Assessing population-level effects of vaccines and other infectious disease prevention measures is important to the field of public health. In infectious disease studies, one person’s treatment may affect another individual’s outcome, that is, there may be interference between units. For example, the use of bed nets to prevent malaria by one individual may have an indirect effect on other individuals living in close proximity. In some settings, individuals may form groups or clusters where interference only occurs within groups, that is, there is partial interference. Inverse probability weighted estimators have previously been developed for observational studies with partial interference. Unfortunately, these estimators are not well suited for studies with large clusters. Therefore, in this paper, the parametric g-formula is extended to allow for partial interference. G-formula estimators are proposed for overall effects, effects when treated, and 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 assuming no unmeasured confounders and that the partial interference takes a particular form (referred to as ‘weak stratified interference’). 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 effects of bed net use on malaria.

KEYWORDS
causal inference, G-formula, herd immunity, observational studies

1 INTRODUCTION

In settings where individuals interact or are connected, one individual’s treatment status may affect another individual’s outcome, that is, interference may be present between individuals. Interference is common in infectious disease research. For instance, if one individual wears a mask, this could affect whether another individual develops COVID-19. 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, that is, there is partial (or clustered) interference. 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; for example, Tchetgen Tchetgen and VanderWeele, Papadogeorgou et al, Barkley et al and Park and Kang.

In the presence of interference, it is of interest to assess the effect of policies that alter the distribution of treatment in the population. For instance, in the Democratic Republic of the Congo, public health officials and policymakers 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 policymakers need to account for possible within-cluster treatment selection dependence. Papadogeorgou et al and Barkley et al 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 computed by multiplying individual propensity score estimates across individuals within the same cluster. When clusters are large, this product of individual propensity scores (each of which is between 0 and 1) will tend to be very small. 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. 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 2013–2014 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. In the analysis presented below, population-level effects of bed net use on malaria are assessed using data from the DRC DHS. Figure 1 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 and 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. Because malaria is spread between humans via the Anopheles mosquito, interference is epidemiologically plausible in this setting; for example, if an individual with malaria elects to use a bed net, then the likelihood of a mosquito transmitting malaria from that individual to another individual may be decreased. Previously, Levitz et al showed that community-level bed net usage was significantly associated with protection against malaria in children younger than 5 years old. The inferential goal of

![Figure 1](image-url) 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.
this paper is to assess the population-level effects of bed net use on malaria while allowing for possible within-cluster interference.

The outline of the remainder of this paper is as follows. Section 2 presents the proposed extension of the g-formula to allow for partial interference. Section 3 presents the simulation results evaluating the performance of the proposed methods in finite samples. In Section 4, the proposed estimators are employed to assess the effect of bed net use on malaria using data from the DRC DHS. Section 5 concludes with a discussion.

2 METHODS

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 \( A_i = (A_{i1}, A_{i2}, \ldots, A_{iN_i}) \) 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 \( N_i \). The covariate vector \( \mathbf{L}_i \) may include summaries of individual-level covariates, such as the average age of individuals within the cluster. 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, that is, there is no interference between clusters, but there may be interference between individuals within the same cluster. For example, one individual's bed net usage may affect whether or not another individual in the same cluster gets malaria. In the DRC analysis, clusters are defined according to household geographical location. Thus, the partial interference assumption is biologically plausible as the Anopheles mosquito has a limited flight range (<10 km) and life span (<1 month), such that interference (if present) is likely restricted to individuals within the same cluster. Let \( A(N_i) \) denote the set of all vectors of length \( N_i \) with binary entries such that \( a_i = (a_{i1}, a_{i2}, \ldots, a_{iN_i}) \in A(N_i) \) is a vector of possible treatment statuses for a cluster of size \( N_i \). For cluster \( i \), let \( Y_i(a_i) \) represent the potential outcome if, possibly counter to fact, the cluster had been exposed to \( a_i \in A(N_i) \), such that \( Y_i(a_i) = Y_i \) when \( A_i = a_i \).

Population-level effects of interventions such as bed nets can be defined by differences in expected potential 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 \( \alpha \) to be the setting where the expected proportion of individuals in a cluster who receive treatment is \( \alpha \), that is, \( E_S(\alpha) = \alpha \), where in general the subscript \( \alpha \) denotes the counterfactual scenario in which the policy \( \alpha \) is implemented.

For example, \( P_{\alpha}(A = a|\mathbf{L} = 1) \) denotes the conditional probability of treatment given covariates \( \mathbf{L} \) in the counterfactual scenario in which policy \( \alpha \) is implemented. There are various ways to define the counterfactual treatment allocation probability \( P_{\alpha}(A = a|\mathbf{L} = 1) \), and the specific policy \( \alpha \) considered in this work is described in Section 2.2. Unlike stochastic policies previously considered in the absence of interference, for example, Muñoz and Van Der Laan,11 Kennedy,12 Wen et al,13 the policy considered here allows for within-cluster treatment selection dependence. For more discussion on other stochastic policies in the presence of partial interference, refer to Lee et al.14 The DRC analysis below considers policies where different proportions of individuals use bed nets.

Under policy \( \alpha \), the treatment assignment within a cluster is allowed to be stochastic, governed by a distribution on \( A \) which may vary across clusters depending on cluster-level covariates \( \mathbf{L} \). For the stratum of clusters in the population defined by \( \mathbf{L} = 1 \) with the cluster size \( n \), the expected potential outcome under policy \( \alpha \) is defined as \( \sum_{a \in A(n)} E \{ Y(a)|\mathbf{L} = 1 \} P_{\alpha}(A = a|\mathbf{L} = 1) \). Here, the conditional expectation of the potential outcome \( Y(a) \) at stratum of \( \mathbf{L} = 1 \) is averaged over all \( a \in A(n) \), with corresponding probabilities \( P_{\alpha}(A = a|\mathbf{L} = 1) \). Then, the average potential outcome in the population under policy \( \alpha \) is defined as

\[
\mu(\alpha) = \int_1 \sum_{a \in A(n)} E \{ Y(a)|\mathbf{L} = 1 \} P_{\alpha}(A = a|\mathbf{L} = 1) dF_L(1)
\] (1)
where \( F_L \) denotes the distribution of baseline covariates \( L \). Effects of interest can be defined by contrasts in \( \mu_a \) for two policies \( \alpha \) and \( \alpha' \), for example,

\[
\delta(\alpha, \alpha') = \mu_\alpha - \mu_{\alpha'}.
\]  

(2)

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 \( \alpha \) versus \( \alpha' \).

