Households or Hotspots? Defining Intervention Targets for Malaria Elimination in Ratanakiri Province, Eastern Cambodia

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Background. Malaria "hotspots" have been proposed as potential intervention units for targeted malaria elimination. Little is known about hotspot formation and stability in settings outside sub-Saharan Africa.

Methods. Clustering of *Plasmodium* infections at the household and hotspot level was assessed over 2 years in 3 villages in eastern Cambodia. Social and spatial autocorrelation statistics were calculated to assess clustering of malaria risk, and logistic regression was used to assess the effect of living in a malaria hotspot compared to living in a malaria-positive household in the first year of the study on risk of malaria infection in the second year.

Results. The crude prevalence of *Plasmodium* infection was 8.4% in 2016 and 3.6% in 2017. Living in a hotspot in 2016 did not predict *Plasmodium* risk at the individual or household level in 2017 overall, but living in a *Plasmodium*-positive household in 2016 strongly predicted living in a *Plasmodium*-positive household in 2017 (Risk Ratio, 5.00 [95% confidence interval, 2.09–11.96], $P < .0001$). There was no consistent evidence that malaria risk clustered in groups of socially connected individuals from different households.

Conclusions. Malaria risk clustered more clearly in households than in hotspots over 2 years. Household-based strategies should be prioritized in malaria elimination programs in this region.

Keywords. malaria; hotspot; malaria elimination; Greater Mekong Subregion; epidemiology.

Malaria elimination targets are focusing attention on the total *Plasmodium* infection burden, including asymptomatic infections [1–3], which are thought to contribute to ongoing transmission [1, 4]. Though the probability of onward transmission is lower [1, 5], asymptomatic infections represent a key challenge for malaria elimination, as they are not systematically detected in routine care [6]. In addition to standard vector control (long-lasting insecticidal nets and indoor residual spraying) and prompt case detection and treatment, there are 2 broad strategies promoted to reduce the parasite reservoir in malaria elimination settings: mass drug administration (MDA), in which entire populations are treated with antimalarial drugs;

and targeted approaches, which aim to focus on "high risk" subgroups. MDA requires substantial resources and intensive community participation strategies to be effective [7–10]. MDA also raises ethical concerns in settings where the vast majority of individuals asked to comply with MDA are uninfected, and therefore unnecessarily exposed to drugs [11]. Alternatively, targeted approaches restrict screening and/or treatment to the population(s) most likely to be infected. Targeted strategies include reactive household-based screening and treatment [12] as well as proactive screening and treatment of at-risk populations [13]. The effectiveness of targeted strategies varies in different epidemiological contexts [14]. The parasite reservoir has also been indirectly targeted through widespread vector control and case detection and treatment, strategies that have historically supported malaria elimination in many countries [15].

"Hotspots" have also been proposed as a unit for targeted intervention [16]. Hotspots are geographical areas of higher-than-expected infection prevalence compared to surrounding areas and can be defined at various spatial scales, from the provincial to subvillage levels [16]. Hotspots may contribute to maintaining the parasite reservoir by individuals residing in hotspots harboring low-density infections that seed ongoing

transmission [16]. However, evidence for the utility of hotspots as an intervention target remains scant; the first trial of its kind showed no effectiveness of hotspot targeting in Kenya [17]. In general, the apparent stability of hotspots varies according to the spatial scale at which they are defined; spatially and temporally stable hotspots at the village or district level have been reported in sub-Saharan African (SSA) [18–20], South Asian [21], and East Asian [22–24] settings. However, there was no consistent evidence for temporal stability of hotspots across sites in SSA [25]. Evidence of stable malaria hotspots in the Greater Mekong Subregion (GMS) that would support hotspot targeting into malaria elimination programs at the subvillage level is limited, despite this region having high heterogeneity of malaria risk [26], and being an international priority region for malaria elimination due to the emergence and spread of artemisinin-resistant *Plasmodium falciparum* malaria [27]. A previous study in 3 villages in western Cambodia found only transient spatial clustering of *Plasmodium* infections at the subvillage level, which the authors partly attributed to transmission occurring mostly away from the village [28]. Other studies in the GMS have either investigated spatial clustering at one time point only [29], or pooled cases from multiple time points into a single analysis [30].

Defining hotspots does pose challenges. Hotspots have mostly been defined based on static house locations in SSA where transmission mostly occurs indoors and at night. This does not reflect the malaria ecology in the GMS, where outdoor evening vector biting predominates, populations frequently move between their houses in the village and at farms, and people may congregate in areas other than their own houses for social events at peak evening biting times [31]. The effect of local-scale mobility on malaria risk has previously been analyzed in terms of spatial clustering of malaria risk at different residence locations [29]. However, this fails to capture effects of individuals from different households regularly spending time together in locations other than their own residences, such as outdoor evening social gatherings at which individuals from multiple households convene [32]. Any effect of this type of local-scale mobility would imply that spatial clustering of malaria would be more accurately detected based on clusters of people who frequently spend time together in the same locations, not only residence location.

