CAUSAL INFERENCE IN CLUSTER-RANDOMIZED TRIALS AND OBSERVATIONAL STUDIES WITH PARTIAL INTERFERENCE

Kayla W. Kilpatrick

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Approved by:

Michael Hudgens

Michael Emch

Kimberly Powers

John Preisser

Haibo Zhou

ABSTRACT

Kayla W. Kilpatrick: Causal Inference In Cluster-Randomized Trials and Observational Studies With Partial Interference
(Under the direction of Michael G. Hudgens)

Vaccine effects or other health-related treatments are important to the field of public health. Causal effects can go beyond simple association to determine whether a treatment is effective in reducing a disease, for example. In infectious diseases, one person's treatment may affect another individual's outcome. This is known as interference. Causal inference with interference can be a powerful tool in the benefits of vaccines or other treatments. This work considers methods for drawing inference about causal effects in cluster-randomized trials and observational studies in the presence of interference.

Cluster-randomized trials are often conducted to assess vaccine effects. Defining estimands of interest before conducting a trial is integral to the alignment between a study's objectives and the data to be collected and analyzed. The first paper considers estimands and estimators for overall, indirect, and total vaccine effects in trials where clusters of individuals are randomized to vaccine or control. The scenario is considered where individuals self-select whether to participate in the trial and the outcome of interest is measured on all individuals in each cluster. Unlike the overall, indirect, and total effects, the direct effect of vaccination is shown in general not to be estimable without further assumptions, such as no unmeasured confounding. An illustrative example motivated by a cluster-randomized typhoid vaccine trial is provided.

In the setting of observational studies with partial interference, inverse probability weighted estimators have previously been developed. Unfortunately, these estimators are not well suited for studies with large clusters. Therefore, in the second paper, the parametric g-formula is extended to allow for partial interference. G-formula estimators are proposed of overall effects,

spillover effects when treated, and spillover effects when untreated. The proposed estimators can accommodate large clusters and do not suffer from the g-null paradox that may occur in the absence of interference. The large sample properties of the proposed estimators are derived, and simulation studies are presented demonstrating the finite-sample performance of the proposed estimators. The Demographic and Health Survey from the Democratic Republic of the Congo is then analyzed using the proposed g-formula estimators to assess the overall and spillover effects of bed net use on malaria.

In the third paper, g-estimation is extended to the case of partial interference where different treatment policies are of interest. This partial interference setting means that individuals within a cluster may interfere with one another, but they cannot interfere with individuals in other clusters. In this setting, prior work has focused on inverse probability weighting and the parametric g-formula. However, inverse probability weighting does not handle large cluster sizes well. The parametric g-formula relies upon a correctly specified outcome model. G-estimation is able to handle larger clusters and is not subject to the g-null paradox, providing an alternative method for this setting. Additionally, g-estimation is doubly robust and is thus more robust to model misspecification than the parametric g-formula. G-estimators of overall effects, spillover effects when treated, and spillover effects when untreated are considered. The large sample properties of the proposed estimators are derived using estimating equation theory. A set of simulation studies are presented to demonstrate the finite-sample performance of the proposed estimators. The 2013-14 Demographic and Health Survey in the Democratic Republic of the Congo is analyzed to determine the causal effect of bed net use on malaria.

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CHAPTER 1: LITERATURE REVIEW

1.1 Introduction to Causal Inference

Causal inference was developed in order to go beyond associations found in general statistical inference and make causal claims. Neyman [1935] started the potential outcomes framework, which was later developed more by Rubin [1974]. In this framework, potential, or counterfactual, outcomes are all possible outcomes for a particular study. Some of these potential outcomes are not observable.

To elucidate this idea, let there be $i = 1, \ldots, n$ individuals in a study with a binary treatment A. Let $A_i = 1$ indicate that individual i received treatment and let $A_i = 0$ indicate that individual i did not receive treatment. For simplicity, let there be a binary outcome Y, where $Y_i = 1$ indicates that individual i experienced the outcome of interest and $Y_i = 0$ indicates that individual i did not experience the outcome of interest. Define the potential outcome for individual i as Y_i^a; $Y_i^{a=1}$ indicates the outcome for individual i that would have been observed if, possibly counter to fact, individual i received treatment. Similarly, $Y_i^{a=0}$ indicates the outcome for individual i that would have been observed if, possibly counter to fact, individual i did not receive treatment. The causal effect of treatment versus no treatment can be written as $Y_i^{a=1} - Y_i^{a=0}$. Under causal consistency, discussed by Cole and Frangakis [2009], the observed outcome can be written in terms of the potential outcomes: $Y = Y^{a=1}A + Y^{a=0}(1 - A)$. If individual i receives treatment, then $Y_i = Y_i^{a=1}$ and $Y_i^{a=0}$ is unobserved since an individual cannot both receive and not receive treatment. This idea is called the fundamental problem of causal inference [Holland, 1986]: since both potential outcomes cannot be observed on the same unit, it is impossible to observe the effect of the treatment on that unit. The treatment effect must therefore be estimated from observed data.

Rubin [1980] detailed the stable unit treatment value assumption (SUTVA), which is frequently used in causal inference framework. This assumption states that there is no interference between units, meaning that the treatment status of one individual does not affect the the outcome of another individual [Cox, 1958]. Under this framework, there is only one version of treatment and one version of control.

Randomized controlled trials (RCTs) are the gold standard in research since randomization enables the comparison of the treated and untreated groups. In RCTs, when the randomization is done properly, association is causation [Hernán and Robins, 2006]. However, it is not always possible to conduct a randomized trial and observational data must be used. Since treated and untreated are generally not comparable in the observed population, association is no longer causation [Hernán and Robins, 2006]. Two common methods for causal inference in observational studies are the parametric G-formula and inverse probability weighting (IPW). A less commonly used method is g-estimation, perhaps due to a lack of off-the-shelf software [Vansteelandt and Joffe, 2014]. The parametric G-formula consists of the g-computation algorithm introduced by Robins [1986] and outcome regression. This method is based on standardization [Hernán and Robins, 2006]. IPW essentially creates a pseudo population where each individual in the study appears twice: once as treated, once as untreated. This is accomplished by weighting the population with the inverse of the conditional probability of receiving the treatment status that each person received [Hernán and Robins, 2006]. Horvitz and Thompson [1952] were the first to create these IPW type estimators. A downfall of the IPW method is that when these weights are small, the estimator becomes very large and difficult to calculate.

A common assumption in observational studies is that the potential outcomes are independent of treatment given a set of measured covariates. Let $\mathbf{L}$ represent the measured covariates. This assumption can be written as $Y^a \perp A|\mathbf{L}$ and is often called conditional exchangeability [Hernán and Robins, 2006]. Since the potential outcomes are only independent of treatment given $\mathbf{L}$, this assumption means that all possible confounders (covariates that affect both the

outcome and treatment) must be in $\mathbf{L}$. In other words, there are no unmeasured confounders. Another assumption that is commonly used is positivity. In words, positivity says that there must be at least one individual for each treatment status for every combination of observed $\mathbf{L}$ [Westreich and Cole, 2010]. In math, this can be represented as $P(A = a|\mathbf{L}) > 0$ for $a \in (0, 1)$ when $f(\mathbf{L}) \neq 0$.

Generally, causal effects can be defined in terms of a contrast function $g(x, y)$ where $g(x, x) = 0$. One such causal contrast is the causal risk difference, which can be defined as $E[Y^{a=1}] - E[Y^{a=0}]$. In order to be a causal effect, the causal contrast must be defined over the same set of units [Rubin, 1974, Frangakis and Rubin, 2002]. A unit could be defined as an individual or a cluster for example. Additionally, in order to be a causal effect, the causal contrast must be in terms of the same outcome under different counterfactual scenarios.

1.2 Causal Inference with Interference

When an individual's treatment status may affect another individual's outcome, this is known as "interference" between individuals [Cox, 1958]. In the context of infectious diseases, one individual's vaccination status could affect whether or not another individual gets infected. In the presence of interference, Halloran and Struchiner [1991] define the direct, indirect, total, and overall effects of treatment. The direct effect of treatment is the effect of treatment that is not attributable to interference. The indirect effect of treatment is typically thought of as the effect of treatment on those who did not receive the treatment, but indirect effects can also be defined in individuals who received treatment. If this effect exists, it is solely due to interference. The total effect is the effect of receiving treatment, as well as the effect of others receiving treatment. Finally, the overall effect is the effect of treatment among all individuals for different counterfactual scenarios. Halloran and Struchiner [1995] define these treatment effects in terms of potential outcomes.

When individuals within groups can interfere with each other but not with individuals in other groups, this is known as "partial interference," as described by Sobel [2006]. This

assumption may be reasonable if the groups of individuals are sufficiently separated by distance or time. If individuals are able to interfere with all other individuals, this is known as general interference. Interference can make the definition of causal estimands difficult. Previously, without interference, there were two potential outcomes that an individual could experience for a binary treatment. With interference, a particular individual can experience much more than two potential outcomes based on the possible treatments that the surrounding individuals receive.

Hudgens and Halloran [2008] proposed estimands of the direct, indirect, total, and overall effects of treatment in a two-stage randomized trial. In these trials, clusters are assigned to a treatment allocation program with the individuals within those clusters subsequently assigned to treatment or control based on the allocation program of their cluster. Under this study design, Hudgens and Halloran [2008] obtain unbiased estimates of the estimands, as well as the variance of the estimators. However, it is not always possible to run a randomized trial. Tchetgen Tchetgen and VanderWeele [2012] developed IPW estimators in observational data where interference may be present. Perez-Heydrich et al. [2014] developed asymptotic variance estimators when the propensity score is modeled using M-estimation theory from Stefanski and Boos [2002]. Liu et al. [2019] proposed doubly robust estimators for causal inference with partial interference.

Causal inference with interference is not only studied in the context of infectious diseases. For example, causal inference has been studied in spatial analyses [Zigler et al., 2012, Graham et al., 2013], medical imaging [Luo et al., 2012], criminology [Verbitsky-Savitz and Raudenbush, 2012], econometrics [Sobel, 2006, Manski, 2013, Arpino and Mattei, 2016], political science [Bowers et al., 2013, Keele and Titiunik, 2015], and social media and network analysis [Ugander et al., 2013, VanderWeele and An, 2013, Toulis and Kao, 2013, Kramer et al., 2014, Eckles et al., 2016, Athey et al., 2018]. These are just a few examples of papers in different fields that use causal inference with interference, but this demonstrates that it is a popular area of study with many interesting problems to solve.

1.3 Cluster-Randomized Trials

Cluster-randomized trials are often conducted when randomizing at the individual level is not feasible or practical [Halloran et al., 2010]. In these trials, individuals are placed into groups depending on particular characteristics, such as a school or residential neighborhood. These groups are then randomized to treatment or control. Cluster-randomized trials allow for the estimation of the treatment's overall impact on a population, which is especially useful when treatments may have indirect effects [Hayes et al., 2000]. In some cluster-randomized vaccine trials, such as those described in Moulton et al. [2001], Diallo et al. [2019], Sur et al. [2009b], the control is also a vaccine. This helps ensure blinding in the study, allowing for clusters to be comparable.

Recently, the International Council on Harmonization (ICH) has published a draft addendum to the E9 guidelines that describes the need to carefully define estimands in clinical trials and provides guidance on possible estimands of interest [for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use., 2019]. This addendum is currently in the process of being revised and finalized. Defining the estimands of interest before conducting a trial helps align the goals of the trial and the data and reduces the chances of using questionable assumptions when analyzing the data [Mehrotra et al., 2016]. There have been papers published that provide examples of estimands of interest in clinical trials; e.g., see Leuchs et al. [2015], Koch and Wiener [2016], Permutt [2016], Phillips et al. [2017].

There have been several papers that describe estimands in cluster-randomized trials. For example, Wu et al. [2014] provide estimands for matched-pair cluster-randomized trials. As previously mentioned, Hudgens and Halloran [2008] provide estimands of different treatment effects in two-stage randomized trials. When individuals can be categorized as always-takers, compliers, and never-takers in clustered encouragement designs, Frangakis et al. [2002] provide estimands of interest. Kang and Keele [2018] discuss cluster-randomized trials with noncompliance where individuals are categorized into the three principal strata as Frangakis et al. [2002], as well as the case where there are only two principal strata when there are no always-takers.

However, the study considered in Kang and Keele [2018] does not have blinding, so the treatment effects of interest, the total and indirect effects, cannot be identified. Due to the lack of blinding, some individuals' principal strata membership is unknown. However, these papers have not considered the causal estimands in cluster-randomized trials with partial interference where individuals are able to choose whether or not to participate in the trial. Chapter 2 of this document concerns itself with such estimands.

While cluster-randomized trials can be useful in certain situations, there are some disadvantages to this trial design. Because individual outcomes within a given cluster may be correlated, clustering must be taken into account as ignoring the correlation within the clusters can result in anti-conservative inference [Bennett et al., 2002]. Because intervention coverage and effect magnitude may vary across populations, cluster-randomized trials may not be generalizable [Hayes et al., 2000]. The disadvantages of cluster-randomized trials mean that it is vital to properly define and incorporate clusters into the design and analysis stages of a trial [Hayes et al., 2000, Campbell et al., 2004]. To aid in this process, the CONSORT guidelines have been extended to cluster-randomized trials [Campbell et al., 2004]. There can also be imbalances in covariates between clusters, but there are methods that can address this problem. Moulton [2004] describes a trial design method for constrained randomization based on covariates that may be related to the trial outcome. Clusters can also be matched to minimize the chance imbalance of covariates. However, this does not always result in perfect balance. Wu et al. [2014] provide a method to correct for covariate imbalances between clustered pairs while still providing causal estimands that are relevant to public health policies. When cluster-randomized trials are not optimal for conducting a study, observational studies can be useful. Chapters 3 and 4 propose causal estimands for observational studies with partial interference.

1.4 Parametric G-Formula

As mentioned above, the parametric G-formula is based on standardization and combines the g-computation algorithm of Robins [1986] with parametric outcome regression [Hernán and

Robins, 2006]. This method provides an alternative way to estimate causal effects other than using the IPW method. The IPW estimator can perform poorly when the weights are small (such as when the positivity assumption is violated), but the parametric G-formula does not suffer from such issues [Westreich et al., 2012]. The parametric G-formula in the case of no interference can be written as $E[Y^a] = \int E[Y|A = a, \mathbf{L} = \mathbf{l}]dF_{\mathbf{L}}(\mathbf{l})$. The estimator corresponding to this estimand can be written as

$$\hat{E}[Y^a] = \int \hat{E}[Y|A = a, \mathbf{L} = \mathbf{l}]d\hat{F}_{\mathbf{L}}(\mathbf{l})$$

or if the distribution of L is empirically estimated,

$$\hat{E}[Y^a] = \frac{1}{n}\sum_{i=1}^{n} \hat{E}[Y_i|A_i = a_i, \mathbf{L}_i]$$

where $\hat{E}[Y_i|A_i = a_i, \mathbf{L}_i]$ can be estimated with an outcome regression model. For a binary outcome Y, a logistic regression could be performed to obtain these estimates. The parametric G-formula has been used to adjust for time-varying confounders in time to event data [Taubman et al., 2009, Young et al., 2011, Westreich et al., 2012, Cole et al., 2013, Garcia-Aymerich et al., 2014, Keil et al., 2014]. When the parametric components are correctly specified, the parametric G-formula estimator is more efficient than the IPW estimator for this setting [Young et al., 2011]. Common parameters of interest are the risk ratio [Taubman et al., 2009, Cole et al., 2013, Garcia-Aymerich et al., 2014] or the hazard ratio [Westreich et al., 2012, Keil et al., 2014]. These parameters typically answer the question of what happens when everyone is treated versus when everyone is not treated.

Unfortunately, the parametric G-formula can suffer from the "g-null paradox." Under this paradox, the necessary parametric models may not be possible to correctly specify under the null hypothesis. This results in the rejection of the null hypothesis in large samples, even if the null hypothesis is true [Robins, 1986, Taubman et al., 2009, Cole et al., 2013]. Another

downfall of the parametric G-formula, as well as any of the other g-methods that use parametric models, is that model misspecification can result in bias [Taubman et al., 2009].

1.5 G-Estimation

G-estimation was proposed for structural nested models in Robins [1989, 1992]. G-estimation allows for time-varying confounding and assumes no unmeasured confounders [Sterne and Tilling, 2002]. Typically, logistic regression models are fit for a range of possible values of ψ, the parameter of interest, where $exp(-\psi_0)$ is the ratio of the survival time for a continuously exposed person to the survival time for someone who was never exposed, with ψ_0 denoting the g-estimate [Sterne and Tilling, 2002]. G-estimation can use information about the exposure distribution a priori [Vansteelandt and Joffe, 2014].

For structural nested mean models, additive rank preservation within the levels of the covariates is important in g-estimation. Additive rank preservation means that the effect of treatment is the same on the additive scale on the outcome for all individuals in the population of interest. A simple structural nested mean model that assumes the average causal effect across strata of L is the following:

$$E[Y^a - Y^{a=0}|A = a, L] = \beta_1 a$$

The additive rank preservation is incorporated with the use of another model:

$$Y_i^A - Y_i^{a=0} = \psi_1 a$$

such that $\psi_1 = \beta_1$. This is equivalent to $Y_i^{a=0} = Y_i^a - \psi_1 a$, or $Y_i^{a=0} = Y - \psi_1 A$ with causal consistency. If this model is correctly specified and ψ_1 known, then $Y_i^{a=0}$ could be calculated for all individuals. However, ψ_1 is typically not known and is the target of inference. For each individual,

$$H(\psi^\dagger) = Y - \psi^\dagger A$$

is computed for all possible values of $\psi^\dagger$, usually over a grid search. For example, separate logistic regression models logit$P[A = 1|H(\psi^\dagger), L] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 L$ can be fit and the value of $H(\psi^\dagger)$ with $\hat{\alpha}_1 \approx 0$ is the counterfactual value of $Y_i^{a=0}$. The corresponding value of $\psi^\dagger$ is then the estimate of the true value of ψ_1. For this setting, there is a closed form solution: $\hat{\psi}_1 = \frac{\sum_i Y_i(A_i - \hat{E}[A_i|L_i])}{\sum_i A_i(A_i - \hat{E}[A_i|L_i])}$, or in estimating equation formatting, the solution to $\sum_i H_i(\psi^\dagger)(A_i - \hat{E}[A_i|L_i]) = 0$. 95% confidence intervals can be constructed by obtaining a subset of the $\psi^\dagger$ where $p > 0.05$ for Wald tests. Alternative tests such as the score or likelihood ratio test could be used instead. Note that g-estimation assumes that conditional exchangeability holds.

When there is effect modification so the average causal effect is not the same for everyone, a two-parameter structural nested mean model can be used:

$$E[Y^a - Y^{a=0}|L] = \beta_1 a + \beta_2 aV$$

where V consists of the components of L that are the effect modifiers. The rank preserving model is then $Y_i^a - Y_i^{a=0} = \psi_1 a + \psi_2 aV$ and we let $H(\psi) = Y - \psi_1 A - \psi_2 AV$. A logistic model logit$P[A = 1|H(\psi^\dagger), L] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 H(\psi^\dagger)V + \alpha_3 L$ can be fit and the goal is to find the combination of values for $\psi_1^\dagger, \psi_2^\dagger$ where $H(\psi^\dagger) \perp A|L$, or where $\hat{\alpha}_1 = \hat{\alpha}_2 = 0$. Generally, there is not a closed form solution to this and numerical search algorithms, such as Nelder-Mead Simplex), need to be used.

Greenland et al. [2008] showed that using g-estimation on randomization status generalizes the intent-to-treat (ITT) analysis when there may be noncompliance in a randomized trial. Ten Have et al. [2007] extended g-estimation to the case of a linear rank preserving model approach with mediation. They found that the method performed well when the assumptions were met, but when the structural interaction assumptions were not met, this method performed poorly. Robins et al. [1992] used g-estimation to estimates parameters of a structural nested failure time model. Witteman et al. [1998] extended g-estimation for time-dependent covariates

to allow for censoring by competing risks. G-estimation can be used to compare counterfactual failure times when always exposed versus never exposed.

