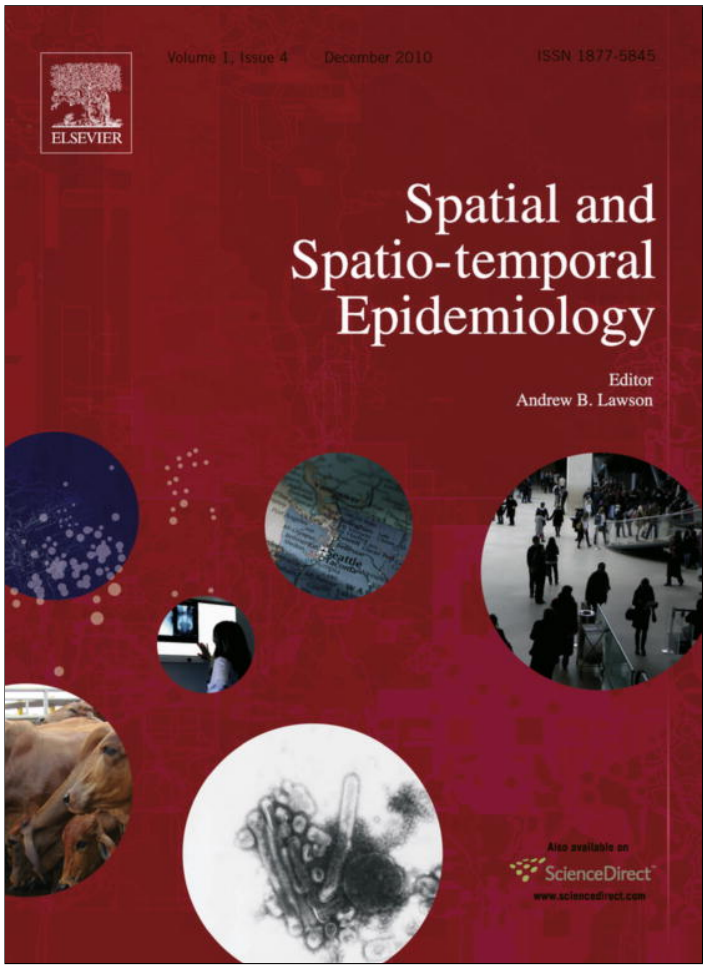

Spatial and Spatio-temporal Epidemiology 1 (2010) 251–259

Contents lists available at ScienceDirect

Spatial and Spatio-temporal Epidemiology

journal homepage: www.elsevier.com/locate/sste

State transition detection in the spatio-temporal incidence of malaria

María-Eugenia Grillet [a,*], Geraldine J. Jordan [b,c], Marie-Josée Fortin [d]

[a] Laboratorio de Biología de Vectores, Instituto de Zoología y Ecología Tropical, Facultad de Ciencias, Universidad Central de Venezuela, Apartado 47058, Caracas 1041-A, Venezuela
[b] Department of Geography and Environment, Mount Allison University, Sackville, NB, Canada E4L 1A7
[c] Geography Program, Trinity Western University, Langley, BC, Canada V2Y 1Y1
[d] Department of Ecology and Evolutionary Biology, University of Toronto, Toronto, ON, Canada M5S 3G5

ARTICLE INFO

Keywords:
Spatial boundary
Epidemic wave
Malaria persistence
Heterogeneity
Population size

ABSTRACT

Mosquito-borne disease spread might exhibit irregular epidemic fronts caused by ecological heterogeneity in the risk factors. To determine *Plasmodium vivax* infection spread in north-eastern Venezuela, we used the State Transition Index (STI) to detect the spatial locations of malaria incidence boundaries and their dynamics over time. Then, we evaluated the role of population size on disease persistence. Boundary locations of malaria were found to be highly spatially variable. Waves of infection were observed in the spatial mosaics of large and small nearby localities due to a strong asynchrony in the epidemic dynamics between both host populations. Our results suggest that the epidemic spatial diffusion follows a hierarchy from large, populated villages (with few or no seasonal parasite fadeouts) to smaller, less populated localities, where infection outbreak was irregular or disease dynamics showed frequent fadeouts. Our findings stress the importance of malaria surveillance and control in these larger communities.

1. Introduction

Understanding the spatial dynamics of an infectious disease is crucial in describing and predicting how infection moves in space and time (Grenfell, 2002; Ostfeld et al., 2008; Smith et al., 2002). Infectious diseases spread on a landscape after the successful invasion of pathogens into a susceptible group of hosts, theoretically determined when basic reproductive ratio of infection, R_0, is greater than unity and density of susceptible hosts exceeds a quantified threshold density (Anderson and May, 1992; Grenfell and Harwood, 1997). The nonlinear dynamics of infectious diseases generate waves even when infections are endemic or locally persistent (Grenfell, 2002) such as indirectly transmitted diseases (Cummings et al., 2004).

Malaria is an infection caused by parasites of the genus *Plasmodium* (Apicomplexa: Plasmodidae) and transmitted among human hosts by the bites of infected female *Anopheles* mosquitoes (Diptera: Culicidae). In the tropics, endemic stable malaria exhibits regular seasonal cycles, multiyear oscillations and changes in period over time. The fluctuations of mosquito populations with seasonality temporally synchronize the dynamics of infection and immunity in a patch of host populations, leading to seasonal fluctuations in malaria parasite prevalence (McKenzie et al., 2001). Longer-term cycles are driven mainly by either intrinsic factors associated with host–pathogen interaction dynamics or extrinsic climatic anomalies such as El Niño Southern Oscillation (ENSO, Hay et al., 2000). Indeed, epidemiological patterns of mosquito-borne pathogens can be highly heterogeneous due to a complex set of interactions among parasites, vectors, and hosts occurring at specific locations and at specific times (Kitron, 1998; Ostfeld et al., 2005). Therefore, as the disease spreads, epidemics would not be completely synchronized in the landscape and the leading front of the epidemic could show irregular patterns,

* Corresponding author. Address: Apartado 47058, 47072, Los Chaguaramos, Caracas 1041-A, Venezuela. Tel.: +58 212 6051404; fax: +58 212 6051204.
E-mail address: maria.grillet@ciens.ucv.ve (M.-E. Grillet).

