Malaria Journal

RESEARCH

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Inter-cluster contamination: a semivariance analysis of community effect ranges of malaria vector control interventions in a four-armed malaria trial in Muleba, Tanzania

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Abstract

Background The presence of a community effect in cluster randomized trials of malaria vector control interventions has led to the implementation of "buffer zones" around clusters to limit the potential for contamination between interventions. No consensus has been reached on how large these buffers need to be to encapsulate the effect.

Methods Nested within a phase-III cluster randomized malaria vector control trial in Northwest Tanzania, this study aims to determine the presence and spatial range of community effects from long-lasting insecticidal net (LLIN) and indoor residual spraying (IRS) interventions on household-level malaria infection in trial clusters four months post-intervention. Effective spatial range estimates of intervention community effects were compared to the 300m buffer distance implemented to limit intervention spillover between clusters in the trial. Geographically-weighted adjusted odds of malaria infection in children aged 0.5–14 years were determined four months post community-level intervention with a randomized allocation comprising one of two LLIN products (Olyset^{TM} LN: 1000mg/m^2 permethrin or Olyset^{TM} Plus LN: 400 + permethrin 800mg/m^2) with either IRS (Actellic$^{®}$300CS: 1000mg/m^2 micro-encapsulated pirimiphos-methyl) or no IRS. Robust semivariances were calculated for each of 48 intervention clusters and fit to semivariogram models by Weighted Least Squares.

Results 6440 children from 2785 households were included in the geographically-weighted logistic regression. Prevalence of *Plasmodium falciparum* infection was 45.9% in the study population. Twenty (20) clusters had significant residual effect ranges, 13 of which were fit to Sine Hole Effect models, indicating periodicity in the study area. Effective range estimates for the study area had a median value of 1210 m (IQR: 958–1691). Clusters with IRS had a higher median range value: 1535 m (IQR: 976–3398) than those without IRS: 1168m (IQR: 829–1504).

Conclusions Significant semivariogram model range estimates extended beyond the trial buffer sizes by a median average of 868 m in LLIN intervention clusters and 1235 m for IRS clusters. This presents a contamination, or spillover, potential for all trialed intervention types that may reduce the statistical power to detect difference between trial

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arms. Future studies should consider the ranges of intervention effects and contamination potential between trial arms when designing buffer areas.

Keywords Malaria, Community effect, Buffer, Semivariance, Spatial analysis

Background

Cluster randomized controlled trials (cRCTs) are frequently used to evaluate the effectiveness of long-lasting insecticidal net (LLIN) and indoor residual spraying (IRS) interventions on clinical and entomological outcomes in different malaria transmission settings. In these trials, groups of households, rather than individuals, are randomly allocated to intervention groups [1]. This design is preferred because these interventions provide community protection through the mass killing of mosquitoes that come into contact with the insecticide [2]. Modelling cluster-level effects allows for the evaluation of this community protection. Further, cluster randomization allows for easier distribution of the trial interventions and creates a better simulation of a real-world rollout of a large-scale malaria intervention.

This localized reduction in malaria vector populations and malaria transmission, induced by the clustering of interventions, has been thoroughly confirmed in multiple settings [3–7], and extends the benefits of high community-level intervention coverage to protect individuals in the community who do not themselves use LLINs or IRS [8]. Spatially, because host-seeking malaria vectors may fly considerable distances [9–11], localized reductions in vector populations may extend the intervention effects outside of the community boundaries, resulting in partial reduction of malaria transmission in neighbouring communities or households [12]. This community effect comes with a drawback when evaluating interventions in a cRCT trial, as the spillover effect between intervention groups, or between intervention and control groups, could cause between-group differences in intervention effects to trend towards the null hypothesis [12].

In malaria vector control trials where intervention clusters are in relatively close proximity, the World Health Organization (WHO) recommends the use of a buffer zone or "fried egg" approach for cRCT design where samples needed for measuring effect size are only drawn from the centre of cluster where the spillover effect is small or absent [13]. Specific recommendations on the size and composition of these buffer zones have not yet been included in any guidance provided. This has led to studies instituting buffers ranging anywhere from 300 [12] to 1500 m [14]. Establishing a consistent measure of the effect distance in malaria vector-control cRCTs is necessary to determine how large these buffer zones should be in future trials.

To obtain a measure of the spatial range of intervention effects in malaria vector control trials, a case study was conducted using data from a cRCT in Muleba, Tanzania, evaluating LLINs alone or in combination with IRS. Semivariogram models were fitted for each trial intervention cluster using the residual odds of malaria infection from a geographically-weighted logistic regression model. This approach, while controlling for likely confounders, seeks to capture the intervention effects in the residual odds of malaria and describe the distances within which significant intervention effects can be detected. By doing so, this study aims to establish an effective range where the effect ceases and provide evidence for the design of future trial buffer areas.

Methods

Data source

Data for this study was collected during a cross-sectional survey four months post-intervention in 2015 as part of a cluster-randomized trial in Muleba, Tanzania. This trial was led by the Pan-African Malaria Vector Research Consortium (PAMVERC), a collaboration between the London School of Hygiene & Tropical Medicine (UK), Kilimanjaro Christian Medical University College (Tanzania) and the National Institute for Medical Research (Tanzania) [15]. The four-armed intervention study investigated the efficacy of a conventional Olyset^{TM} LN, an Olyset^{TM} Plus LN, and each of those nets deployed with IRS. The conventional Olyset^{TM} LN contains a single pyrethroid (1000 mg/m^2 permethrin) [16], while the Olyset^{TM} Plus LN includes permethrin plus piperonyl butoxide (PBO), a synergist which slows the oxidative metabolic process in mosquitoes by inhibiting enzymes that would otherwise break down the permethrin (400 + permethrin 800 mg/m^2) [17]. The IRS formulation used was Actellic$^{®}$300CS (1000 mg/m^2 micro-encapsulated pirimiphos-methyl), an organophosphate insecticide [18]. Complete trial methods and results are discussed elsewhere [15].