To address these research gaps, this study aims to assess the stability of hotspots over 2 dry seasons in 3 villages in eastern Cambodia, and analyze whether incorporating fine-scale mobility data could improve identification and characterization of malaria hotspots.

METHODS

Study Design and Setting
A 2-year repeated population-based survey was conducted in 3 villages (Chamkar San, Tun, Phi) in Ratanakiri Province,

eastern Cambodia. The population mostly comprises ethnic minority (including Jarai, Kreung, and Tompuon) populations that practice slash-and-burn agriculture at forest farms and fields. There is a growing Khmer (ethnic majority) population as well as increasing participation in labor markets [33, 34]. Local vector species include *Anopheles dirus*, *Anopheles minimus*, and *Anopheles barbirostris* [35]. Malaria control activities include long-lasting insecticidal net distributions and free testing and treatment of malaria through the village malaria worker program and at district and provincial health centers.

The study comprised 2 blood screening surveys in the dry seasons of 2016 and 2017, and an individual cross-sectional survey at the midpoint between the 2 blood screening surveys, which included questionnaires on individual and household-level risk factors for *Plasmodium* infection, as well as an individual questionnaire about mobility and contact patterns with other individuals in the same village. Details of the surveys have been published previously [29].

Participants
All individuals residing in the 3 study villages were eligible to participate in the blood screening surveys. All resident individuals aged ≥12 years were eligible to respond to the mobility and contact pattern questionnaire.

Data Collection
Fingerprick blood samples were analyzed by species-specific polymerase chain reaction (PCR) for *Plasmodium* infection (*P. falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*), as previously described [22]. Farm and village house locations were collected by Global Positioning System (GPS) as previously published [29]. Mobility data were collected by taking unique random samples of 10 individuals ("contacts") from the study census lists of each village, and asking each respondent questions about the locations (their own house, in the village, at farms, in the forest) and frequency of meeting the contacts from their village. Prompts were used to assist interviewers and respondents to correctly identify the randomly selected contact, including the selected contact's name, age, and sex, as well as the name of the contact's household head and spouse of the household head.

Data Analysis
Spatial Analysis
The primary outcome was the proportion of household members who were *Plasmodium* positive in each year. Moran I was used to test for global spatial autocorrelation in the distribution of *Plasmodium* infections in each village, separately for each year, each *Plasmodium* species and house location type, that is, village house, farm house, and self-reported main residence. For each village, year, and residence location, Moran I was calculated based on distance matrices for spatial adjacency between households, where a value of 1 was assigned to pairs of

houses within a predefined distance cut-point, or 0 otherwise. Three distance cut-points were used (0.5 km, 1 km, and 2 km) to explore global spatial autocorrelation at different spatial scales. Local clustering detection was performed using Kulldorf spatial scan statistic implemented in SaTScan software [36]. Spatial analysis of the 2016 data has been published [29]; the analysis was repeated for the 2017 data.

The effects of individual *Plasmodium* infection, living in a household with at least one *Plasmodium*-infected individual, or living in a hotspot in 2016, on risk of *Plasmodium* infection in 2017 were investigated using binomial regression with a log-link function and robust variance estimates to account for within-household clustering.

Social Contact Analysis
For each respondent, "contact" was considered to occur if the respondent reported that they met the selected individual at least weekly. To test whether contact with a *Plasmodium*-infected individual increased risk of *Plasmodium* infection, a 2-level logistic regression model was fitted with the respondent's *Plasmodium* infection status as the binary outcome, and the primary exposure was modeled as an interaction between the contact's *Plasmodium* infection status and the occurrence of weekly contact, with secondary analyses for contact specifically at the respondents' house(s) and at the farms and fields. Separate analyses were run for the contact's individual infection status and a contact's household infection status (ie, any household member who was *Plasmodium* positive). A random intercept was included for each respondent to account for the nested data structure of 10 contacts per respondent, with village adjusted for as a fixed effect. Additionally, Moran I was used to test for clustering of infection risk at household level, separately for each village and each year [37]. The cut-point of "at least weekly" contact was used to indicate regular co-location and thus shared risk of exposure to biting vectors. Other cut-points were also investigated, including any contact, monthly contact, and daily contact, but did not substantially change the results.

