N_0$ ,  $\beta_r = \beta$ , and  $p_{rs} = q$ , from (3.1) the infection rate  $\beta_{rs}$  for equal sized households can be written as:

$$\beta_{rs} = \begin{cases} \beta & (r = s), \\ q\beta & (r \neq s), \end{cases} \quad (3.3)$$

where  $0 \leq q \leq 1$ . This formulation of infection rate for equivalent groups is similar to that of a study on an epidemic in a stratified population carried out by Watson (1972). He also showed that the removal rate,  $\gamma_r = \gamma$ , is also the same in case of equivalent groups.

It is realistic that a large community has several households of equal sizes. So, according to above formulation on infection rate for equivalent groups we can assume that the infection rate among all the households of equal sizes will be the same. But infection rates in different sized household should be different. In this project we are dealing with a deterministic epidemic model in such type of population stratified into households with different sizes. Finally we estimate vaccine efficacy and fraction of population has to be vaccinated. Now let us define all notations and parameters that will be used in our model.

### 3.3 Notations and the Models

Let  $m$  be the total number of households and  $m_n$  be the number of households of sizes  $n$  ( $n = 1, 2, \dots, L$ ). Thus,  $N = \sum_{n=1}^L nm_n$  is the total number of population in the community. Assume that a certain proportion of individuals in the community is vaccinated and consequently a minimum proportion of members in every household has been vaccinated. Thus, the members of households are divided into two groups: those who have been vaccinated prior to the outbreak, and those who have remained unvaccinated. As we assumed that epidemic is started in a particular households with a one or few infectives, all other households are considered to be susceptible. Let  $t$  denote the time since the beginning of the epidemic (measured continuously). At each time  $t$ , we define the following dynamic variables:

Let  $a_{n,u}$ ,  $a_{n,v}$  is the prop. of unvaccinated and vaccinated peoples in a household of size  $n$ .

$X_{n,u}(t)$ ,  $X_{n,v}(t)$  = Prop. of unvaccinated and vaccinated susceptible in such household

$Y_{n,u}(t)$ ,  $Y_{n,v}(t)$  = Prop. of unvaccinated and vaccinated infected in household of size  $n$ .

$Z_{n,u}(t)$ ,  $Z_{n,v}(t)$  = Prop. of unvaccinated and vaccinated people who have recovered from infection or immune.

$\beta_{nk,u}$  = infection rate for an unvaccinated susceptible people in households of size  $n$  due to infective in any other households of size  $k$ .

$\beta_{nk,v}$  = infection rate for an vaccinated susceptible people in households of size  $n$  due to infective in any other households of size  $k$ .

$\gamma_n$  = removal rate in any households of size  $n$

**Model 1:** Following Smith *et al.* (1984) we distinguish two models for the action of vaccine. In Model 1 we assume that vaccination reduces the probability of infection given contact with an infective. This model is called *leaky* vaccine model.

Now the deterministic model for general epidemic in unvaccinated peoples of a household

of size  $n$  is derived from the assumption that during small time  $\Delta t$  there are  $X_{n,u}(t)\{\sum_{k=1}^m \beta_{nk,u}(Y_{k,u}(t) + Y_{k,v}(t))\}\Delta t$  infections or adequate contacts between susceptible and infective, where all contacts are equally likely and  $\gamma_n Y_{n,u}(t)\Delta t$  infectives will lose their infection. Thus, the number of susceptibles, infectives, and removed cases at time  $(t + \Delta t)$  can be defined as:

$$\begin{aligned} X_{n,u}(t + \Delta t) &= X_{n,u}(t) - X_{n,u}(t)\left\{\sum_{k=1}^m \beta_{nk,u}(Y_{k,u}(t) + Y_{k,v}(t))\right\}\Delta t + o(\Delta t) \\ Y_{n,u}(t + \Delta t) &= Y_{n,u}(t) + X_{n,u}(t)\left\{\sum_{k=1}^m \beta_{nk,u}(Y_{k,u}(t) + Y_{k,v}(t))\right\}\Delta t - \gamma_n Y_{n,u}(t)\Delta t + o(\Delta t) \\ Z_{n,u}(t + \Delta t) &= Z_{n,u}(t) + \gamma_n Y_{n,u}(t)\Delta t + o(\Delta t) \end{aligned}$$

By definition we can write  $\lim_{\Delta t \rightarrow 0} \frac{X_{n,u}(t+\Delta t) - X_{n,u}(t)}{\Delta t} = \frac{dX_{n,u}(t)}{dt}$ , then the differential equations for unvaccinated group can be written as follows:

$$\frac{dX_{n,u}(t)}{dt} = -X_{n,u}(t)\left\{\sum_{k=1}^m \beta_{nk,u}(Y_{k,u}(t) + Y_{k,v}(t))\right\} \quad (3.4)$$

$$\frac{dY_{n,u}(t)}{dt} = X_{n,u}(t)\left\{\sum_{k=1}^m \beta_{nk,u}(Y_{k,u}(t) + Y_{k,v}(t))\right\} - \gamma_n Y_{n,u}(t) \quad (3.5)$$

$$\frac{dZ_{n,u}(t)}{dt} = \gamma_n Y_{n,u}(t) \quad (3.6)$$

with initial conditions

$$X_{n,u}(t) + Y_{n,u}(t) + Z_{n,u}(t) = a_{n,u}, \forall t \quad (3.7)$$

$$X_{n,u}(0) = a_{n,u}, Y_{n,u}(0) = 0^+, Z_{n,u}(0) = 0 \quad (3.8)$$

where  $0^+$  is very small number.

Similarly, for the epidemic in vaccinated peoples we can assume that during small time  $\Delta t$  there are  $X_{n,v}(t)\{\sum_{k=1}^m \beta_{nk,v}(Y_{k,u}(t) + Y_{k,v}(t))\}\Delta t$  infections or adequate contacts between susceptible and infective, where all contacts are equally likely and  $\gamma_n Y_{n,v}(t)\Delta t$  infectives

will loose their infection. Thus, we can write

$$\frac{dX_{n,v}(t)}{dt} = -X_{n,v}(t) \left\{ \sum_{k=1}^m \beta_{nk,v} (Y_{k,u}(t) + Y_{k,v}(t)) \right\} \quad (3.9)$$

$$\frac{dY_{n,v}(t)}{dt} = X_{n,v}(t) \left\{ \sum_{k=1}^m \beta_{nk,v} (Y_{k,u}(t) + Y_{k,v}(t)) \right\} - \gamma_n Y_{n,v}(t) \quad (3.10)$$

$$\frac{dZ_{n,v}(t)}{dt} = \gamma_n Y_{n,v}(t) \quad (3.11)$$

with initial conditions

$$X_{n,v}(t) + Y_{n,v}(t) + Z_{n,v}(t) = a_{n,v}, \forall t \quad (3.12)$$

$$X_{n,v}(0) = a_{n,v}, Y_{n,v}(0) = 0^+, Z_{n,v}(0) = 0 \quad (3.13)$$

where  $0^+$  is very small number.

### Estimation of transmission rates from final attack rates

Let us first find the size of the susceptible. Substituting (3.6) and (3.11) into (3.4) yields

$$\frac{1}{X_{n,u}(t)} \frac{dX_{n,u}(t)}{dt} = - \sum_{k=1}^m \beta_{nk,u} \left( \frac{dZ_{k,u}(t)}{dt} + \frac{dZ_{k,v}(t)}{dt} \right) / \gamma_k \quad (3.14)$$

Since the population size and length of infectious period are finite, there exists a time  $T$  at which  $Y_{n,u}(T) = Y_{n,v}(T) = 0$  and no new infections can occur. Integrating (3.14) over 0 to  $T$  yields the size of susceptible as follows:

$$\frac{X_{n,u}(T)}{X_{n,u}(0)} = \exp \left[ - \sum_{k=1}^m \beta_{nk,u} \{ Z_{k,u}(T) - Z_{k,u}(0) + Z_{k,v}(T) - Z_{k,v}(0) \} / \gamma_k \right] \quad (3.15)$$

Evaluating (3.15) at the initial conditions, (3.8) and (3.13) and noting that  $Z_{n,u}(T) = a_{n,u} - X_{n,u}(T)$ ; and  $Z_{n,v}(T) = a_{n,v} - X_{n,v}(T)$  yields

$$\frac{Z_{n,u}(T)}{a_{n,u}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,u} \{Z_{k,u}(T) + Z_{k,v}(T)\} / \gamma_k\right] \quad (3.16)$$

Similarly, solving equation (3.9) to (3.13) for vaccinated group we get

$$\frac{Z_{n,v}(T)}{a_{n,v}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,v} \{Z_{k,u}(T) + Z_{k,v}(T)\} / \gamma_k\right] \quad (3.17)$$

Let us define the fraction of vaccinated  $f_k = a_{k,v}/k$  and attack rates in the unvaccinated and vaccinated at the end of outbreak in households of size  $k$ ,  $AR_{k,u} = Z_{k,u}(T)/a_{k,u}$  and  $AR_{k,v} = Z_{k,v}(T)/a_{k,v}$ . Substituting the new values into (3.16)-(3.17) we have

$$AR_{n,u} = 1 - \exp\left[-\sum_{k=1}^m k\beta_{nk,u} \{(1 - f_k)AR_{k,u} + f_k AR_{k,v}\} / \gamma_k\right] \quad (3.18)$$

$$AR_{n,v} = 1 - \exp\left[-\sum_{k=1}^m k\beta_{nk,v} \{(1 - f_k)AR_{k,u} + f_k AR_{k,v}\} / \gamma_k\right] \quad (3.19)$$

Let us assume that removal rate for all household is equals, then  $\gamma_k = \gamma$ . But the removal rates  $\gamma$  for infectives implies that the mean infectious period is  $1/\gamma$ . Let  $\tau = 1/\gamma$  be the average infectious period. We also define transmission rates among unvaccinated and vaccinated as given below:

$$\begin{aligned} \pi_{n,u} &= \sum_{k=1}^m k\beta_{nk,u} \{(1 - f_k)AR_{k,u} + f_k AR_{k,v}\} \\ \pi_{n,v} &= \sum_{k=1}^m k\beta_{nk,v} \{(1 - f_k)AR_{k,u} + f_k AR_{k,v}\} \end{aligned}$$

Then equation (3.18)-(3.19) become

$$AR_{n,u} = 1 - \exp[-\tau\pi_{n,u}] \quad (3.20)$$

$$AR_{n,v} = 1 - \exp[-\tau\pi_{n,v}] \quad (3.21)$$

Taking log transformation in equation (3.20)-(3.21) we get transmission rates for unvaccinated and vaccinated as follows:

$$\pi_{n,u} = \frac{1}{\tau} \ln(1 - AR_{n,u}) \quad (3.22)$$

$$\pi_{n,v} = \frac{1}{\tau} \ln(1 - AR_{n,v}) \quad (3.23)$$

Let  $h_n = m_n/m$  be the proportion of household of size  $n$ . We assume that transmission rates in all households of the same size are identical as infection rates are assumed to be the same. Then equation (3.22)-(3.23) become transmission rates in all households of size  $n$  as follows:

$$\tilde{\pi}_{n,u} = \frac{1}{\tau} \ln(1 - AR_{n,u})h_n \quad (3.24)$$

$$\tilde{\pi}_{n,v} = \frac{1}{\tau} \ln(1 - AR_{n,v})h_n \quad (3.25)$$

Following Haber *et al.* (1991a) we can defined vaccine efficacy in terms of transmission rates. Therefore, the vaccine field efficacy for household of size  $n$  can be defined as

$$VE_n = 1 - \frac{\tilde{\pi}_{n,v}}{\tilde{\pi}_{n,u}} = 1 - \frac{\ln(1 - AR_{n,v})}{\ln(1 - AR_{n,u})}, n = 1, 2, \dots, L \quad (3.26)$$

**Model 2:** In this case we assume that a fraction  $\alpha$  of the vaccinated becomes totally immune and remaining fraction  $(1-\alpha)$  are still susceptible with same level of susceptibility

of unvaccinated. This model is called *all-or-nothing* vaccine Model.

Now the differential equations for unvaccinated group are exactly the same as equation (3.4)-(3.8) and for the vaccinated group (3.9)-(3.13) remained the same, but the initial conditions are

$$X_{n,v}(0) = a_{n,v}(1 - \alpha_n), Y_{n,v}(0) = 0^+, Z_{n,v}(0) = a_{n,v}\alpha_n$$

Therefore, equations (3.16)-(3.17) become

$$\frac{Z_{n,u}(T)}{a_{n,u}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,u} \{Z_{k,u}(T) + Z_{k,v}(T) - Z_{k,v}(0)\} / \gamma_k\right] \quad (3.27)$$

$$\frac{Z_{n,v}(T)}{a_{n,v}(1 - \alpha_n)} = (1 - \alpha_n) \left\{ 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,v} \{Z_{k,u}(T) + Z_{k,v}(T) - Z_{k,v}(0)\} / \gamma_k\right] \right\} \quad (3.28)$$

Substituting  $f_k = a_{k,v}/k$ ,  $AR_{k,u} = Z_{k,u}(T)/a_{k,u}$ ,  $\gamma_k = \gamma = 1/\tau$  and  $AR_{k,v} = [Z_{k,v}(T) - Z_{k,v}(0)] / (1 - \alpha_n)a_{k,v}$  into (3.27)-(3.28) become

$$AR_{n,u} = 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,u} \{(1 - f_k)AR_{k,u} + (1 - \alpha_k)f_k AR_{k,v}\}\right] \quad (3.29)$$

$$AR_{n,v} = (1 - \alpha_n) \left\{ 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,v} \{(1 - f_k)AR_{k,u} + (1 - \alpha_k)f_k AR_{k,v}\}\right] \right\} \quad (3.30)$$

In Model 2, we assumed that the attack rate in  $(1 - \alpha)$  proportion of vaccinated people is the same with that of unvaccinated as  $\beta_{nk,u} = \beta_{nk,v}$ . So, putting  $AR_{k,u} = AR_{k,v}$  into (3.29)(3.30) we get

$$AR_{n,u} = 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,u} \{(1 - \alpha f_k)AR_{k,u}\}\right] \quad (3.31)$$

$$AR_{n,v} = (1 - \alpha_n) AR_{n,u} \quad (3.32)$$

Previously we defined  $h_n = m_n/m$  as the proportion of household of size  $n$ . We assume that attack rate in all households of the same size is identical as infection rates is assumed

to be the same. Then equation (3.31)-(3.32) become as attack rate in all households of size  $n$  as follows:

$$\tilde{AR}_{n,u} = [1 - \exp[-\tau \sum_{k=1}^m k\beta_{nk,u}\{(1 - \alpha f_k)AR_{k,u}\}]]h_n \quad (3.33)$$

$$\tilde{AR}_{n,v} = [(1 - \alpha_n)AR_{n,u}]h_n \quad (3.34)$$

Therefore, the vaccine field efficacy for household of size  $n$  can be defined as

$$VE_n = 1 - \frac{\tilde{AR}_{n,v}}{\tilde{AR}_{n,u}}$$

$$\Rightarrow VE_n = 1 - \frac{AR_{n,v}}{AR_{n,u}}, n = 1, 2, \dots, L \quad (3.35)$$

### 3.4 Summary vaccine efficacy under heterogeneity of vaccine action

In previous section Following Smith *et al.* (1984) and then Haber *et al.* (1991a) we described two models of vaccine action in a population stratified into households depending on whether the vaccine reduced the probability of infection given exposure to infection in all of the vaccinated individuals equally (Model 1) or completely prevented infection in some, while having no effect in others (Model 2). Halloran *et al.* (1991) noted that in the case of Model 2, there are actually two vaccinated strata with different level of susceptibility, where thus the vaccine has a different effect in each of the two strata. Halloran *et al.*(1992) argued that interpretation and estimation of vaccine efficacy is complicated when the vaccine effect is heterogeneous across vaccinated strata. In response to this concern Halloran *et al.* (1992) developed models of vaccine action with a uniform biologic interpretation when the vaccine has heterogeneous effects in the

vaccinated strata. They also argued that vaccine efficacy is a function of the relative susceptibilities in the vaccinated and unvaccinated persons. Under heterogeneity of vaccine effect, they presented a general expression for a summary vaccine efficacy parameter in terms of the vaccine efficacy in the different vaccinated strata weighted by the fraction of the vaccinated sub-populations in each stratum. Extending the method of Haber *et al.* (1991a) for evaluating vaccine efficacy in an outbreak of an acute infectious disease, they also proved that the upper and lower bounds on the summary vaccine efficacy at the beginning of the epidemic are the values obtained when assuming that Model 1 and Model 2 are operating, respectively.