In the DRC analysis, we will consider three different effects of bed nets: the overall effect, the effect when treated, and the effect when untreated. All three effects have the form (2) but differ in how \( Y_i \) is defined. The overall effect compares the average outcome among all individuals in a cluster under policies \( \alpha \) versus \( \alpha' \). 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 policymakers 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 additional treatment effects are also considered. The effect when untreated contrasts average outcomes when an individual is untreated under policy \( \alpha \) versus policy \( \alpha' \). For this effect, \( Y_i \) may be defined by some summary measure of outcomes in untreated individuals. In the DRC analysis of the 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 \( Y_i = 0 \) because no untreated individuals had malaria in those clusters. Similarly, the effect when treated contrasts average outcomes when an individual is treated under policy \( \alpha \) versus policy \( \alpha' \). For the 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.

Causal effects are, in general, defined by contrasts in potential outcomes over the same set of units.\(^{15}\) In this paper, the units are defined to be clusters. While it is natural in many settings to define units as persons or individuals, in the setting considered here, defining units as clusters simplifies matters. In particular, this approach avoids complexities that arise when defining potential outcomes at the individual level, such as nuances regarding casual estimand definitions\(^{16,17}\) and drawing inference in a manner that appropriately allows for within-cluster correlation.

Note the effects as defined here could be non-zero due to interference or dependence between individuals’ treatment propensity and risk of the outcome. For instance, suppose there is no interference and that individuals with a lower risk of some binary outcome are, in general, less likely to get treatment. Then, as the policy \( \alpha \) tends toward 1, only those with the smallest outcome risk will be untreated, such that the mean outcome in the untreated will decrease even in the absence of interference. Nonetheless, the effects defined here could be of interest to policymakers or from a public health perspective, as these effects describe how the average outcome changes across policies.

2.2 Assumptions and identifiability

The following assumptions are made to identify the estimands described above:

**Assumption 1** (Consistency). \( Y_i(a_i) = Y_i \) when \( A_i = a_i \).

**Assumption 2** (Conditional exchangeability). \( Y_i(a_i) \perp A_i | L_i \) for all \( a_i \in A(N_i) \).

The consistency and conditional exchangeability assumptions are analogous to the assumptions commonly made at the individual level when drawing causal inferences in the absence of interference, with the key distinction being that here these assumptions are applied at the cluster level. As in the setting where there is no interference, selection of the covariates \( L \) such that conditional exchangeability is plausible in a particular application may be informed by subject matter knowledge. Causal graphs\(^{18}\), where the nodes/vertices represent cluster-level random variables, may also be used to determine sufficient sets of covariates \( L \) for which conditional exchangeability holds. As discussed in the previous section, the outcome \( Y \) may be defined differently depending on the effect of interest. Thus, the plausibility of
the exchangeability assumption and selection of the particular covariates \( L \) may differ depending on the choice of \( Y \). Section 4 discusses the exchangeability assumption in the context of the malaria example.

**Assumption 3** (Weak stratified interference). \( E \{ Y_i(a_i)|L_i \} = E \{ Y_i(a_i')|L_i \} \) for all \( a_i, a_i' \in \mathcal{A}(N_i) \) such that \( \sum_{j=1}^{N_i} a_{ij} = \sum_{j=1}^{N_i} a_{ij}' \).

The weak stratified interference (WSI) assumption supposes that the conditional expectation of the cluster-level potential outcome given \( L \) depends only on the proportion of individuals treated, but not which particular individuals receive treatment. This assumption is weaker than the usual “stratified interference” assumption, which stipulates that \( Y_i(a_i) = Y_i(a_i') \) for any two vectors \( a_i, a_i' \in \mathcal{A}(N_i) \) such that \( \sum_{j=1}^{N_i} a_{ij} = \sum_{j=1}^{N_i} a_{ij}' \). The stratified interference assumption might be unrealistic in some settings, hence, in this paper, WSI is assumed instead. WSI is a weaker assumption in that stratified interference implies WSI, but that WSI may also hold in settings where stratified interference does not. Note that assuming WSI does not resolve the issue of very small cluster-level propensity scores in large clusters; however, under WSI the proposed method permits inference without using inverse probability weighting and thus avoids the extreme cluster-level propensity score issue.

**Assumption 4** (S model). Let \( \pi = \pi(L; \rho) = g^{-1}(\rho_0 + \rho_1^T L) \), where \( g \) is some invertible, user-specified link function such as logit or probit, and \( \rho = (\rho_0, \rho_1^T) \). Assume

\[
P(S = s|L) = P(S = s|L; \rho) = \left( \frac{N}{N_S} \right)^{\pi(N_s - 1)} (1 - \pi)^{N - N_S}.
\]

(3)

Note (3) will hold if \( A_{ij}|L_i \) for \( j = 1, \ldots, N_i \) are i.i.d. Bernoulli random variables with expectation \( \pi(L_i) \), respectively. In this case, \( A_{ij} \perp A_{ik}|L_i \), that is, the treatment selection of two individuals within the same cluster is conditionally independent. This does not, however, imply marginal independence, that is, \( A_{ij} \perp A_{ik} \). Moreover, provided \( \rho_1 \neq 0 \), in general we would expect marginal dependence between \( A_{ij} \) and \( A_{ik} \). While (3) is assumed in the rest of this paper, alternative parametric models for the conditional distribution of \( S \) given \( L \) could be assumed instead.