Regression modeling was conducted in Stata IC/13. Robust variance estimates were calculated using the vce (cluster) option in Stata. Moran I was calculated in R using the DCluster package. Maps were produced in R using Google Earth satellite images.

Ethical Analysis
Study protocols were approved by the institutional review board (IRB) of the National Ethical Committee on Health Research of Cambodia (approval number 309NECHR), the IRB of the Institute of Tropical Medicine Antwerp (approval number IRB/AB/ac/119), and the Ethical Committee of the University of Antwerp (approval number B300201525582). Written informed consent was obtained to participate in the malariometric survey. Verbal informed consent was obtained to additionally participate in the social contact survey. Minors assented to participate with the informed consent and in the presence of their parent or guardian. All individuals were free to refuse or withdraw participation at any time.

RESULTS

Participants
The study population comprised 1792 individuals in 343 households in 2016, of whom 85.9% had blood samples collected [29] and in 2017, 1117 individuals were reached in 269 households, of whom *Plasmodium* infection data were available for 1102 individuals (Table 1). More than 50% of the population was aged <20 years in both years. There were fewer individuals who resided primarily at their farm houses in 2017 (22%) compared to 2016 (44.6%), reflecting incomplete sampling of the resident population in 2017 (Table 1).

The overall prevalence of malaria in the 3 villages was 3.6% in 2017 and 8.4% in 2016 (Table 2). *Plasmodium vivax* monoinfections accounted for the majority of infections in both surveys (Table 2). *Plasmodium malariae* was more common than *P. falciparum* in Chamkar San and Phi, but was absent in Tun. Mixed infections accounted for 9.3% of infections (0.8% population prevalence) in 2016 and 7.5% of infections (0.3% population prevalence) in 2017.

At the individual level, among participants for whom data was available for both years, 25% (n = 19) of those who were *Plasmodium* positive in 2016 were *Plasmodium* positive in 2017, mostly individuals who had *P. vivax* infections in both years (Supplementary Table 1). Conversely, 51% of individuals who were *Plasmodium* positive in 2017 were *Plasmodium* negative in 2016, mostly with newly detected *P. vivax* infections (38%) (Supplementary Table 1).

At the household level, there were 217 (13.9%) individuals living in 35 households in which at least one person with *Plasmodium* infection was detected in 2017, compared to 679 (37.4%) individuals living in 101 households with at least one person with *Plasmodium* infection in 2016, including 25 households that had *Plasmodium*-positive members in both years.

Spatial Analyses
Several species-specific hotspots and coldspots of *Plasmodium* infection were detected in 2016 [29]. In 2017, only one statistically significant hotspot was detected, which was a cluster of 13 households in an area of radius 0.53 km based on village residence, in which 6 *Plasmodium* infections were detected (Supplementary Table 2). This hotspot had approximately the same location as a *Plasmodium* species hotspot detected in 2016, but in 2016 the hotspot had an 8-fold smaller radius (0.064 km). No *Plasmodium* species–specific hotspots were detected at $P < .15$ (Supplementary Table 2). There was no evidence for

Table 1. Demographic Characteristics and Prevalence of Any *Plasmodium* Infection in the Study Population in 2016 and 2017

Characteristic	2016[a] Population		*Plasmodium* Positive		2017[b] Population		*Plasmodium* Positive	
Village								
Chamkar San	619	(34.54)	31	(5.79)	446	(39.93)	12	(2.69)
Phi	717	(40.01)	53	(8.98)	289	(25.87)	11	(3.94)
Tun	456	(25.45)	45	(10.90)	382	(34.20)	17	(4.51)
Age group, y								
0–4	285	(15.98)	10	(4.07)	154	(13.79)	0	(0.00)
5–9	254	(14.24)	18	(7.93)	182	(16.29)	4	(2.22)
10–14	230	(12.89)	25	(11.85)	174	(15.58)	11	(6.32)
15–19	214	(12.00)	20	(11.83)	124	(11.10)	5	(4.03)
20–29	299	(16.76)	19	(7.42)	178	(15.94)	3	(1.74)
30–39	211	(11.83)	14	(7.87)	123	(11.01)	4	(3.31)
40–49	138	(7.74)	7	(5.93)	69	(6.18)	5	(7.35)
≥50	153	(8.58)	16	(12.50)	113	(10.12)	8	(7.08)
Sex								
Male	903	(50.79)	68	(8.85)	552	(49.42)	25	(4.60)
Female	875	(49.21)	61	(8.05)	565	(50.58)	15	(2.69)
Main residence								
Village	977	(55.39)	57	(6.84)	868	(77.99)	22	(2.56)
Farm	787	(44.61)	72	(10.53)	245	(22.01)	18	(7.59)

Data are presented as No. (%).

