Statistical Methods for Infectious Diseases
Post-infection Vaccine Effects, VE$_P$

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Post-infection Outcomes: Disease

- Disease at all
- Probability of developing disease within some time period after infection
- Rate of progression to disease
- Surrogate outcomes: viral load

Conditional on Developing Clinical Case

- Rate of progression of disease
- Disease severity, extreme example death;
- Number of pox in chickenpox

Contrast with VE_S, or VE_{SP}

- Possible to define the primary outcome of a study based on a clinical case.
- Then comparison is with those who are not a clinical case, some of whom may be infected.
- This has a different interpretation since exposure to infection must be taken into account.

Post-infection Outcomes: Infectiousness

- VE_I as a post-infection outcome
- Level of viral shedding, etc
- much more complex if measured epidemiologically on transmission probability.

Vaccine efficacy for pathogenicity

- Pathogenicity is a measure of the ability of an infectious agent to cause disease
- Can be measured as the probability of developing disease if infected.

$$\widehat{\text{VE}}_P = 1 - \frac{\frac{\text{no. vaccinated cases}}{\text{no. vaccinated infections}}}{\frac{\text{no. unvaccinated cases}}{\text{no. unvaccinated infections}}}$$

- Need to ascertain asymptomatic infections.

Vaccine efficacy for disease severity

- Interest in defining ability to reduce probability of developing severe disease if a clinical case develops

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

- Definition of a severe case and a non-severe case necessary.

Figure: VE$_P$: Death versus Recovery in Smallpox: Greenwood and Yule 1915

TABLE XLIII.

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

Smallpox Death vs Recovery

- Greenwood and Yule (1915) (from Pearson)

$$\begin{aligned}
\widehat{\text{VE}}_P &= 1 - \frac{\frac{\text{no. severe vaccinated cases}}{\text{no. vaccinated cases}}}{\frac{\text{no. severe unvaccinated cases}}{\text{no. unvaccinated cases}}} \\
&= 1 - \frac{\frac{42}{1{,}604}}{\frac{94}{477}} \\
&= 0.87
\end{aligned}$$

Different types of postinfection and postclinical outcomes, VE_P.

Ascertainment can be on infection or on clinical disease, which determines the VE_S

VE_S outcome	Postinfection VE_P outcome	Examples
Infection 0,1	dichotomous	clinical case (0,1) clinical case within time interval (0,1) transmission to other (0,1)
	continuous	malaria parasite density HIV viral load
	time-to-event	time to developing symptoms
Clinical case 0,1	dichotomous	severe disease (0,1) death transmission to other (0,1)
	continuous	malaria parasite density chickenpox: number of lesions
	time-to-event	time to clearing infection

Effect of Pertuss Vaccination on Disease

- Préziosi and Halloran, Effects of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. CID 2003, 37:772–779.
- They propose a scale to assess the global clinical severity of a pertussis cases, rather than analyzing each individual symptom.
- They propose a method of estimating the efficacy of vaccine in reducing the clinical severity of illness, with the condition that the case of pertussis has been confirmed by culture or serologic testing.

Setting and Population

- The Niakhar study area is 150 km southeast of Dakar, Senegal, and includes 30 villages.
- Extended families reside in compounds.
- In January 1993, there were 26,306 residents living in 1800 compounds.
- Surveillance: from March 1983, annual, after 1987 weekly visits to compounds
- Pertussis was endemic, with epidemics every 3–4 years, and 1993 was a pertussis epidemic year.

Surveillance

- Active surveillance conducted in children < 15 years of age by weekly visits to the compounds by trained field workers
- Reported cases in children < 15 years old who had potential pertussis (cough of > 7 days duration)
- Physician then visited to confirm clinically and collect laboratory samples.

Definitions

- Confirmation of pertussis infection by at least 1 of 3 laboratory criteria:
- culture positive
- serology positive
- signs and symptoms of disease in an individual who lived in the same compound as a child who had onset of culture-positive disease within 28 days.
- Severity of illness assessed according to the scale in table 1. Death not included (only 1 death).