Data were collected from a random sample of households in each cluster using interviewer-guided questionnaires on household demographic and socioeconomic status indicators. Up to three children per household were randomly selected for a follow-up clinical and parasitological component which included collection of standard clinical characteristics and testing for

plasmodial infection using malaria rapid diagnostic tests (RDT) (CareStart^{TM} HRP2/pLDH combo, DiaSys, UK) [19].

Study area

The study covered an area of 1433 km^2 between 657023 and 686018 m east of meridian 25 and 187255 to 236686 m south of the equator and included 29311 censused households in the Muleba district of the Kagera region of Tanzania (Fig. 1). Elevation of study households ranged from 1075 to 1654 m above sea level. A series of hills bisects the study region with low-lying households occupying the western areas and along the shore of Lake Victoria in the southeast [20].

Malaria transmission in Muleba is unstable and seasonally variant, with peaks in transmission following heavy seasonal rains that occur from March-May and October-December [21, 22]. A September 2014 pre-intervention survey of children 0.5–14 years of age found a *Plasmodium* spp. infection prevalence of 64.8% (95% CI 61.8–67.8) in the study area [23]. In the same survey, *Plasmodium* spp. infection was also found to be independently associated with elevation, with higher odds of infection in low-lying areas [23].

Anopheles gambiae sensu stricto (*s.s.*) is the dominant malaria vector in the study area, comprising an estimated 89.2% of Anophelines collected pre-intervention [23]. *Anopheles gambiae sensu lato* (*s.l.*) have shown substantial pyrethroid resistance in the study area [24].

Although the 2012 Tanzania census in Muleba found that 22.2% of those 15 years of age or older had never attended school, Muleba had a relatively high literacy rate (62.5%; *Kiswahili*) for the region [25], and a 2010 study showed a high level of community knowledge on malaria transmission, symptoms, and treatment [22]. Farming is the main source of income in Muleba (75.6%) with fishing a distant second (5.2%) [25]. Household construction materials are mixed, with iron (75.1%) or grass (20.9%)

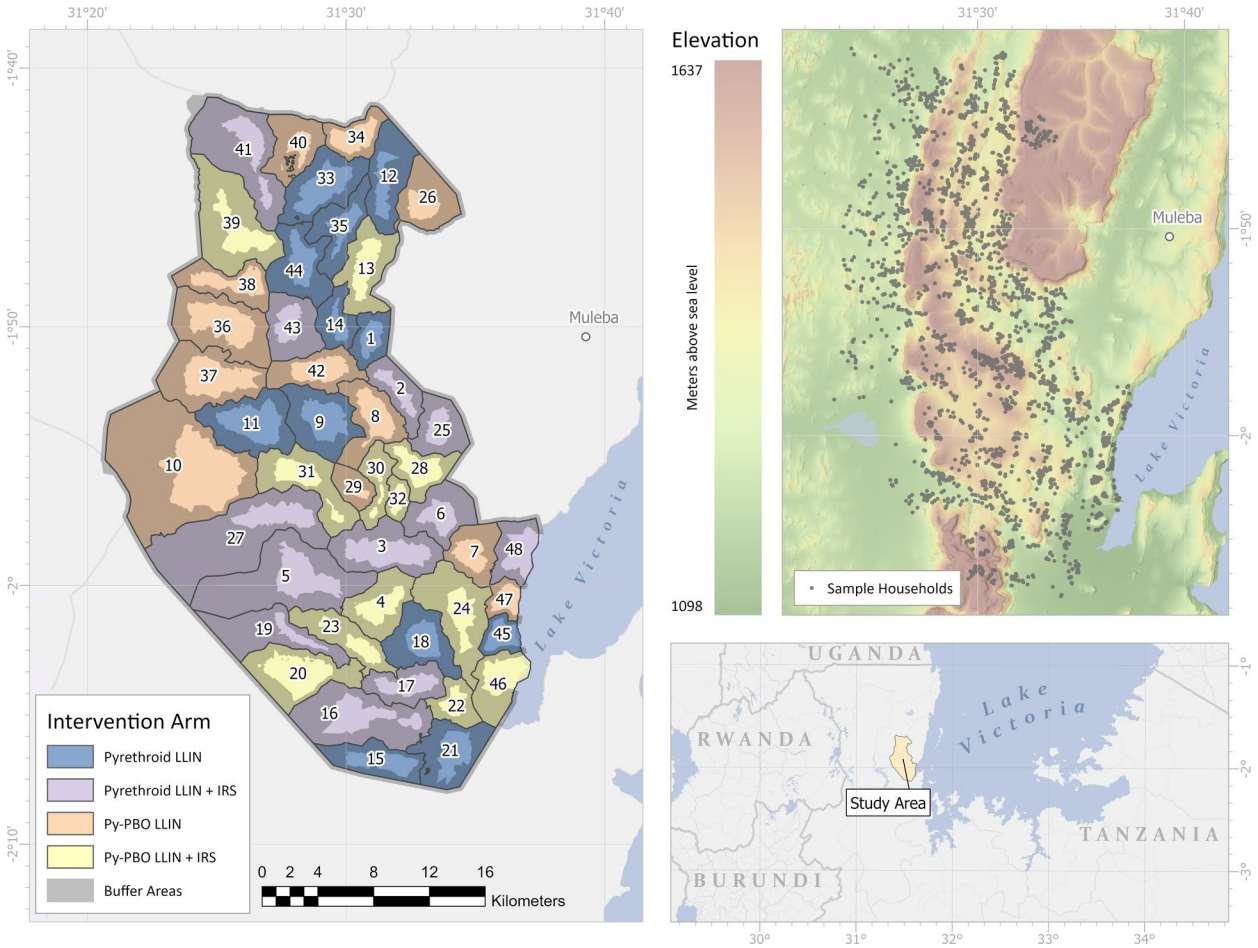

Fig. 1 Study area. Cluster numbers and allocations are shown for the 48 trial clusters with shaded portions representing buffer areas. Household distribution is presented for the four months cross-sectional dataset. Elevation data used in this map was retrieved from ALOS 3D World 30m DSM [20]

roofing, earth (78.7%) or cement (20.0%) flooring, and poles and mud (55.8%), baked (27.1%) or sundried (9.1%) brick walls being the most common [25].

