Causal Vaccine Effects on Binary Post-infection Outcomes

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Abstract

An important component of prophylactic vaccination concerns effects on post-infection outcomes such as disease morbidity or mortality, or secondary transmission to others. As a result, evaluation of many vaccine effects condition on being infected. Conditioning on an event that occurs post-treatment, in our case infection subsequent to assignment to vaccine or control, can result in selection bias. Moreover, because the set of individuals who would become infected if vaccinated is likely not identical to the set of those who would become infected if given control, comparisons that condition on infection do not have a causal interpretation. In this paper we consider identifiability, estimation, and testing of causal vaccine effects on binary post-infection outcomes. Employing the Frangakis and Rubin (2002) principal stratification framework, we define a post-infection causal vaccine efficacy estimand in individuals who would be infected regardless of treatment assignment. The estimand is shown not to be identifiable under the standard assumptions of SUTVA, monotonicity, and independence of treatment assignment. Thus a variety of selection models are developed which identify the estimand. Closed form maximum likelihood estimates are derived under several of these models, including the models which assume maximum possible levels of positive and negative selection bias. Tests for harmful or beneficial causal vaccine effects on binary post-infection outcomes are also developed. The methodology is used to evaluate post-infection vaccine effects in a clinical trial of a rotavirus vaccine candidate and in a field study of a pertussis vaccine.

Keywords: Infectious diseases, Maximum likelihood, Principal stratification, Sensitivity analysis

1 INTRODUCTION

The success of vaccines in reducing the burden of infectious diseases is one of the great achievements in public health. The goal of vaccination is often not to prevent infection, but rather to prevent or ameliorate disease (Clements-Mann 1998). Therefore, many questions of interest in understanding the effects of prophylactic vaccines concern post-infection outcomes, such as severe disease, death, or transmission to others. For example, Kendrick and Eldering (1939) described less severe disease in children inoculated with pertussis vaccine (see also Fine and Clarkson, 1987). More recently, Préziosi and Halloran have estimated the beneficial effects of pertussis vaccination on reducing transmission to others (2003a, see also Halloran, Préziosi, and Chu 2003) and severe disease (2003b) in breakthrough cases. Varicella (chickenpox) vaccination has also been shown to lessen disease severity in individuals that become infected (Vazquez et al. 2001). Assessing candidate HIV vaccine effects on progression to AIDS through both clinical and surrogate post-infection endpoints (Gilbert et al. 2003a) as well as on transmission (Longini, Datta, and Halloran 1996) is crucial for evaluating their potential public health benefit.

Typical analyses of vaccine effects on post-infection endpoints entail including either all individuals under study or only those who have become infected. The former approach enjoys the statistical validity associated with an intent-to-treat (ITT) analysis and provides an assessment
of the overall benefit of vaccination. However such an approach does not distinguish vaccine effects on susceptibility from effects on the post-infection endpoints of interest and may be less sensitive in detecting post-infection vaccine effects than an analysis that conditions on infection.

For these reasons, as an alternative to an ITT-based approach, one might consider an analysis that contrasts post-infection endpoint rates in infected vaccinees and infected controls only. For example, Préziosi and Halloran (2003b) analyzed data from a pertussis vaccine field study in Niakhar, Senegal from January 1 to December 31, 1993, in children aged six months through eight years. During that one year, there were 3845 and 1020 person-years at risk in the vaccinated and unvaccinated children (Préziosi, pers. comm.). Of 548 cases in the vaccinated group, 176 were severe, and of 206 cases in the unvaccinated group, 129 were severe. Préziosi and Halloran (2003b) defined an estimator of vaccine efficacy against severe disease conditional on being infected and having disease as

\[
\hat{VE}_P = 1 - \frac{\text{no. severe vaccinated cases}}{\text{no. vaccinated cases}} \times \frac{\text{no. severe unvaccinated cases}}{\text{no. unvaccinated cases}}.
\]  

(1)

The analysis yields \(\hat{VE}_P = 0.49\), (95% CI 0.40,0.56).

Vesikari et al. (1990) provide a second motivating example in their analysis of a randomized, double-blinded, placebo controlled trial of a Rhesus rotavirus candidate vaccine. The trial was conducted in children two to five months of age from 1985-1987 in Finland with 100 children randomized to each arm. The effect of the vaccine on the clinical course of infection was considered by comparing severity (mild, moderate, or severe) between vaccinees and placebo-treated individuals with confirmed Rotavirus diarrhea using Fisher’s exact test. If severe and moderately severe cases were combined, the approach of Préziosi and Halloran above could also be employed. In particular, of 10 cases in the vaccinated group, five were severe or moderately severe, and of 16 cases in the placebo group, 13 were severe or moderately severe, such that using (1) we have \(\hat{VE}_P = 0.38\), (95% CI -0.11,0.74).

At first glance, both vaccines seem to be protective against severe disease. However, conditioning on an event, such as infection, that occurs subsequent to receipt of vaccine or control could result in selection bias (Halloran and Struchiner 1995). Moreover, because the set of individuals who would become infected if vaccinated is likely not identical to the set of those who would become infected if given control, comparisons that condition on infection do not have a causal interpretation (Frangakis and Rubin 2002). For example, a vaccine might protect only people with strong immune systems, so that infected vaccinees tend to have weaker immune systems on average compared to infected controls. Resulting comparisons of disease severity between infected vaccinees and infected controls could then lead to the false conclusion that vaccination has harmful post-infection effects due solely to the selective effect of the vaccine on
susceptibility to infection (Hudgens et al., 2003; Gilbert et al., 2003b).

Different methods are used to adjust analyses for post-treatment variables such as infection (Robins and Greenland 1992, 1994; Rosenbaum 1984). Our approach is based on an extension of the potential outcomes framework for estimating causal effects (Rubin 1978; Holland 1986). In particular, Frangakis and Rubin (2002) and Rubin (2000) propose a method to adjust for post-treatment variables, called principal stratification, that stratifies on the joint potential post-treatment variables under each of the treatments being considered. The causal effects of one treatment compared to the other on a main outcome of interest are defined within each of these principal strata and are called principal effects. In studying HIV vaccines, Hudgens, Hoering, and Self (2003) and Gilbert, Bosch, and Hudgens (2003b) adopted the principal stratification approach to examine HIV vaccine effects on the continuous post-infection outcome viral load, where the basic principal strata were defined by the joint potential infection outcomes under vaccine and control. In this paper we employ a similar approach in considering identifiability, estimation, and testing of causal vaccine effects on binary post-infection outcomes. In section 2 we define the causal estimand of interest. In section 3, the estimand is shown to not be identifiable without further assumptions regarding the selective mechanism of the vaccine. In section 4 a variety of selection models are developed which identify the estimand. Closed form maximum likelihood estimates are derived under several of these models, including the models which assume maximum possible levels of positive and negative selection bias. We also demonstrate that the estimator given in (1) does not have a causal interpretation unless assumptions are made concerning post-treatment selection bias. Finally, in section 5, we develop tests for harmful or beneficial causal vaccine effects on binary post-infection outcomes. Using these approaches, we analyze the studies of the rotavirus vaccine candidate and the pertussis vaccine.

2 DEFINING VACCINE EFFECTS

Consider a group of individuals \( i = 1, \ldots, n \) where each potentially receives either vaccine or placebo. Following the notation of Rubin (1990a) and similar to the development in Gilbert et al. (2003b), let the vector \( Z = (Z_1, \ldots, Z_n) \) denote the vector of treatment assignments for \( n \) individuals with \( Z_i = v \) if the \( i^{th} \) individual is assigned vaccine and \( Z_i = p \) if the \( i^{th} \) individual is assigned placebo or control. In this paper, assignment is assumed to be equivalent to receipt.

Denote the potential infection outcome of the \( i^{th} \) individual if the study group were assigned \( Z \) as \( S_i(Z) \), where \( S_i(Z) = 0 \) if uninfected and \( S_i(Z) = 1 \) if infected. Then \( \mathbf{S}(Z) \) is the \( n \)-vector of potential infection outcomes if the assignment vector were \( Z \). For simplicity, we will suppress the dependence on \( Z \) by letting \( \mathbf{S} = \mathbf{S}(Z) \). The focus of this work is on evaluating the causal effect of vaccine on a binary outcome \( Y \) that occurs after an individual becomes infected, such
as transmission to another individual, severe disease, or death. Formally, if \( S_i(Z) = 1 \), we define the potential post-infection outcome \( Y_i(Z, S) = 1 \) if the \( i^{th} \) individual would have the worse, i.e. more severe, post-infection outcome of interest given \((Z, S)\), and \( Y_i(Z, S) = 0 \) otherwise. If an individual’s potential infection outcome for an assignment is uninfected, (i.e., \( S_i(Z) = 0 \)), then \( Y_i(Z, S) \) is undefined and denoted by *.