While there is not much in the way of off-the-shelf software for g-estimation, this method can be more flexible and perform better than other methods [Vansteelandt and Joffe, 2014]. Continuous exposures or binary exposures that are correlated with covariates are handled better with g-estimation than with IPW. Additionally, g-estimation performs better than IPW when the positivity assumption may be violated [Vansteelandt and Joffe, 2014]. Compared to the parametric G-formula, g-estimation does not suffer from the g-null paradox [Vansteelandt and Joffe, 2014].

1.6 Motivating Examples

1.6.1 Typhoid Fever

While typhoid fever is not common in the United States, it affects many other countries, particularly developing countries. Crump and Mintz [2010] reported approximately 22 million cases of typhoid fever in the year 2000. Since typhoid fever can be transmitted via contaminated water and food, non-vaccine methods of preventing typhoid include improving sanitation and increasing the presence of safe food and water. As of 2010, there were two available typhoid vaccines in the United States [Crump and Mintz, 2010].

The Vi polysaccharide vaccine was used in the cluster-randomized trial described by Sur et al. [2009b]. This was a phase 4 effectiveness trial that took place in Kolkata, India between 2004 to 2006. Individuals were grouped into a total of 80 geographical clusters based on a census of the population in two wards (administrative units). The clusters were randomized so that 40 clusters were assigned to the Vi vaccine and 40 were assigned to the control, which was an inactivated hepatitis A vaccine. Individuals within those clusters were able to choose whether or not to receive the vaccine to which their cluster was assigned. Sur et al. [2009b] found significant overall, total, and indirect effects of the Vi vaccine. However, this study did not use causal methods and therefore cannot make causal conclusions. We intend to introduce

causal estimand notation to cluster-randomized trials in the context of the Sur et al. [2009b] trial. Assuming partial interference, we can make causal statements about the overall, total, and indirect effects of the Vi vaccine.

1.6.2 Malaria in the Democratic Republic of the Congo

According to the world malaria report for 2018 from the World Health Organization (WHO), there were approximately 219 million cases of malaria worldwide in 2017, with the majority of cases in the WHO African Region [Organization, 2018]. The Democratic Republic of the Congo (DRC) was the country with the second largest percentage of malaria cases and was among three countries with the highest estimated increase in malaria cases. Worldwide, there were approximately 435,000 deaths from malaria in 2017 with 61% of these deaths in children younger than 5 years old [Organization, 2018]. The United States alone contributed $3.1 billion to global control and elimination of malaria. The global burden of malaria is high, so finding methods to reduce malaria cases is vital.

There were 624 million insecticide-treated mosquito nets (ITNs) delivered worldwide between 2015 and 2017 according to the WHO [Organization, 2018]. In Africa in 2017, approximately half of the population used ITNs, but ITN coverage has not increased since 2016. The goal of the research using the 2013-14 DRC Demographic and Health Survey (DHS) is to investigate the cases of malaria in those who use bed nets, those who do not use bed nets, and the entire population as bed net coverage changes.

The 2013-14 Demographic and Health Survey was the second DHS survey in the DRC and took place from November 2013 to February 2014. This was a nationally representative survey intended to gather information about fertility, maternal and child health, sexually transmitted infections, mosquito net usage, malaria, and other health information [Min, 2014]. There were 536 clusters across 26 new provinces (formerly 11 provinces) in the survey. Before combining clusters, the average number of individuals per cluster is approximately 179 with a standard deviation of approximately 30. Children between the ages of 6 to 59 months were tested for

malaria. Blood smear tests and rapid diagnostic tests were used to test for malaria. Before combining clusters, there were approximately 16 children on average with a standard deviation of approximately 5 who tested positive for malaria for both types of tests.

1.7 Summary and Proposed Research

Accounting for the possible presence of interference can allow for the calculation of different treatment effects. This is particularly important for public health policies as there will likely be a mixture of individuals who will and will not choose to receive treatment, such as a vaccine. The proposed methods in this dissertation focus on effects beyond the traditional causal effects defined by comparing the average outcome when all individuals receive treatment versus when all individuals do not receive treatment. Estimators are proposed for both cluster-randomized trials and observational data.

In Chapter 2, estimands for the overall, indirect, and total effects of vaccination are defined for cluster-randomized trials. As there is currently a movement in the literature for clinical trials to carefully define estimands of interest, the estimands in this chapter can be helpful for investigators when designing and analyzing a cluster-randomized trial. The motivating example for this chapter is a cluster-randomized vaccine trial for a Vi polysaccharide (typhoid) vaccine [Sur et al., 2009b]. In this trial, individuals within clusters chose whether or not to participate. The overall, indirect, and total effects of vaccination can be defined within different subgroups of individuals. The proposed methods are applied to simulated data that match exactly the cluster level summary statistics from the motivating example.

In Chapter 3, the G-formula is extended to the case of partial interference when the scientific question of interest is the efficacy of different treatment policies. This may be more relevant to public health policies as there will likely be individuals in the population who do and do not receive treatment. The estimands of interest are shown to be identifiable from observational data. The proposed estimators are shown to be consistent and asymptotically normal using estimation equation theory. The finite-sample performance of the proposed estimators is demonstrated with

simulations. Finally, the proposed estimators is applied to the 2013-14 DRC Demographic and Health Survey to investigate the causal effect of bed net use on malaria.

In Chapter 4, g-estimation is extended to the case of partial interference. The estimands of interest are shown to be identifiable from observed data. The proposed estimators are shown to be consistent and asymptotically normal using estimation equation theory. The proposed estimator is evaluated in simulations and illustrated using the DRC bed net data set.

CHAPTER 2: ESTIMANDS AND INFERENCE IN CLUSTER-RANDOMIZED VACCINE TRIALS

2.1 Introduction

Vaccines are integral to combating a variety of infectious diseases. Quantifying a vaccine's effects is vital to determining its benefits, which can then guide public health policies aimed at reducing the burden of disease. Cluster-randomized trials are often conducted to quantify the effects of a treatment or intervention such as a vaccine. In cluster-randomized trials, individuals are grouped together based on certain characteristics (e.g., neighborhood of residence), and the entire cluster is randomized to treatment or control. The process of randomization ensures that the treatment and control groups are exchangeable. Cluster-randomization is useful when it is impractical or infeasible to randomize at the individual level [Halloran et al., 2010]. Comparisons between randomized clusters can be used to assess the overall impact of an intervention on the population, which is particularly important in settings where an intervention may have indirect (or spillover) effects [Hayes et al., 2000]. For example, in the infectious disease setting, whether one individual is vaccinated could affect the outcome of another individual. Moulton et al. [2001] describe a cluster-randomized trial in the White Mountain Apache Reservation and the Navajo Nation wherein approximately 9000 infants within 38 clusters were randomized by cluster to the vaccine of interest (*Streptococcus pneumoniae* conjugate vaccine) or control (a meningococcal C conjugate vaccine). Diallo et al. [2019] present a cluster-randomized trial of an inactivated influenza vaccine in Senegal in which approximately 7800 enrolled, age-eligible children within 20 clusters were randomized by cluster to the influenza vaccine or control (an inactivated polio vaccine). Sur et al. [2009b] describe a cluster-randomized trial of a typhoid

vaccine in India, with approximately 38000 individuals within 80 clusters randomized by cluster to the typhoid vaccine or control (hepatitis A vaccine).

Because the cluster-randomized trial is a common study design for evaluating vaccine effects, it is important to carefully define the estimands, i.e., parameters of interest, in these trials. Careful definition of the effects of interest prior to the study can aid in study planning and can ensure that the study's goals are achieved [Leuchs et al., 2015]. Recently, there has been increased interest in defining estimands in clinical trials. The International Council on Harmonization (ICH) has published an addendum to the E9 guidelines detailing the use of estimands in clinical trials [for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use., 2019]. This addendum aims to describe the necessity of defining the target estimand before the design and analysis of trials to avoid misalignment of the trial goals and the data, as well as to ensure that estimation of the estimand is possible without relying upon dubious assumptions [Mehrotra et al., 2016].

Leuchs et al. [2015], Koch and Wiener [2016], Permutt [2016], and Phillips et al. [2017] discuss examples of estimands of interest in regulatory clinical trials. Target estimands specifically for cluster-randomized trials have been previously considered for certain designs. Wu et al. [2014] consider estimands for matched-pair cluster-randomized trials. Hudgens and Halloran [2008] consider estimands of the direct, indirect, total, and overall effects of treatment assuming a two-stage randomization scheme. In this design, clusters are randomly assigned to a treatment allocation program, and individuals within the clusters are randomly assigned to treatment based on the cluster-level assignment. In some cluster-randomized trials, individuals may not comply with their randomization assignment or may choose not to participate in the study [Moulton et al., 2001, Sur et al., 2009b,a, PATH, .]. Frangakis et al. [2002] consider clustered encouragement designs, which allow noncompliance, where individuals belong to one of three principal strata: always-takers, compliers, and never-takers. Kang and Keele [2018] also consider cluster-randomized trials with noncompliance. Like Frangakis et al. [2002], they consider the setting where there are the three principal strata mentioned above, and also the

special case where there are no always-takers. Even for this special case, they show the total and indirect (spillover) effects are not identified because principal strata membership is unknown for some individuals.

In this paper, we consider cluster-randomized vaccine trials where individuals choose whether or not to participate in the trial. As illustrated by the examples described above, it is common in cluster-randomized vaccine trials for the control to be another vaccine which is not expected to affect the outcome of interest. For simplicity, below the control vaccine will sometimes be referred to just as a control. Here we consider the particular case where a control vaccine is employed and individuals are blinded, i.e., unaware whether their cluster is randomly assigned to the vaccine of interest or to the control vaccine. In this setting, it is reasonable to assume individual participation behavior is unaffected by randomization, such that there are only two principal strata: always participators and never participators. Thus, our setting is similar to the special case considered by Kang and Keele [2018]. However, because it is assumed an individual will participate or not in the trial regardless of randomization assignment, principal strata membership is known for all individuals; this allows for identification and estimation of overall, total and indirect effects.

Sur et al. [2009b] provides a motivating example of a cluster-randomized vaccine trial where individuals self-select whether to participate. In this trial, clusters of individuals were randomized to either a typhoid vaccine or a control vaccine (for hepatitis A). The presence of a control allowed study blinding, so individuals in the clusters did not know which assignment their cluster received. While some individuals chose not to participate in the trial, outcome data was collected on all individuals. This allows inference about different effects of the vaccine, as described below.

The outline of the remainder of this paper is as follows. In Section 2.2, notation, estimands, estimators, and effects of interest are described. In Section 2.3, the Sur et al. [2009b] cluster-randomized typhoid vaccine trial is considered. Finally, Section 2.4 concludes with a discussion.

2.2 Methods

2.2.1 Notation and Potential Outcomes

Consider a cluster-randomized vaccine trial with n clusters (or groups) of individuals where each cluster is randomly assigned to vaccine or control. For $i = 1, \ldots, n$, let $A_i = 1$ if cluster i is assigned to vaccine and $A_i = 0$ otherwise. Let $Y_i^{a=1}$ denote the potential outcome if cluster i is assigned vaccine, and let $Y_i^{a=0}$ denote the potential outcome if cluster i is assigned control. For example, $Y_i^{a=1}$ could denote the proportion of individuals in cluster i who would develop typhoid within one year after randomization if, possibly counter to fact, cluster i were assigned to vaccine. For now, we leave the particular outcome associated with Y_i^a unspecified. Different specifications of Y_i^a will correspond to different vaccine effects, as described below. Let Y_i denote the observed outcome for cluster i, such that $Y_i = Y_i^{a=1}A_i + Y_i^{a=0}(1 - A_i)$. Below, the subscript i is sometimes dropped for notational convenience.

In cluster-randomized vaccine trials, one individual's vaccination status may affect another individual's outcome, that is, there may be "interference" between individuals [Cox, 1958]. For instance, if one individual receives a typhoid vaccine, this could affect whether or not another individual develops typhoid. Throughout this paper, it is assumed that there is no interference between individuals in different clusters, i.e., there is "partial interference" [Sobel, 2006]. Under this assumption, the outcome Y_i for cluster i depends only on the treatment assigned to cluster i. No assumption is made regarding the form of interference within clusters.

2.2.2 Estimands and Estimators

Vaccine effects, i.e., the causal effects of vaccination, can be defined by contrasts in the expected values of the potential outcomes $Y^{a=1}$ and $Y^{a=0}$. Assuming the n clusters in the trial are randomly sampled from an infinite super-population of clusters, the average treatment

(vaccine) effect is generally defined by

$$\theta = E[Y^{a=1}] - E[Y^{a=0}] \tag{2.1}$$

where $E[X]$ denotes the expected value of X in the super-population of clusters. In words, (2.1) is the difference in the average outcome in the super-population when a cluster receives $a = 1$ compared to when a cluster receives $a = 0$. Alternatively, the n clusters could be considered the finite population of interest and $E[X]$ defined instead to be $n^{-1} \sum_{i=1}^{n} X_i$. The super-population perspective is adopted in this paper, but similar considerations to those provided here apply if the finite population approach is utilized instead. Likewise, estimands other than (2.1) could be considered. For example, for binary Y, the risk ratio $E[Y^{a=1}]/E[Y^{a=0}] = \Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ might be of greater interest than the risk difference (2.1). For instance, Y might be an indicator of whether or not at least one individual in a cluster gets infected [Bjune et al., 1991, Halloran et al., 2002]. More generally, causal effects can by defined by $g(E[Y^{a=1}], E[Y^{a=0}])$ for some contrast function $g(x, y)$ where $g(x, x) = 0$; e.g., $g(x, y) = x - y$ corresponds to (2.1). Below, estimands of the form (2.1) are described, but similar considerations apply for other contrasts.

A few aspects of defining causal effects bear mentioning. First, causal effects are typically defined by contrasts in expected values of the potential outcomes over the same set of units [Rubin, 1974, Frangakis and Rubin, 2002]. In many settings, the unit is defined to be an individual; for example, a unit could be a participant in a randomized controlled trial. Here, we consider the clusters to be the units since randomization is at the cluster level. Note that contrasts in average potential outcomes between different sets of units do not have a causal interpretation. For example, suppose a cluster-randomized vaccine trial is conducted in schools, where students within the same school constitute the clusters. A comparison of the average $Y^{a=1}$ among clusters (schools) in rural areas to the average $Y^{a=0}$ among clusters in urban areas is not a causal effect. Also note that causal effects are contrasts in the expected value of the *same* outcome under different counterfactual scenarios. Contrasts in different outcomes are not

causal effects. For example, a comparison of the average incidence of typhoid when clusters receive vaccine with the average incidence of cholera when clusters receive control would not be a causal effect. We will revisit this point below when discussing direct effects.

The average treatment effect can be estimated by the difference in sample means:

$$\hat{\theta} = \frac{1}{n_1} \sum_{i=1}^{n} Y_i I(A_i = 1) - \frac{1}{n_0} \sum_{i=1}^{n} Y_i I(A_i = 0) \tag{2.2}$$

where $n_a = \sum_{i=1}^{n} I(A_i = a)$ for $a = 0, 1$. This estimator is consistent and unbiased under commonly used randomization schemes, such as a completely randomized experiment where the number of clusters assigned vaccine (treatment) is fixed [Miratrix et al., 2013, Imbens and Rubin, 2015, Athey et al., 2018]. The standard error of $\hat{\theta}$ can be estimated and 95% Wald confidence intervals can be constructed in the usual manner for the difference in means. Equivalently, (2.2) can be obtained by computing the least squares estimate of the slope parameter of simple linear regression of Y on A. A generally more precise estimator can be obtained by regressing Y on A and Z where Z is some vector of baseline covariates. For simplicity, only estimators of the form (2.2) are considered below; see Tsiatis et al. [2008] for further discussion on using baseline covariates to improve efficiency. Note also that (2.2) utilizes only cluster level data and thus avoids the complexities associated with inference based on statistics constructed using individual level data, which require accounting for possible within-cluster correlation (e.g., using mixed effects models or generalized estimating equations).

2.2.3 Overall, Indirect, and Total Effects

In this section, the general approach above is used to define estimands and estimators of the overall, indirect, and total effects. The outcome of interest will depend on the context of the vaccine trial, such as the infection or pathogen of interest, the target population, and so forth. Here, the outcome of interest is generically referred to as disease.

The overall effect compares the average disease outcome among all individuals when a cluster is assigned vaccine versus when a cluster is assigned control. This quantity may be

the most relevant to public health policy because all individuals within clusters are used in the comparison. As it is likely that populations of interest will include a mixture of individuals who would and who would not choose to be vaccinated, the overall effect may be valuable for public health officials and policy makers in assessing the overall impact of a vaccine at the population level.

The overall effect estimand and estimator can be defined in terms of individual level outcomes as follows. Let m_i denote the number of individuals in cluster i. For individual j in cluster i, let $Y_{ij} = 1$ if individual j develops disease, and let $Y_{ij} = 0$ otherwise. Let $Y_{ij}^{a=1}$ indicate the outcome that would have been observed for individual j if cluster i is randomized to vaccine, and define $Y_{ij}^{a=0}$ analogously for control, such that $Y_{ij} = Y_{ij}^{a=1}A_i + Y_{ij}^{a=0}(1 - A_i)$. For the overall effect, the estimand (2.1) can be expressed in terms of individual potential outcomes by defining $Y_i^{a=1} = \sum_{j=1}^{m_i} Y_{ij}^{a=1}/m_i$, and $Y_i^{a=0} = \sum_{j=1}^{m_i} Y_{ij}^{a=0}/m_i$ for cluster i. The overall effect estimator can likewise be expressed in terms of the observed individual-level outcomes by letting $Y_i = \sum_{j=1}^{m_i} Y_{ij}/m_i$.

The indirect effect quantifies the effect of vaccination on individuals who chose not to participate in the trial and, therefore, have no chance of receiving the vaccine. This effect is defined as a contrast in the average outcomes among non-participants when their cluster does or does not receive vaccine [Halloran and Struchiner, 1991]. Because the indirect effect is defined only among individuals who never receive the vaccine, this effect (if present) is solely due to interference. Thus, indirect effects are a type of spillover or peer effect [Sobel, 2006]. Quantifying indirect effects may be of interest from a public health policy perspective because vaccinating some, but not all, individuals within a cluster can still provide benefits to those who are unable or choose not to be vaccinated.

Like the overall effect, the indirect effect estimand and estimator can be defined in terms of individual level outcomes. To do so, first define the potential outcome $S_{ij}^{a=1}$ where $S_{ij}^{a=1} = 1$ if individual j in cluster i would choose to participate in the trial if, possibly counter to fact, cluster i were randomized to vaccine and $S_{ij}^{a=1} = 0$ otherwise. Define $S_{ij}^{a=0}$ analogously.

Denote the observed participation outcome for individual j in cluster i by S_{ij}, such that $S_{ij} = S_{ij}^{a=1}A_i + S_{ij}^{a=0}(1-A_i)$. Assume $S_{ij}^{a=1} = S_{ij}^{a=0}$, i.e., an individual's decision to participate is not affected by whether their cluster is assigned vaccine or control. This assumption may be reasonable in cluster-randomized trials where individuals are blinded, such as the typhoid vaccine trial described in Section 2.3, because in such settings, randomization is not expected to have an effect on an individual's decision to participate in the trial. As mentioned in the Introduction, Frangakis and Rubin [2002] and Kang and Keele [2018] utilize the principal stratification framework when considering non-compliance in cluster-randomized trials. Under the assumption $S_{ij}^{a=1} = S_{ij}^{a=0}$, all individuals belong to one of two principal strata: always participators, i.e., individuals where $S_{ij}^{a=1} = S_{ij}^{a=0} = 1$; and never participators, i.e., individuals where $S_{ij}^{a=1} = S_{ij}^{a=0} = 0$. Fortunately, unlike the setting considered by Kang and Keele, here the principal strata membership of each individual can be inferred directly from the observed data because $S_{ij} = S_{ij}^{a=1} = S_{ij}^{a=0}$.