All data collected in this trial was geocoded in World Geodetic System 1984 (WGS_1984) to allow for geospatial analyses. Initial mapping survey coordinates for each household were imported to ESRI ArcGIS 10.4 [26] and projected into Africa Equidistant Conic projected coordinate system, preserving distances between points as accurately as possible for spatial analyses.

Study population

The first post-intervention household survey was conducted July 2015 (4 months post intervention) during which 3316 households were randomly selected across core and buffer areas of all clusters. Data records for 3282 households were successfully matched to the initial mapping survey, permitting geocoding of the data. A total of 7009 children aged 0.5–14 years completed a following clinical visit, of which 6625 could be linked to post-intervention household survey data for geocoding. One hundred and eighty-five (185) children were missing data on response or explanatory variables used in the principal component or logistic regression analyses, with 10 of those missing data on their RDT status. The final analysed dataset comprised 6440 children from 2785 households across 48 intervention clusters.

Statistical analyses

The residuals from statistical models are a reflection of unmeasured covariates not taken into account by the model. These residuals may have a spatial pattern if observations that are closer together are correlated (more similar) than those that are further apart (spatial autocorrelation). Semivariance models use the model residuals to estimate the range (distance) over which data are correlated in space and can be used to control for spatially correlated confounders in the analysis [27]. In order to achieve this, this study used a two-stage approach to estimate the range effects of interventions. First, multivariable geographically-weighted logistic regression (GWLR) models predicting odds of malaria infection (*P. falciparum* or other *Plasmodium* spp. parasites) were constructed, controlling for factors commonly associated with malaria infection: child age and sex, household elevation, eaves construction, roofing material, and wealth quintile, as well as head of household level of education. These models were constructed without the study arm intervention and without cluster effects with an aim to capture the spatial effects of the interventions in the model residual values, while controlling for other spatially-trending factors. Second, using ordinary residuals derived from the GWLR models, the robust semivariance of all possible household pairs were modelled, grouped by distance ranges between them, to construct semivariogram models of the residual values.

Study population characteristics

Descriptive statistics were developed for variables of interest in the post-intervention clinical cross-sectional sample of children. Age, sex, household elevation, presence of open eaves, household roofing material, head of household schooling, and wealth quintile were all expected to be likely predictors of malaria infection in children due to a review of the extant literature, and findings from a previous analysis of the baseline data from the same trial [23]. All selected variables were checked for spatial autocorrelation through the calculation of a Moran's I statistic in SAS 9.4.

Geographically-weighted regression analysis

The software GWR4 [28] was used to construct multivariable geographically-weighted logistic regression (GWLR) models predicting odds of malaria infection for each sampled child. GWLR is a spatial regression technique that allows the coefficients of independent variables (covariates) to vary across geographic space. The GWLR process constructs separate logistic regression models for each sampled child, weighting the value of each other child in the study area as a function of distance for that model [29]. This creates varied parameter estimates for model covariates and, importantly for these analyses, variation in the residual values for each data point. Ideal spatial weights for the GWLR models were determined by golden section search with an adaptive bi-square bandwidth function [30]. In GWLR, odds ratios represent the local change in the odds of the outcome occurring for a unit change in the predictor variable, varying across space, unlike a standard logistic regression which provides a global odds ratio.

Ordinary residual values were extracted from the results of the GWLR for each datapoint and the dataset was subdivided into clusters, as assigned for intervention allocation. This division of the dataset into clusters has twofold benefits: 1) it allows for the creation of quasi-stationarity in the cluster area as a sub-division of the greater study [31], and 2) for the assessment of cluster means individually—minimizing any spatial effect that could occur between clusters, irrespective of cluster intervention.

Lag distances were calculated for each cluster to ensure a minimum of 50 data pairs per lag distance [32], and pairs whose paired distance exceeded one half the total bounded data distance in each cluster were excluded from this analysis [31]. A Moran's I statistic was calculated in SAS 9.4 to assess the spatial autocorrelation for

the residual odds of malaria for each cluster dataset and the robust semivariance was calculated in SAS 9.4. A one-way analysis of variance (ANOVA) was conducted in SAS 9.4 to establish if there were any significant differences in the analysis characteristics for each allocation group.

Semivariance analysis

Geographic analyses tend to find that proximal samples are more similar than distant ones [33]. Because of this, the spatial distance between sampling locations can be assumed to have some relationship with the correlation of samples collected at those locations. A semivariogram is a model of this spatial relationship in which a derived second-order moment (or semivariance), is plotted against the distance separating those points [34]. If a spatial relationship is able to be defined for a variable of interest, a semivariogram model can be fitted to the data, starting near the origin and extending upwards as some non-negative definite function of distance. This study uses robust estimation of semivariance to limit the influence of outlying values [35].

Robust semivariance estimates were fit to Exponential, Gaussian, Spherical, and Sine Hole Effect model forms by weighted-least squares in SAS 9.4 [36]. These semivariogram models are each characterized by three parameters which compose their basic structure (Fig. 2): the nugget, which represents any variability in samples taken from samples in immediate proximity to each other; the scale, which defines the difference in variability between samples taken proximally and a global average variability in the sample (the combination of nugget and scale parameters define this global variability, generally called the sill); and the range, which is the distance between sample points at which variability reaches the global average [34]. The range parameters for the Exponential and Gaussian models must be interpreted somewhat differently, as they are modelled asymptotically—that is to say, these model forms will never reach the sill, which is instead defined as a limit to their structure. For these models, a separate "effective range" parameter is computed; defined as the point at which the model reaches 90% of the sill value [37].

