BIOMETRIC METHODOLOGY

Biometrics WILEY

Spatial regression and spillover effects in cluster randomized trials with count outcomes

Karim Anaya-Izquierdo[1] | Neal Alexander[2]

[1] Department of Mathematical Sciences, University of Bath, Bath, UK

[2] MRC Tropical Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Correspondence
Neal Alexander, MRC Tropical Epidemiology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK.
Email: neal.alexander@lshtm.ac.uk

Abstract
This paper describes methodology for analyzing data from cluster randomized trials with count outcomes, taking indirect effects as well spatial effects into account. Indirect effects are modeled using a novel application of a measure of depth within the intervention arm. Both direct and indirect effects can be estimated accurately even when the proposed model is misspecified. We use spatial regression models with Gaussian random effects, where the individual outcomes have distributions overdispersed with respect to the Poisson, and the corresponding direct and indirect effects have a marginal interpretation. To avoid spatial confounding, we use orthogonal regression, in which random effects represent spatial dependence using a homoscedastic and dimensionally reduced modification of the intrinsic conditional autoregression model. We illustrate the methodology using spatial data from a pair-matched cluster randomized trial against the dengue mosquito vector *Aedes aegypti*, done in Trujillo, Venezuela.

KEYWORDS
cluster randomized trial, depth, indirect effect, spatial dependence, spillover effect

1 | INTRODUCTION

A cluster randomized trial (CRT) is an experiment in which groups, rather than individuals, are randomized (Hayes and Moulton, 2009). The clusters are usually defined geographically (eg, houses or communities) or institutionally (eg, health facilities or schools). One reason for randomizing by cluster is to achieve a mass or indirect effect (Halloran and Struchiner, 2009), which we take to mean an effect exerted by the intervention on individuals who do not receive it. Another reason is to reduce contamination, that is, some individuals in the control arm receiving an intervention intended for the other arm (Hayes and Moulton, 2009): this is not addressed in the current paper.

We identify indirect effects resulting from proximity between clusters, which we call *spillover indirect effects*. We use the term "spillover" to refer to between-cluster effects.

Others have used this term more generally, to include within-cluster effects, such as those of the interventions on nonparticipants (Benjamin-Chung *et al.*, 2017). Moreover, the terms interference, and indirect effects, have been used as synonyms for spillover (VanderWeele *et al.*, 2012; Perez-Heydrich *et al.*, 2014), that is, more generally than used here. Vanderweele *et al.* (2013) consider spillover effects to be components of indirect effects, which is more similar to the terminology used here, although they use a causal inference framework that is not explicitly spatial. CRTs can be used to estimate certain indirect effects, for example, vaccine herd protection (Longini *et al.*, 1998), and this is more accurate when the clusters are independent, that is, in the absence of "spillover" as defined in the current paper. At the same time, measurement of spillover effects, in the current sense, is important for some classes of intervention, and is a specific objective of some trials (Hawley *et al.*, 2003; McCall, 2011).

We also discuss another type of spillover effect. Independence of the clusters may be violated if they are not sufficiently separated, analogous to agricultural interplot interference (Besag and Kempton, 1986). Ideally, between-cluster independence would be achieved by having sufficiently distant clusters. For example, McCann *et al.* (2018) propose a selection method for candidate clusters that minimizes cross-cluster effects (they use the term contamination for such effects, a definition that is more general than the one stated above). However, it is not always feasible to guarantee that the clusters are independent for practical purposes, yet frequently no allowance is made for this in analysis (Jarvis *et al.*, 2017).

We discuss two types of possible dependence: intracluster correlation (Hayes and Moulton, 2009) and dependence between individual outcomes in different clusters. We call this last type *spillover dependence*. This dependence is assumed to exist prior to the intervention and may arise from: (a) the spatial configuration of the individuals in the trial, (b) contact patterns of infectious diseases and (c) individuals belonging to more than one cluster either sequentially or simultaneously (Silcocks and Kendrick, 2010).

For two-arm CRTs with a count outcome, we propose spatial regression methods to identify, and adjust for, both types of spillover effect, while incorporating the cluster-randomized design. Spillover indirect effects are addressed via an individual-level covariate that measures the degree of surroundedness of individuals in either arm to others in the intervention arm. The estimates of the intervention effects, and of the spillover indirect effects, have simple interpretations in terms of marginal expectations and they are well defined even when the proposed model does not hold. Spillover dependence is addressed via spatially correlated random effects.

2 | METHODOLOGY

2.1 | The proposed individual-level model

When individual level count data are available, generalized linear Poisson models with random effects are commonly used to analyze CRTs, with one random effect per cluster (Hayes and Moulton, 2009). Suppose there are q clusters and a total of n individuals in the trial. The count outcomes are denoted by $Y_1, Y_2, \ldots, Y_n$ and the corresponding denominators by $L_1, \ldots, L_n$, while $\boldsymbol{c}^T = (c_1, \ldots, c_n)$ is the vector of cluster random effects ($\boldsymbol{c}^T$ denotes the transpose of $\boldsymbol{c}$). In this paper, we assume that each outcome is associated with a single geographical point location and that such information is available. We use $\boldsymbol{s}^T = (s_1, s_2, \ldots, s_n)$, a vector of spatially correlated random effects, to model geographical dependence. Conditionally on the random

effects, $Y_1, \ldots, Y_n$ are assumed independent with Poisson distribution and conditional means given by

$$E(Y_i \mid \boldsymbol{c}, \boldsymbol{s}) = L_i \exp\{\alpha + \beta\, t_i + \eta\, d_i\, t_i$$
$$+ \gamma\, d_i\, (1 - t_i) + c_i + s_i\}. \tag{1}$$

The binary variable t_i indicates whether individual i is in a control or intervention cluster ($t_i = 0, 1$, respectively). The variable d_i and its interaction with t_i are introduced to model spillover indirect effects (Section 2.3). The standard regression model for CRTs with count outcomes (Clark and Bachmann, 2010) corresponds to the case where there are no spillover indirect effects ($\gamma = \eta = 0$) and also no geographical dependence ($\sigma_s^2 = 0$ so that $s_i \equiv 0$), namely

$$E(Y_i \mid \boldsymbol{c}) = L_i \exp(\alpha_0 + \tau_0\, t_i + c_i), \tag{2}$$

where the 0 subscripts are introduced to distinguish the parameters from those in (1). We will call Equation (1) the extended model. We use $N_m(\boldsymbol{0}, \boldsymbol{Q})$ to denote the multivariate normal distribution of dimension m with zero mean vector and covariance matrix $\boldsymbol{Q}$, and $\boldsymbol{I}_m$ denotes the identity matrix of dimension $m \times m$. We assume the cluster random effects vector $\boldsymbol{c}$ has the form $\boldsymbol{Z}_c\,\boldsymbol{a}$, where $\boldsymbol{a} \sim N_q(\boldsymbol{0}, \sigma_c^2\, \boldsymbol{I}_q)$ and the cluster design matrix $\boldsymbol{Z}_c$ contains q cluster-level covariates, where the lth covariate is a vector with 1s in entries corresponding to individuals in cluster l, and 0s elsewhere. To model the geographical dependence, we restrict the spatial random effects to have linear form, namely $\boldsymbol{s} = \boldsymbol{Z}_s\,\boldsymbol{b}$, where $\boldsymbol{Z}_s$ is a known matrix with k columns that takes into account the spatial structure and $\boldsymbol{b} \sim N_k(\boldsymbol{0}, \sigma_s^2\, \boldsymbol{I}_k)$. The linear form assumption, and the choice of k (the number of columns of $\boldsymbol{Z}_s$), are discussed in Sections 2.4.3 and 2.4.4.

Let $\boldsymbol{X}$ denote the fixed effects design matrix of the extended model (1). Then the linear predictor can be written in vector form as $\boldsymbol{X}\boldsymbol{\theta} + \boldsymbol{Z}_c\,\boldsymbol{a} + \boldsymbol{Z}_s\,\boldsymbol{b}$, where $\boldsymbol{\theta} = (\alpha, \beta, \eta, \gamma)^T$. We restrict the spatial design matrix $\boldsymbol{Z}_s$ to satisfy the condition $\boldsymbol{X}^T\boldsymbol{Z}_s = \boldsymbol{0}$ so its columns are orthogonal to those of $\boldsymbol{X}$. The orthogonality between fixed and random effects design matrices is required to avoid so-called *spatial confounding* that is discussed in Section 2.4.1.

2.1.1 | Marginal interpretation

By integrating out all the random effects, the extended model (1) can also be thought of as a marginal probability model, known as the multivariate Poisson-lognormal distribution (Aitchison and Ho, 1989). There is no closed-form expression for the density but the marginal means can be

expressed as

$$E(Y_i) = L_i \exp\left\{\alpha + \beta t_i + \eta d_i t_i + \gamma d_i (1 - t_i) + \frac{V_i}{2}\right\},$$
(3)

where we define $V_i := \text{Var}(c_i + s_i) = \sigma_c^2 + \sigma_s^2 z_i^T z_i$ and z_i is the ith row of Z_s. The standard model can also be seen as a marginal model but where $V_i = \text{Var}(c_i) = \sigma_c^2$ does not depend on i. The marginal variance of the extended model is $\text{Var}(Y_i) = E(Y_i)[1 + E(Y_i)\{\exp(V_i) - 1\}]$ which shows that the marginal distribution of Y_i is overdispersed with respect to the Poisson.

2.2 | Intervention effects

In this section, we identify different ways to quantify the effect of the intervention in the population. Their use will depend on the aims of the particular cluster randomized trial. We emphasize that all the intervention effects defined in the following sections (eg, 2.2.1, 2.2.2, and 2.3) are meaningful irrespective of any underlying assumed model. This is because they are defined in terms of marginal expectations of the outcome variable Y_i. In particular, these intervention effects are meaningful even when the extended model does not hold.