The indirect effect is the effect of vaccine in the non-participator principal stratum. The indirect effect has the general form (2.1), with $Y_i^{a=1}$ now defined to be $\big\{\sum_{j=1}^{m_i} Y_{ij}^{a=1} I(S_{ij}^{a=1} = 0)\big\}/\big\{\sum_{j=1}^{m_i} I(S_{ij}^{a=1} = 0)\big\}$ and $Y_i^{a=0}$ defined to be $\big\{\sum_{j=1}^{m_i} Y_{ij}^{a=0} I(S_{ij}^{a=0} = 0)\big\}/\big\{\sum_{j=1}^{m_i} I(S_{ij}^{a=0} = 0)\big\}$. This estimand compares the average disease outcome among non-participators when a cluster is assigned vaccine versus when a cluster is assigned control. Similarly, the indirect effect estimator can be expressed by (2.2) with Y_i defined to be $\big\{\sum_{j=1}^{m_i} Y_{ij} I(S_{ij} = 0)\big\}/\big\{\sum_{j=1}^{m_i} I(S_{ij} = 0)\big\}$.

The total effect measures the effect of treatment in the always participator principal stratum. Because always participators receive the vaccine if and only if their cluster is assigned vaccine, the total effect encompasses both the individual effect of receiving the vaccine as well as the effect of other individuals in the cluster being vaccinated. The total effect estimand and estimator have the same form as the indirect effect estimand and estimator described above, but with $S_{ij}^{a=1} = 0$ replaced by $S_{ij}^{a=1} = 1$, $S_{ij}^{a=0} = 0$ replaced by $S_{ij}^{a=0} = 1$, and $S_{ij} = 0$ replaced by $S_{ij} = 1$. The total effect quantifies the difference in the average disease outcome among always

participators when a cluster is assigned vaccine versus when a cluster is assigned control. The total effect is often the effect of primary interest in this type of trial. An illustration of the overall, indirect, and total effects is given in Figure 2.1.

There are a few special cases of note. In the scenario where all individuals in the population are willing to participate in trials (i.e., there are no non-participators), the indirect effect is not well-defined, and the total and overall effects are equivalent. In some trials, only a subset of individuals may be eligible to be randomized for vaccination. For example, in Sur et al. [2009b], individuals were eligible if they were at least two years of age, were not pregnant or lactating, and did not have an elevated temperature when the vaccine was given. Indirect effects, analogous to that defined above for non-participators, can be defined and estimated in these individuals if their outcome of interest is measured.

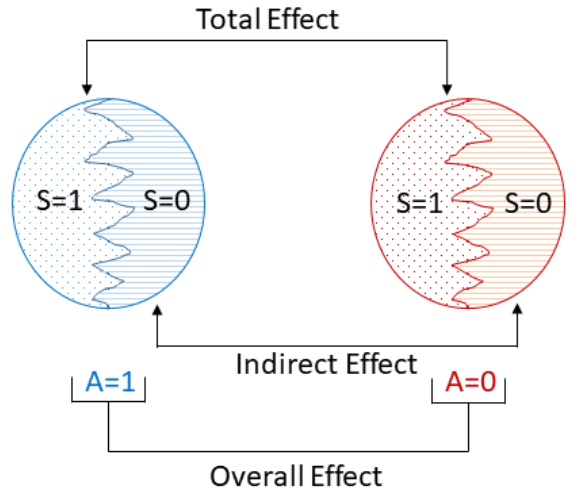

Figure 2.1: Cluster counterfactual comparisons. The left circle represents a cluster if, possibly counter to fact, assigned to vaccine ($A = 1$). The right circle represents a cluster if, possibly counter to fact, assigned to control ($A = 0$). Within each circle, S indicates which individuals chose to participate in the study ($S = 1$ indicates participation, $S = 0$ otherwise). The overall, indirect, and total effects are contrasts in average potential outcomes over different sets of individuals within the clusters.

2.2.4 Direct Effect

The overall, indirect, and total effects each describe an effect of treatment (vaccination) which is at least partially due to interference, if present. The effect of treatment that is not attributable to interference may also be of interest. Such an effect is sometimes referred to as a direct effect. This section describes why it is not possible in general to estimate the direct effect of vaccination in a cluster-randomized trial with self-selection of participation without additional assumptions, such as no unmeasured confounding. Informally, the direct effect compares the average outcome when an individual is vaccinated to the average outcome when an individual is not vaccinated, holding fixed the proportion of other individuals vaccinatedHalloran and Struchiner [1991]. Several formal definitions of the direct effect estimand have been proposed; e.g., see Hudgens and Halloran [2008], VanderWeele and Tchetgen Tchetgen [2011], Liu et al. [2016], Eck et al. [2018] and Sävje et al. [2018].

To develop intuition behind the lack of identifiability of the direct effect, consider the following naive approach. Suppose the proportion of vaccinated individuals with disease is compared to the proportion of unvaccinated individuals with disease in clusters assigned to vaccine by

$$\frac{1}{n_1}\sum_{i=1}^{n}\frac{\sum_{j=1}^{m_i} Y_{ij} I(S_{ij}=1)}{\sum_{j=1}^{m_i} I(S_{ij}=1)} I(A_i=1) - \frac{1}{n_1}\sum_{i=1}^{n}\frac{\sum_{j=1}^{m_i} Y_{ij} I(S_{ij}=0)}{\sum_{j=1}^{m_i} I(S_{ij}=0)} I(A_i=1). \tag{2.3}$$

By the law of large numbers, (2.3) converges to

$$E[Y^{a=1}] - E[\tilde{Y}^{a=1}] \tag{2.4}$$

where $Y_i^{a=1} = \big\{\sum_{j=1}^{m_i} Y_{ij}^{a=1} I(S_{ij}^{a=1}=1)\big\} / \big\{\sum_{j=1}^{m_i} I(S_{ij}^{a=1}=1)\big\}$ and $\tilde{Y}_i^{a=1} = \big\{\sum_{j=1}^{m_i} Y_{ij}^{a=1} I(S_{ij}^{a=1}=0)\big\} / \big\{\sum_{j=1}^{m_i} I(S_{ij}^{a=1}=0)\big\}$. Unfortunately, the estimand (2.4) is not a causal effect, as it comprises a comparison of different cluster-level outcomes, namely $Y_i^{a=1}$ and $\tilde{Y}_i^{a=1}$. As

noted above, for an estimand to have a causal interpretation, the same outcome must be compared under different counterfactual scenarios.

It is conventional, although not incontrovertible [Pearl, 2018], to define causal effects only for a treatment or exposure that is manipulable, i.e., there can be "no causation without manipulation" [Holland, 1986]. If this convention is followed, then in cluster-randomized trials with non-participation, the direct effect of vaccination would only be considered well defined in always participators. Otherwise, to define the relevant potential outcomes would require considering a counterfactual scenario where non-participators receive vaccine. However, for the study design under consideration, always participators receive vaccine if and only if other always participators in their cluster also receive vaccine. Thus it is not possible to observe both (i) a vaccinated always participator and (ii) an unvaccinated always participator, while holding fixed the proportion of other individuals who are vaccinated in the cluster; hence the direct effect is not identifiable without additional assumptions.

On the other hand, if the "no causation without manipulation" convention is not adopted, there are other complications that may arise with estimating the direct effect. In particular, in cluster-randomized trials with non-participation, vaccine coverage within a cluster is dictated by the collective level of individual participation in the study, which is not under the investigator's control. Factors associated with participation may also be associated with the outcome of interest, creating the potential for confounding. Thus causal inference methods for observational studies, such as those assuming no unmeasured confounding, would in general be necessary to draw inference about direct effects. To be concrete, consider the counterfactual scenario (or policy) where individuals independently receive vaccine with probability α. Let A_{ij} denote the vaccination status of individual j in cluster i, and let $\mathbf{A}_i = (A_{i1}, A_{i2}, \ldots, A_{in_i})$. The random vector $\mathbf{A}_i$ takes on values $\mathbf{a}_i$ in the set $\mathcal{A}(n_i) = \{0,1\}^{n_i}$. Let $Y_{ij}(\mathbf{a}_i)$ denote the potential outcome for individual j (in cluster i) corresponding to $\mathbf{a}_i$. The potential outcomes $Y_{ij}(\mathbf{a}_i)$ may also be expressed as $Y_{ij}(\mathbf{a}_{i,-j}, a_{ij})$ where $\mathbf{a}_{i,-j}$ denotes the vector of treatment indicators for all individuals except individual j and a_{ij} is the treatment indicator for individual j. Define the

average outcome for individual j when vaccinated under policy α by

$$Y_{ij}(1;\alpha) = \sum_{\mathbf{b}\in\mathcal{A}(n_i-1)} Y_{ij}(\mathbf{a}_{i,-j} = \mathbf{b}, a_{ij} = 1) P_\alpha(\mathbf{A}_{i,-j} = \mathbf{b})$$

where P_α denotes the probability under policy α. Define $Y_{ij}(0;\alpha)$ analogously such that $Y_{ij}(0;\alpha)$ is the average outcome for individual j when not vaccinated under policy α. Then define the direct effect under policy α to be

$$E[\bar{Y}_i(1;\alpha)] - E[\bar{Y}_i(0;\alpha)] \tag{2.5}$$

In the cluster-randomized trial setting considered in this paper, individuals self-select whether to participate such that it would be dubious to assume treatment received is independent of an individual's potential outcomes. However, in some settings, it might be reasonable to assume there exists some vector of baseline covariates, say $\mathbf{L}_i$, such that the set of potential outcomes for individuals within cluster i are conditionally independent of the treatment selected given these covariates, i.e., $Y_{ij}(\mathbf{a}_i) \perp \mathbf{A}_i \mid \mathbf{L}_i$. This is a cluster level version of the usual no unmeasured confounders assumption. Under this assumption, inverse probability weighted estimators have been proposed which are consistent for (2.5) [Tchetgen Tchetgen and VanderWeele, 2012, Perez-Heydrich et al., 2014].

2.3 Typhoid Vaccine Trial

A cluster-randomized study was conducted to investigate the effectiveness of a Vi polysaccharide typhoid vaccine in Kolkata, India over two years of follow-up from 2004 to 2006 [Sur et al., 2009b]. The control in this trial was an inactivated hepatitis A vaccine. Geographic mapping and a census that characterized and counted all people and households in the study area were used to define 80 clusters. For purposes of randomization, clusters were stratified by ward (an administrative unit of Kolkata) and by the number of residents in certain age groups. Overall, 40 clusters were assigned to Vi vaccine and the other 40 to control. Because data

from the typhoid trial are not publicly available, a simulated data set was constructed (see Data Availability Statement). The data were simulated to match exactly the cluster level summary statistics from the actual trial shown in Table 2.1.

Table 2.1: Summary statistics of a cluster-randomized study in Kolkata from 2004 to 2006 of a Vi typhoid vaccine versus a hepatitis A control vaccine [Sur et al., 2009b]. SD: standard deviation

	Typhoid Vaccine	**Control**
Number of clusters	40	40
Mean $\pm$ SD of people per cluster	777 ± 136	792 ± 142
Mean $\pm$ SD of participants per cluster	472 ± 103	470 ± 104
Number of participants	18869	18804
Number of non-participants	12206	12877
Number of events in participants	34	96
Number of events in non-participants	16	31

Sur et al. [2009b] measure vaccine effects in terms of hazard ratios. However, causal interpretations for hazard ratios are difficult because hazard ratios can depend on time and have an inherent selection bias [Hernán, 2010]. In particular, time-specific hazard ratios compare different subsets of subjects and, as noted above, estimands have a causal interpretation only when comparing potential outcomes between the same set (or subset) of units. Due to these issues, instead of using the hazard ratio to determine the vaccine effects as in Sur et al. [2009b], the risk difference of typhoid over two years is calculated here to quantify vaccine effects.

The overall, indirect, and total effects were estimated using (2.2) with the Y_i definitions provided in section 2.2.3. The effect estimates, estimated standard errors (SEs), and 95% Wald confidence intervals (CIs) are shown in Table 2.2. For example, the overall effect estimate was obtained by taking the difference in the average number of cases of typhoid per 1000 individuals between Vi clusters and control clusters. In particular, Vi clusters had 1.61 cases of typhoid per 1000 people, while control clusters had 4.10 cases of typhoid per 1000 people. Thus, the overall effect estimate is -2.49 cases per 1000 people. The standard error of the overall effect estimate was calculated by $\left\{\hat{\sigma}_0^2 + \hat{\sigma}_1^2\right\}^{1/2}$ where $\hat{\sigma}_a$ denotes the estimated standard error for clusters

assigned $a = 0$ (control), 1 (Vi). Finally, a 95% Wald CI was estimated in the usual manner with a result of (-3.41, -1.58). The overall effect estimate has a straightforward interpretation which may be of interest to public health officials such as epidemiologists. In particular, the number of cases of typhoid per 1000 persons over a two year period is estimated to decrease by 2.5 on average when a cluster receives the Vi vaccine compared to receiving control.

Both participants and non-participants appear to benefit from the Vi vaccine. In particular, over the study period, on average, there were 1.85 cases of typhoid per 1000 participants in Vi clusters, and 5.15 cases of typhoid per 1000 participants in control clusters. Thus, the total effect estimate is -3.30 (95% CI -4.61, -1.99), indicating that assigning a cluster to Vi vaccine causes 3.3 fewer cases of typhoid per 1000 participants compared to assigning a cluster to hepatitis A vaccine. Likewise, Vi clusters had 1.29 cases of typhoid per 1000 non-participants on average, while control clusters had 2.58 cases of typhoid per 1000 non-participants on average over the study period. Taking the difference between these values gives an indirect effect estimate of 1.29 (95% CI 0.19, 2.38). The indirect effect estimate suggests that assigning a cluster to the typhoid vaccine results in 1.29 fewer cases per 1000 non-participants; as non-participants never receive the vaccine, this indicates an indirect (or herd immunity) effect of the typhoid vaccine.

Table 2.2: Estimates of overall, indirect, and total effects, standard errors (SE), and 95% Wald confidence intervals (CI). Effect estimates are differences in typhoid cases per 1000 people per two years.

Effect	**Estimate (SE)**	**95% CI**
Overall	-2.49 (0.47)	(-3.41, -1.58)
Indirect	-1.29 (0.56)	(-2.38, -0.19)
Total	-3.30 (0.67)	(-4.61, -1.99)

On the other hand, the naive direct effect estimator (2.3) equals 0.56 (95% CI -0.44, 1.55). Although not statistically significant, this point estimate implies that the average number of cases of typhoid per 1000 people is higher in vaccinated individuals compared to non-vaccinated

individuals in clusters randomized to the Vi vaccine. However, as described above, this estimate cannot be interpreted as an effect of the vaccine as discussed in Section 2.2.4. For example, perhaps individuals at higher risk of typhoid chose to participate in the trial, or those who participated tended to have different health care seeking behavior. Moreover, the average number of cases of typhoid per 1000 people was also higher in participants compared to non-participants (2.57, 95% CI 1.19, 3.96) in the control clusters, providing direct evidence of confounding. Sur et al. [2009b] reported similar results, with incidence of typhoid higher in participants compared to non-participants, both within Vi vaccine clusters and within control clusters.

2.4 Discussion

Randomized controlled trials are the gold standard in vaccine trials since randomization ensures that the vaccine and control groups are comparable. Carefully defining estimands in clinical trials is vital to ensure accurate interpretation of the resulting treatment effect estimates. Because cluster-randomized trials can be large and expensive to conduct, it is important to formally characterize estimands for use in these trials. This paper considers causal estimands in cluster-randomized trials where interference may be present within clusters. An illustrative example is provided motivated by a recent cluster-randomized typhoid vaccine trial demonstrating inference and interpretation of the overall, total, and indirect effect estimands. These types of analyses can be used to inform public health policies regarding vaccination.

In cluster-randomized trials with self-selection, estimators of the direct effect must account for possible confounding. As described at the end of Section 2.2, a standard method to adjust for confounding is to condition on covariates and assume that conditional on these covariates, participants and non-participants are exchangeable. A possible indirect way to adjust for confounding could involve comparing outcomes between participants and non-participants in the control clusters as an estimate of the confounding bias, if present, similar to negative control approaches described in Lipsitch et al. [2010] and Tchetgen Tchetgen [2013]. Alternatively,

two-stage randomized designs could be considered to eliminate possible confounding when drawing inference about the direct effect. In two-stage randomized experiments, clusters are first randomly assigned to a treatment allocation program, then individuals within those clusters are assigned to treatment or control based on their cluster's treatment allocation program [Hudgens and Halloran, 2008]. Randomization eliminates possible confounding at the cluster and individual level, such that direct, indirect, total, and overall effects can be estimated [Hudgens and Halloran, 2008, Baird et al., 2018, Basse and Feller, 2018]. However, it may not always be feasible to conduct two-stage randomized trials. In addition, the effects estimated by a two-stage randomized experiment are not equivalent to the effects estimated in cluster-randomized trials with participation self-selection and may have less public health relevance [Papadogeorgou et al., 2019, Barkley et al., 2020].

Estimated effects may have greater real-world relevance depending on the estimands of interest and characteristics of individuals in the trials, such as the level of participation. Westreich [2017] provides several examples of population intervention effects defined by contrasts in average potential outcomes under different possible interventions on the distribution of treatment. These population intervention effects may be more germane to real-world policy than the traditional approach of defining causal effects by comparing average outcomes when all individuals in the population receive treatment versus when no individuals receive treatment. The estimands described here for cluster-randomized trials with self-selection are examples of population intervention effects, to the extent that the participation rate in the trial approximates vaccination uptake should the vaccine under evaluation become widely available to the public. For example, in Sur et al. [2009b], about 60% of individuals on average chose to be vaccinated in both Vi and hepatitis A clusters; thus, the overall, total, and indirect effect estimates approximate the effects of vaccinating 60% of the population. Such effect estimates could potentially help inform public health policy decisions regarding vaccination.

Data Availability Statement

Because data from the typhoid trial are not publicly available, a simulated dataset was constructed. This dataset is available at `https://github.com/KilpatrickKW`.

CHAPTER 3: G-FORMULA FOR OBSERVATIONAL STUDIES WITH PARTIAL INTERFERENCE, WITH APPLICATION TO BED NET USE ON MALARIA

3.1 Introduction

In settings where individuals interact or are connected, one individual's treatment status may affect another individual's outcome, i.e., interference may be present between individuals [Cox, 1958]. Interference is common in infectious disease research. For instance, if one individual wears a mask, this could affect whether another individual develops COVID-19 (coronavirus disease 2019). In some settings, it may be reasonable to assume that individuals within a cluster (or group) may interfere with one another, but not with individuals in other clusters, i.e., there is "partial interference" [Sobel, 2006]. Clusters might entail households, villages, schools, or other hierarchical structures. For instance, when assessing the effect of an intervention or exposure in students, it may be reasonable to assume no interference between students in different schools. Under this partial interference setting, several methods have been proposed for drawing inference about causal estimands of treatment effects; e.g., see Tchetgen Tchetgen and VanderWeele [2012], Papadogeorgou et al. [2019], Barkley et al. [2020].

In the presence of interference, it is of interest to assess the effect of policies which alter the distribution of treatment in the population. For instance, in the Democratic Republic of the Congo, public health officials and policy makers may be interested in estimates of malaria risk for different levels of bed net usage in the population. In observational studies where partial interference is present, it may be unlikely that treatment selection among individuals in the same cluster is independent. For example, in household studies of vaccine effects, we might expect vaccine uptake to be positively correlated between individuals in the same household. Therefore, estimands that will be most relevant to policy makers need to account for possible

within-cluster treatment selection dependence. Papadogeorgou et al. [2019] and Barkley et al. [2020] recently proposed such estimands and developed corresponding inferential methods using inverse probability weighted (IPW) estimators. These IPW estimators entail inverse weighting by an estimated group propensity score. Unfortunately, this approach is not well suited for large groups, because in practice the estimated group propensity score is often near zero when there are a large number of individuals in a group [Saul and Hudgens, 2017, Chakladar et al., 2019, Liu et al., 2019]. In the absence of interference, a commonly used alternative to the IPW estimator is the parametric g-formula, which entails combining outcome regression and standardization [Robins, 1986, Hernán and Robins, 2006]. This paper proposes an extension of the parametric g-formula for observational studies where partial interference may be present which is better suited for large clusters compared to IPW.