1877-5845/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.sste.2010.09.007

reflecting spatial variation in the distribution and density of vector and susceptible hosts, degree of local host–vector contact rates and degree of host dispersal.

In a previous study carried out in an endemic-disease area of Venezuela, local transmission of malaria was found to be highly heterogeneous, with disease foci made of localities with cases where there may not be autochthonous transmission (cold spots), foci with high or persistent transmission (hot spots), and foci with moderate-to-low local transmission (cool spots) where the infection would disappear by itself if the locality were isolated (Grillet et al., 2010). Malaria incidence in the hot spots was largely explained by low-elevation terrains, as well as the proximity to and number of mosquito habitats nearby. However, malaria persistence at a locality (that is, maximum number of consecutive weeks a village had malaria cases) was observed only in those hot spots with high human population levels. The spatial structuring of these foci as well as the spatial heterogeneity in malaria persistence led to the issue of spatial and temporal spread of this disease.

In order to better understand the leading edge of the malaria infection spread we present a spatio-temporal analysis of malaria incidence in Venezuela. Specifically, we test whether or not malaria spread from one location to another changes randomly through time. To do so, we use a State Transition Index (STI; Jordan, 2002) that simultaneously detects in space and time epidemiological patterns that highlight areas where causative environmental factors can affect malaria spread. The STI determines locations where malaria incidence persists at neighboring locations (incidence–incidence), spreads or stops (incidence–no incidence) and does not occur (no incidence–no incidence). Moreover, the STI corresponds to a spatio-temporal connectivity measure of malaria state between locations through time. Here, we are mostly interested in the persistence of "incidence–no incidence" links which can be interpreted as boundary locations of malaria spread in the study area.

We propose to use a boundary analysis approach as did Jordan et al. (2008) while studying fire spread discontinuities between neighboring forest plots. Jordan et al. (2008) showed that ecological disturbance boundaries can persist on the landscape and are related to the spatial heterogeneity of topographic barriers which reduce the possibility of disturbance spread. Furthermore, a boundary STI was developed (Jordan, 2002) which we apply here to identify the boundaries between localities where location state (incidence–no incidence) changes so that for a given pair of locations the state shifts (transitions) can be quantified.

A malaria boundary reveals asynchrony and spatial differentiation in the persistence of epidemics among localities. One feature of disease systems that has been shown to produce waves in incidence is spatial heterogeneity in the host population. Epidemiological theory indicates that seasonally driven epidemics will either be completely synchronized across large coupled villages or more irregularly distributed in small centres where infection goes extinct locally and frequently after an epidemic (Anderson and May, 1992; Grenfell et al., 2001). Consequently, spatial boundaries should be expected in spatial mosaics of large, and small neighbor localities. Hence, we also evaluate the relation between the pattern of fadeout of infection (a surrogate for seasonal local parasite extinction) across localities and the village population size.

2. Methods

2.1. Study area and epidemiological data

The study area (332.5 km^2) is located in north-eastern Venezuela where malaria is endemic and produced by *Plasmodium vivax* and transmitted by *Anopheles* (*Nyssorhynchus*) *aquasalis* curry (Grillet et al., 2010). We used weekly data of malaria and associated demographic information for the 29 localities comprising the region from 2001 to 2007. The total number of cases of malaria in the area during this period was 8, 360, with overall malaria incidence rates (cases per 1,000 person-year) ranging from 10 to 44 during this period, and with an epidemic outbreak occurring during 2002. Village-level case data of *P. vivax* malaria from 2001 to 2007 (positive blood smears) were obtained from the Malaria Control Program database, Venezuelan Ministry of Health, where symptomatic cases are detected by passive and active surveillance. The Division of Environmental Health compiles all notifications of malaria consultations on a weekly basis, and considerations are taken in that the locality addresses of the reported cases usually correspond to the dwellings of the infected individuals. Individuals who had more than one positive blood smear for *P. vivax* within the one-year period were considered to have had just a single episode of malaria, avoiding the bias caused by the common relapse phenomenon of this parasite in the tropical area.

This area has an estimated population of 24,788 inhabitants distributed in 29 villages interconnected by primary (paved) and secondary (dirt) roads, with a mountain range to the north reaching up to 600 m of altitude. Vegetation in the south is composed of sparse patches of deciduous forests, some lands cleared for small crops and coconut groves, and large zones of herbaceous and woody swamps, as well as a relatively large undisturbed area of coastal mangroves (Grillet, 2000). High malaria incidences occur during the first 13 weeks of the year (dry season; December to April) and in those settlements located at low altitudes (<130 m) and on gentle slopes where the primary mosquito species vector is very common and abundant (Grillet, 2000; Grillet et al., 2010). Indeed, the number of *An. aquasalis* pre-adult habitats (ponds, mangrove and herbaceous swamps) within 1–3 km radius is highly predictive of malaria risk in the region (Grillet et al., 2010).

2.2. Spatio-temporal analysis

The first step in the spatio-temporal analysis is to determine the spatial connectivity between the locations (village area centroids). Here, we built a Delaunay network to link nearest-neighbor locations (Fortin and Dale, 2005). From these Delaunay links, Voronoi polygons were established by bisecting each of the links (Okabe et al., 2000). Individual bisectors were defined as possible boundary locations between two nearest-neighbors for

each weekly time step. Here, the 29 localities form 29 Voronoi polygons that have in total 60 links between them. Hence, all our spatio-temporal analysis will be based on these 60 potential boundary locations between localities.