2.2.1 | Pairwise intervention effect

We define the individual-level pairwise intervention effect as

$$Pint_{ij} := \log\left\{E(Y_i/L_i)/E(Y_j/L_j)\right\},$$
(4)

where i and j correspond to individuals in the intervention and control arm, respectively. In particular, for the standard model (2) we have that $Pint_{ij} = \tau_0$ for all i, j. However, for the extended model, $Pint_{ij} = \beta + \eta d_i - \gamma d_j + (V_i - V_j)/2$, which varies over (i, j). Specifically, there is dependence on (d_i, d_j) as well as on (V_i, V_j).

2.2.2 | Total intervention effect

Let C_1 and C_0 be the set of indices of individuals in the intervention and control arms, respectively, and let $L_m^+ = \sum_{i \in C_m} L_i$ for $m = 0, 1$. The *total intervention effect* is defined as

$$Tint := \log\left\{\frac{\sum_{i \in C_1} E(Y_i)/L_1^+}{\sum_{j \in C_0} E(Y_j)/L_0^+}\right\},$$
(5)

that is, the logarithm of the ratio between the expected raw rates in the intervention and control arm. There are alternative choices for a total intervention effect (see Chapter 10 of Hayes and Moulton, 2009 and the discussion section in this paper) and we do not evaluate them in this paper. For the extended model (1) the total intervention effect *Tint* can be written as

$$\beta + \kappa(\eta, \gamma, \sigma_s^2),$$
(6)

which from now on we denote by τ, and where

$$\kappa(\eta, \gamma, \sigma_s^2) = \log\left[\frac{\sum_{i \in C_1} L_i \exp\{\eta d_i + (\sigma_s^2/2) z_i^T z_i\}/L_1^+}{\sum_{j \in C_0} L_j \exp\{\gamma d_j + (\sigma_s^2/2) z_j^T z_j\}/L_0^+}\right],$$
(7)

which does not depend on σ_c^2 as it cancels in (7). Based on its factorization in Equation (6), we can interpret τ as the sum of two terms: β, the direct contribution of each intervention and individual; and κ, the contribution of all the indirect effects. In Section 2.3.4, we show that β and κ keep the same interpretations outside the extended model. Under the standard model $\kappa(\eta, \gamma, \sigma_s^2) \equiv 0$ and therefore $Tint = \tau_0$ is the total intervention effect. This highlights the fact that, perhaps contrary to intuition, the parameter β, when the extended model holds, has a different interpretation to that of τ_0 when the standard model holds, both being the multipliers of the intervention variable t_i in each case. As opposed to the pairwise intervention effect $Pint_{ij}$ that in general depends of the chosen pair (i, j), we emphasize the statistical inference regarding the total intervention effect *Tint*, which is a single quantity and is meaningful even under misspecification of either the standard or extended model. Estimates of *Tint* under the standard model are simply estimates of τ_0 while, under the extended model, they are estimates of τ, constructed using expressions (6) and (7). We describe our estimation procedures in Section 3.

2.2.3 | The constant variance property

A special case of the total and pairwise intervention effects in the extended model arises when the variances $\text{Var}(s_i) = \sigma_s^2 z_i^T z_i$ do not depend on i. In this situation, both the total intervention effect parameter τ and all the pairwise intervention effects depend only on fixed effects β, η, and γ and not on any variance component σ_c^2 or σ_s^2. This motivates the following definition:

Definition: The constant variance (CV) property *A model of the form* (1) *has the constant variance property when the spatial variance* $\text{Var}(s_i)$ *does not depend on i.*

A sufficient condition for this property is that the rows of the spatial design matrix Z_s have unit norm, that is, $z_i^T z_i = 1$ for all i. Henceforth, we further restrict our proposed extended model (1) so that the rows of spatial design matrix Z_s have unit norm and therefore the parameter κ in (7) only depends on η and γ and simplifies to

$$\kappa(\eta, \gamma) = \log \left\{ \frac{\sum_{i \in C_1} L_i \exp(\eta \, d_i)/L_1^+}{\sum_{j \in C_0} L_j \exp(\gamma \, d_j)/L_0^+} \right\}, \qquad (8)$$

In Section 2.4.2, we describe an algorithm to make the unit norm restriction on the rows of Z_s consistent with the orthogonality condition on its columns.

2.3 | Spillover indirect effects

CRTs usually include a small number of clusters (perhaps around 20 or 30) and the allocation may be geographically imbalanced in the sense of special spatial configurations. Moreover, some trials have clusters that abut each other, for example, divided by only a narrow street. We are interested in quantifying the indirect effect that such configurations may exert on trial outcomes. Here the question arises of whether intervention locations exert any indirect effect only on control locations, or also on fellow intervention locations. For generality, we allow the effects of intervention locations to differ according to the arm of the nearby locations, and hence define:

Contralateral spillover indirect effect: _An intervention effect exerted on individuals in the control arm via nearby individuals in the intervention arm;_

Ipsilateral spillover indirect effect: _An intervention effect exerted on individuals in the intervention arm, accentuated via nearby individuals that are also in the intervention arm._

To represent these types of indirect effects in the extended model (1), we need a measure d_i of the degree of closeness or surroundedness that each individual spatial location has, with respect to intervention individuals. Two such measures are described next.

2.3.1 | Measures of surroundedness

As a measure of surroundedness, we could use the linear distance from an individual (in either arm) to the closest of those in the intervention arm. However, this does not capture a possible mass effect exerted by, for example, multiple individuals in the intervention arm surrounding one in the control arm. Hence we propose that any surroundedness variable d_i should be defined as the number

of intervention individuals who, in some sense, are around the individual i.

For example, we can use the number of individuals within a specified radius who are in the intervention arm (henceforth the _disc_ measure). We also propose _depth_ (Tukey, 1975) as a measure that does not require a radius to be specified. In general, depth measures the spatial centrality of one point relative to a given set of others. To our knowledge, statistical depth has only been used as a measure of multivariate location, so its use in the context of spatial indirect effects is novel. Here we will assume only two dimensions are relevant and work in the plane, using _Tukey's half space depth: rotating a doubly infinite line through a spatial location of interest, and monitoring the number of spatial locations on each side of it, Tukey's half space depth of the index location is the smallest count occurring on either side as the line is rotated through_ $180°$. This can be computed using the algorithm of Rousseauw and Ruts (1996). For an individual in the control arm, depth is computed with respect to the set of all intervention individuals. For an individual in the intervention arm, the depth is computed with respect to the set of intervention individuals excluding itself. Either of these proposed measures of surroundedness is included in the model as a fixed effect. We elaborate further on these measures in the context of specific geographical configurations used in the simulations in Section 4.

2.3.2 | Pairwise spillover indirect effects

The pairwise spillover indirect effect is exerted by surrounding individuals, acting on the expected individual marginal rates of the outcomes. Although such an effect may be exerted across arms (contralateral), the gradient is defined with reference to individuals in the same arm. So, letting i and j be such individuals ($t_i = t_j$) for which $d_i - d_j = 1$, then the pairwise spillover indirect effect is defined as

$$Sind_{ij} := \log \left\{ E(Y_i/L_i) / E(Y_j/L_j) \right\}. \qquad (9)$$

For clarity, we define $Sind_{ij}^0$ as the pairwise spillover indirect effect for pairs of individuals in the control arm and $Sind_{ij}^1$ as the pairwise spillover indirect effect for pairs of individuals in the intervention arm. Under the extended model, and assuming the CV property, we can write $Sind_{ij}^0 = \gamma$ and $Sind_{ij}^1 = \eta$ so they do not depend on the particular pair of individuals selected, but only on whether the individuals are both in the control or both in the intervention arm. For each extra surrounding individual in the intervention arm, individual i's expected rate changes by a factor of $\exp(\gamma)$ if i is in the control arm, and

by $\exp(\eta)$ if in the intervention arm. In this way, γ then represents the pairwise contralateral spillover indirect effect, and η the pairwise ipsilateral spillover indirect effect.

2.3.3 | Total spillover indirect effects

Let n_1 and n_0 be the number of individuals in the intervention and control arms, respectively. To define a total contralateral indirect effect, we first note that we can assume that the values of the surroundedness variable for individuals in the control arm satisfy $d_1 \leq d_2 \leq \cdots \leq d_{n_0}$. This is always possible via relabeling of the indices in C_0. The total contralateral indirect effect (due to the surroundedness d) can then be defined as

$$Tind_0 := \frac{2}{n_0(n_0 - 1)} \sum_{\{(i,j) \in C_0 \,:\, j < i\}} \log\{E(Y_i/L_i)/E(Y_j/L_j)\}$$

$$= \overline{Sind^0}, \tag{10}$$

that is, the average of all pairwise contralateral indirect effects. The ordering restriction on the surroundedness variable is imposed to be able to interpret this effect as the average effect that increasing the surroundedness variable has on individual rates. The total ipsilateral indirect effect $Tind_1$ can be defined in a similar fashion. In the extended model, the total contralateral and ipisilateral indirect equal $\gamma \bar{\Delta}_0$ and $\eta \bar{\Delta}_1$, respectively, where

$$\bar{\Delta}_0 = \frac{2}{n_0(n_0 - 1)} \sum_{\{(i,j) \in C_0 \,:\, j < i\}} (d_i - d_j),$$

$$\bar{\Delta}_1 = \frac{2}{n_1(n_1 - 1)} \sum_{\{(i,j) \in C_1 \,:\, j < i\}} (d_i - d_j), \tag{11}$$

so they are simple multiples of γ and η, respectively, with corresponding factors equal to the average pairwise difference of the surroundedness variable in the control and intervention arm, respectively. In this way, we can interpret total contralateral and ipsilateral effects geometrically where, for example, the effect of 10 extra surrounding intervention individuals reduce the individual expected response by a factor of $\exp(10\gamma)$ for individuals in the control arm.