We assume that the potential outcomes for each individual \( i \) are independent of the treatment assignment of other individuals, known also as the assumption of no interference between units (Cox 1958). This assumption is obviously violated in many infectious disease settings (Rubin 1978, 1990a; Halloran and Struchiner 1995). However, we make this assumption to clarify the problem in its simplest form. We also assume there are only two possible infection outcomes and, at most, two possible post-infection outcomes. These two assumptions are expressed formally as follows:

**Assumption 1 Stable Unit Treatment Value Assumption (SUTVA) (Rubin 1978; Angrist, Imbens and Rubin 1996).**

*For any two treatment assignments \( Z = (Z_1, \ldots, Z_n) \) and \( Z' = (Z'_1, \ldots, Z'_n) \):

a. If \( Z_i = Z'_i \), then \( S_i(Z) = S_i(Z') \).

b. If \( Z_i = Z'_i \) and \( S_i = S'_i \), then \( Y_i(Z, S) = Y_i(Z', S') \).*

The SUTVA assumption allows us to write \( S_i(Z_i) \) and \( Y_i(Z_i, S_i(Z_i)) \) rather than \( S_i(Z), Y_i(Z, S) \). Under SUTVA, \( S_i(Z_i) = S_i(Z'_i) \) whenever \( Z_i = Z'_i \), so we can write \( Y_i(Z_i) \) instead of \( Y_i(Z_i, S_i(Z_i)) \). Finally, we let \( S_i^{obs} \) denote the observed infection outcome \( S_i(v) \) or \( S_i(p) \), depending on treatment assignment, and analogously \( Y_i^{obs} \) for the observed post-infection outcome.

We define a *basic principal stratification \( P_0 \) according to the joint potential infection outcomes \( S^{fb} = (S(v), S(p)) \) (Frangakis and Rubin 2002). Table 1 summarizes the four possible strata defined by the joint potential infection outcomes, \((S(v), S(p))\), and the strata defined by the joint potential post-infection outcomes within those strata, \((Y(v), Y(p))\). The four possible basic principal strata are composed of immune (not infected under both vaccine and placebo), harmed (infected under vaccine but not placebo), protected (infected under placebo but not vaccine), and doomed individuals (infected under both vaccine and placebo). Since membership in a basic principal stratum is not affected by whether an individual is actually assigned vaccine or placebo, the strata can be used in the same way as pre-treatment covariates, with causal post-infection vaccine effects defined within a basic principal stratum \( S^{fb} \).

In general, causal effects are defined in terms of potential outcomes. From Table 1, we see that the doomed basic principal stratum, \( S^{fb} = (1,1) \), is the only stratum in which both potential post-infection endpoints, and thus their joint distribution, are defined. For this reason,
in our setting, defining post-infection causal vaccine effects makes sense only in the doomed basic principal stratum, $S^{Rb} = (1, 1)$. Thus, following Rubin (2000a), two population-level causal estimands can be validly assessed: (1) the effect of vaccine on infection ($S$) for all participants, and (2) the effect of vaccine on the binary post-infection outcome ($Y$) for those participants who would be infected under both treatment assignments.

To define the first causal estinamd, the individual causal effect of vaccination on infection in individual $i$ might be expressed as a difference or ratio (Rubin, 1990b)

$$S_i(p) - S_i(v), \text{ or } S_i(v)/S_i(p).$$

Vaccine efficacy is typically expressed in terms of a relative risk difference, so that, similar to Struchiner and Halloran (1996), we define the individual causal effect of vaccination on infection as

$$\text{VE}_{S_i} = \frac{S_i(p) - S_i(v)}{S_i(p)} = 1 - \frac{S_i(v)}{S_i(p)},$$

with the convention that $\text{VE}_{S_i} = 0$ when $S_i(v) = S_i(p)$. Recall we assume there is perfect compliance, i.e., assignment to vaccine (control) is equivalent to receipt of vaccine (control). Without this assumption, (2) and (3) would be causal effects of assignment to vaccine. The ramifications of non-compliance on the assessment of causal vaccine effects will not be considered here.

Since for any individual at least one potential outcome is always unobserved, the individual causal effect of vaccine on infection cannot be observed. Therefore one must rely on contrasts between different individuals to estimate average or population level causal effects (Holland 1986). Given the individual causal effect (3), similar to Struchiner and Halloran (1996) and Gilbert et al. (2003b), we define the corresponding population causal vaccine effect by

$$\text{VE}_S = \frac{E\{S(p) - S(v)\}}{E\{S(p)\}} = \frac{E\{S(p)\} - E\{S(v)\}}{E\{S(p)\}} = 1 - \frac{E\{S(v)\}}{E\{S(p)\}}.$$  

We call this the relative average causal effect (RACE) of vaccination on infection. Since $S(v)$ and $S(p)$ are binary, the expectations can be replaced by probabilities and $\text{VE}_S$ can be interpreted as the relative reduction in the probability of infection given vaccine compared to control. An alternative population level causal vaccine effect would be

$$\text{VE}_S^{tt} = E\left\{ \frac{S(p) - S(v)}{S(p)} \right\} = 1 - E\left\{ \frac{S(v)}{S(p)} \right\}.$$  

However this approach will not be pursued here. For development of a population average relative difference causal effect similar to (4), see Robins and Greenland (1989).

Estimation of population average causal effects requires specification of the assignment mechanism (Rubin 1990b), that is, how the individuals were assigned to vaccine or placebo. We assume treatment assignment is independent of the potential outcomes:
**Assumption 2** Z is independent of \{Y(v), Y(p), S(v), S(p)\}.

Here it is understood that \(Y(z)\) does not exist if \(S(z) = 0\) for \(z = v, p\). Randomization is one assignment mechanism where the treatment assignment is independent of the potential outcomes. It now follows that

\[
VE_S = 1 - \frac{E\{S(v)|Z = v\}}{E\{S(p)|Z = p\}} = 1 - \frac{E\{S^{obs}|Z = v\}}{E\{S^{obs}|Z = p\}}.
\]

Next we define three estimands regarding the effect of vaccination on the post-infection outcome \(Y\). Usually, the notation \(VE_I\) is used specifically for vaccine efficacy for infectiousness, i.e., the effect of vaccination on transmission to others (Halloran, Struchiner, Longini, 1997), and \(VE_P\) is used for vaccine efficacy for progression or severity as in (1). Here we use \(VE_I\) throughout the development to refer to vaccine efficacy for any binary post-infection outcome. This enables us to use standard notation for the secondary attack rate (SAR), the probability of transmission from an infected to a susceptible individual. In the following development, SAR is defined more generally as the proportion of infected individuals who develop the worse post-infection outcome.

A typical approach to assessing vaccine effects on post-infection endpoints would be to define a net vaccine effect which conditions on infection, i.e.,

\[
VE_I^{net} = 1 - \frac{E\{Y^{obs}|S^{obs} = 1, Z = v\}}{E\{Y^{obs}|S^{obs} = 1, Z = p\}} = 1 - \frac{E\{Y(v)|S(v) = 1\}}{E\{Y(p)|S(p) = 1\}},
\]

with the second equality following from Assumption (2). However, in general, \(VE_I^{net}\) does not have a causal interpretation since the set of individuals with \(S(v) = 1\) is not necessarily identical to the set of individuals with \(S(p) = 1\) (Rosenbaum 1984; Frangakis and Rubin 2002).

A second typical approach is to define an estimand for the effect of vaccination on different levels of severity of disease or mortality without conditioning on being infected. Such an estimand might be considered intent-to-treat because it does not condition on the post-treatment variable \(S^{obs}\), i.e., it incorporates all individuals according to their treatment assignment. An example of an intent-to-treat estimand is

\[
VE_I^{ITT} = 1 - \frac{E\{Y(v) \times S(v)\}}{E\{Y(p) \times S(p)\}},
\]

where we adopt the convention that \(Y(z) \times S(z) = 0\) if \(S(z) = 0\), \(z = v, p\). This is a general form for what Préziosi and Halloran (2003b) called \(VE_S\) for severity. While \(VE_I^{ITT}\) does have a causal interpretation, it combines vaccine effects on susceptibility and the post-infection outcome as shown by the following relation:

\[
VE_I^{ITT} = 1 - (1 - VE_S)(1 - VE_I^{net}).
\]
We propose a third estimand for the effect of vaccination on a binary post-infection outcome which has a causal interpretation and is separate from vaccine effects on susceptibility. To define the causal \( \text{VE}_I \), we use the basic principal stratification shown in Table 1. In particular, the individual causal vaccine effect on the post-infection outcomes is defined as

\[
\text{VE}_I = 1 - \frac{Y_i(v)}{Y_i(p)},
\]

for individuals within the doomed principal stratum only. Following the development of \( \text{VE}_S \) above, we define the population post-infection causal vaccine effect \( \text{VE}_I \) within the doomed principal stratum as

\[
\text{VE}_I = 1 - \frac{E\{Y(v)|S^{p_s} = (1, 1)\}}{E\{Y(p)|S^{p_s} = (1, 1)\}}. \tag{5}
\]

Like \( \text{VE}_S \), (5) could equivalently be given in terms of probabilities since the post-infection random variables \( Y(v) \) and \( Y(p) \) are assumed to be binary such that \( \text{VE}_I \) can be interpreted as the causal estimand measuring the relative reduction in the probability of the worse post-infection outcome given vaccine compared to placebo in those individuals who would be infected under either treatment assignment. The challenge in estimating principal effects such as (5) lies in identifying those individuals in the doomed basic principal stratum, since at most one potential infection outcome is ever observed for a particular individual. To help overcome this obstacle, we make the following monotonicity assumption:

**Assumption 3 Monotonicity.** The individual causal effect of vaccination on infection is non-negative, i.e., \( \text{VE}_{Si} \geq 0 \) for all \( i \).