Boundaries, or lack of boundary (i.e., connectivity), were classified by comparing the incidence–no incidence of malaria in neighboring locations at a point in time. A boundary exists therefore if no incidence occurs at a location and at least one incidence occurs at the neighboring location. The frequency of boundary occurrence was computed for each link.

To test the significance of boundary persistence, that is, the frequency of boundary occurrences for each link, a binomial test was applied once per link (Fortin, 1994; Crida and Manel, 2007). The number of successes was the frequency of boundary occurrences for each link. The number of trials was the total number of possible times that a boundary could have formed (that is, the total number of time steps) given the number of weeks studied from 2001 with 47 weeks of data to the end of 2007 for a total of 359 weeks. The probability of success on each trial was set to 0.5 and a cumulative distribution function was used to test that there was, at most, the number of successes (as given per each link). Boundaries with $p < 0.05$ were considered to be statistically significant in terms of infrequency. Boundaries with $p > 0.95$ were considered statistically significant in terms of high frequency.

As malaria incidence is proportional to population size, we weighted the frequency of boundary occurrences for each link summing the population sizes of the two localities divided by the total population size of the 29 locations. Then we standardized these weighted boundary occurrence values into z-values to determine where boundaries occur in excess (significant positive values) or rarely (significant negative values) while accounting for population size.

2.3. State Transition Index

While boundary frequency can supply information regarding the incidence of malaria in one location but its absence at a neighboring location at a point over time, boundary frequency does not provide information regarding persistence and oscillations. That is to say, between two locations, a boundary can form in week one, and again in the following week, but from boundary frequency computations alone, one cannot detect if the incidence of malaria was at the same location twice, or if malaria incidence occurred once at one location, and the following week, was absent at that location, but present at its neighbor.

To detect how boundaries change over time, each boundary between neighboring locations was also examined in terms of its formation (or lack of it) in the following week using a subset of the boundaries characterized in the State Transition Index (Jordan, 2002). We examined relevant STI categories in the context of malaria transmission. The spatial component of the STI compares attributes of two spatial neighbors, producing one of four boundary states: B1, B2, B3 and B4 (Fig. 1). The temporal component of the index examines the change in states from 1 week to the next. Each of the spatial states can take on any other (including itself), i.e., B1 to B1, B1 to B2, B1 to B3, etc. Although 16 transitions are possible, we collapsed certain of these transitions (described below) so that the spatio-temporal components could be classified into three meaningful transitions: oscillating, partially oscillating, and spatially persistent for 358 time steps (359 weeks) in which each week is first considered week 1, then week 2 (except for the very last week) (Fig. 1).

(1) *Oscillating:* Incidences where both temporal and spatial boundaries occurred between two locations from week 1 to week 2 were defined as *oscillating* boundaries: B1 to B2 or B2 to B1. This could be interpreted as the existence of asynchrony in the malaria dynamics in time and space (an infection wave) between localities.
(2) *Partially oscillating:* Incidences with only one boundary in space and only one in time were considered *partially oscillating* as any one of the following cases: B1 (or B2) to B4, B4 to B1 (or B2), B1 (or B2) to B3, or B3 to B1 (or B2). Such partially oscillating boundaries were similar to oscillating boundaries, but their patterning was not as distinctive.
(3) *Spatially persistent:* Boundaries persisting in the same location, with one side of the boundary repeatedly showing malaria incidence (i.e., no oscillation in time) were termed *spatially persistent*: B1 to B1, or B2 to B2.

These three boundary transitions were mapped to show their relative spatial distribution.

2.4. Spatial heterogeneity in malaria persistence

We determined the dates of the first malaria cases of the year (epidemic onset) for each locality (e.g., week in rank, number of weeks since the beginning of the year), and for each year. The three largest localities in the region corresponded to the most populated villages (highest number of inhabitants: $n_1 = 9,054$, $n_2 = 4,130$ and $n_3 = 1,964$ inhabitants, respectively). Thus, means were calculated for those three largest localities and for the remaining villages together, for both endemic and epidemic years.

The question of a higher likelihood of disease persistence in large communities and, conversely, its extinction in small villages was explored by calculating the relationship between the mean duration (in weeks) of fadeouts and the population size (number of inhabitants per village) across the 29 villages. A fadeout (seasonal local parasite extinction) corresponded to a period of at least three weeks without a case in a locality (Grenfell and Bolker, 1998). The number of consecutive weeks without cases corresponded to the length of a fadeout period.

3. Results

3.1. Spatio-temporal analysis and STI

Malaria occurrence was highly focal and more prevalent in the southern part of the region during the whole period, with a very contrasting absence or low frequency of diseases