The proposed methods were motivated by the 2013-14 Democratic Republic of the Congo (DRC) Demographic and Health Survey (DHS), a nationally representative survey to gather information about fertility, maternal and child health, sexually transmitted infections, mosquito net (hereafter "bed net") usage, malaria, and other health information [MPSMRM, MSP, and ICF International, 2014]. In the analysis presented below, population level effects of bed net use on malaria are assessed using data from the DRC DHS. Figure 3.2 displays province-level bed net use and the proportion of children who did not use bed nets with malaria. The DHS data were collected at the household level. For the analysis here, a single linkage agglomerative cluster method was used to group individuals into clusters based on their household global positioning system (GPS) coordinates, resulting in a total of 395 clusters with at least one child and measured spatial information and other covariates. After performing this clustering algorithm, covariates and bed net use data are available for approximately 87,500 individuals. Malaria outcome data is available for about 7,500 children between 6 to 59 months (for brevity, henceforth referred to as "children"). Among the clusters with at least one child who did not use a bed net, the prevalence of malaria in children who did not use bed nets is inversely associated with the proportion of bed net usage in the cluster (Spearman correlation $r_s = -0.16, p = 0.002$),

suggesting the possibility of interference within clusters. Previously, Levitz et al. [2018] showed that community-level bed net usage was significantly associated with protection against malaria in children younger than five years old. The inferential goal in this paper is to assess the population-level effects of bed use on malaria when varying the proportion of children who use bed nets.

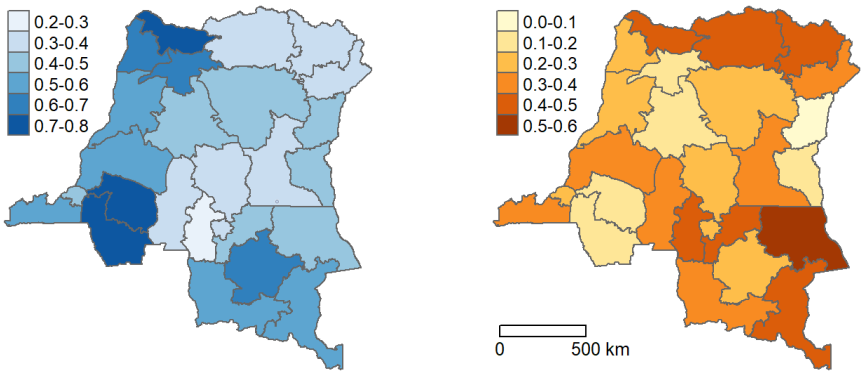

Figure 3.2: Malaria bed net study in the Democratic Republic of the Congo. Left map: province-level bed net usage. Right map: prevalence of malaria in children who do not use bed nets.

The outline of the remainder of this paper is as follows. Section 3.2 presents the proposed extension of the g-formula to allow for partial interference. Section 3.3 presents the simulation results evaluating the performance of the proposed methods in finite samples. In Section 3.4, the proposed estimators are employed to assess the effect of bed net use on malaria using data from the DRC DHS. Section 3.5 concludes with a discussion.

3.2 Methods

3.2.1 Estimands and Effects of Interest

Suppose data is observed on m clusters of individuals, and let N_i denote the number of individuals in cluster i. Suppose some individuals within each cluster may receive treatment (e.g., bed net) and denote the vector of binary treatment indicators in cluster i as $\mathbf{A}_i = (A_{i1}, A_{i2}, \ldots, A_{iN_i})$ with A_{ij} representing the treatment indicator for individual j. Let $S_i = (\sum_{j=1}^{N_i} A_{ij})/N_i$ denote the proportion of treated individuals in cluster i. Let Y_i represent

the outcome at the cluster level. In general, Y_i may be defined differently depending on the outcome of interest. For example, in the analysis of the DRC data, Y_i may be defined as the proportion of children in a cluster with malaria. Let $\mathbf{L}_i$ represent a vector of cluster-level baseline covariates, including N_i. Let $O_i = \{\mathbf{L}_i, S_i, Y_i\}$ be the observed random variables for cluster i, and assume $O_1, \ldots, O_m$ are independent and identically distributed. For notational simplicity, the subscript i is omitted when not needed.

Assume partial interference, i.e., there is no interference between clusters, but there may be interference between individuals within the same cluster. For example, in the DRC analysis, one individual's bed net usage may affect whether or not another individual in the same cluster gets malaria. Let $\mathcal{A}(N_i)$ denote the set of all vectors of length N_i with binary entries such that $\mathbf{a} = (a_{i1}, a_{i2}, \ldots, a_{iN_i}) \in \mathcal{A}(N_i)$ is a vector of possible treatment statuses for a cluster of size N_i. For cluster i, let $Y_i^{\mathbf{a}}$ represent the potential outcome if, possibly counter to fact, the cluster had been exposed to $\mathbf{a} \in \mathcal{A}(N_i)$, such that $Y_i^{\mathbf{a}} = Y_i$ when $\mathbf{A}_i = \mathbf{a}$.

In addition to partial interference, we also assume the cluster level potential outcomes depend only on the proportion of individuals treated, but not which particular individuals receive treatment. That is, $Y_i^{\mathbf{a}} = Y_i^{\mathbf{a}'}$ for any two vectors $\mathbf{a}, \mathbf{a}' \in \mathcal{A}(N_i)$ such that $\sum_{j=1}^{N_i} a_{ij} = \sum_{j=1}^{N_i} a'_{ij}$; this type of assumption is sometimes referred to as "stratified interference" [Hudgens and Halloran, 2008]. For example, in the DRC analysis, we will assume that the prevalence of malaria in a cluster only depends on the proportion of bed net users, not which specific individuals use bed nets. For cluster i, let Y_i^s denote the potential outcome for any $\mathbf{a}$ such that $(\sum_{j=1}^{N_i} a_{ij})/N_i = s$. Assume exchangeability conditional on $\mathbf{L}$ at the cluster level, i.e., $Y^s \perp S|\mathbf{L}$.

Population-level effects of interventions such as bed nets can be defined by differences in expected outcomes when the distribution of treatment is altered. For example, in the absence of interference, the effect of treatment is often defined by the difference in expected outcomes when all individuals receive treatment versus when no individuals receive treatment. Here we consider stochastic policies where individuals receive treatment with some probability between

0 and 1. Define policy α to be the setting where the expected proportion of individuals in a cluster who receive treatment is α, i.e., $E_\alpha(S) = \alpha$, where in general the subscript α denotes the counterfactual scenario in which the policy α is implemented. For example, the DRC analysis below considers policies where different proportions of individuals use bed nets.

The expected outcome in a group of individuals under policy α can be expressed as:

$$\begin{aligned}\mu_\alpha = E_\alpha(Y) &= \int_{\mathbf{l}} \sum_{s \in \mathcal{S}} E_\alpha(Y|S=s, \mathbf{L}=\mathbf{l}) P_\alpha(S=s|\mathbf{L}=\mathbf{l}) dF_{\alpha\mathbf{L}}(\mathbf{l}) \\ &= \int_{\mathbf{l}} \sum_{s \in \mathcal{S}} E_\alpha(Y^s|S=s, \mathbf{L}=\mathbf{l}) P_\alpha(S=s|\mathbf{L}=\mathbf{l}) dF_{\alpha\mathbf{L}}(\mathbf{l})\end{aligned} \tag{3.6}$$

where $\mathcal{S} = \{0, 1/n, 2/n, ..., 1\}$ and $F_{\alpha\mathbf{L}}$ denotes the marginal distribution of baseline covariates under policy α. The first line of (3.6) follows from the law of total expectation and the second line from causal consistency [Cole and Frangakis, 2009]. Effects of interest can be defined by contrasts in μ_α for two policies α and α', e.g.,

$$\delta(\alpha, \alpha') = \mu_\alpha - \mu_{\alpha'}. \tag{3.7}$$

Here, effects are defined as a difference in average potential outcomes, but ratios or other contrasts could be used instead. A primary contrast of interest in the DRC analysis is the difference in the proportion of children infected with malaria under policies α versus α'.

In the DRC analysis, we will consider three different effects of bed nets: the overall effect, the spillover effect when treated, and the spillover effect when untreated. All three effects have the form (3.7) but differ in how Y_i is defined. The overall effect compares the average outcome among all individuals in a cluster under policies α versus α'. As it is likely that populations of interest will include a mixture of individuals who would and who would not choose to receive treatment, the overall effect may be valuable for public health officials and policy makers in assessing the overall impact of increasing treatment coverage among a population. For inference about the overall effect, Y_i is a summary measure of outcomes in all individuals in cluster i.

For the malaria data analysis, Y_i is defined to be the proportion of all children in a cluster with malaria.

Two different spillover effects are also considered. The spillover effect when untreated contrasts average outcomes when an individual is untreated under policy α versus policy α'. For this effect, Y_i may be defined by some summary measure of outcomes in untreated individuals. In the DRC analysis of the spillover effect in the untreated, Y_i will be defined as the proportion of children who do not use bed nets with malaria. If there are no untreated individuals in the cluster, we adopt the convention $Y_i = 0$. Similarly, the spillover effect when treated contrasts average outcomes when an individual is treated under policy α versus policy α'. For the spillover effect when treated in the DRC analysis, Y_i will be the proportion of children who use bed nets with malaria, with $Y_i = 0$ in clusters with no treated individuals.

3.2.2 Identifiability

Additional assumptions are made to draw inference about the estimands described above. Assume $F_L = F_{\alpha L}$, i.e., the distribution of the covariates is the same under the factual and counterfactual policies. Let $\pi_s = g^{-1}(\rho_0 + \rho_1 \mathbf{L})$, where g is some monotone, user-specified link function such as logit or probit, and assume

$$P(S = s|\mathbf{L}) = P(S = s|\mathbf{L}; \rho) = \binom{N}{Ns} \pi_s^{Ns} (1 - \pi_s)^{N - Ns}. \tag{3.8}$$

where $\rho = (\rho_0, \rho_1)$. Likewise, under policy α, let $\pi_{s\alpha} = g^{-1}(\gamma_{0\alpha} + \gamma_{1\alpha}\mathbf{L})$ and assume

$$P_\alpha(S = s|\mathbf{L}) = P_\alpha(S = s|\mathbf{L}; \gamma) = \binom{N}{Ns} \pi_{s\alpha}^{Ns} (1 - \pi_{s\alpha})^{N - Ns}. \tag{3.9}$$

where $\gamma = (\gamma_{0\alpha}, \gamma_{1\alpha})$. The parameters ρ in (3.8) are identifiable from the observable data, whereas the counterfactual parameters γ in (3.9) are not identifiable without additional assumptions. As in Barkley et al. [2020], assume $\rho_1 = \gamma_{1\alpha}$; this assumption implies rank preservation between clusters in treatment propensity. In other words, if treatment adoption is more likely in

cluster i than cluster j, then under counterfactual policy α, treatment adoption will also be more likely in cluster i than cluster j. It follows that $\pi_{s\alpha} = g^{-1}(\gamma_{0\alpha} + \rho_1 \mathbf{L})$ and $\gamma_{0\alpha}$ is the solution to

$$\int_{\mathbf{l}} E_\alpha(S|\mathbf{L} = \mathbf{l}; \gamma_{0\alpha}, \rho_1) dF_{\mathbf{L}} - \alpha = 0 \tag{3.10}$$

where $E_\alpha(S|\mathbf{L} = \mathbf{l}; \gamma_{0\alpha}, \rho_1) = \pi_{s\alpha}$. Finally, let $\pi_y = g^{-1}(\beta_0 + \beta_1 \mathbf{L} + \beta_2 S)$ and assume

$$E(Y|S = s, \mathbf{L} = \mathbf{l}) = E(Y|S = s, \mathbf{L} = \mathbf{l}; \beta) = \pi_y \tag{3.11}$$

where $\beta = (\beta_0, \beta_1, \beta_2)$. For simplicity, an interaction between S and $\mathbf{L}$ is omitted from the model of $E(Y|S = s, \mathbf{L} = \mathbf{l})$ but could be included. Assume that the mean of Y given $S, \mathbf{L}$ is the same under the factual scenario and counterfactual scenario α, i.e., $E(Y|S = s, \mathbf{L} = \mathbf{l}) = E_\alpha(Y|S = s, \mathbf{L} = \mathbf{l})$.

3.2.3 Inference

Estimators for μ_α can be constructed as follows. First estimate the parameters $\rho = (\rho_0, \rho_1)$ of model (3.8) and $\beta = (\beta_0, \beta_1, \beta_2)$ of model (3.11) via maximum likelihood; denote these estimators by $\hat{\rho} = (\hat{\rho}_0, \hat{\rho}_1)$ and $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2)$. Next, for a given policy α, let $\hat{\gamma}_{0\alpha}$ denote the estimator of $\gamma_{0\alpha}$ obtained by finding the solution to (3.10) with $F_{\mathbf{L}}$ replaced by its empirical distribution, i.e., $m^{-1} \sum_{i=1}^{m} \hat{E}_\alpha(S|\mathbf{L}_i; \gamma_{0\alpha}, \hat{\rho}_1) - \alpha = 0$ where $\hat{E}_\alpha(S|\mathbf{L}_i; \gamma_{0\alpha}, \hat{\rho}_1) = g^{-1}(\gamma_{0\alpha} + \hat{\rho}_1 \mathbf{L}_i)$. Let $\hat{P}_\alpha(S = s|\mathbf{L})$ denote (3.9) evaluated using $(\hat{\gamma}_{0\alpha}, \hat{\rho}_1)$, and let $\hat{E}(Y|S = s, \mathbf{L} = \mathbf{l})$ denote (3.11) evaluated using $\hat{\beta}$. Then the g-formula estimator of μ_α is

$$\hat{\mu}_\alpha = \int_{\mathbf{l}} \sum_{s \in \mathcal{S}} \hat{E}(Y|S = s, \mathbf{L} = \mathbf{l}) \hat{P}_\alpha(S = s|\mathbf{L} = \mathbf{l}) d\hat{F}_{\mathbf{L}}(\mathbf{l})$$

where $\hat{F}_{\mathbf{L}}$ denotes the empirical distribution function of $\mathbf{L}$, and the estimator for the effects of interest is $\hat{\delta}(\alpha, \alpha') = \hat{\mu}_\alpha - \hat{\mu}_{\alpha'}$. The estimators $\hat{\rho}, \hat{\beta}$, $\hat{\mu}_\alpha$, $\hat{\mu}_{\alpha'}$, and $\hat{\delta}(\alpha, \alpha')$ are solutions to unbiased estimating equations (see Appendix A). Therefore, it follows from standard large-

sample estimating equation theory that the estimators are consistent and asymptotically Normal [Stefanski and Boos, 2002]. The empirical sandwich estimators, which are consistent estimators of the asymptotic variances, can be used to construct Wald confidence intervals (CIs).

3.2.4 Population Strata

For the DRC malaria example, the methods described above may be applied directly if children are considered the population of interest and we ignore data collected from adults. Such an approach makes inference about counterfactual scenarios regarding the distribution of bed net usage in children and is agnostic to bed net use by others in the clusters. However, the DRC DHS includes bed net data for all individuals, which can be utilized to estimate the effects of bed net usage by all individuals on the risk of malaria in children. To do so, the approach above can simply be modified by changing the definition of S to be the proportion of all individuals in the cluster, not just children, who use bed nets. Alternatively, one may choose to model separately the proportion of children using bed nets (say S_1) and the proportion of other individuals in the cluster using bed nets (say S_2). In particular, the population mean estimand μ_α may be expressed

$$\int_{\mathbf{l}} \sum_{s_2 \in \mathcal{S}_2} \sum_{s_1 \in \mathcal{S}_1} E(Y|S_1 = s_1, S_2 = s_2, \mathbf{L} = \mathbf{l}) P_\alpha(S_1 = s_1|\mathbf{L} = \mathbf{l}, S_2 = s_2) P_\alpha(S_2 = s_2|\mathbf{L} = \mathbf{l}) dF_{\mathbf{L}}(\mathbf{l})$$

where policy α is defined such that individuals in strata 1 and 2 are treated with the same probability: $E_\alpha(S_1) = E_\alpha(S_2) = E_\alpha(S) = \alpha$. Inference proceeds analogous to Sections 3.2.2–3.2.3, but with separate parametric models for S_1 given $\mathbf{L}$, S_2 and for S_2 given $\mathbf{L}$; such an approach is taken in the DRC bed net analysis in Section 3.4.

3.2.5 G-Null Paradox

In the absence of interference, the parametric g-formula may give rise to the so-called g-null paradox. That is, certain parametric models are guaranteed to be misspecified under the null hypothesis of no treatment effect. As a result, the null hypothesis of no treatment effect will be

incorrectly rejected with high probability when the sample size is large [Robins, 1986, Robins and Wasserman, 1997, Taubman et al., 2009].

For the setting considered in this paper, the null hypothesis is that the proportion treated S has no effect on the outcome Y, or that $\mu_\alpha = \mu'_\alpha$ for any two policies α, α'. If S has no effect on Y, then $\beta_2 = 0$ and $E(Y|S = s, \mathbf{L}) = E(Y|\mathbf{L})$. Recall $E(Y|S = s, \mathbf{L}) = E_\alpha(Y|S = s, \mathbf{L})$. Therefore (3.6) reduces to

$$\mu_\alpha = \int_{\mathbf{l}} E(Y|\mathbf{L} = \mathbf{l}) \sum_{s \in \mathcal{S}} P_\alpha(S = s|\mathbf{L} = \mathbf{l}) d_\alpha F_{\mathbf{L}}(\mathbf{l}) = \int_{\mathbf{l}} E(Y|\mathbf{L} = \mathbf{l}) dF_{\mathbf{L}}(\mathbf{l}) \tag{3.12}$$

where the second equality follows because $\sum_{s \in \mathcal{S}} P_\alpha(S = s|\mathbf{L} = \mathbf{l}) = 1$. The right-hand side of (3.12) does not depend on α, so the g-null paradox does not occur here.

3.3 Empirical Evaluation

Simulation studies were conducted to evaluate the finite sample properties of the proposed g-formula estimator. Three separate simulations studies were conducted for the three target estimands: overall effect, spillover effect when treated, and spillover effect when not treated. For the overall effect simulation study, 1000 data sets each with $m = 125$ clusters were stochastically generated as follows:

(i) The number of individuals per cluster N_i was simulated such that $P(N_i = 8) = 0.4, P(N_i = 16) = 0.35,$ and $P(N_i = 20) = 0.25$.

(ii) Two cluster level covariates L_{1i} and L_{2i} were generated, where L_{1i} was Normal with mean 40 and standard deviation 10, and L_{2i} was such that $P(L_{2i} = 0) = 5/18, P(L_{2i} = 1) = 3/18, P(L_{2i} = 2) = 4/18, P(L_{2i} = 3) = 5/18, P(L_{2i} = 4) = 1/18$.

(iii) For each cluster, the number of treated individuals was drawn from a Binomial distribution with parameters N_i and $\pi_{si} = \text{expit}(\rho_0 + \rho_1 L_{1i} + \rho_2 L_{2i})$ where $\rho = (\text{logit}(0.6), -0.01,$

$-0.01)$. The proportion of individuals treated per cluster, S_i, was then calculated by dividing the number of treated individuals by N_i.

(iv) For each cluster, the outcome Y_i was set equal to X_i/N_i where X_i was Binomial with parameters N_i and $\pi_{yi} = \text{expit}(\beta_0+\beta_1 L_{1i}+\beta_2 S_i+\beta_3 L_{2i})$ where $\beta = (\text{logit}(0.6), -0.01, -0.8, -0.01)$.

Correctly specified models of Y given S and $\mathbf{L}$, and of S given $\mathbf{L}$ were fit by maximum likelihood. The asymptotic variance of the estimators was estimated using the empirical sandwich variance estimator, and Wald 95% CIs were calculated with these variance estimates.

