

Identified vaccine efficacy for binary post-infection outcomes under misclassification without monotonicity

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Abstract

In order to meet regulatory approval, new vaccines typically must reduce the total risk of a post-infection outcome like transmission, symptomatic disease, severe illness, or death in randomized, placebo-controlled trials. Because infection is necessary for a post-infection outcome, one can use principal stratification to partition the total causal effect of vaccination into two causal effects: vaccine efficacy against infection, and the principal effect of vaccine efficacy on post-infection outcomes in the patients that would be infected under both placebo and vaccination. Despite the importance of such principal effects to policymakers, these estimands are generally unidentifiable, even under strong assumptions that are rarely satisfied in real-world trials. We develop a novel method to nonparametrically point identify these principal effects while eliminating the monotonicity assumption and allowing for measurement error. Furthermore, our results allow for multiple treatments, and are general enough to be applicable outside of vaccine efficacy. Our method relies on the fact that many vaccine trials are run at geographically disparate health centers, and measure biologically-relevant categorical pretreatment covariates. We show that our method can be applied to a variety of clinical trial settings where vaccine efficacy against

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infection and a post-infection outcome can be jointly inferred. This can yield new insights from existing vaccine efficacy trial data and will aid researchers in designing new multi-arm clinical trials.

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1 Introduction

Phase 3 randomized, placebo-controlled clinical trials are the gold-standard by which vaccine candidates are assessed for efficacy and safety. Such trials are an important source of data about whether vaccines prevent outcomes such as infection and post-infection outcomes like secondary transmission, severe illness, or death. For example, COVID-19 vaccination trials like [Polack et al. \(2020\)](#) and [Baden et al. \(2021\)](#) measured vaccine efficacy against symptomatic disease, as well as severe illness and death. Principal stratification, developed in [Frangakis & Rubin \(2002\)](#), may be used to partition the intention-to-treat effect of vaccination on an outcome like hospitalization into vaccine efficacy against infection and vaccine efficacy against hospitalization given infection in the always-infected stratum; these separate effects help policy makers optimize vaccination programs, communicate with the public, allocate scarce resources, and guide future pharmaceutical therapeutic development ([Lipsitch & Kahn 2021](#)). Methods to infer principal effects for vaccine efficacy were first developed for continuous post-infection outcomes in [Gilbert et al. \(2003\)](#), [Jemai et al. \(2007\)](#), [Shepherd et al. \(2006, 2007\)](#), and further developed for binary post-infection outcomes in [Hudgens & Halloran \(2006\)](#).

Unfortunately, vaccine efficacy against post-infection outcomes, binary or otherwise, is not generally identifiable, even under the assumption that vaccine efficacy against infection is non-negative almost-surely (monotonicity). Moreover, the method requires that both infection and post-infection outcomes are perfectly measured. Neither monotonicity nor error-free measurements can be assumed to hold in vaccine trials. Monotonicity can be violated if a vaccine increases the per-exposure probability of infection for a participant ([Gilbert et al. 2003](#)), which is possible in influenza vaccine trials where the vaccine targets a different antigen than the circulating strain. Another way monotonicity can be violated is if

vaccination increases exposure for certain participants. This can occur in a double-blinded placebo-controlled study where the vaccine is reactogenic and leads to some participants in the vaccine group becoming unblinded.

Measurement error is common in vaccine trials due to the imperfect nature of diagnostic tests for infection ([Kissler et al. 2021](#), [Wang et al. 2020](#)). Post-infection outcomes like symptoms may also be observed with error. For example, in an influenza vaccine trial, many different viruses circulate during influenza season that produce similar symptom profiles.

We develop novel methodology to point identify vaccine efficacy against binary post-infection outcomes without assuming monotonicity while allowing infection and post-infection outcomes to be misclassified. Our framework immediately generalizes to multiple treatments as we will show. We capitalize on the fact that many randomized trials for vaccines are run as multi-center trials (i.e. geographically disparate study sites) ([Francis 1982](#), [Longini Jr et al. 2000](#), [The FUTURE II Study Group 2007](#), [Halloran et al. 2010](#), [Baden et al. 2021](#), [Polack et al. 2020](#)), and typically measure pretreatment covariates relevant to infection. We build on literature for identifying principal stratum effects with covariates ([Rubin 2006](#), [Ding et al. 2011](#), [Jiang et al. 2016](#)), on inferring principal stratum effects in multisite randomized trials ([Wang, Richardson & Zhou 2017](#), [Yuan et al. 2019](#), [Luo et al. 2023](#)), on using covariates to hone large-sample nonparametric bounds ([Zhang & Rubin 2003](#), [Grilli & Mealli 2008](#), [Long & Hudgens 2013](#)), and on identifying causal estimands under unmeasured confounding ([Miao et al. 2018](#), [Shi et al. 2020](#)). Our method also relates to recent literature on inferring causal estimands under measurement error ([Jiang & Ding 2020](#)) and on identification of latent variable models ([Ouyang & Xu 2022](#)).

We show that our method can be used to design randomized trials for comparison of

multiple vaccines against a control, which will be a necessity for public health agencies in future pandemics as well as during the COVID-19 pandemic. Due to recent updates to regulatory guidance from the European Medicines Agency, the authority that authorizes pharmaceuticals in the European Union, principal effects are acceptable target estimands in randomized clinical trials and principal stratification is an acceptable analysis method for these trial data ([Bornkamp et al. 2021](#), [Lipkovich et al. 2022](#)). This means that our methodology can be used by regulatory agencies to design new clinical trials for vaccines that target post-infection outcome VE. As noted by several authors, vaccine efficacy against post-infection outcomes is mathematically analogous to the widely-studied survivor average treatment effects ([Ding et al. 2011](#), [Tchetgen Tchetgen 2014](#), [Ding & Lu 2017](#)), so our methodology can be readily used outside the domain of vaccine efficacy.

2 Vaccine efficacy in two-arm multi-center trials

Two-arm multi-center trials, or trials run in tandem across several disparate health centers where each participant is randomly assigned to receive a vaccine or a placebo, are the most common vaccine efficacy study designs. To fix ideas, we will consider the example of an influenza vaccine trial, where researchers are interested in understanding vaccine efficacy against influenza infection and vaccine efficacy against severe illness caused by influenza infection. Crucially, it is not possible to perfectly observe influenza infection or severe illness. Instead, researchers are limited to using imperfect tests for infection, like polymerase chain reaction (PCR) tests, or serology to detect a participant’s infection status. These methods measure infection with error, with varying levels of sensitivity and specificity. For example, PCRs for COVID-19 have very high specificity, but tend to have sensitivities in the range of 0.6 to 0.8 due to variation among patients in how the virus

populates the nasal cavity, variation in swab quality, and viral RNA dynamics (Kissler et al. 2021, Wang et al. 2020). Depending on the severity of the post-infection outcome, these outcomes may also be mismeasured. For instance, a high proportion of participants report symptoms in vaccine efficacy studies, despite many of these participants testing negative for the target disease. In the presence of high-sensitivity tests, this necessarily means that specificity of symptoms following infection is below 1. This is because it is possible for participants to develop influenza-like severe illness from non-influenza viruses during a clinical trial. Thus our framework assumes that observed infection and severe illness are noisy proxies for true unobservable infection and severe illness states. The next section outlines the data structure for each participant.

Suppose there are n participants in the trial, and we observe the following sextuplet for each participant i : $(\tilde{S}_i, \tilde{Y}_i, Z_i, R_i, A_i, X_i)$, where \tilde{S}_i is binary influenza test result, \tilde{Y}_i is observed binary severe illness status, and Z_i is binary treatment assignment. R_i is a categorical variable indicating the health center with which each participant is associated, A_i is a discrete pre-treatment covariate related to infection under treatment and control, and X_i is a univariate discrete pre-treatment covariate that may represent the intersection of several distinct covariates like age, sex, occupation, and pre-existing conditions. Let R_i take values from 1 to N_r , A_i take values from 1 to N_a , and X_i take values from 1 to N_x . $Z_i = 1$ for individuals assigned to receive vaccination, and $Z_i = 0$ for individuals assigned to placebo.

Let S_i be the latent influenza infection state, and Y_i be the latent influenza-caused severe illness state for each participant. We use the Neyman-Rubin causal model to define S_i , and Y_i as partially-observed realizations of counterfactual outcomes (Neyman 1923, Rubin 1974, 1978, Holland 1986). For an extensive review of statistical approaches to causal inference

through the lens of missing data see [Ding & Li \(2018\)](#). Let any potential treatment plan for all n individuals in the trial be the length- n binary vector \mathbf{z} , where the i^{th} element is the potential treatment status of the i^{th} participant. Accordingly, each individual is associated with a binary counterfactual infection outcome, $S_i(\mathbf{z})$, and a counterfactual severe illness outcome, $Y_i(\mathbf{z}, S_i(\mathbf{z}))$, under treatment status \mathbf{z} . Let the observed treatment status for all n individuals in the trial be the length- n binary vector \mathbf{Z} , where the i^{th} element is the assigned treatment of the i^{th} participant.

Our causal model enforces the constraint that an uninfected individual cannot have severe illness caused by influenza infection. In other words, post-infection outcomes are defined such that they are *caused* by infection from a pathogen of interest ([Gilbert et al. 2003](#), [Hudgens & Halloran 2006](#)). Then $Y_i(\mathbf{z}, 0)$ is undefined for all \mathbf{z} , and is denoted as $Y_i(\mathbf{z}, 0) = \star$. $Y_i(\mathbf{z}, S_i(\mathbf{z}))$ is defined as a binary variable only when $S_i(\mathbf{z}) = 1$, or, equivalently, $Y_i(\mathbf{z}, 1)$. For the remainder of the paper we assume that $S_i(\mathbf{z}) = S_i(\mathbf{z}')$ and $Y_i(\mathbf{z}, S_i(\mathbf{z})) = Y_i(\mathbf{z}', S_i(\mathbf{z}'))$ if $\mathbf{z}_i = \mathbf{z}'_i$. Therefore, we assume the Stable Unit Treatment Value Assumption (SUTVA) holds:

Assumption 2.1 (SUTVA). *There is only one version of each treatment, and counterfactual outcomes are a function of only a unit's respective treatment status, z .*

SUTVA can be satisfied for vaccine efficacy trials by restrictions on participants and recruitment ([Gilbert et al. 2003](#)). Furthermore, recruited participants are a small fraction of the total population at risk of infection ([Zhang et al. 2009](#)). Thus the vector $(S_i(1), Y_i(1, S_i(1)), S_i(0), Y_i(0, S_i(0)))$ is the complete definition of counterfactual outcomes under vaccination and placebo for each individual in the trial.

A second assumption we will make for the rest of the paper is that the study is a randomized experiment. This means that all trial participants have positive probabilities of

being assigned to either vaccine or placebo, and that treatment assignment is unconfounded (Imbens & Rubin 2015).

Assumption 2.2 (Random treatment assignment). *The probability of being assigned to treatment for each individual lies strictly between 0 and 1:*

$$0 < P(Z_i = 1 \mid S_i(1), S_i(0), Y_i(1, S(1)), Y_i(0, S_i(0))) < 1.$$

Treatment assignment is independent of all potential outcomes, or

$$S_i(1), S_i(0), Y_i(1, S_i(1)), Y_i(0, S_i(0)) \perp\!\!\!\perp Z_i.$$

Given Assumption 2.1 and Assumption 2.2, the latent realized values of the counterfactual variables are as follows:

$$S_i = Z_i S_i(1) + (1 - Z_i) S_i(0), \quad Y_i = Z_i Y_i(1, S_i(1)) + (1 - Z_i) Y_i(0, S_i(0)). \quad (1)$$

A third condition that will be assumed to hold is that of non-differential measurement errors for the influenza test result and the severe illness observation.

Assumption 2.3 (Non-differential Misclassification Errors). *Misclassification errors for \tilde{S}_i, \tilde{Y}_i are conditionally independent of all else given the true values S_i, Y_i or*

$$\tilde{S}_i \perp\!\!\!\perp Z_i, S_i^{P_0}, R_i, A_i, Y_i, X_i \mid S_i, \quad \tilde{Y}_i \perp\!\!\!\perp Z_i, S_i^{P_0}, R_i, A_i, S_i, X_i \mid Y_i.$$

Under Assumption 2.3, we may completely characterize the distributions of the noisy outcomes \tilde{S}_i, \tilde{Y}_i via the following four unknown parameters $\text{sn}_S = P(\tilde{S}_i = 1 \mid S_i = 1)$, $\text{sp}_S = P(\tilde{S}_i = 0 \mid S_i = 0)$ and $\text{sn}_Y = P(\tilde{Y}_i = 1 \mid Y_i = 1)$, $\text{sp}_Y = P(\tilde{Y}_i = 0 \mid Y_i = 0)$, or the respective sensitivities and specificities for infection and the post-infection outcome. This assumption can be loosened for infection misclassification as explored in Section 5.

We can thus define several causal estimands of interest related to the latent infection and severe illness states, $S_i(z), Y_i(z)$.

Definition 2.1 (Vaccine efficacy against infection).

$$\text{VE}_S = \mathbb{E}[S_i(0) - S_i(1)] / \mathbb{E}[S_i(0)], \text{ and}$$

Definition 2.2 (Intention-to-treat vaccine efficacy against severe illness).

$$\text{VE}_{ITT} = \mathbb{E}[Y_i(0, S_i(0))S_i(0) - Y_i(1, S_i(1))S_i(1)] / \mathbb{E}[Y_i(0, S_i(0))S_i(0)].$$

where we let $Y_i(z, S_i(z))S_i(z) = 0$ when $S_i(z) = 0$.

Under Assumptions 2.1 to 2.2, the following identities hold

$$\mathbb{E}[S_i(z)] = \mathbb{E}[S_i \mid Z_i = z], \quad \mathbb{E}[Y_i(z)] = \mathbb{E}[Y_i \mid Z_i = z].$$

Given the identities

$$\mathbb{E}[S_i = 1 \mid Z_i = z] = \frac{\mathbb{E}[\tilde{S}_i=1|Z_i=z]+\text{sp}_S-1}{\text{sp}_S+\text{sn}_S-1}, \quad \mathbb{E}[Y_i = 1 \mid Z_i = z] = \frac{\mathbb{E}[\tilde{Y}_i=1|Y_i=z]+\text{sp}_Y-1}{\text{sp}_Y+\text{sn}_Y-1}$$

and known sensitivities and specificities, Definition 2.1, and Definition 2.2 are estimable via plug-in ratio estimators.

2.1 Conditional effects and principal stratification

We might be tempted to define vaccine efficacy against severe illness by comparing the rate of severe illness in vaccinated participants to that of the unvaccinated among patients who have been infected. These quantities are represented as $\mathbb{E}[Y_i \mid S_i = 1, Z_i = 1]$ and $\mathbb{E}[Y_i \mid S_i = 1, Z_i = 0]$. However, as shown in Frangakis & Rubin (2002), the set of participants $\{i \mid S_i = 1, Z_i = 1\}$ is different from the set of participants $\{i \mid S_i = 1, Z_i = 0\}$, which invalidates the contrast as a causal quantity. For a comparison to have a causal interpretation, the *only* systematic difference between the quantities being compared may be the difference in treatment, as in the numerator for VE_S : $\mathbb{E}[S_i(0) - S_i(1)]$. The estimand

$VE_I^{\text{net}} = \mathbb{E}[Y_i(0) | S_i(0) = 1] - \mathbb{E}[Y_i(1) | S_i(1) = 1]$, however, includes both the difference in treatment *and* the systematic difference between groups $\{i | S_i = 1, Z_i = 1\}$ and $\{i | S_i = 1, Z_i = 0\}$. Thus, any difference between $\mathbb{E}[Y_i(0) | S_i(0) = 1]$ and $\mathbb{E}[Y_i(1) | S_i(1) = 1]$ could plausibly be explained by the difference in individual traits between the two groups rather than the difference treatment.

In terms of counterfactual outcomes, the set $\{i | S_i = 1, Z_i = 1\}$ includes trial participants with $(S_i(1) = 1, S_i(0) = 0)$ and those with $(S_i(1) = 1, S_i(0) = 1)$, while the set $\{i | S_i = 1, Z_i = 0\}$ includes those $(S_i(1) = 0, S_i(0) = 1)$ and those with $(S_i(1) = 0, S_i(0) = 0)$. These groups arise in the estimand VE_I^{net} as follows. In order to simplify our notation, we introduce the principal stratum, $S_i^{P_0}$. Let it be defined as the ordered vector of counterfactual infection outcomes for unit i , or

$$S_i^{P_0} = (S_i(1), S_i(0)), S_i(z) \in \{0, 1\}$$

and let the set of all principal strata be denoted as \mathcal{S} . In this case $\mathcal{S} \equiv \{0, 1\}^2$.

Furthermore let $Y_i(z) = Y_i(z, 1)$, and $\theta_{jk} = P(S^{P_0} = (j, k))$. Then:

$$\begin{aligned} VE_I^{\text{net}} &= \mathbb{E}[Y_i(0) - Y_i(1) | S^{P_0} = (1, 1)] \frac{\theta_{11}^2}{(\theta_{11} + \theta_{10})(\theta_{11} + \theta_{01})} \\ &+ (\mathbb{E}[Y_i(0) | S^{P_0} = (1, 1)] - \mathbb{E}[Y_i(1) | S^{P_0} = (1, 0)]) \frac{\theta_{11}\theta_{10}}{(\theta_{11} + \theta_{10})(\theta_{11} + \theta_{01})} \\ &+ (\mathbb{E}[Y_i(0) | S^{P_0} = (0, 1)] - \mathbb{E}[Y_i(1) | S^{P_0} = (1, 1)]) \frac{\theta_{11}\theta_{01}}{(\theta_{11} + \theta_{10})(\theta_{11} + \theta_{01})} \\ &+ (\mathbb{E}[Y_i(0) | S^{P_0} = (0, 1)] - \mathbb{E}[Y_i(1) | S^{P_0} = (1, 0)]) \frac{\theta_{10}\theta_{01}}{(\theta_{11} + \theta_{10})(\theta_{11} + \theta_{01})} \end{aligned}$$

VE_I^{net} is a mixture of contrasts, one of which is a valid causal estimand, $\mathbb{E}[Y_i(0) - Y(1) | S_i^{P_0} = (1, 1)]$.

This mixture is noncausal because some of the contrasts compare outcomes between principal strata.

The solution is to compare potential severe illness outcomes within strata so that the group in which the causal estimand is defined is homogeneous in terms of potential out-

comes. These comparisons are called principal effects ([Frangakis & Rubin 2002](#)).

The only group in which a causal comparison can be made is the $(1, 1)$ stratum, otherwise known as the always-infected stratum. This is because it is the only stratum in which participants have a well-defined post-infection outcome under vaccination and under placebo. Thus we may define vaccine efficacy against severe illness as:

Definition 2.3 (Vaccine efficacy against post-infection outcome).

$$VE_I = \mathbb{E}[Y_i(0) - Y_i(1) \mid S_i^{P_0} = (1, 1)] / \mathbb{E}[Y_i(0) \mid S_i^{P_0} = (1, 1)].$$

The severe illness vaccine efficacy can be seen as the percent change in risk of severe illness conferred by receiving a vaccine conditional on belonging to the always-infected principal stratum. VE_I is a principal effect as defined in [Frangakis & Rubin \(2002\)](#) because it is conditional on a principal stratum.

The fundamental problem of causal inference ([Holland 1986](#)), namely that we cannot observe all counterfactual outcomes for the same individual, prevents the development of a simple ratio estimator because the observed data cannot determine which individuals belong to the always-infected stratum ([Hudgens & Halloran 2006](#)). In fact, in the next section, we will show that no single parameter of the probabilistic model implied by Assumptions [2.1](#) to [2.2](#) can be identified by the data, and that definition [2.3](#) is also not identified by the data.

2.2 Principal effect identifiability

Identifiability is an asymptotic property of a statistical model characterized by a unique map from parameter values to distribution functions. It is a key assumption for much of asymptotic theory, including Bayesian posterior consistency, ([Keener 2010](#), [Van der Vaart 2000](#)), and thus is useful to characterize. [Rothenberg \(1971\)](#) formally defines identifiability:

Definition 2.4 (Parameter identifiability). *A parameter $\theta \in \Theta$ is identifiable if there does not exist a distinct parameter value $\theta' \in \Theta$ for which the density $f(y \mid \theta) = f(y \mid \theta')$ for all observations y .*

To determine the identifiability of vaccine efficacy against a post-infection outcome like severe illness, we define how the counterfactual model governs the observed data distribution. Let $p_{syz} = P(S_i = s, Y_i = y \mid Z_i = z)$ be the observable probabilities of an infection outcome s , a post-infection outcome y given a vaccination status z , and let p_{s+z} be the marginal probability of infection given vaccination, or $P(S_i = s \mid Z_i = z)$. We now define the parameters for the counterfactual probability model. Let $u \in \{(0, 0), (1, 0), (0, 1), (1, 1)\}$, $\theta_u = P(S_i^{P_0} = u)$, and $\beta_z^u = P(Y_i(z) = 1 \mid S_i^{P_0} = u)$. The map from the model parameters to the observable probabilities is:

$$\begin{aligned} p_{110} &= \theta_{(0,1)}\beta_0^{(0,1)} + \theta_{(1,1)}\beta_0^{(1,1)}, & p_{111} &= \theta_{(1,0)}\beta_1^{(1,0)} + \theta_{(1,1)}\beta_1^{(1,1)} \\ p_{100} &= \theta_{(0,1)}\left(1 - \beta_0^{(0,1)}\right) + \theta_{(1,1)}\left(1 - \beta_0^{(1,1)}\right), & p_{101} &= \theta_{(1,0)}\left(1 - \beta_1^{(1,0)}\right) + \theta_{(1,1)}\left(1 - \beta_1^{(1,1)}\right). \end{aligned}$$

The joint distribution of the observed data has only 4 independent quantities, but the probability model has 7 parameters. Thus, the observable probabilities cannot be uniquely mapped to counterfactual probability model parameters, and the model parameters are not identified.

In this formulation VE_I can be written in terms of the observable probabilities and three unidentified parameters $\beta_2^{(0,1)}, \beta_1^{(1,0)}, \theta_{(1,1)}$.

$$VE_I = 1 - \frac{\beta_1^{(1,1)}}{\beta_0^{(1,1)}} = 1 - \frac{p_{111} - \beta_1^{(1,0)}(p_{1+1} - \theta_{(1,1)})}{p_{110} - \beta_0^{(0,1)}(p_{1+0} - \theta_{(1,1)})}. \quad (2)$$

In fact, the structure of the model is such that no single counterfactual model parameter is identifiable without restrictions on the principal stratum proportions. In order to identify

Equation (2) with observed data, one needs to learn $\theta_{(1,1)}, \beta_1^{(1,0)}, \beta_0^{(0,1)}$. The form of the estimand suggests several identification strategies.

One strategy is to assume that no participant is infected when vaccinated and uninfected when given the placebo. This assumption leads to $\theta_{(1,0)} = 0$, $\theta_{(1,1)} = p_{1+1}$, and $\beta_1^{(1,1)} = p_{111}$ (Gilbert et al. 2003, Hudgens & Halloran 2006, Zhou et al. 2016). A consequence of this assumption is that vaccine efficacy against infection is nonnegative with probability 1. VE_I then simplifies to

$$VE_I = 1 - \frac{p_{111}}{p_{110} + \beta_0^{(0,1)}(p_{1+1} - p_{1+0})}, \quad (3)$$

If we further assume that the distribution of severe illness is mean-independent of study site, we can use the variation in infection rates by study site to identify $\beta_0^{(0,1)}$ (Jiang et al. 2016, Yuan et al. 2019).

In some trials monotonicity may be appropriate, but it is not an assumption that is made when assessing vaccine efficacy against infection (Wang, Zhou & Richardson 2017, El Sahly et al. 2021). Accordingly, two separate analyses must be performed to assess the two efficacy estimands. The price for two-step procedures is two-fold: two-step estimators are often less statistically efficient, and it may be harder to communicate results to stakeholders because two sets of assumptions are needed. Assuming monotonicity also complicates using the results of past vaccine efficacy trials as priors for future studies. If past trials have confidence intervals for vaccine efficacy against infection that include negative values, it is not clear how to incorporate this information into a prior over a parameter that excludes negative values by design.