Table 1. Scale used to assess the severity of illness among children with symptoms of pertussis.

Variable	No. of points
Severity of cough	
Typical paroxysms with whoops	4
Typical paroxysms without whoops	3
Atypical paroxysms only	1
Apnea	6
Pulmonary sign[a]	3
Mechanical complication[b]	3
Facial swelling	3
Conjunctival injection	3
Post-tussive vomiting	2
Total score (severity)[c]	
Mild disease	$\leqslant 6$
Severe disease	>6

[a] Bronchitis or bronchopneumonia, as diagnosed by a physician on auscultation.

[b] Subconjunctival hemorrhage or umbilical or unguinal hernia.

[c] The overall median total score was 6 in this study.

VE_P

- Vaccine efficacy in reducing severity was a measure of the decreased severity of breakthrough disease compared with disease in unvaccinated individuals.

$$\widehat{\text{VE}}_P = 1 - \frac{\frac{\text{severe vaccinated cases}}{\text{all vaccinated cases}}}{\frac{\text{severe unvaccinated cases}}{\text{all unvaccinated cases}}}$$

- Sex, age, and type of case (primary or secondary) included in a multivariate analysis using logistic regression and then backtransformed to VE scale; bootstrap for CIs. (Halloran et al 2003)

VE_S

- VE$_S$ (VE$_{SP}$) also computed, the usual estimator, either using all cases or just severe cases.
- Child-years at risk computed for 1993 among susceptible children 6 months up to 8 years old.
- Standard CIs assuming log-normality of relative risks.

Population Selection

- In 1993, 2123 individuals with potential cases of pertussis were identified in 518 of 1800 residential compounds, 98% under 15 years of age.
- Nearly all under 6 months or 9 years and older were unvaccinated, so could these age groups could not be included in comparison.
- Finally, laboratory confirmation necessary.
- In all, 834 children with 837 cases of laboratory-confirmed pertussis were identified.

Estimated VE$_P$

- Based on the median threshold for mild versus severe disease of 6.
- $\text{VE}_P = 1 - \frac{190/594}{149/243} = 0.48$, (95% CI, 39–55)
- Unvaccinated children were twice as likely as vaccinated children to have severe disease.
- Examined sensitivity of results to choice of the threshold value.

Table 4. Number of cases of severe pertussis, among 834 children who had or had not received pertussis vaccine, and efficacy of the vaccine in reducing severity, according to severity score.

Score	No. (%) of cases			Vaccine efficacy,[a] % (95% CI)
	All (n = 837)	In unvaccinated children (n = 243)	In vaccinated children (n = 594)	
>0	738 (88)	233 (96)	505 (85)	11 (8–15)
>1	728 (87)	231 (95)	497 (84)	12 (8–16)
>2	677 (81)	227 (93)	450 (76)	19 (14–23)
>3	559 (67)	205 (84)	354 (60)	29 (23–35)
>4	529 (63)	194 (80)	335 (56)	29 (22–36)
>5	443 (53)	178 (73)	265 (45)	39 (32–46)
>6	339 (41)	149 (61)	190 (32)	48 (39–55)
>7	315 (38)	139 (57)	176 (30)	48 (39–56)
>8	268 (32)	119 (49)	149 (25)	49 (38–58)
>9	151 (18)	76 (31)	75 (13)	60 (47–70)
>10	147 (18)	75 (31)	72 (12)	61 (48–71)
>11	130 (16)	67 (28)	63 (11)	62 (48–72)
>12	31 (4)	20 (8)	11 (2)	78 (54–89)
>13	30 (4)	19 (8)	11 (2)	76 (51–89)
>14	24 (3)	17 (7)	7 (1)	83 (60–93)

NOTE. The scale used to assign the severity score is shown in table 1. The overall median score was 6. A score ⩽6 indicates mild disease; a score >6 indicates severe disease.