2.3.4 | Total residual indirect effect

In this section, we give interpretations to the parameters β, κ, and α in the extended model (1) that are valid even when this model does not hold. Any proposed measure of surroundedness will be a discrete variable that allows individuals to be defined as *isolated* (from the intervention arm) if

$d_i = 0$. Let I_1 and I_0 denote the set of indices corresponding to isolated individuals in the intervention and control arm, respectively. We now define the total intervention effect for isolated individuals:

$$Tiso := \log\left\{ \frac{\sum_{i \in I_1} E(Y_i)/I_1^+}{\sum_{j \in I_0} E(Y_j)/I_0^+} \right\}, \tag{12}$$

where $I_m^+ = \sum_{i \in I_m} L_i$ for $m = 0, 1$, that is, the logarithm of the ratio between the expected rate of isolated individuals in the intervention arm and the expected rate of isolated individuals in the control arm. In the extended model, the total intervention effect for isolated individuals equals β. We can now give an interpretation to the parameter κ defined in (8) that is well defined outside the extended model. We define the total residual indirect effect *Tred* simply as the difference between the total intervention effect *Tint* and the total intervention effect for isolated individuals *Tiso*, that is

$$Tred := Tint - Tiso$$

$$= \log\left[\left\{ \frac{\sum_{i \in C_1} E(Y_i)/L_1^+}{\sum_{j \in C_0} E(Y_j)/L_0^+} \right\} \middle/ \left\{ \frac{\sum_{i \in I_1} E(Y_i)/I_1^+}{\sum_{j \in I_0} E(Y_j)/I_0^+} \right\} \right]. \tag{13}$$

Evidently, in the extended model, the total residual indirect effect *Tred* is simply given by κ, since $\kappa = \tau - \beta$. Expression (13) reveals the intuitive fact that the difference between a total effect (*Tint*) and a *pure* effect (*Tiso*) is a measure of indirect effect. In practice, however, it is possible that there are no isolated individuals in either the intervention or the control arm, that is, either $I_1 = \emptyset$ or $I_0 = \emptyset$. In that case, as there is no information in the data to estimate these effects without an assumed model, we say that the *Tiso* and the *Tred* are *not estimable*. Finally, we define the total average expected count for control isolated individuals as

$$TC_0 = \sum_{i \in I_0} E(Y_i)/I_0^+. \tag{14}$$

This quantity is equal to $\exp(\alpha)$ in the extended model, and $\exp(\alpha_0)$ in the standard model.

2.4 | Spatial modeling

The main reason to incorporate spatial dependence in our extended model is that the randomization units (clusters)

of many trials are defined geographically. In the CRT setting, the main interest is in the estimation of direct and indirect effects of the intervention, with spatial dependence being of interest insofar as it affects such estimation. Technically, the spatial random effects vector s is used to implement a smoother, with the shrinkage estimates of the fixed effects $(\alpha, \beta, \eta, \gamma)$ being interpreted accordingly (see Hodges, 2013, Chapter 10). For this reason, we focus the specification of the spatial dependence within the constrained setting that we have adopted. In this setting, $s = Z_s b$ and Z_s is a matrix to be specified that should satisfy the CV property and should be orthogonal to the fixed effect design matrix X in order to avoid the so-called spatial confounding that is described next.

2.4.1 | Spatial confounding

Adding spatially correlated random effects such as s in the extended model (1) can induce bias in the estimations, and artificially inflate the variances, of the fixed effects of interest $(\alpha, \beta, \eta,$ and $\gamma)$ (Reich *et al.*, 2006; Hodges and Reich, 2010) directly or through the estimation of any of the total effects defined in Sections 2.2.2 and 2.3.3. One reasonable procedure is to retain only random effects that are orthogonal to the fixed effects matrix X. Specifically, let $R^T = (Y_1/L_1, \dots, Y_n/L_n)$ be the random vector of individual rates, then the extended model (1) can be written in vector form as $\log\{E(R|a, b)\} = X\theta + Z_c a + H b$, where the $n \times 4$ design matrix X is assumed to have rank 4, and H is a proposed spatial design $n \times k$ matrix, which we assume has rank $k < n - 4$. Spatial confounding happens when the spatial random effects variance σ_s^2 is large with respect to the residual variation of the model (Hodges and Reich, 2010) and, at the same time, the eigenvectors of HH^T (the covariance matrix of Hb) associated with the largest eigenvalues, are strongly correlated with X.

Following Hughes and Haran, 2013, there exist orthogonal matrices K and L of dimension $n \times 4$ and $n \times (n-4)$, respectively, such that $I_n = KK^T + LL^T$. Then we can write $X\theta + Z_c a + H b = X\theta + K b_1 + Z_c a + L b_2$, where $b_1 = K^T H b$ and $b_2 = L^T H b$. The spatial confounding comes from the fact that K and X span the same column space. We follow the procedure of Reich *et al.* (2006) who suggests deleting the random effect term $K b_1$ altogether from the model in order to avoid spatial confounding. The surviving term is $L b_2 = LL^T H b \sim N_n(0, \Sigma_s)$, where the covariance matrix $\Sigma_s = LL^T HH^T LL^T$ is rank deficient, with rank equal to $\min(k, n-4) = k$. We let Z_s be the $n \times k$ matrix, with the eigenvectors of Σ_s associated with nonzero eigenvalues, and normalized so that each eigenvector has norm equal to its corresponding eigenvalue. This implies that the constructed Z_s has the same dimensions as the ini-

tial H, and $L b_2$ has the same distribution as $Z_s b$, where $b \sim N_k(0, \sigma_s^2 I_k)$. It is easy to show that we can take the eigenvectors of Σ_s to be orthogonal to X, implying that the constructed Z_s satisfies the orthogonality condition $Z_s^T X = 0$.

We note that the presence of an intercept term in the extended model means that the spatial random effect vector $s = Z_s b$, constructed above, satisfies the sum-to-zero condition: $\sum_{i=1}^n s_i = s^T 1_n = b^T Z_s^T 1 = 0$. The orthogonalization implicitly assumes that most of the variability in the outcomes is due to the covariates and not the random effects, so that the latter merely introduce spatial correlation between the outcomes. We should therefore expect the point estimates of the fixed effects under the orthogonalized model to be similar to those under the simpler model with no random effects at all (Reich *et al.*, 2006).

2.4.2 | Construction of orthogonalized models with the CV property

There is a compromise between the column orthogonality condition on Z_s and the unit-norm condition on its rows (the CV property, Section 2.2.3). We provide a simple algorithm to transform an arbitrary $n \times k$ matrix H into a matrix Z_s of the same dimensions that satisfies both conditions and which is close to the original H. First, a spatial random effects vector of the form $s = H_0 b$ has the CV property if the rows of H_0 are of unit length so that the diagonal of the covariance matrix $\text{Var}(s) = \sigma_s^2 H_0 H_0^T$ has all entries equal to 1. Transforming H_0 to $H_1 = \{\text{diag}(H_0 H_0^T)\}^{-1/2} H_0$ ensures that the resulting vector $s = H_1 b$ has the CV property. Now, for the orthogonalization, we proceed as in Section 2.4.1 by constructing H_2 with the normalized eigenvectors of the matrix $LL^T H_1 H_1^T LL^T$. The algorithm consists in repeating, in turn, the transformations to the CV property and to orthogonality, and stops when the maximum absolute angle difference (to 90°) is within a predefined small tolerance. This is an iterative projection algorithm (Bauschke and Borwein, 1996) that targets the intersection between two sets so that if the two sets have nonzero intersection, the iteration converges linearly with the total number of individuals n.

2.4.3 | Choice of the spatial design matrix

There are random effect spatial models available that already have the required linear structure $s = Hb$, such as the one proposed by Silcocks and Kendrick (2010) that addresses the situation of membership of multiple clusters. However, here we are largely motivated by trials that

randomize geographically (eg, houses based on their location) in which single cluster membership can be assumed. Other powerful and widely available spatial modeling strategies such as geostatistical modeling (Diggle and Ribeiro, 2007) for georeferenced data and intrinsic conditional autoregressive (ICAR) models for aereal data, need to be adjusted to satisfy our random effects specific structure.

ICAR models (Reich *et al.*, 2006) use only the spatial neighborhood information in an $n \times n$ adjacency matrix A. If the corresponding set of neighbors forms one connected component, then we can write $s = \frac{1}{\sqrt{n}} \mathbf{1}_n v + H_{\text{ICAR}} w$, where $w \sim N_{n-1}(\mathbf{0}, \sigma_s^2 I_{n-1})$ and $v = \sum_{i=1}^n s_i$ has a flat improper distribution. The matrix H_{ICAR} is of dimension $n \times (n-1)$ and its columns are the eigenvectors of $Q = \text{diag}(A\mathbf{1}_n) - A$ that are associated with positive eigenvalues and also normalized so that their length equals the reciprocal of its corresponding eigenvalue. All the columns in H_{ICAR} are orthogonal to $\mathbf{1}_n$, so imposing the sum-to-zero constraint $\sum_{i=1}^n s_i = 0$ yields the proper model with linear form $s = H_{\text{ICAR}} w$. This is equivalent to removing the spatial confounding with respect to only the intercept fixed effect α.