### An Example

As an example, let us briefly discuss summary vaccine efficacy models of heterogeneous vaccine action defined by Halloran *et al.* (1992). Assume that population in unvaccinated group has equal level of susceptibility  $\beta_0$  and a proportion  $\alpha$  of the vaccinated have susceptibility  $\beta_1$ , while the remaining proportion  $1 - \alpha$  has susceptibility  $\beta_2$ . Different combinations of heterogeneities across vaccinated strata result in different combination of relations among the susceptibilities of vaccinated strata. Using the relations of the susceptibilities in the vaccinated strata different type of vaccine models, the weighted average,  $\bar{\beta}_v$ , of the susceptibilities in the vaccinated fraction, and the summary vaccine efficacy,  $VE_{\bar{\beta}} = 1 - \frac{\bar{\beta}_v}{\beta_0}$ , for each of the vaccine models have been formulated and presented in Table 3.1. All vaccine models presented in Table 3.1 defined by Halloran *et al.* (1992) for randomly mixing population.

The weighted average,  $\bar{\beta}_v$ , is a meaningful population parameter that measures the average susceptibility in a heterogeneous population of vaccinated individuals, and the summary vaccine efficacy,  $VE_{\bar{\beta}}$ , is the average relative reduction in susceptibility. For any given value of  $\alpha$ ,  $\beta_0$ , and  $\beta_1$  it can be shown that  $\alpha(1 - \beta_1/\beta_0) < \alpha$ , and  $(1 - \alpha)\beta_2 <$

Table 3.1: Relation among susceptibility and summary vaccine efficacy in the different models

Model	Name	$\beta_1$	$\beta_2$	$\beta_v$	$VE_{\bar{\beta}}$
1	leaky	$\beta_1 < \beta_0$	no $\beta_2$	$\beta_1$	$1 - \frac{\beta_1}{\beta_0}$
2	all/nothing	$\beta_1 = 0$	$\beta_2 = \beta_0$	$(1 - \alpha)\beta_0$	$\alpha$
3	leaky/nothing	$0 < \beta_1 < \beta_0$	$\beta_2 = \beta_0$	$\alpha\beta_1 + (1 - \alpha)\beta_0$	$\alpha(1 - \frac{\beta_1}{\beta_0})$
4	all/leaky	$\beta_1 = 0$	$0 < \beta_2 < \beta_0$	$(1 - \alpha)\beta_2$	$1 - \frac{(1-\alpha)\beta_2}{\beta_0}$
5	general	$0 \leq \beta_1 \leq \beta_2$	$\beta_1 \leq \beta_2 \leq \beta_0$	$\alpha\beta_1 + (1 - \alpha)\beta_2$	$1 - \frac{\alpha\beta_1 + (1-\alpha)\beta_2}{\beta_0}$

$(1 - \alpha)\beta_0$  when  $\beta_2 < \beta_0$ . Thus, using these results it can be proved from Table 3.1 that

$$VE_{\bar{\beta}}(\text{Model 3}) \leq VE_{\bar{\beta}}(\text{Model 2}) \leq VE_{\bar{\beta}}(\text{Model 4})$$

Holloran *et al.* (1992) discussed the key issues in the interpretation and estimation of  $VE_{\bar{\beta}}$  which includes: (1) whether the strata are determined by a pre-vaccination host condition or by a vaccine-related problem; (2) who is in which vaccinated stratum; and (3) the change in the relative size of the two (or more) vaccinated strata over time due to differential susceptibility.

When the strata are not identifiable, they derived lower and upper bounds for summary vaccine efficacy parameter for the case of an outbreak of an acute infectious disease discussed by Haber *et al.* (1991a). They proved that  $VE_{\bar{\beta}}$  for general model 5 always lies between the efficacies calculated from Models 1 and Model 2, that is,

$$VE_{\beta}^{(2)} \leq VE_{\bar{\beta}}^{(5)} \leq VE_{\beta}^{(1)}$$

Following Halloran *et al.* (1992) we estimate summary vaccine efficacy for general Model 5 from final attack rates of an outbreak of acute, directly transmitted infectious disease in a population stratified into households. We also derive a bound for this summary measures assuming that strata are not identifiable.

### 3.4.1 Notations and model for summary vaccine efficacy in stratified population

To derive summary vaccine efficacy for general Model 5 described in the earlier example we have to modify some notations and initial conditions in vaccinated group as we consider here two strata with different level of susceptibility due to heterogeneous vaccine action. All notations and initial conditions for unvaccinated group will be remained the same.

Let  $\alpha$  be the proportion of vaccinated people that represents strata 1 while  $1 - \alpha$  of vaccinated represent strata 2. Thus, the notations for vaccinated strata 1 and 2 for a particular household size  $n$  are given below:

$X_{n,v}^{(1)}(t), X_{n,v}^{(2)}(t)$  = Prop. of vaccinated susceptible in strata 1 and 2 respectively

$Y_{n,v}^{(1)}(t), Y_{n,v}^{(2)}(t)$  = Prop. of vaccinated infected in strata 1 and 2 respectively

$Z_{n,v}^{(1)}(t), Z_{n,v}^{(2)}(t)$  = Prop. of recovered from infection or immune in strata 1 and 2 respectively.

$\beta_{nk,v}^{(1)}$  = infection rate for a vaccinated susceptible of strata 1 in a households of size  $n$  due to infective in any other households of size  $k$ .

$\beta_{nk,v}^{(2)}$  = infection rate for an vaccinated susceptible of strata 2 in households of size  $n$  due to infective in any other households of size  $k$ .

If Model 5 in the above example is operating then we can write

$$0 \leq \beta_{nk,v}^{(1)} \leq \beta_{nk,v}^{(2)}, \text{ and } \beta_{nk,v}^{(1)} \leq \beta_{nk,v}^{(2)} \leq \beta_{nk,u}$$

Therefore, following the approach of stochastic differential equations applied in previous section, the differential equations for unvaccinated group are:

$$\frac{dX_{n,u}(t)}{dt} = -X_{n,u}(t) \left[ \sum_{k=1}^m \beta_{nk,u} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] \quad (3.36)$$

$$\frac{dY_{n,u}(t)}{dt} = X_{n,u}(t) \left[ \sum_{k=1}^m \beta_{nk,u} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] - \gamma_n Y_{n,u}(t) \quad (3.37)$$

$$\frac{dZ_{n,u}(t)}{dt} = \gamma_n Y_{n,u}(t) \quad (3.38)$$

with initial conditions

$$X_{n,u}(t) + Y_{n,u}(t) + Z_{n,u}(t) = a_{n,u}, \forall t \quad (3.39)$$

$$X_{n,u}(0) = a_{n,u}, Y_{n,u}(0) = 0^+, Z_{n,u}(0) = 0 \quad (3.40)$$

where  $0^+$  is very small number.

Similarly, the differential equations for vaccinated strata 1 are

$$\frac{dX_{n,v}^{(1)}(t)}{dt} = -X_{n,v}^{(1)}(t) \left[ \sum_{k=1}^m \beta_{nk,v}^{(1)} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] \quad (3.41)$$

$$\frac{dY_{n,v}^{(1)}(t)}{dt} = X_{n,v}^{(1)}(t) \left[ \sum_{k=1}^m \beta_{nk,v}^{(1)} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] - \gamma_n Y_{n,v}^{(1)}(t) \quad (3.42)$$

$$\frac{dZ_{n,v}^{(1)}(t)}{dt} = \gamma_n Y_{n,v}^{(1)}(t) \quad (3.43)$$

with initial conditions

$$X_{n,v}^{(1)}(t) + Y_{n,v}^{(1)}(t) + Z_{n,v}^{(1)}(t) = \alpha_n a_{n,v}, \forall t \quad (3.44)$$

$$X_{n,v}^{(1)}(0) = \alpha_n a_{n,v}, Y_{n,v}^{(1)}(0) = 0^+, Z_{n,v}^{(1)}(0) = 0 \quad (3.45)$$

where  $0^+$  is very small number.

Again, the differential equations for vaccinated strata 2 are

$$\frac{dX_{n,v}^{(2)}(t)}{dt} = -X_{n,v}^{(2)}(t) \left[ \sum_{k=1}^m \beta_{nk,v}^{(2)} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] \quad (3.46)$$

$$\frac{dY_{n,v}^{(2)}(t)}{dt} = X_{n,v}^{(2)}(t) \left[ \sum_{k=1}^m \beta_{nk,v}^{(2)} \{Y_{k,u}(t) + Y_{k,v}^{(1)}(t) + Y_{k,v}^{(2)}(t)\} \right] - \gamma_n Y_{n,v}^{(2)}(t) \quad (3.47)$$

$$\frac{dZ_{n,v}^{(2)}(t)}{dt} = \gamma_n Y_{n,v}^{(2)}(t) \quad (3.48)$$

with initial conditions

$$X_{n,v}^{(2)}(t) + Y_{n,v}^{(2)}(t) + Z_{n,v}^{(2)}(t) = (1 - \alpha_n)a_{n,v}, \forall t \quad (3.49)$$

$$X_{n,v}^{(2)}(0) = (1 - \alpha_n)a_{n,v}, Y_{n,v}^{(2)}(0) = 0^+, Z_{n,v}^{(2)}(0) = 0 \quad (3.50)$$

where  $0^+$  is very small number.

### Estimation of transmission rates for summary model from final attack rates

The solution for estimating transmission rate from final attack rates is similar to the approach applied for Model 1 in Section 3.3. Thus, solving equations (3.36)-(3.40) for unvaccinated group, (3.41)-(3.45) for vaccinated strata 1 and (3.46)-(3.50) for strata 2 using the similar fashion applied in previous section we get the following equations:

$$\frac{Z_{n,u}(T)}{a_{n,u}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,u} \{Z_{k,u}(T) + Z_{k,v}^{(1)}(T) + Z_{k,v}^{(2)}(T)\} / \gamma_k\right] \quad (3.51)$$

$$\frac{Z_{n,v}^{(1)}(T)}{\alpha_n a_{n,v}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,v}^{(1)} \{Z_{k,u}(T) + Z_{k,v}^{(1)}(T) + Z_{k,v}^{(2)}(T)\} / \gamma_k\right] \quad (3.52)$$

$$\frac{Z_{n,v}^{(2)}(T)}{(1 - \alpha_n)a_{n,v}} = 1 - \exp\left[-\sum_{k=1}^m \beta_{nk,v}^{(2)} \{Z_{k,u}(T) + Z_{k,v}^{(1)}(T) + Z_{k,v}^{(2)}(T)\} / \gamma_k\right] \quad (3.53)$$

Let us define the fraction of vaccinated  $f_k = a_{k,v}/k$  and attack rates in the unvaccinated and all vaccinated strata at the end of outbreak in households of size  $k$ ,  $AR_{k,u} = Z_{k,u}(T)/a_{k,u}$ ,  $AR_{k,v}^{(1)} = Z_{k,v}^{(1)}(T)/\alpha_k a_{k,v}$ , and  $AR_{k,v}^{(2)} = Z_{k,v}^{(2)}(T)/(1 - \alpha_k)a_{k,v}$ . Substituting the new values and  $\gamma_k = 1/\tau$  into (3.51)-(3.53) we get

$$AR_{n,u} = 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,u} \{(1 - f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1 - \alpha_k) f_k AR_{k,v}^{(2)}\}\right] \quad (3.54)$$

$$AR_{n,v}^{(1)} = 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,v}^{(1)} \{(1 - f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1 - \alpha_k) f_k AR_{k,v}^{(2)}\}\right] \quad (3.55)$$

$$AR_{n,v}^{(2)} = 1 - \exp\left[-\tau \sum_{k=1}^m k \beta_{nk,v}^{(2)} \{(1 - f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1 - \alpha_k) f_k AR_{k,v}^{(2)}\}\right] \quad (3.56)$$

Now let us define transmission rates in terms of final attack rate for unvaccinated, vaccinated strata 1, and strata 2 as follows:

$$\begin{aligned}\pi_{n,u} &= \sum_{k=1}^m k\beta_{nk,u} \{(1-f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1-\alpha_k) f_k AR_{k,v}^{(2)}\} \\ \pi_{n,v}^{(1)} &= \sum_{k=1}^m k\beta_{nk,v}^{(1)} \{(1-f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1-\alpha_k) f_k AR_{k,v}^{(2)}\} \\ \pi_{n,v}^{(2)} &= \sum_{k=1}^m k\beta_{nk,v}^{(2)} \{(1-f_k)AR_{k,u} + \alpha_k f_k AR_{k,v}^{(1)} + (1-\alpha_k) f_k AR_{k,v}^{(2)}\}\end{aligned}$$