[a] Vaccine efficacy in slowing disease progression (VEp) was calculated using the following formula: VEp = 1 − [(severe vaccinated cases/all vaccinated cases)/(severe unvaccinated cases/all unvaccinated cases)].

Secondary results

- VE$_{SP}$ for all cases: 29% (95% CI, 19% – 39%)
- VE$_{SP}$ for severe cases: 64% (95% CI, 55% – 71%)
- Typical to estimate VE$_{SP}$ for range of clinical definitions.
- Difference in interpretation to VE$_P$

Discussion

- Results indicate that pertussis vaccination substantially decreases the severity of breakthrough disease in children who receive 3 doses of vaccine, compared with that in unvaccinated children.
- Majority of vaccinated children who developed pertussis had mild disease.
- Potential for selection bias in the observational study: (1) ascertainment and (2) laboratory confirmation. Both minimal in this case.

Rotavirus vaccine candidate: Vesikari et al. (1990)

- Finland, 1985-1987, children 2 to 5 mos. RCT
- 100 each arm

- 5 of 10 vaccinated cases severe or moderately severe.
- 13 of 16 placebo cases severe or moderately severe.
- 0.38, 95% CI $[-0.11, 0.74]$.

Post-infection Selection Bias

- Pertussis analysis assumed that the vaccinated and unvaccinated children who developed pertussis were comparable.
- However, even in a randomized study, the vaccinated and unvaccinated people who become infected are no longer necessarily comparable if the vaccine has an effect on whether a person gets infected.
- Potential for post-infection selection bias that produces misleading estimates of VE$_P$

Figure: Hudgens, Hoering, Self. On the analysis of viral load endpoints in HIV vaccine trials. Statist. Med. 2003; 22:2281–2298.