Suppose we are interested in causal estimands corresponding to a counterfactual policy \( a \) where the distribution of \( S \) is modified such that a proportion of individuals are treated on average. In particular, motivated by (3), suppose we would like to draw an inference about the counterfactual scenario where

\[
P_a(S = s|L) = P_a(S = s|L; \gamma) = \left( \frac{N}{N_S} \right)^{\pi_a(N_s - 1)} (1 - \pi_a)^{N - N_S},
\]

(4)

where \( \pi_a = g^{-1}(\gamma_{0a} + \gamma_{1a}^T L) \) and \( \gamma = (\gamma_{0a}, \gamma_{1a}^T)^T \). The parameter \( \rho \) in (3) is identifiable from the observable data, whereas the counterfactual parameter \( \gamma \) in (4) are not identifiable without additional assumptions. As in Barkley et al.,

assume \( \rho_1 = \gamma_{1a} \), 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 \( a \), treatment adoption will also be more likely in cluster \( i \) than cluster \( j \). Then, \( \gamma_{0a} \) is obtained from the relationship \( E_a(S) = a \), by solving the equation

\[
\int E_a(S|L = 1; \gamma_{0a}, \rho_1) dF_L(1) - a = 0
\]

(5)

where \( E_a(S|L = 1; \gamma_{0a}, \rho_1) = g^{-1}(\gamma_{0a} + \rho_1^T L) \).

**Assumption 5** (Y model). Let \( \eta = h^{-1}(\beta_0 + \beta_1^T L + \beta_2 S) \) where \( h \) is some invertible, user-specified link function, and \( \beta = (\beta_0, \beta_1^T, \beta_2^T)^T \). Assume

\[
E(Y|S = s, L = 1) = E(Y|S = s, L = 1; \beta) = \eta.
\]

(6)

Note Assumption 5 only supposes that the conditional expectation of \( Y \) given \( S \) and \( L \) has a parametric form, with no additional assumptions placed on the conditional distribution of \( Y \). For simplicity, an interaction between \( S \) and \( L \) is omitted from the model of \( E(Y|S = s, L = 1) \) but could be included. For the analysis in Section 4, binomial regression with the link functions \( g = h = \text{logit} \) are used for the treatment and outcome models.

Under Assumptions 1–4, the causal estimands (1) and (2) are identifiable, that is, can be expressed as functions of the distribution of the observed random variables. In particular, from consistency, conditional exchangeability, and
WSI, it follows that \( E(Y(a_i)|L_i) = E(Y_i|A_i = a_i, L_i) = E(Y_i|S_i = \tilde{a}_i, L_i) \), where \( \tilde{a}_i = N^{-1} \sum_{j=1}^{N_i} a_{ij} \). Therefore, we have the identifiability of \( \mu(a) \) as follows:

\[
\mu(a) = \int \sum_{a \in A(a_i)} E(Y(a)|L = 1)P_a(A = a|L = 1)dF_L(L)
\]

where \( S(n) = \{0/n, 1/n, \ldots, n/n\} \), and \( E(Y|S = s, L = 1) \) and \( F_L(L) \) are identifiable from the observed data \( O_i = \{L_i, S_i, Y_i\}, i = 1, \ldots, m \), and \( P_a(S = s|L = 1) \) is also identifiable since the parameters \( \rho, \gamma_0a \), and thus \( \pi_a = g^{-1}(\gamma_0a + \rho_1^T L) \) are identifiable. The identifiability of the causal effect \( \delta(a, a') \) can be shown similarly. Note that Assumption 5 is not required for identifiability, but it is assumed to facilitate inference as described in the next section.

### 2.3 Inference

Estimators for \( \mu(a) \) can be constructed as follows. First estimate the parameters \( \rho = (\rho_0, \rho_1^T) \) of model (3) and \( \beta = (\beta_0, \beta_1^T, \beta_2^T) \) of model (6) via maximum likelihood; denote these estimators by \( \hat{\rho} = (\hat{\rho}_0, \hat{\rho}_1^T) \) and \( \hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1^T, \hat{\beta}_2^T) \). Next, for a given policy \( a \), let \( \hat{\gamma}_0a \) denote the estimator of \( \gamma_0a \) obtained by finding the solution to (3) with \( F_L \) replaced by its empirical distribution, that is, \( m^{-1} \sum_{i=1}^{m} \hat{E}_a(S_i|L_i; \hat{\gamma}_0a, \hat{\rho}_1) - a = 0 \) where \( \hat{E}_a(S_i|L_i; \gamma_0a, \rho_1) = g^{-1}(\gamma_0a + \rho_1^T L_i) \). Let \( \hat{P}_a(S = s|L_i) \) denote (4) evaluated using \( (\hat{\gamma}_0a, \hat{\beta}_1^T) \), and let \( \hat{E}(Y|S = s, L = 1) \) denote (6) evaluated using \( \hat{\beta} \). Then the g-formula estimator of \( \mu(a) \) is

\[
\hat{\mu}(a) = \int \sum_{s \in S(n)} \hat{E}(Y|S = s, L = 1)\hat{P}_a(S = s|L = 1)dF_L(L)
\]

where \( F_L \) denotes the empirical distribution function of \( L \). Equivalently, the estimator may be written

\[
\hat{\mu}(a) = \frac{1}{m} \sum_{i=1}^{m} \sum_{s \in S(N_i)} \hat{E}(Y_i|S_i = s, L_i)\hat{P}_a(S_i = s|L_i).
\]

The estimator for the effects of interest is \( \hat{\delta}(a, a') = \hat{\mu}(a) - \hat{\mu}(a') \). The estimators \( \hat{\rho}, \hat{\beta}, \hat{\gamma}_0a, \hat{\mu}(a), \hat{\mu}(a') \), and \( \hat{\delta}(a, a') \) are solutions to unbiased estimating equations (see Supporting Information). Therefore, it follows from standard large-sample estimating equation theory that the estimators are consistent and asymptotically Normal. The empirical sandwich estimators, which are consistent estimators of the asymptotic variances, can be used to construct point-wise Wald confidence intervals (CIs).