[a]The population in 2016 reflects the resident population that was included in the census in January 2016, of whom 85.9% had blood collected for malaria testing.

[b]The population in 2017 reflects the population that was reached in the follow-up survey, of whom 1102 (98.7%) had blood collected for malaria testing. Of the 1792 individuals in 2016, 1012 were reached again in 2017, and 105 new individuals were included who were not in the census in 2016, including births and migrants.

global spatial autocorrelation in the distribution of *Plasmodium* infections in either year (Supplementary Table 3).

Descriptively, the spatial distribution of *Plasmodium* infections in 2016 and 2017 combined was scattered, and there was no overt clustering of households that had *Plasmodium*-positive members in both years (Figure 1). Of the 40 *Plasmodium* infections detected in 2017, 22 (55%) were in households identified as being within hotspots in 2016, compared to 30 (75%) in households that had at least 1 *Plasmodium*-infected individual in 2016. There were 9 households that had a *Plasmodium*-positive member in both years but were not located in a hotspot in 2016. There were 10 individuals in 10 households who were *Plasmodium* positive in 2017 who were not living in *Plasmodium*-positive households in 2016, of whom 5 were located inside hotspot areas and 5 outside hotspot areas.

After adjusting for individual and household infection status, living in a hotspot in 2016 did not predict *Plasmodium* risk at the individual level (Risk Ratio [RR], 1.43 [95% confidence interval {CI}, .67–3.05], P = .36) or household level (RR, 1.81 [95% CI, .85–3.85], P = .13) overall (Table 3). However, living in a hotspot in 2016 was a risk factor for living in a *Plasmodium*-positive household in Chamkar San in 2017 (RR, 3.45 [95% CI, 1.18–10.08], P = .024). In Chamkar San and Phi, individual infection in 2016 was the strongest predictor of individual infection risk in 2017, but in Tun, household-level (RR, 4.29 [95% CI, 1.04–17.64], P = .04) but not individual-level (RR, 2.51 [95% CI, .76–8.27], P = .13) infection in 2016 predicted

individual-level infection risk in 2017. Living in a *Plasmodium*-positive household in 2016 was the strongest predictor of living in a *Plasmodium*-positive household in 2017 overall (RR, 5.00 [95% CI, 2.09–11.96], P < .0001) and was more than twice the magnitude of the hotspot effect in Chamkar San and Tun. There were no significant predictors of 2017 household-level *Plasmodium* status in Phi (Table 3).

Social Contact Analyses

Social contact data were available for 712 respondents aged 12 years in 267 households, who were asked about 1445 unique contacts in 349 households, representing 97% of households in the study. Each respondent reported knowing a median of 7 of 10 contacts (interquartile range [IQR], 0.5–0.9), and met with a median of 4 of 10 contacts (IQR, 2–6) on at least a weekly basis. A median of 1 in 10 weekly contacts (IQR, 0–2) occurred at the respondent's house(s), and a median of 1 (IQR, 0–3) at the farms and fields. There was some variation in contact patterns between villages, with more weekly contacts in Tun (median, 6 [IQR, 4–8]) than in Phi (median, 3 [IQR, 2–6]) or Chamkar San (median, 3 [IQR, 1–5]).

When aggregated at household level, there was considerable contact between members from different households (Figure 2). Overall, there was no evidence for an effect of weekly contact with *Plasmodium*-infected individuals (model A1, Table 4), nor when restricting to contact that occurred at the respondent's house(s) or at the farms and fields (models A2 and A3,

Table 2. *Plasmodium* Infection by Village, Species, and Year

	Plasmodium Infection			
Plasmodium Species	2016		2017	
Overall				
All species	129	(8.4)	40	(3.6)
P. falciparum	16	(1.0)	4	(0.4)
P. vivax	75	(4.9)	26	(2.4)
P. malariae	26	(1.7)	7	(0.6)
Mixed	12	(0.8)	3	(0.3)
Chamkar San				
All species	31	(5.8)	12	(2.7)
P. falciparum	2	(0.4)	3	(0.7)
P. vivax	18	(3.4)	3	(0.7)
P. malariae	6	(1.1)	4	(0.9)
Mixed	5	(0.9)	2	(0.4)
Phi				
All species	53	(9.0)	11	(3.9)
P. falciparum	9	(1.5)	1	(0.4)
P. vivax	21	(3.6)	6	(2.2)
P. malariae	20	(3.4)	3	(1.1)
Mixed	3	(0.5)	1	(0.4)
Tun				
All species	45	(10.9)	17	(4.5)
P. falciparum	5	(1.2)	0	(0)
P. vivax	36	(8.7)	17	(4.5)
P. malariae	0	(0)	0	(0)
Mixed	4	(1.0)	0	(0)

Data are presented as No. (%). Missing data were as follows: Chamkar San, n = 86 (13.9%) in 2016, n = 135 (23.3%) in 2017; Phi, n = 127 (17.7%) in 2016, n = 469 (62.7%) in 2017; Tun, n = 44 (9.7%) in 2016, n = 40 (9.6%) in 2017.