The true values of estimands for policies $\alpha \in \{0.4, 0.5, 0.6\}$ were calculated analytically for the data generating process described above. In particular, the true values of $\gamma_{0\alpha}$ are the solutions to (3.10) where $\pi_{s\alpha} = \text{expit}(\gamma_{0\alpha} + \rho_1 L_1 + \rho_2 L_2)$. The counterfactual probabilities $P_\alpha(S = s|\mathbf{L})$ for $s \in \mathcal{S}$ can then be computed via (3.9) based on the true values of $\gamma_{0\alpha}, \rho_1, \rho_2$. Similarly, $E(Y|S = s, \mathbf{L})$ for $s \in \mathcal{S}$ may be evaluated using (3.11) and the true value of β. Finally, the true values of μ_α can be found using (3.6).

Results for the overall effect simulation study are given in the top third of Table 3.3. The average bias of the proposed g-formula estimators was negligible, and the CIs contained the true parameter values for approximately 95% of the simulated datasets. The average of the estimated sandwich standard errors was approximately equal to the empirical standard errors, with standard error ratios of approximately 1.

The simulation study described above was repeated for the spillover effect when treated, with the following modification. In step (iv), the cluster outcome Y_i was set equal to $X_i/(N_i S_i)$ where X_i was Binomial with parameters $N_i S_i$ and π_{yi}. If there were no treated individuals in a cluster, then Y_i was set to 0. Results for the g-formula estimator of the spillover effect when treated are presented in the middle part of Table 3.3. Results are similar to the overall effect, except the standard error for the g-formula estimator of the spillover effect when treated is larger because fewer individuals contribute to the outcome.

Finally, a third simulation study was conducted for the spillover effect when untreated. The simulation steps above were repeated, but with step (iv) modified such that the cluster outcome Y_i was set equal to $X_i/\{N_i(1-S_i)\}$ where X_i was Binomial with parameters $N_i(1-S_i)$ and π_{yi}, with Y_i set to 0 if $S_i = 1$. Results are given in the bottom section of Table 3.3.

Table 3.3: Summary of simulation study results as described in Section 3.3. Truth: true value of the estimand targeted by the estimator. Bias: average bias of the g-formula estimates over 1000 datasets. Cov%: empirical coverage of Wald 95% CIs. ASE: average of estimated sandwich standard errors. ESE: empirical standard error. SER: ASE/ESE.

Estimator	Truth	Bias	Cov%	ASE	ESE	SER
All Individuals						
$\hat{\mu}_{\alpha=0.4}$	0.418	0.000	94%	0.0147	0.0153	0.96
$\hat{\mu}_{\alpha=0.5}$	0.399	-0.000	94%	0.0119	0.0121	0.98
$\hat{\mu}_{\alpha=0.6}$	0.380	-0.000	94%	0.0145	0.0149	0.97
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.4)$	-0.038	-0.001	94%	0.0172	0.0180	0.95
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.5)$	-0.019	-0.000	94%	0.0084	0.0089	0.95
$\hat{\delta}(\alpha = 0.5, \alpha' = 0.4)$	-0.019	-0.000	94%	0.0087	0.0091	0.96
When Treated						
$\hat{\mu}_{\alpha=0.4}$	0.418	-0.002	95%	0.0243	0.0242	1.00
$\hat{\mu}_{\alpha=0.5}$	0.399	-0.001	96%	0.0174	0.0165	1.05
$\hat{\mu}_{\alpha=0.6}$	0.380	0.000	95%	0.0184	0.0178	1.03
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.4)$	-0.038	0.002	93%	0.0255	0.0267	0.96
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.5)$	-0.019	0.001	93%	0.0126	0.0132	0.96
$\hat{\delta}(\alpha = 0.5, \alpha' = 0.4)$	-0.019	0.001	93%	0.0129	0.0135	0.96
When Untreated						
$\hat{\mu}_{\alpha=0.4}$	0.418	-0.001	95%	0.0185	0.0188	0.99
$\hat{\mu}_{\alpha=0.5}$	0.399	-0.000	96%	0.0173	0.0167	1.03
$\hat{\mu}_{\alpha=0.6}$	0.380	0.000	96%	0.0235	0.0231	1.02
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.4)$	-0.038	0.001	94%	0.0248	0.0259	0.96
$\hat{\delta}(\alpha = 0.6, \alpha' = 0.5)$	-0.019	0.000	94%	0.0122	0.0127	0.96
$\hat{\delta}(\alpha = 0.5, \alpha' = 0.4)$	-0.019	0.000	94%	0.0126	0.0131	0.96

3.4 Analysis of Bed Net Use on Malaria in the Democratic Republic of the Congo

The methods described above were applied to the DRC DHS survey to draw inference about the effects of bed nets on malaria in children when varying the proportion of children in this age

range who use bed nets. As mentioned in Section 3.1, a single linkage agglomerative hierarchical cluster method [Everitt et al., 2011] was used to group households of individuals into clusters. The maximum distance between any two households in the same cluster was constrained to not exceed 10 kilometers. This distance was selected based on the maximum flight distance of an *Anopheles* mosquito [Janko et al., 2018]. The GPS coordinates used in the clustering algorithm were randomly displaced from the actual location to prevent participant identification. Rural clusters were displaced up to 5 kilometers, while urban clusters were displaced up to 2 kilometers [MPSMRM, MSP, and ICF International, 2014]. Using this clustering algorithm, there were 395 clusters with at least one child that were not missing spatial information and other covariates. Figure 3.3 displays the number of children per cluster, as well as the proportion of these children who used bed nets; on average, 55% of children utilized bed nets.

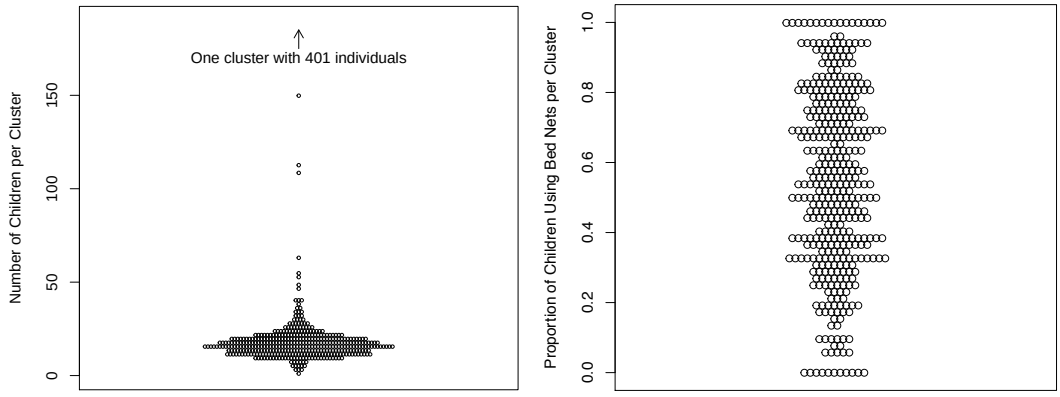

Figure 3.3: Malaria bed net study in the Democratic Republic of the Congo. Left panel: number of children with a measured malaria outcome per cluster. Right panel: proportion of children who used bed nets per cluster.

Because malaria was measured only in children, Y, S, and N for each cluster were defined based only on children with a measured outcome. Exchangeability was assumed conditional on the cluster-level proportion of women, as well as cluster-level averages of building materials (described below), urbanicity, altitude, age, temperature in the month of the survey, total precipitation in a 10 kilometer radius the month before the survey, and proportion of agricultural land cover within a 10 kilometer radius in 2013. The building material variable was defined similar to Levitz et al. [2018] where roof and wall materials were summed for each individual

within a cluster. Natural materials were worth 0 points, rudimentary materials 1 point, and finished materials 2 points. Hence, for each individual, the building material variable was an integer between 0 and 4. The link $g = \text{logit}$ was used for fitting both the treatment and outcome models.

Figure 3.4 displays g-formula estimates of the population mean estimands over a range of policies $\alpha \in [0.1, 0.9]$ in all individuals, when treated, and when untreated. The left panel of Figure 3.4 shows that the overall risk of malaria decreases as α increases, which is not surprising since bed nets are known to protect against malaria and bed net usage increases with α. The middle panel of Figure 3.4 demonstrates that the risk of malaria when treated also decreases as α increases, suggesting the presence of interference. In other words, treated individuals appear to benefit from others in their cluster also using bed nets. On the other hand, there appears to be little or no spillover effect when untreated (right panel Figure 3.4).

Estimates of the overall effects, spillover effects when treated, and spillover effects when untreated for different policies α compared to the current factual policy $\alpha' = 0.55$ are displayed in Figure 3.5. These estimates approximate the expected change in the number of cases of malaria due to increasing or decreasing bed net use relative to current utilization. For example, $\hat{\delta}(\alpha = 0.8, \alpha' = 0.55) = -0.056$ (95% CI $-0.076, -0.035$) indicates that if 80% of children in a cluster were to use bed nets, then we would expect 56 fewer cases of malaria per 1000 children on average. Similarly, for the spillover effect when treated, $\hat{\delta}(\alpha = 0.8, \alpha' = 0.55) = -0.077$ (95% CI $-0.10, -0.054$) indicating we would expect 77 fewer cases of malaria per 1000 treated children on average if 80% of children in a cluster were to use bed nets. On the other hand, the spillover effect when untreated for $\alpha = 0.8$ compared to $\alpha' = 0.55$ is -0.011 (95% CI $-0.045, 0.023$), suggesting no or modest benefit of increasing bed net use to non users.

For sake of comparison, the Barkley et al. [2020] IPW estimator was also applied to the DRC DHS data to estimate the bed net effects. However, the mixed effects model used to estimate the group propensity scores did not converge, hence it was not possible to compute the IPW estimates. Given that the DRC data includes several large clusters, it is not surprising

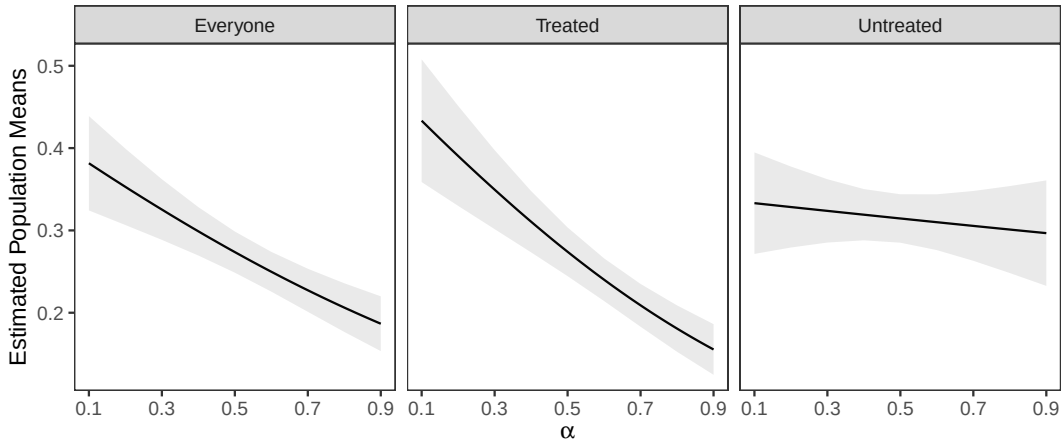

Figure 3.4: Estimates of the population mean estimands from the malaria bed net study. The proportion of treated children is denoted by policy α. The shaded regions indicate 95% confidence intervals.

issues were encountered when attempting to compute the IPW estimator. A possible workaround would be to exclude the large clusters [Chakladar et al., 2019], but this would inefficiently discard data and limit generalizability of the results.

The results above are based on clustering of households such that the maximum distance between any two households in the same cluster was 10 km. Sensitivity analyses were performed where clusters were instead defined based on maximum distances of 5 km and 2.5 km. There were 415 clusters in the 5 km analysis and 445 clusters in the 2.5 km analysis that were not missing spatial information and had at least one child. Population mean estimates were very similar between the 2.5 km, 5 km and 10 km analyses; see Figure 3.6.

To investigate the effect of changing the proportion of the entire population who use bed nets, the 10 kilometer clusters were also analyzed using the methods from Section 3.2.4. The estimated population means for the general population policy compared to the children-only policy are shown in Figure 3.7. Changes in the general population policy are associated with greater changes in the mean outcome in all individuals and when treated compared to the children-only policy. However, the largest difference in estimated population means between the general population policy and the children-only policy is only 0.05. For the spillover effect

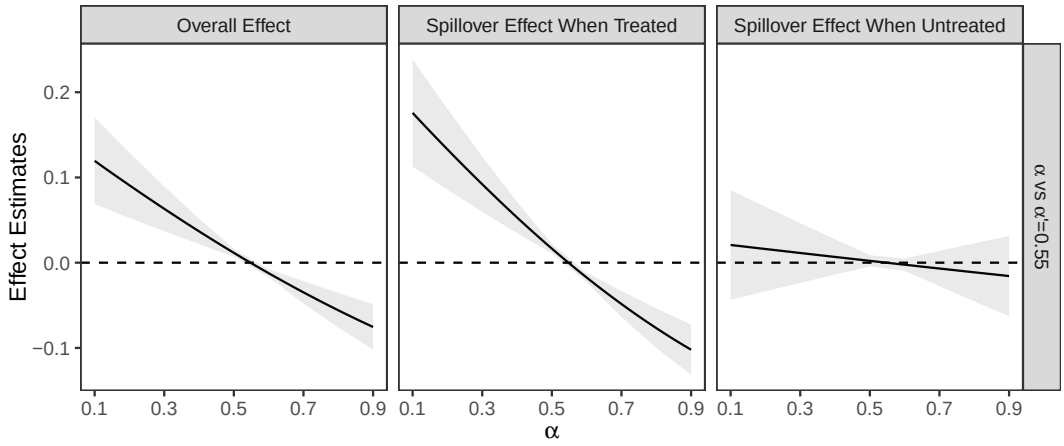

Figure 3.5: Estimated effects from the malaria bed net study. The proportion of treated children is denoted by policy α. Effects contrast α with $\alpha' = 0.55$, the current factual policy. The shaded regions indicate point-wise 95% confidence intervals.

when untreated, the estimates are approximately the same for both the children-only and general population policies.

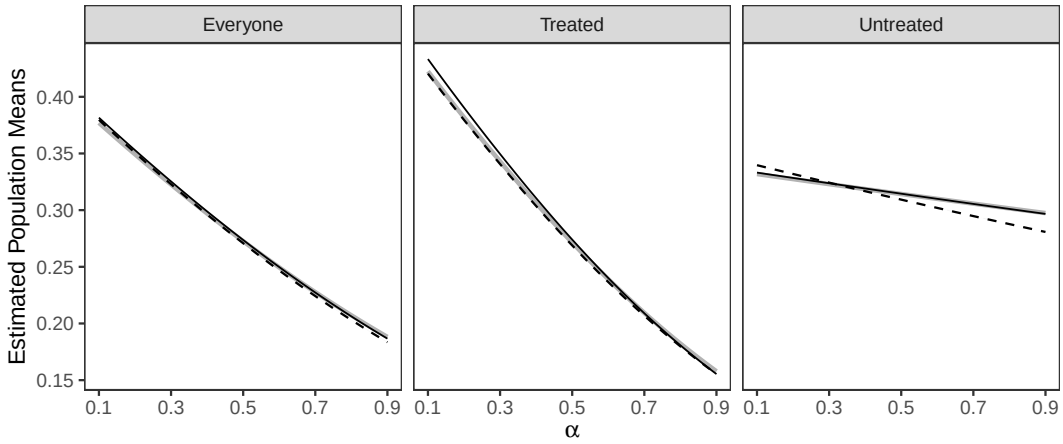

Figure 3.6: Estimates of the population mean estimands from the malaria bed net study. The proportion of treated children is denoted by policy α. Solid black lines represent 10 km, solid gray lines represent 5 km, and dashed lines represent 2.5 km clusters.

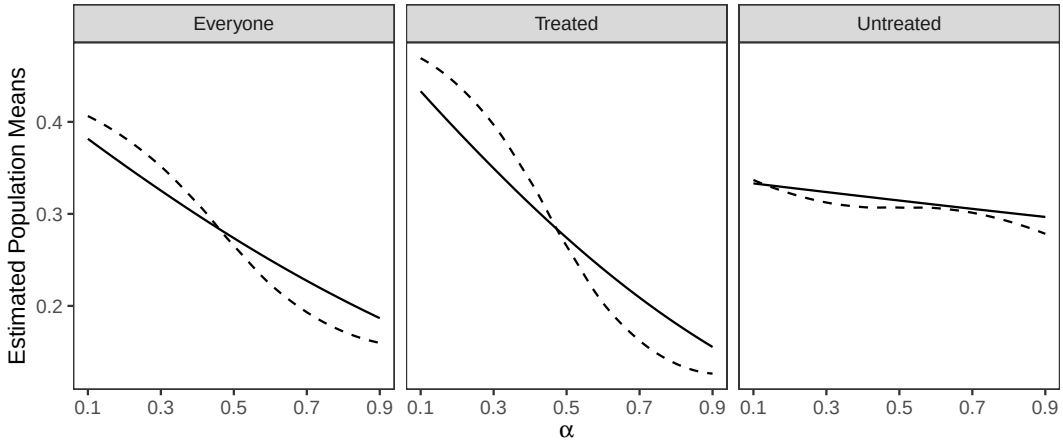

Figure 3.7: Estimates of the population mean estimands from the malaria bed net study for the children-only policy (solid lines) and general population policy (dashed lines).

3.5 Discussion

In the presence of partial interference, the proposed g-formula estimator is an alternative to existing IPW estimators, such as those proposed in Tchetgen Tchetgen and VanderWeele [2012]. The g-formula estimator can accommodate large clusters, unlike IPW estimators [Chakladar et al., 2019, Liu et al., 2019], and does not suffer from the g-null paradox that may occur in the absence of interference. Like the IPW estimators of Papadogeorgou et al. [2019] and Barkley et al. [2020], the proposed methods target counterfactual estimands which allow for within cluster dependence of treatment selection and thus may be more relevant to policy makers. Consistency of the proposed g-formula estimator requires that the parametric models be correctly specified; future research could explore relaxing these parametric assumptions, perhaps by using semiparametric or nonparametric models. While motivated by infectious disease prevention studies, the g-formula methods developed in this paper are applicable in other settings where partial interference may be present.

Supporting Information

Code and Data Availability R code to replicate the simulation study is available at `https://github.com/KilpatrickKW`. The DRC survey data is available upon request at `http://www.dhsprogram.com` and the corresponding spatial data is available at `http://spatialdata.dhsprogram.com`.

CHAPTER 4: G-ESTIMATION WITH PARTIAL INTERFERENCE

4.1 Introduction

In infectious disease research, one individual's treatment status may have an effect on another individual's outcome. This is generally known as "interference" between individuals [Cox, 1958]. A recent example of interference is with the spread of COVID-19 (coronavirus disease 2019). If one individual wears a mask, this can affect whether another individual contracts COVID-19. If individuals are able to be grouped together into clusters, a reasonable assumption may be that the individuals within a particular cluster can interfere with each other, but individuals between clusters cannot interfere with one another. This is known as "partial interference" [Sobel, 2006]. Methods under the partial interference setting have been proposed for causal estimands of treatment effects; e.g., see Tchetgen Tchetgen and VanderWeele [2012], Papadogeorgou et al. [2019], Barkley et al. [2020].

Common methods under the observational setting include inverse probability weighting (IPW) and the parametric g-formula. For example, Tchetgen Tchetgen and VanderWeele [2012], Papadogeorgou et al. [2019], Barkley et al. [2020] provide consistent estimates in the IPW setting. However, the estimator can be unstable when propensity scores are near zero, making it difficult to handle large clusters [Saul and Hudgens, 2017, Chakladar et al., 2019, Liu et al., 2019]. The parametric g-formula provides an alternative method of estimating causal effects that combines the g-computation algorithm of Robins [1986] with parametric outcome regression [Hernán and Robins, 2006]. However, the parametric g-formula requires specifying the outcome model and is not valid if this model is misspecified.

An alternative to IPW and the g-formula is g-estimation. This method was originally proposed for structural nested models [Robins, 1989, Robins et al., 1992]. G-estimation can

perform better than IPW when the positivity assumption may be violated and does not suffer from the g-null paradox [Vansteelandt and Joffe, 2014]. There are doubly robust g-estimators that provide consistent estimators as long as at least one model is correctly specified. A drawback of g-estimation is that it is not commonly used because of the perception that there is a lack of off-the-shelf software. Dukes and Vansteelandt [2018] have provided a method using a gamma generalized linear model to obtain g-estimators of causal mean ratios using generalized estimating equations. However, this does not allow for partial interference. This paper extends existing g-estimation methods for observational studies to the setting where partial interference may be present and allows for more flexible forms of the treatment variable.