Using these transmission rates defined above we solve (3.54)-(3.56) and get

$$\pi_{n,u} = \frac{1}{\tau} \ln(1 - AR_{n,u}) \quad (3.57)$$

$$\pi_{n,v}^{(1)} = \frac{1}{\tau} \ln(1 - AR_{n,v}^{(1)}) \quad (3.58)$$

$$\pi_{n,v}^{(2)} = \frac{1}{\tau} \ln(1 - AR_{n,v}^{(2)}) \quad (3.59)$$

Now we define weighted average of transmission rates of vaccinated group as:

$$\bar{\pi}_{n,v} = \alpha_n \pi_{n,v}^{(1)} + (1 - \alpha_n) \pi_{n,v}^{(2)}$$

### Strata are identifiable and $\alpha$ known

Suppose that  $\alpha$  is known, and that the two strata of vaccinated persons are identified, so that  $AR_{n,v}^{(1)}$  and  $AR_{n,v}^{(2)}$  are also known. Then, the summary vaccine efficacy for Model 5 can be defined as

$$\begin{aligned}\overline{VE}_n &= 1 - \frac{\bar{\pi}_{n,v}}{\pi_{n,u}} \\ &= 1 - \frac{\alpha_n \pi_{n,v}^{(1)} + (1 - \alpha_n) \pi_{n,v}^{(2)}}{\pi_{n,u}}\end{aligned}$$

$$\Rightarrow \overline{VE}_n = 1 - \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(1)})}{\ln(1 - AR_{n,u})} \quad (3.60)$$

### Strata are not identifiable and $\alpha$ unknown

If strata are not identifiable and  $\alpha$  unknown then following Halloran *et al.* (1992) it can be derive bound on summary vaccine efficacy,  $\overline{VE}_n$ . We can show that the lower bound represented by vaccine efficacy,  $VE_n^{(2)}$ , estimated using Model 2 while upper bound represented by vaccine efficacy,  $VE_n^{(1)}$ , estimated using Model 1. That is, bound on  $\overline{VE}_n$  can be written as

$$VE_n^{(2)} \leq \overline{VE}_n \leq VE_n^{(1)}$$

The upper bound assumes that everyone is equally affected by the vaccine, and the lower bound assumes that some are completely protected while others have no protection.

#### Proof:

Let us assume that all assumption on stratified population is remained the same. Also assume that we don't know any thing about  $\alpha$  and attack rates in vaccinated strata 1 and 2. First we prove that  $VE_n^{(1)} \geq \overline{VE}_n$ .

$$\Rightarrow 1 - \frac{\ln(1 - AR_{n,v})}{\ln(1 - AR_{n,u})} \geq 1 - \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(1)})}{\ln(1 - AR_{n,u})}$$

We can say  $\ln(1 - AR_{n,u})$  is negative for  $0 \leq AR_{n,u} \leq 1$ . Therefore, since  $\ln(1 - AR_{n,u})$  is negative we have to prove

$$\ln(1 - AR_{n,v}) \geq \alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(1)}) \quad (3.61)$$

Following Halloran *et al.* (1992), we assume here that if the heterogeneity is due to heterogeneity in a host factor, then (i) the population has been randomly vaccinated with respect to host response to the vaccine, and (ii) if a sample of the population is drawn, then the sampling of the two vaccinated strata as well as the unvaccinated fraction

is done randomly. In this case,  $\overline{AR}_{n,v} = \alpha_n AR_{n,v}^{(1)} + (1 - \alpha_n) AR_{n,v}^{(2)}$  and  $\overline{AR}_{n,v} = AR_{n,v}$ .

That is, the crude estimate is equal to the weighted average.

Let  $x = AR_{n,v}$ ,  $x_1 = AR_{n,v}^{(1)}$ , and  $x_2 = AR_{n,v}^{(2)}$  then inequality in (3.61) implies that

$$\ln(1 - x) \geq \alpha_n \ln(1 - x_1) + (1 - \alpha_n) \ln(1 - x_2)$$

If we again let  $g(x) = \ln(1 - x)$ , where  $g(x)$  is concave function, then above inequality implies that

$$\Rightarrow g(\alpha_n x_1 + (1 - \alpha_n) x_2) \geq \alpha_n g(x_1) + (1 - \alpha_n) g(x_2) \quad (3.62)$$

Thus, to make (3.62) true, we need to show that the function  $g(x) = \ln(1 - x)$  is strictly increasing in  $x$  for all  $0 < x < 1$ . This is true if and only if  $\frac{d^2 g(x)}{dx^2} < 0$ , for all  $0 < x < 1$ .

Thus we have

$$\begin{aligned} \frac{d^2 g(x)}{dx^2} &= \frac{-1}{(1-x)^2} \\ \Rightarrow \frac{d^2 g(x)}{dx^2} &< 0, \text{ for all } 0 < x < 1 \end{aligned}$$

Thus, it implies that (3.62) is true and in turn all implies that  $VE_n^{(1)} \geq \overline{VE}_n$ .

Now we show

$$\begin{aligned} VE_n^{(2)} &\leq \overline{VE}_n \\ \Rightarrow 1 - \frac{AR_{n,v}}{AR_{n,u}} &\leq 1 - \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(2)})}{\ln(1 - AR_{n,u})} \end{aligned}$$

Using this crude estimate,  $\overline{AR}_{n,v} = \alpha_n AR_{n,v}^{(1)} + (1 - \alpha_n) AR_{n,v}^{(2)}$ , in above inequality we can say that we have to prove

$$\begin{aligned} 1 - \frac{\alpha_n AR_{n,v}^{(1)} + (1 - \alpha_n) AR_{n,v}^{(2)}}{AR_{n,u}} &\leq 1 - \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(2)})}{\ln(1 - AR_{n,u})} \\ \Rightarrow \frac{\alpha_n AR_{n,v}^{(1)} + (1 - \alpha_n) AR_{n,v}^{(2)}}{AR_{n,u}} &\geq \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(2)})}{\ln(1 - AR_{n,u})} \quad (3.63) \end{aligned}$$

For  $AR_{n,v}^{(1)} \leq AR_{n,u}$  and also for  $AR_{n,v}^{(2)} \leq AR_{n,u}$  it can be shown that

$$\frac{AR_{n,v}^{(1)}}{AR_{n,u}} \geq \frac{\ln(1 - AR_{n,v}^{(1)})}{\ln(1 - AR_{n,u})} \quad (3.64)$$

and

$$\frac{AR_{n,v}^{(2)}}{AR_{n,u}} \geq \frac{\ln(1 - AR_{n,v}^{(2)})}{\ln(1 - AR_{n,u})} \quad (3.65)$$

Multiply (3.64) by  $\alpha_n$  and (3.65) by  $(1 - \alpha_n)$  and adding together we get inequality (3.63) as follows

$$\Rightarrow \frac{\alpha_n AR_{n,v}^{(1)} + (1 - \alpha_n) AR_{n,v}^{(2)}}{AR_{n,u}} \geq \frac{\alpha_n \ln(1 - AR_{n,v}^{(1)}) + (1 - \alpha_n) \ln(1 - AR_{n,v}^{(2)})}{\ln(1 - AR_{n,u})}$$

Which implies that  $\overline{VE}_n \geq VE_n^{(2)}$ . Thus, for  $AR_{n,v}^{(1)} \leq AR_{n,u}$  and  $AR_{n,v}^{(2)} \leq AR_{n,u}$  it is proved that

$$VE_n^{(2)} \leq \overline{VE}_n \leq VE_n^{(1)}$$

Hence, if we cannot identify the strata and do not know  $\alpha$ , we have an upper and lower bound on the true summary measures,  $\overline{VE}_n$ .

### 3.5 Estimation of fraction of population to be vaccinated to control epidemic

For designing an effective vaccination programme it is important to determine the fraction of population that has to be vaccinated so that there is no epidemic. Thus, the estimation procedures are described below under all vaccine models described in the earlier sections.

#### When Model 1 is operating

We now derive the threshold value  $f_n^*$  for the fraction of vaccinated,  $f_n$ , such that for

$f_n \geq f_n^*$  there will be no epidemic in households of size  $n$ , and for  $f_n < f_n^*$  there will be an epidemic.

Let us define the dynamic variable  $Y_n(t) = Y_{n,u}(t) + Y_{n,v}(t)$ , (\*) which is the total number of infective in households of size  $n$  at time  $t$ . Then taking differentiation we have

$$\frac{dY_n(t)}{dt} = \frac{dY_{n,u}(t)}{dt} + \frac{dY_{n,v}(t)}{dt} \quad (3.66)$$

Using (3.5) and (3.10) and (\*) equation (3.36) becomes

$$\begin{aligned} \frac{dY_n(t)}{dt} &= X_{n,u}(t) \sum_{k=1}^m \beta_{nk,u} Y_k(t) - \gamma_n Y_{n,u}(t) + X_{n,v}(t) \sum_{k=1}^m \beta_{nk,v} Y_k(t) - \gamma_n Y_{n,v}(t) \\ \Rightarrow \frac{dY_n(t)}{dt} &= X_{n,u}(t) \sum_{k=1}^m \beta_{nk,u} Y_k(t) + X_{n,v}(t) \sum_{k=1}^m \beta_{nk,v} Y_k(t) - \gamma_n Y_n(t) \end{aligned} \quad (3.67)$$

It has been shown in a few literatures (Hethcote 1976; Haber *et al.* 1991a) in the field of epidemic modeling that  $Y_n(t)$  is either strictly decreasing (in the case of no epidemic) or strictly increasing to a maximum and strictly decreasing thereafter (in the case of an epidemic). Thus, it has been proved that there will not be an epidemic if  $[\frac{dY_n(t)}{dt}]_{t=0} \leq 0$ .

Let us consider Model 1 and evaluating (3.67) at  $t = 0$ , and using the initial values  $X_{n,u}(0) = a_{n,u}$ , and  $X_{n,v}(0) = a_{n,v}$ , we have

$$\left[ \frac{dY_n(t)}{dt} \right]_{t=0} = a_{n,u} \sum_{k=1}^m \beta_{nk,u} Y_k(0) + \sum_{k=1}^m \beta_{nk,v} Y_k(0) - \gamma_n Y_n(0) \quad (3.68)$$

where  $Y_k(0) = 0^+$  is a very small number.

Let us define  $\pi_{n,u} = \sum_{k=1}^m \beta_{nk,u} Y_k(0)$  and  $\pi_{n,v} = \sum_{k=1}^m \beta_{nk,v} Y_k(0)$ . Substituting  $a_{n,u} =$

$n(1 - f_n)$ ,  $a_{n,v} = nf_n$ , and  $\gamma_n = \gamma = 1/\tau$  and new parameters into (3.68) we have,

$$\left[\frac{dY_n(t)}{dt}\right]_{t=0} = n\tau(1 - f_n)\pi_{n,u} + n\tau f_n\pi_{n,v} - 1 \quad (3.69)$$

Therefore, there will be no epidemic if

$$\begin{aligned} \left[\frac{dY_n(t)}{dt}\right]_{t=0} &= n\tau(1 - f_n)\pi_{n,u} + n\tau f_n\pi_{n,v} - 1 \leq 0 \\ &\Rightarrow n\tau(1 - f_n)\pi_{n,u} + n\tau f_n\pi_{n,v} \leq 1 \\ &\Rightarrow f_n \geq \frac{n\tau\pi_{n,u} - 1}{[\pi_{n,u} - \pi_{n,v}]n\tau} \end{aligned} \quad (3.70)$$

Since  $\pi_{n,u} \geq \pi_{n,v}$  (because we assumed in Model 1 that  $\beta_{nk,u} > \beta_{nk,v}$ ), the inequality (3.70) is satisfied when  $f_n \geq f_n^*$ , where the threshold value  $f_n^*$  is given by

$$\begin{aligned} f_n^* &= \frac{n\tau\pi_{n,u} - 1}{[\pi_{n,u} - \pi_{n,v}]n\tau} \\ \Rightarrow f_n^* &= \frac{1 - 1/n\tau\pi_{n,u}}{1 - \pi_{n,v}/\pi_{n,u}} \\ \Rightarrow f_n^* &= \frac{1 - 1/R_0}{Efficacy} \end{aligned} \quad (3.71)$$

where  $Efficacy = 1 - \pi_{n,v}/\pi_{n,u}$  and  $R_0 = n\tau\pi_{n,u}$  is the basic reproduction number.

### When Model 2 is operating

In Model 2 we use  $X_{n,v}(0) = a_{n,v}(1 - \alpha_n)$ , and  $\beta_{nk,u} = \beta_{nk,v}$ . Then an epidemic will not be occur if

$$n\tau(1 - \alpha_n f_n)\pi_{n,u} \leq 1 \quad (3.72)$$

Solving (3.72) for  $f_n^*$  yields

$$\begin{aligned}
 f_n^* &= \frac{n\tau\pi_{n,u} - 1}{\alpha_n\pi_{n,u}n\tau} \\
 \Rightarrow f_n^* &= \frac{1 - 1/n\tau\pi_{n,u}}{\alpha_n} \\
 \Rightarrow f_n^* &= \frac{1 - 1/R_0}{Efficacy} \tag{3.73}
 \end{aligned}$$

where  $Efficacy = \alpha_n$ , and  $R_0 = n\tau\pi_{n,u}$

### When Summary Model is operating

In summary Model we use  $X_{n,v}^{(1)}(0) = \alpha_n a_{n,v}$ ,  $X_{n,v}^{(2)}(0) = (1 - \alpha_n)a_{n,v}$  and  $\beta_{nk,v}^{(1)} \leq \beta_{nk,v}^{(2)} \leq \beta_{nk,u}$ . Then an epidemic will not occur if

$$\Rightarrow n\tau(1 - f_n)\pi_{n,u} + n\tau f_n \bar{\pi}_{n,v} \leq 1 \tag{3.74}$$

where

$$\bar{\pi}_{n,v} = \alpha_n \pi_{n,v}^{(1)} + (1 - \alpha_n) \pi_{n,v}^{(2)}$$

Solving this equation (3.74) for  $f_n^*$  we get

$$\Rightarrow f_n^* = \frac{1 - 1/R_0}{Efficacy} \tag{3.75}$$

where  $Efficacy = 1 - \bar{\pi}_{n,v}/\pi_{n,u}$ , and  $R_0 = n\tau\pi_{n,u}$ .