Under the sum-to-zero constraint, it is easy to show that the variances of $s = H_{\text{ICAR}} w$ are not constant as a function of i so that the ICAR specification above does not have the CV property. After enforcing this property using the algorithm in Section 2.4.2, the resulting random effect is no longer ICAR. Geostatistical models, conversely, naturally satisfy the CV property and can be written in the form $s = H_{\text{GEO}} b$ (Lindgren *et al.*, 2011), but the orthogonality condition needs to be enforced. Furthermore, the covariance matrix in geostatistical models depends on σ_s^2 as well as a scale and a smoothness parameters so, unless those extra parameters are known, the algorithm in Section 2.4.2 cannot be used and further modification is needed (see Hodges and Reich, 2010, for a related discussion).

2.4.4 | Dimension reduction in the spatial model

We now discuss the choice of the number of columns of the spatial design matrix. The number of columns in a selected H can be substantially reduced by discarding columns in the span of H that give rise to negative dependence when there is no interest in modeling this (Hughes and Haran, 2013), as is the case in many CRT applications. The choice is guided by the spectrum of the modified Moran's operator $P^\perp A P^\perp$ (Hughes and Haran, 2013), where A is the adjacency matrix of the neighborhood structure and $P^\perp$ is the projector matrix onto the space orthogonal to

the column span of X. Moran's operator $P^\perp A P^\perp$ appears in the numerator of a generalized form of Moran's I statistic: $I_A(s) \propto (s^T P^\perp A P^\perp s)/(s^T P^\perp s)$. The standardized spectrum of Moran's operator comprises all possible values of $I_A(s)$, and the eigenvectors comprise all possible mutually distinct patterns of spatial dependence. Positive (negative) eigenvalues correspond to varying degrees of positive (negative) spatial dependence. If positive spatial correlation is of interest, then we can further restrict the spatial design matrix Z_s to have the additional property that the diagonal elements of $Z_s^T (P^\perp A P^\perp) Z_s$ are all positive. This can lead to a substantial reduction on the original number of columns (Hughes and Haran, 2013). In this way, an initial matrix H can be transformed to a matrix with the desired three properties, using a modified version of the algorithm in Section 2.4.2 where the orthogonalization steps are followed by column selection where only columns that give rise to positive spatial dependence are selected. This last step preserves orthogonality.

In summary, we propose that, in the absence of a specific spatial design, one should start with H_{ICAR} and transform it, using the iterative procedure described above, into a column-reduced matrix that satisfies both the CV and orthogonality properties. As shown by Hughes and Haran (2013), the resulting models are attractive for spatial modeling, for example, in retaining only positive spatial associations and also with smooth patterns of spatial variation at various scales. As we assume point spatial data are available for each individual, we define the neigborhood structure from the corresponding Voronoi tessellation (Bivand *et al.*, 2008). This partitions the continuous plane into a set of regions called *tiles* where each tile is a convex polygon, defined as the subset of the plane for which the given location is closer than any other. We propose to use *queen type* neighbors instead of *rook type* (Bivand *et al.*, 2008) as the former are more consistent with our definition of surroundedness.

3 | STATISTICAL INFERENCE

To fit the extended model (1) to a given dataset, we use Bayesian inference for generalized linear mixed models as described in Fong *et al.* (2010) and, more specifically, *integrated nested Laplace approximations* (INLA; Rue *et al.*, 2009), which is an efficient alternative to MCMC in our our situation of only two hyperparameters (σ_c^2 and σ_s^2). For the fixed effects, we assign a flat improper prior for the intercept α and independent $N_1(0, 0.001)$ priors for β, η, and γ. For the random effect standard deviations σ_c and σ_s, we use independent exponential priors. These are weakly informative priors (called penalized complexity

priors, Simpson *et al.*, 2017) that favor the standard model in order to avoid fitting artificial spatial and cluster dependence. This is in contrast to commonly used Gamma priors for the precisions ($1/\sigma_c^2$ and $1/\sigma_s^2$) that do not allow very small values of the standard deviations and therefore can cause overfitting. Following Simpson *et al.* (2017), the penalty is given by the magnitude of the marginal standard deviation of the random effect, that is, after integrating out the prior.

INLA naturally produces marginal posterior densities for the fixed effects, which, in turn, implies marginal posteriors for the total contralateral and ipsilateral indirect effects that depend only on γ and η, respectively. To compute marginal posteriors of the total intervention effect τ and the total residual indirect effect κ, which are nonlinear functions of β, η, and γ, we use the Monte Carlo sampling procedure implemented in the INLA package in R (The R-INLA Project, 2019). This generates independent samples from the joint posterior of the fixed effects (based on a Gaussian approximation) so that we can apply Equations (6) and (8) to obtain samples from the marginal posteriors of τ and κ. The approximation is particularly good in our case as neither τ nor κ depends functionally on the hyperparameters σ_c^2 or σ_s^2.

4 | SIMULATION STUDY

We performed a simulation study in order to evaluate the operating characteristics of our method. We performed six sets of simulations: one for each measure of surroundedness described in Section 2.3.1 (disc and depth, each included as a fixed effect) and one for each of three spatial configurations. In line with similar simulation studies (Paciorek, 2010; Hughes and Haran, 2013), we assume the spatial configuration of the trial is a unit square grid in which each square represents an individual and groups of squares represent clusters. Moreover, we use square clusters so that the neighborhood structure is obvious. In order to prevent artifactual behavior of the depth being induced by the regular grid layout of the square centroids (Rousseauw and Ruts, 1996), we perturbed the individual centroids slightly.

We use a completely balanced design with 18 clusters in each arm and with nine individuals per cluster giving a total of 324 individuals. The three cluster configurations shown in Figure 1 were chosen to illustrate different patterns of surroundedness, rather than being "typical" spatial randomizations (although, as discussed in Section 6, this notion is not trivial to define).

With the aim of assessing the robustness of the proposed method, the generating model was not the extended model. However, an intervention effect and indirect effects

were present (details are in the Supporting Information section). Within each set, two models were fit: the full extended model (1), and the standard model (2). The latter was introduced to measure the influence of ignoring spillover indirect effects when they are present in the data. In this situation, as discussed in Section 2.2.2, estimates of the parameter τ_0 in the standard model are actually estimating the total intervention effect *Tint*. Results for the disc measure of surroundedness are shown in Figure 2. For the three configurations, in terms of the posterior median, the method was able to correctly estimate the target parameters (thick vertical line): the total intervention effect *Tint* (when using the standard or extended model) and the total contralateral and ipsilateral indirect effects ($Tind_0$ and $Tind_1$, respectively). However, for the *Ring* configuration, there seem to be a small bias in estimating *Tint* for the extended model that is corrected by using depth instead of the disc measure of surroundedness (corresponding histograms are in the Supporting Information section). This reflects the clear differences in values for both measures of surroundedness as shown in Figure 1. The only small bias that remains, when using both measures of surroundedness, is when estimating the total contralateral indirect effect $Tind_0$. Other differences not shown by the histograms are structural and are related to estimating other parameters such as the total residual indirect effect (*Tred*) and the total intervention effect for isolated individuals (*Tiso*). When using the disc measure, there were no isolated individuals in the intervention arm in the three configurations considered. As described in Section 2.3.4, this means that *Tred* and *Tiso* are not estimable and therefore the corresponding estimates of the parameters κ and β are still well defined but are estimating a different population parameter. This was not the case for the depth, as some individuals are defined as isolated under this measure.

In further simulations, we allowed the cluster sizes to vary, in terms of both numbers of individuals and spatial area. The conclusions remained the same, with no indication that this variation induced bias in the results.