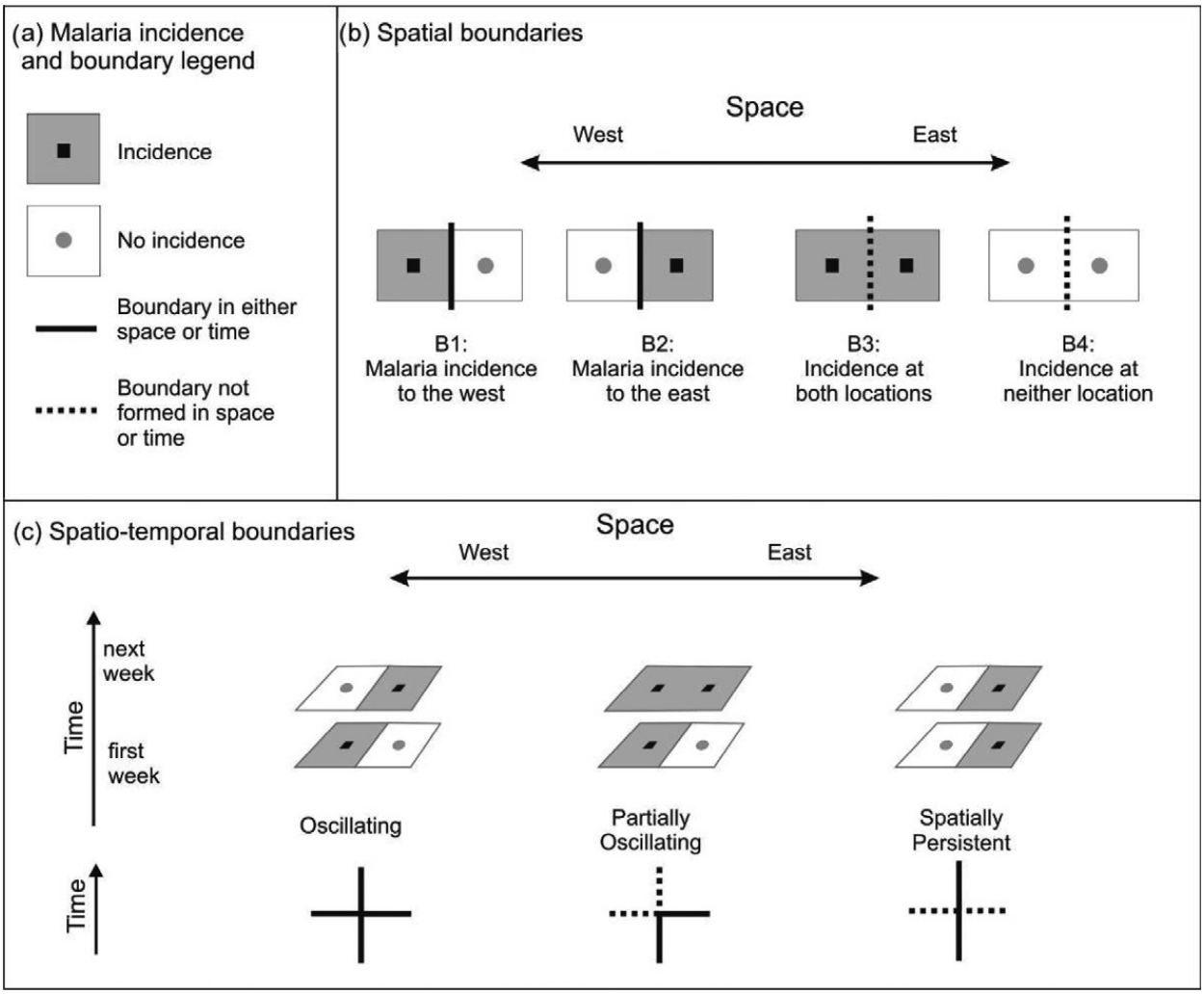

Fig. 1. Schematic illustration of boundary definition and the State Transition Index (after Jordan, 2002) showing how: (a, b) adjacent locations can have different types of boundaries in space and (c) state transition types can be detected through time.

in the north area (see location frequencies on Fig. 2). The observed malaria boundary frequency (Fig. 2a) shows that there were 60 links between nearest-neighbor localities. A total of 21,540 potential boundaries existed over the 359 weeks. However, over total number of weeks, 35.5% boundary formation was detected – incidence/no incidence – ($n = 7,615$). The results of the binomial test show 41 out of 60 links are statistically infrequent ($p < 0.05$) and seven out of 60 links are statistically frequent ($p > 0.95$). Most of the infrequent boundaries occur to the north (Fig. 2c), while the more frequent boundaries are found heterogeneously located throughout the east and south-central region of the study area (Fig. 2b). The landscape in those areas is dominated by large zones of herbaceous swamps and coastal mangroves both suitable aquatic habitats for mosquito species (see Fig. 2). By contrast, few or lack of boundaries (as expected) were observed in the north shore where malaria incidence was low or absent.

Using the STI, we were able to classify the potential 60 boundary locations according to the three types of state transition: oscillation ($n_o = 653$ for 3% over the 7 years), partial oscillation ($n_{po} = 6931$ for 32.3% over the 7 years), and spatial persistence ($n_{sp} = 3472$ for 16.2% over the 7 years). The distributions of oscillation boundary frequency, partial oscillating and spatial persistence boundaries frequency are shown in Fig. 3. The overall distribution of the links between localities varies across the study area. Oscillating links are found to the south-central area and mostly oriented in a north–south direction. Partially oscillating boundaries exhibit a similar pattern, with higher frequencies of partial oscillating existing in the south-central area, and also with a tendency to be north–south oriented. Spatially persistent boundaries have their highest frequency surrounding a relatively high population locality ($n = 1964$ inhabitants) to the east of the study area. Many of the higher frequency spatially persistent boundaries are oriented east–west (except for those to the east of the study area), suggesting a substantial divide in malaria incidence between the north and south ends of the study area.

The map of weighted and standardized frequency of boundary occurrences for each link (Fig. 4) reveals differences with the unweighted map (Fig. 2a): only five of the seven frequent boundaries are significant (positive), but new significant boundaries are detected. Indeed, when we account for the population size, significant spatial boundaries are observed in the south-central, east and west ends of the