Monotonicity may be violated if some participants are inadvertently unblinded during a vaccine trial due to post-vaccine side effects (also known as reactogenicity). Participants who experience strong side effects may infer they have received the vaccine and may take

fewer prophylactic precautions than if they had been in the placebo group.

Further complications arise from the fact that infection and post-infection outcomes are observable only through proxy variables, \tilde{S}_i and \tilde{Y}_i with unknown sensitivities and specificities. Let the observable probabilities $q_{syz} = P(\tilde{S}_i = s, \tilde{Y}_i = y \mid Z_i = z)$ be defined as

$$\begin{aligned} q_{syz} = & \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \text{sn}_Y^y (1 - \text{sn}_Y)^{1-y} p_{11z} + \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y p_{10z} \\ & + \text{sp}_S^{1-s} (1 - \text{sp}_S)^s \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y p_{0*z}. \end{aligned}$$

As above, let $q_{+yz} = P(\tilde{Y}_i = y \mid Z_i = z)$, $q_{s+z} = P(\tilde{S}_i = s \mid Z_i = z)$, and $\tilde{\beta}_z^u = P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = u)$. Under this probability model, the causal estimand of interest, or vaccine efficacy against severe illness caused by influenza, is

$$\text{VE}_I = 1 - \frac{q_{+11} - (1 - \text{sp}_Y) - (\tilde{\beta}_1^{(1,0)} - (1 - \text{sp}_Y))(\frac{q_{1+1} - (1 - \text{sp}_S)}{\text{sn}_S + \text{sp}_S - 1} - \theta_{(1,1)})}{q_{+10} - (1 - \text{sp}_Y) - (\tilde{\beta}_0^{(0,1)} - (1 - \text{sp}_Y))(\frac{q_{1+0} - (1 - \text{sp}_S)}{\text{sn}_S + \text{sp}_S - 1} - \theta_{(1,1)})} \quad (4)$$

This expression involves nonidentifiable causal parameters $\tilde{\beta}_0^{(0,1)}, \tilde{\beta}_1^{(1,0)}, \theta_{(1,1)}$ as well as the unidentifiable measurement error parameters $\text{sn}_S, \text{sp}_S, \text{sp}_Y$.

Thus, one cannot identify the estimand of interest without additional information. The next section outlines how we can use the structure of multisite randomized trials for vaccine efficacy to infer post-infection outcome vaccine efficacy.

2.3 Incorporating study-site and covariate information

Enrollment criteria for vaccine efficacy trials typically stipulate that patients with a history of infection or a recent infection with the pathogen of interest are excluded from the trial. Furthermore, multisite studies typically rely on study sites themselves to recruit patients for the trial, which mean that site-specific full patient accrual may occur at different times (Weinberger et al. 2001). Because enrollment is conditional on the patient-specific lack of infection and intersite patient enrollment may systematically differ, patients at different

study sites can have different times at risk for infection prior to the study. To the extent there is patient-level frailty in time to infection, this can lead to patients who are enrolled later in the study as being less frail than those enrolled earlier. It is reasonable to assume that patient frailty is related to principal strata, and thus it is reasonable to assume that study site is not independent of principal strata given covariates.

Another reason to expect that the distribution of principal strata is not independent of study site is variation in exposure to the pathogen of interest between study sites. Variation in disease prevalence during the trial can lead to variation in rates of infection, and, subsequently, principal strata at the study site. Multi-scale spatial variation of disease prevalence is a hallmark of infectious disease ([Bauer & Wakefield 2018](#)). Thus, if study sites are sufficiently separated geographically, it is reasonable to expect that the study site variable is predictive of exposure during the duration of the trial. This variation in exposure should lead to variation in principal strata due to differences in exposure.

Assumption 2.4 (Study site relevance). $S_i^{P_0}$ is conditionally dependent on study site affiliation and baseline covariates, or $R_i \not\perp S_i^{P_0} \mid X_i$.

This is a common assumption in multi-site principal stratification modeling, but it is one that is especially reasonable in vaccine efficacy trials. See [Yuan et al. \(2019\)](#) and references therein.

Another key feature of vaccine efficacy trials is that patients' susceptibility to the pathogen of interest is assessed via comprehensive baseline measurements of correlates of protection. For example, in influenza trials it is common to measure the pre-season, pre-vaccination (i.e. baseline) influenza antibody concentrations via hemagglutination inhibition (HAI) assays or neuraminidase inhibition (NAI) assays against different strains of influenza ([Monto et al. 2009](#)). These assays are categorical measurements generated

from serial two-fold dilutions of patient serum samples; high titer values are associated with lower infection risk, and can be considered surrogates for past infections and/or past influenza vaccinations (Zelner et al. 2019). Given the fact that the participants will be inoculated against influenza, it is reasonable that the measurements of these values are not independent of principal strata. We will call these measurements A_i , and assume that $A_i \not\perp S_i^{P_0} \mid X_i$. The structure of multisite randomized trials is such that we make two further assumptions about the joint distribution of covariate values A_i and potential post-infection outcomes $(Y_i(1), Y_i(0))$. Formally,

Assumption 2.5 (Covariate homogeneity). *A_i is conditionally independent of the study site and treatment assignment given the principal stratum and baseline covariates, or $A_i \perp R_i, Z_i \mid S_i^{P_0}, X_i$, and*

Assumption 2.6 (Causal Homogeneity). *Conditional on principal stratum $S_i^{P_0}$ and A_i, X_i , the potential outcomes $(Y_i(1), Y_i(0))$ are independent of R_i , or $(Y_i(1), Y_i(0)) \perp R_i \mid S_i^{P_0}, A_i, X_i$.*

These two assumptions are crucial for the nonparametric identifiability of vaccine efficacy against post-infection outcomes. Both assumptions depend on the validity of the measurements A_i being a good proxy for infection risk frailty and post-infection outcome frailty conditional on principal stratum.

Assumption 2.5 is equivalent to assuming that individuals' covariate measurements A_i are exchangeable within strata defined by $(X_i = x, S_i^{P_0} = u)$; it is thus similar to the assumption of no unmeasured confounders in observational trials. The randomization of treatment assignment assures the independence of A_i and Z_i . The conditional independence of A_i and R_i given other baseline covariates and principal stratum means that A_i must measure baseline biological predisposition to infection and predisposition for vaccine efficacy against infection; if these characteristics are captured by A_i , then conditional on principal

stratum, or the joint measurement of infection under placebo and infection under treatment, there should be no variation between study sites. The independence assumption may be characterized as A_i being a measure of susceptibility to infection, while R_i affects the frailty of infection conditional on being susceptible. A priori, there is no reason to assume that susceptibility to infection, conditional on principal stratum varies by study site. (Longini & Halloran 1996, Aalen et al. 2008).

Assumption 2.6 is equivalent to assuming conditional exchangeability of $Y_i(z)$ within strata defined by $(X_i = x, S_i^{P_0} = u, A_i = k)$ (Saarela et al. 2023). Assumption 2.6 is commonly assumed in vaccine efficacy trials (Tsiatis & Davidian 2022), and is justifiable given the conditioning on A_i and other pretreatment covariates. We may loosen Assumption 2.5 by employing a parametric model for $A_i | R_i, S_i^{P_0}, X_i$. This is discussed more in Section 3.2.

Under Assumptions 2.3 to 2.6, we can define the joint distribution of influenza test results, reported severe illness, and pre-season antibody concentration given treatment assignment and study site membership.

Let $\theta_u^{r,x} = P(S_i^{P_0} = u | R_i = r, X_i = x)$ for $u \in \{(0,0), (1,0), (0,1), (1,1)\}$. Let $u_z = P(S_i(z) = 1 | S_i^{P_0} = u)$. Let $a_k^{u,x} = P(A_i = k | S_i^{P_0} = u, X_i = x)$, and $\beta_{z,k}^{u,x} = P(Y_i(z) = 1 | S_i^{P_0} = u, A_i = k, X_i = x)$. Further, recall $\text{sn}_S = P(\tilde{S}_i = 1 | S_i = 1)$, $\text{sp}_S = P(\tilde{S}_i = 0 | S_i = 0)$ and $\text{sn}_Y = P(\tilde{Y}_i = 1 | Y_i = 1)$, $\text{sp}_Y = P(\tilde{Y}_i = 0 | Y_i = 0)$. Let the probability of observing an influenza test result s and a covariate level k given treatment assignment z , study site membership r and pretreatment covariates x , or $q_{sk|zrx} = P(\tilde{S}_i = s, A_i = k | Z_i = z, R_i = r, X_i = x)$, be defined as:

$$q_{sk|zrx} = \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \sum_{u|u \in \mathcal{S}, u_z=1} a_k^{u,x} \theta_u^{r,x} + \text{sp}_S^{1-s} (1 - \text{sp}_S)^s \sum_{u|u \in \mathcal{S}, u_z=0} a_k^{u,x} \theta_u^{r,x}.$$

Similarly, we define the probability of observing a reported severe illness outcome y given treatment assignment z , study site membership r , and pretreatment covariates x , or

$q_{y|kzrx} = P(\tilde{Y}_i = y \mid Z_i = z, R_i = r, A_i = k, X_i = x)$, as:

$$q_{y|kzrx} = \text{sn}_Y^y (1 - \text{sn}_Y)^{1-y} \sum_{u|u \in \mathcal{S}, u_z=1} \beta_{z,k}^{u,x} \theta_u^{r,x} \\ + \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y (\sum_{u|u \in \mathcal{S}, u_z=1} (1 - \beta_{z,k}^{u,x}) \theta_u^{r,x} + \sum_{u|u \in \mathcal{S}, u_z=0} \theta_u^{r,x}).$$

In designing a clinical trial in which a primary or secondary endpoint is severe illness, limiting the definition of severe illness to encompass only the most extreme illness can at once increase the sensitivity and specificity of reporting.

2.3.1 Identifiability of expanded model

Given assumptions Assumptions 2.3 to 2.6, we will show that the joint variation in observed antibody concentrations and infection rates across study sites identifies the joint distribution of principal strata proportions and covariate values by study site. Then, given sufficient variation in principal strata proportions between study sites, the distribution of post-infection potential outcomes can be identified as well.

The proof depends on representing the observed distribution $q_{sk|zr}$ as a 3-way array and using a modified tensor decomposition uniqueness theorem from Kruskal (1977). Kruskal's theorem defines sufficient conditions for the uniqueness of the *triple product* decomposition of L , where this product is defined in Definition 2.5.

Definition 2.5 (Array triple product). *Let the array triple product with resulting array $L \in \mathbb{R}^{I \times J \times K}$ be defined between matrices $A \in \mathbb{R}^{I \times M}$, $B \in \mathbb{R}^{J \times M}$, $C \in \mathbb{R}^{K \times M}$. The operation is represented as $L = [A, B, C]$. As a result, the $(i, j, k)^{\text{th}}$ element of L , L_{ijk} , is defined the sum of three-way-products of elements a_{im}, b_{jm}, c_{km} , i.e.:*

$$L_{ijk} = \sum_{m=1}^M a_{im} b_{jm} c_{km}.$$

The sufficient conditions concern the *Kruskal ranks* of the matrices A, B, C , defined in Definition 2.6.

Definition 2.6 (Kruskal rank). *Let the Kruskal rank of a matrix $B \in \mathbb{R}^{I \times M}$ be $k_B \in [0, 1, 2, \dots, M]$, and let k_B be the maximum integer such that every set of k_B columns of B are linearly independent.*

Kruskal rank is stricter than matrix rank. To see why, consider a matrix with M columns of which two are repeated. At most the rank of the matrix can be $M - 1$, but Kruskal rank can be at most 1. A corollary of the definition is that if a matrix is full column rank, its Kruskal rank equals its column rank.

Let L be the 3-way array representing $q_{sk|zrx}$, where we fix $X_i = x$ for each unique value of X_i . The array's dimensions are $4 \times N_a \times N_r$ and is defined so that the $(j, k, r)^{\text{th}}$ element $P(S_i = \mathbb{1}(j \leq 2), A_i = k \mid Z = j - 1 \bmod 2, R_i = r, X_i = x)$. If we look at the matrix that results from fixing the third array index, also known as the *3-slab* and denoted as $L_r \in \mathbb{R}^{4 \times N_a}$, we can see a possible decomposition of this array. Let $\sum_{u_z=s} a_k^{u,x} \theta_u^{r,x}$ denote the sum over elements $u \in \{(0,0), (1,0), (0,1), (1,1)\}$ such that $P(S_i(z) = 1 \mid S_i^{P_0} = u)$. The let L_r be defined as

$$\begin{array}{ccc} (a = 1) & \dots & (a = N_a) \\ \left[\begin{array}{ccc} (1 - \text{sp}_S) \sum_{u_0=0} a_1^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_0=1} a_1^{u,x} \theta_u^{r,x} & \dots & (1 - \text{sp}_S) \sum_{u_0=0} a_{N_a}^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_0=1} a_{N_a}^{u,x} \theta_u^{r,x} \\ (1 - \text{sp}_S) \sum_{u_1=0} a_1^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_1=1} a_1^{u,x} \theta_u^{r,x} & \dots & (1 - \text{sp}_S) \sum_{u_1=0} a_{N_a}^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_1=1} a_{N_a}^{u,x} \theta_u^{r,x} \\ \text{sp}_S \sum_{u_0=0} a_1^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_0=1} a_1^{u,x} \theta_u^{r,x} & \dots & \text{sp}_S \sum_{u_0=0} a_{N_a}^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_0=1} a_{N_a}^{u,x} \theta_u^{r,x} \\ \text{sp}_S \sum_{u_1=0} a_1^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_1=1} a_1^{u,x} \theta_u^{r,x} & \dots & \text{sp}_S \sum_{u_1=0} a_{N_a}^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_1=1} a_{N_a}^{u,x} \theta_u^{r,x} \end{array} \right] \end{array} \begin{array}{l} (s = 1, z = 0) \\ (s = 1, z = 1) \\ (s = 0, z = 0) \\ (s = 0, z = 1) \end{array}.$$

This structure allows L to be defined as the triple product of three matrices:

$$P_2(\tilde{S} \mid Z, S^{P_0}) \in \mathbb{R}^{4 \times 4}, P_2^x(A \mid S^{P_0}) \in \mathbb{R}^{N_a \times 4}, P_2^x(S^{P_0} \mid R) \in \mathbb{R}^{4 \times N_r}.$$

The matrix $P_2(\tilde{S} \mid Z, S^{P_0})$ is defined as

$$P_2(\tilde{S} \mid Z, S^{P_0}) = \begin{bmatrix} (0,0) & (1,0) & (0,1) & (1,1) \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S & \text{sn}_S \\ 1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S & 1 - \text{sn}_S \\ \text{sp}_S & 1 - \text{sn}_S & \text{sp}_S & 1 - \text{sn}_S \end{bmatrix} \begin{matrix} (s=1, z=0) \\ (s=1, z=1) \\ (s=0, z=0) \\ (s=0, z=1) \end{matrix}. \quad (5)$$

The matrices $P_2^x(A \mid S^{P_0}), P_2^x(S^{P_0} \mid R)$ are defined

$$P_2^x(A \mid S^{P_0}) = \begin{bmatrix} a_1^{(0,0),x} & a_1^{(1,0),x} & a_1^{(0,1),x} & a_1^{(1,1),x} \\ a_2^{(0,0),x} & a_2^{(1,0),x} & a_2^{(0,1),x} & a_2^{(1,1),x} \\ \vdots & \vdots & \vdots & \vdots \\ a_{N_a}^{(0,0),x} & a_{N_a}^{(1,0),x} & a_{N_a}^{(0,1),x} & a_{N_a}^{(1,1),x} \end{bmatrix}, \quad P_2^x(S^{P_0} \mid R) = \begin{bmatrix} \theta_{(0,0)}^{r_1,x} & \theta_{(0,0)}^{r_2,x} & \cdots & \theta_{(0,0)}^{r_{N_r},x} \\ \theta_{(1,0)}^{r_1,x} & \theta_{(1,0)}^{r_2,x} & \cdots & \theta_{(1,0)}^{r_{N_r},x} \\ \theta_{(0,1)}^{r_1,x} & \theta_{(0,1)}^{r_2,x} & \cdots & \theta_{(0,1)}^{r_{N_r},x} \\ \theta_{(1,1)}^{r_1,x} & \theta_{(1,1)}^{r_2,x} & \cdots & \theta_{(1,1)}^{r_{N_r},x} \end{bmatrix}.$$

We show in Lemma C.3 that when $P_2(\tilde{S} \mid Z, S^{P_0}), P_2^x(A \mid S^{P_0}), P_2^x(S^{P_0} \mid R)$ satisfy certain Kruskal rank conditions, along with reasonable conditions on sn_S and sp_S , the joint distributions $P(S_i^{P_0} = u, A_i = k \mid Z_i = z, R_i = r, X_i = x), P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = u, A_i = k, X_i = x)$ are strictly identified. Furthermore, we show that sn_S, sp_S , and sp_Y are also identified. Formally,

Theorem 2.7 (Identifiability of causal model parameters). *Suppose that Assumptions 2.3 to 2.6 hold. If both sn_S, sp_S lie in $[0, 1/2)$ or both lie in $(1/2, 1]$, $P_2^x(A \mid S^{P_0})$ is Kruskal rank 3 or greater for all x and $P_2^x(S^{P_0} \mid R)$ is rank 4 for all x , then both sn_S, sp_S are identifiable, as are the following distributions: $P(S_i^{P_0} = (m, n) \mid R_i = r, X_i = x), P(A_i = k \mid S_i^{P_0} = (m, n), X_i = x), k \in \{1, \dots, N_a\}, r \in \{1, \dots, N_r\}, (m, n) \in \{(0, 0), (1, 0), (1, 0), (1, 1)\}$. Furthermore, if sn_Y is unknown (known), distributions $P(Y_i(z) = 1 \mid S_i^{P_0} = u, A_i = k, X_i = x)$ are identifiable up to an unknown (known) common constant, $r_Y = \text{sn}_Y + \text{sp}_Y - 1$.*

A consequence of Theorem 2.7 is that the marginal distribution of reported severe illness

among the always-infected stratum is identified, or $P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), X_i)$. To see why, note that the conditional counterfactual distributions for $\tilde{Y}_i(z) \mid S_i^{P_0} = (1, 1), A_i, X_i$ are identified, along with the distribution of $A_i \mid S_i^{P_0} = (1, 1), X_i$. The following corollary marginalizes over A_i to yield identifiability of the population distribution $\tilde{Y}_i(z) \mid S_i^{P_0} = (1, 1), X_i$:

Corollary 2.8. *By the conditions set forth in Theorem 2.7, $P(A_i = k \mid S_i^{P_0} = (1, 1), X_i = x)$ and $P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), A_i = k, X_i = x)$ are identifiable for $k \in \{1, \dots, N_a\}$. Let $P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), X_i = x) = \sum_k P(A_i = k \mid S_i^{P_0} = (1, 1), X_i = x)P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), A_i = k, X_i = x)$. Then $P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), X_i = x), P(A_i = k \mid S_i^{P_0} = (1, 1), X_i = x)$, and $P(\tilde{Y}_i(z)_i = 1 \mid S_i^{P_0} = (1, 1), A_i = k, X_i = x)$ are identifiable.*

Given that the marginal distribution of reported severe illness for the always-infected stratum is identified, along with sp_Y , we can write the estimand of interest, the vaccine efficacy against severe illness within the always-infected stratum explicitly. To see why, note that for any latent binary random variable Q and its measurement, \tilde{Q} with associated sensitivity sn_Q and specificity sp_Q , we have the following identity:

$$P(Q = 1) = \frac{P(\tilde{Q} = 1) - (1 - \text{sp}_Q)}{\text{sn}_Q + \text{sp}_Q - 1}. \quad (6)$$

Then employing Equation (6) yields:

$$\begin{aligned} \text{VE}_I &= 1 - \frac{\mathbb{E}[Y_i(1) \mid S_i^{P_0} = (1, 1)]}{\mathbb{E}[Y_i(0) \mid S_i^{P_0} = (1, 1)]} \\ &= 1 - \frac{\mathbb{E}[\tilde{Y}_i(1) \mid S_i^{P_0} = (1, 1)] - (1 - \text{sp}_Y)}{\mathbb{E}[\tilde{Y}_i(0) \mid S_i^{P_0} = (1, 1)] - (1 - \text{sp}_Y)}. \end{aligned}$$

We have thus shown that VE_I is point identified without needing to identify sn_Y . This estimand marginalizes over the population distribution of X_i , which may be known, or may be estimated.

Moreover, the identifiability of the conditional counterfactual distributions $P(\tilde{Y}_i(z) = 1 \mid S_i^{P_0} = (1, 1), A_i = k, X_i = x)$ allows for causal effect heterogeneity by covariate A_i .

Definition 2.7 (Conditional VE against post-infection outcome Y).

$$\text{VE}_I(k) = 1 - \frac{\mathbb{E}[\tilde{Y}_i(1) \mid S_i^{P_0} = (1, 1), A_i = k] - (1 - \text{sp}_Y)}{\mathbb{E}[\tilde{Y}_i(0) \mid S_i^{P_0} = (1, 1), A_i = k] - (1 - \text{sp}_Y)}$$

Again this estimand marginalizes over X_i .

2.4 Asymptotic variance for VE_I

For the moment, suppose that our target of inference in VE_I . Let $\hat{\beta}_z^{(1,1)}$ be the estimator for $\mathbb{E}[\tilde{Y}_i(z) \mid S_i^{P_0} = (1, 1)]$ and let $\widehat{\text{sp}}_Y$ be the estimator for $(1 - \text{sp}_Y)$. One can show that a valid estimator for the vector $(\text{sp}_Y, \beta_z^{(0,1)}, \beta_z^{(1,0)}, \beta_z^{(1,1)})$ is the least-squares estimator obtained by projecting the site-specific counts of severe illness conditional on $Z_i = z$ onto the column space of the estimated matrix $P_{N_z}^x(S^{P_0} \mid R)$, or the proportions of principal strata by study site. This estimator naturally marginalizes over A_i . The plug-in estimator therefore has the form

$$\widehat{\text{VE}}_I = 1 - \frac{\hat{\beta}_1^{(1,1)} - \widehat{\text{sp}}_Y}{\hat{\beta}_0^{(1,1)} - \widehat{\text{sp}}_Y}.$$

We can use the delta method to characterize the asymptotic variance of the estimator.

$$\begin{aligned} \text{Var}(\widehat{\text{VE}}_I) = \frac{1}{(r_Y \beta_0^{(1,1)})^2} & \left(\text{Var}(\hat{\beta}_1^{(1,1)}) + (1 - \text{VE}_I)^2 \text{Var}(\hat{\beta}_0^{(1,1)}) + \text{VE}_I^2 \text{Var}(\widehat{\text{sp}}_Y) \right. \\ & - 2(1 - \text{VE}_I) \text{Cov}(\hat{\beta}_1^{(1,1)}, \hat{\beta}_0^{(1,1)}) - 2\text{VE}_I \text{Cov}(\hat{\beta}_1^{(1,1)}, \widehat{\text{sp}}_Y) \\ & \left. + 2\text{VE}_I \text{Cov}(\hat{\beta}_0^{(1,1)}, \widehat{\text{sp}}_Y) \right). \end{aligned}$$

Given the symmetry of the estimators, $\text{Cov}\left(\hat{\beta}_0^{(1,1)}, \widehat{\text{sp}}_Y\right) = \text{Cov}\left(\hat{\beta}_1^{(1,1)}, \widehat{\text{sp}}_Y\right)$, so the asymptotic variance simplifies to

$$\begin{aligned} \text{Var}\left(\widehat{\text{VE}}_I\right) = \frac{1}{(r_Y \beta_0^{(1,1)})^2} & \left(\text{Var}\left(\hat{\beta}_1^{(1,1)}\right) + (1 - \text{VE}_I)^2 \text{Var}\left(\hat{\beta}_0^{(1,1)}\right) + \text{VE}_I^2 \text{Var}\left(\widehat{\text{sp}}_Y\right) \right. \\ & \left. - 2(1 - \text{VE}_I) \text{Cov}\left(\hat{\beta}_1^{(1,1)}, \hat{\beta}_0^{(1,1)}\right) \right). \end{aligned}$$

Under the causal null hypothesis of $\beta_0^{(1,1)} = \beta_1^{(1,1)} \implies \text{VE}_I = 0$, this expression simplifies to the following

$$\text{Var}\left(\widehat{\text{VE}}_I\right) = \frac{1}{(r_Y \beta_0^{(1,1)})^2} \left(\text{Var}\left(\hat{\beta}_1^{(1,1)}\right) + \text{Var}\left(\hat{\beta}_0^{(1,1)}\right) - 2\text{Cov}\left(\hat{\beta}_1^{(1,1)}, \hat{\beta}_0^{(1,1)}\right) \right).$$

We show in the appendix that the asymptotic variance-covariance matrix for $(\hat{\beta}_z^{(1,1)}, \widehat{\text{sp}}_Y)$ can be partly characterized in terms of N_r and the Moore-Penrose inverse of $P_{N_z}^x(S^{P_0} | R)$. As shown in Section I.0.1, the variance of the estimator increases in the number of study sites, N_r , though if we consider study sites to be drawn from a superpopulation of study sites as they do in Yuan et al. (2019), then increasing the number of study sites allows for more precise estimation of the matrix of second moments of $P_{N_z}^x(S^{P_0} | R)$.