Under this assumption, an individual who would get infected under vaccine would also get infected under placebo, so the harmed principal stratum \( S^{p_s} = (1, 0) \) is empty. In the context of possible noncompliance with treatment assignment, Angrist et al. (1996) and Imbens and Rubin (1997) made a monotonicity assumption akin to Assumption 3, which immediately eliminates the basic principal stratum of defiers, people who would always take the opposite of their treatment assignment. By Assumption 3, we are not assuming that the individual post-infection causal effect of vaccination is non-negative. Rather, we allow that vaccination could have a negative, that is harmful, causal effect on the post-infection outcome. One of our goals is to identify the conditions under which it could be determined that the post-infection causal effect is negative.

Under Assumption 3, for each possible observed combination of \( (Z_i, S_i^{obs}) \), we can deduce certain characteristics of the corresponding basic principal strata:

- \( (Z_i = p, S_i^{obs} = 0) \rightarrow S^{p_s} = (0, 0) \) (since \( \text{VE}_{Si} \geq 0 \)) immune
- \( (Z_i = p, S_i^{obs} = 1) \rightarrow S^{p_s} = (0, 1) \) or \( S^{p_s} = (1, 1) \) protected or doomed
- \( (Z_i = v, S_i^{obs} = 0) \rightarrow S^{p_s} = (0, 1) \) or \( S^{p_s} = (0, 0) \) protected or immune
- \( (Z_i = v, S_i^{obs} = 1) \rightarrow S^{p_s} = (1, 1) \) (since \( \text{VE}_{Si} \geq 0 \)) doomed
Thus the infected vaccine recipients will immediately provide information about the distribution of the post-infection outcome \( Y(v) \) in the doomed principal stratum. However, getting a handle on \( Y(p) \) in \( S^{P_b} = (1, 1) \) is still problematic since infected placebo recipients may be members of either the protected or doomed principal stratum. In the following sections we derive models that allow us to identify the distribution of \( Y(p) \) in the doomed principal stratum, and in turn, the post-infection causal vaccine effect \( VE_I \) given in (5).

3 IDENTIFIABILITY AND ESTIMATION OF VACCINE EFFECTS

In this section, we investigate identifiability and estimation of the estimands defined in the previous section.

3.1 Parameterization

Let the parameters \( \theta \) govern the probabilities associated with the basic principal strata. In our case, the stratum \( S^{P_b} = (1, 0) \) is empty, so let \( \theta = (\theta^{00}, \theta^{01}, \theta^{11}) \) where

\[
\Pr\{S^P_i = (i, j); \theta \} = \theta^{ij} \text{ for } i, j = 0, 1; i \leq j.
\]

(6)

Next let the parameters \( \phi = (\phi^{00}, \phi^{01}, \phi^{10}, \phi^{11}) \) govern the probabilities associated with the joint potential post-infection outcomes in the doomed basic principal stratum \( S^{P_b} = (1, 1) \), where

\[
\Pr\{(Y(v), Y(p)) = (k, m); S^{P_b} = (1, 1); \phi \} = \phi^{km} \text{ for } k, m = 0, 1.
\]

(7)

Let the parameters \( \gamma = (\gamma^0, \gamma^1) \) govern the probabilities associated with the two possible potential post-infection outcomes under placebo in the protected basic principal stratum, \( S^{P_b} = (0, 1) \), where

\[
\Pr\{Y(p) = i; S^{P_b} = (0, 1); \gamma \} = \gamma^l \text{ for } l = 0, 1.
\]

(8)

Finally, let the law of \( Z \) be given by \( \Pr\{Z = z; \psi \} = \psi^z \) for \( z = v, p \).

Under this parameterization, the causal estimand of vaccine efficacy for susceptibility is

\[
VE_S = 1 - \frac{\theta^{11}}{\theta^{01} + \theta^{11}}.
\]

Based on the definition of the causal estimand \( VE_I \) given in (5), we are not interested in the joint probabilities \( \phi^{km} \) \((k, m = 0, 1)\), but rather just two of the marginal probabilities. In particular, under the parameterization above

\[
VE_I = 1 - \frac{\phi^{11}}{\phi^{11}}.
\]

(9)
where
\[
\Pr\{Y(v) = 1|S^F = (1, 1)\} = \phi^{10} + \phi^{11} = \phi^1.
\]
and
\[
\Pr\{Y(p) = 1|S^F = (1, 1)\} = \phi^{01} + \phi^{11} = \phi^1.
\]
We also have
\[
\text{VE}^\text{net}_I = 1 - \frac{\phi^1}{\gamma^1 \text{VE}_S + \phi^1 (1 - \text{VE}_S)},
\]
and
\[
\text{VE}^{III}_I = 1 - \frac{\phi^1 (1 - \text{VE}_S)}{\gamma^1 \text{VE}_S + \phi^1 (1 - \text{VE}_S)}.
\]

3.2 Identifiability

Without further assumptions \(\text{VE}_I\) is not identifiable from the observable random variables \((Y^{\text{obs}}, S^{\text{obs}}, Z)\). To see this, first write the probability function for the observable random variables \(\Pr[Z = z, S^{\text{obs}} = s, Y^{\text{obs}} = y; \theta, \gamma, \phi, \psi]\) as

\[
\begin{align*}
&\theta^{00}\psi^p I(z = p, s = 0, y \text{ does not exist}) \\
+ &\{\theta^{01} + \theta^{11} - (\theta^{01}\gamma^1 + \theta^{11}\phi^1)\}\psi^p I(z = p, s = 1, y = 0) \\
+ & (\theta^{01}\gamma^1 + \theta^{11}\phi^1)\psi^p I(z = p, s = 1, y = 1) \\
+ & (\theta^{00} + \theta^{01})\psi^v I(z = v, s = 0, y \text{ does not exist}) \\
+ & \theta^{11}(1 - \phi^1)\psi^v I(z = v, s = 1, y = 0) \\
+ & \theta^{11}\phi^1\psi^v I(z = v, s = 1, y = 1),
\end{align*}
\]

(10)

where \(I(\cdot)\) is the usual indicator function. Next, suppose we have \(\theta^{01} = \theta^{11}, \phi^1 = \epsilon, \) and \(\gamma^1 = 1 - \epsilon\) for some \(\epsilon \in (0, 1)\). Then the probability function given in (10) is constant for different values of \(\epsilon\). Moreover, \(\text{VE}_I = 1 - \phi^1/\epsilon\) depends on the choice of \(\epsilon\), indicating \(\text{VE}_I\) is not identifiable. On the other hand, one can show that the estimands \(\text{VE}_S, \text{VE}^{III}_I, \) and \(\text{VE}^\text{net}_I\) are identifiable without further assumptions.

3.3 Estimation

Suppose we observe \(n\) independent and identically distributed realizations of \((Z, S^{\text{obs}}, Y^{\text{obs}})\), where \(Y^{\text{obs}}\) is undefined or does not exist if \(S^{\text{obs}} = 0\). There are six observed combinations of \((Z, S^{\text{obs}}, Y^{\text{obs}})\). Let \(n_{kj}(z)\) be the number of each combination observed in the study population where \(k = 0, 1\) is the observed infection outcome \(S^{\text{obs}}; j = 0, 1, *\) is the observed post-infection outcome \(Y^{\text{obs}}\); and \(z = v, p\). That is,
\[ n_{0i}(p) = \sum_i I(Z_i = p, S_i^{obs} = 0, Y_i^{obs} \text{ does not exist}) \]
\[ n_{10}(p) = \sum_i I(Z_i = p, S_i^{obs} = 1, Y_i^{obs} = 0) \]
\[ n_{11}(p) = \sum_i I(Z_i = p, S_i^{obs} = 1, Y_i^{obs} = 1) \]

\[ n_{0i}(v) = \sum_i I(Z_i = v, S_i^{obs} = 0, Y_i^{obs} \text{ does not exist}) \]
\[ n_{10}(v) = \sum_i I(Z_i = v, S_i^{obs} = 1, Y_i^{obs} = 0) \]
\[ n_{11}(v) = \sum_i I(Z_i = v, S_i^{obs} = 1, Y_i^{obs} = 1) \]

where the summations are over \( i = 1, \ldots, n \). We assume each of the six combinations is observed at least once, i.e., \( n_{kj}(z) > 0 \) for \( k = 0, 1, j = 0, 1, * \), and \( z = v, p \). Let \( n(p) = n_{0i}(p) + n_{10}(p) + n_{11}(p) \) and \( n(v) = n_{0i}(v) + n_{10}(v) + n_{11}(v) \) denote the number of individuals assigned to placebo and vaccine. Let \( n_{1i}(p) = n_{10}(p) + n_{11}(p) \) and \( n_{1i}(v) = n_{10}(v) + n_{11}(v) \) denote the number of infected individuals assigned placebo and vaccine. Let

\[ AR_z = \frac{n_{1i}(z)}{n(z)} \text{ for } z = v, p, \]

i.e., \( AR_z \) is the observed attack rate in the group assigned treatment \( z \). Finally, let

\[ SAR_z = \frac{n_{11}(z)}{n_{1i}(z)} \text{ for } z = v, p, \]

i.e., \( SAR_z \) is the observed secondary attack rate in the group infected given treatment \( z \).