In cases where all four model structures were deemed to be a questionable fit, a Power model was considered. The Power model is characterized by a continuous upward construction, with no sill or range parameters, and is largely indicative of nonstationarity in the model data [38]. Clusters with no significant spatial range estimate, for which a Power model is not the appropriate fit, are considered to have "pure nugget" effects [32]. These clusters show no definable spatial trend and may suggest a lack of community protection from the trial intervention.

Significant range parameter estimates from the best fitting model were used to calculate effective range estimates for each cluster, according to the parameter estimate of the corresponding model. These resulting effective ranges were grouped by intervention allocation and compared to the 300 m spillover buffer used in the main trial design.

Results

Characteristics of study population

A total of 2953 children tested positive for malaria parasites (*P. falciparum* or other) for an overall prevalence of 45.9% (N = 6440) (Table 1). Sample children had a median age of 6 years (IQR 4–10) and were evenly split by sex (51.1% Female). All variables of interest had a significant spatial trend in the study population (Moran's I $p < 0.05$) (Suppl 1).

Geographically-weighted logistic regression

All covariates of interest were used to compute a GWLR models; odds ratios are computed as minimum, median, maximum and intra-quartile range (IQR). Variations in the odds ratios in the GWLR model indicate spatial variation in the effect of each covariate. A golden section search identified 439 nearest-neighbours as the optimal sample bandwidth. Local adjusted odds ratio estimates for each variable can be seen in Table 2 with eave type, household roofing material, and head of household schooling showing the greatest spatial variability in covariate effects.

Semivariance analysis

Fitted semivariogram models for twenty (20) clusters had significant estimates for the residual odds of malaria effect range indicating a defined spatial trend (Fig. 3).

The remaining clusters did not have significant range estimates: two (2) clusters had fitted models with non-significant range estimates, twenty-two (22) fitted models had "pure nugget" effects—suggesting no spatial trend, and four were fit with Power models and thus had a spatial trend that exceeded one half the maximum data range for estimation of the variogram. Of the clusters that were fit with significant range estimates, 5 were from Pyrethroid-only LLIN clusters, 5 from Py-PBO LLIN clusters, 5 from Py-PBO LLIN + IRS clusters, and 5 from Pyrethroid-only LLIN + IRS clusters (Table 3).

Effective range estimates from all clusters had a median value of 1210 m (IQR: 958–1691). Clusters without IRS had a median value of 1168 m (IQR: 829–1504), and clusters with IRS 1535 m (IQR: 976–3398). Clusters with Py-PBO LLIN and Py-PBO LLIN + IRS

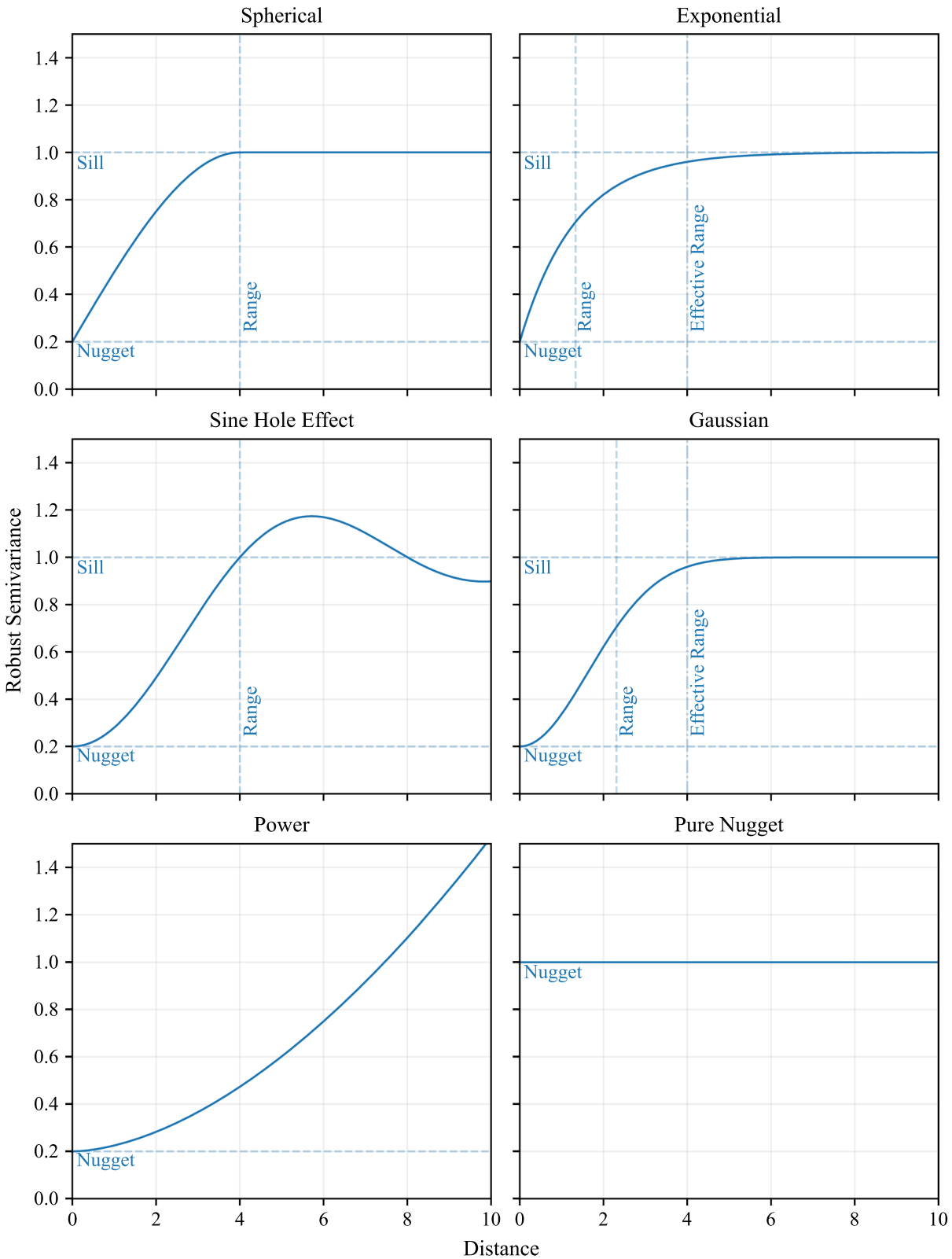

Fig. 2 Semivariogram model forms. The Spherical, Exponential, Sine Hole Effect, and Gaussian models depicted have a Nugget of 0.2, a Scale of 0.8 (for a combined Sill of 1), and an Effective Range of 4. Note that the Range parameter estimates for the Exponential and Gaussian model forms appear shorter, due to their asymptotic construction