The identifiability results presented in this section are in fact a special case of identifiability results related to multiarm multisite trials. Because of this, the discussion of the proof and the implications are deferred until the next section, which outlines the generalization to two or more treatments.

3 Vaccine efficacy in multiarm, multisite trials

Many vaccine trials involve more than two treatment arms. For example, Monto et al. (2009) compares the absolute and relative vaccine efficacy of an inactivated influenza vaccine and a live attenuated influenza vaccine against two placebo arms. The results of trials

such as these can inform public health vaccine policy as well as suggest new directions for vaccine development.

Mirroring the notation presented in Section 2, for n total participants we observe the following sextuplet for each participant i : $(\tilde{S}_i, \tilde{Y}_i, Z_i, R_i, A_i, X_i)$. Like Section 2, \tilde{S}_i, \tilde{Y}_i are imperfectly observed proxies for true infection status, S_i , and true severe illness status, Y_i . In contrast to Section 2, Z_i is a categorical variable with $N_z \geq 2$ categories representing treatment assignment. Let $Z_i \in \{z_1, \dots, z_{N_z}\}$. The variables R_i, A_i, X_i , study site membership, pretreatment measurement of susceptibility to infection, and other pretreatment covariates, are defined as in Section 2. True infection status S_i and true severe illness status Y_i are assumed to be partially-observable realizations of counterfactual variables $S_i(\mathbf{z}), Y_i(\mathbf{z}, S_i(\mathbf{z}))$, where \mathbf{z} is a given n -vector of treatment assignments for each individual. The counterfactual variables are so-named because these variables are defined for *any* \mathbf{z} , which is possibly different from the collection of observed treatment assignments $\{Z_1, \dots, Z_n\}$. Our causal model enforces the constraint that $Y_i(\mathbf{z}, 0) = \star$ for all \mathbf{z} , meaning that severe illness is caused by an influenza infection; without an influenza infection there can be no severe illness caused by influenza.

Like Section 2, we assume **SUTVA**, as is typical in vaccine trials (Gilbert et al. 2003); we also continue to assume **Non-differential Misclassification Errors**. Furthermore, we assume random treatment assignment in the multiarm setting.

Assumption 3.1 (Random treatment assignment multiple treatment). *The probability of being assigned to treatment for each individual lies strictly between 0 and 1:*

$$0 < P(Z_i = z_j \mid S_i(z_1), Y_i(z_1, S(z_1)), \dots, S_i(z_{N_z}), Y_i(z_{N_z}, S(z_{N_z}))) < 1$$

for all $z_j \in \{z_1, \dots, z_{N_z}\}$.

Treatment assignment is independent of all potential outcomes, or

$$S_i(z_1), Y_i(z_1, S(z_1)), \dots, S_i(z_{N_z}), Y_i(z_{N_z}, S(z_{N_z})) \perp\!\!\!\perp Z_i.$$

Assumption 2.1 and assumption 3.1 allows us to write the variables S_i, Y_i as

$$S_i = \sum_{j=1}^{N_z} S_i(z_j) \mathbb{1}(Z_i = z_j), \quad Y_i = \sum_{j=1}^{N_z} Y_i(z_j, S_i(z_j)) \mathbb{1}(Z_i = z_j). \quad (7)$$

In keeping with the expanded set of treatments, let principal stratum, $S_i^{P_0}$, be defined as the ordered N_z -vector of counterfactual infection outcomes for unit i , or

$$S_i^{P_0} = (S_i(z_1), S_i(z_2), \dots, S_i(z_{N_z})), \quad S_i(z_j) \in \{0, 1\}, \quad 1 \leq j \leq N_z,$$

and let the set of all principal strata be denoted as \mathcal{S} . When the set of principal strata is not restricted $\mathcal{S} \equiv \{0, 1\}^{N_z}$. As in Section 2.2, let u be an element of \mathcal{S} , and let $u_j \equiv P(S_i(z_j) = 1 \mid S_i^{P_0} = u)$.

It is typical to restrict the set of principal strata as the size of \mathcal{S} grows because the dimension of the parameter space grows quickly. For example, monotonicity assumptions can be generalized to three treatments, as in Yuan et al. (2019) or Cheng & Small (2006). Another strain of research places strong assumptions on treatment ordering, such as Luo et al. (2023) and Wang, Richardson & Zhou (2017). We do not make such assumptions and allow for an unrestricted space of principal strata.

In the multiarm setting, we will modify our definition for the vaccine efficacy estimands. Vaccine efficacy against infection is now defined for any two treatments, z_j and z_k :

Definition 3.1 (Vaccine efficacy against infection z_j versus z_k).

$$\text{VE}_{S,jk} = 1 - \mathbb{E}[S_i(z_j)] / \mathbb{E}[S_i(z_k)].$$

Vaccine efficacy against severe illness is well-defined for any principal stratum u and any two treatments z_j and z_k such that $P(S_i(z_j) = S_i(z_k) = 1 \mid S_i^{P_0} = u)$. The principal

strata that admit a well-defined principal effect is defined as:

$$\mathcal{U} \equiv \{u \in \mathcal{S} \mid \sum_{u=1}^{2^{N_z}} u_u > 1\}.$$

Then for any $u \in \mathcal{U}$ we may define the following principal effect for any two treatments z_j and z_k such that $u_j u_k = 1$:

Definition 3.2 (Vaccine efficacy against post-infection outcome Y).

$$\text{VE}_{I,jk}^u = 1 - \mathbb{E}[Y_i(z_j) \mid S_i^{P_0} = u] / \mathbb{E}[Y_i(z_k) \mid S_i^{P_0} = u].$$

$\text{VE}_{I,jk}^u$ is a principal effect as defined in [Frangakis & Rubin \(2002\)](#) because it is conditional on a principal stratum u . For example, when $N_z = 3$, there are 8 principal strata, three of which would admit comparisons between two treatments: $(1, 1, 0)$, $(0, 1, 1)$, $(1, 0, 1)$, and one of which would allow for comparisons between all three treatments: $(1, 1, 1)$. For patients with $S_i^{P_0} = (1, 1, 0)$, $u_1 = 1, u_2 = 1, u_3 = 0$. Given that $u_1 u_2 = 1$, we may compare $Y(z_1)$ to $Y(z_2)$ among this group of patients. Like the two-arm setting, in which $S_i^{P_0} = (1, 1)$ is the “always-infected” stratum, the stratum $S_i^{P_0} = \{1\}^{N_z}$ is the “always-infected” stratum in the multiarm trial.

To give a concrete example about how one might use the expanded definition of vaccine efficacy against severe illness, we will use [Monto et al. \(2009\)](#) as an example. [Monto et al. \(2009\)](#) treated the four-arm trial as a three-arm trial by combining the two separate placebo arms into one unified arm. Given that both placebo arms received inert treatments, albeit via different routes of administration, this is a reasonable assumption. The aim of the trial was to measure the absolute and relative efficacies against symptomatic influenza; thus, it is of interest to infer the relative efficacy against severe illness given influenza infection for the two competing vaccines. The following causal estimand captures this effect:

$$\frac{\mathbb{E}[Y_i(z_2) \mid S_i^{P_0} = (1, 1, 1)] - \mathbb{E}[Y_i(z_3) \mid S_i^{P_0} = (1, 1, 1)]}{\mathbb{E}[Y_i(z_1) \mid S_i^{P_0} = (1, 1, 1)]} = \text{VE}_{I,31}^{(1,1,1)} - \text{VE}_{I,21}^{(1,1,1)}. \quad (8)$$

As in Section 2, we will assume **Causal Homogeneity**:

Assumption 3.2 (Causal Homogeneity for multiarm trials). *Conditional on principal stratum $S_i^{P_0}$, A_i , and X_i the potential outcomes $(Y_i(z_1), \dots, Y_i(z_{N_z}))$ are independent of R_i , or $(Y_i(z_1), \dots, Y_i(z_{N_z})) \perp\!\!\!\perp R_i \mid S_i^{P_0}, A_i, X_i$.*

In order to expand the causal model, we shall update some of the notation introduced in Section 2 to the multiarm trial. Let $\theta_u^{r,x} = P(S_i^{P_0} = u \mid R_i = r, X_i = x)$ where $u \in \{0, 1\}^{N_z}$, and $\beta_{j,k}^{u,x} = P(Y_i(z_j) = 1 \mid S_i^{P_0} = u, A_i = k, X_i = x)$. Let $u_j = P(S_i(z_j) = 1 \mid S_i^{P_0} = u)$. Then $\beta_{j,k}^{u,x}$ is only defined for j such that $u_j = 1$. Further, let $a_k^{u,x} = P(A_i = k \mid S_i^{P_0} = u, X_i = x)$. Let $q_{sk|jrx} = P(\tilde{S}_i = s, A_i = k \mid Z_i = z, R_i = r, X_i = x)$ be defined as

$$q_{sk|jrx} = \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \sum_{u|u \in \mathcal{S}, u_j=1} a_k^{u,x} \theta_u^{r,x} + \text{sp}_S^{1-s} (1 - \text{sp}_S)^s \sum_{u|u \in \mathcal{S}, u_j=0} a_k^{u,x} \theta_u^{r,x}.$$

The observable probabilities $q_{y|kjr} = P(\tilde{Y}_i = y \mid Z_i = z_j, R_i = r, A_i = k, X_i = x)$, which marginalize over the observed infection test results, are defined:

$$\begin{aligned} q_{y|kjr} &= \text{sn}_Y^y (1 - \text{sn}_Y)^{1-y} \sum_{u|u \in \mathcal{S}, u_j=1} \beta_{j,k}^{u,x} \theta_u^{r,x} \\ &\quad + \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y (\sum_{u|u \in \mathcal{S}, u_j=1} (1 - \beta_{j,k}^{u,x}) \theta_u^{r,x} + \sum_{u|u \in \mathcal{S}, u_j=0} \theta_u^{r,x}) \end{aligned}$$

3.1 Identifiability of multiarm, multi-site trials

Our strategy will be the same as in Section 2. Fixing x , we can rewrite $q_{sk|jrx}$ as a 3-way array, L and subsequently use Kruskal rank conditions to characterize the uniqueness of the array decomposition. Let L be the 3-way array representing $q_{sk|jrx}$. The array's dimensions are $2N_z \times N_a \times N_r$ and is defined so that the $(j, k, r)^{\text{th}}$ element $P(S_i = 1 (j \leq N_z), A_i = k \mid Z = z_{j-1 \bmod N_z+1}, R_i = r, X_i = x)$. Again, we look to the β -slab, denoted as $L_r \in \mathbb{R}^{2N_z \times N_a}$, to yield a possible decomposition of this array. As above, let $\sum_{u_z=s} a_k^{u,x} \theta_u^{r,x}$ denote the sum

over elements $u \in \mathcal{S}$ such that $P(S_i(z) = 1 \mid S_i^{P_0} = u)$. Let L_r be defined as

$$\begin{array}{c}
 (a = 1) \qquad \qquad \qquad \dots \qquad \qquad \qquad (a = N_a) \\
 \left[\begin{array}{ccc}
 (1 - \text{sp}_S) \sum_{u_{z_1}=0} a_1^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_1}=1} a_1^{u,x} \theta_u^{r,x} & \dots & (1 - \text{sp}_S) \sum_{u_{z_1}=0} a_{N_a}^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_1}=1} a_{N_a}^{u,x} \theta_u^{r,x} \\
 (1 - \text{sp}_S) \sum_{u_{z_2}=0} a_1^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_2}=1} a_1^{u,x} \theta_u^{r,x} & \dots & (1 - \text{sp}_S) \sum_{u_{z_2}=0} a_{N_a}^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_2}=1} a_{N_a}^{u,x} \theta_u^{r,x} \\
 \vdots & \ddots & \vdots \\
 (1 - \text{sp}_S) \sum_{u_{z_{N_z}}=0} a_1^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_{N_z}}=1} a_1^{u,x} \theta_u^{r,x} & \dots & (1 - \text{sp}_S) \sum_{u_{z_{N_z}}=0} a_{N_a}^{u,x} \theta_u^{r,x} + \text{sn}_S \sum_{u_{z_{N_z}}=1} a_{N_a}^{u,x} \theta_u^{r,x} \\
 \text{sp}_S \sum_{u_{z_1}=0} a_1^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_1}=1} a_1^{u,x} \theta_u^{r,x} & \dots & \text{sp}_S \sum_{u_{z_1}=0} a_{N_a}^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_1}=1} a_{N_a}^{u,x} \theta_u^{r,x} \\
 \text{sp}_S \sum_{u_{z_2}=0} a_1^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_2}=1} a_1^{u,x} \theta_u^{r,x} & \dots & \text{sp}_S \sum_{u_{z_2}=0} a_{N_a}^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_2}=1} a_{N_a}^{u,x} \theta_u^{r,x} \\
 \vdots & \ddots & \vdots \\
 \text{sp}_S \sum_{u_{z_{N_z}}=0} a_1^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_{N_z}}=1} a_1^{u,x} \theta_u^{r,x} & \dots & \text{sp}_S \sum_{u_{z_{N_z}}=0} a_{N_a}^{u,x} \theta_u^{r,x} + (1 - \text{sn}_S) \sum_{u_{z_{N_z}}=1} a_{N_a}^{u,x} \theta_u^{r,x}
 \end{array} \right] \begin{array}{l} (s = 1, z = z_1) \\ (s = 1, z = z_2) \\ \vdots \\ (s = 1, z = z_{N_z}) \\ (s = 0, z = z_1) \\ (s = 0, z = z_2) \\ \vdots \\ (s = 0, z = z_{N_z}) \end{array}
 \end{array}$$

Following the same logic as Section 2, we can define matrices encoding the distribution of principal strata by study site, and the distribution of pre-season titers by principal stratum. In order to define these matrices such that they share a common ordering along the axes defined by the principal strata, we shall use the the natural ordering of the binary vectors $S_i^{P_0}$: the base-10 representation of the principal stratum. In order to formalize this ordering, we define a map, $\varpi_m(j)$, which generates the m -digit binary representation of the integer j as a length- m binary vector. We also define its inverse, $\varpi_m(u)^{-1}$, where u is an element of \mathcal{S} .

Definition 3.3 (Base-10 to binary map). *Let the operator ϖ_m be defined as $\varpi_m(\cdot) : j \rightarrow \{0, 1\}^m, j \in \mathbb{N}, j \leq 2^m - 1$ with elements $\varpi_m(j)_i \in \{0, 1\}$, so $\varpi_m(j)$ is the base-2 representation of j with m digits represented as a binary m -vector. The binary representation is indexed so the i^{th} element of the vector corresponds to the digit for 2^{i-1} . Let the inverse operator $\varpi_m^{-1}(\cdot) : \{0, 1\}^m \rightarrow j$, or the binary to base-10 conversion. Let digit i of $\varpi_m(\cdot)$ represent the digit for 2^{i-1} .*

For example, $\varpi_3(4) = (0, 0, 1)$, $\varpi_5(4) = (0, 0, 1, 0, 0)$, and $\varpi_3((0, 0, 1))^{-1} = \varpi_5((0, 0, 1, 0, 0))^{-1} =$

4. In order to see how \mathcal{S} is ordered, suppose that $N_z = 3$ so $\mathcal{S} \equiv \{0, 1\}^3$. Then the third and fourth elements of the ordered set of principal strata are $(0, 1, 0)$ and $(1, 1, 0)$ respectively.

With this ordering defined, let the matrix $P_{N_z}^x(A | S^{P_0})$ in $\mathbb{R}^{N_a \times 2^{N_z}}$ encode the distributions $A_i | S_i^{P_0}, X_i$ with $(k, j)^{\text{th}}$ element $P_{N_z}(A_i = k | S_i^{P_0} = \varpi_{N_z}(j-1), X_i = x)$. Let the matrix $P_{N_z}^x(S^{P_0} | R)$ in $\mathbb{R}^{2^{N_z} \times N_r}$ encode the distribution $S_i^{P_0} | R_i, X_i$ with $(k, j)^{\text{th}}$ element $P_{N_z}^x(S_i^{P_0} = \varpi_{N_z}(k-1) | R_i = j, X_i = x)$.

Finally, let matrix $P_{N_z}(\tilde{S} | Z, S^{P_0}) \in \mathbb{R}^{2^{N_z} \times 2^{N_z}}$ with $(k, j)^{\text{th}}$ element $\text{sn}_S^{\varpi_{N_z}(j-1)k} (1 - \text{sp}_S)^{1 - \varpi_{N_z}(j-1)k} \mathbb{1}(k \leq N_z) + (1 - \text{sn}_S)^{\varpi_{N_z}(j-1)k - N_z} \text{sp}_S^{1 - \varpi_{N_z}(j-1)k - N_z} \mathbb{1}(k > N_z)$.

Let $P_{N_z}^x(S^{P_0} | R = r)$ be the r^{th} column of matrix $P_{N_z}^x(S^{P_0} | R)$. Then L_r can be represented in matrix form as

$$L_r = P_{N_z}(\tilde{S} | Z, S^{P_0}) \text{diag}(P_{N_z}^x(S^{P_0} | R = r)) P_{N_z}^x(A | S^{P_0})^T$$

This structure again allows us to define L as the triple product of these three matrices, each of which have columns that correspond to principal strata:

$$L = [P_{N_z}(\tilde{S} | Z, S^{P_0}), P_{N_z}^x(A | S^{P_0}), P_{N_z}^x(S^{P_0} | R)^T].$$

The conditions for the identifiability of the model parameters are outlined below:

Theorem 3.3. *Let $N_z \geq 2$. Suppose Assumptions 2.3 to 2.1, Assumption 2.5, Assumption 3.1, and Assumption 3.2 hold. If both sn_S, sp_S lie in $[0, 1/2)$ or both lie in $(1/2, 1]$, $P_{N_z}^x(A | S^{P_0})$ is at least Kruskal rank $2^{N_z} - 1$ and $P_{N_z}^x(S^{P_0} | R)$ is rank 2^{N_z} for all x then the counterfactual distributions $P(S_i^{P_0} = u | R_i = r, X_i = x)$, $P(A_i = k | S_i^{P_0} = u, X_i = x)$ are identifiable as are the quantities $\text{sn}_S, \text{sp}_S, \text{sp}_Y, \text{VE}_{I,jk}^u(k)$, and $\text{VE}_{I,jk}^u$. Furthermore, if sn_Y is unknown (known), distributions $P(Y_i(z_j) = 1 | S_i^{P_0} = u, A_i = k, X_i = x)$ are identifiable up to an unknown (known) common constant, $r_Y = \text{sn}_Y + \text{sp}_Y - 1$.*

Theorem 3.3 allows for a more realistic model of infection measurement than [Hudgens & Halloran \(2006\)](#) and does not require any restrictions on the space of principal strata.

The primary benefit of an unrestricted principal strata distribution is that we can jointly infer vaccine efficacy against infection and vaccine efficacy against a post-infection outcome. This will aid in designing comprehensive randomized trials for vaccine efficacy.

The proof of Theorem 3.3, shown in Section E is related to the methods in Jiang et al. (2016) and Ding et al. (2011). Ding et al. (2011) addresses problems of identifiability in survivor average treatment effects, which is mathematically analogous to vaccine efficacy for post-infection outcomes, by measuring covariates that are related to the principal strata. Jiang et al. (2016) identifies principal causal effects in binary surrogate endpoint evaluations. Despite not being mathematically identical to vaccine efficacy, binary surrogacy endpoint evaluation is ultimately a problem in identification of principal causal effects. Most importantly, the proof does not encode any restrictions on the distribution of secondary outcomes, otherwise known in our case as the post-infection outcomes. This makes the result applicable to categorical or continuous post-infection outcomes, and, more broadly, to principal stratification problems outside the scope of vaccine efficacy.

The identifiability results in Theorem 3.3 suggest the following so-called transparent parameterization¹: $(\beta_{j,k}^{u,x}, \text{sp}_Y, \text{sn}_Y) \rightarrow (\tilde{p}_{j,k}^{u,x} = (\text{sn}_Y + \text{sp}_Y - 1)\beta_{j,k}^{u,x} + (1 - \text{sp}_Y), \text{sp}_Y, \text{sn}_Y)$. The quantities $\tilde{p}_{j,k}^{u,x} = P(\tilde{Y}_i = 1 \mid Z_i = z_j, S_i^{P_0} = u, A_i = k)$ and sp_Y are identified by the data, while sn_Y is not. This yields the following asymptotic identification regions for sn_Y and $\beta_{j,k}^{u,x}$:

$$\text{sn}_Y \in \left(\max_{x,u,j,k} (\tilde{p}_{j,k}^{u,x}), 1 \right), \quad \beta_{j,k}^{u,x} \in \left(\frac{\tilde{p}_{j,k}^{u,x} - (1 - \text{sp}_Y)}{\text{sp}_Y}, \frac{\tilde{p}_{j,k}^{u,x} - (1 - \text{sp}_Y)}{\max_{x,u,j,k} (\tilde{p}_{j,k}^{u,x}) + \text{sp}_Y - 1} \right) \quad (9)$$

This may be useful for policymakers interested in absolute risk of post-infection outcomes to forecast the burden on healthcare centers under different vaccination policies.

We will present a final corollary that will be useful in our applied examples:

¹See (Gustafson 2015) for more details on inference in partially identified Bayesian models

Corollary 3.4. *Suppose in addition to Assumptions 2.3 to 2.1, Assumption 2.5, Assumption 3.1, and Assumption 3.2, researchers do not directly observe A_i , but instead observe a misclassified version of A_i , \tilde{A}_i , such that the following nondifferential error assumption holds: $\tilde{A}_i \perp\!\!\!\perp \tilde{S}_i, \tilde{Y}_i, Y_i(z_j, S(z_j)), R_i, Z_i, S_i^{P_0} \mid A_i, X_i$. If both sn_S, sp_S lie in $[0, 1/2)$ or both lie in $(1/2, 1]$, $P_{N_z}^x(\tilde{A} \mid S^{P_0})$ is at least Kruskal rank $2^{N_z} - 1$ and $P_{N_z}^x(S^{P_0} \mid R)$ is rank 2^{N_z} for all x then the counterfactual distributions $P(S_i^{P_0} = u \mid R_i = r, X_i = x)$, $P(\tilde{A}_i = k \mid S_i^{P_0} = u, X_i = x)$ are identifiable as are the quantities $\text{sn}_S, \text{sp}_S, \text{sp}_Y$, and $\text{VE}_{I,jk}^u$. Furthermore, if sn_Y is unknown (known), distributions $P(Y_i(z_j) = 1 \mid S_i^{P_0} = u, \tilde{A}_i = k, X_i = x)$ are identifiable up to an unknown (known) common constant, $r_Y = \text{sn}_Y + \text{sp}_Y - 1$.*

The proof, shown in Section E, follows directly from the proof of Theorem 3.3 and the nondifferential misclassification error assumption for A .

While misclassified \tilde{A} precludes learning heterogeneous treatment effects, marginalizing over the identifiable distribution $\tilde{A}_i \mid S^{P_0}, X_i$ will yield the average post-infection vaccine efficacy.

3.2 Models, priors and sensitivity analyses

Under the assumptions laid out in Section 3 the observational model is a multinomial random variable for each study site and treatment group.