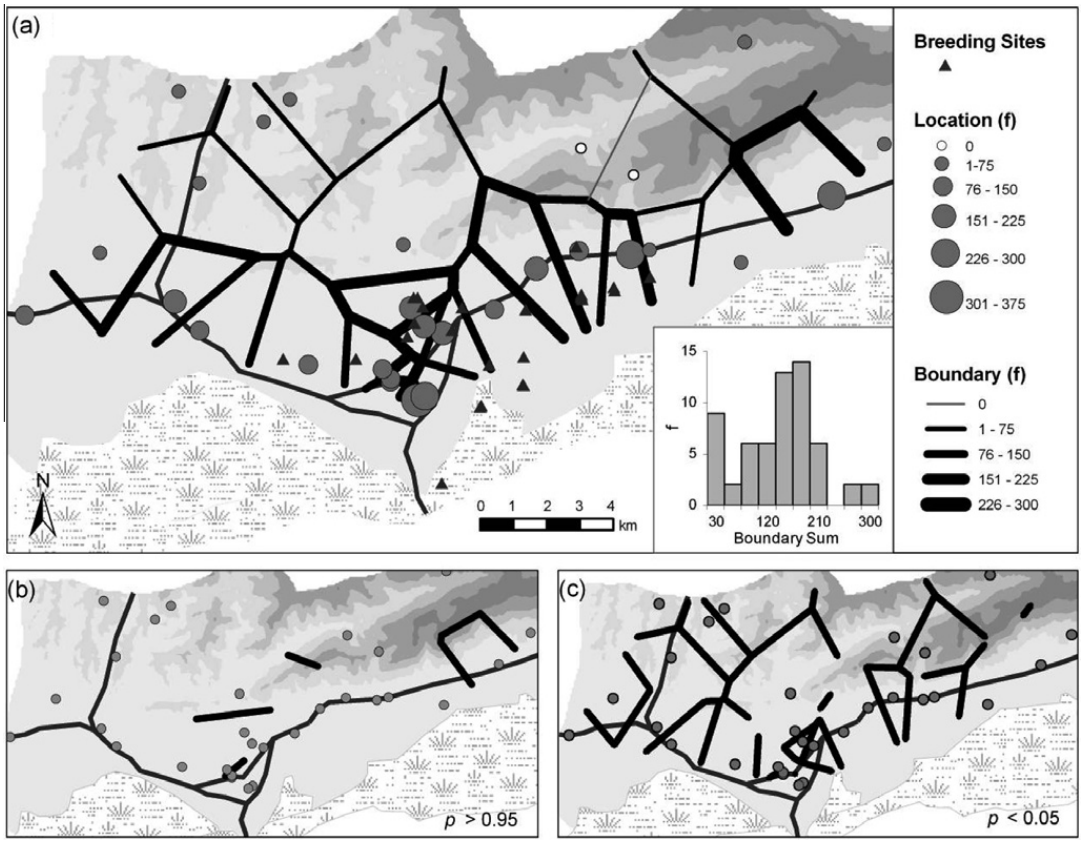

Fig. 2. Frequency of malaria incidence at each location over the entire time period (location (f)). Boundary frequency between locations (boundary (f)): (a) overall frequency of boundaries where the inset shows a histogram of the boundary distribution; (b) significant boundary locations that are most frequent then based on a binomial test ($p > 0.95$); and (c) significant boundary locations that are less frequent then based on a binomial test ($p < 0.05$). Landscape features such as elevation, wetlands and mosquito breeding sites are shown.

region (Fig. 4). The *z*-values help to determine which of the spatio-temporal boundary behaviors (oscillation, partial oscillation and persistent) are more (positively significant) or less (negatively significant) frequent.

3.2. Spatial heterogeneity in malaria persistence

Dates of first cases in the less populated localities aggregate during endemic years, the epidemic year, and for the more populated localities aggregate during both endemic and epidemic years were 3.6 (standard error = 0.51), 2.6 ($SE = 0.88$), 2.1 ($SE = 0.88$) and 1.0 ($SE = 0.0$), respectively. First malaria cases were reported sooner in the three more populated localities than other small localities during the epidemic year (2002) and the rest of the endemic period but these differences were not significant.

The mean duration of fadeout for *P. vivax* infection across the 29 localities within the study area are illustrated in Fig. 5. Fadeout declined significantly with population size ($R^2 = 0.72$, $p < 0.05$) indicating that small localities (<2000 inhabitants) experienced frequent and durable extinctions, while larger villages experienced few short extinctions.

4. Discussion

In this study, the boundary analysis allowed us to detect in space and time areas of strong change in malaria incidence (Figs. 2–4) identifying spatial locations where local propagation of diseases is seemingly affected by a combination of local heterogeneity of the environmental malaria risk factors and the intrinsic factors associated with host–pathogen interaction dynamics. Furthermore, the STI enabled us to reveal the existence of epidemic waves (i.e., oscillating boundaries) and apparent spatial thresholds to epidemic disease spread (i.e., spatially persistent boundaries) in the occurrence of *P. vivax* infection in the study region. Overall, malaria outbreaks were irregular in small localities where disease dynamics showed frequent fadeouts, by contrast, larger localities showed synchronic and regular malaria epidemics with few or no fadeouts (Fig. 5). Malaria boundaries were significantly observed in some spatial mixture of large and small nearby localities (south-central, east and west area), indicating that the coupling of large and small centres may thus be one of the critical feature generating waves in this seasonal mosquito-borne disease. These results have deep implications both for the spatio-temporal dynamics and for the persistence of infection, and for the design of malaria control strategies.

4.1. Malaria boundaries and spatio-temporal disease spread

Most of the boundaries were oriented in a north–south direction, suggesting that waves of infection spread, mainly and longitudinally along the main road and have