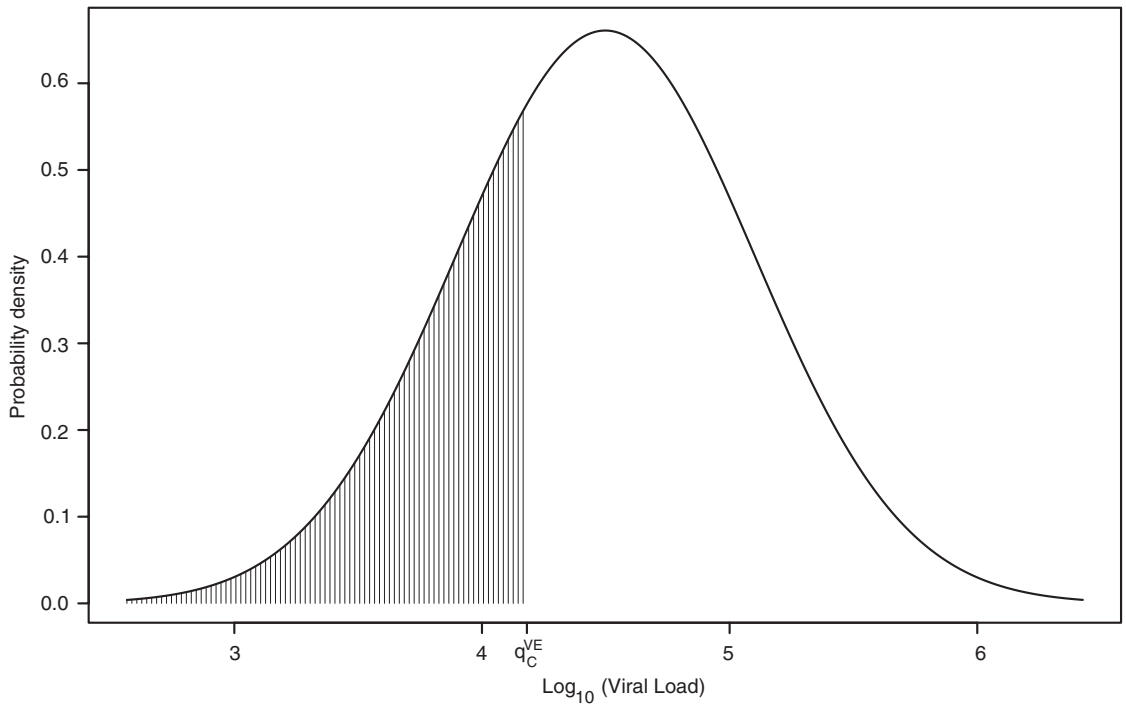


Figure 1. Viral load distributions for infected participants under a selection model. The normal distribution represents the viral loads of the infected controls. The shaded area represents the potential viral loads of the VE $\times$ 100 per cent that are protected by the vaccine. The unshaded area (after appropriate rescaling) represents the viral load distribution of the infected vaccinees.

Consequences

- In HIV vaccine case, possibility of discarding a potentially useful vaccine candidate
- In pertussis case, possible bias in estimates of VE$_P$ which could either over- or underestimate the public health benefits.

Causal Vaccine Effects

- Gilbert, Bosch, Hudgens. Sensitivity analysis for the assessment of causal vaccine effects on viral load in HIV vaccine trials. Biometrics. 2003; 59:531– 541, and Shepherd et al 2006.
- $\longrightarrow$ Continuous postinfection outcome of viral load.
- Hudgens and Halloran. Causal vaccine effects on binary postinfection outcomes. JASA. 2006; 101:51-64.
- $\longrightarrow$ Binary postinfection outcomes such as severity, etc
- $\longrightarrow$ Easier to present

What is an individual causal effect?

- Difference in potential outcomes in individual i under one treatment compared to another treatment.
- Formally, for $i = 1, \ldots, n$,

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

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

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

Causal Inference and SUTVA

- Stable Unit Treatment Value Assumption (Rubin 1980)
  - The potential outcomes in an individual is independent of the treatment assignment of others; no interference between units (Cox 1958)
  - All treatments and their potential outcomes are represented in the model.
- Then the representation with just two potential outcomes is adequate.

Fundamental Problem of Causal Inference

- We cannot observe both potential outcomes for person i
- So, define population average causal effect we can identify
- Then specify an assignment mechanism, for example randomization

Population Average Causal Effect

- Under randomization and SUTVA,

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

- identifiable from the data

Basic Principal Strata

- A *basic principal stratification* P_0 is defined according to the joint potential infection outcomes $S^{P_0} = (S(v), S(p))$ (Frangakis and Rubin 2002).

- The next table summarizes the four basic principal strata defined by the joint potential infection outcomes, $(S(v), S(p))$, and the strata defined by the joint potential post-infection outcomes, $(Y(v), Y(p))$, within each principal stratum.

- 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^{P_0}.

Basic principal stratification P_0 based on the potential infection outcomes $(S(v), S(p))$ with potential post-infection strata based on $(Y(v), Y(p))$ (Hudgens and Halloran 2006).

Potential infection strata		Potential post-infection strata	
Basic principal stratum, S^{P_0}	Potential infection outcomes $(S(v), S(p))$	Potential post-infection outcomes $(Y(v), Y(p))$	Post-infection interpretation
immune	(0,0)	$(*,*)$	always undefined
harmed	(1,0)	$(0,*)$	not severe vaccine, undefined placebo
		$(1,*)$	severe vaccine, undefined placebo
protected	(0,1)	$(*,0)$	undefined vaccine, not severe placebo
		$(*,1)$	undefined vaccine, severe placebo
doomed	(1,1)	(0,0)	never severe
		(1,0)	harmed by vaccine
		(0,1)	helped by vaccine
		(1,1)	always severe

Causal VE$_S$

- The population casual vaccine efficacy to prevent infection $S = 1$:

$$\text{VE}_S = 1 - \frac{\Pr(S(1) = 1)}{\Pr(S(0) = 1)}, \tag{1}$$

  the relative average causal effect (RACE) of vaccination on infection (Hudgens and Halloran 2006).
- Under randomization, it follows that