It is interesting that denominator of formula for  $f^*$  in case of all three models is the vaccine efficacy. Again the basic reproduction number  $R_0$  will be the same for all three models as it is function of transmission rate for unvaccinated, average length of infectious

period and household size. Because transmission rate in unvaccinated group for all three models are the same according to the definition of these models described earlier. We also assumed that length of infectious periods is same in case of all models. That is, the estimate of fraction of population has to be vaccinated depends on vaccine efficacy and basic reproduction number. Thus, if transmission rate and length of infectious periods are known or estimated from previous study on a similar population, we can easily estimate  $f^*$  using estimated vaccine efficacy. We can see in all models that the threshold  $f^*$  is positive only if the basic reproduction number  $R_0 > 1$ , which is the condition required to guarantee that an epidemic will occur in the absence of vaccination. For details of estimation and interpretation on such threshold value see Haber *et al.* (1991a).

### 3.6 Conclusion

In this chapter we discussed method for estimating vaccine efficacy in terms of transmission probability in a population partitioned into households. We also estimated the threshold value of fraction of people that has to be vaccinated to stop epidemic. In the next chapter application of the methods for estimating vaccine efficacy will be provided with the help of simulated data as well as numerical solution of stochastic differentials described earlier in this chapter. Details of simulation study will also be discussed.

# Chapter 4

## Estimating vaccine efficacy using both simulation study and numerical solution of differential equations

### 4.1 Introduction

In Chapter 3 we discussed methods of estimating vaccine efficacy in a population stratified into households in theoretical perspective. Three models has been described for vaccine efficacy using a deterministic approach of epidemic modeling. In this chapter we simulate an epidemic process in a population partitioned into households and then estimate vaccine efficacy from simulated epidemic. Details of stochastic simulation study are described in Section 4.1. Section 4.2 describe the estimation and interpretation of results. We also estimate vaccine efficacy from numerical approximation of stochastic differential equations applied in earlier chapter. Section 4.3 demonstrates the procedures and interpretation of results of numerical approximation of vaccine models. In Section 4.4 we compare the results of simulation study and numerical approximation. In Section 4.5 we also estimate the fraction of population to be vaccinated using the results found

from both simulation study and numerical analysis. Section 4.6 concludes the chapter.

## 4.2 Description of simulation study

Stochastic simulation is useful to model the paths of the numbers of susceptible, infectious and recovered individuals in an epidemic with known rates of infection and recovery. In our project the simulation study was conducted to generate an epidemic process in a population partitioned into households. Initially we considered 5 households with different size 1, 2, 3, 4, 5. That is, one from each size. We assumed that initially one infective exists in any one of the 5 households and epidemic start from this infective. So, all other households' members either vaccinated or not are considered as susceptible. Structure of initial households used in simulation has been presented in Table 4.1. The notations "S", "I", and "R" used for number of susceptibles, infectives, and removal cases in each household. Subscript "u" and "v" used for unvaccinated and vaccinated. With this initials household structured and initial infection and removal rates given in Table 4.2 we generate the path of epidemic in every households for a length of periods 10.

Table 4.1: Structure of initial household used in simulation

HH size	Su	Iu	Ru	Sv	Iv	Rv
1	0	0	0	1	0	0
2	1	0	0	1	0	0
3	1	1	0	1	0	0
4	2	0	0	2	0	0
5	2	0	0	3	0	0

In the simulation study we assumed higher frequency of mixing within households than between households and thus overall mixing is non-homogeneous. As a result, we set higher infection rate within household than between households. Again we assumed that probability of mixing of individual of household of size greater is higher compared to the

Table 4.2: Initial values of  $\beta_{nk,u}$  and  $\beta_{nk,v}$  when Model 1 and Model 2 used in simulation

	Unvaccinated ( $\beta_{nk,u}$ )					Vaccinated ( $\beta_{nk,v}$ )				
	k=1	k=2	k=3	k=4	k=5	k=1	k=2	k=3	k=4	k=5
n=1	0.42	0.19	0.29	0.31	0.33	0.11	0.05	0.06	0.08	0.11
n=2	0.19	0.48	0.33	0.35	0.37	0.05	0.12	0.10	0.11	0.13
n=3	0.29	0.33	0.56	0.39	0.40	0.06	0.10	0.16	0.12	0.14
n=4	0.31	0.35	0.39	0.65	0.43	0.10	0.11	0.12	0.17	0.15
n=5	0.33	0.37	0.40	0.43	0.75	0.11	0.13	0.14	0.15	0.19

individual of households of smaller size. We assumed that vaccination is not random and at least a minimum proportion of individuals in every households has been vaccinated. In this regards Haber *et al.* (1991b) showed that estimates of vaccine efficacy in stratified population is unaffected if vaccination is considered to be fixed rather than random. We also assumed that mixing pattern of individual doesn't depend on vaccination status. The initial infection rates for within household and between household contacts used in simulation study have been given in a matrix which is presented by Table 4.2.

In stochastic epidemic theory, time  $t$  use as index parameter and number of susceptible, infective and removals are act as states of the process. At each time period states of the process is observed. According to the stochastic model for stratified population described in Section 2.3.2 of Chapter 2, the simulation process counts the number of infectives,  $I_{n,u}(t+1)$ , among unvaccinated in household of size  $n$  ( $n = 1, \dots, 5$ ) at time  $(t+1)$  as the binomial r.v.  $\text{Bin}(S_{n,u}(t), 1 - \exp(-\tau(\sum_{k=1}^5 \beta_{nk,u}(I_{k,u}(t) + I_{k,v}(t))))$ ), where  $\tau = 1/\gamma = 5$  ( $\gamma = 0.2$ , removal rate) is assumed as the average length of infectious period for all households. So, the number of susceptibles at time  $(t+1)$  is  $S_{n,u}(t+1) = S_{n,u}(t) - I_{n,u}(t+1)$  and number of removal at  $(t+1)$ ,  $R_{n,u}(t+1) = (S_{n,u}(t) + I_{n,u}(t) + R_{n,u}(t)) - (S_{n,u}(t+1) + I_{n,u}(t+1))$ . Similarly, the number of infectives among vaccinated at time  $(t+1)$  was counted as binomial r.v.  $\text{Bin}(S_{n,v}(t), 1 - \exp(-\tau(\sum_{k=1}^5 \beta_{nk,v}(I_{k,u}(t) + I_{k,v}(t))))$ ) and susceptibles and removals cases can be counted accordingly.

To simulate the process we used R programming Language. R codes are given in the

appendix. The R codes in Figure A1 given in appendix used to generate the epidemic process in all households. Figures A2, A3, A4 in appendix were used to estimate vaccine efficacy parameters using three models described in the earlier chapter. All results are computed from average of 100 simulations. The sample of epidemic process in each household can be viewed a few epidemic curve. Figure 4.1-4.5 demonstrate the epidemic path in the households of size 5, 4, 3, 2, and 1 respectively. That is, one figure represent epidemic in one household. As we assumed a proportion of members in every households has been vaccinated the simulated epidemic curve has been presented separately for vaccinated and unvaccinated in each household. Every graph placed in the left side represents the epidemic path for unvaccinated while the right one represents vaccinated group.

Figure 4.1: A sample simulated epidemic path in both unvaccinated and vaccinated in a household of size 5



The benefits of carrying out a large number of simulations mean is that we get reasonably smooth lines for the number of susceptible individuals, recovered individuals and infective individuals and so can fairly accurately describe what the dynamics of the population

Figure 4.2: A sample simulated epidemic path in both unvaccinated and vaccinated in a household of size 4

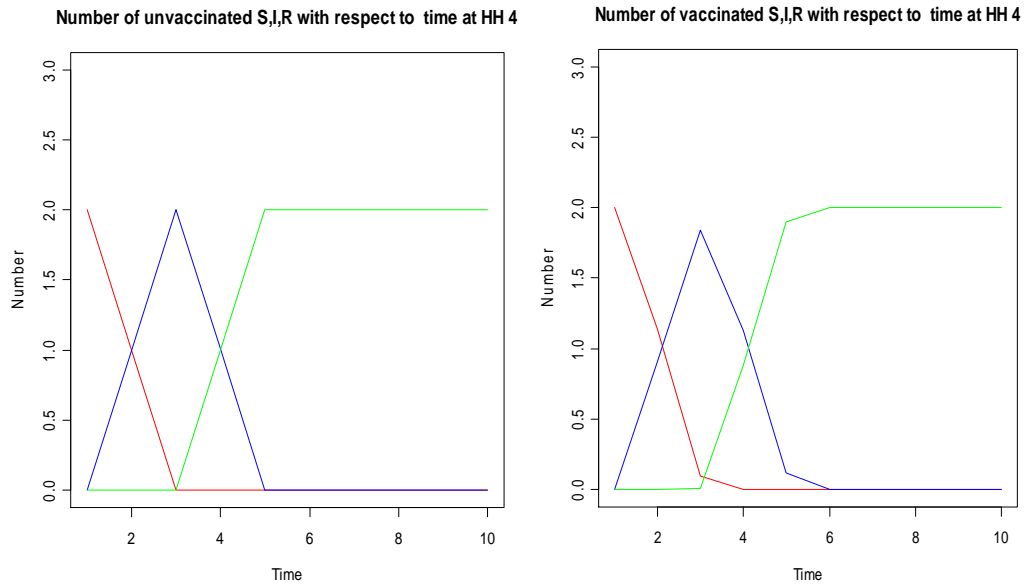
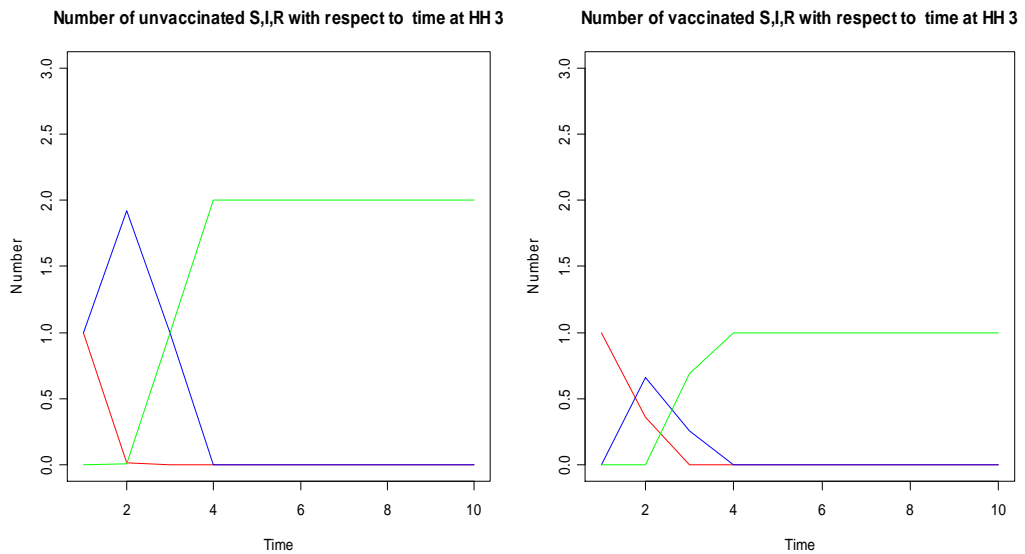


Figure 4.3: A sample simulated epidemic path in both unvaccinated and vaccinated in a household of size 3



are showing. In all graphs the red line is the number of susceptible individuals, the blue line the number of infective individuals and the green line the number of recovered individuals. From all Figures 4.1-4.5 we can see that the number of susceptible individuals decreases as we would expect with time. The number of infective individuals increases quite rapidly and then decreases so that there are no infective individuals. As indicated

Figure 4.4: A sample simulated epidemic path in both unvaccinated and vaccinated in a household of size 2

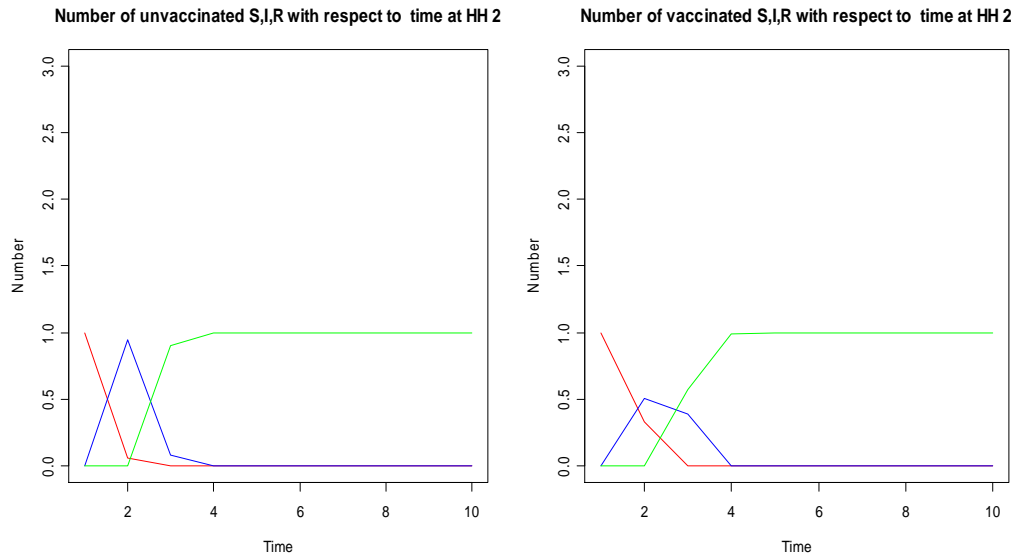
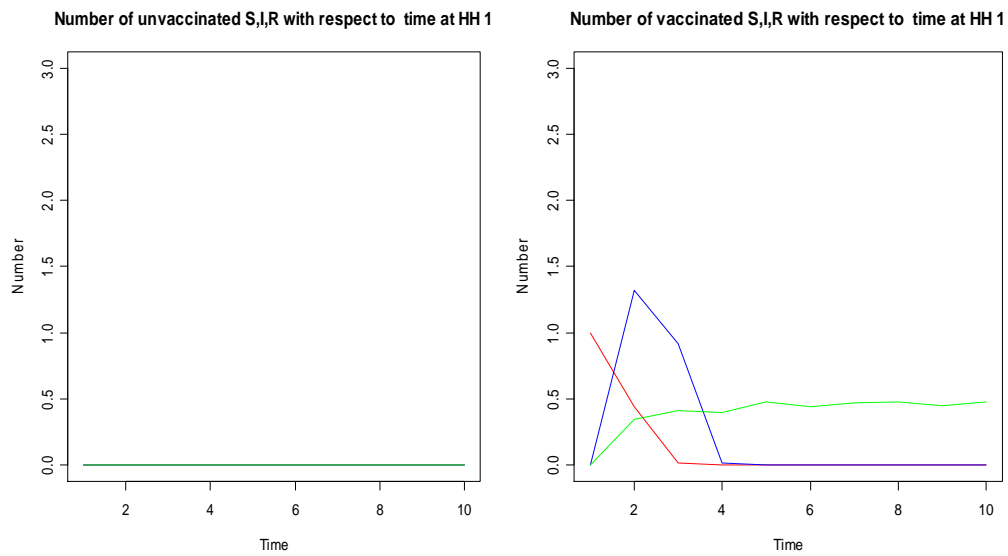


Figure 4.5: A sample simulated epidemic path in both unvaccinated and vaccinated in a household of size 1



by the initial distribution of the population the number of recovered individuals starts at zero and increases quite rapidly. The number of susceptible individuals and recovered individuals remains constant once there are no infective individuals in the population. The graph representing the epidemic situation in unvaccinated group of household of size 1 is different. That is, this graph don't shows the path for infectives and removals. Because there was no susceptible, result in no infectives and removals. Only the member in this household considered as vaccinated.