5 | APPLICATION: TRUJILLO TRIAL

In this section, we apply the above methods to a CRT of interventions against *Aedes* mosquitoes, which are vectors of dengue and Zika viruses. In Trujillo, Venezuela, Kroeger *et al.* (2006) randomized pairs of clusters of households to a package of window curtains and water container covers treated with insecticide, or to control (no intervention). A total of 18 clusters were defined geographically and pair-matched in a semi-quantitative manner, based primarily on baseline indices of infestation of water containers by
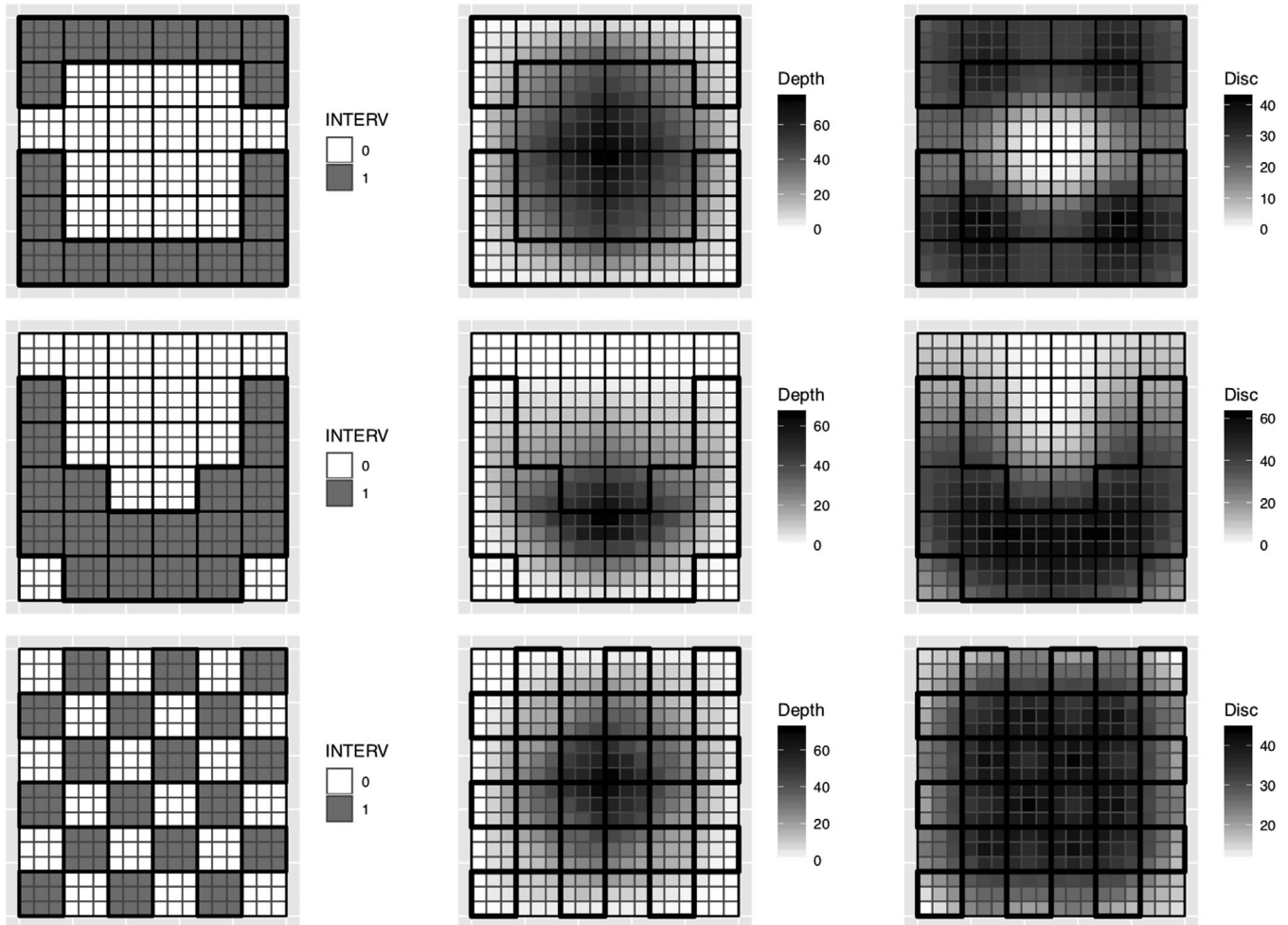
FIGURE 1 *Three configurations* used in the simulation study (leftmost column of three panels), and the depth and disc measures of surroundedness (middle and right columns, respectively). *In the left column*, the first configuration (top), which we call *Ring*, the control clusters (white) are almost completely surrounded by the intervention ones (gray). In the second configuration (middle), called *Crater*, control clusters are again contiguous, but tending to lie on one side of the space, with the interventions clusters on the other. In the third configuration (bottom), called *Chessboard*, control and intervention clusters alternate regularly over the study region. *The middle column* shows values of the depth measure of surroundedness. Darker values show higher values. *The right column* shows values of the disc measure, that is, number of individuals in the intervention arm who lie within a radius of each individual. Here the radius is set at 0.12, the study area having unit side. Again, darker values show higher values

mosquito larvae and pupae, but also on residential conditions such as the size and density of houses. The pairing, together with the randomization within each pair, agglomerated the clusters into two contiguous regions per arm, with one control region being interdigitated with one intervention region. Point geo-reference information was available for each house site (latitude and longitude) and this was used to construct the corresponding Voronoi tesselation (Figure 3).

The primary outcome was the number of containers per house that were positive for immature stages of the mosquito. The house in this trial corresponds to the more general term "individual" as used in the current paper. When this outcome is aggregated, for example, to the clus-

ter level, and expressed per 100 houses, this is called the Breteau index. The flight range of *Aedes* mosquitoes is in the hundreds of meters (Honório *et al.*, 2003), which is the same order of magnitude as the size of the area of the current trial. Daily human movements within urban areas are likely to be larger, and relevant for dengue transmission (Stoddard *et al.*, 2013). Hence people may be infected outside the study area, but such outcomes were not endpoints for the current trial. The final entomological survey was done 12 months after the interventions were implemented. The original report analyzed the cluster-level changes in Breteau index from baseline to the final survey, and found no significant difference between control and intervention arms (Kroeger *et al.*, 2006).
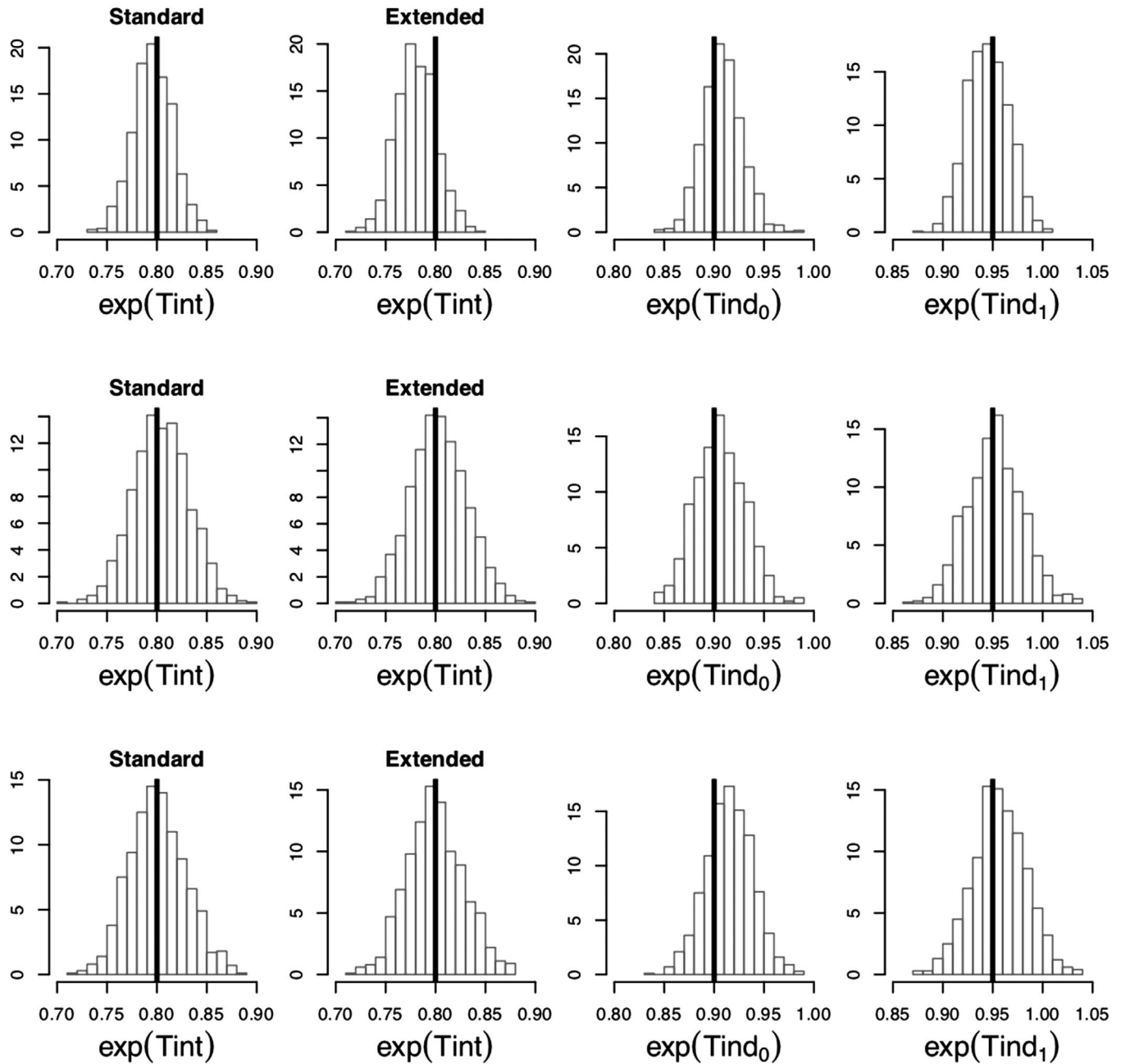
FIGURE 2 Simulation results. Histograms of posterior medians from 1000 independent replicates. Top, middle, and bottom rows correspond to Ring, Crater, and Chessboard configurations (see Figure 1), respectively, and all for disc measure of surroundedness ($r = 0.12$). Thick vertical lines indicate population (target) parameters values

In a post hoc analysis, the original report found some evidence of a contralateral spillover indirect effect, in that initially positive houses (ie, with immature mosquito stages) in the control arm within 50 m of the nearest intervention house were 3.5 times as likely to be free of vectors than more distant initially positive control houses 1 month after the intervention, although this difference was not statistically significant (Kroeger *et al.*, 2006).