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

Causal post-infection vaccine efficacy estimand

- Vaccine effect on disease progression within the doomed basic principal stratum:

$$\text{VE}_P = 1 - \frac{E\{Y(v)|S^{P_0} = (1,1)\}}{E\{Y(p)|S^{P_0} = (1,1)\}}$$

- Pro:
  - Causal effect
  - Not subject to selection bias
  - Separates VE$_S$ and disease progression
- Con:
  - Can not identify individuals in $S^{P_0} = (1,1)$ (doomed)

Steps Toward Identification

- Assume that vaccine does no harm for infection, harmed stratum empty (monotonicity)
- $\longrightarrow$ infected vaccine recipients in harmed stratum, numerator of causal VE$_P$ identifiable.
- $\longrightarrow$ only infected placebos recipients can be in one of two strata, denominator of causal VE$_P$ not identifiable

Basic principal stratification P_0 based on the potential infection outcomes $(S(v), S(p))$ with potential post-infection strata based on $(Y(v), Y(p))$ (Hudgens and Halloran 2006).

Potential infection strata			Potential post-infection strata	
Basic principal stratum, S^{P_0}	Potential infection outcomes $(S(v), S(p))$		Potential post-infection outcomes $(Y(v), Y(p))$	Post-infection parameter
immune	(0,0)	θ_{00}	$(*,*)$	always undefined
protected	(0,1)	θ_{01}	$(*,0)$	γ_0
			$(*,1)$	γ_1
doomed	(1,1)	θ_{11}	(0,0)	ϕ_{00}
			(1,0)	ϕ_{10}
			(0,1)	ϕ_{01}
			(1,1)	ϕ_{11}

Unindentifiable causal VE$_P$

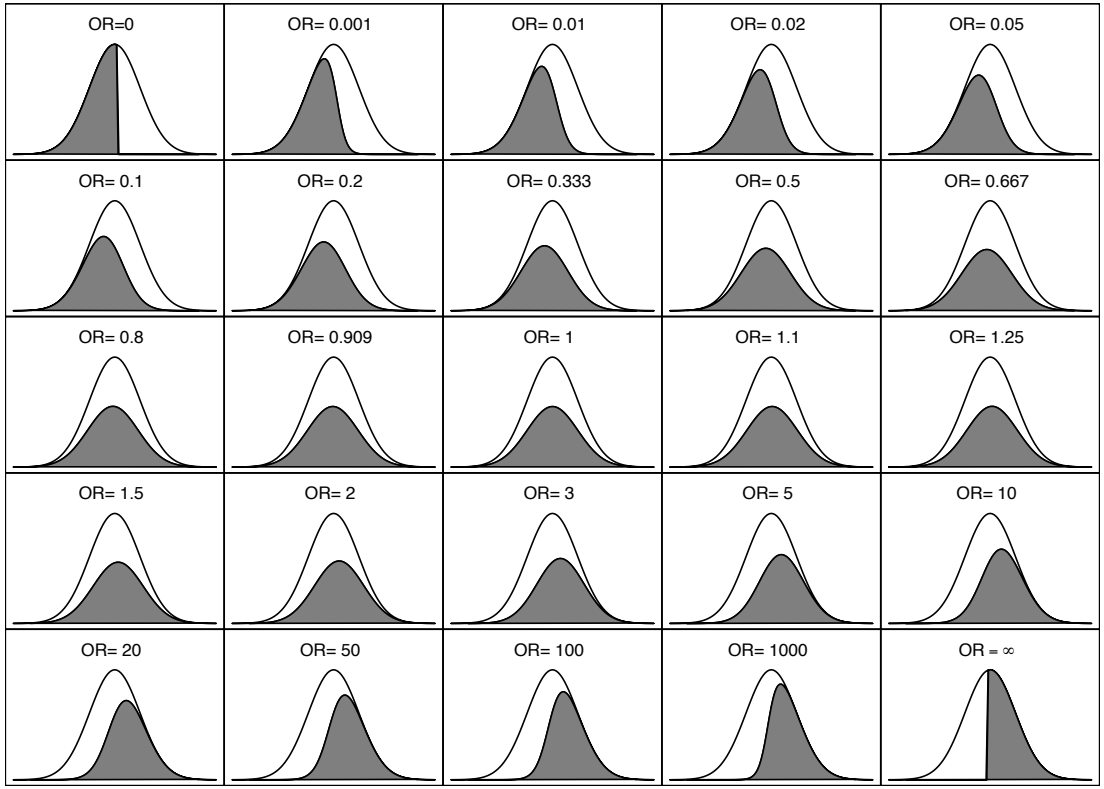
$$\widehat{\mathrm{VE}}_P = 1 - \frac{PAR_v}{??}$$