### 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 $\mu(\alpha)$ may be expressed

$$\int \sum \sum E(Y|S_1 = s_1, S_2 = s_2, L = 1)P_a(S_1 = s_1|L = 1, S_2 = s_2)P_a(S_2 = s_2|L = 1) dF_L(I)$$

where the policy $a$ here is defined such that individuals in strata 1 and 2 are treated with the same probability: $E_a(S_1) = E_a(S_2) = E_a(S) = a$. More generally, one could consider different policies $a_1$ and $a_2$ for the two population strata. Inference proceeds analogous to Sections 2.2 and 2.3, but with separate parametric models for $S_1$ given $L$, $S_2$ and for $S_2$ given $L$; such an approach is taken in the DRC bed net analysis in Section 4.

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.$^{2,1,22}$

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 $\alpha$, $\alpha'$. If $S$ has no effect on $Y$, then $\beta_2 = 0$ and $E(Y|S = s, L) = E(Y|L)$. Therefore,

$$\mu(\alpha) = \int E(Y|L = 1) \sum_{s \in S(\alpha)} P_a(S = s|L = 1) dF_L(I) = \int E(Y|L = 1) dF_L(I)$$

where the second equality follows because $\sum_{s \in S(\alpha)} P_a(S = s|L = 1) = 1$. The right-hand side of (7) does not depend on $\alpha$, so the g-null paradox does not occur here.

3 EMPIRICAL EVALUATION
Simulation studies were conducted to evaluate the finite sample properties of the proposed g-formula estimator. Three separate simulation studies were conducted for the three target estimands: overall effect, effect when treated, and 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 $\pi_i = \expit(\rho_0 + \rho_1 L_{1i} + \rho_2 L_{2i})$ where $\rho = (\logit(0.6), -0.01, -0.01)^T$. 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 $\eta_i = \expit(\beta_0 + \beta_1 L_{1i} + \beta_2 S_i + \beta_3 L_{2i})$ where $\beta = (\logit(0.6), -0.01, -0.8, -0.01)^T$.

Correctly specified models of $Y$ given $S$ and $L$, and of $S$ given $L$ were fit by maximum likelihood. The asymptotic variance of the estimators was estimated using the empirical sandwich variance estimator, and point-wise 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 $Y_{0a}$ are the solutions to (5) where $\alpha_a = \expit(\gamma_{0a} + \rho_1 L_1 + \rho_2 L_2)$. The counterfactual probabilities $P_a(S = s|L)$ for $s \in S(N)$ can then be computed via (4) based on the true values of $\gamma_{0a}, \rho_1, \rho_2$. 

Similarly, \( E(Y|S=s, L) \) for \( s \in S(N) \) may be evaluated using (6) and the true value of \( \beta \). Finally, the true values of \( \mu(\alpha) \) can be found using (1).

Results for the overall effect simulation study are given in the top third of Table 1. 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 effect when treated, with the following modification. In step (iv), the cluster outcome \( Y_i \) was set equal to \( X_i^1/(N_i S_i) \) where \( X_i^1 \) was Binomial with parameters \( N_i S_i \) and \( \eta_i \). If there were no treated individuals in a cluster, then \( Y_i \) was set to 0. Results for the g-formula estimator of the effect when treated are presented in the middle part of Table 1. Results are similar to the overall effect, except the standard error for the g-formula estimator of the effect when treated is larger because fewer individuals contribute to the outcome.

Finally, a third simulation study was conducted for the 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 \( X_i^0/[N_i(1-S_i)] \) where \( X_i^0 \) was Binomial with parameters \( N_i(1-S_i) \) and \( \eta_i \), with \( Y_i \) set to 0 if \( S_i = 1 \). Results are given in the bottom section of Table 1.

Additional simulation studies were conducted to compare the g-formula estimator with the IPW estimator of Barkley et al.\(^5\) The same data generating process described above was repeated, with the exception of steps (iii) and (iv) where instead the treatment status for each individual was generated as a Bernoulli random variable with expectation \( \pi_y = \expit(\rho_0 + \rho_1 L_{11} + \rho_2 L_{21}) \) where \( \rho = (\logit(0.6), -0.01, -0.01)\)\(^6\), and similarly, individual outcomes were generated as

| TABLE 1 | Summary of simulation study results as described in Section 3. |
|----------|-------------------------------------------------------------|
| **Estimand** | **Truth** | **Bias** | **Cov%** | **ASE** | **ESE** | **SER** |
| All individuals | | | | | | |
| \( \mu(\alpha = 0.4) \) | 0.418 | 0.000 | 94% | 0.0147 | 0.0153 | 0.96 |
| \( \mu(\alpha = 0.5) \) | 0.399 | −0.000 | 94% | 0.0119 | 0.0121 | 0.98 |
| \( \mu(\alpha = 0.6) \) | 0.380 | −0.000 | 94% | 0.0145 | 0.0149 | 0.97 |
| \( \delta(\alpha = 0.6, \alpha' = 0.4) \) | −0.038 | −0.001 | 94% | 0.0172 | 0.0180 | 0.95 |
| \( \delta(\alpha = 0.6, \alpha' = 0.5) \) | −0.019 | −0.000 | 94% | 0.0084 | 0.0089 | 0.95 |
| \( \delta(\alpha = 0.5, \alpha' = 0.4) \) | −0.019 | −0.000 | 94% | 0.0087 | 0.0091 | 0.96 |
| When treated | | | | | | |
| \( \mu_1(\alpha = 0.4) \) | 0.418 | −0.002 | 95% | 0.0243 | 0.0242 | 1.00 |
| \( \mu_1(\alpha = 0.5) \) | 0.399 | −0.001 | 96% | 0.0174 | 0.0165 | 1.05 |
| \( \mu_1(\alpha = 0.6) \) | 0.380 | 0.000 | 95% | 0.0184 | 0.0178 | 1.03 |
| \( \delta_1(\alpha = 0.6, \alpha' = 0.4) \) | −0.038 | 0.002 | 93% | 0.0255 | 0.0267 | 0.96 |
| \( \delta_1(\alpha = 0.6, \alpha' = 0.5) \) | −0.019 | 0.001 | 93% | 0.0126 | 0.0132 | 0.96 |
| \( \delta_1(\alpha = 0.5, \alpha' = 0.4) \) | −0.019 | 0.001 | 93% | 0.0129 | 0.0135 | 0.96 |
| When untreated | | | | | | |
| \( \mu_0(\alpha = 0.4) \) | 0.418 | −0.001 | 95% | 0.0185 | 0.0188 | 0.99 |
| \( \mu_0(\alpha = 0.5) \) | 0.399 | −0.000 | 96% | 0.0173 | 0.0167 | 1.03 |
| \( \mu_0(\alpha = 0.6) \) | 0.380 | 0.000 | 96% | 0.0235 | 0.0231 | 1.02 |
| \( \delta_0(\alpha = 0.6, \alpha' = 0.4) \) | −0.038 | 0.001 | 94% | 0.0248 | 0.0259 | 0.96 |
| \( \delta_0(\alpha = 0.6, \alpha' = 0.5) \) | −0.019 | 0.000 | 94% | 0.0122 | 0.0127 | 0.96 |
| \( \delta_0(\alpha = 0.5, \alpha' = 0.4) \) | −0.019 | 0.000 | 94% | 0.0126 | 0.0131 | 0.96 |