Table 1 Characteristics of the study population across intervention arms, four months post-intervention/N = 6440 children, 2785 households

Individual characteristics	Pyrethroid LLIN	Py-PBO LLIN	Pyrethroid LLIN + IRS	Py-PBO LLIN + IRS
Malaria infection prevalence, positive RDT	893/1656 (54%)	665/1605 (41%)	745/1582 (47%)	650/1597 (41%)
Plasmodium falciparum	435/893 (49%)	334/665 (50%)	321/745 (43%)	309/650 (48%)
P. falciparum or mixed *Plasmodium* spp.	458/893 (51%)	331/665 (50%)	424/745 (57%)	341/650 (52%)
Median age, years (IQR; N)	7 (4–10; 723)	7 (4–10; 699)	6 (3–10; 670)	6 (4–10; 693)
Female	848/1656 (51%)	803/1605 (50%)	787/1582 (50%)	850/1597 (53%)
Household characteristics				
Median elevation, meters above sea level (IQR; N)	1334 (1287–1367; 723)	1290 (1234–1376; 670)	1274 (1243–1348; 699)	1339 (1228–1400; 693)
Households with open eaves	462/723 (64%)	463/670 (69%)	443/699 (63%)	426/693 (61%)
Households with grass/leaves & partial metal roofing	125/723 (17%)	156/670 (23%)	126/699 (18%)	134/693 (19%)
Households where the head of household has no formal education	168/723 (23%)	218/670 (33%)	231/699 (33%)	187/693 (27%)
Households in the lowest wealth quintile	123/723 (17%)	142/670 (21%)	121/699 (17%)	158/693 (23%)
Households in buffer areas	328/723 (45%)	312/670 (47%)	281/699 (40%)	303/693 (44%)

Data are n/N (%), unless otherwise noted

LLIN = Long-lasting insecticidal net. *Py-PBO* = Pyrethroid + Piperonyl butoxide. *IRS* = Indoor residual spraying. *RDT* = Malaria Rapid Diagnostic Test. *IQR* = Inter-quartile range

Table 2 Geographically-weighted logistic regression model predicting malaria infection (any *Plasmodium* spp.) in the study population, controlling for common confounders/Global N = 6440 children [Local n = 439 children]

	Adjusted odds ratios					
Variable	Min	Q1	Median	Q3	Max	IQR
Age (vs one year younger)	0.96	1.09	1.13	1.18	1.33	0.37
Sex (male vs female)	0.32	0.69	0.87	1.12	1.63	1.32
Elevation (vs 100 m lower)	0.08	0.31	0.50	0.68	2.29	2.21
Household has Open Eaves (open vs closed)	0.50	1.10	1.45	1.87	3.73	3.23
Roofing Material (natural vs metal)	0.24	0.67	0.93	1.29	3.67	3.43
Head of Household Schooling (vs one category lower)	0.28	0.61	0.83	1.10	4.83	4.55
Wealth Quintile (vs one category poorer)	0.64	0.82	0.88	0.95	1.20	0.56

All data is presented as exponentiated odds, or Odds Ratios representing a single step increase for each covariate

Q = Quartile. *IQR* = Inter-quartile range

had higher median effective range estimates than Pyrethroid-only LLIN clusters at 1190 m (IQR: 829–1538) versus 1146 m (IQR: 1041–1504) for non-IRS and 1717 m (IQR:940–2815) versus 1353 m (IQR: 1176–3398) for IRS clusters (Table 4).

Most clusters with significant range estimates were fit with Sine Hole Effect models (Table 5). While this may be due to the irregular sampling pattern of households in the study area [39], it could also indicate underlying anisotropic trends producing periodicity in the contamination effect [40]. Spatial variation should be mostly controlled for in the GWLR analysis, however this is not a perfect solution and some spatial clustering of the residual odds of malaria persists in the final dataset (Suppl 2).

Discussion

This study examined the distance of potential spillover effects, or contamination, between intervention clusters in a four-armed 48-cluster randomized controlled trial of malaria vector control interventions by comparing the range of semivariance models across intervention groups. Results showed that nearly half of the clusters (42%) in the study area exhibited a clear spatial trend in the residual geographically-weighted odds of malaria infection. These results are in agreement with previous studies demonstrating a community effect in malaria vector control trials [7, 8, 12, 41, 42], while also supporting the idea that these community effects may be sensitive to a number of contextual factors [43–45].