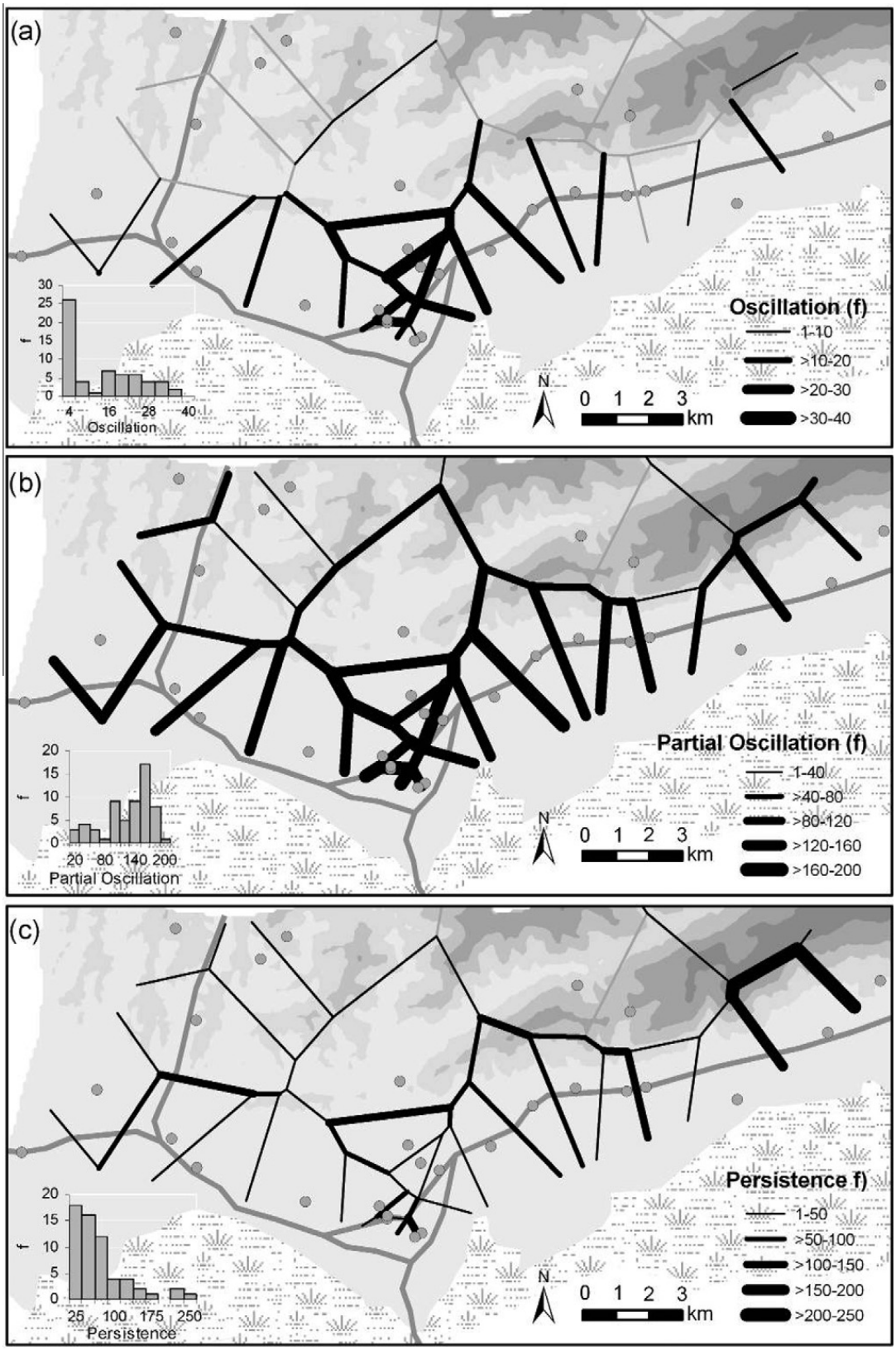

Fig. 3. Maps of frequency of the three types of boundary state transition: (a) oscillation; (b) partial oscillation; and (c) spatial persistence. In each panel, the inset shows a histogram of the boundary distribution. Landscape features such as elevation and wetlands are shown.

less of a tendency to move northward into the less connected and less populated areas. However, boundaries locations of malaria spread were highly heterogeneous and spatially located toward the south-central, eastern and western areas of the region where local clustering of *P. vivax* cases were previously detected (Grillet et al.,

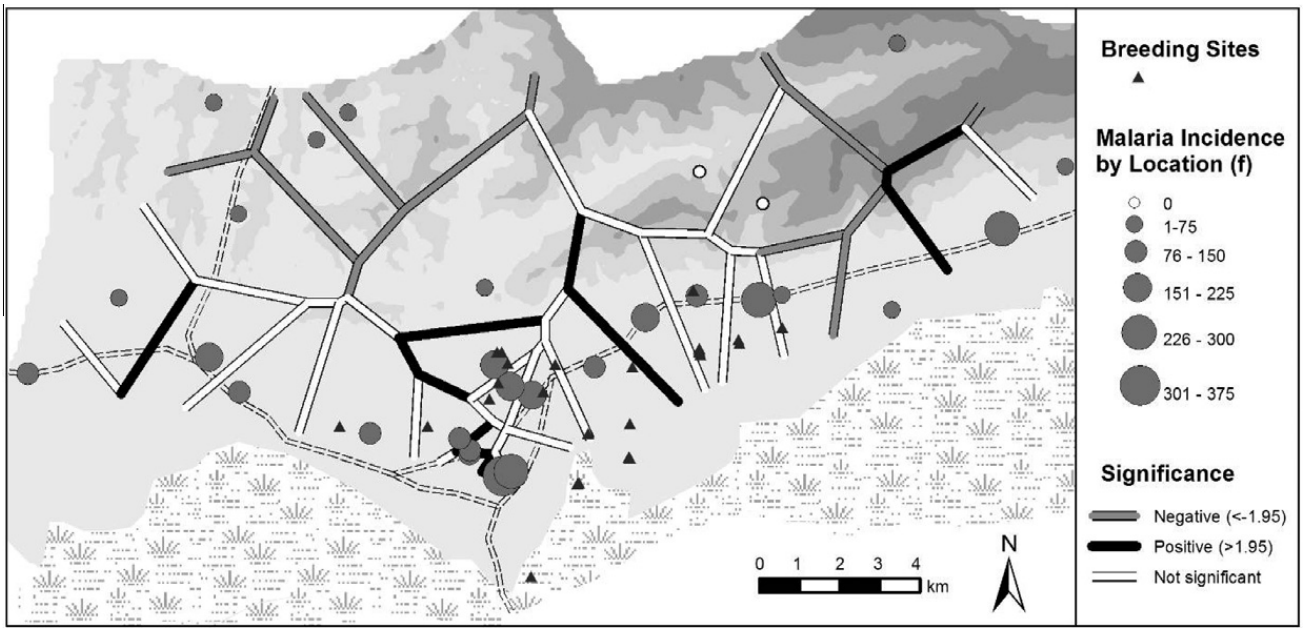

Fig. 4. Weighted and standardized frequency of malaria incidence at each location over the entire time period: significant positive ($z > 1.95$), significant negative ($z > 1.95$), and not significant boundaries. Landscape features such as elevation, wetlands and mosquito aquatic habitats are shown as well as the frequency of malaria incidence over the entire time period (location (f)).