Maximum likelihood estimates (MLEs) of the identifiable vaccine efficacy estimands can be found by maximizing the likelihood

\[ L(\theta, \gamma, \phi) \propto \prod_{i=1}^{n} \Pr[y_i^{obs} = y_i, s_i^{obs} = s_i | Z_i = z_i; \theta, \gamma, \phi], \]

subject to constraints on \( \theta, \gamma, \phi \) that ensure (6-8) are probability functions. Using the results from the appendix, it follows that the MLE of \( \text{VE}_S \) is given by

\[ \hat{\text{VE}}_S = \left\{ \begin{array}{ll}
1 - \frac{AR_v}{AR_p} & \text{if } \frac{n_{0i}(v)}{n(v)} \geq \frac{n_{0i}(p)}{n(p)}, \\
0 & \text{otherwise}.
\end{array} \right. \quad (11) \]

Further, the MLEs of \( \text{VE}_T^{ITT} \) and \( \text{VE}_T^{net} \) are

\[ \hat{\text{VE}}_T^{net} = 1 - \frac{SAR_v}{SAR_p}, \quad (12) \]

and

\[ \hat{\text{VE}}_T^{ITT} = 1 - (1 - \hat{\text{VE}}_S) \frac{SAR_v}{SAR_p}, \quad (13) \]
or equivalently

$$\widehat{VE}_{I}^{ITT} = \begin{cases} 
\widehat{VE}_{I}^{net} & \text{if } \widehat{VE}_{S} = 0, \\
1 - \frac{n_{11}(v)/n(v)}{n_{11}(p)/n(p)} & \text{if } \widehat{VE}_{S} > 0.
\end{cases} \quad (14)$$

The causal estimand $VE_{I}$ is not identifiable because $\phi^{1}$, the denominator of the right side of (9), is not identifiable. On the other hand, $\phi^{1}$, the numerator of the right side of (9), can be identified by the observable random variables. The corresponding MLE is given by

$$\hat{\phi}^{1} = SAR_{v},$$

i.e., the observed secondary attack rate in the vaccine arm.

Finally, while $\phi^{1}$ is not identifiable, we can identify

$$\Pr[Y(p) = 1|S(p) = 1; \theta, \gamma, \phi] = \widehat{VE}_{S}\gamma^{1} + (1 - \widehat{VE}_{S})\phi^{1}. \quad (16)$$

The MLE of (16) is $SAR_{p}$ such that any feasible pair $(\hat{\gamma}^{1}, \hat{\phi}^{1})$ that satisfies

$$SAR_{p} = \widehat{VE}_{S}\hat{\gamma}^{1} + (1 - \widehat{VE}_{S})\hat{\phi}^{1}, \quad (17)$$

is an MLE of $(\gamma^{1}, \phi^{1})$. In the following section we introduce selection models which identify $(\gamma^{1}, \phi^{1})$. These models add an additional constraint to the parameters such that there is only one feasible pair $(\hat{\gamma}^{1}, \hat{\phi}^{1})$ that satisfies (17). Since the value of the likelihood will remain the same, we will have the unique MLE of $\phi^{1}$ and, therefore, $VE_{I}$. Before proceeding, we revisit our examples.

### 3.4 Applications

#### 3.4.1 Rotavirus candidate vaccine

In the rotavirus candidate vaccine study (Vesikari et al., 1990), the observed data were

\[
\begin{align*}
  n_{0a}(p) &= 84 & n_{0a}(v) &= 90 \\
  n_{10}(p) &= 3 & n_{10}(v) &= 5 \\
  n_{11}(p) &= 13 & n_{11}(v) &= 5 
\end{align*}
\]

From (11), $\widehat{VE}_{S} = 1 - (10/100)/(16/100) = 0.375$. It then follows from (14) that $\widehat{VE}_{I}^{ITT} = 1 - (5/100)/(13/100) = 0.62$. The secondary attack rates are $SAR_{v} = \hat{\phi}^{1} = 5/10 = 0.50$ and $SAR_{p} = 13/16 = 0.81$ such that $\widehat{VE}_{I}^{net} = 1 - (5/10)/(13/16) = 0.385$.

To consider estimation of $VE_{I}$, Table 2 shows the relation of the observed data to the basic principal strata and the strata of joint potential post-infection outcomes within each basic principal stratum. By Assumptions 1-3, we know the following:
• All $n_{10}(v) + n_{11}(v) = 10$ belong to the doomed stratum $S^{R_b} = (1, 1)$.
• All $n_{0s}(p) = 84$ belong to the immune stratum $S^{R_b} = (0, 0)$.
• The $n_{0s}(v) = 90$ could belong to $S^{R_b} = (0, 0)$ or $S^{R_b} = (0, 1)$.
• The $n_{10}(p) + n_{11}(p) = 16$ could belong to $S^{R_b} = (0, 1)$ or $S^{R_b} = (1, 1)$.

Ignoring statistical variability, by Assumption 2 (independence), since there are 10 vaccine recipients in the doomed stratum, there are 10 placebo recipients in the doomed stratum as well. Since there are 84 placebo recipients in the immune stratum, there are 84 vaccine recipients in the immune stratum as well. So there must be 6 from each of the vaccinated and unvaccinated groups in the protected stratum. Thus, we can estimate the size of the unobserved principal stratum $S^{R_b} = (0, 1)$. However, we do not know which 6 of the 16 infected placebo recipients are in protected stratum $S^{R_b} = (0, 1)$ or which 10 of the 16 are in the doomed stratum $S^{R_b} = (1, 1)$. This illustrates the need for further assumptions to identify $VE_I$.

### 3.4.2 Pertussis vaccine

The pertussis vaccine analysis of Préziosi and Halloran (2003b) included exactly one year of follow-up, the calendar year 1993, so the person-years at risk are a close approximation to the number of persons at risk. Thus, we use the person-years at risk for $n(v)$ and $n(p)$. Although vaccine status was not randomized, there was no evidence of systematic differences between the vaccinated and unvaccinated groups, so that Assumption 2 (independence) might be reasonable. Active surveillance to find cases makes it unlikely that ascertainment bias plays a role. (See Préziosi and Halloran (2003b) for further discussion). The observed data are

$$
\begin{align*}
    n_{0s}(p) &= 814 & n_{0s}(v) &= 3297 \\
    n_{10}(p) &= 77 & n_{10}(v) &= 372 \\
    n_{11}(p) &= 129 & n_{11}(v) &= 176
\end{align*}
$$

From (11), $\widehat{VE}_S = 1 - (548/3845)/(206/1020) = 0.29$. The secondary attack rates are $SAR_v = \hat{\phi} = 176/548 = 0.32$ and $SAR_p = 129/206 = 0.63$ such that $\widehat{VE}_I^{net} = 1 - (176/548)/(129/206) = 0.49$, which is the same as $\widehat{VE}_P$ given in (1). Finally $\widehat{VE}_I^{ITT} = 1 - (176/3845)/(129/1020) = 0.64$, which Préziosi and Halloran (2003b) called $\widehat{VE}_S$ for severity.

### 4 SELECTION BIAS MODELS

In this section, we make additional assumptions about the selective effect of the vaccine on susceptibility to infection that identify $VE_I$. We begin in section 4.1 by assuming there is no
selective vaccine effect. In section 4.2 we present two extreme models that assume maximum possible levels of positive and negative selection bias and, in turn, yield bounds on the MLE of the causal estimand in a fashion similar to Manski (1990), Balke and Pearl (1997), and Hudgens et al. (2003). In section 4.3, we present three approaches to sensitivity analysis which allow a range of selective effects. The different methods are then applied to the two vaccine examples.

4.1 No selection bias

The simplest assumption is that there is no selection, that is, the probability of the post-infection outcome conditional on infection under placebo is independent of infection status under vaccine:

\[
\Pr \left\{ Y(p) = y | S^{P_0} = (1, 1) ; \phi \right\} = \Pr \left\{ Y(p) = y | S^{P_0} = (0, 1) ; \gamma \right\} \quad \text{for } y = 0, 1,
\]

which implies that \( \phi^1 = \gamma^1 \). Moreover, assumption (18) identifies \( \text{VE}_I \), and it follows immediately from (17) that the resulting MLE is

\[ \hat{\phi}^1 = \text{SAR}_p. \]  

From (15), (19), and the definition of \( \text{VE}_I \) given by (9), it follows that the MLE of \( \text{VE}_I \) equals \( \hat{\text{VE}}_I^{\text{net}} \) as given in (12). In other words, under the assumption of no selection bias as specified by (18), the MLE of the causal vaccine effect is the usual secondary attack rate ratio estimate one obtains when conditioning on infection.