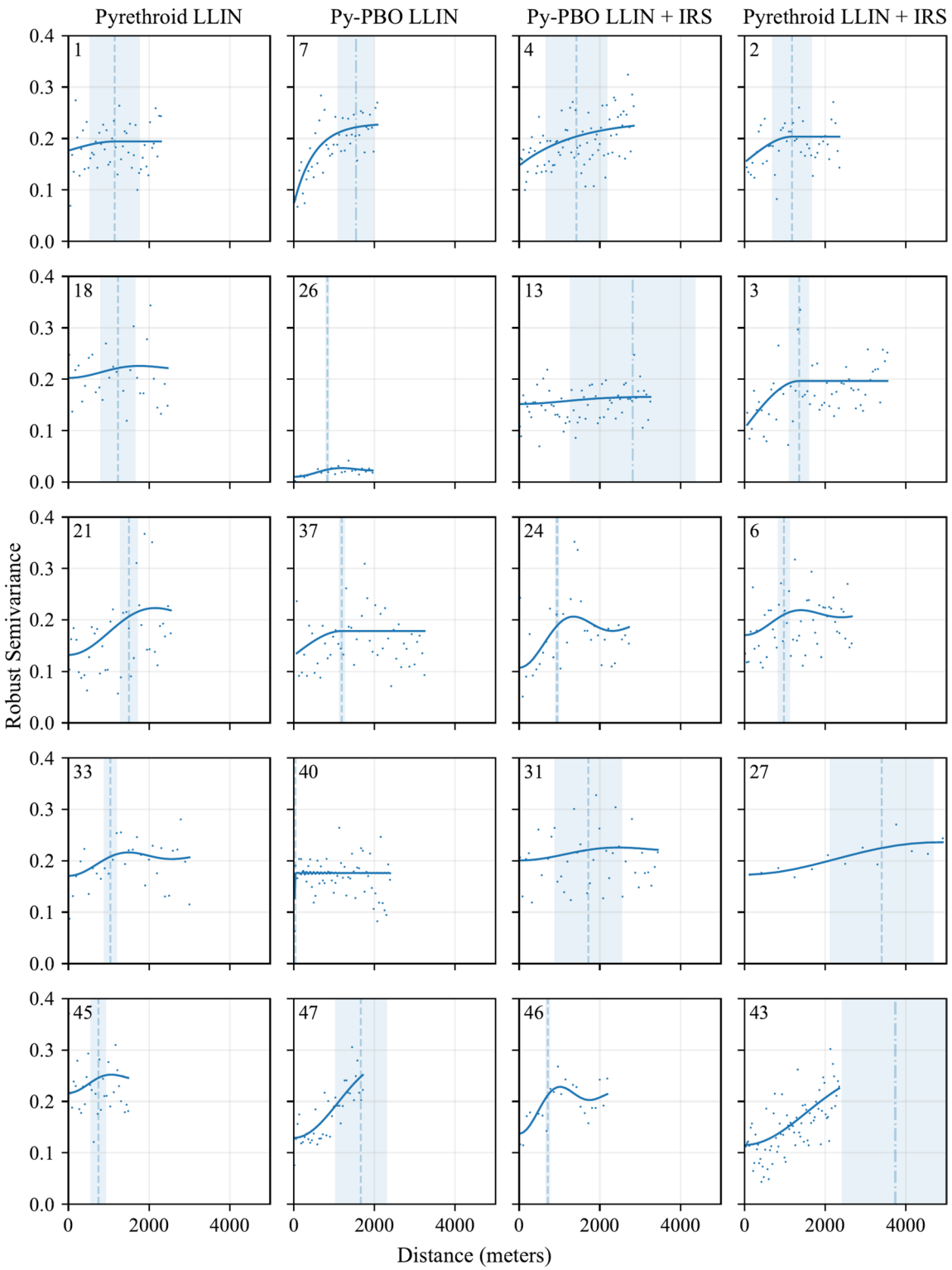

Fig. 3 Fitted semivariogram models with significant range parameters. Solid lines demonstrate the WLS-fitted semivariogram models of robust semivariance estimates for distance-lagged residual malaria infection (points). Shaded areas show the 95% confidence interval of either range estimates (dashed lines) or effective range estimates (dot-dash lines) as appropriate to the fitted model. $n = 20$ clusters

Table 3 Fitted robust variogram model parameter estimates of residual odds of malaria infection any (*Plasmodium* spp.) by intervention allocation and cluster/N = 6440 children

				Nugget		Scale		Range (m)			Effective Range
Intervention	**Cluster**	**n**	**Form**	**Estimate**	**pvalue**	**Estimate**	**pvalue**	**Estimate**	**95% CI**	**pvalue**	**(m)**
Pyrethroid LLIN											
	1	143	SPH	0.18	.	0.02	.	1146	(520–1772)	0.0006	1146
	9	145	SPH	0.19	<.0001	0.00	0.9999	1341	(1341–1341)	.	.
	11	114	GAU	0.17	.	0.01	.	1643	(0–3755)	0.1237	.
	12	169	SPH	0.16	<.0001	0.01	0.0900	1824	(1824–1824)	.	.
	14	173	SPH	0.11	<.0001	0.03	<.0001	1017	(1017–1017)	.	.
	15	121	POW	0.02	<.0001						
	18	105	SHE	0.20	.	0.02	.	1229	(795–1663)	<.0001	1229
	21	109	SHE	0.13	.	0.07	.	1504	(1281–1727)	<.0001	1504
	33	135	SHE	0.17	.	0.04	.	1041	(878–1204)	<.0001	1041
	35	175	GAU	0.19	<.0001	0.00	0.4476	1651	(1651–1651)	.	.
	44	145	EXP	0.16	<.0001	0.07	<.0001	1320	(1320–1302)	.	.
	45	122	SHE	0.22	.	0.03	.	741	(548–934)	<.0001	741
Py-PBO LLIN											
	7	146	EXP	0.07	<.0001	0.16	<.0001	513	(362–663)	<.0001	1538
	8	147	EXP	0.19	<.0001	0.00	0.9999	1406	(1406–1406)	.	.
	10	51	SPH	0.18	0.0015	0.00	1.0000	1402	(1402–1402)	.	.
	26	127	SHE	0.01	.	0.01	.	829	(784–875)	<.0001	829
	29	145	SPH	0.08	<.0001	0.00	0.9998	649	(649–649)	.	.
	34	145	EXP	0.19	<.0001	0.00	0.9999	1260	(1260–1260)	.	.
	36	122	SHE	0.16	<.0001	0.01	0.0437	1745	(1745–1745)	.	.
	37	151	SHE	0.13	<.0001	0.05	<.0001	1190	(1113–1267)	<.0001	1190
	38	144	EXP	0.20	<.0001	0.00	0.9999	1276	(1276–1276)	.	.
	40	137	SHE	0.10	<.0001	0.07	.	44	(43–44)	<.0001	44
	42	137	EXP	0.21	<.0001	0.00	0.9999	1523	(1523–1523)	.	.
	47	130	SHE	0.13	.	0.12	.	1665	(1021–2309)	<.0001	1665
Py-PBO LLIN + IRS											
	4	158	EXP	0.15	.	0.09	.	1419	(653–2185)	0.0004	4257
	13	170	GAU	0.15	.	0.01	.	1625	(723–2528)	0.0006	2815
	20	117	GAU	0.18	<.0001	0.00	0.9999	1734	(1734–1734)	.	.
	22	98	EXP	0.17	.	0.04	.	852	(0–1736)	0.0583	.
	23	135	SPH	0.17	<.0001	0.00	0.5854	1738	(1738–1738)	.	.
	24	116	SHE	0.11	<.0001	0.08	<.0001	940	(891–990)	<.0001	940
	28	131	SHE	0.19	<.0001	0.02	0.0024	1393	(1393–1393)	.	.
	30	138	POW	0.06	<.0001						
	31	140	SHE	0.20	.	0.02	.	1717	(879–2555)	0.0002	1717
	32	146	POW	0.06	<.0001						
	39	139	SPH	0.20	<.0001	0.00	0.9999	1948	(1948–1948)	.	.
	46	109	SHE	0.14	<.0001	0.07	<.0001	709	(649–768)	<.0001	709
Pyrethroid LLIN + IRS											
	2	126	SPH	0.15	.	0.05	.	1176	(684–1667)	<.0001	1176
	3	137	SPH	0.10	.	0.09	.	1353	(1098–1607)	<.0001	1353
	5	122	SPH	0.19	<.0001	0.01	0.3246	2101	(2101–2101)	.	.
	6	145	SHE	0.17	.	0.04	.	976	(821–1131)	<.0001	976
	16	120	POW	0.08	<.0001						
	17	111	SPH	0.16	<.0001	0.00	0.9999	1237	(1237–1237)	.	.
	19	120	EXP	0.22	<.0001	0.03	0.0314	2069	(2069–2069)	.	.