Let $\tilde{n}_{syk}(j, r, x)$ be $\sum_{i=1}^n \mathbb{1}(\tilde{S}_i = s) \mathbb{1}(\tilde{Y}_i = y) \mathbb{1}(Z_i = z_j) \mathbb{1}(R_i = r) \mathbb{1}(A_i = k) \mathbb{1}(X_i = x)$, and let the error-free partially-observed causal model probabilities $p_{syk|jrx} = P(S_i = s, Y_i = y, A_i = k \mid Z_i = z_j, R_i = r, X_i = x)$ be defined as:

$$p_{1yk|jrx} = \sum_{u|u \in \mathcal{S}, u_j=1} a_k^{u,x} \theta_u^{r,x} (\beta_{j,k}^{u,x})^y (1 - \beta_{j,k}^{u,x})^{1-y}, \quad p_{0* k|jrx} = \sum_{u|u \in \mathcal{S}, u_j=0} a_k^{u,x} \theta_u^{r,x}, \quad (10)$$

where we note that $p_{01k|jrx} = 0$ for all k, j, r . Then we define the observable joint probabilities

$q_{syk|jrx} = P(\tilde{S}_i = s, \tilde{Y}_i = y, A_i = k \mid Z_i = z_j, R_i = r, X_i = x)$ as

$$q_{syk|jrx} = \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \text{sn}_Y^y (1 - \text{sn}_Y)^{1-y} p_{11kjrx} + \text{sn}_S^s (1 - \text{sn}_S)^{1-s} \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y p_{10kjrx} \\ + \text{sp}_S^{1-s} (1 - \text{sp}_S)^s \text{sp}_Y^{1-y} (1 - \text{sp}_Y)^y p_{0*kjrx},$$

This allows us to define the observational model as:

$$(\tilde{n}_{001}(j, r, x), \tilde{n}_{011}(j, r, x), \tilde{n}_{101}(j, r, x), \tilde{n}_{111}(j, r, x), \dots, \tilde{n}_{00N_a}(j, r, x), \tilde{n}_{01N_a}(j, r, x), \tilde{n}_{10N_a}(j, r, x), \tilde{n}_{11N_a}(j, r, x)) \sim \\ \text{Multinomial}(n(j, r, x) \mid q_{001|jrx}, q_{011|jrx}, q_{101|jrx}, q_{111|jrx}, \dots, q_{00N_a|jrx}, q_{01N_a|jrx}, q_{10N_a|jrx}, q_{11N_a|jrx}), \quad (11) \\ j \in \{1, \dots, N_z\}, r \in \{1, \dots, N_r\}, x \in \{1, \dots, N_x\}$$

The post-infection severe-illness models can be formulated as saturated logistic regressions:

$$\log \frac{P(Y_i(z_j) = 1 \mid S_i^{P_0} = u, A_i = k, X_i = x)}{P(Y_i(z_j) = 0 \mid S_i^{P_0} = u, A_i = k, X_i = x)} = \alpha_j^{u,x} + \delta_{j,k}^{u,x}, \quad \beta_{j,k}^{u,x} = \frac{e^{\alpha_j^{u,x} + \delta_{j,k}^{u,x}}}{1 + e^{\alpha_j^{u,x} + \delta_{j,k}^{u,x}}}, \\ \delta_{j,1}^{u,x} = 0 \quad \forall j, u, x.$$

We may also implement a James-Stein-type estimator that asymptotically reduces to the saturated logistic regression:

$$\log \frac{P(Y_i(z_j) = 1 \mid S_i^{P_0} = u, A_i = k, X_i = x)}{P(Y_i(z_j) = 0 \mid S_i^{P_0} = u, A_i = k, X_i = x)} = \alpha_j^u + \epsilon_{j,k}^{u,x}, \quad \epsilon_{j,k}^{u,x} \sim N(0, \tau_\epsilon^2) \quad \forall j, u, x, k.$$

The model can accommodate deviations from Assumption 2.6 through an additive term $\epsilon_r^{u,x}$ capturing heterogeneity between study sites:

$$\log \frac{P(Y_i(z_j) = 1 \mid S_i^{P_0} = u, A_i = k, R_i = r, X_i = x)}{P(Y_i(z_j) = 0 \mid S_i^{P_0} = u, A_i = k, R_i = r, X_i = x)} = \alpha_j^{u,x} + \delta_{j,k}^{u,x} + \epsilon_r^{u,x}, \\ \epsilon_r^{u,x} \sim \text{Normal}(0, (\tau_\epsilon^u)^2).$$

We can fix $\tau_\gamma^{u,x}$ to several values for sensitivity analysis, as developed in Jiang et al. (2016).

We may write the probability models for $S_i^{P_0} \mid R_i, X_i$ and $A_i \mid S_i^{P_0}, X_i$ as two saturated

multinomial regressions, given Assumption 2.5 that $A_i \perp\!\!\!\perp R_i, Z_i \mid S_i^{P_0}, X_i$.

$$\begin{aligned} \log \frac{P(S_i^{P_0} = u \mid R_i = r, X_i = x)}{P(S_i^{P_0} = u_0 \mid R_i = r, X_i = x)} &= \mu_u^r + \eta_u^x + \eta_u^{r,x} \\ \log \frac{P(A_i = k \mid S_i^{P_0} = u, X_i = x)}{P(A_i = k_0 \mid S_i^{P_0} = u, X_i = x)} &= \nu_k^u + \gamma_k^x + \gamma_k^{u,x}, \end{aligned}$$

where

$$\theta_u^{r,x} = \frac{e^{\mu_u^r + \eta_u^x + \eta_u^{r,x}}}{\sum_{w \in \mathcal{S}} e^{\mu_w^r + \eta_w^x + \eta_w^{r,x}}}, \mu_{u_0}^r = 0 \forall r, \quad a_k^{u,x} = \frac{e^{\nu_k^u + \gamma_k^x + \gamma_k^{u,x}}}{\sum_{m=1}^{N_a} e^{\nu_m^u + \gamma_m^x + \gamma_m^{u,x}}}, \nu_{k_0}^u = 0 \forall u.$$

Note that $\eta_{u_0}^x, \gamma_{k_0}^x, \eta_{u_0}^{r,x}, \gamma_{k_0}^{r,x}, \gamma_{k_0}^{u,x}$ are all zero for all x . Furthermore, for given reference categories x_0, u_0, r_0 , $\eta_u^{x_0}, \gamma_k^{x_0}$ are zero for all u, k , while $\eta_u^{r_0,x}$ is zero for all x , η_u^{r,x_0} is zero for all r , γ_k^{u,x_0} is zero for all u and $\gamma_k^{u_0,x}$ is zero for all x . This leads to a tidy representation of the log-odds of belonging to stratum u vs. u_0 conditional on $A_i = k, R_i = r, X_i = x$:

$$\log \frac{P(S_i^{P_0} = u \mid A_i = k, R_i = r, X_i = x)}{P(S_i^{P_0} = u_0 \mid A_i = k, R_i = r, X_i = x)} = \mu_u^r + \nu_k^u - \nu_{k_0}^{u_0} + \gamma_k^{u,x} - \gamma_{k_0}^{u_0,x} + \eta_u^x + \eta_u^{r,x}.$$

If we suspect deviations from Assumption 2.5, we can add an interaction between A_i and R_i in the multinomial regression model for A_i :

$$\log \frac{P(A_i = k \mid R_i = r, S_i^{P_0} = u, X_i = x)}{P(A_i = k_0 \mid R_i = r, S_i^{P_0} = u, X_i = x)} = \nu_k^u + \gamma_k^x + \gamma_k^{u,x} + \epsilon_k^r, \quad \epsilon_k^r \sim \text{Normal}(0, (\tau_\epsilon^k)^2) \forall r. \quad (12)$$

4 Design and analysis of vaccine efficacy studies

There are several real-world applications for Theorem 3.3 in vaccine efficacy studies. The first is for quantifying vaccine efficacy against post-infection outcomes like severe illness, medically-attended illness or death, which is the primary motivation for the methods we have developed here. A second is to quantify the impact on vaccination on secondary transmission to household contacts. In both of these hypothetical trials, we imagine that participants are prospectively monitored for infection as well as the post-infection outcome

of interest. The infection monitoring might involve regular diagnostic testing or analysis of blood specimens for signs of infection.

A guiding philosophy we follow below is in using Bayesian models to design clinical trials with good Frequentist properties, as is discussed in [Berry \(2011\)](#). Thus, we chose our rejection region for our test statistic so as to limit our Type 1 error to no more than 0.05.

4.1 Vaccine efficacy against severe illness trial design

To show how our model can be used to design a vaccine efficacy study, we consider determining the sample size for two hypothetical clinical trials: one three-arm trial inspired by [Monto et al. \(2009\)](#), and a two-arm trial inspired by [Polack et al. \(2020\)](#). [Monto et al. \(2009\)](#) investigated vaccine efficacy against symptomatic influenza infection in a three-arm, double-blind placebo-controlled randomized trial. [Polack et al. \(2020\)](#) presented the results of the COVID-19 Pfizer vaccination trial, which measured vaccine efficacy against symptomatic infection using a two-arm double-blind placebo-controlled randomized trial. All trials are designed so as to jointly test the efficacy against infection and the efficacy against severe symptoms for the always-infected group.

In order to design our hypothetical trials, we simulate 200 datasets under the alternative hypothesis for each sample size and measure the proportion of datasets in which we reject the null hypothesis. For both trials, we will target a power of 0.8 against an alternative hypothesis that the vaccine efficacy against symptoms is equal to 0.6 for the always-infected stratum (i.e. $S_i^{P_0} = (1, 1, 1)$ and $S_i^{P_0} = (1, 1)$). We reject the null when the posterior probability is 0.85 or larger that vaccine efficacy against severe illness is above 0.1 and that the vaccine efficacy against infection is greater than 0.3. We can write the rejection region for $\text{Data} = \{(\tilde{S}_i, \tilde{Y}_i, Z_i, R_i, A_i, X_i), 1 \leq i \leq n\}$ as $\{\text{Data} : P(\text{VE}_{I,31}^{(1,1,1)} > 0.1, \text{VE}_{S,31} > 0.3 \mid$

Data) $\geq c\}$ for the three-arm trial and $\{\text{Data} : P(\text{VE}_{I,21}^{(1,1)} > 0.1, \text{VE}_{S,21} > 0.3 \mid \text{Data}) \geq k\}$ for the two-arm trial. More details on the choice of k is given in the next two subsections. Broadly, our decision criterion is akin to that used in [Polack et al. \(2020\)](#), namely that the posterior probability is greater than 0.986 that vaccine efficacy against confirmed COVID-19 is greater than 0.3. For example, in the two-arm scenario $k = 0.85$ adequately controls the Type 1 error for a null hypothesis of no vaccine efficacy against severe illness.

We use the model defined in Equation (11); the computational details are discussed in Section H. Given the results of Theorem 3.3, we can determine the number of study sites and the number of levels for A_i that need to be observed in order to point identify the causal estimand of interest. For the three-arm trial, we need at least 8 study sites and a covariate with at least 7 levels, while for the two-arm trial we need only 4 study sites and a covariate with at least 3 levels. In the two-arm study we simulated data from 8 sites, while in the three-arm trial we simulated data from 16 sites.

4.1.1 Two-arm trial

In the two arm trial, we sample the study-site-specific principal strata proportions from a Dirichlet distribution. The distribution's mean corresponds to the vector:

$$(P(S_i^{P_0} = (0, 0)), P(S_i^{P_0} = (0, 1)), P(S_i^{P_0} = (1, 0)), P(S_i^{P_0} = (1, 1))),$$

where $S_i^{P_0} = (S_i(1) = i, S_i(0) = j)$. The mean is set to $(0.78, 0.1, 0.02, 0.1)$, while the variance for each category is $P(S_i^{P_0} = (i, j))(1 - P(S_i^{P_0} = (i, j)))/101$. These parameter settings result in a cumulative incidence of 16%.

We fitted three models, which are described in detail in the appendix. Both included terms to account for possible deviations from assumption Assumption 2.5, and both employ a hierarchical model for the probability of severe disease conditional on principal stratum

and covariates. One model allows for an unrestricted set of principal strata, while the other two assume monotonicity, namely that $P(S_i^{P_0} = (1, 0)) = 0$. Of these two models that assume monotonicity, one assumes severe disease and infection are observed without error, while the other employs a measurement error model identical to the model proposed in this paper. In the results below, the unrestricted model is *full*, while the model that incorrectly assumes monotonicity and assumes perfect measurements is *mono-wo-meas-error*. The model that assumes monotonicity but allows for measurement error is called *mono-w-meas-error*. Given monotonicity assumption, neither monotonic model models the distribution for A_i ; they do, however, condition on A_i when learning the distribution of the post-infection outcome. We measured coverage of the 95% posterior credible intervals, bias and mean squared error of the posterior median of the target estimand, namely vaccine efficacy against severe illness in the always-infected stratum $S_i^{P_0} = (1, 1)$, and vaccine efficacy against infection. The data were simulated under two alternative hypotheses and two null hypotheses. VE against severe illness was ≈ 0.6 under one alternative hypothesis, and the alternative hypothesis had a VE against severe illness of ≈ -0.6 . Alternatively, under both null hypotheses VE against severe disease is equal to zero, while one has a VE against infection of ≈ 0.5 , and the other has a VE against infection ≈ 0.06 . Within these hypotheses we further stratified the simulations by two conditions: one in which Assumption 2.5 held and one in which Assumption 2.5 was violated.

Bias and MSE under both alternative hypotheses are presented in Figures 1 to 2. The figures show that under most scenarios, the full model has lower bias and MSE compared to the other models, though there are exceptions. The notable exceptions are at sample sizes of 20,000, and 40,000 under the null hypotheses. In these cases, monotonic models have smaller MSEs. This is due to the fact that the models which assume monotonicity

have far fewer parameters than the joint model, and while it may be a bit biased, this increased bias is small compared to the decrease in variance.

The coverage plots in Figure 3 show that the posterior credible intervals generated by the incorrect models have coverage far below the nominal rates under both alternative hypotheses, but the coverage is at or above the nominal rates under both null hypotheses. The full model achieves and sometimes exceeds the nominal coverage in all scenarios. Because it is a stated goal of the model to jointly infer VE_S and VE_I , the coverage plots show that it is at a minimum necessary to use a model that allows an unrestricted causal model to achieve nominal coverage.

The power calculations are presented in Table 1, which shows power as a function of the sample size and the various hypotheses. Despite the increased MSE under the null hypothesis, the full model does not have significantly inflated Type I errors compared to the *mono* models. The full model displays higher power uniformly across scenarios and sample sizes.

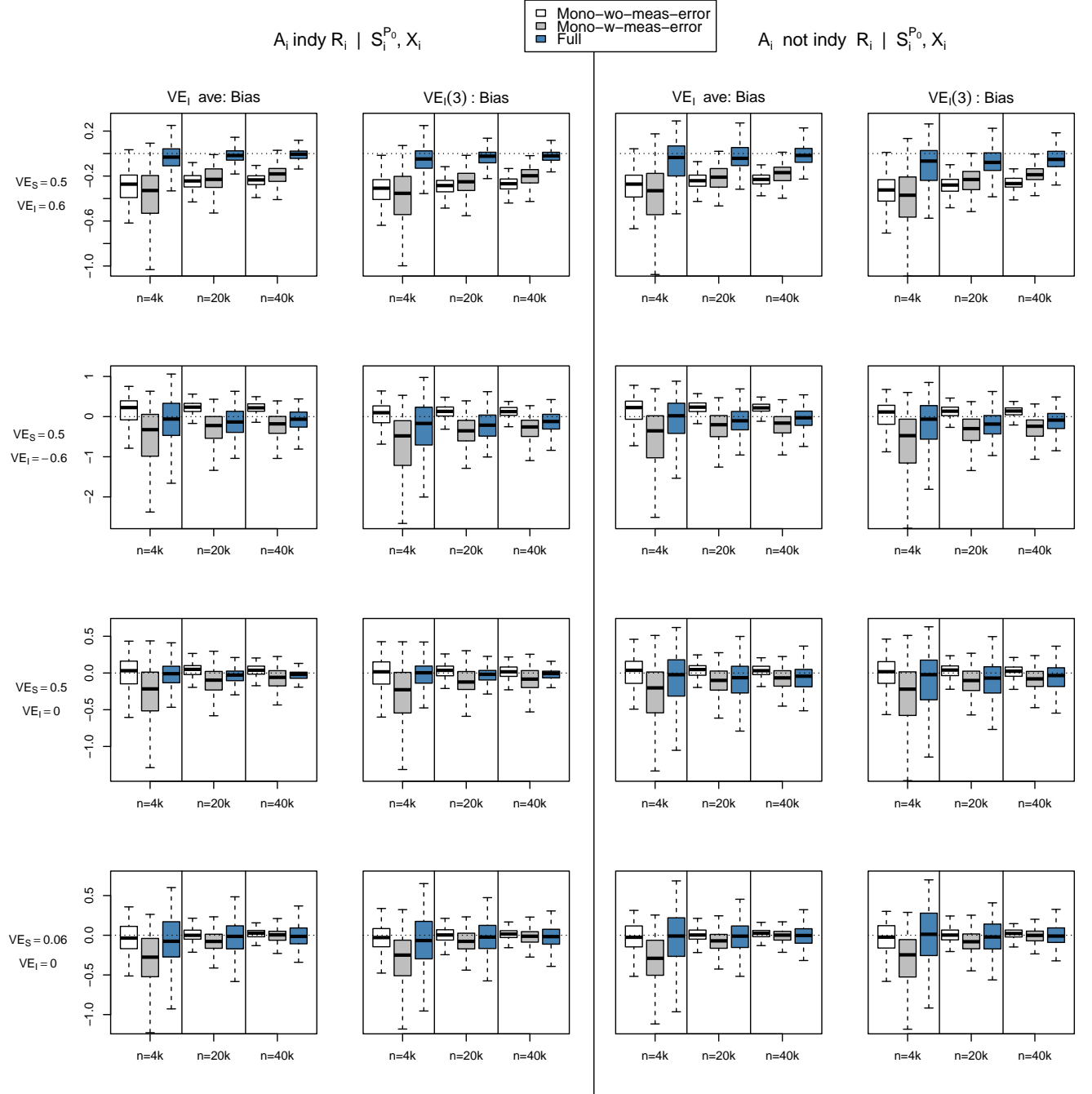


Figure 1: Boxplots collecting bias across simulated datasets for posterior median VE_I and $VE_I(3)$. Each boxplot bar summarizes the bias of an estimator across 200 datasets under a single sample size and hypothesis combination. The blue bar indicates bias under the full model, while the white bar indicates bias under the model employing a monotonicity assumption. Rows of the graph correspond to different hypotheses, while the columns correspond to whether or not Assumption 2.5 holds.

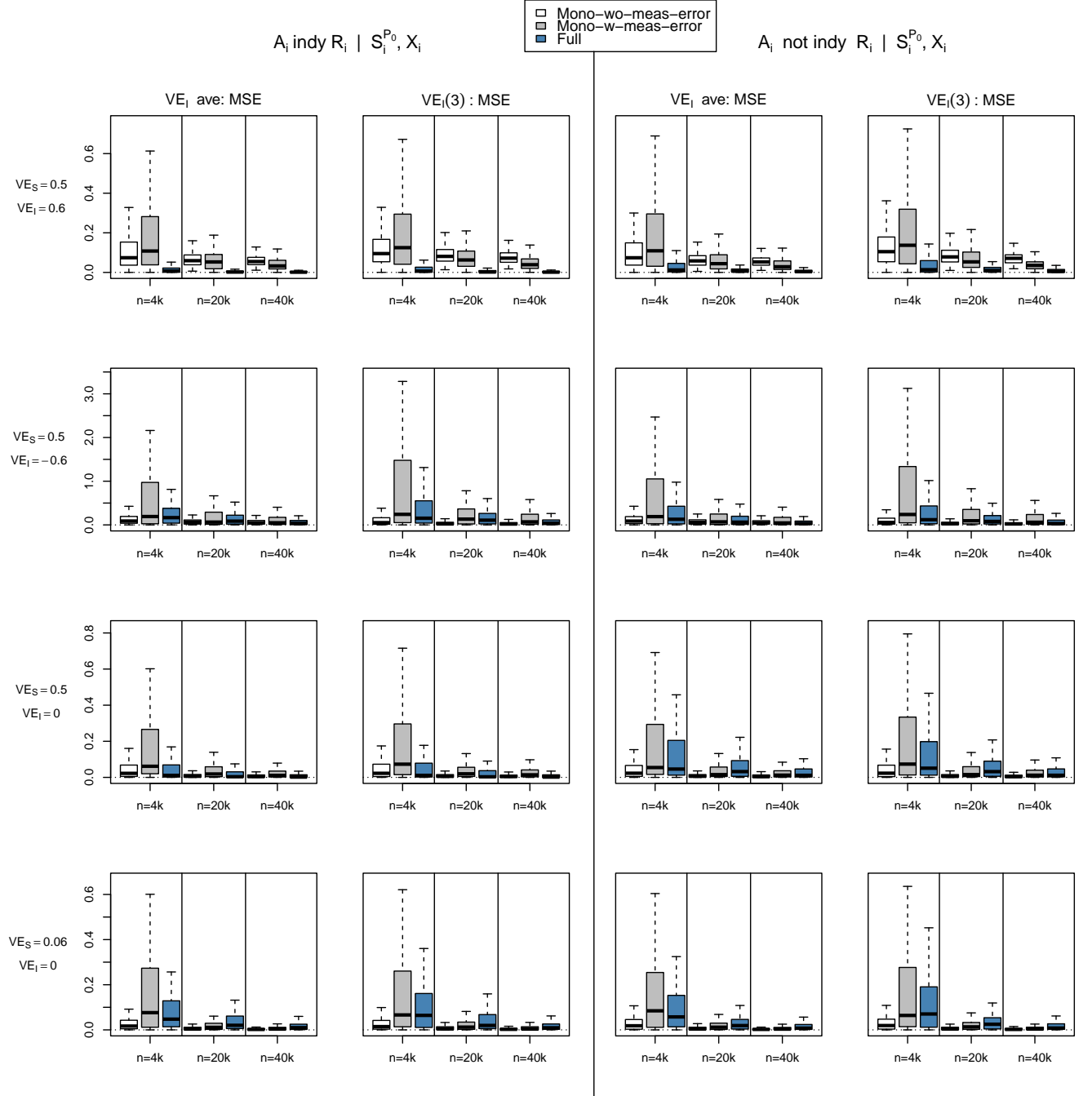


Figure 2: Boxplots collecting mean squared error across simulated datasets for posterior median VE_I and $VE_I(3)$. Each boxplot bar summarizes the bias of an estimator across 200 datasets under a single sample size and hypothesis combination. The blue bar indicates bias under the full model, while the white bar indicates bias under the model employing a monotonicity assumption. Rows of the graph correspond to different hypotheses, while the columns correspond to whether or not Assumption 2.5 holds.