Table 4). There was no evidence for household-level increased *Plasmodium* infection risk due to contact with *Plasmodium*-positive households in the regression analyses (models B1, B2, and B3, Table 4). When analyzing clustering of *Plasmodium* infection risk among socially connected households, there was no evidence of social clustering in Chamkar San or Phi. In Tun, there was evidence of social clustering of *Plasmodium* infection in 2016, but not 2017 (Table 5).

DISCUSSION

This study combined spatial and social contact patterns to investigate fine-scale heterogeneity in malaria risk at the subvillage level. This study found minimal evidence of stable spatial clustering of *Plasmodium* infection in "hotspots" over 2 dry seasons in 3 villages in Ratanakiri Province, eastern Cambodia, and there was no evidence that incorporating social contact patterns, which could indicate shared exposures, improves understanding of clustering of malaria risk at the subvillage level. A salient finding is that in the second year of the study, when *Plasmodium* infection prevalence halved, the spatial distribution of infections was more scattered, and hotspots became less apparent than in the first year. Other authors have cautioned that statistical power for cluster detection is weak in low-prevalence

settings, and thus recommended a low threshold for acting on any apparent clustering despite lack of clear statistical evidence [25]. However, this presumes that apparent spatial clustering of malaria cases is a meaningful intervention target, even in the absence of statistical evidence [16, 38]. While the temporal stability of hotspots has been observed at larger spatial scales in SSA settings [20], the findings of our study do not support the spatial focalization of malaria risk to subvillage level in this low-prevalence setting. Compared to SSA settings, the lack of stable hotspots in general may be explained by differences in vector ecology or other environmental characteristics. Despite the negative findings of the social contact analysis, there may be an influence of small-scale human mobility on hotspot instability given that vector exposure is linked to early evening outdoor activities conducted in the vicinity of houses [35]; any shifts in the composition of groups of people who regularly spend time in the same outdoor locations in the evenings may explain the lack of temporal stability of hotspots.

These findings have implications for the key operational research question of whether the parasite reservoir can be identified and targeted at the village and subvillage levels. Malaria risk did appear to become more focal over time, but clustering occurred within households, not hotspots, with 75% of *Plasmodium* infections detected in the second year of the study arising in households in which at least one infection was detected in the first year. This is supported by a previous analysis on the same population showing that the strongest determinants of *Plasmodium* infection were household characteristics, rather than individual or village characteristics [39], and a study in low-transmission settings in Uganda that also indicated the importance of household-level heterogeneity in malaria risk [40]. A well-implemented household-based strategy based on active case detection and presumptive treatment of all household members, coupled with sustained and improved provision of vector control tools especially for higher-risk households, may achieve further reductions and even local interruption of transmission, and may be more feasible to sustain than MDA. Though households appear to be a relatively stable unit of clustering of infection, we are unable to directly infer whether clustering occurs due to indoor transmission within houses, or is due to shared evening activities or other exposures among household members.