The motivation behind the methods proposed in this paper was the 2013-14 Democratic Republic of the Congo (DRC) Demographic and Health Survey (DHS), with the question of interest focusing on the effect of bed net use on malaria [MPSMRM, MSP, and ICF International, 2014]. This was a nationally representative survey to gather health information, including data about mosquito net usage and malaria. Data were collected at the household level. Only children between 6 to 59 months, referred to as "children" for brevity, were tested for malaria, but covariates and bed net use data were collected for all individuals. In the presented analysis, a single linkage agglomerative cluster method based on household global positioning system (GPS) coordinates was used to group individuals into clusters, resulting in a total of 395 clusters with at least one child and measured spatial information and other covariates. After this algorithm is performed, there are approximately 87,500 individuals with about 7,500 children with non-missing malaria outcomes (about 96% of children in this age range) in the survey. Community-level bed net usage has previously been shown to be significantly associated with malarial protection in children younger than five years old [Levitz et al., 2018]. In the DRC data, the proportion of malaria in children who do not use bed nets is inversely associated with the proportion of bed net usage in the cluster for clusters with at least one child who did not use a bed net (Spearman correlation of $r_s = -0.16, p = 0.002$), suggesting that there may be interference within clusters. Figure 4.8 displays this inverse relationship. The inferential goal is

to assess the population-level effects of bed use on malaria when varying the proportion of bed net users.

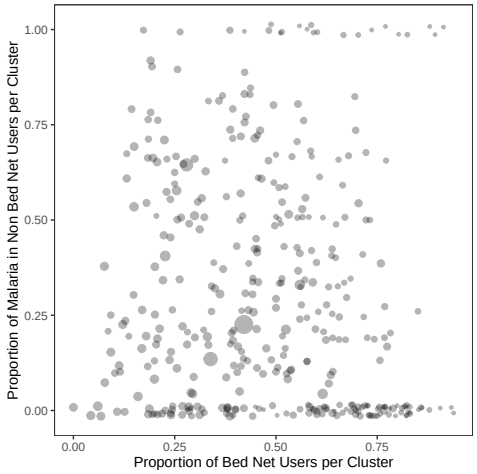

Figure 4.8: Malaria Bed Net Study in the Democratic Republic of the Congo. This figure displays bed net usage of the entire cluster vs prevalence of malaria in children who do not use bed nets. Points have been vertically jittered by 0.015. Circle size corresponds to the number of children who do not use bed nets in the cluster, with larger circle sizes indicating larger numbers.

The outline of the remainder of this paper is as follows. In Section 4.2, notation, estimands, estimators, and effects of interest are described. Simulation results for the proposed estimators in finite samples are presented in Section 4.3. In Section 4.4, the proposed estimators are applied to the DRC data to investigate the effect of bed net use on malaria. A discussion is presented in Section 4.5.

4.2 Methods

4.2.1 Notation and Assumptions

Let there be N_i individuals in cluster i for $i = 1, \ldots, m$. Some individuals within each cluster may receive treatment, such as a bed net. Denote the binary treatment indicator for individual j in cluster i by A_{ij}, and let $\mathbf{A}_i = (A_{i1}, A_{i2}, \ldots, A_{iN_i})$ represent the vector of treatment indicators for all individuals in the cluster. Denote the proportion of treated individuals in cluster i by $S_i = (\sum_{j=1}^{N_i} A_{ij})/N_i$. Represent the outcome at the cluster level by Y_i. Depending

on the outcome of interest, Y_i can be defined differently. In the DRC analysis, Y_i may be defined as the proportion of children with malaria in a cluster. Let $\mathbf{L}_i$ represent a vector of cluster-level covariates, including N_i. Denote the observed random variables for cluster i by $O_i = \{\mathbf{L}_i, S_i, Y_i\}$, and assume there are m observed independent and identically distributed copies $O_1, \ldots, O_m$. For ease of notation, the subscript i is omitted when not needed.

Assume that there is no interference between clusters, but there may be interference between individuals within the same cluster, i.e., partial interference. For example, one individual's bed net usage may affect if another individual in the same cluster gets malaria in the DRC analysis. Let $\mathcal{A}(N_i)$ denote the set of all vectors of N_i binary entries for a cluster of size N_i, where a vector of potential treatment statuses is $\mathbf{a}_i = (a_{i1}, a_{i2}, \ldots, a_{iN_i}) \in \mathcal{A}(N_i)$. Let $Y_i^{\mathbf{a}}$ represent the potential outcome if, possibly counter to fact, cluster i had been exposed to $\mathbf{a}_i \in \mathcal{A}(N_i)$. When $\mathbf{A}_i = \mathbf{a}_i$, $Y_i^{\mathbf{a}} = Y_i$. Cluster i has 2^{N_i} potential outcomes.

Assume that only the proportion of treated individuals is important, not the particular individuals themselves. This assumption is also known as stratified interference [Hudgens and Halloran, 2008]. For any two vectors $\mathbf{a}_i, \mathbf{a}_i' \in \mathcal{A}(N_i)$ where $\sum_{j=1}^{N_i} a_{ij} = \sum_{j=1}^{N_i} a_{ij}'$, $Y^{\mathbf{a}} = Y^{\mathbf{a}'}$. Let Y_i^s represent the potential outcome for any $\mathbf{a}$ where $(\sum_{j=1}^{N_i} a_{ij})/N_i = s$ for cluster i. Assume exchangeability conditional on $\mathbf{L}$ at the cluster level, i.e.,

$$Y^s \perp S | \mathbf{L} \text{ for } s \in \{0, 1/N, 2/N, \ldots 1\}. \tag{4.13}$$

This assumption reduces the number of potential outcomes for cluster i to $N_i + 1$.

4.2.2 Estimands and Effects of Interest

Ratios of expected outcomes when the proportion of treated individuals is changed can provide information about the population-level effects on interventions, such as bed net use in the DRC data. Treatment effects in the absence of interference are often defined as contrasts in expected outcomes when all individuals receive treatment versus where no individuals receive

treatment. This paper considers a range of contrasts where the proportion of treated individuals, S, varies.

Assuming exchangeability conditional on $\mathbf{L}$ as given in (4.13), consider the following structural model

$$\frac{E[Y^s|\mathbf{L}]}{E[Y^0|\mathbf{L}]} = \exp(\psi f(s)) \tag{4.14}$$

for $s \in \{0, 1/N, 2/N, \ldots, 1\}$ where ψ is a row vector of parameters of interest and f is a some (column) vector-valued function of s. For example, $f(s) = (s, s^2, s^3)^\top$. The special case $f(s) = s$ is the model considered by Dukes and Vansteelandt [2018]. In the DRC analysis, the causal contrast of interest for the case where $f(s) = s$, $\exp(\psi s)$, is the ratio of the expected proportion of individuals with malaria when proportion s of individuals are treated compared to the scenario when no individuals are treated.

For all effects, the estimand of the effect can be written as (4.14) with different definitions of Y. The overall effect compares the average disease outcome among all individuals in a cluster when s individuals are treated versus when no individuals are treated. This effect may be the most relevant to public health policy because it is likely that there will be a mixture of individuals who would and who would not choose to receive treatment in a population of interest. For inference about the overall effect, the proportion of outcomes in all individuals in a cluster is represented by Y_i. In the DRC analysis, Y_i is the proportion of all children with malaria.

Spillover effects can be defined among only untreated individuals in a cluster and among only treated individuals in a cluster. The effect of treatment, if one exists, that untreated individuals may experience from being surrounded by other treated individuals is quantified by the spillover effect when untreated. Let Y_i be the proportion of outcomes in untreated individuals in cluster i for the spillover effect when untreated, and let $Y_i = 0$ if there are no untreated individuals in the cluster. For the DRC analysis, the proportion of children who do not use bed nets with malaria will be Y_i. The spillover effect when treated can be defined analogously. In the DRC analysis, the proportion of children who use bed nets with malaria will be Y_i. In addition,

for the spillover effect when treated, $s^* = 1 - s$ is used in place of s. This effect compares the proportion of individuals with malaria when the proportion of treated individuals is s^* to that when all individuals are treated.

4.2.3 Estimators

Suppose we fit by maximum likelihood a correctly specified finite dimensional model for $S|\mathbf{L}$ with parameter vector ρ. Let $e(\mathbf{L};\rho)$ denote $E[S|\mathbf{L}]$ with parameters ρ. In this paper, S is assumed to follow a binomial distribution with parameters N and $e(\mathbf{L};\rho) = \text{expit}(\rho_0 + \rho_1\mathbf{L})$. Denote the maximum likelihood estimate of ρ as $\hat{\rho}$. Consider the model

$$E[Y|\mathbf{L}, S] = \exp(\omega(\mathbf{L}) + \psi f(S)) \tag{4.15}$$

where $\omega(\mathbf{L})$ is the unknown effect of $\mathbf{L}$ in the true outcome model. Extending the method in Dukes and Vansteelandt [2018] to handle a general function $f(S)$ in the case of partial interference, a consistent estimator of ψ can be obtained by fitting a gamma generalized linear model with a log link for the outcome Y

$$E[Y|S, \mathbf{L}] = \exp(\beta_0 + \beta_1 E\{f(S)|\mathbf{L};\hat{\rho}\} + \psi f(S)). \tag{4.16}$$

The estimator $\hat{\psi}_{SR}$ is the solution to

$$\sum_{i=1}^{n} d(\mathbf{L}_i;\hat{\rho},\hat{\beta}_0,\hat{\beta}_1)[f(S_i) - E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\}][Y_i \exp(-\psi f(S_i)) - g(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1)] = 0 \tag{4.17}$$

where $d(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1) = \exp(-\hat{\beta}_0 - \hat{\beta}_1 E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\})$, $g(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1) = \exp(\hat{\beta}_0 + \hat{\beta}_1 E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\})$, and $\hat{\beta} = (\hat{\beta}_0,\hat{\beta}_1)$ are the maximum likelihood estimates for the model in (4.16). The estimate of ψ from fitting the gamma generalized linear model in (4.16) is equivalent to finding the value of ψ that solves (4.17). Dukes and Vansteelandt [2018] show this equivalence in the appendix of their paper for the case when $f(S) = S$. The more general

case considered here is shown in Appendix B. If the model for $S|\mathbf{L}$ is correctly specified and model (4.15) holds, then $\hat{\psi}_{SR}$ is a consistent estimator for ψ. Following Dukes and Vansteelandt [2018], this estimator will be referred to hereafter as the "singly robust" estimator because it requires both the $S|\mathbf{L}$ model and model (4.15) to be correct. If either $S|\mathbf{L}$ or (4.15) do not hold, then (4.17) is not necessarily unbiased and therefore $\hat{\psi}_{SR}$ is not consistent.

A doubly robust estimator can be constructed as well by fitting a gamma generalized linear model with a log link for the outcome Y and adjusting for all covariates $\mathbf{L}$ as follows

$$E[Y|S,\mathbf{L}] = \exp(\beta_0 + \beta_1 E\{f(S)|\mathbf{L};\hat{\rho}\} + \beta_L\mathbf{L} + \psi f(S)). \tag{4.18}$$

The estimate of ψ from fitting the gamma generalized linear model in (4.18) is equivalent to finding the value of $\hat{\psi}_{DR}$ that solves

$$\sum_{i=1}^{n} \widetilde{d}(\mathbf{L}_i;\hat{\rho},\hat{\beta}_0,\hat{\beta}_1)[f(S_i) - E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\}][Y_i\exp(-\psi f(S_i)) - \widetilde{g}(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1)] = 0 \tag{4.19}$$

where $\widetilde{d}(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1) = \exp(-\hat{\beta}_0 - \hat{\beta}_1 E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\} - \hat{\beta}_L\mathbf{L}_i)$, $\widetilde{g}(\mathbf{L};\hat{\rho},\hat{\beta}_0,\hat{\beta}_1) = \exp(\hat{\beta}_0 + \hat{\beta}_1 E\{f(S_i)|\mathbf{L}_i;\hat{\rho}\} + \hat{\beta}_L\mathbf{L}_i)$, and $\hat{\beta} = (\hat{\beta}_0,\hat{\beta}_1,\hat{\beta}_L)$ are the maximum likelihood estimates for the model in (4.18). As long as either the outcome model for the untreated $E[Y|\mathbf{L},S=0] = \exp(\beta_0 + \beta_L\mathbf{L})$ or the treatment model $S|\mathbf{L}$ is correctly specified, but not necessarily both, then $\hat{\psi}_{DR}$ is consistent for ψ. This estimator is therefore doubly robust. Finally, the estimators for the effects of interest can be defined as $\exp(\hat{\psi}f(s))$ for $s \in \{0, 1/N, 2/N, \ldots, 1\}$ using either $\hat{\psi}_{SR}$ or $\hat{\psi}_{DR}$. An exponential model can be fit instead of a gamma generalized linear model for the outcome as the estimates will be the same in either case. In Appendix B, these estimators are shown to be consistent and asymptotically Normal using standard large-sample estimating equation theory as described by [Stefanski and Boos, 2002]. The empirical sandwich estimators, which are consistent estimators of the asymptotic variances, can be used to construct Wald confidence intervals (CIs). These standard error estimates account for estimating $e(\mathbf{L})$, so the variance estimator is not conservative.

4.3 Simulations

In order to evaluate finite sample properties of the proposed g-estimator, simulation studies were performed for the special case when $f(s) = s$. Two separate studies were done for two of the target estimands: the overall effect and the spillover effect when untreated. Since the spillover effect when treated is essentially the same process as the spillover effect when untreated, with the exception of recoding the treatment variable, it was omitted for the simulation studies. For the overall effect simulation study, 1000 datasets of $m = 350$ clusters were stochastically generated as follows:

(i) The number of individuals per cluster N_i was simulated such that $P(N_i = 40) = 0.4, P(N_i = 50) = 0.35,$ and $P(N_i = 60) = 0.25$.

(ii) Two cluster level covariates L_{1i} and L_{2i} were generated with L_{1i} following a Normal distribution with mean 40 and standard deviation 10, and L_{2i} such that $P(L_{2i} = 0) = 5/18, P(L_{2i} = 1) = 3/18, P(L_{2i} = 2) = 4/18, P(L_{2i} = 3) = 5/18, P(L_{2i} = 4) = 1/18$.

(iii) For each cluster, the number of treated individuals was drawn from a Binomial distribution with parameters N_i and $e(\mathbf{L}_i; \rho) = \text{expit}(\rho_0 + \rho_1 L_{1i} + \rho_2 L_{2i})$ where $(\rho_0, \rho_1, \rho_2) = (\text{logit}(0.55), -0.01, -0.01)$. For each cluster, the proportion of individuals treated per cluster, S_i, was calculated by dividing the number of treated individuals by N_i.

(iv) For each cluster, the outcome Y_i was set equal to X_i/N_i where X_i was Poisson with parameter $\lambda_{yi} = \exp(\beta_0 + \psi S_i + \beta_1 L_{1i} + \beta_2 L_{2i})$ where $(\beta_0, \psi, \beta_1, \beta_2) = (\log(0.6N_i), -0.6, -0.01, -0.01)$.

This process was repeated for the spillover effect when untreated. For this effect, Y_i was set equal to $X_i/\{N_i(1 - S_i)\}$ where X_i was Poisson with parameter λ_{yi} with $\beta_1 = \log(0.6\{N_i(1 - S_i)\})$. If there were no untreated individuals, then $Y_i = 0$.

Binomial regression models for S were fit with main effects for L_1, L_2 to calculate fitted values $e(\mathbf{L}; \hat{\rho})$. Gamma regression models with a log-link for Y were fit with main effects for $S, e(\mathbf{L}; \hat{\rho})$. In the case of the doubly robust estimator, these models had main effects for $S, e(\mathbf{L}; \hat{\rho}), L_1$. As noted in Dukes and Vansteelandt [2018], including both $e(\mathbf{L}; \hat{\rho})$ and all covariates $\mathbf{L}$ can sometimes result in failed convergence or unstable estimates due to collinearity. This was the case here when including both L_1, L_2, so just L_1 was used instead. Note that these models were correctly specified. The asymptotic variance of the estimators was calculated using the empirical sandwich variance estimator, which is described in Appendix B. Wald-type 95% CIs were calculated with these variance estimates.

In the case where the model for S is misspecified, the true treatment model uses $e(\mathbf{L}; \rho) = \text{probit}^{-1}(-0.002L_1^2 + 0.5\sqrt{L_2})$. A binomial regression model for S is then fit with main effects for L_1, L_2 as before. In the case where the model for Y is misspecified, the true outcome model uses $\lambda_y = \exp(\log(0.3K) + \psi S - 0.5I(55 > L_1 > 35) + 0.005I(L_2 < 3))$ where $K = N$ for the overall effect or $\{N_i(1 - S_i)\}$ for the spillover effect when untreated. Gamma regression models are then fit as mentioned above.

The estimates for each dataset were compared to the true value of ψ with a summary of these results in Table 4.4. For the singly robust estimator, the average bias is negligible when the $S|\mathbf{L}$ model is correctly specified, and the Wald-type 95% CIs contained the true parameter values in approximately 95% of the simulated datasets. When the $S|\mathbf{L}$ model is not correctly specified, the estimator is biased and coverage is below 90%, as expected. For the doubly robust estimator, the average bias of the estimators was negligible when both models are correctly specified, when the $E[Y|\mathbf{L}, S = 0]$ model is correctly specified (but the $S|\mathbf{L}$ model is incorrect), and when the treatment model $S|\mathbf{L}$ is correctly specified (but $E[Y|\mathbf{L}, S = 0]$ is incorrect). For these scenarios, the Wald-type 95% CIs contained the true parameter values in approximately 95% of the simulated datasets. When both models are misspecified, the estimators are biased with poor coverage. The average of the estimated sandwich standard errors was approximately equal to the empirical standard errors, with standard error ratios of approximately 1. These

simulations demonstrate that the estimators performed well. Additional simulations for the overall effect for the case when $f(s) = s + s^2$ can be seen in Appendix B.

Table 4.4: Summary of simulation study results as described in Section 4.3. Truth: true value of ψ targeted by the estimator. Bias: average bias of the g-estimates over 1000 datasets. Cov%: empirical coverage of Wald 95% CIs. ASE: average of estimated sandwich standard errors. ESE: empirical standard error. SER: ASE/ESE. Group: group of interest where All denotes all individuals, Untreated denotes untreated individuals.

Scenario	Group	Bias	Relative Bias	Cov%	ASE	ESE	SER
Singly robust							
S model correct	All	0.003	-0.5%	96%	0.20	0.19	1.03
	Untreated	-0.002	0.3%	94%	0.28	0.29	0.95
S model incorrect	All	0.41	-68%	76%	0.34	0.36	0.96
	Untreated	0.42	-70%	80%	0.41	0.43	0.95
Doubly Robust							
Both correct	All	0.003	-0.5%	96%	0.20	0.19	1.05
	Untreated	-0.003	0.5%	94%	0.28	0.29	0.96
S model incorrect	All	-0.027	4.5%	94%	0.35	0.36	0.97
	Untreated	-0.017	2.8%	93%	0.42	0.44	0.96
Y model incorrect	All	-0.003	0.5%	97%	0.35	0.31	1.15
	Untreated	-0.030	5%	95%	0.44	0.42	1.07
Both incorrect	All	1.5	-250%	17%	0.50	0.53	0.94
	Untreated	1.5	-250%	28%	0.58	0.59	0.97

4.4 Analysis of Bed Net Use on Malaria in the Democratic Republic of the Congo

To measure the effects of bed nets on malaria in children when varying the proportion of children who use bed nets in the DRC, the methods described above can be applied. Individuals within 10 kilometers are grouped into larger clusters using a single linkage agglomerative cluster method, as mentioned in Section 4.1. The maximum distance between any two households in the same cluster was constrained to not exceed 10 kilometers The maximum flight distance of an *Anopheles* mosquito is 10 kilometers, which was the basis for this choice of distance [Janko et al., 2018]. In order to prevent identification of participants, the GPS coordinates in the data that were used in this algorithm are randomly displaced from the real location. Rural clusters

were displaced up to 5 kilometers, while urban clusters were displaced up to 2 kilometers [MPSMRM, MSP, and ICF International, 2014]. There were 395 clusters with at least one child and were not missing spatial information and other covariates after this clustering algorithm. Partial interference is assumed at the cluster level. Figure 4.9 displays the number of children per cluster, as well as the proportion of these children who use bed nets.