Note: 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.
For each simulated dataset, the proposed g-formula estimator and the Barkley et al. IPW estimator were computed. The simulation setting considered here as shown in Table 2. While the IPW estimator is consistent as the number of clusters grows large, there are no established theoretical results showing the IPW estimator is consistent when the size of the clusters increases while the number of clusters is held fixed. Moreover, the IPW estimator entails inverse weighting by cluster propensity scores, which tend to decrease as the cluster sizes increase, leading to greater variability and increased bias for the simulation setting considered here as shown in Table 2.

### Summary of simulation study results comparing g-formula and IPW as described in Section 3.

| Estimand | Truth | G-formula bias | G-formula ESE | IPW bias | IPW ESE |
|----------|-------|----------------|---------------|----------|---------|
| 125 clusters of sizes 8, 16, 20 | | | | | |
| \(\mu(\alpha = 0.4)\) | 0.418 | -0.000 | 0.015 | -0.003 | 0.035 |
| \(\mu(\alpha = 0.5)\) | 0.399 | 0.000 | 0.012 | -0.001 | 0.014 |
| \(\mu(\alpha = 0.6)\) | 0.380 | 0.000 | 0.014 | -0.003 | 0.024 |
| \(\delta(\alpha = 0.6, \alpha' = 0.4)\) | -0.038 | 0.001 | 0.017 | 0.000 | 0.037 |
| \(\delta(\alpha = 0.6, \alpha' = 0.5)\) | -0.019 | 0.000 | 0.009 | -0.003 | 0.020 |
| \(\delta(\alpha = 0.5, \alpha' = 0.4)\) | -0.019 | 0.000 | 0.009 | 0.003 | 0.029 |
| 125 clusters of sizes 20, 50, 100 | | | | | |
| \(\mu(\alpha = 0.4)\) | 0.418 | -0.000 | 0.011 | -0.006 | 0.247 |
| \(\mu(\alpha = 0.5)\) | 0.399 | 0.000 | 0.007 | 0.002 | 0.016 |
| \(\mu(\alpha = 0.6)\) | 0.380 | 0.000 | 0.011 | -0.008 | 0.266 |
| \(\delta(\alpha = 0.6, \alpha' = 0.4)\) | -0.038 | 0.000 | 0.018 | -0.002 | 0.362 |
| \(\delta(\alpha = 0.6, \alpha' = 0.5)\) | -0.019 | 0.000 | 0.009 | -0.006 | 0.262 |
| \(\delta(\alpha = 0.5, \alpha' = 0.4)\) | -0.019 | 0.000 | 0.009 | 0.004 | 0.240 |
| 125 clusters of sizes 40, 100, 200 | | | | | |
| \(\mu(\alpha = 0.4)\) | 0.418 | 0.000 | 0.010 | -0.032 | 0.299 |
| \(\mu(\alpha = 0.5)\) | 0.399 | 0.000 | 0.005 | -0.005 | 0.021 |
| \(\mu(\alpha = 0.6)\) | 0.380 | 0.000 | 0.010 | -0.047 | 0.172 |
| \(\delta(\alpha = 0.6, \alpha' = 0.4)\) | -0.038 | -0.001 | 0.018 | -0.015 | 0.339 |
| \(\delta(\alpha = 0.6, \alpha' = 0.5)\) | -0.019 | -0.000 | 0.009 | -0.042 | 0.166 |
| \(\delta(\alpha = 0.5, \alpha' = 0.4)\) | -0.019 | -0.000 | 0.009 | 0.027 | 0.291 |

Note: Truth: true value of the estimand targeted by the estimator. Bias: average bias of the g-formula and IPW estimates over 1000 datasets. ESE: empirical standard error. Results are for all individuals (overall effect).

Bernoulli random variables with mean \(\eta_{ij} = \expit(\beta_0 + \beta_1 L_{ij} + \beta_2 S_i + \beta_3 L_{2j})\) where \(\beta = (\logit(0.6), -0.01, -0.8, -0.01)'\). For each simulated dataset, the proposed g-formula estimator and the Barkley et al. IPW estimator were computed. Results in the top panel of Table 2 show both estimators are approximately unbiased, but the ESE of the IPW estimator is roughly twice as large.

Because the IPW estimator is known to not perform well in the presence of large clusters (as in the bed net study), the simulation study described in the previous paragraph was repeated, but in step (i), the number of individuals per cluster \(N_i\) was simulated under two additional scenarios: (i) \(P(N_i = 20) = 0.4, P(N_i = 50) = 0.35, P(N_i = 100) = 0.25,\) and (ii) \(P(N_i = 40) = 0.4, P(N_i = 100) = 0.35, P(N_i = 200) = 0.25.\) For these simulations, the bias of the IPW estimator increased as the cluster size increased, and the ESE was an order of magnitude larger than the g-formula estimator for most estimands; see the middle and bottom panels of Table 2. While the IPW estimator is consistent as the number of clusters grows large, there are no established theoretical results showing the IPW estimator is consistent when the size of the clusters increases while the number of clusters is held fixed. Moreover, the IPW estimator entails inverse weighting by cluster propensity scores, which tend to decrease as the cluster sizes increase, leading to greater variability and increased bias for the simulation setting considered here as shown in Table 2.