There are several limitations to this study. This analysis was based on infections detected by PCR only. Serology markers may provide more stable measures of hotspots in endemic settings [41], though the utility of serology for estimating exposure in settings with rapidly declining transmission is unclear. A possible explanation for the lack of spatial or social contact-related clustering of malaria risk is that the extent to which asymptomatic infections contribute to transmission remains unclear [5]. The spatial and social contact patterns of the proportionally few symptomatic infections may be more important
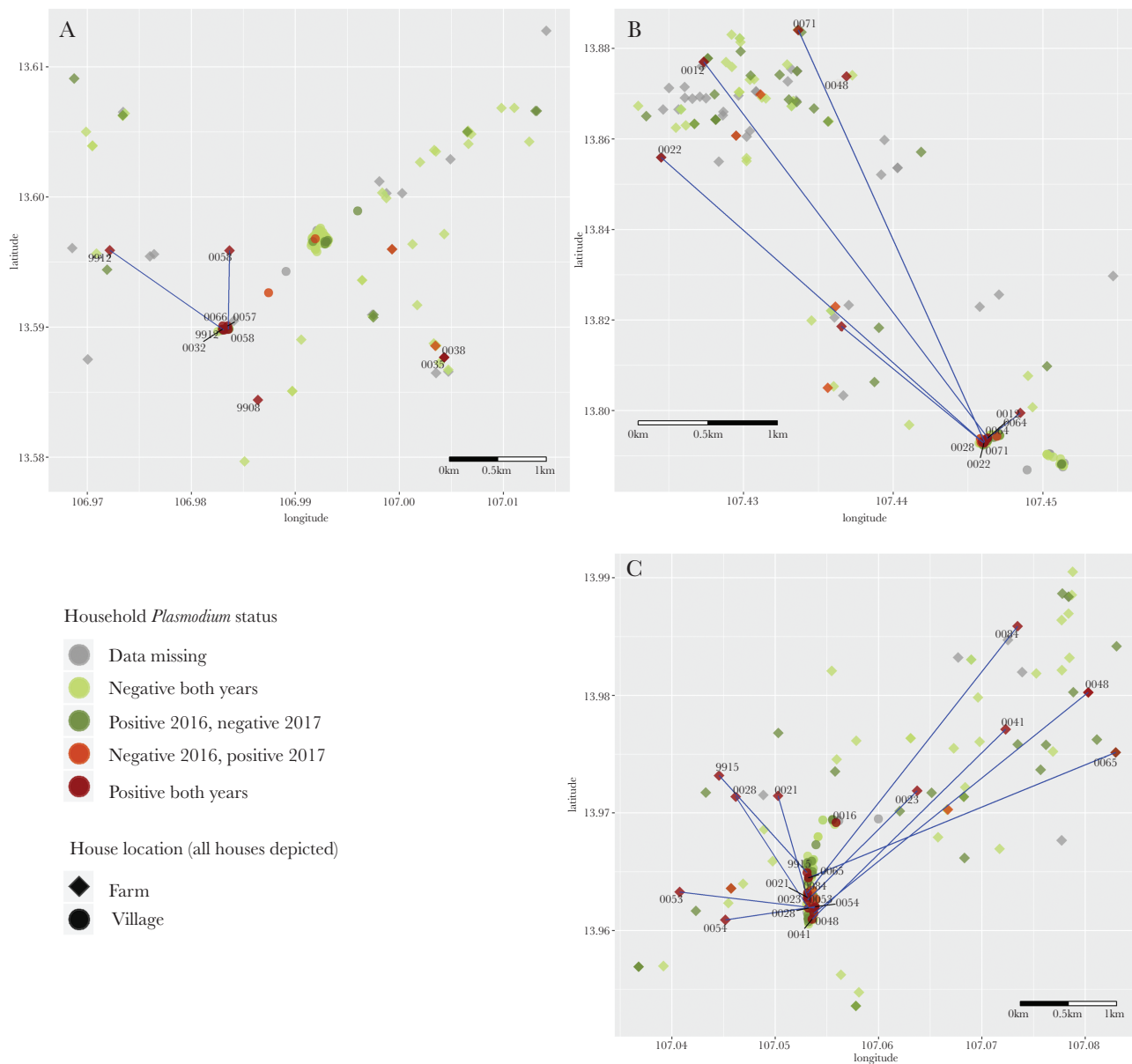
Figure 1. Distribution of *Plasmodium* infections at the household level in 2016 and 2017, in Chamkar San (*A*), Phi (*B*), and Tun (*C*), Cambodia.

for understanding the distribution of the parasite reservoir. Additionally, the spatial analyses were based on Euclidean distances and did not take local topographical features into account, which may have affected vector dispersion. As most infections were *P. vivax* infections, for which it was not possible to separate new infections from relapsing infections, and as a considerable proportion of infections were due to *P. malariae*, which can persist for several years, the lack of detection of social or spatial clustering may also relate to the elapsed time since infections were acquired. The response rate in the second year of the survey was lower than in the first year, substantially so in Phi. This was in large part caused by a low willingness of the inhabitants of Phi to participate in the second survey. The data from Phi are included for completeness but only the findings

from Chamkar San and Tun should be considered reliable. The small number of infections detected in the second year, particularly for *P. falciparum,* precluded species-specific statistical analyses. The decline in prevalence between the first and second year remains unexplained. As per national guidelines, no treatment was given for PCR-positive, rapid diagnostic test–negative (asymptomatic) malaria detected in the first survey. No change in the provision of malaria testing or treatment, or general health services occurred during the study period that could account for the observed change in prevalence. Finally, as there was no temporal dimension to the social contact data, it was not possible to directly investigate whether spending time with a *Plasmodium*-infected individual increased the risk of a new infection. More comprehensive assessment of fine-scale mobility

Table 3. Determinants of *Plasmodium* Infection Status at Individual and Household Level, 2017