Table 3 (continued)

Intervention	Cluster	n	Form	Nugget		Scale		Range (m)			Effective Range
				Estimate	pvalue	Estimate	pvalue	Estimate	95% CI	pvalue	(m)
	25	144	EXP	0.23	<.0001	0.00	0.9999	1153	(1153–1153)	.	.
	27	134	SHE	0.17	.	0.05	.	3398	(2107–4689)	0.0002	3398
	41	147	SPH	0.14	<.0001	0.01	0.0913	2746	(2746–2746)	.	.
	43	177	GAU	0.12	.	0.16	.	2158	(1388–2927)	<.0001	3738
	48	122	SPH	0.13	<.0001	0.00	0.9999	1171	(1171–1171)	.	.

Table 4 Effective range estimates of residual odds of malaria infection (any *Plasmodium* spp.) by intervention allocation/N = 48 clusters

	Effect ranges (m)					
	Min	Q1	Median	Q3	Max	IQR
Whole Dataset	44	958	1210	1691	4257	733
Non-IRS Clusters	44	829	1168	1504	1665	675
Pyrethroid LLIN	741	1041	1146	1229	1504	188
Py-PBO LLIN	44	829	1190	1538	1665	291
IRS Clusters	709	976	1535	3398	4.257	2422
Py-PBO LLIN + IRS	709	940	1717	2815	4257	1875
Pyrethroid LLIN + IRS	976	1176	1353	3398	3738	2222

Table 5 Semivariogram model fitted forms by intervention allocation/N = 48 clusters

	Significant Range Models				Non-Significant Range Models				
	SPH	GAU	EXP	SHE	SPH	GAU	EXP	SHE	POW
Pyrethroid LLIN	1	0	0	4	3	2	1	0	1
Py-PBO LLIN	0	0	1	4	2	0	4	1	0
Py-PBO LLIN + IRS	0	1	1	3	2	1	1	1	2
Pyrethroid LLIN + IRS	2	1	0	2	4	2	0	0	1
Total	3	2	2	13	11	5	6	2	4

This study has presented a unique, detailed analysis of the potential effect ranges of malaria vector control interventions for each of the 48 clusters in the study area, rather than examining specific subsets or global trends. Each cluster was uniformly assessed and modelled to produce range estimates that allow for localized variations within the study area—and within intervention arm. Furthermore, while most previous examinations of the effective range of vector control interventions restrict their assessment of effects to households in some immediate proximity (e.g., households within a set distance [41] or discordant household pairs [42]), the semivariance approach examines all household pairs within half the bounded distance of the cluster area to develop robust estimates of the model effect range [31].

The overall model effect range of 1210 m (IQR: 958–1691) found in this analysis suggests that the 300 m buffer ranges used in the trial under study [15] would be inadequate to completely prevent contamination between groups. One kilometre buffers, as were previously used in Muleba [46] and more recently in Benin [47], or 1500 m, as were employed in the western Kenyan highlands [14], would be much more appropriate in terms of encapsulating the majority of the modelled effects. However, there is a trade-off between larger buffer distances and operational factors as increasing the size of the study area and the number of study clusters directly impacts trial costs. Further to this, the semivariance ranges calculated using trial data reflect the effective level of global statistical variance which may not necessarily equate to biologically

meaningful differences in malaria transmission rates or malaria outcomes across the full range distance. Simulations and retrospective studies that have suggested contamination effects at a much smaller spatial scale, and having little impact on trial outcomes [48, 49]. These results are not necessarily incongruous with the findings in this study, but further analysis is needed to determine the impact of the present spillover on trial results.