The current re-analysis again uses the final survey data that included data from 702 house sites. Another

independent random effect was included in the extended model (1) to account for the cluster pairing. For prior sensitivity, we tried three different priors for the standard deviation of the spatial random effects σ_s. The priors were set such that the corresponding marginal standard deviations were 0.3, 0.05, and 0.01, which corresponds to weak, medium, and strong penalties to the spatial model as compared to the model with no spatial random effects. For the cluster and pairing random effects, we only used (independent) priors with weak penalty as this reflects
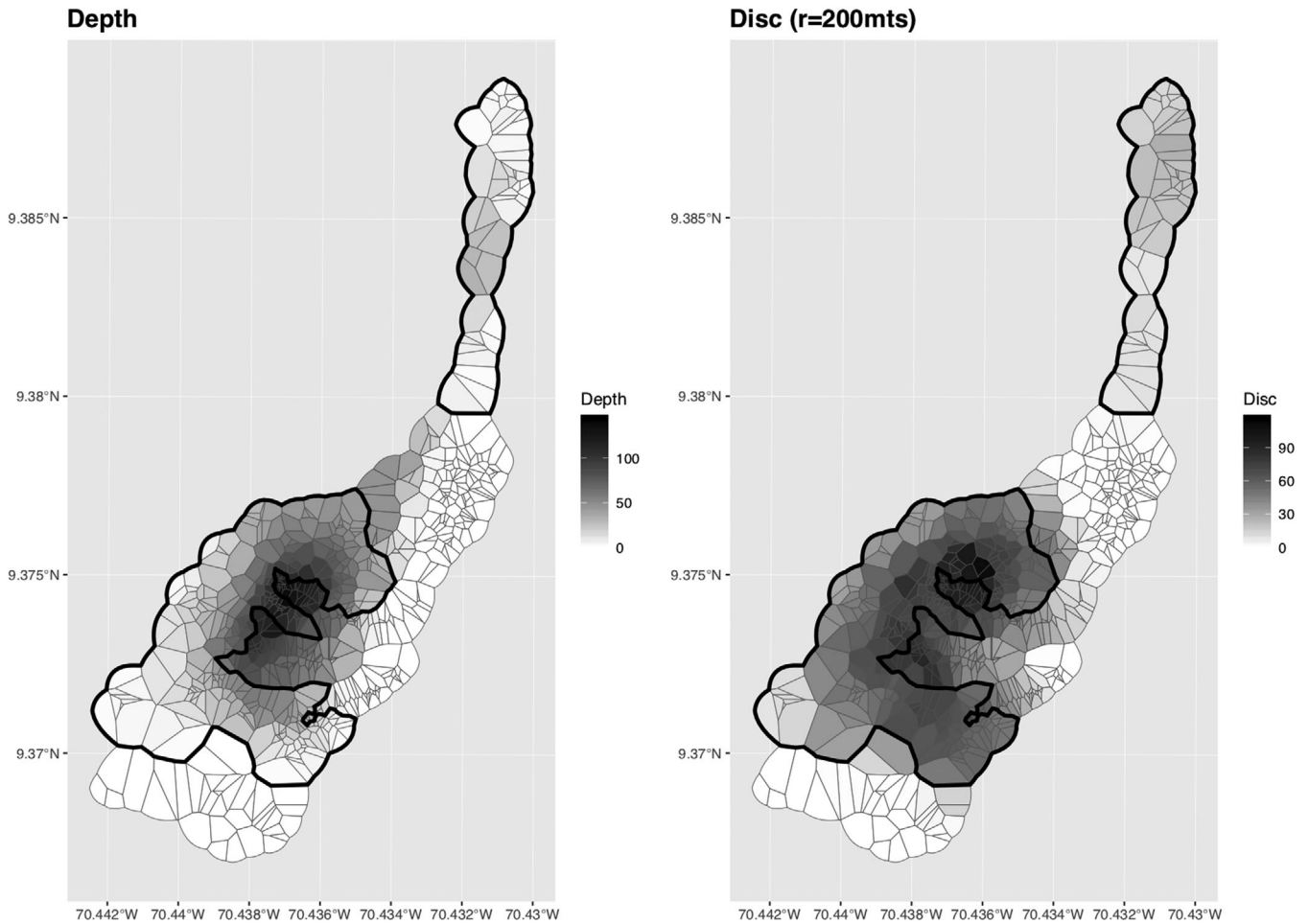
FIGURE 3 Voronoi tesselation of the Trujillo trial, with each tile representing a house site. Also shown are the choropleth maps of the depth (left) and disc (right) measures of surroundedness. Intervention regions are those inside the thick black boundary

the prior belief, in cluster randomized trials, that there is dependence within clusters and, for this particular trial, dependence within pairs. To obtain the posterior of the total intervention effect τ, as described in Section 3, we draw an independent sample of size 10 000 form the corresponding posterior marginals. All the orthogonalized models, as described in Section 2.4.4, were constructed by transforming the full ICAR design matrix derived from the neighborhood structure of the Voronoi tesselation.

Figure 4 shows 95% posterior density intervals (quantile based) of the exponential of the total intervention effect (*Tint*), fitting the data with the standard model (2), the standard model (2) but with orthogonal spatial random effects and with the extended model (1) with the depth and disc measures of surroundedness (the latter with radius 200 m and both for the three levels of prior information). All the posterior intervals, apart from the standard model, cross the null value of 1, with medians on the beneficial side. Spatial dependence seems to be important. As pointed out in Section 2.4.1, orthogonalization only intends to

increase the estimated variance of the fixed effects without major changes in the point estimates. In the extended model, most of the extra estimated variability is attributed to the added covariates (the surroundedness measure to model indirect effects), which are ignored in the standard models. Including indirect effects (ie, generalizing the standard model into the extended one) makes the intervals slightly wider when using the depth measure and much wider when using the disc measure of surroundedness. In other words, the difference in interval length implies, in this case, a strong indication of the presence of disc indirect effects but a weak indication of the presence of depth indirect effects.

The difference in interval length between extended depth and disc models is mainly due to the nature of the surroundedness measure itself. As shown in Figure 3, the range of values of the disc measure are comparable to those of the depth measure, but are spread more widely across the central part of the Trujillo area. In these terms, this area of the trial resembles the *Crater* configuration in
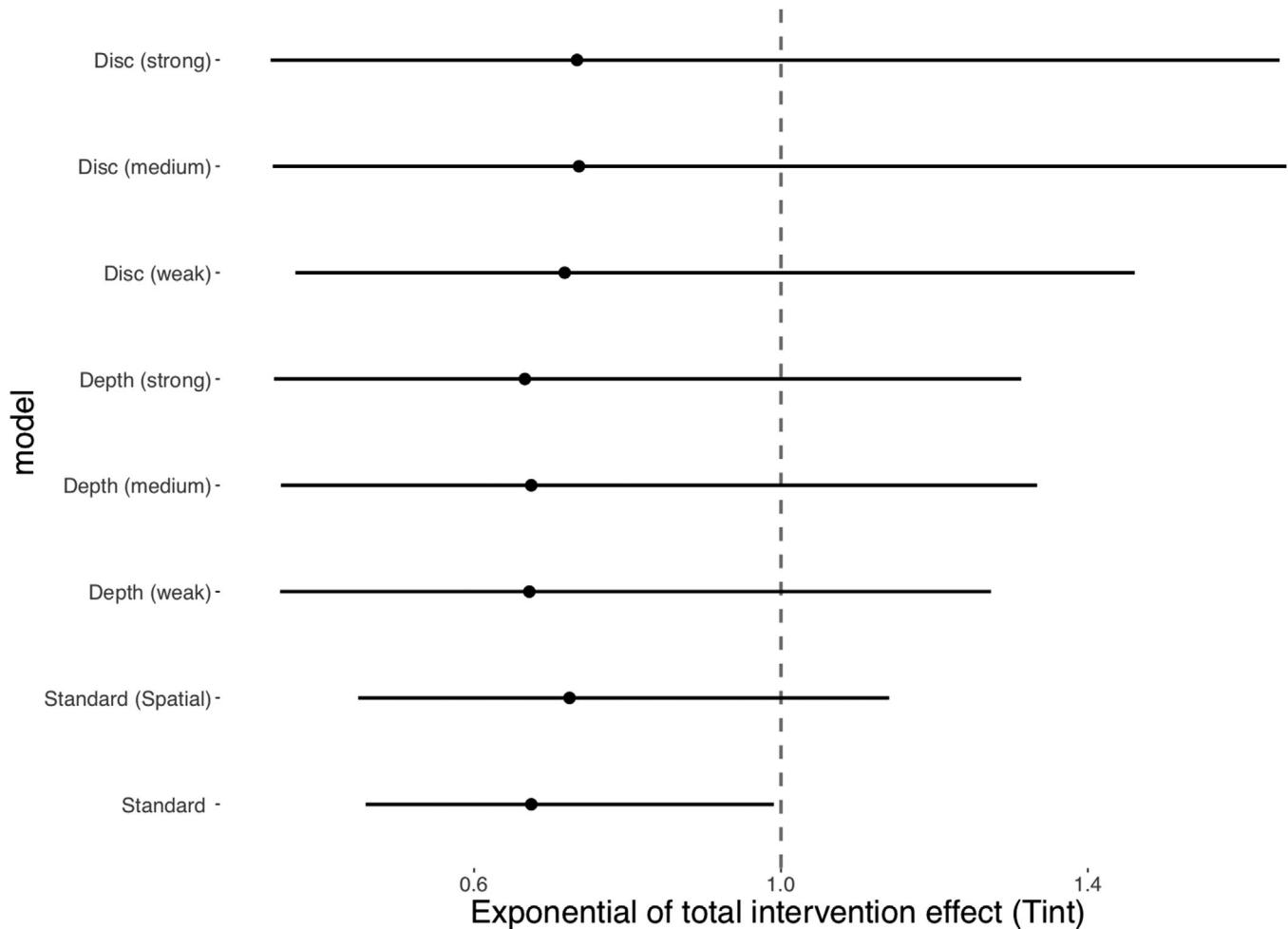
FIGURE 4 Note that 95% posterior density intervals for the exponential of the total intervention effect (*Tint*) in models fitted to data from the Trujillo trial. The points are the posterior medians. The upper three intervals are from models with the disc measure of surroundedness (radius 200 m), and the middle three for models with depth. Each measure was fitted with priors with strong, medium, or weak penalties. The bottom two intervals are from the standard model with and without spatial dependence

Figure 1. As opposed to the models with depth measure, the effect of the prior penalty seems to be larger in the models with the disc measure, in which a stronger penalty implies a wider posterior interval for the total intervention effect.

Overall, in terms of posterior probability, it is clear that models with the depth measure provide stronger posterior evidence of a beneficial effect of the intervention as a whole.