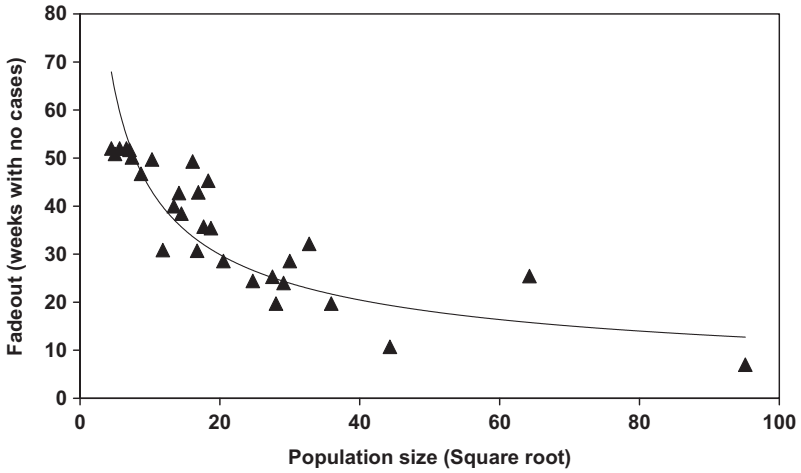

Fig. 5. Annual fadeout (mean) of *Plasmodium vivax* infection (>3 weeks without malaria case reports) for each locality plotted against population size (square root transformed). Line: Data were fitted to power function, $R^2 = 0.72$, $p < 0.05$.

2010). Local transmission in those diseases pockets accounted for most malaria transmission (73–86 %) during the whole period. At a very local scale (i.e., <5 km), the risk of malaria is mainly determined by mosquito behavior and ecology, especially the distribution of blood-meal hosts and aquatic habitats. Parasite transmission potential by mosquitoes is indeed maximized when water and humans are both available (Le Menach et al., 2005), but the heterogeneous distribution of larval habitats produces significant variations in vector-host contact over relatively short distances. High local levels of *P. vivax* transmission are more likely in those localities having high cluster of mosquito pre-adult habitats (Grillet et al., 2010).

Spatial transmission of mosquito-borne diseases is ultimately tied to movement patterns and density of hosts and insect vectors. Landscape features that influence vector density or dispersal are the very determinants of the rate of local disease spread. Spatial heterogeneity and the rate of long-distance movement of the host, which might vary among localities depending on their human demographic or geographic features (e.g., network and degree of connectivity between villages), can determine spatio-temporal patterns of epidemics at larger spatial scale and produce epidemic fronts in malaria incidence. Our results suggest that the spatial pattern of effective malaria infection and the spatial spread between localities depend on the regional coupling of human population local movements (through the main road) and the local population density as it has been observed in other micro-parasite infections (Grenfell and Harwood, 1997). In this area, main road

villages have significantly more malaria than secondary road villages. However, distance-based coupling of these localities seem to be largely dependent of the population size, with movements between or from large villages being more common than between small ones. The three largest localities in the region localized in the south-central, east and western area, respectively, correspond to the most populated villages where most services exist (main markets, health care centres and main schools). All these facilities are absent in the 26 other less populated localities.

Malaria boundaries, notably the STI categories (oscillating and spatially persistent), revealed asynchrony and spatial differentiation in the timing of epidemics among localities. While malaria epidemics were completely synchronized in the three large localities where there were regular epidemics (few or not fadeouts), *P. vivax* infections were more irregular in small localities where disease dynamics showed frequent fadeouts. This confirmed previous results indicating that although high local levels of infection are likely in those areas in the landscape where suitable conditions for local transmission exist (such as the south shore where the wetlands predominate), sustained and persistent levels of infection were only observed in those villages with certain population levels (Grillet et al., 2010). Although non-conclusive due to the high frequency of small localities in comparison with the largest one in this small region, our current results suggest that, below 2000 inhabitants, local parasite extinction is more likely to occur frequently. Therefore, most of the malaria cases observed annually in those small localities seem to be imported cases from larger villages. Indeed, larger populations were associated with earlier epidemic onset than less-dense villages suggesting a higher likelihood of local spatial diffusion of malaria from more populated to less populated villages (Grenfell and Bolker, 1998). In deterministic epidemic models, the stochastic threshold for parasite persistence is particularly relevant (Anderson and May, 1992; Grenfell and Harwood, 1997; Grenfell et al., 2001). In small populations within a larger network of villages where an infectious disease is endemic, demographic stochasticity can lead to the extinction of the pathogen in the deep troughs between epidemics even when R_0 is greater than unity (Anderson and May, 1992). Given the seasonal fluctuations in malaria, an appropriate threshold for the stochastic persistence of *P. vivax* could therefore be the host population size (Conlan and Grenfell, 2007). Indeed, our results agreed with recent works evaluating the notion of a critical community size to sustain epidemics of mosquito-borne infections such as malaria and dengue (Cummings et al., 2004; Chowell et al., 2008, 2009).