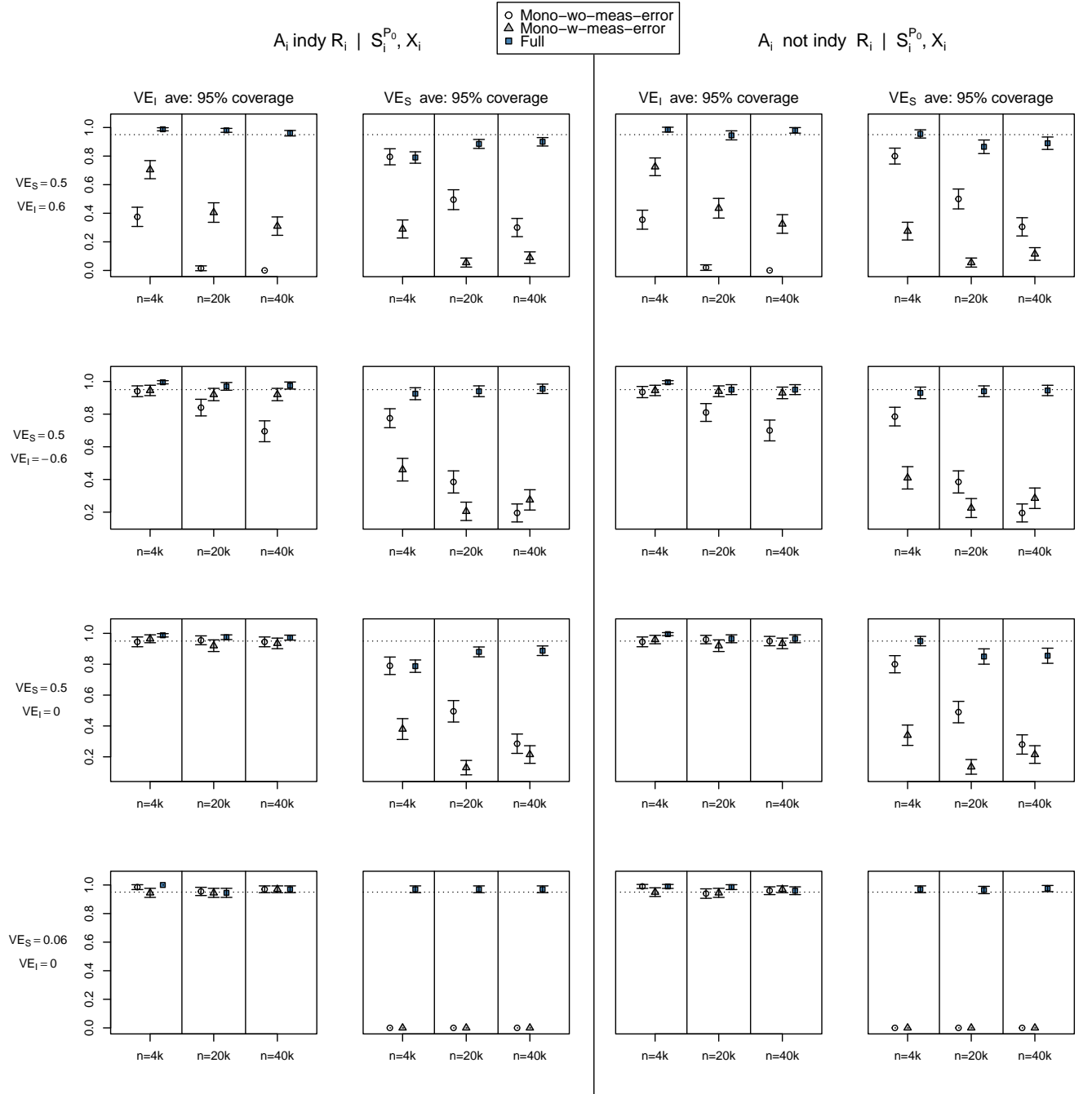


Figure 3: Posterior credible interval coverage across simulated datasets for VE_I and VE_S (95% intervals). Each point and error bar summarizes the coverage of the credible 200 datasets under a single sample size and hypothesis combination. The blue square points indicate the full model coverage, while the white points indicate the coverage under the model employing a monotonicity assumption. Rows of the graph correspond to different hypotheses, while the columns correspond to whether or not Assumption 2.5 holds.

Table 1: Power and Type I error rates for sample sizes of 4,000 through 40,000. Hypothesis indicates whether the alternative or the null hypothesis was used to generate the datasets, the column $A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$ indicates whether Assumption 2.5 holds, and the Model column indicates whether the full model or the models that incorrectly assume monotonicity were fitted. The k column indicates the cutoff value used to control Type I error; these values are specific to each model and are set so as to control the Type I error under the null across all sample sizes and $A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$ scenarios. Values for $VE_I = 0.6$ indicate power, while $VE_I = 0$ indicate Type I error.

Hypothesis	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$?	Model	k	4,000	20,000	40,000
$VE_I = 0.6$	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.925	0.23	0.77	0.90
		<i>mono-w-meas-error</i>	0.75	0.34	0.80	0.95
		<i>full</i>	0.85	0.53	0.92	1.00
	$A_i \not\perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.925	0.23	0.78	0.92
		<i>mono-w-meas-error</i>	0.75	0.35	0.81	0.96
		<i>full</i>	0.85	0.59	0.95	1.00
$VE_I = 0$	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.925	0.03	0.01	0.01
		<i>mono-w-meas-error</i>	0.75	0.03	0.02	0.04
		<i>full</i>	0.85	0.03	0.04	0.01
	$A_i \not\perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.925	0.05	0.01	0.01
		<i>mono-w-meas-error</i>	0.75	0.04	0.03	0.03
		<i>full</i>	0.85	0.03	0.04	0.01

While these results show that one needs fairly large sample sizes to achieve 80% power for the estimands of interest in both scenarios, this is expected because the always-infected principal strata, $(1,1)$, are only 10% of their respective populations in our simulation studies. Despite the full model having more parameters than either the *mono-w-meas-error* or *mono-wo-meas-error*, it generates the most powerful test in all scenarios while adequately controlling the type I error. In order to achieve Type I error control, the *mono-wo-meas-error* model requires a much smaller rejection region, or, equivalently, a larger value of k compared to the other two models. This reduces its power, and results in the *mono-wo-meas-error* having the smallest power among the models.

This highlights the extent to which power calculations, and bias and MSE for our models are dependent on principal strata proportions. Even though the proportion of individuals who are harmed by the vaccine is only 2%, the effect on models that assume monotonicity is quite drastic in terms of bias, MSE, and especially coverage.

Furthermore, though the sample sizes are large, randomized vaccine trials of similar magnitude have been run. For example, the trial presented in [Polack et al. \(2020\)](#) included approximately 43,500 participants. This highlights the fact that our model can be used to infer post-infection outcome vaccine efficacy from large real-world studies.

4.1.2 Three-arm trial

In the three arm trial, we sample the study-site-specific principal strata proportions from a Dirichlet distribution. The distribution's mean corresponds to the vector:

$$\begin{aligned} & (P(S_i^{P_0} = (0, 0, 0)), P(S_i^{P_0} = (1, 0, 0)), P(S_i^{P_0} = (0, 1, 0)), P(S_i^{P_0} = (1, 1, 0)), \\ & P(S_i^{P_0} = (0, 0, 1)), P(S_i^{P_0} = (1, 0, 1)), P(S_i^{P_0} = (0, 1, 1)), P(S_i^{P_0} = (1, 1, 1)) \end{aligned}$$

where $S_i^{P_0} = (S_i(0) = i, S_i(1) = j, S_i(2) = k)$. The mean is set to $(0.7, 0.13, 0.01, 0.01, 0.01, 0.01, 0.01, 0.12)$, while the variance for each category is $P(S_i^{P_0} = (i, j, k))(1 - P(S_i^{P_0} = (i, j, k)))/101$, as above. These parameter settings result in a population-average cumulative incidence of 19%.

We simulated data under two scenarios of varying study population size of 4,000, 40,000, and 80,000 participants. In all scenarios, $VE_{S,21} = 0.45$, $VE_{S,21} = 0.41$ and $VE_{I,21}^{(1,1,1)} = 0$. In one scenario, $VE_{I,21}^{(1,1,1)} = 0.52$, while $VE_{I,21}^{(1,1,1)} = 0$ in the null scenario. The data is generated so that Assumption 2.5 holds.

We fitted the same three models we fitted above, but the monotonicity assumption is more severe for the three-arm trial compared to the two-arm trial because only four parameters can be estimated from the observed data. The monotonic models assume that

$$P(S_i^{P_0} = (0, 1, 0)) = P(S_i^{P_0} = (0, 0, 1)) = P(S_i^{P_0} = (1, 0, 1)) = P(S_i^{P_0} = (0, 1, 1)) = 0,$$

thus misclassifying about 4% of the population.

In order to compare the models' performance, we measured $VE_{I,21}^{(1,1,1)}$ and $VE_{I,31}^{(1,1,1)}$, as

well as conditional VE $VE_{I,21}^{(1,1,1)}(k)$ and $VE_{I,31}^{(1,1,1)}(k)$ for $k = 5$. We also compared inferences for the VE against infection estimands, $VE_{S,21}$ and $VE_{S,31}$ respectively.

Figure 4 shows that the bias of the *full* model was the smallest in nearly every scenario for the chosen parameters. Meanwhile, the Figure 5 results are more mixed; the figure shows that the MSE is smallest for the full model when sample size exceeds 4,000 for the VE_S parameters, but that the MSE for the VE_I and conditional causal estimand is larger when the causal null hypothesis holds. In Figure 6 we see that the full model attains the nominal coverage for the VE_I parameters, while the monotonic models fail to achieve nominal coverage for these parameters. All models fail to achieve the nominal coverage for the VE_S parameters, but the *full* model's coverage improves as the sample size increases.

Table 2: Power and Type I error rates for sample sizes of 4,000 through 80,000 for the three-arm treatment simulation study. Hypothesis indicates whether the alternative or the null hypothesis was used to generate the datasets, the column $A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$ indicates whether Assumption 2.5 holds, and the Model column indicates whether the full model or the two models that incorrectly assume monotonicity were fitted. The k column shows the cutoff value that determines the rejection region; the value is chosen so as to control Type I error across all sample sizes for each model. Values for $VE_{I,31}^{(1,1,1)} = 0.52$ indicate power, while $VE_{I,31}^{(1,1,1)} = 0$ indicate Type I error. By design, all methods will have Type I error less than or equal to 5%.

Hypothesis	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$	Model	k	4,000	40,000	80,000
$VE_{I,31}^{(1,1,1)} = 0.52$	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.99	0.02	0.68	0.94
		<i>mono-w-meas-error</i>	0.94	0.02	0.75	0.97
		<i>full</i>	0.93	0.00	0.83	0.98
$VE_{I,31}^{(1,1,1)} = 0$	$A_i \perp\!\!\!\perp R_i \mid S_i^{P_0}$	<i>mono-wo-meas-error</i>	0.99	0.00	0.03	0.03
		<i>mono-w-meas-error</i>	0.94	0.00	0.04	0.03
		<i>full</i>	0.93	0.00	0.04	0.03

Table 2 shows the pitfalls of the smaller MSE values from the *mono-wo-meas-error* model, namely that in order to control the Type I error we need a much smaller rejection region. This leads to lower power compared to the other two models. In keeping with the results in the two-arm trial, the full model has the highest power among all the models, with the exception of the 4,000 participant scenario. The results show that one could run a

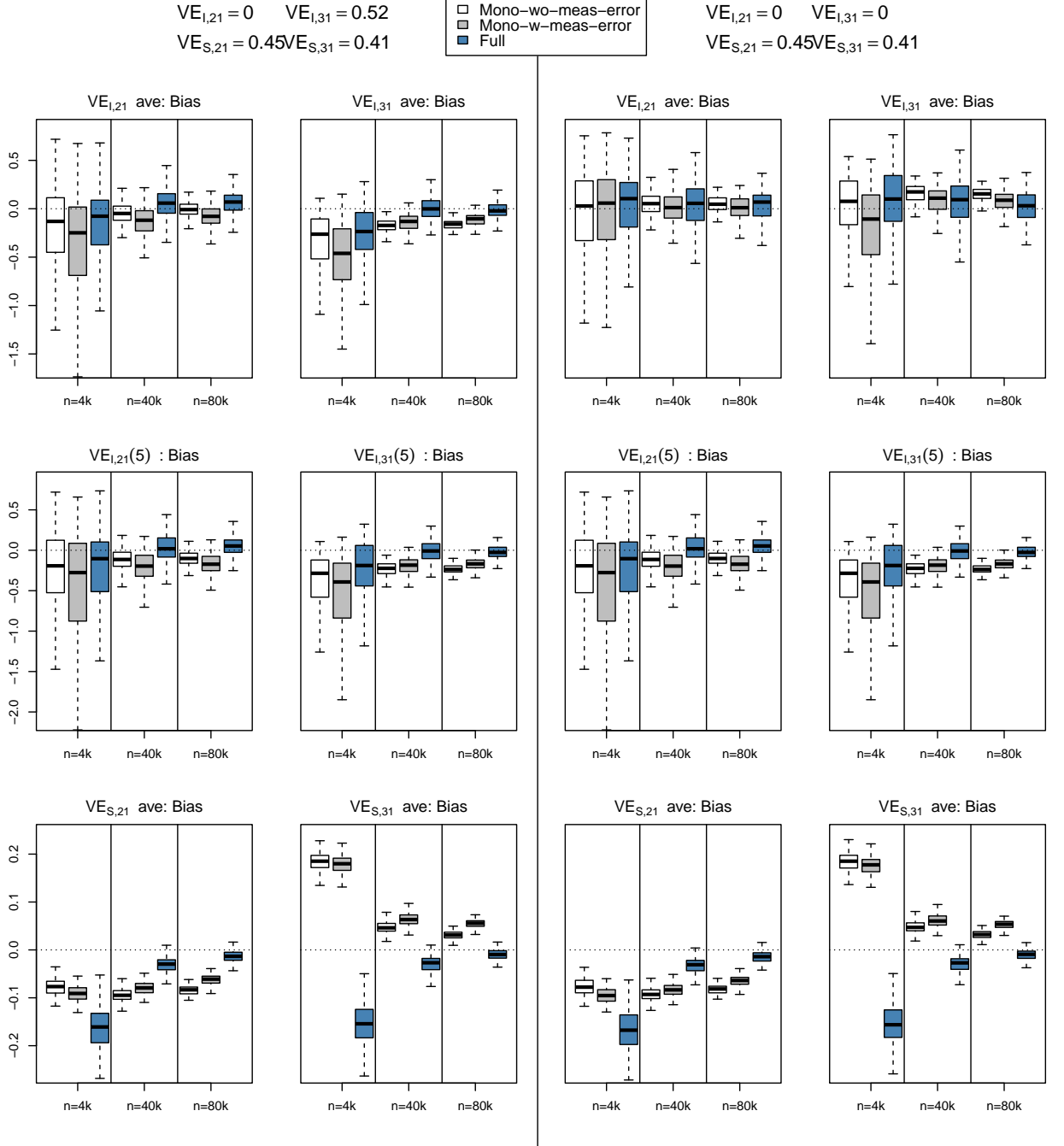


Figure 4: Boxplots collecting bias across simulated datasets for posterior median $VE_{I,21}^{(1,1,1)}$ and $VE_{I,31}^{(1,1,1)}$ in the top row, $VE_{I,21}^{(1,1,1)}(k)$ and $VE_{I,31}^{(1,1,1)}(k)$ in the middle row, and $VE_{S,21}$ and $VE_{S,31}$ in the final row. Each boxplot bar summarizes the bias of an estimator across 200 datasets under a single sample size and hypothesis combination. The blue bar indicates bias under the full model, while the white bar indicates bias under the model employing a monotonicity assumption. The columns correspond to whether the null hypothesis of $VE_{I,31}^{(1,1,1)} = 0$ holds.

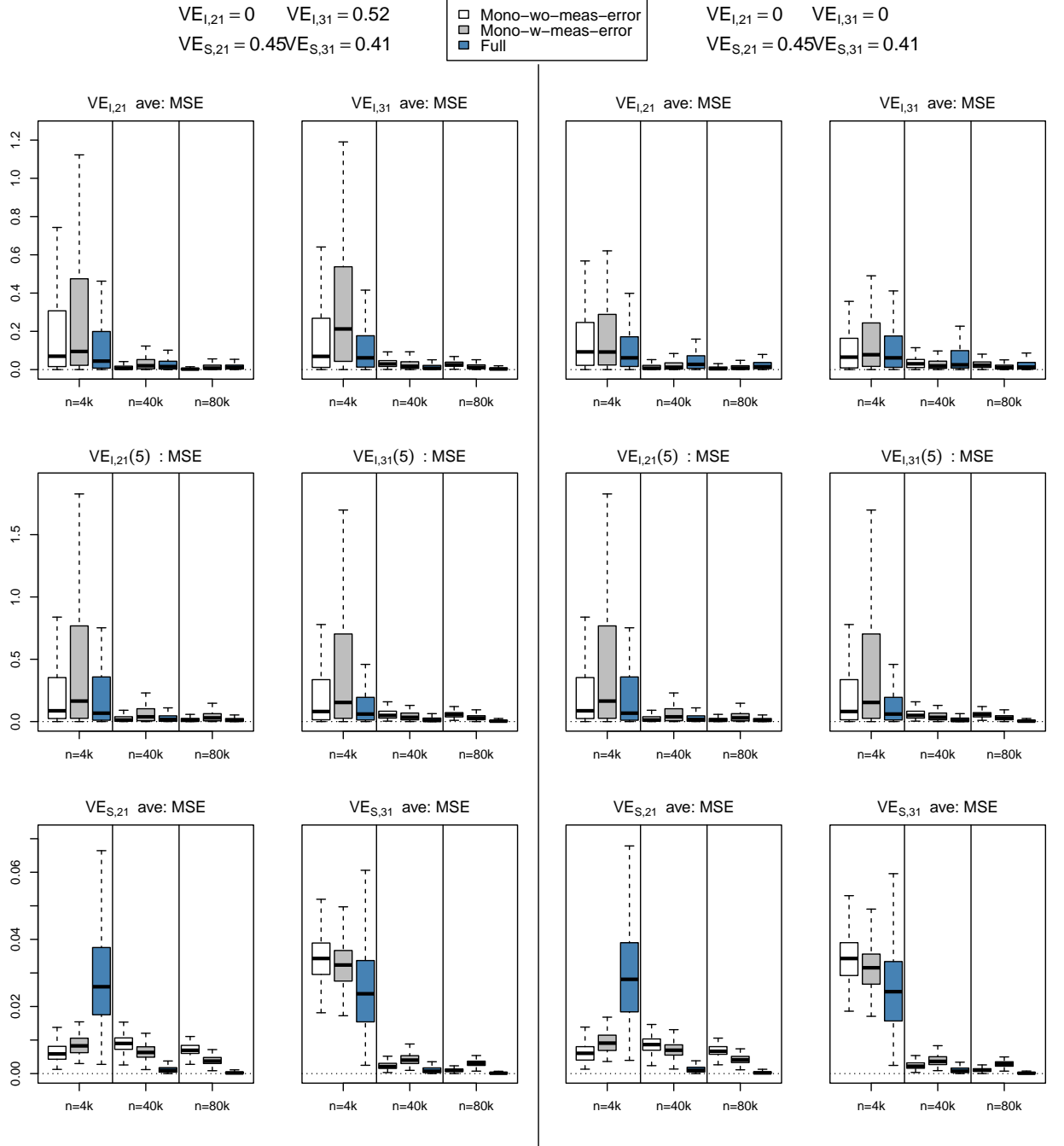


Figure 5: Boxplots collecting mean squared error across simulated datasets for posterior median $VE_{I,21}^{(1,1,1)}$ and $VE_{I,31}^{(1,1,1)}$ in the top row, $VE_{I,21}^{(1,1,1)}(k)$ and $VE_{I,31}^{(1,1,1)}(k)$ in the middle row, and $VE_{S,21}$ and $VE_{S,31}$ in the final row. Each boxplot bar summarizes the bias of an estimator across 200 datasets under a single sample size and hypothesis combination. The blue bar indicates bias under the full model, while the white bar indicates bias under the model employing a monotonicity assumption. The columns correspond to whether the null hypothesis of $VE_{I,31}^{(1,1,1)} = 0$ holds.

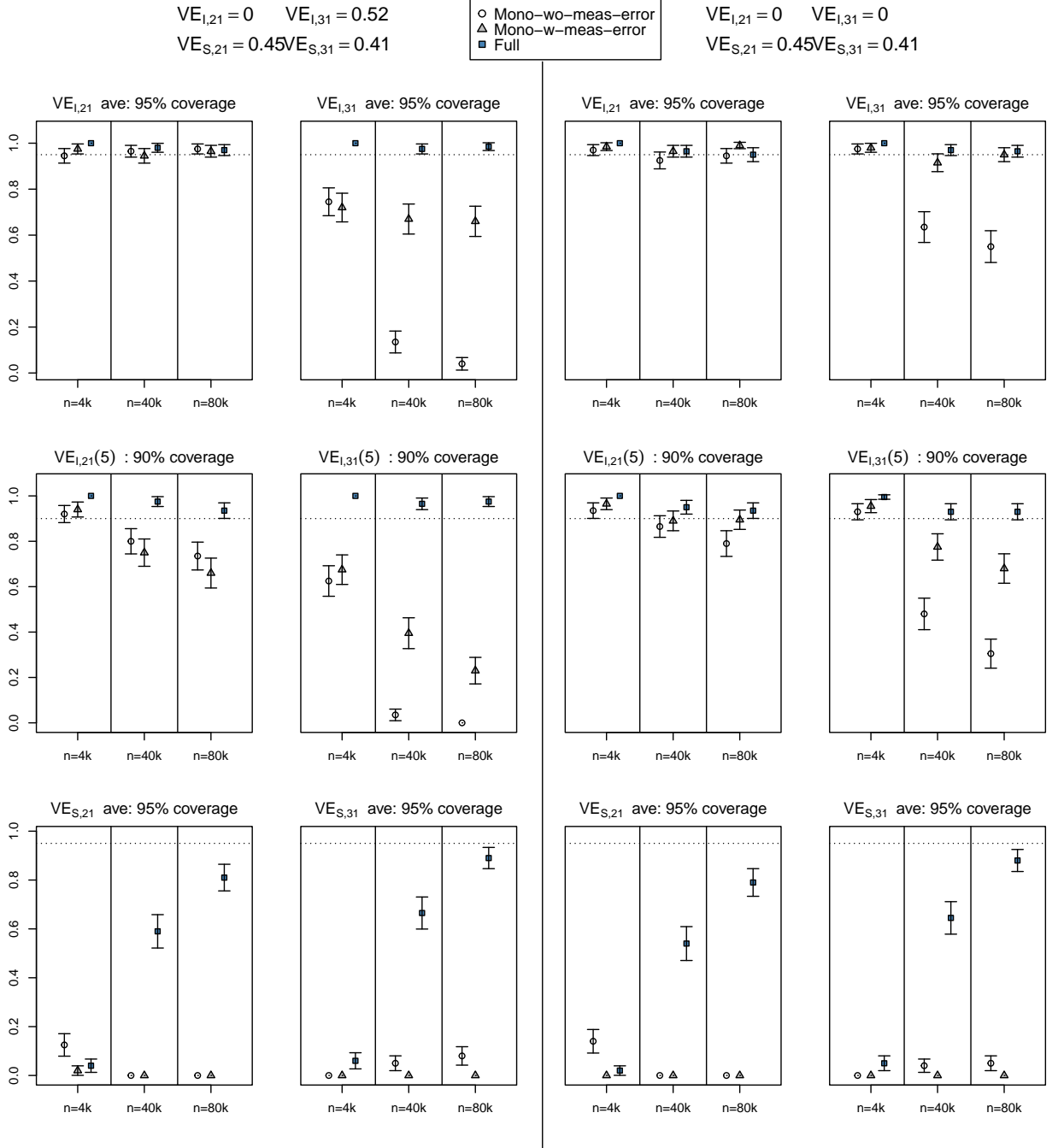


Figure 6: Posterior credible interval coverage across simulated datasets for $VE_{I,21}^{(1,1,1)}$ and $VE_{I,31}^{(1,1,1)}$ (95% intervals) in the top row, $VE_{I,21}^{(1,1,1)}(k)$ and $VE_{I,31}^{(1,1,1)}(k)$ in the middle row, and $VE_{S,21}$ and $VE_{S,31}$ in the final row (all 90% intervals). Each point and error bar summarizes the coverage of the credible 200 datasets under a single sample size and hypothesis combination. The blue square points indicate the full model coverage, while the white points indicate the coverage under the model employing a monotonicity assumption. The columns correspond to whether the null hypothesis of $VE_{I,31}^{(1,1,1)} = 0$ holds.

trial with 40,000 to achieve 80% power. Recent vaccine trials show that trials of 40,000 are feasible and successful, further demonstrating the applicability of our model to real-world trials.

5 Discussion

Policymakers and public health experts can use vaccine efficacy for post-infection outcomes to design more precise vaccination programs. Our method makes inferring these causal estimands feasible in real-world multi-arm trials where outcomes are measured with error and vaccines cannot be assumed to have a nonnegative effect on infection for every individual. The power of our method is reflected in its flexibility to be applied to vaccine trials with multiple treatments as well as various post-infection outcomes. Although we focus on binary post-infection outcomes here, our method is readily extensible to ordinal and continuous measures, such as immune response as measured by antibody titer. Accordingly, when paired with a parametric likelihood for continuous post-infection outcomes, our method may be more statistically efficient than models identified by likelihood assumptions alone, like that of [Zhang et al. \(2009\)](#). Furthermore, our identifiability results are nonparametric, though we use parametric Bayesian estimators in our examples. One can use these methods to design and analyze clinical trials, as we show in [Section 4](#).