Steps Toward Identification

- Bounds on estimates of VE_P are set on extremes of how the infected placebo recipients could be distributed.
  $\longrightarrow \widehat{VE}_P^{upper}$ and $\widehat{VE}_P^{lower}$
- Then sensitivity analysis can be done by varying degree of selection bias.
- Perhaps expert opinion can be brought to bear.
- Inference proceeds using usual methods.

Sensitivity analysis

- Gilbert et al.(2003b), Shepherd et al (2006), and Shepherd et al (2007) adapted methods for sensitivity similar to that of Scharfstein, et al (1999) and Robins, et al (2000) for continuous outcomes.
- In this approach, the sensitivity analysis is performed by varying a selection bias parameter β over a range.
- In particular the odds ratio, OR $= \exp(\beta)$, is varied from 0 to $+\infty$, with no selection bias being at OR $= 1$.
- The odds ratio is interpreted as given infection in the placebo arm, for a one unit increase in the Y outcome, the odds of being infected if randomized to the vaccine arm multiplicatively increases by OR $= \exp(\beta)$.



Distribution of the potential post-infection outcome Y in the infected control group in the protected stratum and the infected control group in the doomed stratum for different values of the selection bias odds ratio $\exp(\beta)$. The shaded area represents the distribution of the potential Y outcome in the infected control group in the doomed stratum. The area under the clear distribution is that in the protected stratum.

VE_P^{net}

- The approach to assessing vaccine effects on post-infection endpoints based on the observed data is the *net* vaccine effect estimand which conditions on infection, i.e.,

$$\text{VE}_P^{net} = 1 - \frac{E\left\{Y^{obs} | S^{obs} = 1, Z = v\right\}}{E\left\{Y^{obs} | S^{obs} = 1, Z = p\right\}} = 1 - \frac{E\left\{Y(v) | S(v) = 1\right\}}{E\left\{Y(p) | S(p) = 1\right\}},$$

  with the second equality following from the randomization assumption.

- In general, VE_P^{net} does not have a causal interpretation.

VE_P^{ITT}

- $\text{VE}_{SP,CI}$ is an example of an intent-to-treat ITT estimand. Formally,

$$\text{VE}_{SP,CI} = \text{VE}_P^{ITT} = 1 - \frac{E\{Y(v) \times S(v)\}}{E\{Y(p) \times S(p)\}},$$

  where the convention sets $Y(z) \times S(z) = 0$ if $S(z) = 0$, $z = v, p$.