4.2. Spatio-temporal scale and malaria control

Malaria by *P. vivax* was reinitiated (after its successful control in 1960s) in north-eastern Venezuela from an established focus of malaria in southern Venezuela (Barrera et al., 1999). Since the mid-1980s, this disease has spread in this geographical region, where a consolidated seasonal cycle of endemic transmission is maintained and alternated by epidemic periods (e.g., 2002 year). The application of a general control strategy has reduced considerably the number of malaria cases in this area but transmission remains in persistent foci that are potential sources of outbreaks and that could extend to other regions if environmental conditions change (Grillet et al., 2009). Thus, an important factor in evaluating the success of malaria control is the spatial scale of malaria transmission (Carter et al., 2000). We have previously demonstrated that the risk of malaria transmission is spatially and temporally oriented (Barrera et al., 1999; Grillet et al., 2010). Additionally, here, we found that the small populated townships appear to act as barriers to local diffusion of malaria, by isolating the epidemics and concentrating the force of infection in a few, more populated, localities (hot spots). All these findings together make clear that malaria control interventions need to be spatially and temporally targeted. Concentrating the control strategies in these large "core" patches will offset their role as reservoir of *P. vivax* infection in space (region) and in those malaria epidemic troughs.

Acknowledgments

We are grateful to the logistic support provided by the Minister of Health of Venezuela and for the laboratory assistance provided by M. Herrera, J. Martínez, J. Berti, A. Zorrilla, M. El Souki and A. Mejía. This study was supported by Venezuelan Council for Scientific and Technological Research(G-2000001541 and UC-2008000911-3), the Council for Sciences and Humanities Development (PI-030064412006), and Invensys Systems Latin America Corporation(LOCTI 2007–2009). The perspectives presented in this publication are those of the author and do not represent the official position of the funding institutions.

References

Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press; 1992.
Barrera R, Grillet ME, Rangel Y, Berti J, Aché A. Temporal and spatial patterns of malaria re-infection in northeastern Venezuela. Am J Trop Med Hyg 1999;61:784–90.
Carter R, Mendis KN, Roberts D. Spatial targeting of interventions against malaria. Bull W Health Org 2000;78:1401–11.
Chowell G, Munayco CV, Escalante AA, McKenzie E. The spatial and temporal patterns of *falciparum* and *vivax* malaria in Perú: 1994–2006. Mal J 2009;8(142):1–19.
Chowell G, Torre CA, Munayco-Escate C, Suarez-Ognio L, Lopez-Cruz R, Hyman JM, et al. Spatial and temporal dynamics of dengue fever in Perú: 1994–2006. Epidemiol Infect 2008;136:1667–77.
Conlan AJK, Grenfell BT. Seasonality and the persistence and invasion of measles. Proc R Soc B 2007;274:133–1141.
Crida A, Manel S. WOMBSOTF: an R package that implements the Wombling method to identify genetic boundary. Mol Ecol Notes 2007;7:588–91.
Cummings DAT, Irizarry RA, Huang NE, Endy TP, Nisalak A, Ungchusak K, et al. Travelling waves in the occurrence of dengue haemorrhagic fever in Thailand. Nature 2004;427:344–7.
Fortin MJ, Dale MRT. Spatial analysis: a guide for ecologists. New York: Cambridge University Press; 2005.
Fortin MJ. Edge detection algorithms for two-dimensional ecological data. Ecology 1994;75:956–65.
Grenfell BT, Bjornstad ON, Kappey J. Travelling waves and spatial hierarchies in measles epidemics. Nature 2001;414:716–23.
Grenfell BT, Bolker BM. Cities and villages: infection hierarchies in a measles metapopulation. Ecol Lett 1998;1:63–70.
Grenfell BT, Harwood J. Metapopulation dynamics of infectious diseases. Trends Ecol Evol 1997;12:395–9.
Grenfell BT. Rivers dam waves of rabies. PNAS 2002;99(6):3365–7.

Grillet ME, Barrera R, Martínez J, Berti J, Fortin MJ. Disentangling the effect of local and global spatial variation on a mosquito-borne infection in a neotropical heterogeneous environment. Am J Trop Med Hyg 2010;82(2):194–201.

Grillet ME, Martínez J, Barrera R. Focos calientes de transmisión de malaria: Implicaciones para un control orientado y efectivo en Venezuela. Bol Mal Salud Amb 2009;45:27–36.

Grillet ME. Environmental factors associated with the spatial and temporal distribution of *Anopheles aquasalis* and *Anopheles oswaldoi* in wetlands of an endemic malaric area in northeastern Venezuela. J Med Entomol 2000;37(2):231–8.

Hay SH, Myers MF, Burke DS, Vaughn DW, Endy T, Ananda N, et al. Etiology of interepidemic periods of mosquito-borne disease. Proc Natl Acad Sci 2000;97:9335–9.

Jordan GJ, Fortin MJ, Lertzman K. Spatial pattern and persistence of historical fire boundaries in southern interior, British Columbia. Environ Ecol Stat 2008;15:523–35.

Jordan GJ. Space, time and uncertainty: detecting and characterizing boundaries in forest fire disturbances. Ph.D.. Burnaby: Simon Fraser University; 2002.

Kitron U. Landscape ecology and epidemiology of vector-borne diseases: tools for spatial analysis. J Med Entomol 1998;35:435–45.

Le Menach A, McKenzie FE, Flahault A, Smith DL. The unexpected importance of mosquito oviposition behavior for malaria: non-productive larval habitats can be sources for malaria transmission. Malar J 2005;4:1–11.

McKenzie EF, Killeen GF, Beier JC, Bossert WH. Seasonality, parasite diversity, and local extinctions in *Plasmodium falciparum* malaria. Ecology 2001;82(10):2673–81.

Okabe A, Boots B, Sugihara K, Chiu SN. Spatial tesselations: concepts and applications of Voronoi diagrams. Chinchester: John Wiley and Sons; 2000.

Ostfeld RS, Galss GE, Keesing F. Spatial epidemiology: an emerging (or re-emerging) discipline. Trends Ecol Evol 2005;20:328–36.

Ostfeld RS, Keesing F, Eviner V, editors. Infectious disease ecology: effects of ecosystems on disease and of disease on ecosystems. Princeton: Princeton University Press; 2008.

Smith DL, Lucey B, Waller LA, Childs JE, Real LA. Predicting the spatial dynamics of rabies epidemics on heterogeneous landscapes. Proc Natl Acad Sci USA 2002;99:3668–72.