4.2 Upper and lower bounds

To derive the MLE of \( \text{VE}_I \) under the upper bound selection bias model, we assume that either (i) all placebo recipients in the doomed principal stratum have the worse post-infection outcome or (ii) all placebo recipients in the protected principal stratum have the better post-infection outcome. The first case is depicted in the top left panel of figure 1, the second in the top right panel. Probabilistically, this extreme selection model is equivalent to assuming either

\[ \Pr \left\{ Y(p) = 1 | S^{P_0} = (1, 1) \right\} = \phi^1 = 1, \]  

or

\[ \Pr \left\{ Y(p) = 1 | S^{P_0} = (0, 1) \right\} = \gamma^1 = 0. \]  

Under the model that assumes either (20) or (21), \( \phi^1 \) is identifiable. Moreover, from (17) it follows that the MLE of \( \VE_I \) assuming either (20) or (21) is given by:

\[
\widehat{\VE_I}^{\text{upper}} = \begin{cases} 
1 - SAR_v & \text{if } \widehat{\VE}_S > 1 - SAR_p, \\
\widehat{\VE}_I^{\text{ITT}} & \text{if } 0 < \widehat{\VE}_S \leq 1 - SAR_p, \\
\widehat{\VE}_I^{\text{net}} & \text{if } \widehat{\VE}_S = 0.
\end{cases}
\] (22)

Similarly, we can derive the MLE of \( \VE_I \) under the lower bound selection bias model by assuming that under assignment to placebo, the worse post-infection outcome occurs either with probability zero in the doomed principal stratum,

\[ \Pr[Y(p) = 1| S^p = (1, 1)] = \phi^1 = 0, \] (23)

or with probability one in the protected principal stratum,

\[ \Pr[Y(p) = 1| S^p = (0, 1)] = \gamma^1 = 1. \] (24)

The model in (23) corresponds to the lower left panel of figure 1, model (24) to the lower right panel. This model renders \( \phi^1 \) identifiable and from (17) the resulting unique MLE of \( \VE_I \) is

\[
\widehat{\VE}_I^{\text{lower}} = \begin{cases} 
-\infty & \text{if } \widehat{\VE}_S > SAR_p, \\
1 - SAR_v / \left\{ \frac{SAR_v - \widehat{\VE}_S}{1 - \widehat{\VE}_S} \right\} & \text{if } 0 < \widehat{\VE}_S \leq SAR_p, \\
\widehat{\VE}_I^{\text{net}} & \text{if } \widehat{\VE}_S = 0.
\end{cases}
\] (25)

In summary, even though \( \VE_I \) is not identifiable from the data in hand, these extreme selection bias models provide bounds on the MLE. Moreover, we have derived the circumstances when the upper bound will be negative (suggesting harm) and when the lower bound will be positive (suggesting benefit). For example, \( \widehat{\VE}_I^{\text{upper}} \) will be negative iff \( 0 \leq \widehat{\VE}_S \leq 1 - SAR_p \) and \( \widehat{\VE}_I^{\text{ITT}} < 0 \). Similarly, \( \widehat{\VE}_I^{\text{lower}} \) will be positive iff \( 0 \leq \widehat{\VE}_S \leq SAR_p \) and \( SAR_v < (SAR_p - \widehat{\VE}_S)/(1 - \widehat{\VE}_S) \). On the other hand, for large \( \widehat{\VE}_S \) (i.e. \( \max\{SAR_p, 1 - SAR_p\} \)) \( \widehat{\VE}_I^{\text{upper}} \) will be always positive and \( \widehat{\VE}_I^{\text{lower}} \) will be always negative, indicating further assumptions about the selective effect of the vaccine must be made to draw inference on \( \VE_I \).

### 4.3 Sensitivity analyses

Estimating the causal vaccine effect under an extreme degree of selection bias is useful in bounding the estimate of the possible post-infection effect above and beyond any possible selective
effects. However, the true degree of selection bias is likely less than the extreme models above, such that using $\text{VE}_T^{upper}$ or $\text{VE}_T^{lower}$ may lead to conservative inference. Therefore, we consider sensitivity analyses that allow selection models which range from no selection to the extreme models above.

### 4.3.1 Log odds ratio of infection

Our first approach is similar to that of Scharfstein, Robins, and Rotnitzky (1999) and Robins, Rotnitzky, and Scharfstein (2000) and adapted by Gilbert et al. (2003b). We define a sensitivity model in terms of the log odds ratio of infection under vaccine given infection under assignment to placebo with post-infection endpoint $Y(p) = 1$ versus $Y(p) = 0$, i.e.,

$$
\exp(\beta) = \frac{\Pr[S(v) = 1|Y(p) = 1, S(p) = 1]}{\Pr[S(v) = 0|Y(p) = 1, S(p) = 1]} \frac{\Pr[S(v) = 0|Y(p) = 0, S(p) = 1]}{\Pr[S(v) = 0|Y(p) = 0, S(p) = 1]}.
$$

(26)

For example, if $\beta = 2$, then for individuals infected under placebo, the odds of being in the doomed strata are doubled if the worse post-infection outcome occurs. In terms of our parameterization, this implies

$$
\phi^{-1} = \frac{\gamma^1 \exp(\beta)}{\gamma^0 + \gamma^1 \exp(\beta)}.
$$

(27)

For fixed $\beta$, one can solve equations (17) and (27) for $\phi^{-1}$ and, in turn, $\text{VE}_T$. While a closed form solution does not appear to exist, a simple one-dimensional line search can be employed. A sensitivity analysis can then be performed by repeating this process over a range of different $\beta$s.

The selection models given in sections 4.1-4.2 are special cases of the class of logistic selection models given by (26) when $\beta = 0$ (no selection), $\beta \to \infty$ (upper bound) or $\beta \to -\infty$ (lower bound). For example, letting $\beta \to \infty$ implies either

$$
\Pr[S(v) = 1|Y(p) = 0, S(p) = 1] \to 0,
$$

(28)

or

$$
\Pr[S(v) = 0|Y(p) = 1, S(p) = 1] \to 0.
$$

(29)

If (28) holds, this in turn implies $\Pr[Y(p) = 1|S^{pb} = (1,1)] \to 1$, which gives (20). On the other hand, if (29) holds, this implies $\Pr[Y(p) = 1|S^{pb} = (0,1)] \to 0$, which yields (21). Thus we recover the extreme upper selection bias model.

### 4.3.2 Conditioning on $\gamma^1$ as the sensitivity analysis parameter

Section 4.3.1 posits the existence of a model relating the post-infection endpoint distributions between the doomed and protected strata. Alternatively, one might simply condition on the
nuisance parameter $\gamma^1$ which governs the post-infection endpoint distribution in the protected stratum. Assuming $\gamma^1$ is known renders $\phi^{-1}$ and, hence, VE$_I$ identifiable. From (17), the resulting MLE of VE$_I$ is

$$\hat{\text{VE}}_I = 1 - \frac{SAR_p - \gamma^1 \hat{\text{VE}}_S}{1 - \hat{\text{VE}}_S},$$

(30)

where $\gamma^1$ varies between

$$\max \left\{ 0, \frac{SAR_p - (1 - \hat{\text{VE}}_S)}{\hat{\text{VE}}_S} \right\} \leq \gamma^1 \leq \min \left\{ 1, \frac{SAR_p}{\hat{\text{VE}}_S} \right\},$$

(31)

with the left side of (31) giving rise to $\text{VE}^\text{upper}_I$ and the right side of (31) giving rise to $\text{VE}^\text{lower}_I$.

### 4.3.3 Complete data model

A third approach to the sensitivity analysis regards the unknown basic principal strata membership of the infected placebo recipients as missing data and formulates the sensitivity analysis in terms of the complete data likelihood. The observed data are $n_{10}(p)$ and $n_{11}(p)$. If we could know the basic principal stratum membership, the complete data would be $n^d_{10}(p)$ and $n^d_{11}(p)$, the number of infected placebo recipients in the doomed stratum with $Y(p) = 0$ and $Y(p) = 1$, and $n^p_{10}(p)$ and $n^p_{11}(p)$ the corresponding number in the protected stratum. Given the complete data, $\phi^{-1}$ becomes identifiable. The complete data log likelihood for $(\Theta, \Phi, \Gamma)$ is given by

$$n_{0*}(p) \log(\theta^{00}) + n^p_{10}(p) \log(\theta^{01} \gamma^0) + n^p_{11}(p) \log(\theta^{01} \gamma^1) + n^d_{10}(p) \log(\theta^{11} (1 - \phi^{-1})) + n^d_{11}(p) \log(\theta^{11} \phi^{-1})$$

$$+ n_{0*}(v) \log(\theta^{00} + \theta^{01}) + n_{10}(v) \log(\theta^{11} (1 - \phi^{-1})) + n_{11}(v) \log(\theta^{11} \phi^{-1}),$$

(32)

which factors in terms of $\Theta$, $\Phi$, and $\Gamma$, say $l(\Theta)$, $l(\Phi)$, and $l(\Gamma)$. Maximizing $l(\Phi)$ yields the same MLE $\phi^{-1} = \text{SAR}_v$ as before. It also yields the MLE

$$\hat{\phi}^{-1} = \frac{n^d_{11}(p)}{n^d_{10}(p) + n^d_{11}(p)},$$

(33)

the secondary attack rate under placebo in the doomed stratum. The sensitivity analysis involves estimating VE$_I$ using (33) for all possible complete data configurations consistent with the assumptions and the constraints implied by the observed data. Molenberghs et al. (2001) call this set of point estimates the region of ignorance. They call the collection of confidence intervals or other measures of precision together with the region of ignorance the region of uncertainty.
4.4 Applications, continued

4.4.1 Rotavirus candidate vaccine

For these data, $\hat{VE}_S > 1 - SAR_p$, so from (22), $\hat{VE}_I^{upper} = 1 - SAR_e = 0.50$. On the other hand, $0 < \hat{VE}_S \leq SAR_p$, so from (25),

$$\hat{VE}_I^{lower} = 1 - \frac{5/10}{(10/100)/(16/100)} = 0.29.$$ 

For these data, not taking statistical variability into account, the lower bound for $VE_I$ is evidence that even in the presence of extreme selection bias, the vaccine has a protective effect against severe diarrheal disease if a child becomes infected.