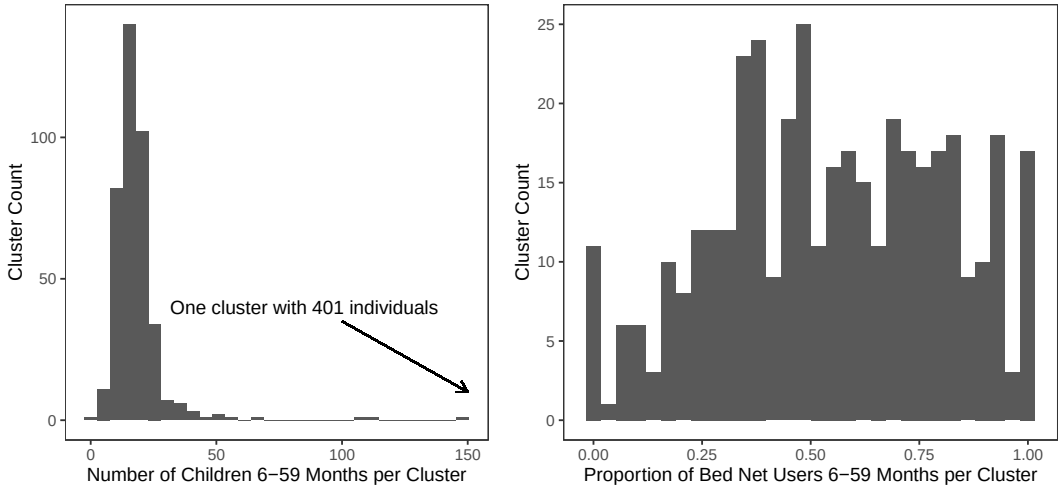

Figure 4.9: Malaria Bed Net Study in the Democratic Republic of the Congo. Left panel: number of children with a measured malaria outcome per cluster. Right panel: proportion of children who use bed nets per cluster.

For each cluster, Y, S, and N were defined based only on children with a measured outcome because malaria was only measured in children. Exchangeability was assumed conditional on the cluster-level proportion of women, as well as cluster-level averages of building material, urbanicity, altitude, age, temperature in the month of the survey, total precipitation in a 10 kilometer radius the month before the survey, and proportion of agricultural land cover within a 10 kilometer radius in 2013. The building material variable was defined as the sum of roof and wall materials for each individual within a cluster, similar to Levitz et al. [2018]. Natural materials were worth 0 points, rudimentary materials 1 point, and finished materials 2 points, so the building material variable is an integer between 0 and 4 points.

Causal mean ratios conditional on $\mathbf{L}$ can be constructed using $\hat{\psi}_{SR}$ and $\hat{\psi}_{DR}$ for the overall effect, spillover effect when treated, and spillover effect when untreated. While the methods

presented in Section 4.2 involve a comparison to the case when no children are treated (or when all children are treated in the case of the spillover effect when treated), this may not be of interest to policy makers. Instead, the analysis presented here compares the estimated mean proportion of children in each group of interest with malaria when a given proportion of children are treated versus the case in the actual data where 55% of children are treated on average. First, the choice of $f(S)$ was investigated to see if this affects the results in the malaria dataset. The estimated causal mean ratios $\exp(\hat{\psi}(f(S) - f(0.55)))$ for different functions $f(S)$ can be seen in Figure 4.10 for $f(S) = S$, $S + S^2, S + S^2 + S^3$, and $I(0.2 < S \leq 0.4) + I(0.4 < S \leq 0.6) + I(0.6 < S \leq 0.8) + I(0.8 < S \leq 1)$. For example, the estimated causal mean ratio for $f(S) = S + S^2$ is $\exp(\hat{\psi}_0(S - 0.55) + \hat{\psi}_1(S^2 - 0.55^2))$. The functional form of S can change the behavior of the estimated causal mean ratio. For the flexible models, the estimated causal mean ratio increases and then decreases, while for the simple case $f(S) = S$, this ratio decreases. In comparison with the piecewise constant model, the quadratic and cubic models appear to fit better than linear model.

Figure 4.11 displays the estimated causal mean ratios when $f(S) = S + S^2$. For the overall effect, this ratio compares the estimated mean proportion of all children with malaria when a given proportion of children are treated versus when 55% of children are treated. For the spillover effect when treated, this ratio compares the estimated mean proportion of treated children with malaria when a given proportion of children are treated versus when 55% of children are treated. The spillover effect when untreated is defined similarly with untreated children as the population and the comparison of interest is to the case when 55% of children are treated. The estimated ratios increase and then decrease as the proportion treated increases. For comparisons where the proportion of children treated is greater than 55%, all confidence intervals in Figure 4.11 exclude 1, indicating that if more than 55% of children in this population used bed nets, there is a significant protective effect of bed net use in all children, in treated children, and in untreated children.

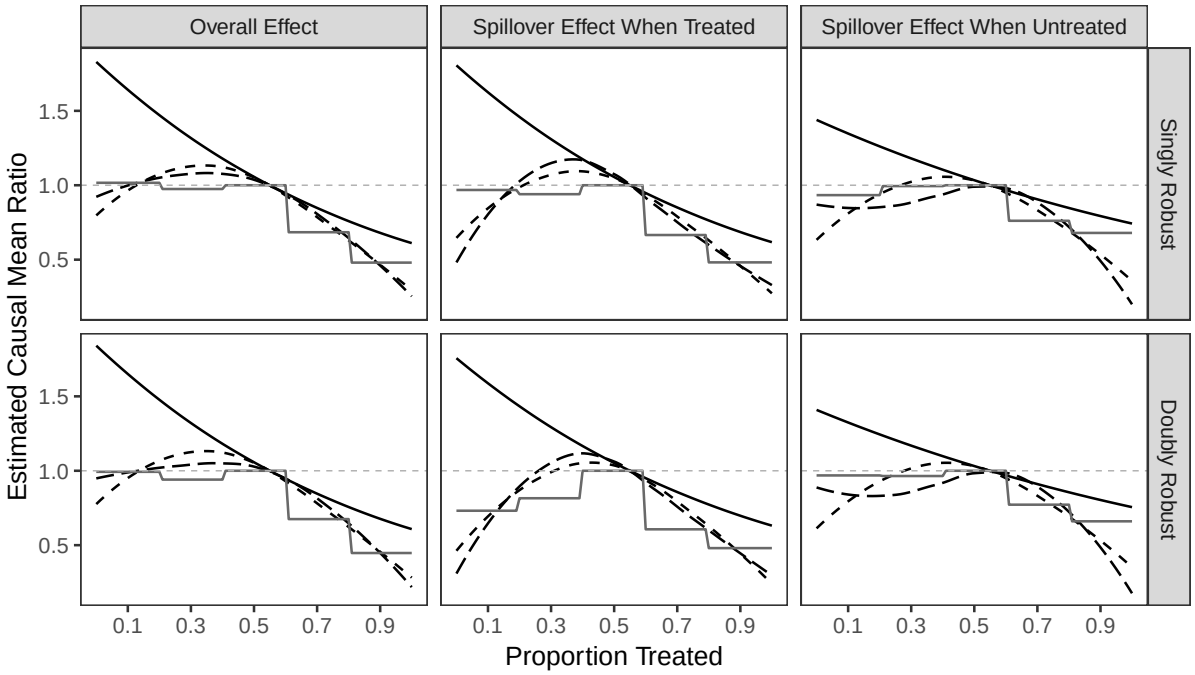

Figure 4.10: Estimated Causal Mean Ratios Using Different Functions of Treatment from the Malaria Bed Net Study. The plotted lines are the estimated causal mean ratios $\exp(\hat{\psi}(f(S) - f(0.55)))$ for different functions $f(S)$. Solid black lines represent $f(S) = S$, dashed lines represent $f(S) = S + S^2$, long dashed lines represent $f(S) = S + S^2 + S^3$, and solid dark gray lines represent $f(S) = I(0.2 < S \leq 0.4) + I(0.4 < S \leq 0.6) + I(0.6 < S \leq 0.8) + I(0.8 < S \leq 1)$. The overall effect, spillover effect when untreated, and spillover effect when treated compare the expected proportion of malaria cases in all children, untreated children, and treated children, respectively, when the proportion treated is a given value compared to the expected proportion of malaria cases when 55% of children are treated.

Sensitivity analyses were performed to investigate if the choice of 10 kilometers for the single linkage agglomerative clustering algorithm affects the results in the malaria dataset. The clustering algorithm was performed using 5 kilometers and 2.5 kilometers as well. There were 415 clusters for the 5 km analysis and 445 clusters for the 2.5 km analysis that were not missing spatial information and have at least one child. The estimated causal mean ratios where $f(S) = S + S^2$ can be seen in Figure 4.12 and are very similar to those when using 10 km, with a maximum absolute difference of 0.12 for the singly robust results and 0.11 for the doubly robust results. The conclusions are the same for all choices of distance.

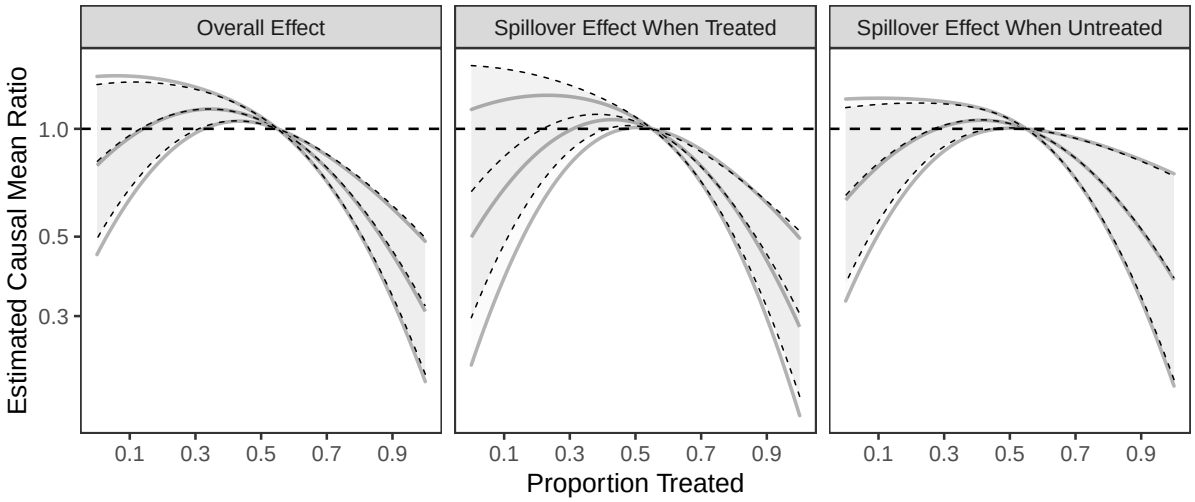

Figure 4.11: Estimated Causal Mean Ratios from the Malaria Bed Net Study. Shaded regions indicate 95% CIs. Dashed black lines represent the singly robust estimator, and solid gray lines represent the doubly robust estimator. The overall effect, spillover effect when treated, and spillover effect when untreated compare the expected proportion of malaria cases in all children, treated children, and untreated children, respectively, when the proportion treated is a given value compared to the expected proportion of malaria cases when 55% of children are treated.

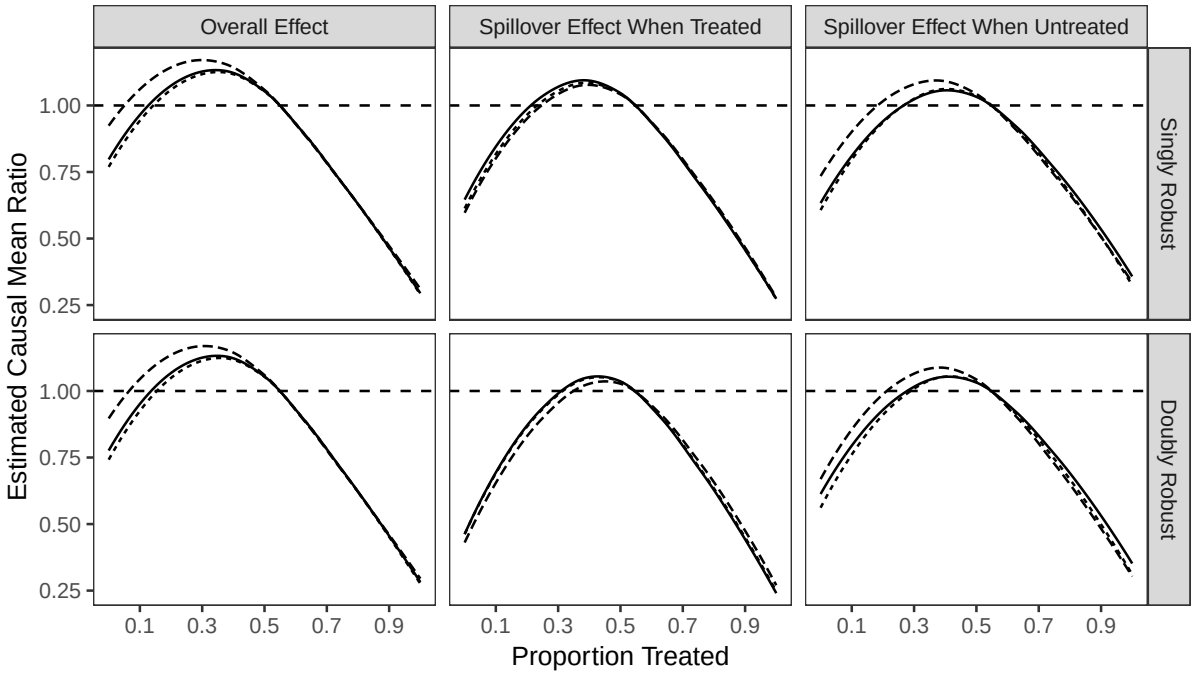

Figure 4.12: Sensitivity Analysis for Estimated Causal Mean Ratios from the Malaria Bed Net Study. Solid lines represent 10 km, dotted lines represent 5 km, and dashed lines represent 2.5 km. The overall effect, spillover effect when treated, and spillover effect when untreated compare the expected proportion of malaria cases in all children, treated children, and untreated children, respectively, when the proportion treated is a given value compared to the expected proportion of malaria cases when 55% of children are treated.

4.5 Discussion

G-estimation is an alternative to IPW and the parametric g-formula. Unlike IPW, the proposed estimator can handle large cluster sizes [Saul and Hudgens, 2017, Chakladar et al., 2019, Liu et al., 2019]. The proposed estimator is also not subject to the g-null paradox, unlike the parametric g-formula. Both IPW and the parametric g-formula rely upon parametric models. G-estimation is a semi-parametric approach and is more flexible than IPW or the parametric g-formula. Both singly and doubly robust estimators are provided here with a general function of the treatment variable that allows for more flexible models. In order for the estimators to be consistent, the appropriate parametric models must be correctly specified; future research could explore relaxing the parametric assumptions further.

The causal effects of treatment mentioned in this paper may be of interest to policy makers. Populations of interest may have a mixture of those who would and would not choose to be treated, so public health officials could investigate treatment effects in different parts of these populations. Recently, IPW and g-formula methods for the partial interference setting in observational studies have been proposed [Barkley et al., 2020, Kilpatrick and Hudgens, 2021]. Both methods consider counterfactual scenarios that change the distribution of treatment according to different policies. However, this paper does not consider this type of stochastic intervention, so some effect estimates may not make sense depending on cluster size, i.e., the effect estimates for a proportion treated of 50% may not make sense for an odd sized cluster. However, the causal mean ratio curves presented above can still help guide policy makers. The methods presented in this paper are focused on the infectious disease setting, but the methods can also be applied to other settings with partial interference.

Code and Data Availability

R code to replicate the more complex simulation study in Appendix B is available at `https://github.com/KilpatrickKW`. The DRC survey data is available upon request

at http://www.dhsprogram.com and the corresponding spatial data is available at http://spatialdata.dhsprogram.com.

CHAPTER 5: CONCLUSION

Causal inference can be a powerful tool to evaluate treatment effects. In a real world setting, it is likely that some individuals can interfere with each other, i.e., one individual's treatment can affect another individual's outcome. The proposed methods in this dissertation assume partial interference where individuals can be placed into groups, and individuals within the same group can interfere with each other but not with individuals in other groups. By accounting for the possible presence of interference, different treatment effects can be calculated. Since the real world population will likely be made up of individuals who will and will not choose to receive treatment, calculating different treatment effects in these different populations can be useful for public health policies. In this dissertation, methods are proposed to go beyond the usual causal effect that compares the average outcome when all individuals are treated versus when no individuals are treated.

The first setting considered in this dissertation was cluster-randomized trials. Estimands for the overall, indirect, and total effects of vaccination are defined. This chapter can be useful for investigators when designing and analyzing a cluster-randomized trials, especially since there is currently a movement in clinical trials literature to carefully define estimands of interest. A Vi polysaccharide (typhoid) vaccine trial was the motivating example for this chapter [Sur et al., 2009b]. Individuals within clusters chose whether or not to participate in this trial. The number of cases of typhoid per 1000 persons over a two year period was found to decrease when receiving the Vi vaccine for all individuals, for non-participants, and for participants. Future research related to this chapter could be to develop methods accounting for possible confounding in order to define the estimator of the direct effect.

We then move to the setting of observational studies for the following two chapters. In Chapter 3, we extend the G-formula to the case of partial interference when the scientific question of interest is the efficacy of different treatment policies. The estimands of interest were shown to be identifiable from observational data, and the proposed estimators were shown to be consistent and asymptotically normal using estimation equation theory. The proposed estimators were applied to the 2013-14 DRC Demographic and Health Survey to investigate the causal effect of bed net use on malaria. As the proportion of children who use bed nets increases, the expected number of cases of malaria decreased for all children and treated children. For non users, increasing bed net use seems to either have no benefit or a modest benefit. For this chapter, future research could include using semiparametric or nonparametric models in order to relax the parametric assumptions made here.

Finally, in Chapter 4, g-estimation is extended to the case of partial interference where the question of interest is again the effect of different treatment policies. We showed that the estimands of interest are identifiable from observed data, and that the proposed estimators are consistent and asymptotically normal. The proposed estimators were applied to 2013-14 DRC Demographic and Health Survey to again investigate the causal effect of bed net use on malaria. Using this method, the estimated causal mean ratios were found to decrease as the proportion of bed net users increased, indicating that there are fewer cases of malaria as more individuals use bed nets. Future research building from this chapter could be to explore relaxing the parametric assumptions further.