2016 Status	2017 *Plasmodium*-Positive Individual			2017 *Plasmodium*-Positive Household		
	RR	(95% CI)	*P* Value	RR	(95% CI)	*P* Value
All villages						
Individual *Plasmodium* negative	Ref.	…		Ref.	…	
Individual *Plasmodium* positive	6.46	(2.85–14.65)	< .0001	1.12	(.86–1.46)	.39
Household *Plasmodium* negative	Ref.	…		Ref.	…	
Household *Plasmodium* positive	2.00	(.73–5.50)	.18	5.00	(2.09–11.96)	< .0001
Outside hotspot	Ref.	…		Ref.	…	
Inside hotspot	1.43	(.67–3.05)	.36	1.81	(.85–3.85)	.13
Chamkar San						
Individual *Plasmodium* negative	Ref.	…		Ref.	…	
Individual *Plasmodium* positive	13.90	(3.40–56.90)	< .0001	0.89	(.71–1.11)	.30
Household *Plasmodium* negative	Ref.	…		Ref.	…	
Household *Plasmodium* positive	1.95	(.26–14.15)	.51	8.95	(2.55–31.36)	.001
Outside hotspot	Ref.	…		Ref.	…	
Inside hotspot	1.81	(.55–5.90)	.33	3.45	(1.18–10.08)	.024
Phi						
Individual *Plasmodium* negative	Ref.	…		Ref.	…	
Individual *Plasmodium* positive	21.75	(2.84–166.61)	.003	0.96	(.56–1.66)	.89
Household *Plasmodium* negative	Ref.	…		Ref.	…	
Household *Plasmodium* positive	0.30	(.04–2.55)	.27	2.81	(.50–15.88)	.24
Outside hotspot	Ref.	…		Ref.	…	
Inside hotspot	1.16	(.23–5.83)	.85	0.83	(.16–4.42)	.83
Tun						
Individual *Plasmodium* negative	Ref.	…		Ref.	…	
Individual *Plasmodium* positive	2.51	(.76–8.27)	.13	1.24	(.88–1.74)	.21
Household *Plasmodium* negative	Ref.	…		Ref.	…	
Household *Plasmodium* positive	4.29	(1.04–17.65)	.044	5.50	(1.32–22.84)	.019
Outside hotspot	Ref.	…		Ref.	…	
Inside hotspot	1.52	(.48–4.84)	.47	2.36	(.81–6.85)	.12

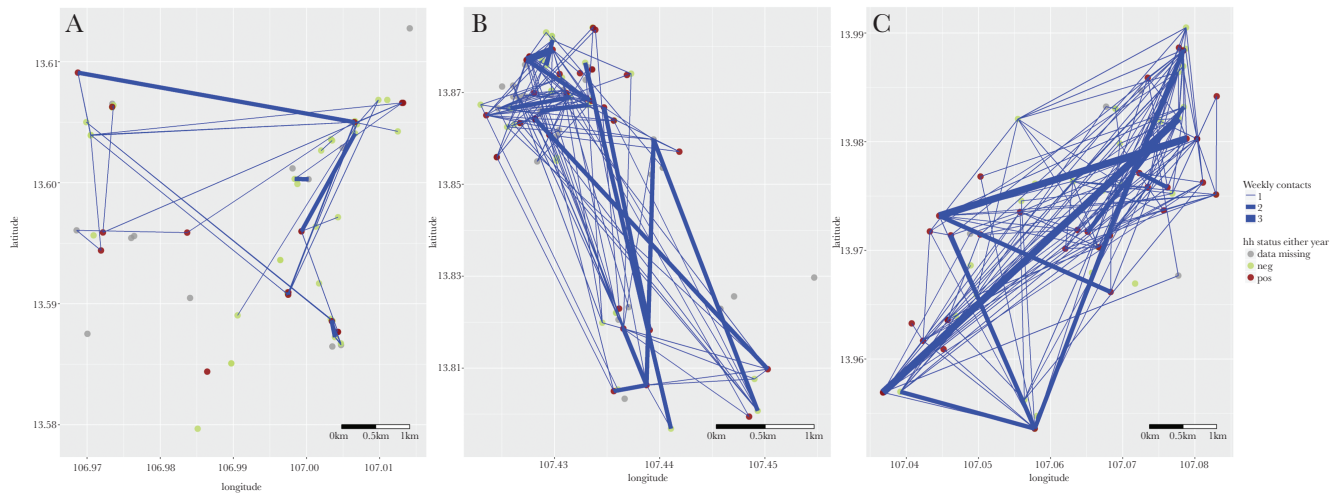Abbreviations: CI, confidence interval; RR, Risk Ratio.