5.1 Limitations and extensions

The model currently assumes that post-infection outcome specificity is constant across study sites, but this may not reflect the reality of some vaccine trials. An extension to the model is to allow misclassification rates that differ by values of covariates X , by treatment assignment Z as well as by study site R . The identifiability results readily generalize to

models including X and Z , but more work is required to understand how varying specificities by R impacts the identifiability results presented here. For instance, if a vaccine changes how the virus populates the nasal cavity, we might expect that PCR tests from nasopharyngeal swabs will be less sensitive in the vaccinated group. More work is needed to further generalize the procedure to categorical intermediate outcomes, which would allow for more general vaccine efficacy against transmission study designs (VanderWeele & Tchetgen Tchetgen 2011), as well as applications beyond vaccine efficacy to noncompliance in multi-arm trials where the exclusion restriction could be violated (Cheng & Small 2006).

A Proofs and further details for simulation studies

We define our notation for principal stratification in vaccine efficacy (VE) in section B. In section F, we give general properties of the Kruskal rank, and extensions to Kruskal (1977) theorems that we derived. We apply these extensions in the context of principle stratification for VE in section C. The proof of our main result, Theorem 3.3, is given in section E. These proofs are based on results in Section F and Section C.

B Notation and definitions

In the following proofs, we have omitted the subscript i from random variables to simplify our notation. We have also elided conditioning on $X_i = x$; the proofs shown in Section E are understood to be conditional on $X_i = x$. Let z be the N_z -category discrete variable taking values in the set $\{z_1, \dots, z_{N_z}\}$ representing treatment, and let Z be treatment assignment. The principal stratum, S^{P_0} is defined as $(S(z_1), \dots, S(z_{N_z}))$, $S(z_j) \in \{0, 1\}$. Let \mathcal{S} be the set of principal strata, which is equal to $\{0, 1\}^{N_z}$ when there are no monotonicity assumptions;

let $u \in \mathcal{S}$.

Let the set of treatments be $\{z_1, \dots, z_{N_z}\}$, with $z \in \{z_1, \dots, z_{N_z}\}$

Let A have N_a levels and take values in the set $\{1, \dots, N_a\}$. Let $P(A \mid R)$ be the $N_a \times N_r$ matrix with $(i, j)^{\text{th}}$ element equal to $P(A = i \mid R = j)$ and let $P(A = k \mid R)$ be the $N_r \times N_r$ diagonal matrix with $(i, i)^{\text{th}}$ diagonal element $P(A = k \mid R = i)$. Let $P(\tilde{A} = k \mid R)$ be defined similarly. Let $P_{N_z}(A \mid S^{P_0})$ be the $N_a \times 2^{N_z}$ matrix with $(i, j)^{\text{th}}$ element equal to $P(A = i \mid S^{P_0} = \varpi_{N_z}(j - 1))$, and let $P_{N_z}(S^{P_0} \mid R)$ be the $2^{N_z} \times N_r$ matrix with $(i, j)^{\text{th}}$ element equal to $P(S^{P_0} = \varpi_{N_z}(i - 1) \mid R = j)$. Let $P_{N_z}(A = k \mid S^{P_0})$ be the $2^{N_z} \times 2^{N_z}$ diagonal matrix with $(i, i)^{\text{th}}$ element $P(A = k \mid S^{P_0} = \varpi_{N_z}(i - 1))$ and let $P_{N_z}(\tilde{A} = k \mid S^{P_0})$ be defined similarly. Let $P(y \mid R, Z = z)$ be the $1 \times R$ matrix with element $(1, j)^{\text{th}}$ equal to $P(y \mid R = j, Z = z)$, and similarly let $P_{N_z}(y \mid S^{P_0}, Z = z)$ be the 1×2^{N_z} matrix with element $(1, j)^{\text{th}}$ equal to $P(y \mid S^{P_0} = \varpi_{N_z}(j - 1), Z = z)$. Let $P(y \mid R, Z = z, A = k)$ be the $1 \times R$ matrix with $(1, j)^{\text{th}}$ element equal to $P(y \mid R = j, Z = z, A = k)$, and similarly let $P_{N_z}(y \mid S^{P_0}, Z = z, A = k)$ be the 1×2^{N_z} matrix with element $(1, j)^{\text{th}}$ equal to $P(y \mid S^{P_0} = \varpi_{N_z}(j - 1), Z = z, A = k)$. Let the matrix $P_{N_z}(S \mid Z, S^{P_0})$ be in $\mathbb{R}^{2N_z \times 2^{N_z}}$ where column denotes principal stratum $S^{P_0} = \varpi_{N_z}(j - 1)$ and row represents a combination $(s, z) \in \{(1, 1), (1, 2), \dots, (1, N_z), (0, 1), \dots, (0, N_z)\}$, with $(i, j)^{\text{th}}$ element denoted $P_{N_z}(S \mid Z, S^{P_0})_{ij}$ defined as

$$P_{N_z}(S \mid Z, S^{P_0})_{ij} = \varpi_{N_z}(j - 1)_i \mathbb{1}(i \leq N_z) + (1 - \varpi_{N_z}(j - 1)_{i-N_z}) \mathbb{1}(i > N_z),$$

and let $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ be in $\mathbb{R}^{2N_z \times 2^{N_z}}$ with $(i, j)^{\text{th}}$ element denoted $P_{N_z}(\tilde{S} \mid Z, S^{P_0})_{ij}$ defined:

$$\begin{aligned} P_{N_z}(\tilde{S} \mid Z, S^{P_0})_{ij} = & \text{sn}_S^{\varpi_{N_z}(j-1)_i} (1 - \text{sp}_S)^{1 - \varpi_{N_z}(j-1)_i} \mathbb{1}(i \leq N_z) \\ & + (1 - \text{sn}_S)^{\varpi_{N_z}(j-1)_{i-N_z}} \text{sp}_S^{1 - \varpi_{N_z}(j-1)_{i-N_z}} \mathbb{1}(i > N_z). \end{aligned}$$

Let B^+ be the Moore-Penrose inverse of the matrix B , $\mathbf{1}_m$ be the m -vector of 1s, $\mathbf{0}_m$ be the m -vector of 0s, and \mathbf{I}_m be the $m \times m$ dimensional identity matrix.

C Kruskal rank properties related to VE

In this section, we show that (a) the Kruskal rank of the matrix $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ is 3 for $N_z \geq 2$ when $\text{sn}_S + \text{sp}_S \neq 1$ and (b) the column domains of $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ are not invariant to column permutation when $\text{sn}_S, \text{sp}_S > 0.5$ or $\text{sn}_S, \text{sp}_S < 0.5$ for $N_z \geq 2$.

Lemma C.1 (Kruskal rank $P_2(\tilde{S} \mid Z, S^{P_0})$). *The Kruskal rank of*

$$\begin{array}{cccc} (0,0) & (1,0) & (0,1) & (1,1) \\ \left[\begin{array}{cccc} 1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S & \text{sn}_S \\ \text{sp}_S & 1 - \text{sn}_S & \text{sp}_S & 1 - \text{sn}_S \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S & 1 - \text{sn}_S \end{array} \right] & \begin{array}{l} (s=1, z=1) \\ (s=1, z=2) \\ (s=0, z=1) \\ (s=0, z=2) \end{array} \end{array} \quad (13)$$

is 3 as long as $\text{sn}_S + \text{sp}_S \neq 1$.

Proof. All subsets of 3 columns of the matrix $P_2(\tilde{S} \mid Z, S^{P_0})$ are of the form:

$$\begin{bmatrix} a & c & e \\ b & d & f \\ 1-a & 1-c & 1-e \\ 1-b & 1-d & 1-f \end{bmatrix}. \quad (14)$$

These submatrices have a common maximal minor of

$$a(d-f) - c(b-f) + e(b-d).$$

The quantities a, b, c, d, e, f are the elements of the 2×3 matrix

$$\begin{bmatrix} a & c & e \\ b & d & f \end{bmatrix} \quad (15)$$

in which $(a, b)^T, (c, d)^T, (e, f)^T$ are any 3 columns drawn without replacement from the 2×4 submatrix of Equation (13):

$$\begin{bmatrix} 1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S & \text{sn}_S \end{bmatrix}. \quad (16)$$

These minors are all equal to (up to a factor of -1):

$$(1 - \text{sn}_S - \text{sp}_S)^2,$$

which can be seen after a brute-force calculation. The minors are nonzero for all $\text{sn}_S, \text{sp}_S \in [0, 1]$ such that $\text{sn}_S + \text{sp}_S \neq 1$. Thus, by the determinantal rank definition, all 3 column matrices are rank 3. In contrast, the determinant of $P_2(\tilde{S} \mid Z, S^{P_0})$ is 0 for all values of sn_S, sp_S . Thus by the definition of Kruskal rank in Definition 2.6, $k_{P_2(\tilde{S} \mid Z, S^{P_0})} = 3$. \square

Lemma C.2 (Kruskal rank $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$, $N_z \geq 2$). *The Kruskal rank of $P(\tilde{S} \mid Z, S^{P_0})$ for $N_z \geq 2$ is 3 as long as $\text{sn}_S + \text{sp}_S \neq 1$.*

Proof. We proceed by induction. For $N_z = 2$, Lemma C.1 shows that the Kruskal rank is 3. Let $N_z = n$ for $n > 2$. Recall that $P_n(\tilde{S} \mid Z, S^{P_0})$ is the $2n \times 2^n$ matrix with column j

$$\begin{bmatrix} s_j \\ \mathbf{1}_n - s_j \end{bmatrix}$$

with the i^{th} element of s_j denoted s_{ij} and defined as:

$$s_{ij} = \text{sn}_S^{\varpi_n(j-1)_i} (1 - \text{sp}_S)^{1 - \varpi_n(j-1)_i}.$$

The induction hypothesis is that the Kruskal rank of $P_n(\tilde{S} \mid Z, S^{P_0})$ is 3. The columns of $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$ are of the form

$$\begin{bmatrix} s_j \\ 1 - \text{sp}_S \\ \mathbf{1}_n - s_j \\ \text{sp}_S \end{bmatrix}$$

for $j \in \{1, \dots, 2^n\}$, and

$$\begin{bmatrix} s_{j-2^n} \\ \text{sn}_S \\ \mathbf{1}_n - s_{j-2^n} \\ 1 - \text{sn}_S \end{bmatrix}$$

for $j \in \{2^n + 1, \dots, 2^{n+1}\}$. The 3-column submatrices of $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ made from column j, ℓ, m indices fall into several classes. When $j, \ell, m \in \{1, \dots, 2^n\}$, $j, \ell, m \in \{2^n + 1, \dots, 2^{n+1}\}$ or $j, \ell \in \{1, \dots, 2^n\}, m \in \{2^n + 1, \dots, 2^{n+1}\} \setminus \{j + 2^n, \ell + 2^n\}$, $j \in \{1, \dots, 2^n\}, m, \ell \in \{2^n + 1, \dots, 2^{n+1}\} \setminus \{j + 2^n\}$ all matrices are rank 3 by the induction hypothesis. When $j, \ell \in \{1, \dots, 2^n\}$ but $m \in \{j + 2^n, \ell + 2^n\}$ the submatrix is

$$\begin{bmatrix} s_j & s_\ell & s_{m-2^n} \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell & \mathbf{1}_n - s_{m-2^n} \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S \end{bmatrix}.$$

WLOG, let $m = j + 2^n$. This leads to the submatrix:

$$\begin{bmatrix} s_j & s_\ell & s_j \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell & \mathbf{1}_n - s_j \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S \end{bmatrix}.$$

The rank of this submatrix is

$$\begin{aligned}
\text{rank} \begin{bmatrix} s_j & s_\ell & s_j \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell & \mathbf{1}_n - s_j \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S \end{bmatrix} &= \text{rank} \begin{bmatrix} s_j & s_\ell & s_j \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell & \mathbf{1}_n - s_j \\ 1 & 1 & 1 \end{bmatrix} \\
&= \text{rank} \begin{bmatrix} s_j & s_\ell & s_j \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell & \mathbf{1}_n - s_j \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ 0 & 0 & 1 - \frac{\text{sn}_S}{1 - \text{sp}_S} \end{bmatrix} \\
&\geq \text{rank} \begin{bmatrix} s_j & s_\ell \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_\ell \\ 1 - \text{sp}_S & 1 - \text{sp}_S \\ 0 & 0 \end{bmatrix} + \text{rank} \left(1 - \frac{\text{sn}_S}{1 - \text{sp}_S} \right) \\
&= 3.
\end{aligned}$$

The inequality follows from Lemma G.1. Other scenarios follow similarly. \square

Lemma C.3 (Domain restriction lemma). *If $\text{sn}_S, \text{sp}_S \in [0, 0.5)$ or $\text{sn}_S, \text{sp}_S \in (0.5, 1]$, the matrix $P_{N_z}(\tilde{S} \mid Z, S^{P_0}) \in \mathbb{R}^{2N_z \times 2N_z}$ has column domains that are not invariant to column permutation.*

Proof. We prove Lemma C.3 by induction on N_z . The base case is $N_z = 2$. Let P be a 4×4

permutation matrix and let $P_2(\tilde{S} \mid Z, S^{P_0})$ be

$$\begin{array}{cccc}
(0,0) & (1,0) & (0,1) & (1,1) \\
\left[\begin{array}{cccc}
1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S \\
1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S & \text{sn}_S \\
\text{sp}_S & 1 - \text{sn}_S & \text{sp}_S & 1 - \text{sn}_S \\
\text{sp}_S & \text{sp}_S & 1 - \text{sn}_S & 1 - \text{sn}_S
\end{array} \right] & \begin{array}{l} (s=1, z=1) \\ (s=1, z=2) \\ (s=0, z=1) \\ (s=0, z=2) \end{array}
\end{array} \quad (17)$$

Recall from the definition in Section B that the column indices $\{1, 2, 3, 4\}$ of $P_2(\tilde{S} \mid Z, S^{P_0})$ map to the following principal strata S^{P_0} : $\varpi_2(0), \varpi_2(1), \varpi_2(2), \varpi_2(3)$. In other words, column index j is mapped to S^{P_0} via the relation $\varpi_2(j-1)$. We consider permutation matrix P without loss of generality, and other cases are similarly shown,

$$P = \begin{bmatrix} 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix}$$

Let $\mathcal{C} = [0, 1]$, and let \mathcal{A} be one of two half intervals of $[0, 1]$: $[0, 0.5]$ or $(0.5, 1]$. Let $\mathcal{B} = \mathcal{C} \setminus \mathcal{A}$. Note that $P_2(\tilde{S} \mid Z, S^{P_0})$ maps $\mathcal{C} \times \mathcal{C}$ to a matrix with elements in \mathcal{C} . Let $1 - \text{sp}_S \in \mathcal{A}$ and let $\text{sn}_S \in \mathcal{B}$ and suppose that the column domains for $P_2(\tilde{S} \mid Z, S^{P_0})$ are not invariant after permutation by matrix P . Then we have the following domain for the map given by $P_2(\tilde{S} \mid Z, S^{P_0})$:

$$\begin{array}{cccc}
(0,0) & (1,0) & (0,1) & (1,1) \\
P_2(\tilde{S} \mid Z, S^{P_0})|_{\mathcal{A} \times \mathcal{B}}: \mathcal{A} \times \mathcal{B} \rightarrow & \left[\begin{array}{cccc}
\mathcal{A} & \mathcal{A} & \mathcal{A} & \mathcal{A} \\
\mathcal{A} & \mathcal{A} & \mathcal{A} & \mathcal{A} \\
\mathcal{B} & \mathcal{B} & \mathcal{B} & \mathcal{B} \\
\mathcal{B} & \mathcal{B} & \mathcal{B} & \mathcal{B}
\end{array} \right]
\end{array}$$

However, we have,

$$\bar{P}_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}} = P_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}} P \quad (18)$$

$$= \begin{matrix} & \begin{matrix} (0,0) & (1,0) & (0,1) & (1,1) \end{matrix} \\ \begin{matrix} \begin{bmatrix} 1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S \\ 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S & \text{sn}_S \\ \text{sp}_S & 1 - \text{sn}_S & \text{sp}_S & 1 - \text{sn}_S \\ \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S & 1 - \text{sn}_S \end{bmatrix} \end{matrix} & \begin{bmatrix} 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix} \end{matrix} \quad (19)$$

$$= \begin{matrix} & \begin{matrix} (0,0) & (1,0) & (0,1) & (1,1) \end{matrix} \\ \begin{matrix} \begin{bmatrix} \text{sn}_S & 1 - \text{sp}_S & \text{sn}_S & 1 - \text{sp}_S \\ \text{sn}_S & 1 - \text{sp}_S & 1 - \text{sp}_S & \text{sn}_S \\ 1 - \text{sn}_S & \text{sp}_S & 1 - \text{sn}_S & \text{sp}_S \\ 1 - \text{sn}_S & \text{sp}_S & \text{sp}_S & 1 - \text{sn}_S \end{bmatrix} \end{matrix} & \end{matrix}. \quad (20)$$

But we see that the column domains are invariant after column permutation:

$$\bar{P}_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}}: \mathcal{A} \times \mathcal{B} \rightarrow \begin{matrix} & \begin{matrix} (0,0) & (1,0) & (0,1) & (1,1) \end{matrix} \\ \begin{bmatrix} \mathcal{A} & \mathcal{A} & \mathcal{A} & \mathcal{A} \\ \mathcal{A} & \mathcal{A} & \mathcal{A} & \mathcal{A} \\ \mathcal{B} & \mathcal{B} & \mathcal{B} & \mathcal{B} \\ \mathcal{B} & \mathcal{B} & \mathcal{B} & \mathcal{B} \end{bmatrix} & \begin{matrix} (s=1, z=1) \\ (s=1, z=2) \\ (s=0, z=1) \\ (s=0, z=2) \end{matrix} \end{matrix}$$

In order for the columns $\bar{P}_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}}$ to be on the same domain as $P_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}}$, a necessary and sufficient condition is that sn_S and $1 - \text{sp}_S$ are on the same domain. In other words, $\{\text{sn}_S \in \mathcal{A}, \text{sp}_S \in \mathcal{B}\}$ or $\{\text{sn}_S \in \mathcal{B}, \text{sp}_S \in \mathcal{A}\}$.

Thus $\bar{P}_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}}$ maps $(\text{sn}_S, \text{sp}_S)$ to the same space that $P_2(\tilde{S} \mid Z, S^{P_0}) \mid_{\mathcal{A} \times \mathcal{B}}$.

We contradict our statement that the columns are not invariant to permutation.

The case for $N_z > 2$. Let $N_z = n > 2$ and let the column domains of $P_n(\tilde{S} \mid Z, S^{P_0})$ be not invariant to permutation. Furthermore suppose that $\text{sn}_S, \text{sp}_S \in \mathcal{A}$ or $\text{sn}_S, \text{sp}_S \in \mathcal{B}$. Then matrix $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$ has columns

$$\begin{bmatrix} s_j \\ 1 - \text{sp}_S \\ \mathbf{1}_n - s_j \\ \text{sp}_S \end{bmatrix}$$

for $j \in \{1, \dots, 2^n\}$ and

$$\begin{bmatrix} s_{j-2^n} \\ \text{sn}_S \\ \mathbf{1}_n - s_{j-2^n} \\ 1 - \text{sn}_S \end{bmatrix}$$

for $j \in \{2^n + 1, \dots, 2^{n+1}\}$. Permuting any two columns $j, k \in \{1, \dots, 2^n\}$ or $j, k \in \{2^n + 1, \dots, 2^{n+1}\}$ yields different column domains given the induction hypothesis. If $j \in \{1, \dots, 2^n\}$ and $k = j + 2^n$, then the columns are

$$\begin{bmatrix} s_j & s_j \\ 1 - \text{sp}_S & \text{sn}_S \\ \mathbf{1}_n - s_j & \mathbf{1}_n - s_j \\ \text{sp}_S & 1 - \text{sn}_S \end{bmatrix}$$

Let the domain of s_j be \mathcal{D} , and let $\mathcal{D}^c = [0, 1]^n \setminus \mathcal{D}$ be the domain of $\mathbf{1}_n - s_j$. Then the domains are

$$\begin{bmatrix} \mathcal{D} & \mathcal{D} \\ \mathcal{A} & \mathcal{B} \\ \mathcal{D}^c & \mathcal{D}^c \\ \mathcal{B} & \mathcal{A} \end{bmatrix}$$

if $\text{sp}_S, \text{sn}_S \in \mathcal{B}$ and

$$\begin{bmatrix} \mathcal{D} & \mathcal{D} \\ \mathcal{B} & \mathcal{A} \\ \mathcal{D}^c & \mathcal{D}^c \\ \mathcal{A} & \mathcal{B} \end{bmatrix}$$

if $\text{sp}_S, \text{sn}_S \in \mathcal{A}$. These two columns are not invariant to permutation. Because no two columns may be interchanged without a change in domain, right multiplying $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$ by any $2^{n+1} \times 2^{n+1}$ permutation matrix $P \neq \mathbf{I}_{n+1}$ to will yield a matrix with different column domains than $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$. \square

D Rank properties related to VE

In this section we show that when $N_z \geq 2$ the rank of $P_{N_z}(\tilde{S} \mid Z, S^{P_0}) = N_z + 1$ when $\text{sn}_S + \text{sp}_S \neq 1$.