Figures 5 and 6 show 95% posterior intervals for the pairwise contralateral and ipsilateral effects, $Sind_{ij}^0$ and $Sind_{ij}^1$, respectively, and for the same depth and disc models. As mentioned above, there is strong posterior evidence, in particular from the disc model, of an ipsilateral effect, that is, of locations in the intervention arm benefiting from being surrounded by other intervention locations, which was not a conclusion of the original analysis.

6 | DISCUSSION

Geographically demarcated clusters are the most common choice for cluster-randomized trials (Hayes and Moulton, 2009). At the design stage, the clusters should ideally be sufficiently far apart to render spatial correlation negligible, as required by the standard analytic assumption of between-cluster independence. However, this may well be impractical, because the scale of spatial correlation can be up to tens of kilometers (Alexander *et al.*, 2003; Clemens *et al.*, 2006) and, in fact, may well be unknown at the design stage. Spatial aspects have been largely overlooked in the analysis of CRTs, beyond some incomplete ad hoc approaches (Benjamin-Chung *et al.*, 2017; Jarvis *et al.*, 2017).

We have distinguished two possible consequences of spatial proximity in a CRT. *Spillover dependence* refers
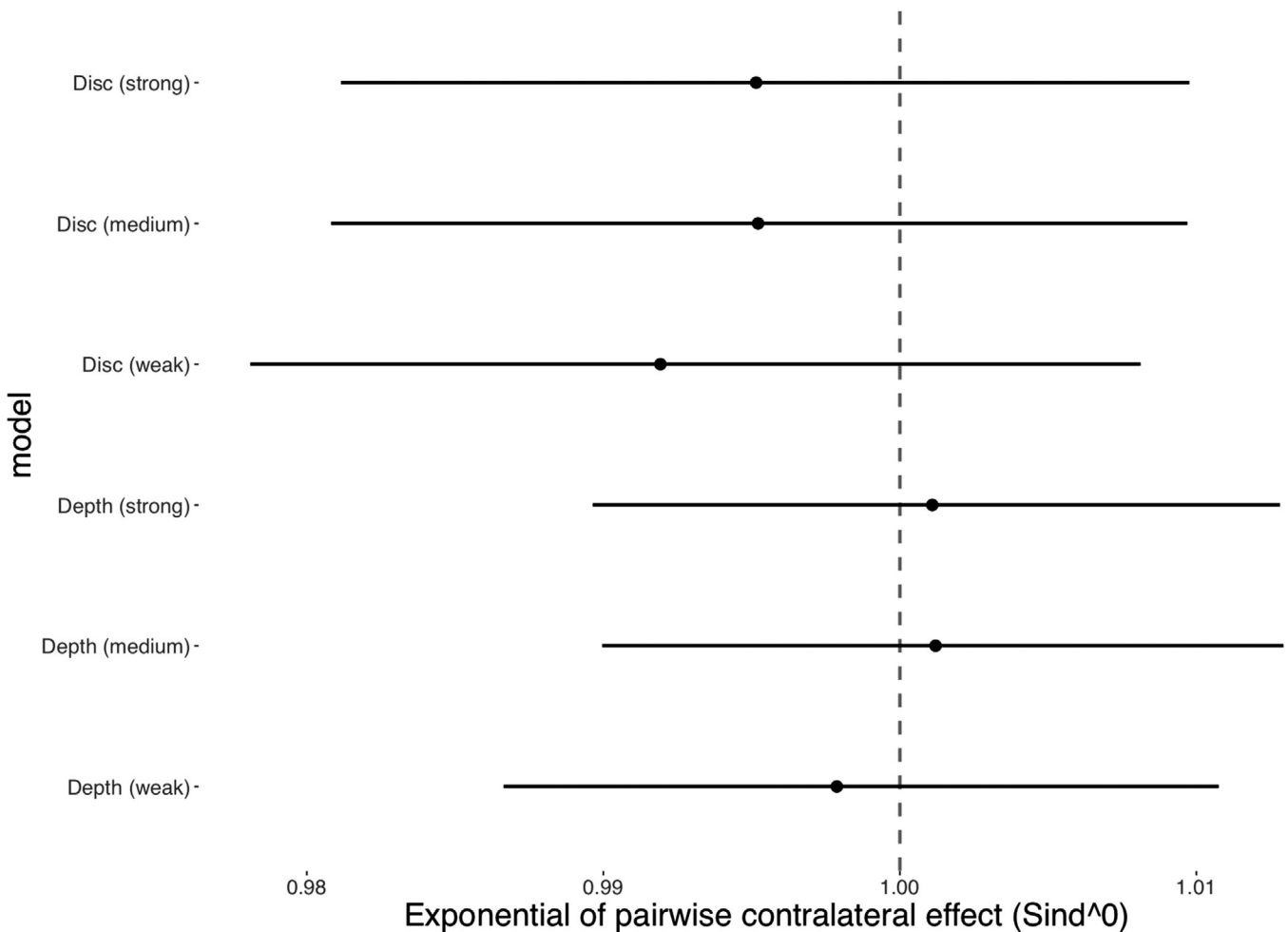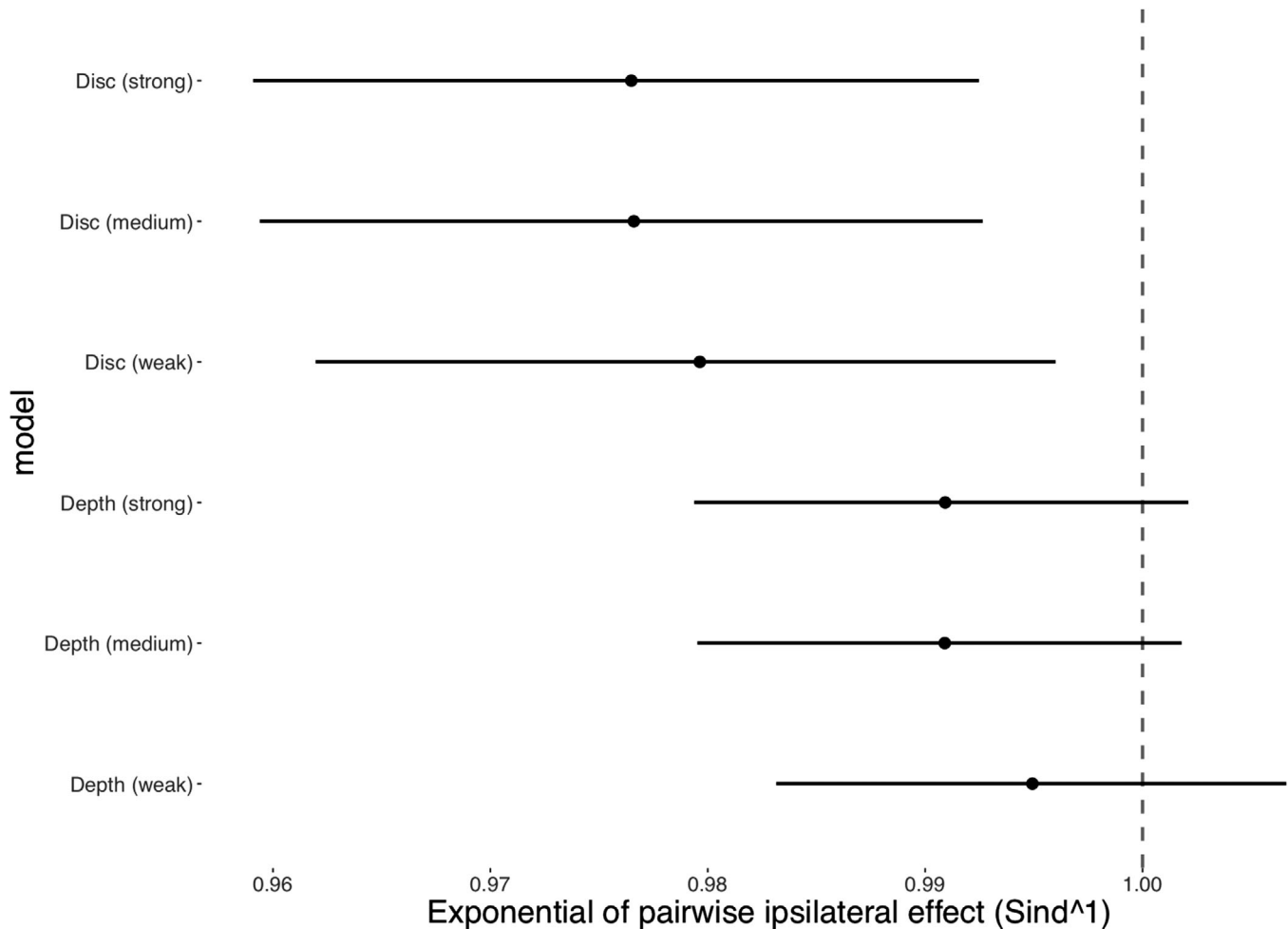
FIGURE 5 Posterior 95% intervals for the exponential of the pairwise contralateral effect, for different models fitted to data from the Trujillo trial. The upper three intervals are from models with the disc measure of surroundedness (radius 200 m), and the lower three for models with depth. Each measure was fitted with strong, medium, or weak prior distributions

to between-cluster dependence in individual outcomes, and *spillover indirect effects* increase or decrease the intervention effect, depending on the degree of surroundedness of individuals by other individuals in the intervention arm. We propose a new spatial regression model that incorporates both these phenomena, and whose intervention effects have a marginal interpretation (as opposed to being cluster-specific), as well as being well defined even when the proposed model is misspecified. We estimate, and adjust for, spillover indirect effects via a novel application of the statistical concept of depth (Tukey, 1975), and also using a simple measure of surroundedness based on the number of intervention individuals within a certain radius. The framework assumes spatial point data, although both surroundedness measures proposed can also be defined for areal data. For example, provided the centroids are good representatives of each area, for example, each lies within the area to it refers, we can use them

to compute either of the two surroundedness measures. Minor modifications would also be required (eg, defining balls instead of discs and planes instead of lines) to define surroundedness in three-dimensional space (ie, including elevation).