Table 4.3: Values of  $\beta_{nk,u}$ ,  $\beta_{nk,v}^{(1)}$ , and  $\beta_{nk,v}^{(2)}$  when *summary* vaccine model used in simulation

k		k=1	k=2	k=3	k=4	k=5
$\beta_{nk,u}$	n=1	0.42	0.19	0.29	0.31	0.33
	n=2	0.19	0.48	0.33	0.35	0.37
	n=3	0.29	0.33	0.56	0.39	0.40
	n=4	0.31	0.35	0.39	0.65	0.43
	n=5	0.33	0.37	0.40	0.43	0.75
$\beta_{nk,v}^{(1)}$	n=1	0.11	0.05	0.06	0.08	0.11
	n=2	0.05	0.12	0.10	0.11	0.13
	n=3	0.06	0.10	0.16	0.12	0.14
	n=4	0.10	0.11	0.12	0.17	0.15
	n=5	0.11	0.13	0.14	0.15	0.19
$\beta_{nk,v}^{(2)}$	n=1	0.15	0.07	0.08	0.10	0.12
	n=2	0.07	0.19	0.12	0.15	0.16
	n=3	0.08	0.12	0.25	0.16	0.19
	n=4	0.10	0.15	0.17	0.32	0.22
	n=5	0.12	0.16	0.19	0.22	0.39

The main purpose of this study is estimating vaccine efficacy in a population stratified into households. Subsequently, we defined three vaccine models in the earlier chapter on the basis of vaccine action. Thus, vaccine efficacy is estimated from simulated outbreak in each households using those three models. In *leaky* vaccine model (Model 1), as we assumed vaccine reduce susceptibility, we set higher infection rate for unvaccinated compared to vaccinated as initial of simulation process. In *all-or-nothing* vaccine model (Model 2) we set  $\alpha = 0.6$ , proportion of completely immune due to vaccine and assumed equal infection rate for remaining proportion,  $(1 - \alpha)$ , with unvaccinated. Finally, for *summary* vaccine model as we assumed the proration  $\alpha$  (called strata 1) and the remaining proportion  $(1 - \alpha)$  (called strata 2) of vaccinated have different vaccine action we considered three different sets of infection rates for unvaccinated, vaccinated strata 1 and strata 2. That is, infection rate among unvaccinated is greater than both of vaccinated strata 1 and 2, while infection rate in strata 1 is greater compared to strata 2. Three sets of infection rates were used in simulation study when summary vaccine models was operating. The initial values of infection rates have been presented in Table 4.3. Finally, we estimate vaccine efficacy from simulated epidemics using all three models. But those three models were used separately in simulation. Next section we describe the estimation

of vaccine efficacy from simulated data.

### 4.3 Estimation of vaccine efficacy from simulated epidemics

After simulating epidemics we estimate vaccine efficacy from the final outcome of epidemic. We used three different models mention earlier to estimate vaccine efficacy. As those three models were used separately R codes used in simulation are also presented separately in the appendix. R codes presented by Figures A2, A3, A4 in appendix were used to estimate vaccine efficacy parameters using Model 1, Model 2 and summary model respectively.

Every simulation of epidemic path using initials susceptibles, infectives, and removals gives us the eventual number of outbreak for each household of sizes 1, 2, 3, 4, and 5. Using the household's final outbreak size we estimate attack rates in both unvaccinated and vaccinated group using formula (3.18)-(3.19) for Model 1, (3.33)-(3.34) for Model 2, and (3.54)-(3.56) for summary vaccine model. Transmission rates are then calculated using formula (3.24)-(3.25) for Model 1 and (3.57)-(3.59) for summary model. It is not necessary to calculate transmission rate for Model 2 as it measures vaccine efficacy in terms of attack rate. Finally vaccine efficacy then estimated from transmission rates and attack rates using formula (3.26) for Model 1, (3.35) for Model 2 and (3.60) for summary vaccine model. During simulation, estimates of vaccine efficacy was varying from one simulation run to another run as household final outbreak size were varying associated with simulation run. Thus, the final estimates of vaccine efficacy parameters were taken from the average 100 simulations run. Accordingly, standard error is also computed for all estimators of vaccine efficacy parameters. We estimate vaccine efficacy for each household of different sizes using all models. Results of estimated vaccine efficacy from

simulated epidemics have been presented in Table 4.4.

Table 4.4: Estimated vaccine efficacy from simulated data for all models

HH size	Model 1		Model 2		Summary Model	
	VE	SE	VE	SE	VE	SE
n=1	0.740	0.0022	0.601	0.00001	0.715	0.0131
n=2	0.692	0.0013	0.600	0.000	0.654	0.0155
n=3	0.690	0.0009	0.601	0.00002	0.676	0.0252
n=4	0.702	0.0028	0.602	0.0001	0.632	0.0432
n=5	0.689	0.0041	0.600	0.0000	0.689	0.0878

The estimates of vaccine efficacy using three models differ from each others. For each household, Model 1 gives greatest estimates of vaccine efficacy, followed by summary vaccine model while Model 2 gives lowest estimates. That is, Model 2 gives lower bound for summary vaccine models while Model 1 gives upper bound. Estimation through simulations study gives lower standard error for all vaccine efficacy estimators of all models. Estimates for vaccine efficacy have different interpretations for Model 1 and Model 2. For example, in case of household of size 5, estimate of vaccine efficacy using Model 2 is 0.600, then the interpretation is that 60% of the vaccinated are completely protected from infection. For Model 1 the estimate is 0.689, then the interpretation is that the transmission rate given exposure to one infective is reduced by 68.1%.

Again, estimates of vaccine efficacy between households of different size differ slightly for every model. For Model 2 estimates between the households almost the same. It is due to the fact that we assumed constant protection of vaccine across the all households. For both Model 1 and summary models, household of size 1 gives greatest estimates while for Model 1 household size of 5 gives lowest and for summary model household of size 3 gives lowest estimates of vaccine efficacy.

Though household of different size gives different estimates of vaccine efficacy but estimates for all households of the same size will be equal as we assumed transmission rates in all household of same size are equal. A simulation study for estimating vaccine efficacy

in 400 households of equal size 5 conducted by Haber *et al.* (1991b) estimated the same estimates for . Therefore, if we consider a large community with several households, for example 500, of sizes 1, 2, 3, 4, and 5 then the results we have estimated from simulation study can be generalized for such large community.

## 4.4 Estimation of vaccine efficacy from numerical analysis

We also estimate vaccine efficacy from numerical solution of differential equations (3.4)-(3.26) for Model 1, (3.27)-(3.35) for Model 2, and (3.36)-(3.60) for summary model that are discussed in Chapter 3. All initial conditions used in stochastic simulations like household structure given in Table 4.1 and parameters value given in Table 4.2 and Table 4.3 are remained the same for this numerical solutions. In numerical analysis we observed the results of initial susceptibles, infectives and removals at each small time interval  $\Delta t = 0.1$  up to end of time 10. We also find the solution taking more small time interval  $\Delta t = 0.01$  to observe whether any difference exist in approximation. In both cases, the number of susceptibles, infectives and removal cases among vaccinated and unvaccinated at each household are computed at time  $(t + \Delta t)$  using the recursive formula as given below

$$\begin{aligned} S_{n,u}(t + \Delta t) &= S_{n,u}(t) - S_{n,u}(t) \left\{ \sum_{k=1}^m \beta_{nk,u} (I_{k,u}(t) + I_{k,v}(t)) \right\} \Delta t \\ I_{n,u}(t + \Delta t) &= I_{n,u}(t) + S_{n,u}(t) \left\{ \sum_{k=1}^m \beta_{nk,u} (I_{k,u}(t) + I_{k,v}(t)) \right\} \Delta t - \gamma I_{n,u}(t) \Delta t \\ R_{n,u}(t + \Delta t) &= R_{n,u}(t) + \gamma I_{n,u}(t) \Delta t \end{aligned}$$

In both cases, at the end of period 10 we got eventual number of susceptibles, infectives and removals. From those final outbreak size we estimate household attack rates,

transmission rates and finally estimate vaccine efficacy for three models using the same formula mentioned in simulation study that are used to estimate those rates and vaccine efficacy. But here we took results of one run as numerical analysis gives the same results for every run. Vaccine efficacies for three models estimated from the numerical analysis are given in Table 4.5. For Model 2 we set  $\alpha = 0.6$ , proportion of immune due to vaccine. For summary models  $\alpha$  is considered as the proportion of vaccinated with lower susceptibility compared to the remaining proportion of vaccinated,  $(1 - \alpha)$ , and unvaccinated. R programming language was also used to find the solution.

Table 4.5: Estimated vaccine efficacy from numerical analysis for all models: Model 1(M1), Model 2(M2), Summary Model (SM)

HH size	$\Delta t=0.1$			$\Delta t=0.01$		
	VE (M1)	VE (M2)	VE (SM)	VE (M1)	VE (M2)	VE (SM)
n=1	0.745	0.600	0.715	0.745	0.600	0.715
n=2	0.691	0.600	0.649	0.691	0.600	0.649
n=3	0.693	0.600	0.641	0.693	0.600	0.641
n=4	0.709	0.600	0.632	0.710	0.600	0.632
n=5	0.680	0.600	0.669	0.679	0.600	0.669

Estimates of vaccine efficacy from numerical analysis for three models differ significantly but gives almost similar estimates in both cases of time interval. Only estimates for household of sizes 4 and 5 differ slightly at the 2nd digit. Vaccine efficacy for Model 2 gives the exact results of  $\alpha = 0.6$ . Estimates between households also differ slightly.

## 4.5 Comparisons of results between simulation study and numerical analysis

In stochastic simulation the estimates of parameters usually vary from one simulation run to other one. Thus, we estimated vaccine efficacy from the average of 100 simulations. On the other hand, numerical analysis gives the same result in every run. Thus, we estimate

vaccine efficacy from one run of numerical analysis. The estimate of vaccine efficacy from both approach slightly differ particularly for Model 1 and summary model. This kind of dissimilarity in results of numerical analysis and simulation study may happen. But in terms of robustness we prefer estimates of simulation study as it can be generalized to whole population.

## 4.6 Estimation of fraction of population to be vaccinated

In Chapter 3 we also discussed estimation of the threshold value of the fraction of the population that has to be vaccinated to stop epidemic. In this section we estimate the fraction of population to be vaccinated using the estimated vaccine efficacy from simulation study and numerical analysis. Estimation procedures described in Chapter 3 indicates that estimation of such fraction depends on vaccine efficacy and basic reproduction number  $R_0$ . By definition of basic reproduction number we know that an epidemic will occur if  $R_0 > 1$  in the absence of vaccination. Here we estimate the fraction of population to be vaccinated to stop such epidemic. To estimate that fraction we assume that the basic reproduction number at  $R_0 = 2$ . Again we already have estimated vaccine efficacy in Table 4.4 and table 4.5. Thus, using the formula (3.71) for Model 1, (3.73) Model 2, and (3.75) for summary model we can estimate the fraction of population to be vaccinated. The estimates of the fraction  $f^*$  of the population that has to be vaccinated to stop epidemic for all threes models has been presented in Table 4.6. All estimates in Table 4.6 show that more than 70% of population has to be vaccinated before starting an epidemic to stop it. These estimates are based on the current estimates of vaccine efficacy found from simulation study and numerical analysis. These estimates of fraction of population will be change if there is any change in estimates of vaccine efficacy.

Table 4.6: Estimates of fraction of population to be vaccinated using Model 1(M1), Model 2 (M2) and Summary Model (SM)(Basic reproduction number assumed as  $R_0 = 2$ )

HH size	Simulation results			Numerical analysis		
	$f^*$ (M1)	$f^*$ (M2)	$f^*$ (SM)	$f^*$ (M1)	$f^*$ (M2)	$f^*$ (SM)
n=1	0.678	0.831	0.699	0.671	0.833	0.699
n=2	0.727	0.833	0.765	0.723	0.833	0.770
n=3	0.730	0.831	0.776	0.721	0.833	0.780
n=4	0.719	0.830	0.790	0.705	0.833	0.791
n=5	0.732	0.833	0.752	0.735	0.833	0.747

## 4.7 Conclusion

In this chapter an application of vaccine models described in Chapter 3 is provided using simulated data as well as numerical solution of stochastic differential equations. Details of simulation study and estimation procedures of vaccine efficacy have been described. We also discussed the interpretations of results found from simulation study and numerical analysis. In the next chapter we will discuss the robustness of the methods and models that we applied to estimates vaccine efficacy in a population stratified into households comparing to the methods and findings of other studies taken in similar population.

# Chapter 5

## Discussion and Conclusion

Estimation of vaccine efficacy parameters depends on several assumptions related to structure of population, mixing patterns either random or not, the routes of transmission of infection agent, vaccine response, strategy of vaccination programme, study design, sampling procedures etc. Most published works on vaccine efficacy assumed random mixing throughout the population. In real world situation non-random mixing in a population is common because population is usually partitioned into different groups or obviously into households. The present work considered an epidemic of acute, directly transmitted disease in a closed population of a large community that stratified into households of different sizes. Then estimation of vaccine efficacy is described assuming a vaccine that lowers the transmission rate to vaccinated persons but does not affect the infectiousness of those vaccinated persons who became infected. Following Smith *et al.* (1984) and then Haber *et al.* (1991a) we firstly define two vaccine models in terms of transmission rates and household final attack rates. The transmission rate is actually defined in terms of log transformation of final attack rates. Model 1, called *leaky* vaccine model defined by equation (3.26), assumes that everyone is equally affected by the vaccine, and Model 2, called *all-or-nothing* vaccine model defined by equation (3.35), assumes that some of vaccinated completely protected while others have no protection.

For both models estimation of transmission rates from attack rates and then estimation of vaccine efficacy parameter has been discussed by a deterministic approach proposed by Haber *et al.* (1991a).

Again, following Halloran *et al.* (1992) we define another vaccine model in terms of attack rates, called *summary* vaccine model, on the basis of heterogeneity of vaccine action. This vaccine model assume that vaccine action varies across the vaccinated strata. Thus, a fraction,  $\alpha$ , of vaccinated assumed to have lower susceptibility prior to start outbreak compared to remaining proportion,  $1 - \alpha$ , of vaccinated but both strata have lower susceptibility compared to unvaccinated. An weighted average of attack rate and then transmission rate for vaccinated has been calculated from attack rates and transmission rates of two vaccinated strata. Finally, vaccine efficacy defined comparing transmission rates of unvaccinated and weighted transmission rates of vaccinated. We also discussed estimation of *summary* vaccine efficacy when strata are identifiable and  $\alpha$  is known as well when strata are identifiable and  $\alpha$  unknown. When strata are identifiable and  $\alpha$  known we can easily estimate attack rates in strata 1 and strata 2 from final outbreak size and thus *summary* vaccine efficacy was defined by equation (3.60) in terms of attack rates. On the other hand, when strata are not identifiable and  $\alpha$  unknown at time  $t = 0$  we derived a bound for *summary* vaccine efficacy where Model 1 represents upper bound while Model 2 represents the corresponding lower bound. The mathematical proof of this inequality has been provided in Chapter 3.

This study provides an application of estimating vaccine efficacy in a stratified population through both simulation study and numerical analysis. The simulation study was carried out considering 5 initial households of each from one of sizes 1, 2, 3, 4, and 5 and initial infection rates within and between households. The simulated epidemic paths ,from the average of 100 simulations, in each household were presented by epidemic curve(Figure 4.1-4.5). Throughout the study we assumed that vaccination is not random

, i.e., at least a proportion of population has been vaccinated. We also assumed that mixing distribution doesn't depend on vaccination status. Estimates of vaccine efficacy based on household final attack rates found from simulation study differ slightly between households of different sizes. This phenomena holds true for all models. The estimates of vaccine efficacy for all models have smaller bias. But comparatively Model 2 gives smaller bias. This finding is analogous to those of Haber *et al.* (1991b) and Haber *et al.* (1995) conducted in a stratified population considering all strata are of equal size. Through a simulation study they showed that estimates are not affected if mixing distribution depends on vaccination status. Simulation results of their model also showed that Model 2 gives smaller bias than Model 1. But they didn't apply *summary* model of heterogeneity vaccine actions. On the other hand, both simulation and numerical analysis results of the present study showed that estimates between models differ slightly. Model 2 gives the lowest estimate of vaccine efficacy while Model 1 gives the highest. That is, estimate based on Model 2 provides the lower bound for *summary* vaccine model while Model 1 provides the upper bound. Halloran *et al.* (1992) also estimated such lower and upper bounds for *summary* vaccine efficacy using Model 2 and Model 1 respectively via a simulation of epidemics in a randomly mixing closed population.

Again, we also estimate vaccine efficacy from a numerical analysis of stochastic differential equations. We find the solution taking time interval  $\Delta t = 0.1$  and also  $\Delta t = 0.01$ . For both cases provide the approximately the same results. The estimates of vaccine efficacy from numerical analysis also differ slightly by size of households. Model 2 provides the lower bound for *summary* vaccine model while Model 1 provides upper bound. Using estimated vaccine efficacies found from both simulation and numerical analysis and basic reproduction number at  $R_0 = 2$  we also estimate the fraction of population to be vaccinated before starting an outbreak. All estimates indicate that at least 70% of population at each household has to be vaccinated to stop an epidemic. Haber *et al*

(1991a) also estimates such fraction in a study on measures of effectiveness of vaccination programme in a randomly mixing population.

This study provides the estimation of vaccine efficacy in a population assumed to be partitioned into households. In practice the population can also be partitioned in terms of demographic, socioeconomic, and others social factors. For example, usually children are more likely to become infected compared to adults (McLean *et al.* 1988; Anderson *et al.* 1984). Conversely, vaccine may have different action between children and adults (Anderson *et al.*, 1984). So, within household children and adult can form two strata and may have different transmission rate and also vaccine action. Therefore, vaccine efficacy can be estimated considering such population partitioned into two steps: household then children and adults.

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# Appendix

The function *singlesim* in Figure A 1 gives the number of both unvaccinated and vaccinated susceptible, infectives and recovered individuals for each household after a single time interval. Then *onecompsim* gives the same items after each single interval up to size  $N_{steps}=10$ .

The function *fsim* does *onecompsim* repeatedly 100 simulations times.

The function *graph* plots a graph for each of the *onecompsim*'s carried out in *fsim*.

The function *mean* finds the mean number of susceptible, infective, and recovered individuals at each interval using each of the simulations in *fsim*.

The *allgraph* function plots the mean values for each of the number of susceptible individuals, infective individuals and recovered individuals on the same set of axes.

The function *VEM1* in Figure A 2 gives estimates vaccine efficacy of average of 100 simulations using Model 1. But before executing this code we have to execute function *singlesim* and then *onecompsim* to generate epidemic paths. Similarly, *VEM2* and *VESM* presented by Figure A 3 and Figure A 4 give estimates vaccine efficacy using Model 2 and summary model.

## Figure A 1: R codes for generating epidemics process in a population partitioned into households

```
singlesim<-function(b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
  b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
  b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,b23v,
  b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,b44v,
  b45v,b51v,b52v,b53v,b54v,b55v,
  S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,
  S3v,I3v,R3v, S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v){
r<-0.20
tau<-1/r
a1u<-rbinom(1,S1u,1-exp(-tau*(b11u*(I1u+I1v)+b12u*(I2u+I2v)+
  b13u*(I3u+I3v)+b14u*(I4u+I4v)+b15u*(I5u+I5v))))
a1v<-rbinom(1,S1v,exp(-tau*(b11v*(I1u+I1v)+b12v*(I2u+I2v)+
  b13v*(I3u+I3v)+b14v*(I4u+I4v)+b15v*(I5u+I5v))))
b1u<-r*I1u
b1v<-r*I1v
a2u<-rbinom(1,S2u, 1-exp(-tau*(b21u*(I1u+I1v)+b22u*(I2u+I2v)+
  b23u*(I3u+I3v)+b24u*(I4u+I4v)+b25u*(I5u+I5v))))
a2v<-rbinom(1,S2v, 1-exp(-tau*(b21v*(I1u+I1v)+b22v*(I2u+I2v)+
  b23v*(I3u+I3v)+b24v*(I4u+I4v)+b25v*(I5u+I5v))))
b2u<-r*I2u
b2v<-r*I2v
a3u<-rbinom(1,S3u, 1-exp(-tau*(b31u*(I1u+I1v)+b32u*(I2u+I2v)+
  b33u*(I3u+I3v)+b34u*(I4u+I4v)+b35u*(I5u+I5v))))
```

```

a3v<-rbinom(1,S3v, 1-exp(-tau*(b31v*(I1u+I1v)+b32v*(I2u+I2v)+
b33v*(I3u+I3v)+b34v*(I4u+I4v)+b35v*(I5u+I5v))))
b3u<-r*I3u
b3v<-r*I3v
a4u<-rbinom(1,S4u,1-exp(-tau*(b41u*(I1u+I1v)+b42u*(I2u+I2v)+
b43u*(I3u+I3v)+b44u*(I4u+I4v)+b45u*(I5u+I5v))))
a4v<-rbinom(1,S4v, 1-exp(-tau*(b41v*(I1u+I1v)+b42v*(I2u+I2v)+
b43v*(I3u+I3v)+b44v*(I4u+I4v)+b45v*(I5u+I5v))))
b4u<-r*I4u
b4v<-r*I4v
a5u<-rbinom(1,S5u,1-exp(-tau*(b51u*(I1u+I1v)+b52u*(I2u+I2v)+
b53u*(I3u+I3v)+b54u*(I4u+I4v)+b55u*(I5u+I5v))))
a5v<-rbinom(1,S5v,1-exp(-tau*(b51v*(I1u+I1v)+b52v*(I2u+I2v)+
b53v*(I3u+I3v)+b54v*(I4u+I4v)+b55v*(I5u+I5v))))
b5u<-r*I5u
b5v<-r*I5v
d<-runif(1)
ran1u<-max(a1u*d,b1u*d)
ran1v<-max(a1v*d,b1v*d)
ran2u<-max(a2u*d,b2u*d)
ran2v<-max(a2v*d,b2v*d)
ran3u<-max(a3u*d,b3u*d)
ran3v<-max(a3v*d,b3v*d)
ran4u<-max(a4u*d,b4u*d)
ran4v<-max(a4v*d,b4v*d)
ran5u<-max(a5u*d,b5u*d)
ran5v<-max(a5v*d,b5v*d)

z<-c(S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,
S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v)

j<-ifelse(c(ran1u>a1u&ran1u<=a1u+b1u,ran1u>a1u&ran1u<=a1u+b1u,
ran1u>a1u&ran1u<=a1u+b1u,ran1v>a1v&ran1v<=a1v+b1v,
ran1v>a1v&ran1v<=a1v+b1v,ran1v>a1v&ran1v<=a1v+b1v,
ran2u>a2u&ran2u<=a2u+b2u,ran2u>a2u&ran2u<=a2u+b2u,
ran2u>a2u&ran2u<=a2u+b2u,ran2v>a2v&ran2v<=a2v+b2v,
ran2v>a2v&ran2v<=a2v+b2v,ran2v>a2v&ran2v<=a2v+b2v,
ran3u>a3u&ran3u<=a3u+b3u,ran3u>a3u&ran3u<=a3u+b3u,
ran3u>a3u&ran3u<=a3u+b3u,ran3v>a3v&ran3v<=a3v+b3v,
ran3v>a3v&ran3v<=a3v+b3v,ran3v>a3v&ran3v<=a3v+b3v,
ran4u>a4u&ran4u<=a4u+b4u,ran4u>a4u&ran4u<=a4u+b4u,
ran4u>a4u&ran4u<=a4u+b4u,ran4v>a4v&ran4v<=a4v+b4v,
ran4v>a4v&ran4v<=a4v+b4v,ran4v>a4v&ran4v<=a4v+b4v,
ran5u>a5u&ran5u<=a5u+b5u,ran5u>a5u&ran5u<=a5u+b5u,
ran5u>a5u&ran5u<=a5u+b5u,ran5v>a5v&ran5v<=a5v+b5v,
ran5v>a5v&ran5v<=a5v+b5v,ran5v>a5v&ran5v<=a5v+b5v),
c(S1u,I1u-1,R1u+1,S1v,I1v-1,R1v+1,S2u,I2u-1,R2u+1,S2v,I2v-1,
R2v+1,S3u,I3u-1,R3u+1,S3v,I3v-1,R3v+1,S4u,I4u-1,R4u+1,
S4v,I4v-1,R4v+1,S5u,I5u-1,R5u+1,S5v,I5v-1,R5v+1),z)

l<-ifelse(c(ran1u<=a1u,ran1u<=a1u,ran1u<=a1u,ran1v<=a1v,ran1v<=a1v,

```

```

ran1v<=a1v,ran2u<=a2u,ran2u<=a2u,ran2u<=a2u,ran2v<=a2v,
ran2v<=a2v,ran2v<=a2v,ran3u<=a3u,ran3u<=a3u,ran3u<=a3u,
ran3v<=a3v,ran3v<=a3v,ran3v<=a3v,ran4u<=a4u,ran4u<=a4u,
ran4u<=a4u,ran4v<=a4v,ran4v<=a4v,ran4v<=a4v,ran5u<=a5u,
ran5u<=a5u,ran5u<=a5u,ran5v<=a5v,ran5v<=a5v,ran5v<=a5v),
c(S1u-1,I1u+1,R1u,S1v-1,I1v+1,R1v,S2u-1,I2u+1,R2u,S2v-1,I2v+1,
R2v, S3u-1,I3u+1,R3u,S3v-1,I3v+1,R3v,S4u-1,I4u+1,R4u,S4v-1,
I4v+1,R4v,S5u-1,I5u+1,R5u,S5v-1,I5v+1,R5v),z)

x<-ifelse(c(ran1u<=a1u,ran1u<=a1u,ran1u<=a1u,ran1v<=a1v,ran1v<=a1v,
ran1v<=a1v,ran2u<=a2u,ran2u<=a2u,ran2u<=a2u,ran2v<=a2v,
ran2v<=a2v,ran2v<=a2v,ran3u<=a3u,ran3u<=a3u,ran3u<=a3u,
ran3v<=a3v,ran3v<=a3v,ran3v<=a3v,ran4u<=a4u,ran4u<=a4u,
ran4u<=a4u,ran4v<=a4v,ran4v<=a4v,ran4v<=a4v,ran5u<=a5u,
ran5u<=a5u,ran5u<=a5u,ran5v<=a5v,ran5v<=a5v,ran5v<=a5v),l,j)
q<-ifelse(j==z&l==z,z,x)
g<-ifelse(c(ran1u==0,ran1u==0,ran1u==0,ran1v==0,ran1v==0,ran1v==0,
ran2u==0,ran2u==0,ran2u==0,ran2v==0,ran2v==0,ran2v==0,
ran3u==0,ran3u==0,ran3u==0,ran3v==0,ran3v==0,ran3v==0,
ran4u==0,ran4u==0,ran4u==0,ran4v==0,ran4v==0,ran4v==0,
ran5u==0,ran5u==0,ran5u==0,ran5v==0,ran5v==0,ran5v==0),z,q)
g}

onecompsim<-function(Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,
I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,
R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,
b51u,b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,
b21v,b22v,b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,
b41v,b42v,b43v,b44v, b45v,b51v,b52v,b53v,b54v,b55v){
P<-array(0,c(Nsteps,30))
Z<-array(0,c(Nsteps,30))
Y<-array(0,c(Nsteps,30))
P[1,]<-c(S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,
S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v)
for(i in 2:Nsteps){
P[i,]<-singlesim(P[i-1,1],P[i-1,2],P[i-1,3],P[i-1,4],P[i-1,4],P[i-1,6],
P[i-1,7],P[i-1,8],P[i-1,9],P[i-1,10],P[i-1,11],P[i-1,12],
P[i-1,13],P[i-1,14],P[i-1,15],P[i-1,16],P[i-1,17],
P[i-1,18],P[i-1,19],P[i-1,20],P[i-1,21],P[i-1,22],
P[i-1,23],P[i-1,24],P[i-1,25],P[i-1,26],P[i-1,6],
P[i-1,28],P[i-1,29],P[i-1,30])}
P}

fisim<-function(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,
S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,
I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,
b51u,b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,