Lemma D.1 (Rank $P_2(\tilde{S} \mid Z, S^{P_0})$). *The rank of $P_2(\tilde{S} \mid Z, S^{P_0})$, defined in Equation (13), is 3 as long as $\text{sn}_S + \text{sp}_S \neq 1$.*

Proof. The determinant of $P_2(\tilde{S} \mid Z, S^{P_0})$ is 0. The determinant of the 3-minor $M_{4,4}$ is $(1 - \text{sn}_S - \text{sp}_S)^2$ which is nonzero as long as $\text{sn}_S + \text{sp}_S \neq 1$. \square

Lemma D.2 (Rank $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$, $N_z \geq 2$). *The rank of $P(\tilde{S} \mid Z, S^{P_0})$ for $N_z \geq 2$ is $N_z + 1$ as long as $\text{sn}_S + \text{sp}_S \neq 1$.*

Proof. We proceed by induction. For $N_z = 2$, Lemma D.1 shows that the rank is 3. Let $N_z = n$ for $n > 2$. Recall that $P_n(\tilde{S} \mid Z, S^{P_0})$ is the $2n \times 2^n$ matrix with column j

$$\begin{bmatrix} s_j \\ \mathbf{1}_n - s_j \end{bmatrix}$$

with the i^{th} element of s_j denoted s_{ij} and defined as:

$$s_{ij} = \text{sn}_S^{\varpi_n(j-1)i} (1 - \text{sp}_S)^{1-\varpi_n(j-1)i}.$$

The induction hypothesis is that the rank of $P_n(\tilde{S} \mid Z, S^{P_0})$ is $n + 1$. The columns of $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$ are of the form

$$\begin{bmatrix} s_j \\ 1 - \text{sp}_S \\ \mathbf{1}_n - s_j \\ \text{sp}_S \end{bmatrix}$$

for $j \in \{1, \dots, 2^n\}$, and

$$\begin{bmatrix} s_{j-2^n} \\ \text{sn}_S \\ \mathbf{1}_n - s_{j-2^n} \\ 1 - \text{sn}_S \end{bmatrix}$$

for $j \in \{2^n + 1, \dots, 2^{n+1}\}$. After a row permutation we can express $P_{n+1}(\tilde{S} \mid Z, S^{P_0})$ as a block matrix:

$$\begin{bmatrix} P_n(\tilde{S} \mid Z, S^{P_0}) & P_n(\tilde{S} \mid Z, S^{P_0}) \\ (1 - \text{sp}_S)\mathbf{1}_{2^n}^T & \text{sn}_S\mathbf{1}_{2^n}^T \\ \text{sp}_S\mathbf{1}_{2^n}^T & (1 - \text{sn}_S)\mathbf{1}_{2^n}^T \end{bmatrix}$$

Recall that by construction the sum of the i^{th} row with the $(i + n)^{\text{th}}$ row of $P_n(\tilde{S} \mid Z, S^{P_0})$ is $\mathbf{1}_{2^n}^T$ for $i \leq n$. Then by Lemma [G.2](#), $\text{rank}(P_{n+1}(S \mid Z, S^{P_0}))$ is

$$\begin{aligned} \text{rank}(P_{n+1}(S \mid Z, S^{P_0})) &= \text{rank}(P_n(S \mid Z, S^{P_0})) + \text{rank}\left(\begin{bmatrix} \text{sn}_S\mathbf{1}_{2^n}^T \\ (1 - \text{sn}_S)\mathbf{1}_{2^n}^T \end{bmatrix} - \begin{bmatrix} (1 - \text{sp}_S)\mathbf{1}_{2^n}^T \\ \text{sp}_S\mathbf{1}_{2^n}^T \end{bmatrix}\right) \\ &= n + 1 + 1 \end{aligned} \tag{21}$$

$$= n + 1 + 1 \tag{22}$$

given that $\text{sn}_S + \text{sp}_S \neq 1$. □

E Main results

Proof. Proof of Theorem 3.3

Define the three way array L with dimensions $2N_z \times N_a \times N_r$ and $(i, j, r)^{\text{th}}$ element $P(\tilde{S} = \mathbb{1}(i \leq N_z), A = k \mid Z = z_{i-N_z \mathbb{1}(i > N_z)}, R = r)$. Recall that the definition of matrix $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ requires that column j be

$$\begin{bmatrix} s_j \\ \mathbf{1}_{N_z} - s_j \end{bmatrix}$$

where the i^{th} element of s_j is denoted as s_{ij} and is defined as:

$$s_{ij} = \text{sn}_S^{\varpi_{N_z}(j-1)_i} (1 - \text{sp}_S)^{1 - \varpi_{N_z}(j-1)_i}$$

Let the matrices $P_{N_z}(S^{P_0} \mid R)^T, P_{N_z}(A \mid S^{P_0})$ be defined as in Section B. Then

$$P(\tilde{S} = \mathbb{1}(i \leq N_z), A = k \mid Z = z_{i-N_z \mathbb{1}(i > N_z)}, R = r) = \sum_{j=1}^{2^{N_z}} P_{N_z}(\tilde{S} \mid Z, S^{P_0})_{i,j} P_{N_z}(S^{P_0} \mid R)_{r,j}^T P_{N_z}(A \mid S^{P_0})_{k,j}.$$

Given that $\text{sn}_S + \text{sp}_S \neq 1$, as shown in Lemma C.2, $k_{P_{N_z}(\tilde{S} \mid Z, S^{P_0})} = 3$ and $\text{rank}(P_{N_z}(\tilde{S} \mid Z, S^{P_0})) = N_z + 1$. Furthermore, by assumptions stated in Theorem 3.3, $\text{rank}(P_{N_z}(S^{P_0} \mid R)^T) = 2^{N_z}$ and $P_{N_z}(S^{P_0} \mid R)^T \in \mathbb{R}^{N_r \times 2^{N_z}}$ so by Definition 2.6, $k_{P_{N_z}(S^{P_0} \mid R)^T} = 2^{N_z}$. Given that $k_{P_{N_z}(A \mid S^{P_0})} \geq 2^{N_z} - 1$ as stated in Theorem 3.3, the conditions in Corollary F.3 hold:

$$\min(3, 2^{N_z}) + 2^{N_z} - 1 \geq 2^{N_z} + 2 \tag{23}$$

$$\min(3, 2^{N_z} - 1) + 2^{N_z} \geq 2^{N_z} + 2 \tag{24}$$

$$\tag{25}$$

and

$$\text{rank}(P_{N_z}(S \mid Z, S^{P_0})) + \text{rank}(P_{N_z}(S^{P_0} \mid R)) + \text{rank}(P_{N_z}(A \mid S^{P_0})) \quad (26)$$

$$\geq N_z + 1 + 2^{N_z} + 2^{N_z} - 1 \quad (27)$$

$$= N_z + 2^{N_z+1} \quad (28)$$

by the fact that $\text{rank}(P_{N_z}(A \mid S^{P_0})) \geq k_{(P_{N_z}(A \mid S^{P_0}))}$. Also

$$N_z + 2^{N_z+1} - 2(2^{N_z} - 1) = N_z - 1 \quad (29)$$

$$\geq \begin{cases} \min(N_z - 2, \text{rank}(P_{N_z}(A \mid S^{P_0})) - k_{(P_{N_z}(A \mid S^{P_0}))}) \\ \min(N_z - 2, 0) \end{cases}. \quad (30)$$

Given that $P_{N_z}(A \mid S^{P_0})$ has columns that sum to 1, and $P_{N_z}(S^{P_0} \mid R)^T$ has rows that sum to 1, we can apply Corollary F.3 to the 3-way array L . Applying Corollary F.3 yields that the triple-product decomposition $[P_{N_z}(\tilde{S} \mid Z, S^{P_0}), P_{N_z}(A \mid S^{P_0}), P_{N_z}(S^{P_0} \mid R)^T]$ is unique up to a common column permutation. However, Theorem 3.3 states the assumption that sn_S, sp_S lie in a common half-interval. By Lemma C.3, the only permutation matrix consistent with the column domain of $P_{N_z}(\tilde{S} \mid Z, S^{P_0})$ is the identity matrix. We conclude that the 3-way decomposition of L , $[P_{N_z}(\tilde{S} \mid Z, S^{P_0}), P_{N_z}(A \mid S^{P_0}), P_{N_z}(S^{P_0} \mid R)^T]$, is unique. It follows that two different decompositions $[P_{N_z}(\tilde{S} \mid Z, S^{P_0}), P_{N_z}(A \mid S^{P_0}), P_{N_z}(S^{P_0} \mid R)^T]$ and $[P_{N_z}(\tilde{S} \mid Z, S^{P_0})', P_{N_z}(A \mid S^{P_0})', (P_{N_z}(S^{P_0} \mid R)^T)']$ yield different L s. By the fact that L is a complete characterization of the data distribution $P(\tilde{S} = s, A = k \mid Z = z_j, R = r)$ and Definition 2.4 the parameter set $[P_{N_z}(\tilde{S} \mid Z, S^{P_0}), P_{N_z}(A \mid S^{P_0}), P_{N_z}(S^{P_0} \mid R)^T]$ is strictly identifiable.

Define the matrix $P(\tilde{Y} \mid Z, R, A = k)$ with dimensions $N_z \times N_r$ with elements $P(\tilde{Y} = y \mid R = r, Z = z, A = k)$

$$P(\tilde{Y} \mid Z, R, A = k)_{i,r} = P(\tilde{Y} = 1 \mid Z = z_i, R = r, A = k).$$

Let the matrix $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)$ be in $\mathbb{R}^{N_z \times 2^{N_z}}$ for all $k \in \{1, \dots, N_a\}$ with elements

$$P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)_{i,j} = \varpi_{N_z}(j-1)_i r_Y P(Y = 1 \mid Z = z_i, S^{P_0} = \varpi_{N_z}(j-1), A = k) + (1 - \text{sp}_Y) \quad (31)$$

where $r_Y = \text{sp}_Y + \text{sn}_Y - 1$. Then

$$P(\tilde{Y} = 1 \mid Z = z_i, A = k, R = r) = \sum_{j=1}^{2^{N_z}} P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)_{i,j} P_{N_z}(S^{P_0} \mid R)_{j,r} \times P_{N_z}(A = k \mid S^{P_0})_{j,j} / P(A = k \mid R = r).$$

Recalling the definitions of diagonal matrices $P(A = k \mid R)$ and $P_{N_z}(A = k \mid S^{P_0})$, the expression can be rewritten as matrix multiplication:

$$P(\tilde{Y} \mid Z, R, A = k) = P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k) P_{N_z}(A = k \mid S^{P_0}) P_{N_z}(S^{P_0} \mid R) P(A = k \mid R)^{-1}. \quad (32)$$

Given our assumption that $P_{N_z}(S^{P_0} \mid R)$ is full row rank, $P_{N_z}(S^{P_0} \mid R) P_{N_z}(S^{P_0} \mid R)^+ = \mathbf{I}_{2^{N_z}}$.

We assume without loss of generality that $P(A = k \mid S^{P_0} = u) > 0 \forall k, u$, so $P_{N_z}(A = k \mid S^{P_0})$ is invertible, and that $P(A = k \mid R = r) > 0 \forall k, r$ so $P(A = k \mid R)$ is invertible.

$$P(\tilde{Y} \mid Z, R, A = k) P(A = k \mid R) P_{N_z}(S^{P_0} \mid R)^+ P_{N_z}(A = k \mid S^{P_0})^{-1} = P_{N_z}(\tilde{Y} \mid Z, A = k, S^{P_0}) \quad (33)$$

If to the contrary that $P(A = k \mid S^{P_0} = u) = 0$ for some k and u , we adopt the convention that $P(\tilde{Y} = y \mid Z = z, S^{P_0} = u, A = k)$ is undefined. We can then reduce the set of principal strata included in the sum to include only those for which $P(A = k \mid S^{P_0} = u) > 0$. It follows from the full-row-rank assumption on $P_{N_z}(S^{P_0} \mid R)$ that the matrix formed from any subset of rows of this matrix is still full row-rank. Given the modified matrices, Equation (33) will hold with the reduced set of principal strata. We can use a similar technique when $P(A = k \mid R = r) = 0$ for some combination of k and r . This condition is empirically testable.

It then follows the definition of $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)$ in Equation (31) that sp_Y is identifiable, as are the parameters $r_Y P(Y = 1 \mid Z = z_j, S^{P_0} = \varpi_{N_z}(j - 1), A = k)$ for all $z_j, j \in \{1, \dots, 2^{N_z}\}$ and k .

Let any allowable post-infection outcome vaccine efficacy estimand, necessarily where $u_j u_l = 1$, be defined as

$$\text{VE}_{I,jl}^u(k) = 1 - \frac{\mathbb{E}[Y(z_j) \mid S^{P_0} = u, A = k]}{\mathbb{E}[Y(z_l) \mid S^{P_0} = u, A = k]}.$$

By Assumptions 2.1 to 2.2 $P(Y = 1 \mid Z = z, S^{P_0} = u, A = k) = P(Y(z) = 1 \mid S^{P_0} = u, A = k)$ for all $z \in \{z_1, \dots, z_{N_z}\}$ and $\mathbb{E}[Y(z) \mid S^{P_0} = u, A = k] = P(Y(z) = 1 \mid S^{P_0} = u, A = k)$. Note that $\text{sp}_Y = 1 - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)_{1,1}$ by our definition of $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)$ in Equation (31). This is because the first column of $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)$ corresponds to the principal stratum that is always uninfected, or $S^{P_0} = \varpi(0)$, which results in $P(\tilde{Y} = 1 \mid Z = z, S^{P_0} = \varpi(0), A = k) = 1 - \text{sp}_Y$ for all z, k . The first row of the matrix $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)$ corresponds to $\tilde{Y} = 1$. Then

$$P(Y = 1 \mid Z = z, S^{P_0} = u, A = k) = \frac{P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)_{z,j} - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, A = k)_{1,1}}{r_Y}$$

where $j = \varpi_{N_z}^{-1}(u) + 1$, so $\text{VE}_{I,jl}^u(k)$ is identifiable. \square

Proof. Proof of Corollary 3.4

By the conditions set forth in Corollary 3.4 we have that

$$P(\tilde{S} = \mathbb{1}(i \leq N_z), \tilde{A} = k \mid Z = z_{i-N_z \mathbb{1}(i > N_z)}, R = r) = \sum_{j=1}^{2^{N_z}} P_{N_z}(\tilde{S} \mid Z, S^{P_0})_{i,j} P_{N_z}(S^{P_0} \mid R)_{r,j}^T P_{N_z}(\tilde{A} \mid S^{P_0})_{k,j}.$$

This decomposition holds because of our nondifferential misclassification assumption, namely

$\tilde{A} \perp\!\!\!\perp S^{P_0}, \tilde{S}, R, Z \mid A$, which allows for the following complete characterization of $\tilde{A} \mid S^{P_0}$:

$$P(\tilde{A} = k \mid S^{P_0} = u) = \sum_{\ell=1}^{N_z} P(\tilde{A} = k \mid A = \ell) P(A = \ell \mid S^{P_0} = u).$$

Recall that sn_S, sp_S lie in the same half interval of $[0, 1]$, so by the same logic as Section E, the distributions $P(\tilde{S} = 1 \mid Z = z, S^{P_0} = u), P(\tilde{A} = k \mid S^{P_0} = u), P(S^{P_0} = u \mid R = r)$ are identifiable. Define the matrix $P(\tilde{Y} \mid Z, R, \tilde{A} = k)$ with dimensions $N_z \times N_r$ with elements $P(\tilde{Y} = y \mid R = r, Z = z, \tilde{A} = k)$

$$P(\tilde{Y} \mid Z, R, \tilde{A} = k)_{i,r} = P(\tilde{Y} = 1 \mid Z = z_i, R = r, \tilde{A} = k).$$

Let the matrix $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)$ be defined in the same way as Equation (31). Then

$$P(\tilde{Y} = 1 \mid Z = z_i, \tilde{A} = k, R = r) = \sum_{j=1}^{2^{N_z}} P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{i,j} \quad (34)$$

$$\times P_{N_z}(S^{P_0} \mid R)_{j,r} P_{N_z}(\tilde{A} = k \mid S^{P_0})_{j,j} / P(\tilde{A} = k \mid R = r) \quad (35)$$

which can be represented as matrix multiplication, recalling the definitions of matrices $P_{N_z}(\tilde{A} = k \mid S^{P_0})$, and $P(\tilde{A} = k \mid R)$:

$$P(\tilde{Y} \mid Z, R, \tilde{A} = k) = P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k) P_{N_z}(\tilde{A} = k \mid S^{P_0}) P_{N_z}(S^{P_0} \mid R) P(\tilde{A} = k \mid R)^{-1} \quad (36)$$

Given our assumption that $P_{N_z}(S^{P_0} \mid R)$ is full row rank, $P_{N_z}(S^{P_0} \mid R) P_{N_z}(S^{P_0} \mid R)^+ = \mathbf{I}_{2^{N_z}}$. Without loss of generality we assume that $P(\tilde{A} = k \mid R = r) > 0 \forall k, r$, which is estimable from observed data and $P(\tilde{A} = k \mid S^{P_0} = u) > 0 \forall k, u$, which is identified via the . Then:

$$P(\tilde{Y} \mid Z, R, \tilde{A} = k) P(\tilde{A} = k \mid R) P_{N_z}(S^{P_0} \mid R)^+ P_{N_z}(\tilde{A} = k \mid S^{P_0})^{-1} = P_{N_z}(\tilde{Y} \mid Z, \tilde{A} = k, S^{P_0}) \quad (37)$$

It then follows the definition of $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)$ that sp_Y is identifiable, as are the parameters $r_Y P(Y = 1 \mid Z = z_j, S^{P_0} = \varpi_{N_z}(j - 1), \tilde{A} = k)$ for all $j \in \{1, \dots, 2^{N_z}\}$ and $k \in \{1, \dots, N_a\}$.

Let any allowable post-infection outcome vaccine efficacy estimand, necessarily where $u_j u_l = 1$, be defined as

$$\text{VE}_{I,jl}^u = 1 - \frac{\mathbb{E}[Y(z_j) \mid S^{P_0} = u]}{\mathbb{E}[Y(z_l) \mid S^{P_0} = u]}.$$

By Assumptions 2.1 to 2.2 $P(Y = 1 \mid Z = z, S^{P_0} = u, \tilde{A} = k) = P(Y(z) = 1 \mid S^{P_0} = u, \tilde{A} = k)$ and $\mathbb{E}[Y(z) \mid S^{P_0} = u, \tilde{A} = k] = P(Y(z) = 1 \mid S^{P_0} = u, \tilde{A} = k)$ for all $z \in \{z_1, \dots, z_{N_z}\}$. Note that $\text{sp}_Y = 1 - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{1,1}$ by our definition of $P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)$ in Equation (31). Then

$$P(Y = 1 \mid Z = z, S^{P_0} = u, \tilde{A} = k) = \frac{P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{z,j} - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{1,1}}{r_Y}$$

where $j = \varpi_{N_z}^{-1}(u) + 1$. Then

$$\text{VE}_{I,jl}^u = 1 - \frac{\sum_k (P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{z,j} - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{1,1}) P(\tilde{A} = k \mid S^{P_0} = u)}{\sum_k (P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{z,l} - P_{N_z}(\tilde{Y} \mid Z, S^{P_0}, \tilde{A} = k)_{1,1}) P(\tilde{A} = k \mid S^{P_0} = u)}.$$

□

Lemma E.1 (Identifiability of counterfactual post-infection outcome expectations). *Suppose $P(S_i^{P_0} = u \mid R = r)$ is known*

F Kruskal rank properties

In the section that follows, we use properties and several theorems and lemmas that are proven in Kruskal (1977). Where appropriate we will indicate on which pages the proofs of the theorems and lemmas can be found.

Lemma F.1 (Rank lemma). *Let*

$$H_{AB}(n) = \min_{\text{card}(A')=n} \{\text{rank}(A') + \text{rank}(B')\} - n$$

for an integer n where A' is an n -column subset of the matrix A and B' is the same column-index subset of a matrix B . For any diagonal matrix $D \in \mathbb{R}^{n \times n}$ with rank δ ,

$$\text{rank}(ADB^T) \geq H_{AB}(\delta).$$

See proof on p. 121 in [Kruskal \(1977\)](#).

F.1 Kruskal's triple-product decomposition uniqueness theorem

Theorem F.2 (Kruskal triple product decomposition uniqueness). *Let matrices A, B, C be defined as in Definition 2.5, with respective ranks r_A, r_B, r_C , and let array L also be defined as in Definition 2.5. Suppose that $k_A \leq r_A, k_B \leq r_B$, and $k_C \leq r_C$. Then if*

$$r_A + r_B + r_C - (2M + 2) \geq \begin{cases} \min(r_A - k_A, r_B - k_B) \\ \min(r_A - k_A, r_C - k_C) \end{cases},$$

$\min(k_A, k_B) + r_C \geq M + 2$, and $\min(k_A, k_C) + r_B \geq M + 2$ the decomposition $L = [A, B, C]$ is unique up to column permutation matrix P and column scaling Λ, G, N such that ΛGN is the identity matrix. In other words, L can be represented as the triple product of any three matrices $[\tilde{A}, \tilde{B}, \tilde{C}]$ such that $[\tilde{A} = AP\Lambda, \tilde{B} = BPG, \tilde{C} = CPN]$. See proof in [Kruskal \(1977\)](#) on page 126.

F.2 Corollary to Theorem F.2

Corollary F.3 (Uniqueness with column and row sum conditions). *Suppose B has rows that sum to 1 and C has columns that sum to 1, or $B\mathbf{1}_{R \times 1} = \mathbf{1}_{J \times 1}$, and $\mathbf{1}_{1 \times K}C = \mathbf{1}_{1 \times R}$. If the rank conditions in Theorem F.2 on A, B, C also hold, and C is full column rank then $[A, B, C]$ is the unique triple product decomposition of array L up to a common column permutation.*

Proof. Suppose that $L = [A, B, C]$ and that $[\bar{A}, \bar{B}, \bar{C}]$ is another decomposition of L , where \bar{B}, \bar{C} satisfy the respective row- and column-sum constraints. Let $r_{\bar{B}}, r_{\bar{C}}$ be the ranks of \bar{B} and \bar{C} respectively. Definition 2.5 implies that $\text{Adiag}(xC)B^T = \bar{\text{Adiag}}(x\bar{C})\bar{B}^T$ for all $x \in \mathbb{R}^{1 \times I}$. If for any $y \in \mathbb{R}^{1 \times K}$ such that $y\bar{C} = 0 \implies yC = 0$ then $\text{col}(C) \subset \text{col}(\bar{C})$, $\text{null}(C) \supset \text{null}(\bar{C})$, and $r_C \leq r_{\bar{C}}$. If $y\bar{C} = 0$ then

$$\bar{\text{Adiag}}(y\bar{C})\bar{B}^T = 0 \implies \text{Adiag}(yC)B^T = 0$$

Recall the definition of $H_{AB}(n)$ from Lemma F.1. Kruskal (1977) shows that the condition on the ranks and Kruskal ranks above imply the following inequalities (proof omitted):

$$k_A \geq \max(R - r_B + 2, R - r_C + 2), \quad (38)$$

$$k_B \geq R - r_C + 2, \quad (39)$$

$$k_C \geq R - r_B + 2, \quad (40)$$

$$H_{AB}(n) \geq R - r_C + 2 \text{ if } n \geq R - r_C + 2 \quad (41)$$

$$H_{AC}(n) \geq R - r_B + 2 \text{ if } n \geq R - r_B + 2 \quad (42)$$

$$H_{BC}(n) \geq 1 \text{ if } n \geq 1 \quad (43)$$

The inequality eq. (41) implies that when $H_{AB}(n) < R - r_C + 2$ then $n < R - r_C + 2$. When $n < R - r_C + 2$, the inequalities eqs. (38) to (40) and the definition of $H_{AB}(n)$ imply that $H_{AB}(n) = n$. Then

$$\begin{aligned} 0 &= \text{rank}(\text{Adiag}(yC)B^T) \\ &\geq H_{AB}(\text{rank}(\text{diag}(yC))) \geq 0, \end{aligned}$$

where the second to last inequality comes from Lemma F.1 and the last inequality comes from the definition of $H_{AB}(n)$. This implies $yC = 0$. Let the function $w(y)$ for a generic vector y return the number of nonzero entries in the vector y . Let v be any vector such

that $w(v\bar{C}) \leq R - \bar{K}_0 + 1$. Then we'll show that $w(vC) \leq w(v\bar{C})$.

$$R - r_C + 1 \geq R - \bar{K}_0 + 1 \geq w(v\bar{C}) = \text{rank}(\text{diag}(v\bar{C})) \quad (44)$$

$$\geq \text{rank}(\text{Adiag}(y\bar{C})\bar{B}^T) = \text{rank}(\text{Adiag}(yC)B^T) \quad (45)$$

$$\geq H_{AB}(\text{rank}(\text{diag}(vC))) = H_{AB}(w(vC)). \quad (46)$$

The final line implies that $H_{AB}(w(vC)) = w(vC)$, which shows that $w(v\bar{C}) \geq w(vC)$ when $R - \bar{K}_0 + 1 \geq w(v\bar{C})$.

Given this condition, Kruskal's permutation lemma (proved on page 134 of [Kruskal \(1977\)](#)) shows that for any matrices C and \bar{C} that satisfy the inequality, $\bar{C} = CP_C N$ where P_C is a permutation matrix and N is a diagonal nonsingular scaling matrix. If we have the stronger condition that every two columns of C are linearly independent then P_C and N are unique. Our matrices satisfy these conditions, so we have that $\bar{C} = CP_C N$, and a similar argument can be used to show $\bar{B} = BP_B M$

Given that we also have the condition that $\mathbf{1}_{1 \times K} C = \mathbf{1}_{1 \times R}$ and $\mathbf{1}_{1 \times K} \bar{C} = \mathbf{1}_{1 \times R}$, then this implies that $\bar{C} = CP_C$ because $\mathbf{1}_{1 \times K} \bar{C} = \mathbf{1}_{1 \times K} CP_C N = \mathbf{1}_{1 \times R} N$ which only equals $\mathbf{1}_{1 \times R}$ if $N = \mathbf{I}_{R \times R}$.

Furthermore, if $r_B = R$, the equation $B\nu = \mathbf{1}_{J \times 1}$ has a unique solution in $\nu \in \mathbb{R}^{R \times 1}$, namely $\nu = \mathbf{1}_{R \times 1}$. This implies that M is the identity matrix, as the condition $\bar{B}\mathbf{1}_{R \times 1} = \mathbf{1}_{J \times 1}$ results in:

$$\mathbf{1}_{J \times 1} = \bar{B}\mathbf{1}_{R \times 1} \quad (47)$$

$$= BP_B M \mathbf{1}_{R \times 1} \quad (48)$$

$$\implies P_B M \mathbf{1}_{R \times 1} = \mathbf{1}_{R \times 1}. \quad (49)$$

Given that M is a nonsingular diagonal matrix and P_B is a permutation matrix, M must be the identity to solve the equation $P_B M \mathbf{1}_{R \times 1} = \mathbf{1}_{R \times 1}$.