The methodology proposed can be easily adapted to deal with total intervention effects defined in a different manner. For example, we can define the total intervention effect as a weighted average of expected rates at the cluster level (Hayes and Moulton, 2009) or as a simple average of all the pairwise intervention effects. However, the latter case would give unduly importance to large pairwise intervention effects that is not usually the objective in cluster randomized trials. CRT researchers would define total effects in such a way that, even though there are a few large pairwise effects, the intervention may still be considered effective as long as the total effects are small. Intervention effects may also be defined as *geometrical* averages instead

FIGURE 6 Posterior 95% intervals for the exponential of the pairwise ipsilateral effect, for different models fitted to data from the Trujillo trial. Labeling is as for Figure 5

of traditional arithmetic averages (see Hayes and Moulton, 2009, p.152).

In the Trujillo trial, there is some evidence that locations benefited indirectly from surrounding locations receiving the intervention. Despite being randomized, the clusters in each arm are distributed in just two contiguous regions. Restricted randomization could be used to achieve an allocation that addresses this or other concerns (see McCann *et al.* (2018) for one such proposed method). An alternative criterion could relate to geographical balance, in the intuitive sense of avoiding large contiguous regions of clusters from a single arm, although this notion may be hard to quantify. For example, despite lying in few contiguous regions, 17 of the 18 Trujillo clusters border at least one in the opposite arm. One approach may be to impose a minimum proportion of between-cluster boundaries that separate clusters in different arms, hence tending to reduce the size of contiguous single-arm regions.

We hope these methods will prove useful in those trials in which spatial correlation is inherent. Such analyses would provide more robust estimates of intervention effects, as well as quantifying the contribution of indirect effects, which are likely to be of interest when deciding whether to implement interventions at full scale.

DATA AVAILABILITY STATEMENT

The data that support the findings in this paper are available from the corresponding author upon reasonable request.

ORCID

Karim Anaya-Izquierdo https://orcid.org/0000-0001-9718-5256

Neal Alexander https://orcid.org/0000-0002-6707-7876

REFERENCES

Aitchison, J. and Ho, H. (1989) The multivariate Poisson-lognormal distribution. *Biometrika*, 76, 643–653.

Alexander, N., Moyeed, R., Hyun, P., Dimber, Z., Bockarie, M., Stander, J., Grenfell, B., Kazura, J. and Alpers, M. (2003) Spatial variation of *Anopheles*-transmitted *Wuchereria bancrofti* and *Plasmodium falciparum* infection densities in papua new guinea. *Filaria J*, 2. Available at: https://doi.org/10.1186/1475-2883-2-14.

Bauschke, H. and Borwein, J. (1996) On projection algorithms for solving convex feasibility problems. *SIAM Review*, 38, 367–426.

Benjamin-Chung, J., Abedin, J., Berger, D., Clark, A., Jimenez, V., Konagaya, E., Tran, D., Arnold, B.F., Hubbard, A.E., Luby, S.P., Miguel, E. and Colford, J.M., Jr. (2017) Spillover effects on health outcomes in low- and middle-income countries: a systematic review. *International Journal of Epidemiology*, 46, 1251–1276.

Besag, J. and Kempton, R. (1986) Statistical analysis of field experiments using neighbouring plots. *Biometrics*, 42, 231–251.

Bivand, R., Pebesma, E. and Gómez-Rubio, V. (2008) *Applied Spatial Data Analysis with R*. New York, NY: Springer.

Clark, A. and Bachmann, M. (2010) Bayesian methods of analysis for cluster randomized trials with count outcome data. *Statistics in Medicine*, 29, 199–209.

Clemens, A., Moyeed, R. and Brooker, S. (2006) Bayesian geostatistical prediction of the intensity of infection with *Schistosoma mansoni* in East Africa. *Parasitology*, 133, 711–719.

Diggle, P. and Ribeiro, P., Jr. (2007) *Model-Based Geostatistics*. Berlin: Springer.

Fong, Y., Rue, H. and Wakefield, J. (2010) Bayesian inference for generalized linear mixed models. *Biostatistics*, 11, 397–412.

Halloran, M. I., Jr. and Struchiner, C. (2009) *Design and Analysis of Vaccine Studies*. Berlin: Springer.

Hawley, W., Phillips-Howard, P., ter Kuile, F., Terlouw, D., Vulule, J., Ombok, M., Nahlen, B., Gimnig, J., Kariuki, S., Kolczak, M. and Hightower, A. (2003) Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. *American Journal of Tropical Medicine and Hygiene*, 68, 121–127.

Hayes, R. and Moulton, L. (2009) *Cluster Randomised Trials*. Boca Raton, FL: Chapman and Hall/CRC.

Hodges, J. (2013) *Richly Parameterized Linear Models: Additive, Time Series, and Spatial Models Using Random Effects*. Boca Raton, FL: Chapman and Hall/CRC.

Hodges, J. and Reich, B. (2010) Adding spatially-correlated errors can mess up the fixed effect you love. *The American Statistician*, 64, 325–334.

Honório, N.A., Silva, W., Leite, P.J., Gonçalves, J.M., Lounibos, L.P. and Lourenço-de Oliveira, R. (2003) Dispersal of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) in an urban endemic dengue area in the State of Rio de Janeiro, Brazil. *Memórias do Instituto Oswaldo Cruz*, 98, 191–8.

Hughes, J. and Haran, M. (2013) Dimension reduction and alleviation of confounding for spatial generalized linear mixed models. *Journal of the Royal Statistical Society: Series B*, 75, 139–159.

Jarvis, C., Di Tanna, G., Lewis, D., Alexander, N. and Edmunds, W. (2017) Spatial analysis of cluster randomised trials: a systematic review of analysis methods. *Emerging Themes in Epidemiology*, 14, 12.

Kroeger, A., Lenhart, A., Ochoa, M., Villegas, E., Alexander, N., Levy, M., Alexander, N. and McCall, P.J. (2006) Effective control of dengue vectors with curtains and water container covers treated with insecticide in Mexico and Venezuela: cluster randomised trials. *British Medical Journal*, 332, 1247–1252.

Lindgren, F., Rue, H. and Lindstrom, J. (2011) An explicit link between Gaussian fields and Gaussian Markov random fields: the stochastic PDE approach. *Journal of the Royal Statistical Society: Series B*, 73, 423–498.

Longini, I.M., Sagatelian, K., Rida, W.N. and Halloran, M.E. (1998) Optimal vaccine trial design when estimating vaccine efficacy for susceptibility and infectiousness from multiple populations. *Statistics in Medicine*, 17, 1121–1136.

McCall, P. (2011) Can insecticide-treated curtains prevent transmission of dengue? *ISRCTN Registry*. Available at: https://doi.org/10.1186/ISRCTN08474420.

McCann, R., van den Berg, H., Takken, W., Chetwynd, A., Giorgi, E., Terlouw, D. and Diggle, P. (2018) Reducing contamination risk in cluster-randomized infectious disease-intervention trials. *International Journal of Epidemiology*, 47, 2015–2024.

Paciorek, C. (2010) The importance of scale for spatial-confounding bias and precision of spatial regression estimators. *Statistical Science*, 25, 107–125.

Perez-Heydrich, C., Hudgens, M., Halloran, M., Clemens, J., Ali, M. and Emch, M.E. (2014) Assessing effects of cholera vaccination in the presence of interference. *Biometrics*, 70, 731–744.

Reich, B.J., Hodges, J.S. and Zadnik, V. (2006) Effects of residual smoothing on the posterior of the fixed effects in disease-mapping models. *Biometrics*, 62, 1197–1206.

Rousseauw, P. and Ruts, I. (1996) AS 307: bivariate location depth. *Journal of the Royal Statistical Society: Series C*, 45, 516–526.

Rue, H., Martino, S. and Chopin, N. (2009) Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *Journal of the Royal Statistical Society: Series B*, 71, 319–392.

Silcocks, P. and Kendrick, D. (2010) Spatial effects should be allowed for in primary care and other community-based cluster RCTS. *BMC Trials*, 11, 55.

Simpson, D., Rue, H., Riebler, A., Martins, T.G. and Sørbye, S.H. (2017) Penalising model component complexity: a principled, practical approach to constructing priors. *Statistical Science*, 32, 1–28.

Stoddard, S.T., Forshey, B.M., Morrison, A.C., Paz-Soldan, V.A., Vazquez-Prokopec, G.M., Astete, H., Reiner, R.C.J., Vilcarromero, S., Elder, J.P., Halsey, E.S., Kochel, T.J., Kitron, U. and Scott, T.W. (2013) House-to-house human movement drives dengue virus transmission. *Proceedings of the National Academy of Sciences USA*, 110, 994–999.

The R-INLA Project (2019) *The R-INLA package.* Available at: http://www.r-inla.org/ [accessed 1 November 2019].

Tukey, J. (1975) Mathematics and the picturing of data. *Proceeding of the International Congress of Mathematicians*, 2, 523–531.

Vanderweele, T., Hong, G., Jones, S. and Brown, J. (2013) Mediation and spillover effects in group-randomized trials: a case study of the 4rs educational intervention. *Journal of the American Statistical Association*, 108, 469–482.

VanderWeele, T., Tchetgen Tchetgen, E. and Halloran, M. (2012) Components of the indirect effect in vaccine trials: identification of contagion and infectiousness effects. *Epidemiology*, 23, 751–761.

SUPPORTING INFORMATION

R code, and figures referenced in Section 4, are available with this paper at the Biometrics website on Wiley Online Library.