## 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 1,
a single linkage agglomerative hierarchical cluster method\textsuperscript{23} 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 km. This distance was selected based on the maximum flight distance of an \textit{Anopheles} mosquito.\textsuperscript{24} 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 km, while urban clusters were displaced up to 2 km.\textsuperscript{9} Using this clustering algorithm, there were 395 clusters with at least one child that were not missing spatial information and other covariates. Figure 2 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.

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-km radius the month before the survey, and proportion of agricultural land cover within a 10-km radius in 2013. The building material variable was defined similarly to Levitz et al,\textsuperscript{10} 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 conditional exchangeability assumption supposes that, within strata of clusters defined by levels of these eight covariates, the proportion of children using bed nets is essentially randomized.

These covariates were selected based on prior research showing that each covariate is predictive of both the exposure and the outcome. Gender has been found to be associated with malaria; in particular, pregnant women may attract more malaria-carrying mosquitoes and have decreased malaria immunity.\textsuperscript{24–28} Women, and in particular pregnant women, have been found to use bed nets more often.\textsuperscript{27,29} Age is associated with malaria prevalence in several studies, with children being particularly vulnerable due to low malaria immunity.\textsuperscript{10,24–28} Children under 5 years old, along with older adults, tend to be more likely to use bed nets.\textsuperscript{29,31} Housing quality and urbanicity are both associated with malaria prevalence, where traditional homes or sleeping outside are associated with increased malaria risk.\textsuperscript{10,24,26} Individuals sleeping in temporary housing such as tents or those in poor, rural areas may not be able to afford bed nets or housing that prevents mosquito entry,\textsuperscript{26,28} while individuals in urban areas may be more inclined to use bed nets due to increased exposure to education and health systems.\textsuperscript{27} Altitude, temperature, precipitation, and agricultural land cover are all associated with malaria prevalence, with more favorable climates for malaria parasites and mosquito larvae leading to increased malaria risk.\textsuperscript{10,24,26,28} In areas where the perceived malaria risk is low due to unfavorable conditions for mosquitoes or malaria parasites, bed net use may be decreased.\textsuperscript{31} Additionally, in warmer temperatures, individuals may choose not to use bed nets if it’s too hot when using them or if they sleep outdoors.\textsuperscript{28,31}

In addition to conditional exchangeability, WSI was assumed conditional on the same set of covariates as the conditional exchangeability assumption. The WSI assumption supposes that within the strata of clusters having the same covariate values, the expected cluster-level malaria outcome depends only on the proportion of children using bed nets but not on which particular children use bed nets.
Figure 3 displays g-formula estimates and corresponding point-wise 95% confidence intervals 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 shows that the overall risk of malaria decreases as $\alpha$ increases, which is not surprising since bed nets are known to protect against malaria and bed net usage increases with $\alpha$. The middle panel of Figure 3 demonstrates that the risk of malaria when treated also decreases as $\alpha$ increases. On the other hand, there appears to be little or no effect when untreated (right panel of Figure 3).

Estimates and point-wise 95% confidence intervals of the overall effects, effects when treated, and effects when untreated for different policies $\alpha$ compared to the current factual policy $\alpha' = 0.55$ are displayed in Figure 4. 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 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 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 the sake of comparison, the Barkley et al\textsuperscript{5} 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,

![Figure 3](image-url)

**Figure 3** Estimates of the population mean estimands from the malaria bed net study. The proportion of treated children is denoted by policy $\alpha$. The shaded regions indicate point-wise 95% confidence intervals.

![Figure 4](image-url)

**Figure 4** Estimated effects from the malaria bed net study. The proportion of treated children is denoted by policy $\alpha$. Effects contrast $\alpha$ with $\alpha' = 0.55$, the current factual policy. The shaded regions indicate point-wise 95% confidence intervals.
hence it was not possible to compute the IPW estimates. Given that the DRC data includes several large clusters, it is not surprising issues were encountered when attempting to compute the IPW estimator. See Saul and Hudgens\(^3\)\(^2\) for further discussion related to computational issues of partial interference IPW estimators. A possible workaround would be to exclude the large clusters,\(^3\)\(^3\) but this would inefficiently discard data and limit the generalizability of the results.

The results above are based on the 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 and 2.5 km. There were 415 clusters in the 5 km analysis and 449 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, 5, and 10 km analyses; see Figure 5.

The g-formula approach relies on the correct specification of the outcome model, and thus, assessing the robustness of results to model specification is essential when using this method in practice. Various sensitivity analyses of the DRC data did not result in meaningful changes in the conclusions. For example, the results in Supplementary Figures S1 and S2 show the population mean estimates were similar to the original estimates when each of the eight covariates was individually dropped from the outcome model. The sensitivity of the results to the specified outcome regression link function was also assessed. Results in Supplementary Figure S3 show that when the probit link function was used instead of the logit link function for treatment and outcome models, the estimates were almost identical to the original scenario. Finally, an interaction term between \(S\) and the average total precipitation in a 10 km radius at the month before the survey was included in the outcome model, and the estimates did not appreciably change relative to the original estimates from the model without the interaction term (Supplementary Figure S3).

To investigate the effect of changing the proportion of the entire population who use bed nets, the 10-km clusters were also analyzed using the methods from Section 2.4 with separate parametric models fit for \(S_1\) given \(L\), \(S_2\) and for \(S_2\) given \(L\). The estimated population means for the general population policy compared to the children-only policy are shown in Figure 6. 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 effect when untreated, the estimates are approximately the same for both the children-only and general population policies.

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.\(^3\) The g-formula estimator can accommodate large clusters,
FIGURE 6  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).

unlike IPW estimators,\textsuperscript{33,34} 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\textsuperscript{4} and Barkley et al,\textsuperscript{5} the proposed methods target counterfactual estimands, which allow for within-cluster dependence of treatment selection and thus may be more relevant to policymakers. 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.