Figure 2a shows the sensitivity analysis of $\hat{VE}_I$ as a function of the odds ratio $e^\theta$ as described in section 4.3.1. Figure 3a shows the sensitivity analysis of $\hat{VE}_I$ as a function of $\gamma^1$ as described in section 4.3.2. From (31), the range for $\gamma^1$ is [0.5,1,0] in this example. For these figures, profile likelihood based confidences intervals were computed numerically assuming the usual $\chi^2$ limiting distribution of the likelihood ratio. The vertical dotted line in figures 2 and 3 corresponds to the assumption of no selection bias. In particular, in figure 3, $\hat{\gamma}^1$ corresponds to the MLE of $\gamma^1$ under the assumption of no selection bias. The pointwise 95% confidence intervals cover 0 over nearly the entire range of both sensitivity analyses, thus one cannot conclude that the vaccine has a protective effect against severe disease.

Table 3 shows the estimates for $VE_I$ obtained by fitting all possible configurations of the complete data that are consistent with the observed data, the assumptions, and the constraints as described in section 4.3.3. In particular, the complete data configurations are constrained by, on the one hand, $n_{11}(p) = n_{11}^L(p) + n_{11}^R(p) = 13$ and $n_{10}(p) = n_{10}^L(p) + n_{10}^R(p) = 3$. On the other hand, by Assumptions 2 and 3, of the total 16 in the combined protected and doomed strata, 6 are in the protected stratum and 10 are in the doomed stratum. There are only four such configurations. The $VE_I$ estimates are computed using (9), (15), and (33) with the region of ignorance comprised of the four $VE_I$ estimates. For this data set, the assumption of no selection bias does not correspond to any possible complete data configuration. On the other hand, the extreme lower and upper bound estimates $\hat{VE}_I^{lower}$ and $\hat{VE}_I^{upper}$ are included in the region of ignorance.

4.4.2 Pertussis vaccine

For these data, $0 \leq \hat{VE}_S \leq 1 - SAR_p$, so from (22), $\hat{VE}_I^{upper} = \hat{VE}_I^{ITT} = 0.64$. On the other hand, $0 \leq \hat{VE}_S \leq SAR_p$, so from (25), $\hat{VE}_I^{lower} = 0.32$. Figures 2b and 3b show the sensitivity
analyses of \( \widehat{\text{VE}}_I \) as described in sections 4.3.1 and 4.3.2. In both figures, the lower limits of the pointwise 95\% confidence intervals are well above zero over the range of both selection models, suggesting pertussis vaccination causes significant protection against severe disease in children who would develop pertussis regardless of vaccination. The sensitivity analysis using the complete data likelihood would proceed similarly as for the rotavirus vaccine candidate, with many more possible data configurations and taking the unequal sizes of the vaccinated and unvaccinated arms into account.

5 TESTING

In this section, we consider a testing procedure to assess whether there is significant evidence of a causal vaccine effect on the binary post-infection endpoint of interest. Our approach is based on that in Hudgens et al. (2003) for testing for a causal effect of vaccination on a continuous post-infection endpoint. Suppose one wants to test the null hypothesis of no harmful causal vaccine effect with respect to the post-infection endpoint of interest, i.e., \( H_0 : \text{VE}_I \geq 0 \), or, equivalently

\[
H_0 : \Pr[Y(v) = 1|S^{Fr} = (1, 1)] \leq \Pr[Y(p) = 1|S^{Fr} = (1, 1)].
\]

(34)

One possible test statistic is based on contrasts in estimates of the probabilities in (34) under the extreme upper selection bias model given in Section 4.2, i.e.,

\[
T_{upper} = SAR_v - \min\{1, \frac{SAR_p}{1 - \widehat{\text{VE}}_S}\},
\]

with sufficiently large values of \( T_{upper} \) resulting in the rejection of (34). Similarly, if one wants to test the null hypothesis of no beneficial causal effect of the vaccine on the post-infection endpoint, i.e., \( H_0 : \text{VE}_I \leq 0 \), or equivalently,

\[
H_0 : \Pr[Y(p) = 1|S^{Fr} = (1, 1)] \leq \Pr[Y(v) = 1|S^{Fr} = (1, 1)],
\]

(35)

then it follows from Section 4.2 that a corresponding test statistic is

\[
T_{lower} = \max\{0, \frac{SAR_p - \widehat{\text{VE}}_S}{1 - \widehat{\text{VE}}_S}\} - SAR_v,
\]

with sufficiently large values of \( T_{lower} \) resulting in rejecting (35). Two sided testing for any post-infection causal vaccine effect can be undertaken using the test statistic \( T = \max\{T_{upper}, T_{lower}\} \). The NPMLE bootstrap procedures detailed in Hudgens et al. (2003) can readily be adapted to assess the significance probability associated with these test statistics.
5.1 Simulation study

Finite sample operating characteristics of the test statistic $T_{\text{lower}}$ were evaluated by computer simulation. We considered one-sided procedures associated with testing (35) at the 0.05 level of significance using the NPMLE bootstrap procedure for approximating critical values. The probability of rejecting the null hypothesis under each study condition was estimated from 10,000 simulated data sets. For each simulation, bootstrap samples of size $B = 500$ were generated.

We assumed 1000 trial participants in each arm, i.e., $n(p) = n(v) = 1000$. Each data set was generated by first sampling the number of infected placebo and vaccine recipients, $n_1(p)$ and $n_1(v)$, from binomial distributions with means $n(p)(\theta^{01} + \theta^{11})$ and $n(v)\theta^{11}$, respectively. The binary post-infection outcomes were then generated from a Bernoulli distribution with expectation $\Pr[Y(p) = 1|S(p) = 1] = 0.6$ for each infected placebo recipient. The infected vaccinee post-infection endpoints were generated from a Bernoulli distribution with expectation

$$\Pr[Y(v) = 1|S(v) = 1] = \frac{\Pr[Y(p) = 1|S(p) = 1] - \text{VE}_S}{1 - \text{VE}_S} - \Delta,$$

where $\Delta = 0$ corresponds to the boundary of the null hypothesis region (35) under the extreme lower selection bias model of Section 4.2. For simulations under the alternative hypotheses, a positive $\Delta$–mean shift was used. Values of $\text{VE}_S$ and $\Delta$ were chosen to ensure that (36) was non-negative. In particular, parameters and corresponding values that were varied in the simulation study were:

- expected number of infected placebo recipients: $n(p)(\theta^{01} + \theta^{11}) = 45, 90, 135, 180$,
- protective efficacy of the vaccine against infection: $\text{VE}_S = 0, 0.3, 0.5$,
- departure from the $H_0$ as indexed by the magnitude of the location shift: $\Delta = 0, 0.1, 0.2$.

Table 4 gives the simulated size and power of $T_{\text{lower}}$ when using the NPMLE bootstrap approach. Generally, the testing procedure gives slightly inflated false positive rates compared to the nominal 0.05 significance level, especially where there are few infections. Thus caution should be employed when applying this testing procedure to smaller studies, e.g., the rotavirus example. Not surprisingly, power increases with the expected number of infected placebo recipients and decreases with increasing $\text{VE}_S$.

It has been suggested (Gilbert et al. 2003b; Hudgens et al. 2003) that employing a testing approach that conditions on infection (e.g., using $T_{\text{lower}}$) might be more powerful in detecting post-infection vaccine effects compared to an unconditional (or ITT) approach which effectively combines individuals who are uninfected with those who are infected but do not have the post-infection endpoint of interest. To this end, we conducted a simulation study to compare the
power of the conditional approach based on $T^{lower}$ with an unconditional approach using Fisher's exact test (FET). In particular, the proportion of all vaccinees with the post-infection endpoint of interest was compared with the analogous proportion in all placebo recipients via FET as a test of the null hypothesis $H_0 : \text{VE}_{IT} \leq 0$. The simulation study assumed the vaccine had no effect on susceptibility (i.e. $\text{VE}_S = 0$) allowing direct comparison of the power of the two approaches to detect post-infection vaccine effects. The results given in Table 5 indicate that the conditional approach is more sensitive.

5.2 Applications, continued

Applying our testing procedure to the rotavirus vaccine example gives $t^{lower} = 0.2$ and a corresponding p-value of 0.21, based on $B = 100,000$ bootstrap samples. Thus, there is no significant statistical evidence for a causal benefit of rotavirus vaccine on disease severity in this example. On the other hand, for the pertussis example, $t^{lower} = 0.15$ with a corresponding p-value of 0.02 (based on $B = 100,000$ bootstrap samples), suggesting there is significant statistical evidence for a causal benefit of pertussis vaccine on disease severity. Both of these results are consistent with the sensitivity analysis results given in section 4.4.