We now have $\bar{C} = CP_C$ and $\bar{B} = BP_B$. We can apply Kruskal's permutation matrix proof from pages 129-130 in [Kruskal \(1977\)](#) to show that $P_C = P_B = P$. The following two identities hold for any diagonal scaling matrices M, N , any permutation matrix P , and any vector v :

$$M \text{diag}(v) N = \text{diag}(v M N) \quad (50)$$

$$P \text{diag}(v) P^T = \text{diag}(v P^T). \quad (51)$$

Given Equations (50) to (51) and the condition that $L = [A, B, C] = [\bar{A}, \bar{B}, \bar{C}]$, then, for all vectors $v \in \mathbb{R}^{1 \times J}$,

$$B \text{diag}(vA) C^T = \bar{B} \text{diag}(v\bar{A}) \bar{C}^T \quad (52)$$

$$= B P \text{diag}(v\bar{A}) P^T C^T \quad (53)$$

$$= B \text{diag}(v\bar{A} P^T) C^T. \quad (54)$$

The equality $B \text{diag}(vA) C^T = B \text{diag}(v\bar{A} P^T) C^T$ implies

$$B \text{diag}(v(A - \bar{A} P^T)) C^T = 0 \quad (55)$$

for all v . Furthermore,

$$0 = \text{rank}(B \text{diag}(v(A - \bar{A} P^T)) C^T) \quad (56)$$

$$\geq H_{BC}(\text{rank}(\text{diag}(v(A - \bar{A} P^T))) \geq 0. \quad (57)$$

The last line follows from Lemma [F.1](#). Then using the implication from eq. (43) that if $H_{BC}(n) < 1 \implies n = 0$, $\text{rank}(\text{diag}(v(A - \bar{A} P^T))) = 0$ or $v(A - \bar{A} P^T) = 0$ for all v . This further implies that

$$A = \bar{A} P^T$$

or

$$\bar{A} = AP.$$

□

G Supporting lemmas and definitions from other work

Lemma G.1 (Block rank lemmas [Tian \(2004\)](#)). Let $A \in \mathbb{R}^{m \times n}$, $B \in \mathbb{R}^{m \times k}$, $C \in \mathbb{R}^{l \times n}$.

$$\text{rank} \begin{pmatrix} A & B \\ C & 0 \end{pmatrix} = \text{rank}(B) + \text{rank}(C) + \text{rank}((I - BB^+)A(I - C^+C))$$

If $\text{range}(B) \subseteq \text{range}(A)$ and $\text{range}(C^T) \subseteq \text{range}(A^T)$

$$\text{rank} \begin{pmatrix} A & B \\ C & D \end{pmatrix} = \text{rank}(A) + \text{rank}(D - CA^+B)$$

Lemma G.2 (Block rank lemma extension). Let $A \in \mathbb{R}^{m \times n}$, $B \in \mathbb{R}^{m \times k}$, $C \in \mathbb{R}^{l \times n}$. If $\text{range}(C^T) \subseteq \text{range}(A^T)$

$$\text{rank} \begin{pmatrix} A & A \\ C & D \end{pmatrix} = \text{rank}(A) + \text{rank}(D - C)$$

Proof. Given that $\text{range}(C^T) \subseteq \text{range}(A^T)$, we can apply the second block rank lemma from [Lemma G.1](#) with $B = A$.

$$\text{rank} \begin{pmatrix} A & A \\ C & D \end{pmatrix} = \text{rank}(A) + \text{rank}(D - CA^+A).$$

By supposition, $\text{range}(C^T) \subseteq \text{range}(A^T)$ and A^+A is the projection matrix onto the column space of A^T . Then $CA^+A = C$, and the statement follows. □

H Details behind numerical examples

We have three simulation scenarios where we vary the sample size to determine the power: a two-arm trial to determine vaccine efficacy against severe symptoms, a three-arm trial

to determine relative vaccine efficacy against severe symptoms, and a two-arm trial to determine vaccine efficacy against transmission. All trials are designed such that the assumptions of Theorem 3.3 are satisfied, so the three-arm trial includes 16 study sites, and a categorical covariate with 7 levels, and both two-arm trials include 8 study sites, and a categorical covariate with 3 levels. Within each scenario we suppose that A , the categorical covariate, to be measured perfectly. In addition, we assume a 3-level, pretreatment categorical covariate has been measured for each participant. We simulate from the parametric model defined in Section 3.2, which requires that we specify μ_u^r , or the log-odds of belonging to stratum u relative to base stratum u_0 for each study site r . Let the ordered collection of log-odds of being in stratum u relative to stratum u_{2N_z} for the reference covariate level $x = 1$ be $\mu^r = (\mu_{u_1}^r, \mu_{u_2}^r, \dots, \mu_{u_{2N_z-1}}^r, 0)$.

Let softmax be the function from $v \in \mathbb{R}^L$ to the $L + 1$ -dimensional probability simplex, defined elementwise for the i^{th} element as:

$$\text{softmax}(v)_i = \frac{e^{v_i}}{\sum_{l=1}^L e^{v_l}}$$

and let softmax^{-1} be the inverse function from $\theta \in$ the $L + 1$ -dimensional simplex to \mathbb{R}^L , where the i^{th} element, $i < L + 1$ is defined as

$$\text{softmax}(\theta)_i^{-1} = \log(\theta_i) - \log(\theta_{L+1})$$

Let $\theta_u^{r,x} = P(S^{P_0} = u \mid R = r, X = x)$, and let $\theta^{r,x}$ be the ordered vector $(\theta_{u_1}^{r,x}, \theta_{u_1}^{r,x}, \dots, \theta_{u_{2N_z}}^{r,x})$

. For the 2-arm trials, the population principal strata proportions are as follows:

$$\theta^{r,1} \stackrel{\text{iid}}{\sim} \text{Dirichlet}((78, 10, 2, 10)) \forall r$$

while for the 3-arm trials, the proportions are

$$\theta^{r,1} \stackrel{\text{iid}}{\sim} \text{Dirichlet}((70, 13, 1, 1, 1, 1, 1, 12)) \forall r$$

Assuming equal proportions of participants in each treatment group, these parameter settings equate to a cumulative true incidence of roughly 0.16 and 0.19, respectively. Recall from Section 3.2 that $\eta^x \in \mathbb{R}^{2^{N_z}}$, so η_u^x is the change in log-odds of belonging to principal stratum u vs. u_0 relative to $x = 1$. We set $\eta_{2^{N_z}}^x = 0$ for identifiability. Then let $\mu_u^r = \text{softmax}^{-1}(\theta^{r,1})$,

$$\theta^{r,x} = \text{softmax}(\mu_u^r + \eta^x),$$

where for all $x > 1$

$$\eta_i^x \stackrel{\text{iid}}{\sim} \text{Normal}(0, 1), i < 2^{N_z}, \eta_{2^{N_z}}^x = 0.$$

Let the N_a -vector $a^{u,x}$ be defined elementwise as $a_k^{u,x}$ where $a_k^{u,x} = P(A = k \mid S^{P_0} = u, X = x)$.

$$a^{u,1} \stackrel{\text{iid}}{\sim} \text{Dirichlet}(4\mathbf{1}_{N_a}) \forall u,$$

and $\nu^u = \text{softmax}^{-1}(a^{u,1})$. Then recall that $\gamma^x \in \mathbb{R}^{N_a}$ such that γ_k^x is the change in log-odds of $A = k$ relative to $A = k_0$, and that $\gamma_{N_a}^x = 0$ for identifiability. Then

$$a^{u,x} = \text{softmax}(\nu^u + \gamma^x),$$

and for all $x > 1$

$$\gamma_i^x \stackrel{\text{iid}}{\sim} \text{Normal}(0, 1), i < N_a, \gamma_{N_a}^x = 0.$$

For data generating process that does not adhere to the **Covariate homogeneity** assumption, $a^{u,x,r}$ is generated as follows

$$\begin{aligned} a^{u,x,r} &= \text{softmax}(\nu^u + \gamma^x + \varepsilon^r) \\ \varepsilon_k^r &\sim \text{Normal}(0, \sigma_\varepsilon^2) \forall r > 1, k < N_a \\ \varepsilon_{N_a}^r &= 0 \forall r \\ \varepsilon_k^1 &= 0 \forall k \end{aligned} \tag{58}$$

We set $\sigma_\varepsilon = \{0.5, 1, 2\}$ for our simulation study scenarios.

Finally, recall that

$$\log \frac{P(Y(z_j) = 1 \mid S^{P_0} = u, A = k, X = x)}{P(Y(z_j) = 0 \mid S^{P_0} = u, A = k, X = x)} = \alpha_j^u + \delta_{j,k}^u + \omega_j^x,$$

where ω_j^x is the change in log-odds of $Y(z_j) = 1$, all else being equal, compared to $x = 1$.

In all of our simulations, $\omega_j^x = (x - 1) \log(1.1)$ for all j . For the 2-arm trial example, we let $\alpha_1^{(1,1)} = \log(0.3/0.7)$, $\alpha_2^{(1,1)} = \log(0.3/0.7) + \log(0.4)$, and $\delta_{1,k}^{(1,1)} = (k - 1) \log(0.925)$, $\delta_{2,k}^{(1,1)} = (k - 1) \log(0.825)$. Further, we let $\alpha_1^{(1,0)} = \log(0.15/0.85)$, $\alpha_2^{(0,1)} = \log(0.2/0.8)$, and $\delta_{1,k}^{(1,0)} = (k - 1) \log(0.925)$, and $\delta_{2,k}^{(0,1)} = 0$

For the 3-arm trial example, we let $\alpha_1^{(1,1,1)} = \log(0.3/0.7)$, $\alpha_2^{(1,1,1)} = \log(0.3/0.7)$, $\alpha_3^{(1,1,1)} = \log(0.3/0.7) + \log(0.4)$, and $\delta_{j,k}^{(1,1,1)} = (k - 1) \log(0.925)$ for $j = 1, 2, 3$. Further, we let $\alpha_1^{(1,0,1)} = \log(0.2/0.8)$, $\alpha_3^{(1,0,1)} = \log(0.1/0.9)$, $\alpha_1^{(1,1,0)} = \log(0.3/0.7)$, $\alpha_2^{(1,1,0)} = \log(0.15/0.85)$, $\alpha_2^{(0,1,1)} = \log(0.25/0.75)$, $\alpha_3^{(0,1,1)} = \log(0.08/0.92)$, $\alpha_3^{(0,0,1)} = \log(0.25/0.75)$, $\alpha_2^{(0,1,0)} = \log(0.25/0.75)$, $\alpha_1^{(1,0,0)} = \log(0.1/0.9)$ and $\delta_{j,k}^u = 0$ for all $k, u \in \{(1, 0, 0), (0, 1, 0), (1, 1, 0), (0, 0, 1), (1, 0, 1), (0, 1, 1)\}$, and all allowable j

In the 2- and 3-arm trial examples that pertain to inferring vaccine efficacy against severe symptoms, we set $\text{sn}_S = 0.8$, $\text{sp}_S = 0.99$ which reflects the sensitivity and specificity of a typical PCR collected via nasopharyngeal swab ([Kissler et al. 2021](#)), and $\text{sn}_Y = 0.99$, $\text{sp}_S = 0.9$ to reflect the fact that most severe illness caused by the pathogen of interest will be reported, but that there are many severe illness episodes that are reported that may be caused by other pathogens. These lead to a true rate of severe illness of 0.04 but a rate of reported severe illness of 0.14. For comparison [Monto et al. \(2009\)](#) symptom reporting data shows that 10% of participants reported at least one severe symptom, but the cumulative incidence was 0.07.

For each hypothetical participant in a study site $R = r$ in our study we draw data in

the following manner

$$\begin{aligned}
Z_i &\stackrel{\text{iid}}{\sim} \text{Categorical}\left(\frac{1}{N_z} \mathbf{1}_{N_z}\right) \\
X_i &\stackrel{\text{iid}}{\sim} \text{Categorical}\left(\frac{1}{3} \mathbf{1}_3\right) \\
S_i^{P_0} \mid R = r, X = x &\stackrel{\text{iid}}{\sim} \text{Categorical}(\theta^{r,x}) \\
A_i \mid S^{P_0} = u, X = x &\stackrel{\text{iid}}{\sim} \text{Categorical}(a^{u,x}) \\
Y_i \mid S^{P_0} = u, A = k, X = x, Z = j &\stackrel{\text{iid}}{\sim} \text{Bernoulli}(\text{inv_logit}(\alpha_j^u + \delta_{j,k}^u + \omega_x)) \\
\tilde{Y}_i \mid Y = y &\stackrel{\text{iid}}{\sim} \text{Bernoulli}(y \text{sn}_Y + (1 - y)(1 - \text{sp}_Y)) \\
\tilde{S}_i \mid S^{P_0} = u, Z = j &\stackrel{\text{iid}}{\sim} \text{Bernoulli}(u_j \text{sn}_S + (1 - u_j)(1 - \text{sp}_S)) \\
\tilde{A}_i \mid A = a &\stackrel{\text{iid}}{\sim} \text{Categorical}(p_{N_a}^a)
\end{aligned} \tag{59}$$

and we do this for all sites $R \in \{1, \dots, N_r\}$.

We fit the model defined in Equation (11). Recall

$$A_i \mid S_i^{P_0} = u, X_i = x, R_i = r \sim \text{Categorical}(\boldsymbol{\pi}_{u,x,r}) \tag{60}$$

$$S_i^{P_0} \mid R_i = r, X_i = x \sim \text{Categorical}(\boldsymbol{\rho}_{r,x}) \tag{61}$$

$$Y_i(z_j) \mid S_i^{P_0} = u, A_i = k, X_i = x \sim \text{Bernoulli}(\beta_{j,k}^{u,x}) \tag{62}$$

where we define $\boldsymbol{\pi}_{u,x,r}$ as in Equation (12):

$$\begin{aligned}
\boldsymbol{\pi}_{u,x,r} &= \text{softmax}(\boldsymbol{\nu}^u + \boldsymbol{\gamma}^x + \boldsymbol{\gamma}^{u,x} + \boldsymbol{\epsilon}^r) \\
\epsilon_k^r &\sim \text{Normal}(0, \sigma_\epsilon^2) \quad \forall r > 1, k < N_a \\
\gamma_k^{u,x} &\sim \text{Normal}(0, \sigma_\gamma^2) \quad \forall u, x > 1, k < N_a \\
\sigma_\epsilon &\sim \text{StudentT}^+(3, 0, 0.1), \quad \sigma_\gamma \sim \text{StudentT}^+(3, 0, 0.1) \\
\epsilon_{N_a}^r &= 0 \forall r, \quad \epsilon_k^1 = 0 \forall k, \quad \gamma_k^x = 0 \forall x, \quad \gamma_k^1 = 0 \forall k, \quad \gamma_{N_a}^{u,x} = 0 \forall u, x, \quad \gamma_k^{u,1} = 0, \quad \gamma_k^{1,x} = 0 \forall k
\end{aligned} \tag{63}$$

We define a hierarchical model for $\beta_{j,k}^{u,x}$ as:

$$\begin{aligned}
\text{logit}\beta_{j,k}^{u,x} &= \alpha_j^u + \epsilon_{j,k}^{u,x} \\
\epsilon_{j,k}^{u,x} &\sim \text{Normal}(0, \tau_\epsilon^2) \\
\tau_\epsilon &\sim \text{Normal}^+(0, 5^2) \\
\alpha_j^u &\sim \text{Normal}(0, 1.7^2)
\end{aligned} \tag{64}$$

We use the following priors:

$$\begin{aligned}
\text{sn}_S &\sim \text{Beta}(0.5, 1, 4, 2) \\
\text{sp}_S &\sim \text{Beta}(0.5, 1, 10, 2) \\
\text{sn}_Y &\sim \text{Beta}(0.5, 1, 1, 1) \\
\text{sp}_Y &\sim \text{Beta}(0.5, 1, 4, 2) \\
\boldsymbol{\rho}_{r,x} &\stackrel{\text{iid}}{\sim} \text{Dirichlet}((7, 1, 1, 1)^T), \forall r, x \\
\nu_k^u &\sim \text{Normal}(0, 1.3^2), \forall u, 1 \leq k < N_a \\
\gamma_k^x &\sim \text{Normal}(0, 1.3^2), \forall x > 1, 1 \leq k < N_a
\end{aligned} \tag{65}$$

where $\text{Beta}(0.5, 1, 4, 2)$ is the shifted, scaled Beta distribution in which the first two arguments define the support of the distribution, and the second two parameters are shape parameters. For example, for sn_S this corresponds to $\chi \sim \text{Beta}(4, 2)$ and $\text{sn}_S = (1 - 0.5)\chi + 0.5$.

When $N_z = 3$, the prior for $\boldsymbol{\rho}_{r,x}$ changes to:

$$\boldsymbol{\rho}_{r,x} \stackrel{\text{iid}}{\sim} \text{Dirichlet}((2, 1/3 \mathbf{1}_{2^{N_z-1}}^T)^T), \forall r, x$$

We use Stan for inference ([Team 2021](#)) using the `cmdstanr` package ([Gabry & Češnovar 2022](#)) in R ([R Core Team 2022](#)). Four MCMC chains were run for each model on each scenario. All models for the two-arm trials were run for 3,000 warmup and 3,000 post-warmup iterations; nearly all \hat{R} statistics ([Gelman et al. 2013](#)) were below 1.01, as recommended by

[Vehtari et al. \(2020\)](#). The maximum \hat{R} recorded across all two-arm trials was 1.04. For the three-arm trials, all models were run for 3,000 warmup and 12,000 post-warmup iterations. Nearly all \hat{R} statistics were below 1.01 with a maximum \hat{R} recorded across all three-arm trials was 1.02.

I Asymptotic variance derivations

Lemma I.1 (Affine transformation of vectorized normal). *Suppose $X \in \mathbb{R}^{n \times p}$, $\text{vec}(X) \sim N(0, \Sigma)$ for a positive definite matrix Σ . Given a matrix $D \in \mathbb{R}^{k \times n}$ with $\text{rank } D = k$ and a matrix $C \in \mathbb{R}^{p \times m}$ with $\text{rank } C = m$, $\text{vec}(DXC) \sim N(0, (C^T \otimes D)\Sigma(C \otimes D^T))$ where $(C^T \otimes D)\Sigma(C \otimes D^T)$ is positive definite.*

Proof. $\text{vec}(DXC) = (C^T \otimes D)\text{vec}(X)$. Affine transformations of multivariate normal vectors, $Y = BZ$, where $Z \sim N(0, \Sigma)$ and B is a full-row rank matrix leads to $Y \sim N(0, B\Sigma B^T)$, $B\Sigma B^T$ positive definite. Then

$$\text{vec}(DXC) \sim N(0, (C^T \otimes D)\Sigma(C \otimes D^T)).$$

The rank of $C^T \otimes D = \text{rank } C^T \text{rank } D = mk$. The dimensions of $C^T \otimes D$ are $mk \times np$, so $C^T \otimes D$ is full-row rank. \square

Lemma I.2 (Limiting distribution of least squares estimator). *Let $b = X\omega$ where X is full column rank with elements in \mathbb{R} and $\omega \neq 0$. Given estimators \hat{X}, \hat{b} the least-squares estimator for ω , $\hat{\omega}$, is $(\hat{X}^T \hat{X})^{-1} \hat{X}^T \hat{b}$. Let $X^+ = (X^T X)^{-1} X^T$, $\text{vec}(\sqrt{N} D_X (\hat{X} - X)) \xrightarrow{d} \text{Normal}(0, \Sigma)$, and $\sqrt{N} D_b (\hat{b} - b) \xrightarrow{d} \text{Normal}(0, C)$ where D_X, D_b are positive definite diagonal scaling matrices. Then*

$$\sqrt{N}(\hat{\omega} - \omega) \xrightarrow{d} \text{Normal}(0, (\omega^T \otimes X^+ D_X^{-1})\Sigma(\omega \otimes (X^+ D_X^{-1})^T) + X^+ D_b^{-1} C (X^+ D_b^{-1})^T).$$

Proof. $\omega(X, b) = (X^T X)^{-1} X^T b$, so we can linearize this function in X and b , following the logic in [Bonhomme et al. \(2016\)](#):

$$\omega(X + dX, b + db) = \omega(X, b) + d(X^T X)^{-1} X^T b + (X^T X)^{-1} (dX^T) b + (X^T X)^{-1} X^T db$$

For a square invertible matrix Ω , $d\Omega^{-1} = -\Omega^{-1} d\Omega \Omega^{-1}$ so

$$d(X^T X)^{-1} = -(X^T X)^{-1} d(X^T X) (X^T X)^{-1} \quad (66)$$

$$= -(X^T X)^{-1} (dX^T X + X^T dX) (X^T X)^{-1} \quad (67)$$

Then,

$$\begin{aligned} \omega(X + dX, b + db) &= \omega(X, b) - (X^T X)^{-1} (dX^T X + X^T dX) (X^T X)^{-1} X^T b \\ &\quad + (X^T X)^{-1} (dX^T) b + (X^T X)^{-1} X^T db + o(1) \\ &= \omega(X, b) + (X^T X)^{-1} dX^T (I - XX^+) b + X^+ dX X^+ b \\ &\quad + X^+ db + o(1) \end{aligned}$$

Note that $(I - XX^+)b = (I - XX^+)X\omega = 0$ and $D_X^{-1}D_X = D_b^{-1}D_b = I$ So

$$\sqrt{N}(\hat{\omega} - \omega) = X^+ D_X^{-1} \sqrt{N} D_X (\hat{X} - X) \omega + X^+ D_b^{-1} \sqrt{N} D_b (\hat{b} - b) + o_p(1) \quad (68)$$

By assumption,

$$\sqrt{N} D_b (\hat{b} - b) \xrightarrow{d} N(0, C), \text{vec} \left(\sqrt{N} D_X (\hat{X} - X) \right) \xrightarrow{d} \text{Normal}(0, \Sigma),$$

so

$$\text{vec} \left(X^+ D_X^{-1} \sqrt{N} D_X (\hat{X} - X) \omega \right) \xrightarrow{d} \text{Normal}(0, (\omega^T \otimes X^+ D_X^{-1}) \Sigma (\omega \otimes (X^+ D_X^{-1})^T)) \quad (69)$$

$$X^+ D_b^{-1} \sqrt{N} D_b (\hat{b} - b) \xrightarrow{d} N(0, X^+ D_b^{-1} C (X^+ D_b^{-1})^T) \quad (70)$$

given that $\text{vec} \left(X^+ D_X^{-1} \sqrt{N} D_X (\hat{X} - X) \omega \right) = X^+ D_X^{-1} \sqrt{N} D_X (\hat{X} - X) \omega$, we get

$$\sqrt{N}(\hat{\omega} - \omega) \xrightarrow{d} \text{Normal}(0, (\omega^T \otimes X^+ D_X^{-1}) \Sigma (\omega \otimes (X^+ D_X^{-1})^T) + X^+ D_b^{-1} C (X^+ D_b^{-1})^T) \quad (71)$$

□

I.0.1 Interpretation for VE modeling

When considering Lemma I.2 in the context of the two-arm model presented in the paper, the vector ω is the vector

$$(\text{sp}_Y, \beta_z^{(0,1)}, \beta_z^{(1,0)}, \beta_z^{(1,1)})$$

, the matrix X is $P_{N_z}^x(S^{P_0} \mid R)$, and the matrix D_X in Lemma I.2 is the square-root of the proportion of individuals assigned to a study site $R_i = r$. D_b is the proportion of people assigned to a study site $R_i = r$ and $Z_i = z$. If the design of the study calls for equal proportions of individuals spread out between study sites and equal numbers of people assigned to treatment and control for each study site, then $D_b = (2N_r)^{-\frac{1}{2}}\mathbf{I}_{N_r}$ and $D_X = (N_r)^{-\frac{1}{2}}\mathbf{I}_{N_r}$. This simplifies the expression above to:

$$\sqrt{N}(\hat{\omega} - \omega) \xrightarrow{d} \text{Normal}(0, N_r((\omega^T \otimes X^+) \Sigma(\omega \otimes (X^+)^T) + 2X^+ C(X^+)^T)) \quad (72)$$

This highlights that variance increases as a function of N_r due to distributing people over more sites. This effect is in tension with the Moore-Penrose inverse X^+ because if we take the view that study sites are drawn from a superpopulation of study sites with a generating distribution for proportions of principal strata, the more study sites we have, the better estimate of the inverse of the second moment matrix $X^T X$.

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