```

```

        b21v,b22v,b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,
        b41v,b42v,b43v,b44v,b45v,b51v,b52v,b53v,b54v,b55v){
Q<-array(0,c(Nsteps,30,Simulations))
for(i in 1:Simulations){
Q[, ,i]<-oncompsim(Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,
        I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,
        S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
        b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
        b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,
        b51u,b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,
        b21v,b22v,b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,
        b41v,b42v,b43v,b44v,b45v,b51v,b52v,b53v,b54v,b55v)}
print(Q)}

# a is for which part of three indicators:susceptible,
infective, removal in each household we want to plot,(a=1,...,30).
e.g, if we want to plot susceptible of HH 5 only then a=28,
for infective a=29, and for removal, a=30 and so on.

function(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,
        I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,
        S5u,I5u,R5u,S5v,I5v,R5v,b11u,b12u,b13u,b14u,b15u,b21u,
        b22u,b23u,b24u,b25u,b31u,b32u,b33u,b34u,b35u,b41u,b42u,
        b43u,b44u b45u,b51u,b52u,b53u,b54u,b55u,b11v,b12v,b13v,
        b14v,b15v,b21v,b22v,b23v,b24v,b25v,b31v,b32v,b33v,b34v,
        b35v,b41v,b42v,b43v,b44v,b45v,b51v,b52v,b53v,b54v,b55v,a){
plot(fisim(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,
        I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,
        R4v,S5u,I5u,R5u,S5v,I5v,R5v,
        b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
        b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
        b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
        b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
        b44v,b45v,b51v,b52v,b53v,b54v,b55v) [, a, 1] ,axes=FALSE,type="l" ,
        ylim=c(0,S5u+I5u+R5u))axis(2,0:(S5u+I5u+R5u))
axis(1)
for(i in 2:Simulations){
lines(fisim(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,
        R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,
        I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
        b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
        b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
        b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
        b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
        b44v,b45v,b51v,b52v,b53v,b54v,b55v) [,a,i])}
}
mean<-function(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,
        S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,
        I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
        b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
        b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,

```

```

        b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
        b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
        b44v,b45v,b51v,b52v,b53v,b54v,b55v,a){
Q<-1:Nsteps*0
for(i in 1:Nsteps){
Q[i]<-sum(fisim(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v, S2u,
I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,
S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
b44v,b45v,b51v,b52v,b53v,b54v,b55v)[i,a,])/Simulations}
Q}
meangraph<-function(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
b44v,b45v,b51v,b52v,b53v,b54v,b55v,a){
plot(mean(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
b44v,b45v,b51v,b52v,b53v,b54v,b55v,a),
type="l",col="red",ylim=c(0,S5v+I5v+R5v),xlab="Time",
ylab="Number",main="Number of S,I,R with respect to time")}

allgraph<-function(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
b44v,b45v,b51v,b52v,b53v,b54v,b55v){
plot(mean(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
b44v,b45v,b51v,b52v,b53v,b54v,b55v,28),
type="l",col="red",ylim=c(0,S5v+I5v+R5v),xlab="Time",
ylab="Number",main="Number of vaccinated

```

```

S,I,R with respect to time at HH 5")
lines(mean(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
  S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
  S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
  b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
  b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
  b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
  b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
  b44v,b45v,b51v,b52v,b53v,b54v,b55v,29),col="blue")
lines(mean(Simulations,Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
  S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
  S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
  b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
  b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
  b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
  b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
  b44v,b45v,b51v,b52v,b53v,b54v,b55v,30),col="green")}]

```

**Figure A 2: R codes for estimating vaccine efficacy using Model 1**

```

VEM1<-function(Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,
  S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,R3u,S3v,I3v,R3v,
  S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v,
  b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,b24u,b25u,
  b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u b45u,b51u,
  b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,b21v,b22v,
  b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,b42v,b43v,
  b44v,b45v,b51v,b52v,b53v,b54v,b55v){
  VE1<-numeric(100)
  VE2<-numeric(100)
  VE3<-numeric(100)
  VE4<-numeric(100)
  VE5<-numeric(100)
  for (j in 1:100){
    P<-array(0,c(Nsteps,30))
    Z<-array(0,c(Nsteps,30))
    Y<-array(0,c(Nsteps,30))
    P[1,]<-c(S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,S3u,I3u,
      R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,R5u,S5v,I5v,R5v)
    for(i in 2:Nsteps){
      P[i,]<-singlesim(P[i-1,1],P[i-1,2],P[i-1,3],P[i-1,4],P[i-1,4],P[i-1,6],
        P[i-1,7],P[i-1,8],P[i-1,9],P[i-1,10],P[i-1,11],P[i-1,12],
        P[i-1,13],P[i-1,14],P[i-1,15],P[i-1,16],P[i-1,17],P[i-1,18],
        P[i-1,19],P[i-1,20],P[i-1,21],P[i-1,22],P[i-1,23],P[i-1,24],
        P[i-1,25],P[i-1,26],P[i-1,6],P[i-1,28],P[i-1,29],P[i-1,30])}

    f1<-1/1
    f2<-1/2
    f3<-1/3
    f4<-2/4
    f5<-3/5
    AR1u<-0

```

```

AR1v<-P [Nsteps,6] /1
AR2u<-P [Nsteps,9] /1
AR2v<-P [Nsteps,12] /1
AR3u<-P [Nsteps,15] /2
AR3v<-P [Nsteps,18] /1
AR4u<-P [Nsteps,21] /2
AR4v<-P [Nsteps,24] /2
AR5u<-P [Nsteps,27] /2
AR5v<-P [Nsteps,30] /3

phi1u<-1*b11u*((1-f1)*AR1u+f1*AR1v)+2*b12u*((1-f2)*AR2u+f2*AR2v)+
3*b13u*((1-f3)*AR3u+f3*AR3v)+4*b14u*((1-f4)*AR4u+f4*AR4v)+
5*b15u*((1-f5)*AR5u+f5*AR5v)
phi2u<-1*b21u*((1-f1)*AR1u+f1*AR1v)+2*b22u*((1-f2)*AR2u+f2*AR2v)+
3*b23u*((1-f3)*AR3u+f3*AR3v)+4*b24u*((1-f4)*AR4u+f4*AR4v)+
5*b25u*((1-f5)*AR5u+f5*AR5v)
phi3u<-1*b31u*((1-f1)*AR1u+f1*AR1v)+2*b32u*((1-f2)*AR2u+f2*AR2v)+
3*b33u*((1-f3)*AR3u+f3*AR3v)+4*b34u*((1-f4)*AR4u+f4*AR4v)+
5*b35u*((1-f5)*AR5u+f5*AR5v)
phi4u<-1*b41u*((1-f1)*AR1u+f1*AR1v)+2*b42u*((1-f2)*AR2u+f2*AR2v)+
3*b43u*((1-f3)*AR3u+f3*AR3v)+4*b44u*((1-f4)*AR4u+f4*AR4v)+
5*b45u*((1-f5)*AR5u+f5*AR5v)
phi5u<-1*b51u*((1-f1)*AR1u+f1*AR1v)+2*b52u*((1-f2)*AR2u+f2*AR2v)+
3*b53u*((1-f3)*AR3u+f3*AR3v)+4*b54u*((1-f4)*AR4u+f4*AR4v)+
5*b55u*((1-f5)*AR5u+f5*AR5v)

phi1v<-1*b11v*((1-f1)*AR1u+f1*AR1v)+2*b12v*((1-f2)*AR2u+f2*AR2v)+
3*b13v*((1-f3)*AR3u+f3*AR3v)+4*b14v*((1-f4)*AR4u+f4*AR4v)+
5*b15v*((1-f5)*AR5u+f5*AR5v)
phi2v<-1*b21v*((1-f1)*AR1u+f1*AR1v)+n2*b22v*((1-f2)*AR2u+f2*AR2v)+
3*b23v*((1-f3)*AR3u+f3*AR3v)+4*b24v*((1-f4)*AR4u+f4*AR4v)+
5*b25v*((1-f5)*AR5u+f5*AR5v)
phi3v<-1*b31v*((1-f1)*AR1u+f1*AR1v)+2*b32v*((1-f2)*AR2u+f2*AR2v)+
3*b33v*((1-f3)*AR3u+f3*AR3v)+4*b34v*((1-f4)*AR4u+f4*AR4v)+
5*b35v*((1-f5)*AR5u+f5*AR5v)
phi4v<-1*b41v*((1-f1)*AR1u+f1*AR1v)+2*b42v*((1-f2)*AR2u+f2*AR2v)+
3*b43v*((1-f3)*AR3u+f3*AR3v)+4*b44v*((1-f4)*AR4u+f4*AR4v)+
5*b45v*((1-f5)*AR5u+f5*AR5v)
phi5v<-1*b51v*((1-f1)*AR1u+f1*AR1v)+n2*b52v*((1-f2)*AR2u+f2*AR2v)+
3*b53v*((1-f3)*AR3u+f3*AR3v)+4*b54v*((1-f4)*AR4u+f4*AR4v)+
5*b55v*((1-f5)*AR5u+f5*AR5v)

tau<-1/r
AR11u<- 1-exp(-tau*phi1u)
AR11v<-1-exp(-tau*phi1v)
AR22u<- 1-exp(-tau*phi2u)
AR22v<-1-exp(-tau*phi2v)
AR33u<- 1-exp(-tau*phi3u)
AR33v<-1-exp(-tau*phi3v)
AR44u<- 1-exp(-tau*phi4u)
AR44v<-1-exp(-tau*phi4v)

```

```

AR55u<- 1-exp(-tau*phi5u)
AR55v<-1-exp(-tau*phi5v)
ARF<-c(AR11u,AR11v,AR22u,AR22v,AR33u,AR33v,AR44u,AR44v,AR55u,AR55v)
#print(ARF)
VE1[j]<-1-(log(1-AR11v)/log(1-AR11u))
VE2[j]<-1-(log(1-AR22v)/log(1-AR22u))
VE3[j]<-1-(log(1-AR33v)/log(1-AR33u))
VE4[j]<-1-(log(1-AR44v)/log(1-AR44u))
VE5[j]<-1-(log(1-AR55v)/log(1-AR55u))
}
ve1<-sum(VE1)/100
ve2<-sum(VE2)/100
ve3<-sum(VE3)/100
ve4<-sum(VE4)/100
ve5<-sum(VE5)/100
se1<-sqrt(var(VE1))
se2<-sqrt(var(VE2))
se3<-sqrt(var(VE3))
se4<-sqrt(var(VE4))
se5<-sqrt(var(VE5))
SE<-c(se1,se2,se3,se4,se5)
VE<-c(ve1,ve2,ve3, ve4, ve5)
print(VE)
print(SE)
}

```

**Figure A 3: R codes for estimating vaccine efficacy using Model 2**

```

VEM2<-function(Nsteps,S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,
S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,S5u,I5u,
R5u,S5v,I5v,R5v,b11u,b12u,b13u,b14u,b15u,b21u,b22u,b23u,
b24u,b25u,b31u,b32u,b33u,b34u,b35u,b41u,b42u,b43u,b44u,
b45u,b51u,b52u,b53u,b54u,b55u,b11v,b12v,b13v,b14v,b15v,
b21v,b22v,b23v,b24v,b25v,b31v,b32v,b33v,b34v,b35v,b41v,
b42v,b43v,b44v,b45v,b51v,b52v,b53v,b54v,b55v){
VE1<-numeric(100)
VE2<-numeric(100)
VE3<-numeric(100)
VE4<-numeric(100)
VE5<-numeric(100)
for (j in 1:100){
P<-array(0,c(Nsteps,30))
Z<-array(0,c(Nsteps,30))
Y<-array(0,c(Nsteps,30))
P[1,]<-c(S1u,I1u,R1u,S1v,I1v,R1v,S2u,I2u,R2u,S2v,I2v,R2v,
S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,
S5u,I5u,R5u,S5v,I5v,R5v)
for(i in 2:Nsteps){
P[i,]<-singlesim(P[i-1,1],P[i-1,2],P[i-1,3],P[i-1,4],P[i-1,4],P[i-1,6],
P[i-1,7],P[i-1,8],P[i-1,9],P[i-1,10],P[i-1,11],P[i-1,12],