6 DISCUSSION

For vaccine studies in which the effect of vaccination on binary post-infection outcomes is of interest, our results will enable researchers to quantify the soundness and limitations of their findings. Combining principal stratification with a maximum likelihood approach, we derived methods for estimating the causal effect of vaccination on post-infection outcomes in those individuals who would be infected under vaccine and placebo. We derived closed forms for the upper and lower bounds of the MLE of the causal estimand and methods for sensitivity analyses under varying selection bias assumptions. These results indicate specific assumptions under which traditionally employed efficacy estimators have a causal interpretation. For example, under the assumption of no selection bias, the usual net post-infection efficacy estimator is the MLE of our causal estimand. We also developed a test for a harmful or beneficial causal vaccine effects on the post-infection endpoint. Provided Assumptions 1-3 are satisfied, the results are applicable to treatments other than vaccination and binary post-treatment outcomes other than infection.

Correctly assessing vaccine effects on post-infection endpoints has important public health consequences. For example, there is precedent and concern for vaccine induced immune responses causing disease enhancement (Kliks et al. 1989, Burke 1992, Mascola et al. 1993, Nabel 2001).
If the estimated net post-infection vaccine effect suggested a possible harmful effect, a vaccine could be wrongfully discounted if in fact the apparent negative effect were due to selection bias. Our methods could be employed to determine whether such an observed effect is consistent with selection bias. On the other hand, if the estimated net vaccine effect were positive, one might be less compelled to distinguish (i) a selective effect of the vaccine on infection from (ii) the causal effect of the vaccine in the doomed principal stratum, since either effect is beneficial from a public health perspective. Disentangling (i) from (ii) could be quite valuable from a scientific viewpoint, however. For example, our analysis of the pertussis vaccine study provides evidence that vaccination has an effect on disease severity above and beyond that attributable to selection bias, suggesting vaccination produces an immune response that directly hinders severe symptoms such as paroxysms with whoops. This could suggest directions for further biologic research. Another example arises in HIV where researchers are considering both antibody and T-cell based vaccines (McMichael, Mwau, and Hanke 2002; Nabel 2001) under the hypothesis that the former will protect from infection and the latter from disease or death. If a combination vaccine proves effective in reducing the risk of morbidity or mortality, researchers will be interested in understanding the mechanism of protection, i.e., to which vaccine component is such an effect attributable. Analysis revealing a significant post-infection causal vaccine effect in the doomed stratum would provide evidence of T-cell based protection. Separating (i) and (ii) might also be helpful in predicting the success of particular vaccination programs (Hayes, Alexander, Bennett, and Cousens 2000).

Further research is needed on the consequences of relaxing several key assumptions. Regarding Assumption 1, SUTVA is clearly violated in many vaccine field studies (Rubin 1990a; Halloran and Struchiner 1995). When SUTVA is violated, the basic principal strata are not well-defined, since an individual can have different potential infection outcomes under the same treatment assignment. Regarding Assumption 2 (independence), many vaccine field studies are not randomized. The effect of nonrandom allocation of the vaccine could be explored through additional sensitivity analyses and other approaches for observational studies (Rosenbaum 1995). Relaxing Assumption 3, monotonicity, to allow for a harmful vaccine effect on infection would make identifiability and estimation of the post-infection causal estimand VEf more difficult. However, a vaccine that increases susceptibility to infection would be unacceptable from a public health standpoint, so that concerns about post-infection selection bias become less relevant. Finally, we have assumed that assignment to a treatment is equivalent to receipt of that treatment. The increased complexity of defining, identifying, and estimating causal effects in the presence of noncompliance (Angrist et al. 1996) would likely necessitate further exclusion restriction assumptions, e.g., given the actual treatment received, assignment to treatment carries no additional information. Additional research is also needed to incorporate baseline covariates and allow for missing or mismeasured infection or post-infection outcomes.
Although we have handled the post-infection outcomes of transmission and disease severity or death similarly in this paper, there are important differences. In particular, vaccine efficacy for infectiousness, VE\textsubscript{I}, involves transmission to another susceptible individual, while vaccine efficacy for severity or progression, VE\textsubscript{P}, involves only the infected individual. Thus, unlike VE\textsubscript{P}, VE\textsubscript{I} can depend on the characteristics of the individuals susceptible to secondary infection as well as the type of contacts between individuals. Also, an infected individual could expose more than one individual, so that there could be several potential post-infection outcomes, one for each exposed individual. For example, in Prëziosi and Halloran (2003a), over 20 individuals are exposed to one infected individual in some cases. Alternatively, an infected individual may expose no other susceptibles, so then the potential post-infection outcome would be undefined. Our method needs to be extended to such multiple outcomes and possible dependencies.

In most vaccine studies in humans, whether or not an individual becomes infected is not under the control of the investigator. The potential post-infection outcomes for individuals who would not get infected under either vaccine or placebo are undefined, or a priori counterfactual (Frangakis and Rubin 2002), resulting in our defining the post-infection causal estimand in the doomed stratum only. However, there are a few infectious agents with which human participants can be challenged in vaccine studies as well as infection challenge animal experiments. For these types of studies, more appropriate might be the approach of Robins and Greenland (1992,1994) in which they assume that the post-treatment variable is controllable, that is, the investigator can force the individuals to take on any possible value of the post-treatment variable. Comparison of the different approaches is an outstanding research question.

**APPENDIX: MAXIMUM LIKELIHOOD ESTIMATION**

Let $\xi = \theta^{01} \gamma^1 + \theta^{11} \phi^1$ and consider maximizing the log likelihood

$$
\begin{align*}
n_{0s}(p) & \log(\theta^{00}) \\
+ n_{10}(p) & \log(\theta^{01} + \theta^{11} - \xi) \\
+ n_{11}(p) & \log(\xi) \\
+ n_{0s}(v) & \log(\theta^{00} + \theta^{01}) \\
+ n_{10}(v) & \log(\theta^{11}(1 - \phi^1)) \\
+ n_{11}(v) & \log(\theta^{11} \phi^1)
\end{align*}
$$

subject to the constraints

$$
\theta^{00} + \theta^{01} + \theta^{11} = 1,
$$

(37)
\[ 0 \leq \theta^{ij} \ (i, j = 0, 1; i \leq j), \]  
\[ 0 \leq \xi \leq \theta^{01} + \theta^{11}, \]  
\[ 0 \leq \phi^1 \leq 1. \]  

The maximum of \( \phi^1 \) is given by \( \hat{\phi}^1 = n_{11}(v)/n_1(v) \), such that we are left with the simpler problem of maximizing

\[
l(\theta, \xi) = n_{01}(p) \log(\theta^{00}) + n_{10}(p) \log(\theta^{01} + \theta^{11} - \xi) + n_{11}(p) \log(\xi) + n_{00}(v) \log(\theta^{00} + \theta^{01}) + n_1(v) \log(\theta^{11}),
\]

subject to (37-39).

The function \( l(\theta, \xi) \) is concave over the convex parameter space defined by (37-39) such that the MLE exists and the (first order) Kuhn-Tucker conditions are necessary and sufficient for optimality (Fletcher 1987; Gentleman and Geyer, 1994). In particular, define Lagrange multipliers \( \lambda_0, \lambda_1, \ldots, \lambda_5 \) and Lagrangian function

\[ L(\theta, \xi) = l(\theta, \xi) + \lambda_0(1 - \sum \theta^{ij}) + \lambda_1 \theta^{00} + \lambda_2 \theta^{01} + \lambda_3 \theta^{11} + \lambda_4 \xi + \lambda_5 (\theta^{01} + \theta^{11} - \xi), \]

where the summation is over \( i, j = 0, 1 \) such that \( i \leq j \). Then \( (\hat{\theta}, \hat{\xi}) \) is a MLE iff it is a feasible point according to (37-39) and satisfies

\[
\frac{\partial L(\theta, \xi)}{\partial \theta^{ij}} = 0 \ (i, j = 0, 1; i \leq j),
\]

\[
\frac{\partial L(\theta, \xi)}{\partial \xi} = 0,
\]

\[
\lambda_i \geq 0 \ (i = 1, \ldots, 5),
\]

and

\[
\lambda_0(1 - \sum \theta^{ij}) = \lambda_1 \theta^{00} = \lambda_2 \theta^{01} = \lambda_3 \theta^{11} = \lambda_4 \xi = \lambda_5 (\theta^{01} + \theta^{11} - \xi) = 0.
\]

Clearly we must have \( \hat{\theta}^{00}, \hat{\theta}^{11} \) and \( \hat{\xi} \) strictly greater than zero to maximize \( l(\theta, \xi) \), such that \( \lambda_1 = \lambda_3 = \lambda_4 = 0 \). Similarly, we must have \( \hat{\xi} < \hat{\theta}^{01} + \hat{\theta}^{11} \), such that \( \lambda_5 = 0 \) as well. Multiplying equations (41) and (42) by \( \theta^{ij} \) and \( \xi \) and summing, i.e.,

\[
\sum \theta^{ij} \frac{\partial L(\theta, \xi)}{\partial \theta^{ij}} + \xi \frac{\partial L(\theta, \xi)}{\partial \xi} = 0,
\]
can be shown to yield \( \lambda_0 = n \). It follows that \((\hat{\theta}, \hat{\xi})\) is a MLE iff it satisfies (37-39) and

\[
\frac{\partial l(\theta, \xi)}{\partial \theta^{00}} = \frac{n_{00}(p)}{\theta^{00} + \theta^{01}} = n, \tag{45}
\]

\[
\frac{\partial l(\theta, \xi)}{\partial \theta^{01}} = \frac{n_{10}(p)}{\theta^{01} + \theta^{11} - \xi} + \frac{n_{00}(p)}{\theta^{00} + \theta^{01}} \leq n, \tag{46}
\]

\[
\frac{\partial l(\theta, \xi)}{\partial \theta^{11}} = \frac{n_{10}(p)}{\theta^{01} + \theta^{11} - \xi} + \frac{n_{10}(v) + n_{11}(v)}{\theta^{11}} = n, \tag{47}
\]

\[
\frac{\partial l(\theta, \xi)}{\partial \xi} = \frac{n_{11}(p)}{\xi} - \frac{n_{10}(p)}{\theta^{01} + \theta^{11} - \xi} = 0. \tag{48}
\]