- considered ITT because it does not condition on the post-treatment variable S^{obs}.
- has a causal interpretation, but combines vaccine effects on susceptibility and post-infection outcomes. Formally,

$$\text{VE}_P^{ITT} = 1 - (1 - \text{VE}_S)(1 - \text{VE}_P^{net}).$$

MLEs

$$\widehat{\text{VE}}_S = \begin{cases} 1 - \frac{AR_v}{AR_p} & \text{if } AR_v \leq AR_p, \\ 0 & \text{otherwise.} \end{cases} \tag{2}$$

$$\widehat{\text{VE}}_P^{net} = 1 - \frac{PAR_v}{PAR_p}. \tag{3}$$

$$\widehat{\text{VE}}_P^{ITT} = 1 - (1 - \widehat{\text{VE}}_S)\frac{PAR_v}{PAR_p}. \tag{4}$$

Bounds on Causal VE$_P$

$$\widehat{\text{VE}}_P^{upper} = \begin{cases} 1 - PAR_v & \text{if } \widehat{\text{VE}}_S > 1 - PAR_p, \\ \widehat{\text{VE}}_P^{ITT} & \text{if } 0 < \widehat{\text{VE}}_S \leq 1 - PAR_p, \\ \widehat{\text{VE}}_P^{net} & \text{if } \widehat{\text{VE}}_S = 0. \end{cases} \tag{5}$$

$$\widehat{\text{VE}}_P^{lower} = \begin{cases} -\infty & \text{if } \widehat{\text{VE}}_S > PAR_p, \\ 1 - PAR_v / \left\{ \frac{PAR_p - \widehat{\text{VE}}_S}{1 - \widehat{\text{VE}}_S} \right\} & \text{if } 0 < \widehat{\text{VE}}_S \leq PAR_p, \\ \widehat{\text{VE}}_P^{net} & \text{if } \widehat{\text{VE}}_S = 0. \end{cases} \tag{6}$$