The approach used in this paper requires only cluster-level covariates, exposures, and outcomes, and thus may be of particular utility in settings where individual-level data is not available and only cluster-level variables are observed. As noted by one reviewer, the approach in this paper accommodates partial interference by essentially reframing as a ’classic causal inference’ problem where the clusters as units and i.i.d. unit-level data are observed. Moreover, the g-formula estimator could easily be adapted to the no interference setting where the exposure is a fraction between 0 and 1.

The analysis of the DRC Demographic and Health Survey data in Section 4 provides evidence that increasing the proportion of children who use bed nets reduces the proportion of children with malaria. The protective effect of bed nets was found to be more pronounced in children who use bed nets compared to children who do not. These results complement existing research on the population-level effects of bed nets. For example, community-level effects of bed net use have previously been found to affect the overall risk of malaria among individuals within the community.\textsuperscript{35,36} Additionally, previous studies have shown that community-level bed net coverage can have indirect (ie, spillover) protective effects.\textsuperscript{37-40} Similar to the results in this paper, Escamilla et al\textsuperscript{41} found that the protective association of community-level bed net coverage with malaria morbidity in Malawi was greater among children who used bed nets compared to children who did not. Likewise, using the same DRC data as in this paper, Levitz et al\textsuperscript{10} found community-level bed net use was associated with a lower prevalence of malaria, and in individuals who used bed nets, the odds of malaria were further diminished. The DRC data analysis presented in Section 4 extends these previous association-type analyses of population-level bed net usage to inference about the different causal effects of bed nets. Such inference quantifies the expected number of malaria cases prevented for different levels of bed net coverage when individuals use bed nets as well as when individuals do not, thus providing a clearer interpretation of and additional insight into the population-level impact of bed nets for investigators and policymakers.

There are several possible areas of further methodological research related to this paper. For example, the consistency of the proposed g-formula estimator requires that the parametric models be correctly specified. These models make explicit assumptions on the cluster-level data generating process (DGP) without explicitly imposing any assumptions on the individual-level DGP. That said, individual-level DGPs that do not marginalize to the assumed cluster-level DGP are implicitly assumed to not hold. Future research could explore relaxing these parametric assumptions, perhaps by using semiparametric or nonparametric (ie, machine learning) methods. In no interference setting, Kennedy\textsuperscript{12}
considers estimands similar to the estimands in this paper corresponding to average potential outcomes when the proportion treated is increased. Kennedy proposes nonparametric doubly robust estimators, which tend to have smaller bias but larger variance than the parametric approach considered in this paper. Extensions of the proposed method which relax the partial interference assumption and thereby allowing for more general (eg, spatial) interference could be considered. The method developed here considers only a univariate exposure, such as bed net usage in the malaria study, and makes no assumptions about other possible exposures. Future research could extend the methods in this paper to draw inference about the joint effects of multivariate exposures in the presence of partial interference. In the context of malaria, such methods could be used to assess the effects of policies on bed net usage and other risk factors for malaria, such as spraying of insecticides or other approaches to mosquito control. The RTS, S/AS01 malaria vaccine was recently recommended for widespread use by the World Health Organization, and it would also be of interest to assess the joint effect of bed nets and vaccination. As the total number of bed nets may be limited in practice, it may be helpful to extend the proposed methods to estimate an optimal bed net allocation strategy based on cluster characteristics, subject to some constraints on the total number of bed nets available. Finally, the approach in this paper defines the unit as the cluster, which has advantages but does not easily permit inference about the direct effect. G-formula based estimates of direct effects could be developed, presumably based on individual-level potential outcomes.

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DATA AVAILABILITY STATEMENT

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.

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REFERENCES

1. Cox DR. Planning of Experiments. New York: Wiley; 1958.
2. Sobel ME. What do randomized studies of housing mobility demonstrate? Causal inference in the face of interference. J Am Stat Assoc. 2006;101(476):1398-1407.
3. Tchetgen Tchetgen EJ, VanderWeele TJ. On causal inference in the presence of interference. Stat Methods Med Res. 2012;21(1):55-75.
4. Papadogeorgou G, Mealli F, Zigler CM. Causal inference with interfering units for cluster and population level treatment allocation programs. Biometrics. 2019;75(3):778-787.
5. Barkley BG, Hudgens MG, Clemens JD, Ali M, Emch ME. Causal inference from observational studies with clustered interference, with application to a cholera vaccine study. Ann Appl Stat. 2020;14(3):1432-1448.
6. Park C, Kang H. Efficient semiparametric estimation of network treatment effects under partial interference. Biometrika. 2022;109(4):1015-1031.
7. Robins J. A new approach to causal inference in mortality studies with sustained exposure period — application to control of the healthy worker survivor effect. Math Model. 1986;7:1393-1512.
8. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health. 2006;60(7):578-586.
9. Ministère du Plan et Suivi de la Mise en oeuvre de la Révolution de la Modernité (MPSMRM), Ministère de la Santé Publique (MSP), and ICF International. République Démocratique du Congo Enquête Démographique et de Santé (EDS-RDC) 2013-2014 [Dataset]. CDPR61SD, CDGE61FL. Rockville, Maryland, 2014.
10. Levitz L, Janko M, Mwandagalirwa K, et al. Effect of individual and community-level bed net usage on malaria prevalence among under-fives in the Democratic Republic of Congo. Malar J. 2018;17(1):39.
11. Muñoz ID, Van Der Laan M. Population intervention causal effects based on stochastic interventions. Biometrics. 2012;68(2):541-549.
12. Kennedy EH. Nonparametric causal effects based on incremental propensity score interventions. *J Am Stat Assoc.* 2019;114(526):645-656.

13. Wen L, Marcus JL, Young JG. Intervention treatment distributions that depend on the observed treatment process and model double robustness in causal survival analysis. *Stat Methods Med Res.* 2023;32(3):509-523.