This analysis demonstrated that there is a difference in the model effect ranges of IRS (1535 m, IQR: 976–3398) and non-IRS (1168 m, IQR: 829–1504) interventions, which suggests that that spillover effects will be larger in cRCT vector control trials with higher coverage and stronger efficacy. Indeed, IRS had a much quicker impact on prevalence [15], with its effect being detectable at four-month compared to the arms that received only LLINs. It is important to note that the IRS arm was not exclusively IRS; it assessed the combined effect of IRS and LLINs. This combination likely resulted in higher overall coverage of at least one intervention compared to arms with LLINs alone (non-IRS), as IRS does not require a continued commitment to use once applied. More consistent community coverage, and therefore a more robust community protective effect as seen elsewhere [50], could explain the difference in model effect ranges identified between IRS and non-IRS arms. Alternatively, there may have been differential impacts of the trial interventions based on the vector species composition of the study area, as has been seen in a comparable study area [51]. While *An. gambiae s.s.* were far and away the dominant vector species in the study area, *Anopheles arabiensis* and *Anopheles funestus s.l.* were also present [23]. Given the different flight patterns and resting behaviours of these vector species [10, 52], a concentration of a particular species in a given cluster could have influence on cluster-specific semivariance effect ranges—even if these differences are adequately controlled for in other trial analyses. It should be noted that this analysis was conducted four months post-intervention when IRS still showed a clear protective benefit (OR 0.50 (95% CI 0.31–0.82) compared to no IRS) [15]. With a waning efficacy of interventions over time, it would be expected that community effect ranges would similarly diminish.

The large discrepancies in modelled effect range distances between clusters in the same intervention group are likely due to a combination of factors including the spatial arrangement of sampling points (and cluster households more broadly) due to topography and/or unobserved localized factors that may be significantly associated with malaria, including differences in vector populations (e.g. host preference, insecticide resistance), or intervention coverage and usage [53]. Indeed, given the mechanism of community effects through a combination of mass killing and reduction in mean age of vectors [2, 54], which in turn greatly reduces the population of infectious mosquitoes and local entomological inoculation rates [55–57], vector population characteristics may greatly influence the estimated effect ranges. This study has used robust semivariance estimates to minimize this effect [35], as well as reporting median values and interquartile ranges to provide conservative estimates. Median estimates of the model effect ranges for each intervention type align reasonably with the expected dispersal ranges of *An. gambiae s.l.* [58], supporting the plausibility that these spatial trends are predominantly representative of community-level intervention effects on malaria transmission. While it is possible that there are indeed effects ranging as far as four kilometres from cluster households, these numbers should be considered in the picture of the group estimates as one might consider an outlying variable in any dataset [59].

Limitations

While care has been taken in the GWLR model to include commonly identified factors associated with malaria infection in the study area, unmodelled spatial factors are likely present in the study area that could create an underlying non-stationary trend—impacting the direct interpretability of these results as intervention effects [34]. The use of "model range" throughout presumes that the bulk of any spatial trends remaining in the model residuals are due to the effects of the intervention, but care should be taken in generalizing these results—especially to areas with substantively different vector species compositions.

This study excluded clusters with non-significant model range estimates in the analysis of effective semivariance ranges. These data models are likely underpowered, due to a lack of sufficient data density in the semivariance estimation of each cluster [60], and may also be indicative of some form of residual spatial trend. As this secondary analysis was conceived after data collection, a more robust sample was not possible. Future studies targeting semivariance analysis could undertake a larger sample to evaluate these trends.

This study did not incorporate entomological data, given the relatively sparse geographical coverage of households that were sampled for mosquitoes compared to those that were included in the malaria survey. Future studies would benefit from examining spatial range effects of vector control interventions on malaria vector population indices to enable a more mechanistic understanding of these effects.

Conclusions

This study, which uses a robust semivariance approach to estimate the potential range effects of LLIN and IRS interventions on malaria prevalence, provides a strong indication that there may be a substantially larger community effect to vector-control interventions than previously thought. The estimated ranges of intervention spillover effects on malaria infection from a trial in Muleba, Tanzania, which reflect the distance over which malaria vector control interventions have an impact on malaria prevalence, extend substantially beyond current best practices for trial cluster buffer sizes. This is especially the case for intervention clusters utilizing IRS in this study. Contamination of effects between adjacent clusters, as exhibited in this study, may be causing measured intervention effects to trend towards the mean in cluster-randomized vector control trials, impacting the capacity of trials to determine significance differences between interventions under study. Future research should be incorporated into malaria vector control trials to estimate range effects for different types of LLIN and IRS interventions and account for these effects in the interpretation of trial results.

Abbreviations

AICc	Akaike information criterion (corrected)
ANOVA	Analysis of variance
AOR	Adjusted odds ratio
cRCT	Cluster randomized-control trial
EXP	Exponential
GAU	Gaussian
GWLR	Geographically-weighted logistic regression analysis
IQR	Inter-quartile range
IRS	Indoor residual spraying
LLIN	Long-lasting insecticidal net
OR	Odds ratio
PAMVERC	Pan-African malaria vector research consortium
PBO	Piperonyl butoxide
POW	Power
Py-PBO	Pyrethroid and piperonyl butoxide
RDT	Malaria rapid diagnostic test
SHE	Sine hole effect
SPH	Spherical
UK	United Kingdom
WGS_1984	World geodetic system 1984
WHO	World health organization
WLS	Weighted least squares

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-025-05438-y.

Additional file1

Author contributions

CT, MK, and NP conceptualized and developed the analyses for this study. NP, ELM, JFM, JDC, and AM collected the data. CT analysed the data and produced the first draft of the manuscript. MK, AJ, AZ, and NP critically evaluated the analysis methods and provided revisions for the first draft of the manuscript. CT, EL, JFM, AM, IK, FWM, JDC, and MR revised the manuscript. All authors reviewed and approved the manuscript prior to publication.

Funding

Funding for this project was provided by the University of Ottawa Access to Research Networks.

Availability of data and materials

The datasets used for analysis in this study are available from PAMVERC upon reasonable request. The corresponding author would be pleased to facilitate this communication.

Declarations

Ethics approval and consent to participate

Ethics approval for these secondary analyses was provided the University of Ottawa Science and Health Sciences Research Ethics Board (Ethics File Number H-06-18-806).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 16 April 2025 Accepted: 30 May 2025
Published online: 09 June 2025

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