Figure 2. Spatial location, contact patterns, and *Plasmodium* status at the household level, in Chamkar San (*A*), Phi (*B*), and Tun (*C*), Cambodia. Figure shows weekly contacts that occur between individuals in different houses that were reported to occur at either village or farm houses. Farm house locations only are displayed. Blue lines indicate at least weekly contact between members of 2 different households; lines are weighted by number of contacts between 2 households. Abbreviations: hh, household; neg, negative; pos, positive.

Table 4. Association Between Respondent *Plasmodium* Infection and at Least Weekly Contact With *Plasmodium*-Infected Individual (Model A), and Respondent's Household *Plasmodium* Infection Status and at Least Weekly Contact With Any Member of a *Plasmodium*-Positive Household (Model B), by Location of Contact

Individual Contact Models	OR[a]	(95% CI)	P Value	Household Contact Models	OR[a]	(95% CI)	P Value
A1. Contact's *Plasmodium* status, weekly contact				B1. Contact's household status, weekly contact			
Plasmodium negative, <weekly contact	Ref	…		HH *Plasmodium* negative, <weekly contact	Ref	…	
Plasmodium negative, ≥weekly contact	1.16	(.39–3.43)	.79	HH *Plasmodium* negative, ≥weekly contact	1.28	(.34–4.8)	.72
Plasmodium positive, <weekly contact	1.05	(.14–7.73)	.96	HH *Plasmodium* positive, <weekly contact	1.01	(.26–4.01)	.99
Plasmodium positive, ≥weekly contact	1.06	(.15–7.38)	.95	HH *Plasmodium* positive, ≥weekly contact	1.36	(.35–5.36)	.66
A2. Contact's *Plasmodium* status, weekly contact at respondent's household				B2. Contact's household status, weekly contact at respondent's household			
Plasmodium negative, <weekly hh contact	Ref	…		HH *Plasmodium* negative, <weekly hh contact	Ref	…	
Plasmodium negative, ≥weekly hh contact	0.85	(.19–3.82)	.84	HH *Plasmodium* negative, ≥weekly hh contact	0.77	(.14–4.33)	.77
Plasmodium positive, <weekly hh contact	0.96	(.22–4.06)	.95	HH *Plasmodium* positive, <weekly hh contact	0.97	(.42–2.25)	.95
Plasmodium positive, ≥weekly hh contact	1.06	(.03–35.62)	.97	HH *Plasmodium* positive, ≥weekly hh contact	0.94	(.15–5.86)	.95
A3. Contact's *Plasmodium* status, weekly contact at farms/fields				B3. Contact's household status, weekly contact at farms/fields			
Plasmodium negative, <weekly ff contact	Ref	…		HH *Plasmodium* negative, <weekly ff contact	Ref	…	
Plasmodium negative, ≥weekly ff contact	1.38	(.42–4.53)	.59	HH *Plasmodium* negative, ≥weekly ff contact	1.23	(.28–5.49)	.79
Plasmodium positive, <weekly ff contact	0.97	(.23–4.04)	.97	HH *Plasmodium* positive, <weekly ff contact	0.95	(.37–2.47)	.92
Plasmodium positive, ≥weekly ff contact	1.18	(.07–19.15)	.91	HH *Plasmodium* positive, ≥weekly ff contact	1.47	(.32–6.73)	.62

Abbreviations: CI, confidence interval; ff, farm and field; hh, respondent's household; HH, contact's household; OR, odds ratio.

[a]ORs adjusted for village to control for differences in malaria prevalence between the 3 villages. Effect of social contact with a *Plasmodium*-infected individual on respondent's risk of *Plasmodium* infection should be apparent as an OR significantly greater than 1 for exposure to a *Plasmodium*-positive individual with whom contact occurs at least weekly. All other ORs should approximately equal 1.

Table 5. Autocorrelation Statistics for Clustering of *Plasmodium* Species Infections in Socially Connected Households

	P Values for Social Contact, Moran I	
Location	2016	2017
Chamkar San	.41	.88
Phi	.40	.85
Tun	.001	.52

patterns could be conducted with GPS tracking or comprehensive mobility diaries, but either approach was logistically too intensive to administer in the scope of this study.

CONCLUSIONS

In this study in a low-transmission setting in eastern Cambodia, there was no clear evidence for clustering of malaria risk based on spatial location of residence or social contact patterns that could be used to identify the malaria parasite reservoir. Instead, *Plasmodium* infection clustered most strongly within households. Household-based malaria prevention, including vector control as well as diagnosis and treatment interventions, should be prioritized as part of regional malaria control and elimination strategies.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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