APPENDIX A: TECHNICAL DETAILS FOR CHAPTER 3

The g-formula estimators in Section 3.2.3 can be shown to be consistent and asymptotically Normal using standard large-sample estimating equation theory. Let $\theta = (\rho, \gamma_{0\alpha}, \gamma_{0\alpha'}, \beta, \mu_\alpha, \mu_{\alpha'}, \delta(\alpha, \alpha'))$. Estimating functions for $\hat{\rho}$ and $\hat{\beta}$ are given by score equations corresponding to the binomial models $P(S = s|\mathbf{L}; \rho)$ and $P(Y = y|S = s, \mathbf{L}; \beta)$. Denote these score equations by $\psi_\rho(O; \theta)$ and $\psi_\beta(O; \theta)$. For policy α, let $\psi_{\gamma_{0\alpha}}(O; \theta) = E_\alpha(S|\mathbf{L} = \mathbf{l}; \gamma_{0\alpha}, \rho_1) - \alpha$ where $E_\alpha(S|\mathbf{L} = \mathbf{l}; \gamma_{0\alpha}, \rho_1) = \text{expit}(\gamma_{0\alpha} + \rho_1 \mathbf{L})$, and let

$$\psi_{\mu_\alpha}(O; \theta) = \sum_{s \in \mathcal{S}} E(Y|S = s, \mathbf{L}; \beta) P_\alpha(S = s|\mathbf{L}; \gamma_{0\alpha}, \rho) - \mu_\alpha.$$

Define $\psi_{\delta(\alpha,\alpha')}(O; \theta) = \psi_{\mu_\alpha}(O; \theta) - \psi_{\mu_{\alpha'}}(O; \theta)$, and let $\psi_\theta = (\psi_\rho, \psi_{\gamma_{0\alpha}}, \psi_{\gamma_{0\alpha'}}, \psi_\beta, \psi_{\mu_\alpha}, \psi_{\mu_{\alpha'}}, \psi_{\delta(\alpha,\alpha')})^\top$. Then the estimator $\hat{\theta} = (\hat{\rho}, \hat{\gamma}_{0\alpha}, \hat{\gamma}_{0\alpha'}, \hat{\beta}, \hat{\mu}_\alpha, \hat{\mu}_{\alpha'}, \hat{\delta}(\alpha, \alpha'))$ is the solution to the vector estimating equation $\sum_{i=1}^m \psi_\theta(O; \theta) = \mathbf{0}$.

It is straightforward to show these estimating equations are unbiased. Because $\psi_\rho(O; \theta)$ and $\psi_\beta(O; \theta)$ are score equations, $\int \psi_\rho(O; \theta) dF_O(O) = 0$ and $\int \psi_\beta(O; \theta) dF_O(O) = 0$ where $F_O(O)$ denotes the distribution of the observed variables O. For policy α, $\gamma_{0\alpha}$ is the solution to (3.10), implying $E\{\psi_{\gamma_{0\alpha}}(O; \theta)\} = 0$. Next note

$$\begin{aligned}
E\{\psi_{\mu_\alpha}(O; \theta)\} &= E\{\sum_{s \in \mathcal{S}} E_\alpha(Y|S = s, \mathbf{L}) P_\alpha(S = s|\mathbf{L})\} - \mu_\alpha \\
&= E\{\sum_{s \in \mathcal{S}} E_\alpha(Y^s|S = s, \mathbf{L}) P_\alpha(S = s|\mathbf{L})\} - \mu_\alpha \\
&= E\{\sum_{s \in \mathcal{S}} E_\alpha(Y^s|\mathbf{L}) P_\alpha(S = s|\mathbf{L})\} - \mu_\alpha \\
&= \int_{\mathbf{l}} \sum_{s \in \mathcal{S}} E_\alpha(Y^s|\mathbf{L} = \mathbf{l}) P_\alpha(S = s|\mathbf{L} = \mathbf{l}) dF_{\mathbf{L}}(\mathbf{l}) - \mu_\alpha \\
&= 0
\end{aligned}$$

where the first equality holds assuming the $Y|S, \mathbf{L}$ and $S|\mathbf{L}$ models are correctly specified and that $E_\alpha(Y|S = s, \mathbf{L} = \mathbf{l}) = E(Y|S = s, \mathbf{L} = \mathbf{l})$, the second equality by causal consistency, the third equaltiy from conditional exchangeability, and the last equality from the definition of μ_α.

From standard large-sample estimating equation theory, it follows that under suitable regularity conditions, $\hat{\theta} \rightarrow_p \theta$ and $\sqrt{m}(\hat{\theta} - \theta) \rightarrow_d N(0, \Sigma)$ where $\Sigma = U^{-1}W(U^{-\top})$ for $U = E\{-\dot{\psi}_\theta(O;\theta)\}$, where $\dot{\psi}_\theta(O;\theta) = \partial\psi_\theta(O;\theta)/\partial\theta^\top$, and $W = E\{\psi_\theta(O;\theta)^{\otimes 2}\}$ [Stefanski and Boos, 2002]. The asymptotic variance Σ can be consistently estimated by the empirical sandwich variance estimator $\widehat{\Sigma} = \widehat{U}^{-1}\widehat{W}(\widehat{U}^{-\top})$ where $\widehat{U} = m^{-1}\sum_{i=1}^m -\dot{\psi}_\theta(O_i;\hat{\theta})$ and $\widehat{W} = m^{-1}\sum_{i=1}^m \psi_\theta(O_i;\hat{\theta})^{\otimes 2}$.

APPENDIX B: TECHNICAL DETAILS FOR CHAPTER 4

The estimators in Section 4.2.3 can be shown to be consistent and asymptotically Normal using standard large-sample estimating equation theory [Stefanski and Boos, 2002]. Under the assumptions in Section 4.2, the model in equation (4.14) is equivalent to assuming $E(Y|S,\mathbf{L}) = \exp(w(\mathbf{L}) + \psi f(S))$ for some unspecified function $w(\mathbf{L})$. The goal is to draw inference about ψ based on m iid copies of $O = (\mathbf{L}, S, Y)$. Suppose we fit by maximum likelihood a correct specified finite dimensional model for $S|\mathbf{L}$ with parameter vector ρ. Next fit Gamma glm $E(Y|S,\mathbf{L}) = \mu$ where $\mu = \exp(\beta_0 + \beta_1 E\{f(S)|\mathbf{L};\hat{\rho}\} + \psi f(S))$ and where $\hat{\rho}$ is MLE of ρ. Let $\rho = (\rho_0, \rho_1)$ and $\beta = (\beta_0, \beta_1, \beta_L)$ where β_L is only included if using the doubly robust estimator. Let $\theta = (\rho, \beta, \psi)$. Estimating functions for $\hat{\theta}$ are given by score equations; denote these score equations by $\gamma_\rho(O;\rho)$, $\gamma_\beta(O;\theta)$, $\gamma_\psi(O;\theta)$. Let $\gamma_\theta = (\gamma_\rho, \gamma_\beta, \gamma_\psi)^\top$. The estimator $\hat{\theta} = (\hat{\rho}, \hat{\beta}, \hat{\psi})$ is the solution to the vector estimating equation $\sum_{i=1}^m \gamma_\theta(O;\theta) = \mathbf{0}$, i.e.,

$$0 = \sum_i \begin{pmatrix} \gamma_\rho(O_i;\rho) \\ \gamma_{\beta_0}(O_i;\rho,\beta_0,\beta,\psi) \\ \gamma_{\beta_1}(O_i;\rho,\beta_0,\beta,\psi) \\ \gamma_\psi(O_i;\rho,\beta_0,\beta,\psi) \end{pmatrix} = \sum_i \begin{pmatrix} \gamma_\rho(O_i;\rho) \\ Y_i\mu_i^{-1} - 1 \\ E\{f(S)|\mathbf{L}_i;\rho\}(Y_i\mu_i^{-1} - 1) \\ f(S_i)(Y_i\mu_i^{-1} - 1) \end{pmatrix}$$

Note that this is equivalent to solving

$$0 = \sum_i \begin{pmatrix} \gamma_\rho(O_i;\rho) \\ \gamma_{\beta_0}(O_i;\rho,\beta_0,\beta,\psi) \\ \gamma_{\beta_1}(O_i;\rho,\beta_0,\beta,\psi) \\ \gamma^*_\psi(O_i;\rho,\beta_0,\beta,\psi) \end{pmatrix} = \sum_i \begin{pmatrix} \gamma_\rho(O_i;\rho) \\ Y_i\mu_i^{-1} - 1 \\ E\{f(S)|\mathbf{L}_i;\rho\}(Y_i\mu_i^{-1} - 1) \\ (f(S_i) - E\{f(S)|\mathbf{L}_i;\rho\})(Y_i\mu_i^{-1} - 1) \end{pmatrix}$$

It is straightforward to show that the estimating equations are unbiased. Define β_0^* and β_1^* to be values of β_0 and β_1 such that $E(\gamma_{\beta_0}(O;\rho,\beta_0^*,\beta_1^*,\psi) = 0$ and $E(\gamma_{\beta_1}(O;\rho,\beta_0^*,\beta_1^*,\psi) = 0$. Because $\gamma_\rho(O;\rho)$ and $\gamma_\beta(0;\theta)$ are score equations, $\int \gamma_\rho(O;\rho)dF_O(O) = 0$ and $\int \gamma_\beta(O;\theta)dF_O(O)$

$= 0$ where $F_O(O)$ denotes the distribution of the observed variables O. Next note

$$\gamma^*_\psi(O;\rho,\beta^*_0,\beta^*_1,\psi) = d(\mathbf{L};\rho,\beta^*_0,\beta^*_1)\{f(S) - E\{f(S)|\mathbf{L};\rho\}\}(Y\exp(-\psi f(S)) - g(\mathbf{L};\rho,\beta^*_0,\beta^*_1))$$

where $d(\mathbf{L};\rho,\beta_0,\beta_1) = \exp(-\beta_0 - \beta_1 E\{f(S)|\mathbf{L};\rho\})$ and $g(\mathbf{L};\rho,\beta_0,\beta_1) = \exp(\beta_0 + \beta_1 E\{f(S)|\mathbf{L};\rho\})$. From Robins [1994] it follows that $E(\gamma^*_\psi(O;\rho,\beta^*_0,\beta^*_1,\psi)) = 0$ if the treatment model and structural models above are correctly specified. Using obvious shorthand

$$\begin{aligned} E(\gamma^*_\psi) &= E_{S,\mathbf{L}}[d(f(S) - E\{f(S)|\mathbf{L};\rho\})\{E(Y\exp(-\psi f(S))|S,\mathbf{L}) - g\}] \\ &= E_{S,\mathbf{L}}[d(f(S) - E\{f(S)|\mathbf{L};\rho\})\{\exp(w(\mathbf{L})) - g\}] = 0 \end{aligned}$$

where first equality holds by the assumed structural model and the second equality holds assuming the treatment model is correct.

Consider the estimator from above, but suppose now that instead we fit Gamma glm $E(Y|S,\mathbf{L}) = \mu$ where $\mu = \exp(\beta_0 + \beta_1 E\{f(S)|\mathbf{L};\hat{\rho}\} + \beta_L\mathbf{L} + \psi f(S))$. The estimator $\hat{\theta} = (\hat{\rho},\hat{\beta},\hat{\psi})$ is the solution to estimating equations listed above with the addition of $\gamma_{\beta_L}(O_i;\rho,\beta_0,\beta_1,\psi) = \mathbf{L}_i(Y_i\mu_i^{-1} - 1)$. Define β^*_0, β^*_1, and β^*_L to be values of β_0, β_1 and β_L such that $E(\gamma_\beta(O;\rho,\beta^*_0,\beta^*_1,\beta^*_2,\psi)) = 0$ for $\gamma_{\beta_0},\gamma_{\beta_1},\gamma_{\beta_L}$. By the previous arguments, $\hat{\psi}$ is CAN for ψ if the treatment model is correctly specified. Alternatively, suppose we can assume that

$$E(Y|\mathbf{L},S=0) = \exp(\beta_0 + \beta_L\mathbf{L})$$

such that $\beta^*_0 = \beta_0, \beta^*_1 = 0, \beta^*_L = \beta_L$. Then it follows that $E(Y_i\mu_i^{-1}|S_i,\mathbf{L}_i) = 1$, implying $E(\gamma_\beta) = 0$ and $E(\gamma^*_\psi) = 0$ even if the treatment model is misspecified. Thus $\hat{\psi}$ is CAN for ψ if the treatment model is correct or the $Y|S=0,\mathbf{L}$ model is correct, i.e., the estimator is doubly robust.

It follows from standard large-sample estimating equation theory that under suitable regularity conditions, $\hat{\theta} \to_p \theta$ and $\sqrt{m}(\hat{\theta} - \theta) \to_d N(0,\Sigma)$ where $\Sigma = U^{-1}W(U^{-\top})$ for

$U = E\{-\dot{\gamma}_\theta(O;\theta)\}$, where $\dot{\gamma}_\theta(O;\theta) = \partial\gamma_\theta(O;\theta)/\partial\theta^\top$, and $W = E\{\gamma_\theta(O;\theta)^{\otimes 2}\}$ [Stefanski and Boos, 2002]. The asymptotic variance Σ can be consistently estimated by the empirical sandwich variance estimator $\widehat{\Sigma} = \widehat{U}^{-1}\widehat{W}(\widehat{U}^{-\top})$ where $\widehat{U} = m^{-1}\sum_{i=1}^{m} -\dot{\gamma}_\theta(O_i;\hat{\theta})$ and $\widehat{W} = m^{-1}\sum_{i=1}^{m}\gamma_\theta(O_i;\hat{\theta})^{\otimes 2}$.

Additional Simulations

Additional simulations were performed for the overall effect when $f(s) = s + s^2$. Steps (i)-(iv) in Section 4.3 were performed using true values of $\psi_0 = -3, \psi_1 = 1.5$ for $\lambda_y = \exp(\beta_0 + \beta_1 L_{1i} + \beta_2 L_{2i} + \psi_0 S_i + \psi_1 S_i^2)$. When the model for S model is misspecified, the true treatment model uses $e(\mathbf{L};\rho) = \text{probit}^{-1}(-0.4I(55 > L_1 > 35) + 0.2I(L_2 < 3))$. When the model for Y is misspecified, the true outcome model uses $\lambda_y = \exp(\log(0.7N) + \psi_0 S + \psi_1 S^2 - 0.5I(55 > L_1 > 35) + 0.3I(L_2 < 3))$. Binomial regression models for S were fit with main effects for L_1, L_2. Gamma regression models with a log link for Y were fit with main effects for $S, S^2, E[S|\mathbf{L};\hat{\rho}], E[S^2|\mathbf{L};\hat{\rho}]$. In the case of the doubly robust estimator, these models also had main effects for both L_1, L_2. These estimators performed as expected. The singly robust estimator may be robust to some misspecifications, but this could be due to the choice of parameters and is not guaranteed.

Scenario	ψ	Group	Bias	Relative Bias	Cov%	ASE	ESE	SER
Singly robust								
S model correct	ψ_0	All	-0.014	0.5%	94%	2.29	2.33	0.98
	ψ_1	All	0.012	0.8%	94%	2.57	2.65	0.97
S model incorrect	ψ_0	All	-0.26	8.7%	94%	1.31	1.32	0.99
	ψ_1	All	0.28	18%	94%	1.43	1.45	0.99
Doubly Robust								
Both correct	ψ_0	All	-0.019	0.6%	94%	2.29	2.34	0.98
	ψ_1	All	0.016	1.1%	94%	2.57	2.66	0.96
S model incorrect	ψ_0	All	0.042	-1.4%	94%	1.32	1.34	0.99
	ψ_1	All	-0.057	-3.8%	94%	1.44	1.46	0.98
Y model incorrect	ψ_0	All	0.069	-2.3%	93%	2.14	2.28	0.94
	ψ_1	All	-0.085	-5.7%	93%	2.40	2.57	0.93
Both incorrect	ψ_0	All	0.97	-32%	85%	1.16	1.26	0.92
	ψ_1	All	0.61	40%	89%	1.24	1.34	0.93

Sample R Code

The full code used for the simulations in the previous section is available at `https://github.com/KilpatrickKW`. The following code demonstrates how to fit both models and find standard error estimates using the geex package in R.

```
#------------------------------------------------------------------------
# Fit S|L model
#------------------------------------------------------------------------
s_model_rhos<-glm(S~L1+L2,data=simdataset,family="binomial",weights = N)
rho_hat<- s_model_rhos$coef
simdataset$e_L<-expit(rho_hat["(Intercept)"]+rho_hat["L1"]*simdataset$L1+
rho_hat["L2"]*simdataset$L2)

# now find E[S^2|L]
ehat_s<-list()
sum_over_s<-list()
for (i in simdataset$cluster){
Nval<-simdataset$N[i] #max num in cluster
for (s in 1:(Nval+1)){
pmf_s<-dbinom(s-1,size=Nval,prob=simdataset$e_L[i])
summand<-((s-1)/Nval)^2*pmf_s
sum_over_s[s]<-summand
}
ehat_s[[i]]<-sum(unlist(sum_over_s))
sum_over_s<-list()
}
simdataset$e_L_squared<-unlist(ehat_s)
#------------------------------------------------------------------------
# Fit Y model
#------------------------------------------------------------------------
```

```
#singly robust version
g_est<-geem(Y~e_L+e_L_squared+S+S2,family = Gamma(link="log"),id=cluster,
data = simdataset)
beta_hat<-coefficients(g_est)[c("(Intercept)","e_L","e_L_squared")]
psi_hat<-coefficients(g_est)[c("S","S2")]

#doubly robust version
g_est_dr<-geem(Y~e_L+e_L_squared+L1+L2+S+S2,family = Gamma(link="log"),
id=cluster, data = simdataset)
beta_hat_dr<-coefficients(g_est_dr)[c("(Intercept)","e_L","e_L_squared",
"L1","L2")]
psi_hat_dr<-coefficients(g_est_dr)[c("S","S2")]
#-------------------------------------------------------------------------
# Find SEs using geex
#-------------------------------------------------------------------------
estfun_gf <- function(data,models){
S <- data$S
S2 <- data$S2
Y <- data$Y
X_s<-cbind(rep(1, length(Y)),data$L1,data$L2,data$N)
function(theta){
# s score equations
pi_score_s<-expit(theta[1]*X_s[,1]+theta[2]*X_s[,2]+theta[3]*X_s[,3])
score_int_s<-X_s[,4]*(S-pi_score_s)*X_s[,1]
score_L1_s<-X_s[,4]*(S-pi_score_s)*X_s[,2]
score_L2_s<-X_s[,4]*(S-pi_score_s)*X_s[,3]

#now we need E(S|L)
e_L<-pi_score_s
#now find E(S^2|L)
ehat_s<-list()
sum_over_s<-list()
for (i in length(Y)){
```

```
Nval<-data$N[i] #max num in cluster
for (s in 1:(Nval+1)){
pmf_s<-dbinom(s-1,size=Nval,prob=e_L[i])
summand<-((s-1)/Nval)^2*pmf_s
sum_over_s[s]<-summand
}
ehat_s[[i]]<-sum(unlist(sum_over_s))
sum_over_s<-list()
}
e_L_squared<-unlist(ehat_s)

# singly robust for Y
mu_inv<-exp(-theta[4]-theta[5]*e_L-theta[6]*e_L_squared-theta[7]*S-
theta[8]*S2)
score_int_y<-Y*mu_inv-1
score_eL_y<-e_L*(Y*mu_inv-1)
score_eLsquared_y<-e_L_squared*(Y*mu_inv-1)
score_psi<-S*(Y*mu_inv-1)
score_psi_1<-S2*(Y*mu_inv-1)

# doubly robust for Y
mu_inv_dr<-exp(-theta[9]-theta[10]*e_L-theta[11]*e_L_squared-
theta[12]*X_s[,2]-theta[13]*X_s[,3]-theta[14]*S-theta[15]*S2)
score_int_y_dr<-Y*mu_inv_dr-1
score_eL_y_dr<-e_L*(Y*mu_inv_dr-1)
score_eLsquared_y_dr<-e_L_squared*(Y*mu_inv_dr-1)
score_L1_y_dr<-X_s[,2]*(Y*mu_inv_dr-1)
score_L2_y_dr<-X_s[,3]*(Y*mu_inv_dr-1)
score_psi_dr<-S*(Y*mu_inv_dr-1)
score_psi_1_dr<-S2*(Y*mu_inv_dr-1)

c(score_int_s, score_L1_s, score_L2_s,
score_int_y, score_eL_y, score_eLsquared_y,
```

```
score_psi, score_psi_1,
score_int_y_dr, score_eL_y_dr, score_eLsquared_y_dr, score_L1_y_dr,
score_L2_y_dr, score_psi_dr, score_psi_1_dr)}}

geex_results<-m_estimate(
estFUN = estfun_gf,
data  = simdataset,
roots = c(rho_hat, beta_hat, psi_hat, beta_hat_dr, psi_hat_dr),
compute_roots = FALSE)

psi_se<-sqrt(geex_results@vcov[7,7])
psi_1_se<-sqrt(geex_results@vcov[8,8])
psi_dr_se<-sqrt(geex_results@vcov[14,14])
psi_1_dr_se<-sqrt(geex_results@vcov[15,15])
```

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