```

P[i-1,13],P[i-1,14],P[i-1,15],P[i-1,16],P[i-1,17],P[i-1,18],  
P[i-1,19],P[i-1,20],P[i-1,21],P[i-1,22],P[i-1,23],P[i-1,24],  
P[i-1,25],P[i-1,26],P[i-1,6],P[i-1,28],P[i-1,29],P[i-1,30])}

f1<-n1v/n1  
f2<-n2v/n2  
f3<-n3v/n3  
f4<-n4v/n4  
f5<-n5v/n5  
alpha<-0.6

AR1u<-0  
AR1v<-(P[Nsteps,6]-alpha\*1)/1\*(1-alpha)  
AR2u<-P[Nsteps,9]/1  
AR2v<-(P[Nsteps,12]-alpha\*1)/1\*(1-alpha)  
AR3u<-P[Nsteps,15]/1  
AR3v<-(P[Nsteps,18]-alpha\*2)/2\*(1-alpha)  
AR4u<-P[Nsteps,21]/2  
AR4v<-(P[Nsteps,24]-alpha\*2)/2\*(1-alpha)  
AR5u<-P[Nsteps,27]/2  
AR5v<-(P[Nsteps,30]-alpha\*3)/3\*(1-alpha)

phi1u<-1\*b11u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b12u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b13u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b14u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b15u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi2u<-1\*b21u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b22u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b23u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b24u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b25u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi3u<-1\*b31u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b32u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b33u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b34u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b35u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi4u<-1\*b41u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b42u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b43u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b44u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b45u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi5u<-1\*b51u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b52u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b53u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b54u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b55u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)

phi1v<-1\*b11u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b12u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b13u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b14u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b15u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi2v<-1\*b21u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b22u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b23u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b24u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b25u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi3v<-1\*b31u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b32u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b33u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b34u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b35u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi4v<-1\*b41u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b42u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b43u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b44u\*  
\*((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b45u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)  
phi5v<-1\*b51u\*((1-f1)\*AR1u+(1-alpha)\*f1\*AR1v)+2\*b52u\*((1-f2)\*AR2u+  
(1-alpha)\*f2\*AR2v)+3\*b53u\*((1-f3)\*AR3u+(1-alpha)\*f3\*AR3v)+4\*b54u\*  
((1-f4)\*AR4u+(1-alpha)\*f4\*AR4v)+5\*b55u\*((1-f5)\*AR5u+(1-alpha)\*f5\*AR5v)

```

AR11u<- 1-exp(-tau*phi1u)
AR11v<-(1-alpha)*(1-exp(-tau*phi1v))
AR22u<- 1-exp(-tau*phi2u)
AR22v<-(1-alpha)*(1-exp(-tau*phi2v))
AR33u<- 1-exp(-tau*phi3u)
AR33v<-(1-alpha)*(1-exp(-tau*phi3v))
AR44u<- 1-exp(-tau*phi4u)
AR44v<-(1-alpha)*(1-exp(-tau*phi4v))
AR55u<- 1-exp(-tau*phi5u)
AR55v<-(1-alpha)*(1-exp(-tau*phi5v))
VE1[j]<-1-(AR11v/AR11u)
VE2[j]<-1-(AR22v/AR22u)
VE3[j]<-1-(AR33v/AR33u)
VE4[j]<-1-(AR44v/AR44u)
VE5[j]<-1-(AR55v/AR55u)}

ve1<-sum(VE1)/100
ve2<-sum(VE2)/100
ve3<-sum(VE3)/100
ve4<-sum(VE4)/100
ve5<-sum(VE5)/100
se1<-sqrt(var(VE1))
se2<-sqrt(var(VE2))
se3<-sqrt(var(VE3))
se4<-sqrt(var(VE4))
se5<-sqrt(var(VE5))
SE<-c(se1,se2,se3,se4,se5)
VE<-c(ve1,ve2,ve3, ve4, ve5)

print(VE)
print(SE)
}

```

**Figure A 4: R codes for estimating vaccine efficacy using Summary Model**

```

VESM<-function(Nsteps,S1u,I1u,R1u,S1v,I1v,R1v, S2u,I2u,R2u,S2v,I2v,R2v,
S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,
S5u,I5u,R5u,S5v,I5v,R5v,b11u,b12u,b13u,b14u,b15u,b21u,
b22u,b23u,b24u,b25u,b31u,b32u,b33u,b34u,b35u,b41u,b42u,
b43u,b44u,b45u,b51u,b52u,b53u,b54u,b55u,b11v1,b12v1,b13v1,
b14v1,b15v1,b21v1,b22v1,b23v1,b24v1,b25v1,b31v1,b32v1,
b33v1,b34v1,b35v1,b41v1,b42v1,b43v1,b44v1,b45v1,b51v1,
b52v1,b53v1,b54v1,b55v1,b11v2,b12v2,b13v2,
b14v2,b15v2,b21v2,b22v2,b23v2,b24v2,b25v2,b31v2,b32v2,
b33v2,b34v2,b35v2,b41v2,b42v2,b43v2,b44v2,b45v2,b51v2,
b52v2,b53v2,b54v2,b55v2){
VE1<-numeric(100)
VE2<-numeric(100)
VE3<-numeric(100)

```

```

VE4<-numeric(100)
VE5<-numeric(100)
for(j in 1:100){
P<-array(0,c(Nsteps,30))
Z<-array(0,c(Nsteps,30))
Y<-array(0,c(Nsteps,30))
P[1,]<-c(S1u,I1u,R1u,S1v,I1v,R1v, S2u,I2u,R2u,S2v,I2v,R2v,
        S3u,I3u,R3u,S3v,I3v,R3v,S4u,I4u,R4u,S4v,I4v,R4v,
        S5u,I5u,R5u,S5v,I5v,R5v)
for(i in 2:Nsteps){
P[i,]<-singlesim(P[i-1,1],P[i-1,2],P[i-1,3],P[i-1,4],P[i-1,4],P[i-1,6],
                P[i-1,7],P[i-1,8],P[i-1,9],P[i-1,10],P[i-1,11],P[i-1,12],
                P[i-1,13],P[i-1,14],P[i-1,15],P[i-1,16],P[i-1,17],P[i-1,18],
                P[i-1,19],P[i-1,20],P[i-1,21],P[i-1,22],P[i-1,23],P[i-1,24],
                P[i-1,25],P[i-1,26],P[i-1,6],P[i-1,28],P[i-1,29],P[i-1,30])}

lambda<-0.6
n1v1<-1*lambda
n1v2<-1*(1-lambda)
n2v1<-1*lambda
n2v2<-1*(1-lambda)
n3v1<-2*lambda
n3v2<-2*(1-lambda)
n4v1<-2*lambda
n4v2<-2*(1-lambda)
n5v1<-3*lambda
n5v2<-3*(1-lambda)
r<-0.20
tau<-1/r
f1<-1/1
f2<-1/2
f3<-1/3
f4<-2/4
f5<-3/5

AR1u<-0
AR1v1<-P[Nsteps,6]*lambda/n1v1
AR1v2<-P[Nsteps,6]*(1-lambda)/n1v2
AR2u<-P[Nsteps,9]/1
AR2v1<-P[Nsteps,12]*lambda/n2v1
AR2v2<-P[Nsteps,12]*(1-lambda)/n2v1
AR3u<-P[Nsteps,15]/2
AR3v1<-P[Nsteps,18]*lambda/n3v1
AR3v2<-P[Nsteps,18]*(1-lambda)/n3v2
AR4u<-P[Nsteps,21]/2
AR4v1<-P[Nsteps,24]*lambda/n4v1
AR4v2<-P[Nsteps,24]*(1-lambda)/n4v2
AR5u<-P[Nsteps,27]/2
AR5v1<-P[Nsteps,30]*(1-lambda)/n5v1
AR5v2<-P[Nsteps,30]*(1-lambda)/n5v2

phi1u<-1*b11u*((1-f1)*AR1u+lambda*f1*AR1v1+(1-lambda)*f1*AR1v2)+2*b12u*((1-f2)

```

$$\begin{aligned}
& *AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b13u*((1-f3)*AR3u+f3*\lambda* \\
& AR3v1+(1-\lambda)*f3*AR3v2)+4*b14u*((1-f4)*AR4u+\lambda*f4*AR4v1+(1-\lambda)* \\
& *f4*AR4v2)+5*b15u*((1-f5)*AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{2u} & <-1*b21u*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+2*b22u*((1-f2) \\
& *AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b23u*((1-f3)*AR3u+f3*\lambda* \\
& *AR3v1+(1-\lambda)*f3*AR3v2)+4*b24u*((1-f4)*AR4u+\lambda*f4*AR4v1+(1-\lambda)* \\
& f4*AR4v2)+5*b25u*((1-f5)*AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{3u} & <-1*b31u*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+2*b32u*((1-f2) \\
& *AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b33u*((1-f3)*AR3u+f3*\lambda* \\
& *AR3v1+(1-\lambda)*f3*AR3v2)+4*b34u*((1-f4)*AR4u+\lambda*f4*AR4v1+(1-\lambda)* \\
& *f4*AR4v2)+5*b35u*((1-f5)*AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{4u} & <-1*b41u*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+2*b42u* \\
& ((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b43u*((1-f3)* \\
& AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+4*b44u*((1-f4)*AR4u+ \\
& \lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+5*b45u*((1-f5)*AR5u+\lambda* \\
& *f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{5u} & <-1*b51u*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+ \\
& 2*b52u*((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b53u* \\
& ((1-f3)*AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+4*b44u*((1-f4)*AR4u \\
& +\lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+5*b55u*((1-f5)*AR5u+\lambda*f5 \\
& *AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{1v1} & <-1*b11v1*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+ \\
& 2*b12v1*((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b13v1* \\
& ((1-f3)*AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+4*b14v1*((1-f4) \\
& *AR4u+\lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+5*b15v1*((1-f5) \\
& *AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{2v1} & <-1*b21v1*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+ \\
& 2*b22v1*((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+ \\
& 3*b23v1*((1-f3)*AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+ \\
& 4*b24v1*((1-f4)*AR4u+\lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+ \\
& 5*b25v1*((1-f5)*AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{3v1} & <-1*b31v1*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+ \\
& 2*b32v1*((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b33v1 \\
& *((1-f3)*AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+4*b34v1*((1-f4) \\
& *AR4u+\lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+5*b35v1*((1-f5)*AR5u+ \\
& \lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{4v1} & <-1*b41v1*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+ \\
& 2*b42v1*((1-f2)*AR2u+\lambda*f2*AR2v1+(1-\lambda)*f2*AR2v2)+3*b43v1* \\
& ((1-f3)*AR3u+f3*\lambda*AR3v1+(1-\lambda)*f3*AR3v2)+4*b44v1* \\
& ((1-f4)*AR4u+\lambda*f4*AR4v1+(1-\lambda)*f4*AR4v2)+5*b45v1*((1-f5) \\
& *AR5u+\lambda*f5*AR5v1+(1-\lambda)*f5*AR5v2) \\
\\
\phi_{5v1} & <-1*b51v1*((1-f1)*AR1u+\lambda*f1*AR1v1+(1-\lambda)*f1*AR1v2)+
\end{aligned}$$

$$\begin{aligned}
& 2*b52v1*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2) \\
& +3*b53v1*((1-f3)*AR3u+f3*lmbda*AR3v1+(1-lmbda)*f3*AR3v2) \\
& +4*b54v1*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b55v1*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{phi1v2} <- 1*b11v2*((1-f1)*AR1u+lmbda*f1*AR1v1+(1-lmbda)*f1*AR1v2)+ \\
& 2*b12v2*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2)+ \\
& 3*b13v2*((1-f3)*AR3u+f3*lmbda*AR3v1+(1-lmbda)*f3*AR3v2)+ \\
& 4*b14v2*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b15v2*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{phi2v2} <- 1*b21v2*((1-f1)*AR1u+lmbda*f1*AR1v1+(1-lmbda)*f1*AR1v2)+ \\
& 2*b22v2*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2)+ \\
& 3*b23v2*((1-f3)*AR3u+f3*lmbda*AR3v1+(1-lmbda)*f3*AR3v2)+ \\
& 4*b24v2*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b25v2*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{phi3v2} <- 1*b31v2*((1-f1)*AR1u+lmbda*f1*AR1v1+(1-lmbda)*f1*AR1v2)+ \\
& 2*b32v2*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2)+ \\
& 3*b33v2*((1-f3)*AR3u+f3*lmbda*AR3v2+(1-lmbda)*f3*AR3v2)+ \\
& 4*b34v2*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b35v2*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{phi4v2} <- 1*b41v2*((1-f1)*AR1u+lmbda*f1*AR1v1+(1-lmbda)*f1*AR1v2)+ \\
& 2*b42v2*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2)+ \\
& 3*b43v2*((1-f3)*AR3u+f3*lmbda*AR3v1+(1-lmbda)*f3*AR3v2)+ \\
& 4*b44v2*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b45v2*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{phi5v2} <- 1*b51v2*((1-f1)*AR1u+lmbda*f1*AR1v1+(1-lmbda)*f1*AR1v2)+ \\
& 2*b52v2*((1-f2)*AR2u+lmbda*f2*AR2v1+(1-lmbda)*f2*AR2v2)+ \\
& 3*b53v2*((1-f3)*AR3u+f3*lmbda*AR3v1+(1-lmbda)*f3*AR3v2)+ \\
& 4*b54v2*((1-f4)*AR4u+lmbda*f4*AR4v1+(1-lmbda)*f4*AR4v2)+ \\
& 5*b55v2*((1-f5)*AR5u+lmbda*f5*AR5v1+(1-lmbda)*f5*AR5v2) \\
\\
\text{AR11u} <- 1-\exp(-\tau*\text{phi1u}) \\
\text{AR11v1} <- 1-\exp(-\tau*\text{phi1v1}) \\
\text{AR11v2} <- 1-\exp(-\tau*\text{phi1v2}) \\
\text{AR22u} <- 1-\exp(-\tau*\text{phi2u}) \\
\text{AR22v1} <- 1-\exp(-\tau*\text{phi2v1}) \\
\text{AR22v2} <- 1-\exp(-\tau*\text{phi2v2}) \\
\text{AR33u} <- 1-\exp(-\tau*\text{phi3u}) \\
\text{AR33v1} <- 1-\exp(-\tau*\text{phi3v1}) \\
\text{AR33v2} <- 1-\exp(-\tau*\text{phi2v2}) \\
\text{AR44u} <- 1-\exp(-\tau*\text{phi4u}) \\
\text{AR44v1} <- 1-\exp(-\tau*\text{phi4v1}) \\
\text{AR44v2} <- 1-\exp(-\tau*\text{phi4v2}) \\
\text{AR55u} <- 1-\exp(-\tau*\text{phi5u}) \\
\text{AR55v1} <- 1-\exp(-\tau*\text{phi5v1}) \\
\text{AR55v2} <- 1-\exp(-\tau*\text{phi5v2}) \\
\text{AR11v} <- lmbda*\log(1-\text{AR11v1})+(1-lmbda)*\log(1-\text{AR11v2}) \\
\text{AR22v} <- lmbda*\log(1-\text{AR22v1})+(1-lmbda)*\log(1-\text{AR22v2})
\end{aligned}$$

```

AR33v<-lambda*log(1-AR33v1)+(1-lambda)*log(1-AR33v2)
AR44v<-lambda*log(1-AR44v1)+(1-lambda)*log(1-AR44v2)
AR55v<-lambda*log(1-AR55v1)+(1-lambda)*log(1-AR55v2)
VE1[j]<-1-AR11v/log(1-AR11u)
VE2[j]<-1-AR22v/log(1-AR22u)
VE3[j]<-1-AR33v/log(1-AR33u)
VE4[j]<-1-AR44v/log(1-AR44u)
VE5[j]<-1-AR55v/log(1-AR55u)
}
ve1<-sum(VE1)/100
ve2<-sum(VE2)/100
ve3<-sum(VE3)/100
ve4<-sum(VE4)/100
ve5<-sum(VE5)/100
se1<-sqrt(var(VE1))
se2<-sqrt(var(VE2))
se3<-sqrt(var(VE3))
se4<-sqrt(var(VE4))
se5<-sqrt(var(VE5))
SE<-c(se1,se2,se3,se4,se5)
VE<-c(ve1,ve2,ve3, ve4, ve5)
print(VE)
print(SE)
}

```