14. Lee C, Zeng D, Hudgens MG. Efficient nonparametric estimation of stochastic policy effects with clustered interference. *J Am Stat Assoc.* 2024;1–23. In press. doi:10.1080/01621459.2024.2340789

15. Rubin DB. Causal inference using potential outcomes: design, modeling, decisions. *J Am Stat Assoc.* 2005;100(469):322-331.

16. VanderWeele TJ, Tchetgen Tchetgen EJ. Effect partitioning under interference in two-stage randomized vaccine trials. *Stat Probab Lett.* 2011;81(7):861-869.

17. Crawford FW, Morozova O, Buchanan AL, Spiegelman D. Interpretation of the individual effect under treatment spillover. *Am J Epidemiol.* 2019;188(8):1407-1409.

18. Richardson TS, Robins JM. Single world intervention graphs (SWIGs): a unification of the counterfactual and graphical approaches to causality. Center for the Statistics and the Social Sciences, University of Washington Series Working Paper, 128(30):2013.

19. Hudgens MG, Halloran ME. Toward causal inference with interference. *J Am Stat Assoc.* 2008;103(482):832-842.

20. Stefanski LA, Boos DD. The calculus of M-estimation. *Am Stat.* 2002;56(1):29-38.

21. Robins JM, Wasserman L. Estimation of effects of sequential treatments by reparameterizing directed acyclic graphs. Proceedings of the Thirteenth Conference on Uncertainty in Artificial Intelligence. 1997.

22. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *Int J Epidemiol.* 2009;38(6):1599-1611.

23. Everitt BS, Landau S, Leese M, Stahl D. *Cluster Analysis.* Fifth ed. Chichester, United Kingdom: John Wiley & Sons Ltd; 2011.

24. Janko MM, Irish SR, Reich BJ, et al. The links between agriculture, *anopheles* mosquitoes, and malaria risk in children younger than 5 years in the Democratic Republic of the Congo: a population-based, cross-sectional, spatial study. *Lancet Planetary Health.* 2018;2(2):e74-e82.

25. Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. *Lancet.* 2000;355(9192):1972.

26. Smith J, Mumbengegwi D, Haindongo E, et al. Malaria risk factors in northern Namibia: the importance of occupation, age and mobility in characterizing high-risk populations. *PLoS One.* 2021;16(6):1-23.

27. Kuse K, Chikako T, Bacha R, Hagan JJr, Seidu AA, Ahinkorah B. Multilevel modelling of individual, community and regional level factors associated with insecticide-treated net usage among pregnant women in Ethiopia. *Healthcare.* 2022;10(8):1418.

28. CDC: Center for Disease Control and Prevention. Parasites-Malaria. [https://www.cdc.gov/parasites/malaria/index.html](https://www.cdc.gov/parasites/malaria/index.html) 2023.

29. Olapeju B, Choiriyah I, Lynch M, et al. Age and gender trends in insecticide-treated net use in sub-Saharan Africa: a multi-country analysis. *Malar J.* 2018;17(423):1-12.

30. Carneiro I, Roca-Feltz A, Griffin J, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. *PLoS One.* 2010;5(2):1-10.

31. Xu JW, Liao YM, Liu H, Nie RH, Havumaki J. Use of bed nets and factors that influence bed net use among Jinuo ethnic minority in southern China. *PLoS One.* 2014;9(7):e103780.

32. Saul BC, Hudgens MG. A recipe for interference: start with causal interference. Add interference. Mix well with R. *J Stat Softw.* 2017;82(2):1-21. doi:10.18637/jss.v082.i02

33. Klinkard S, Hudgens MG, Halloran ME, Clemens JD, Ali M, Emch ME. Inverse probability weighted estimators of vaccine effects accommodating partial interference and censoring. *Biostatistics.* 2022;78:777-788.

34. Liu L, Hudgens MG, Saul B, Clemens JD, Ali M, Emch ME. Doubly robust estimation in observational studies with partial interference. *Stat.* 2019;8(1):e214.

35. Binka FN, Kubaje A, Adjuk M, et al. Impact of permethrin impregnated bednets on child mortality in Kassena-Nankan district, Ghana: a randomized controlled trial. *Trop Med Int Health.* 1996;1(2):147-154.

36. Hii JLK, Smith T, Younatsou P, et al. Area effects of bednet use in a malaria-endemic area in Papua New Guinea. *Trans R Soc Trop Med Hyg.* 2001;95(1):7-13.

37. Binka FN, Indome F, Smith T. Impact of spatial distribution of permethrin-impregnated bed nets on child mortality in rural northern Ghana. *Am J Trop Med Hyg.* 1998;59(1):80-85.

38. Howard SC, Ommombo J, Nevill C, Some ES, Donnelly CA, Snow RW. Evidence for a mass community effect of insecticide-treated bednets on the incidence of malaria on the Kenyan coast. *Trans R Soc Trop Med Hyg.* 2000;94(4):357-360.

39. Maxwell CA, Musuya E, Sudi M, Njunwa KJ, Carneiro IA, Curtis CF. Effect of community-wide use of insecticide-treated nets for 3–4 years on malarial morbidity in Tanzania. *Tropical Med Int Health.* 2002;7(12):1003-1008.

40. Hawley WA, Phillips-Howard PA, Ter Kuile FO, et al. Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. *Am J Trop Med Hyg.* 2003;68(4):121-127.

41. Escamilla V, Alker A, Dandalo L, et al. Effects of community-level bed net coverage on malaria morbidity in Lilongwe, Malawi. *Malar J.* 2017;16(142):1-9.

42. Wang Y, Samii C, Chang H, Aronow P. Design-based inference for spatial experiments with interference. *arXiv preprint arXiv:2010.13599* 2020.

43. Leung MP. Rate-optimal cluster-randomized designs for spatial interference. *Ann Stat.* 2022;50(5):3064-3087.
44. Maxmen A. Scientists hail historic malaria vaccine approval—but point to challenges ahead. *Nature*. 2021. doi:10.1038/d41586-021-02755-5

45. Ananth A. *Optimal treatment assignment rules on networked populations*. Technical Report, working paper 2020.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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