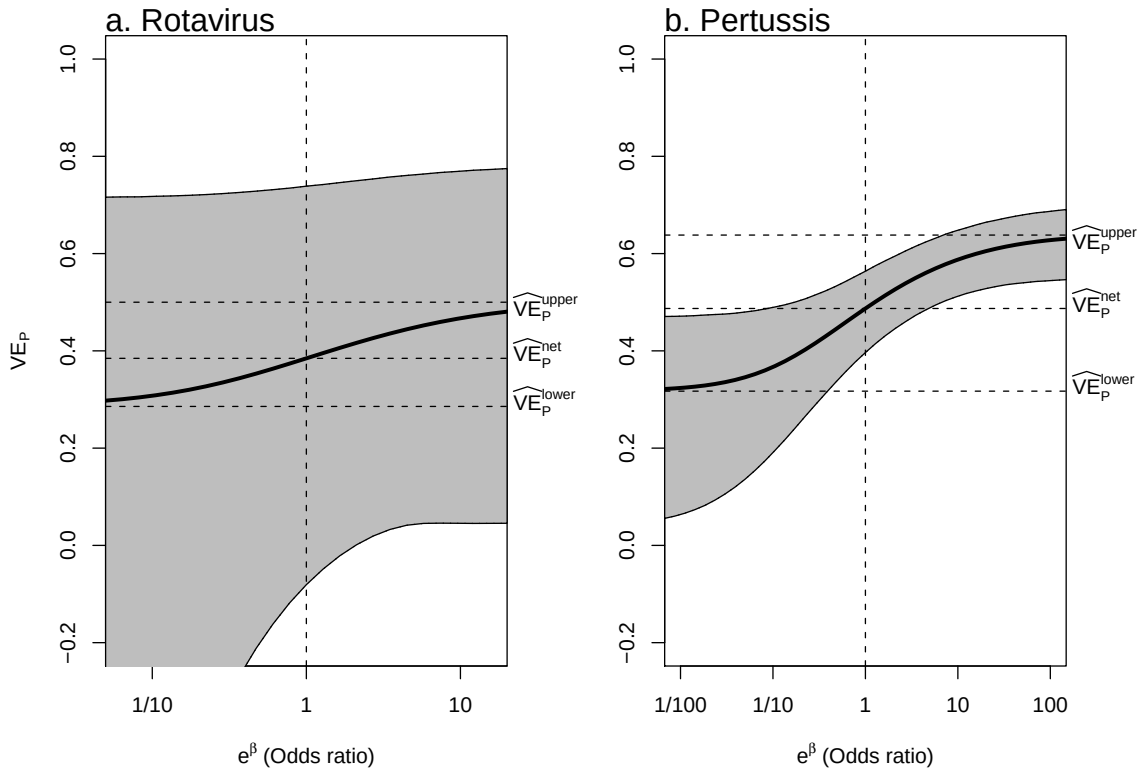


Figure: Sensitivity analysis using the odds ratio of having the severe post-infection endpoint under placebo in the doomed versus protected principal strata. The vertical dotted line corresponds to the assumption of no selection bias.

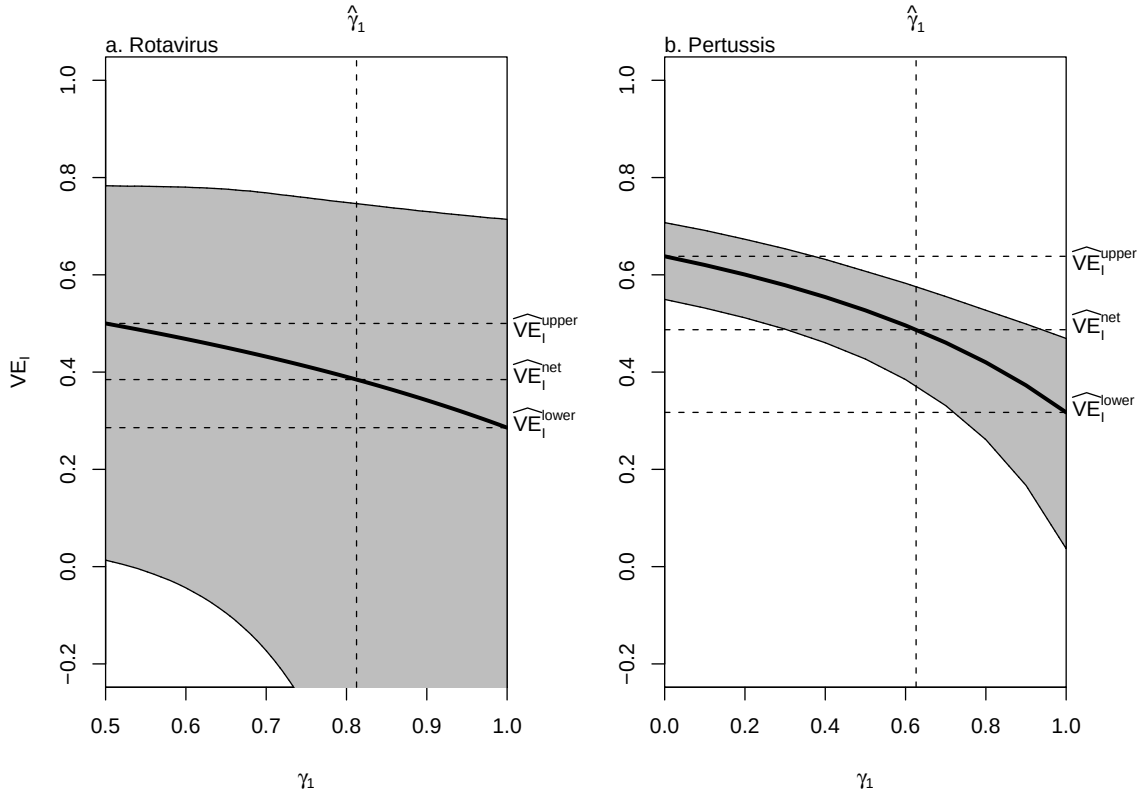


Figure: Sensitivity analysis assuming $\gamma_1 = \Pr\left\{Y(p) = 1 | S^{P_0} = (0,1); \boldsymbol{\gamma}\right\}$ is known. The vertical dotted line gives the MLE of γ_1 under the assumption of no selection bias.

Thank You!