One can show that the MLE of \( \theta \) has the following closed form that depends on the data. In particular, if

\[
\frac{n_{00}(v)}{n(v)} > \frac{n_{00}(p)}{n(p)},
\]

then the MLEs are given by

\[
\hat{\theta}^{00} = \frac{n_{00}(p)}{n(p)}, \quad \hat{\theta}^{01} = \frac{n_{00}(v)}{n(v)} - \frac{n_{00}(p)}{n(p)}, \quad \hat{\theta}^{11} = 1 - \frac{n_{00}(v)}{n(v)}.
\]

Otherwise

\[
\hat{\theta}^{00} = \frac{n_0(p) + n_{00}(v)}{n}, \quad \hat{\theta}^{01} = 0, \quad \hat{\theta}^{11} = 1 - \frac{n_0(p) + n_{00}(v)}{n}.
\]

In either case, the MLE of \( \xi \) is given by

\[
\hat{\xi} = \frac{n_{11}(p)}{n_1(p)} (\hat{\theta}^{01} + \hat{\theta}^{11}),
\]

which implies equation (17).

References


Table 1: Basic principal stratification $P_0$ based on the potential infection outcomes $(S(v), S(p))$ with potential post-infection strata based on $(Y(v), Y(p))$.

<table>
<thead>
<tr>
<th>Potential infection strata</th>
<th>Potential infection outcomes $(S(v), S(p))$</th>
<th>Potential post-infection outcomes $(Y(v), Y(p))$</th>
<th>Post-infection interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>immune</td>
<td>(0,0)</td>
<td>(<em>,</em>)</td>
<td>always undefined</td>
</tr>
<tr>
<td>harmed</td>
<td>(1,0)</td>
<td>(0,*)</td>
<td>not severe vaccine, undefined placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,*)</td>
<td>severe vaccine, undefined placebo</td>
</tr>
<tr>
<td>protected</td>
<td>(0,1)</td>
<td>(*,0)</td>
<td>undefined vaccine, not severe placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(*,1)</td>
<td>undefined vaccine, severe placebo</td>
</tr>
<tr>
<td>doomed</td>
<td>(1,1)</td>
<td>(0,0)</td>
<td>never severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,0)</td>
<td>harmed by vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0,1)</td>
<td>helped by vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,1)</td>
<td>always severe</td>
</tr>
</tbody>
</table>
Table 2: Rotavirus vaccine example (Vesikari, et al, 1990). Relation of observed data to the basic principal strata of the joint potential infection outcomes and the strata of joint potential post-infection outcomes. The shaded regions correspond to membership within the basic strata with observations outside the shaded regions having unknown stratum. Numbers in [ ] are not observed, but follow from Assumptions 1-3 and the observed data.

<table>
<thead>
<tr>
<th>Basic principal stratum, $S^R$</th>
<th>Potential infection outcomes $(S(v), S(p))$</th>
<th>$n(v) = 100$</th>
<th>Potential post-infection outcomes $(Y(v), Y(p))$</th>
<th>Placebo $n(p) = 100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>immune</td>
<td>$(0,0)$</td>
<td>[84]</td>
<td>$(\star, \star)$</td>
<td>$n_{0\star}(p) = 84$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>${n_{1\star}(p) = 3}$</td>
</tr>
<tr>
<td>protected</td>
<td>$(0,1)$</td>
<td>[6]</td>
<td>$(\star, 0)$</td>
<td>$n_{1\star}(p) = 5$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$(\star, 1)$</td>
<td>${n_{11}(p) = 5}$</td>
</tr>
<tr>
<td>doomed</td>
<td>$(1,1)$</td>
<td>10</td>
<td>$n_{10}(v) = 5$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$n_{11}(v) = 5$</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Assumed underlying complete data and estimates of causal VE_I under different selection model assumptions in the infected placebo recipients for rotavirus candidate vaccine data. The shaded regions correspond to membership within the basic strata with observations outside the shaded regions having unknown stratum. Numbers in [ ] are not observed, but follow from Assumptions 1-3 and the observed data.

<table>
<thead>
<tr>
<th>Basic principal stratum, S^\empty</th>
<th>Potential infection outcomes (S(c), S(p))</th>
<th>Potential post-infection outcomes (Y(c), Y(p))</th>
<th>Infected placebo recipients observed</th>
<th># in S^\empty</th>
<th>( z = p )</th>
<th>Assumed underlying complete data</th>
<th>no selection bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>protected</td>
<td>(0,1)</td>
<td>(*,0)</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1.125</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(*,1)</td>
<td></td>
<td>6</td>
<td>5</td>
<td>4.875</td>
<td>4</td>
</tr>
<tr>
<td>doomed</td>
<td>(1,1)</td>
<td>(0,0)</td>
<td></td>
<td>3</td>
<td>2</td>
<td>1.875</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1,0)</td>
<td></td>
<td>7</td>
<td>8</td>
<td>8.125</td>
<td>9</td>
</tr>
</tbody>
</table>

\( \hat{\text{VE}}_I \) 0.29 0.375 0.38 0.44 0.50
Table 4: Simulated size and power of $T_{lower}$ when using the NPMLE bootstrap approach. Results are based on 10,000 simulations with $B = 500$ bootstrap samples per simulation. The expected number of infected placebo recipients is denoted by $n(p)(\theta^0 + \theta^{11})$ and the magnitude of the location shift is denoted by $\Delta$. The simulations assumed $\Pr[Y(p) = 1|S(p) = 1] = 0.6$.

<table>
<thead>
<tr>
<th>$n(p)(\theta^0 + \theta^{11})$</th>
<th>$\Delta = 0$</th>
<th>$\Delta = 0.1$</th>
<th>$\Delta = 0.2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$VE_S$</td>
<td>$VE_S$</td>
<td>$VE_S$</td>
</tr>
<tr>
<td>45</td>
<td>0.04 0.10 0.09</td>
<td>0.22 0.21 0.16</td>
<td>0.50 0.37 0.26</td>
</tr>
<tr>
<td>90</td>
<td>0.05 0.08 0.07</td>
<td>0.33 0.25 0.19</td>
<td>0.72 0.49 0.35</td>
</tr>
<tr>
<td>135</td>
<td>0.05 0.07 0.07</td>
<td>0.42 0.28 0.20</td>
<td>0.86 0.59 0.42</td>
</tr>
<tr>
<td>180</td>
<td>0.05 0.07 0.07</td>
<td>0.51 0.32 0.23</td>
<td>0.93 0.70 0.50</td>
</tr>
</tbody>
</table>
Table 5: Simulated size and power comparing $T_{lower}$, which conditions on infection, and Fisher’s exact test (FET), which does not condition on infection. Both tests are one-sided and performed at the $\alpha = 0.05$ significance level. Results are based on 10,000 simulations with $B = 500$ bootstrap samples per simulation for $T_{lower}$. The expected number of infected placebo recipients is denoted by $n(p)(\theta_{01} + \theta_{11})$ and the magnitude of the location shift is denoted by $\Delta$. The simulations assumed a true $VE_S = 0$ and $Pr[Y(p) = 1|S(p) = 1] = 0.6$.

<table>
<thead>
<tr>
<th>$n(p)(\theta_{01} + \theta_{11})$</th>
<th>$\Delta = 0$</th>
<th>$\Delta = 0.1$</th>
<th>$\Delta = 0.2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T_{lower}$</td>
<td>$FET$</td>
<td>$T_{lower}$</td>
</tr>
<tr>
<td>45</td>
<td>0.04</td>
<td>0.03</td>
<td>0.22</td>
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<tr>
<td>90</td>
<td>0.05</td>
<td>0.04</td>
<td>0.33</td>
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<tr>
<td>135</td>
<td>0.05</td>
<td>0.05</td>
<td>0.42</td>
</tr>
<tr>
<td>180</td>
<td>0.05</td>
<td>0.04</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Figure captions:

Figure 1. Maximum positive and negative selection bias models.

Figure 2. Sensitivity analysis using the odds ratio of infection under vaccine given infection under assignment to placebo with post-infection endpoint $Y(p) = 1$ versus $Y(p) = 0$ as described in section 4.3.1. The vertical dotted line corresponds to the assumption of no selection bias.

Figure 3. Sensitivity analysis assuming $\gamma^1 = \Pr \{Y(p) = 1 | S^{p_0} = (0,1) ; \gamma \}$ is known as described in section 4.3.2. The vertical dotted line gives the MLE of $\gamma^1$ under the assumption of no selection bias.
Figure 1:

Upper bound for $V_{E_i}$

Lower bound for $V_{E_i}$
Figure 2:

(a) Rotavirus

(b) Pertussis
Figure 3: