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Seasonal dynamics and microgeographical spatial heterogeneity of malaria along the China-Myanmar border

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Abstract

Malaria transmission is heterogeneous in the Greater Mekong Subregion with most of the cases occurring along international borders. Knowledge of transmission hotspots is essential for targeted malaria control and elimination in this region. This study aimed to determine the dynamics of malaria transmission and possible existence of transmission hotspots on a microgeographical scale along the China-Myanmar border. Microscopically confirmed clinical malaria cases were recorded in five border villages through a recently established surveillance system between January 2011 and December 2014. A total of 424 clinical cases with confirmed spatial and temporal information were analyzed, of which 330 (77.8%) were *Plasmodium vivax* and 88 (20.8%) were *Plasmodium falciparum*, respectively. The *P. vivax* and *P. falciparum* case ratio increased dramatically from 2.2 in 2011 to 4.7 in 2014, demonstrating that *P. vivax* malaria has become the predominant parasite species. Clinical infections showed a strong bimodal seasonality. There were significant differences in monthly average incidence rates among the study villages with rates in a village in China being 3-8 folds lower than those in nearby villages in Myanmar. Spatial analysis revealed the presence of clinical malaria hotspots in four villages. This information on malaria seasonal dynamics and transmission hotspots should be harnessed for planning targeted control.

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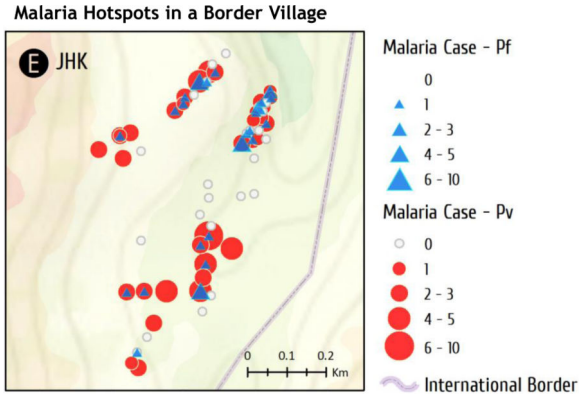
Graphical Abstract



Keywords

Clinical malaria; seasonality; hotspot; China-Myanmar border

1. Introduction

Malaria is a serious vector-borne disease and a major public health problem in many tropical countries (WHO, 2014). Intensive intervention during the past two decades has led to a dramatic decrease in global malaria incidence. Countries like China and Thailand have entered the malaria elimination phase (Cui et al., 2012a; Cui et al., 2012b; Zhou et al., 2014a). As malaria transmission further declines, control measures will increasingly rely on accurate knowledge of risk factors as well as the ability to define high-risk areas and populations for targeted interventions (Bousema et al., 2010; Bousema et al., 2012; Marsh, 2010; Moonen et al., 2010; Mosha et al., 2014).

Intensified malaria control has also resulted in a major change in malaria epidemiology with an increasing proportion of *Plasmodium vivax* malaria. Of the four human malaria species, *P. vivax* is the most common and has the widest geographic range (Battle et al., 2012; Gething et al., 2012; Guerra et al., 2010). It is mostly found outside of Africa and is especially prevalent in Southeast Asia. This parasite is less responsive to control interventions and much more difficult to eliminate when compared to *P. falciparum*, partly due to the noted ability of *P. vivax* to form dormant liver stages that cause relapses (Chaves et al., 2008). The increased proportions of *P. vivax* malaria in Southeast Asia will be a formidable challenge for the malaria elimination course in these countries.

In the Greater Mekong Subregion (GMS), Myanmar has the highest regional malaria burden and is a key source of malaria exportation (Cui et al., 2012a; Cui et al., 2012b; Delacollette et al., 2009). As a consequence of shared borders, low malaria transmission countries such as China (Zhang et al., 2014b) and Thailand will continually face the challenges of managing cross-border malaria introduction (Parker et al., 2015; Wangdi et al., 2015; Zhou et al., 2005; Zhou et al., 2014a). China is entering the malaria elimination phase with a very low malaria incidence rate (< 0.3 cases per 1,000,000p erson year in 2013). However, the

China-Myanmar border area has the highest malaria incidence rate (1.2 and ~10.3 cases per 1,000,000 person year in Yunnan Province and in four border counties, respectively). Therefore, border malaria control is crucial to malaria elimination in China (Zhang et al., 2014a). Southwestern Yunnan, which shares ~ 4,000 km of border with Myanmar, Laos and Vietnam, is the most malaria prevalent province in China (Feng et al., 2015; Zhang et al., 2014a). Border malaria – high malaria transmission along the international borders is a common phenomenon in all the GMS nations, which requires in-depth studies and coordinated international efforts. Since border regions represent the biggest reservoirs for malaria, and frequent malaria introductions by migratory human populations are extremely difficult to monitor, border malaria constitutes one of the biggest obstacles for malaria elimination in these countries. Some border regions in Myanmar were not reached by the national malaria control program, and internal political and military conflicts further exacerbate malaria situations in these border regions. Influx of refugees from areas of higher malaria endemicity as the result of military conflicts may inevitably accompany massive malaria introduction. Therefore, timely, detailed mapping of malaria epidemiology in the border regions is essential for identifying malaria transmission hotspots and guiding targeted control efforts. However, malaria epidemiology studies conducted so far in this region mostly focused on malaria in China on large scales (Bi et al., 2013a; Clements et al., 2009; Hui et al., 2009; Li et al., 2013; Lin et al., 2009; Xu et al., 2015; Zhou et al., 2014a). Though these studies depicted the overall trends of malaria situation, better understanding of malaria transmission on a microgeographic level (e.g., villages) would provide unprecedented opportunities for local health department officials to execute targeted control efforts. In this study, as our continued efforts to monitor malaria transmission in the China-Myanmar border area, we performed longitudinal malaria case detections in villages along the border in order to map malaria transmission on a much finer scale. It will offer more accurate information for local disease control organizations to carry out malaria control operations including mosquito control, drug distribution, and health education.

2. Materials and methods

2.1. Study area and population

The total population (permanent residents) in Lai Zar and Na Bang (NB) is about 20,000 and 1,500 (from the 2012 census), respectively. Malaria surveillance was carried out between January 2011 and December 2014 in five closely located villages along the China-Myanmar border: JHK, MSY, SSL, SY in Kachin State, Myanmar, and NB in Yingjiang County, Yunnan Province, China (Fig. 1). JHK, MSY and SY are the rural Myanmar villages in the study area, and SSL is a randomly selected suburban area of Lai Zar town. NB consists of three natural villages, where malaria cases were analyzed in this study. The catchment population of each of the four Myanmar villages ranged from ~120 to ~480. The selected villages all had higher malaria incidence in the past. This region has a subtropical climate with January through March as the dry and cold months, and June to August as the rainy season. Annual rainfall is about 1500 mm, and average annual temperature is 22.7°C. Average monthly temperature is the lowest (~15°C) in January, which gradually rises to 24°C in May, and remains at that level through September before gradually declining in October to December.

2.2. Malaria surveillance

Demographic data of the study villages in Myanmar were surveyed and updated monthly through seasonal census surveys and weekly/biweekly household visits. Information gathered includes age, sex, onset date of a febrile illness, parasite species, final diagnosis, asexual stage parasitemia and gametocytemia. The latitude and longitude of each household was taken using a handset GPS device. Malaria infection data included clinical malaria infections both from passive case surveillance (PCS) and active case surveillance (ACS). PCS was conducted at five clinics, and only patients from the study villages were included in the final data. ACS was conducted through weekly (April to September) and biweekly (October to March) home visits to assess clinical malaria. During the survey, individuals who were diagnosed with malaria by clinicians (for PCS) or who showed malaria symptoms (for ACS), and who agreed to sign a consent and/or assent form (for minors under the age of 18) were included in the study. We collected all cases occurred during the survey period, and cases potentially resulted from relapses were treated as new cases. Trained nurses collected blood samples by a standard finger-prick method, and thick and thin smears were prepared on labeled slides for parasite species identification. A clinical malaria case was defined as an individual with malaria-related symptoms (fever, i.e., axillary temperature ≥ 37.5°C, chills, severe malaise, headache or vomiting) at the time of examination or 1-2 days prior to the examination with a *Plasmodium*-positive blood smear (Afrane et al., 2013; Zhou et al., 2015). Parasites were identified microscopically by two experienced technologists. For quality control purpose, a third microscopist confirmed parasite identification by random analysis of ~ 5% of the slides (Afrane et al., 2013; Zhou et al., 2015).

2.3. Statistical and spatial analysis

Clinical malaria incidence rates were calculated as cases per 1,000 populations per year (month) based on the populations from the August 2012 demographic survey. Differences in monthly malaria incidence rates among villages were compared using nonparametric Kruskal-Wallis ANOVA and Median test, while Duncan's range test was used to test the pair-wise difference between villages. Friedman's nonparametric ANOVA was used to test inter-year differences in malaria incidence in MSY. The odds ratio with a 95% CI was used.Analysis of spatial clustering in clinical malaria was performed by using hot spot analysis Getis-Ord'sGi*(d) statistics (Cartabia et al., 2012; Dhimal et al., 2014; Haque et al., 2014; Haque et al., 2012; Kelly-Hope et al., 2009; Ruktanonchai et al., 2014; Saxena et al., 2012). Statistical analysis and spatial clustering were conducted using STATISTICA 10.0 (StatSoft Inc., Tulsa, OK, USA) and ArcGIS 10.3 for Desktop (ESRI, Redlands, CA, USA), respectively.

2.4. Ethical approval

Ethical clearance was granted by the institutional review boards of Kunming Medical University, China, University of California, Irvine, and Pennsylvania State University, USA, and the local Bureau of Health, Kachin State, Myanmar. Informed consent was obtained during the survey both orally and in writing from adult individuals, while for children it was obtained from their parents or guardians.

3. Results

3.1. Malaria incidence and parasite prevalence

A newly established malaria surveillance system was in place at the study villages in order to monitor malaria transmission on the international border. A total of 424 clinical malaria cases were detected by microscopy during the study period. Among them, 271 (64%) and 153 (36%) were from male and female patients, respectively, and the median age was 19. Of the 424 cases, 330 (77.8%) were *P. vivax*, 88 (20.8%) *P. falciparum*, and six (1.4%) mixed *P. vivax* and *P. falciparum* infections. More than 90% of malaria cases were diagnosed at the clinicians (for PCS), of which 340 cases had household locations. Since this was a retrospective study, household locations could not be obtained for 84 cases (19.8%, 84/424).

Clinical malaria incidence rates varied drastically among villages (Table 1) (Kruskal-Wallis ANOVA with the Median test $\chi^2 = 26.57$, d.f. = 4, $P < 0.0001$). JHK (96.0 cases per 1,000 person year) had a 7-fold higher malaria incidence rate than NB (18.1 cases per 1,000 person year). NB had the lowest malaria incidence rate amongst the study villages. Overall, villages in Myanmar had significantly higher incidence rates than NB in China (Duncan's range test, $P < 0.05$).

3.2. Temporal trend in clinical malaria

The overall clinical malaria incidence showed distinct seasonality with the peak season from April to October (Fig. 2). Despite that these villages are closely located from each other, the peak malaria month and year varied among villages. Specifically, the highest peak occurred in SY in 2012, JHK in 2013, and SSL in 2014, respectively (Fig. 2). MSY was the only village where incidence rates increased continuously from 2011 to 2014, with average incidence rates being 23.4, 41.7, 93.7, and 112.0 cases per 1,000 person years, respectively (Friedman ANOVA $\chi^2 = 8.07$, d.f. = 3, $P < 0.05$).

Changes in *P. vivax/P. falciparum* (Pv/Pf) ratio were significant over the four-year period (Table 2). In Myanmar, the Pv/Pf ratio increased from 1.6 in 2011 to 2.7, 3.6, and 4.91 in 2012, 2013 and 2014, respectively. The odds ratio also increased from 2.4 (95% CI [0.7, 7.9], $P = 0.14$) in 2011 to 23.3 (95% CI [12.2, 44.2], $P < 0.0001$) in 2014. In China, however, the *Pv/Pf* ratio decreased from 2011 to 2013 (Table 2).

3.3. Hotspots of clinical malaria

Spatial distribution of malaria cases varied significantly both among villages and within a particular village (Fig. 3). The locations of *P. falciparum* and *P. vivax* cases are mapped in Fig. 3. The median number of cases in each village was JHK 1.5, MSY 0, SY 0, SSL 0, and NB 0, respectively. In NB, SY, and SSL, there was at most one case per household, while most households had no malaria. In contrast, in both JHK and MSY, malaria cases at the household level ranged from zero to more than 10 cases during the study period. Furthermore, most households in JHK had experienced at least one episode of malaria during the study period.

Getis-Ord's analysis showed the presence of evident malaria hotspots ($z > 2.58$, $P < 0.01$) in four villages, JHK, MSY, SSL, and NB, whereas clustering of malaria cases was marginal ($1.65<z<1.96$, $P < 0.10$) in SY (Fig. 4). Interestingly, malaria cases clustered in the village center of JHK, whereas the clusters were located at the gateways of the remaining four villages.

4. Discussion

Motivated by recent achievements in malaria control, several nations in the GMS are pursuing malaria elimination with China taking the lead and aiming to achieve this goal by 2020. Malaria morbidity has continued to decline over the past two decades in China, with the majority of malaria concentrated in western Yunnan (Bi et al., 2013a). International border areas have become key control points for malaria elimination in China (Cui et al., 2012a; Cui et al., 2012b; Zhang et al., 2014a; Zhou et al., 2014a; Zhou et al., 2008). Investigation of malaria incidence in border counties of Yunnan province, China revealed that clinical *P. falciparum* malaria was closely associated with travel to Myanmar, whereas local *P. vivax* transmission remained (Xu et al., 2015; Zhou et al., 2014a).This highlights the need for both strengthened local control efforts as well as tightened monitoring near international borders to prevent malaria introduction (Mosha et al., 2014; Wangdi et al., 2015).

At the last stage of malaria elimination, control programs must shift focus from high coverage of interventions to seeking out infections and interrupting transmission. Targeted intervention is probably the most cost-effective way to rid of the source of parasites (Bousema et al., 2010; Bousema et al., 2012; Cotter et al., 2013; Mosha et al., 2014). However, targeted intervention requires accurate and timely information for identifying the target areas (Bousema et al., 2010; Bousema et al., 2012; Cotter et al., 2013). In China, a malaria elimination surveillance system was set up with a “1-3-7” approach to meet the challenges in communicating and monitoring surveillance and response activities (Cao et al., 2014).The disease control programs will have massive data gathering and dissemination responsibilities, and timely analysis and communications are essential (Cao et al., 2013; Zhou et al., 2014b). In this aspect, spatial and temporal maps to track populations at risk of malaria at local levels would be of great value.

Our analysis of malaria epidemiology on a micro-geographical scale revealed significant malaria transmission heterogeneity in both time and space. First, malaria in this area has clear seasonality with the peak malaria season coincident with the rainy season, which is likely a reflection of the climatic pattern. Yet, it is surprising that peak malaria incidence also had considerable variations among different villages and in different years and months. This may be attributed to an insufficient malaria management system that focuses on epidemics rather than systematic interventions. In several villages, annual malaria incidence in 2012-2014 was much higher than 2011, suggesting of insufficient control efforts, probably as a consequence of military conflicts taken place in recent years between the local and central governments. Second, our spatial analysis clearly showed the presence of malaria transmission hotspots in most of the villages. The strongly aggregated distribution of malaria in JHK and MSY may be attributed to the existence of mosquito breeding habitats,

which were associated with high *Anopheles* mosquito abundance as detected in our mosquito surveys in 2011 to 2013. In this area, twenty species of *Anopheles* mosquitoes were identified, with *An. minimus* s.l. accounting for 85% of the total collections (54–91 % of total captures in different villages). Mosquito densities varied from 0.05 to 3.00 females per trap per night, with strong seasonality in all sites and a density peak from June to August. Species richness peaked from April to August according to our previously reports (Bi et al., 2013b; Wang et al., 2015; Yu et al., 2013).

Interestingly, most of the hotspots were located in the crossroad or junctions areas. For example, the hotspot in JHK coincides with the major junction of roads to China, the camps for internally displaced people, and inland of Myanmar. It is possible that such hotspots may facilitate local and distant spread of malaria. Finally, the increase of malaria incidence in these villages in recent years accompanied the increase of Pv/Pf ratio, indicating increased transmission of vivax malaria in these villages. The emergence of drug-resistant parasites in this region (Yuan et al., 2014) and less stringent uses of primaquine for radical care because the presence of a significant portion of the local ethnic population with glucose-6-phosphate dehydrogenase deficiency (Li et al., 2015) may be partially responsible for the increased vivax cases in this region, which underlines the urgency for implementation of more effective *P. vivax* control measures (Waltmann et al., 2015; Zhou et al., 2014a). Furthermore, current treatment of *P. falciparum* was effective, which may contribute to the decrease in falciparum malaria, similar to what has been found in Thailand (Phimpraphi et al., 2008; Wang et al., 2015; Zhou et al., 2005).The migration flow between two countries is huge, estimated to be at least 20-fold higher than Lai Zar's residents, and 300-fold higher than NB's residents based on local records from the border control (unpublished). Our study is limited in that we did not collect data on cross-border movement of the study participants, and therefore could not differentiate indigenous from imported cases. Such information is important for a better understanding of malaria transmission at the border region.

In conclusion, this study investigated temporal and spatial patterns of malaria transmission in villages along the China-Myanmar border. While malaria here has an overall seasonal trend, there were considerable variations in the peak transmission month between the villages. Spatial analysis identified clear hotspots of malaria clinical cases within most studied villages. Malaria incidence rates were significantly higher in the Myanmar villages than in the neighboring village in China. These findings further depicted a scenario of border malaria in the GMS. Difference in malaria transmission levels between the two sides of the border emphasizes the threat of cross-border malaria introduction. These findings are vital for health workers on both sides of the border to implement targeted malaria intervention and to develop a strategy for controlling and eliminating “border malaria” in the GMS countries.

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Highlights

- Malaria cases in 5 villages along the China-Myanmar border were mapped.
- *P. vivax*/*P. falciparum* ratio increased dramatically during the four study years.
- Monthly incidence rates differed greatly among the study villages.
- Myanmar villages had much higher malaria incidence rates than a village in China.
- Spatial analysis revealed hotspots of clinical malaria incidences in four villages.

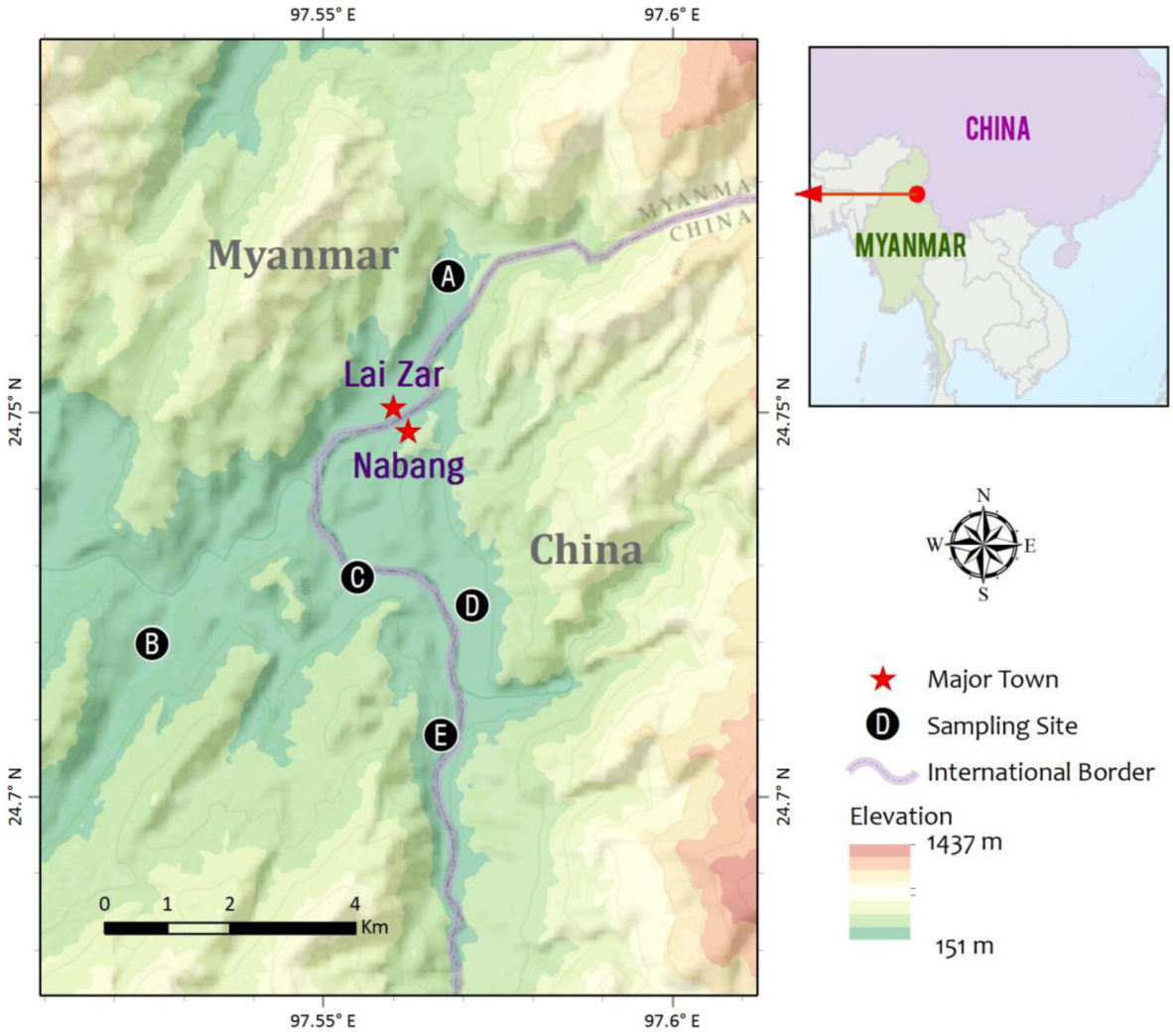

Fig. 1.

Locations of study villages SSL (A), SY (B), MSY (C), NB (D), and JHK (E) along the China-Myanmar border.

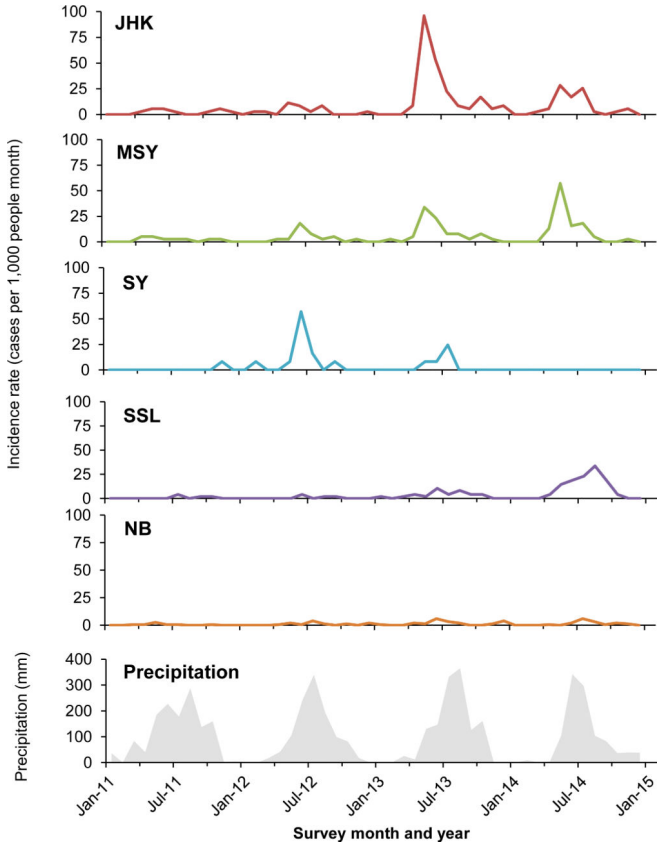

Fig. 2.

Temporal trends of malaria incidence rate (cases per 1,000 persons per year) in different villages from 2011 to 2014.

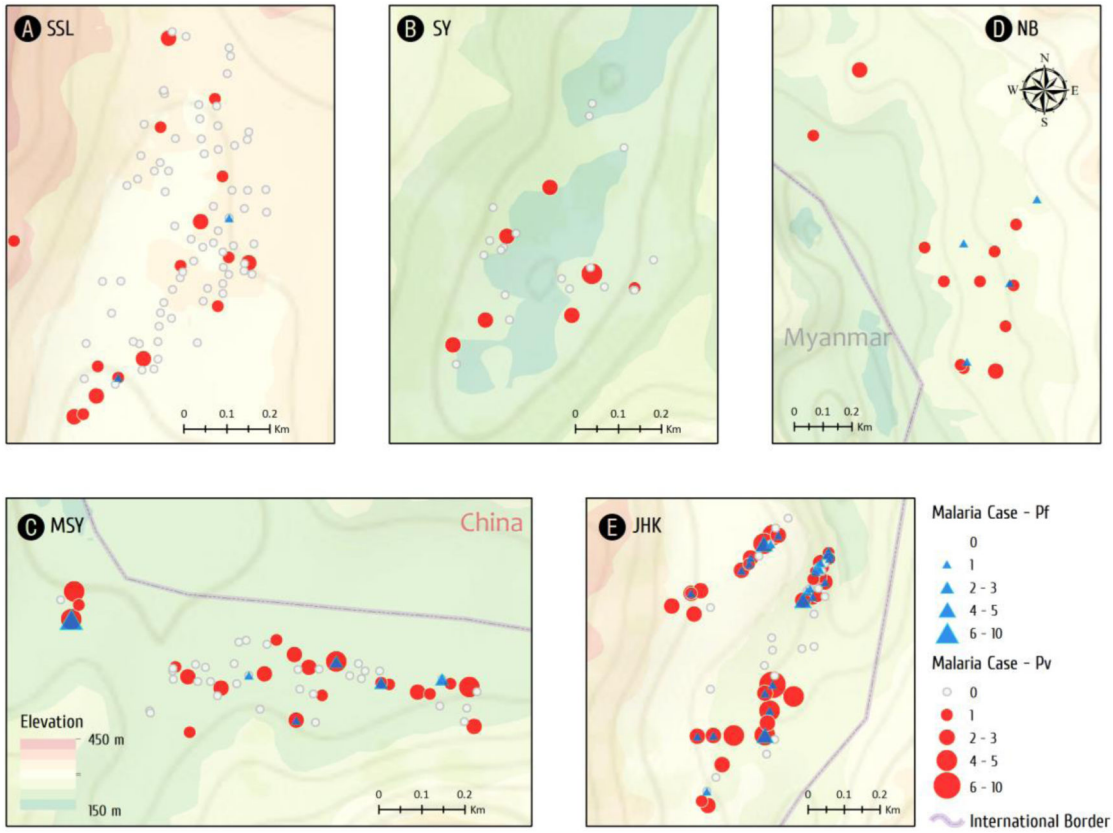

Fig. 3.

Spatial distribution of malaria cases in each village at the household level. Malaria cases were pooled from 2011 to 2014. Symbol sizes correspond to the numbers of malaria cases. P. falciparum and P. vivax cases are shown as blue triangles and red circles, respectively.

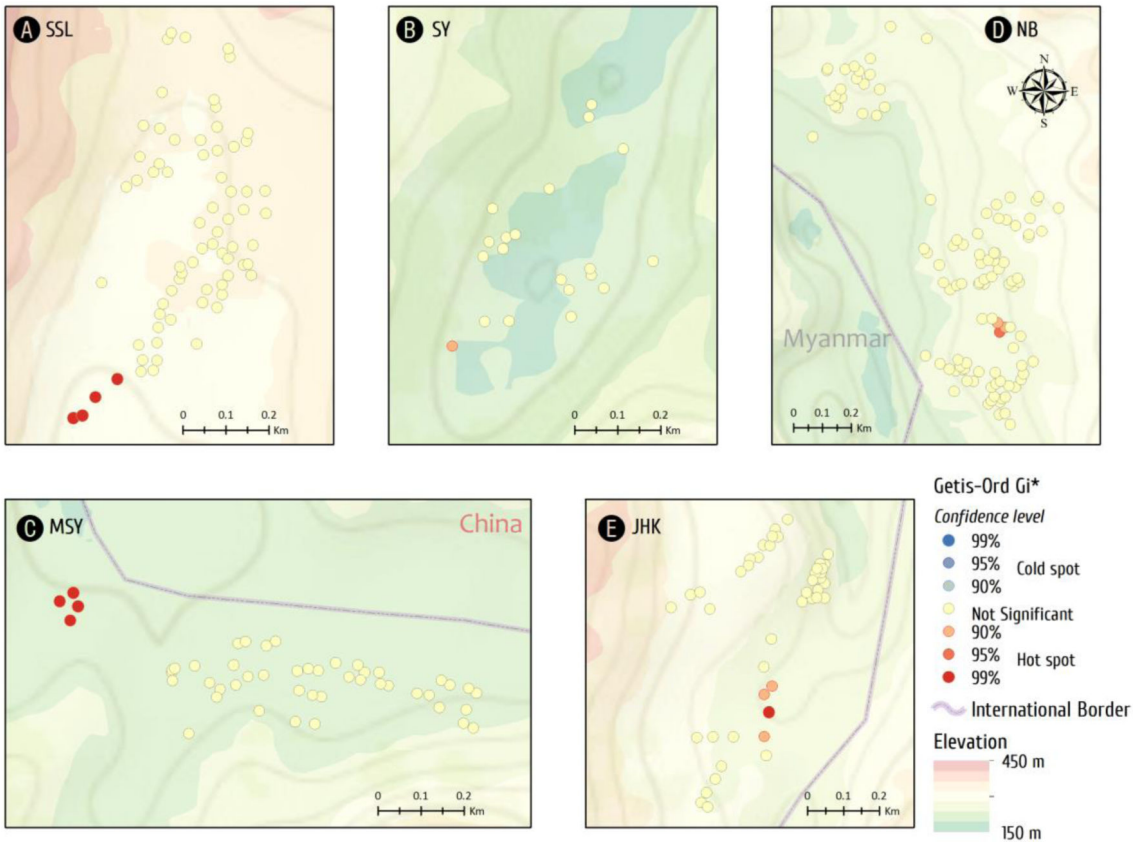

Fig. 4.

Hot and cold spots of malaria incidents detected by Getis-OrdGi* analysis at the household level. Dot colors indicate different significance levels. Reddish dots indicate hot spots, bluish dots indicate cold spots, and yellow dots represent “not significant”.

Table 1

Clinical cases from 2011 to 2014 by village and parasite species.

Site	Population†	Blood slides examined	Clinical cases				Case rate‡
			Total	Pv	Pf	Pv+Pf	
JHK	354	743	136	37	96	3	96.0
MSY	384	964	104	23	79	2	67.7
SSL	476	1713	84	8	76	0	44.1
SY§	123	135	18	5	12	1	48.8
NB$	1,500	170	82	15	67	0	13.7

Pv, *P. vivax*; Pf, *P. falciparum*, Pv+Pf, mixed infections of *P. vivax* and *P. falciparum.*

†Population from a 2012 demographic survey.

‡Case rate: cases per 1,000 population per year.

§2014 cases were not available.

$Population included only permanent residents, while cases included all suspected malaria infections.

Table 2

Changes in *P. vivax* and *P. falciparum* (Pv/Pf) incidence ratio over time.

Site	Year	Pv/Pf	Odds ratio [95% CI]	*P* value
Overall				
	2011	2.20	4.84 [1.68, 13.93]	0.0027
	2012	3.21	8.75 [3.90, 19.61]	<0.0001
	2013	3.47	11.64 [7.02, 19.28]	<0.0001
	2014	4.66	21.16 [12.38, 36.19]	<0.0001
	Total	3.70	14.35 [10.47, 19.69]	<0.0001
Myanmar				
	2011	1.56	2.42 [0.74, 7.91]	0.1407
	2012	2.73	6.18 [2.46, 15.51]	<0.0001
	2013	3.63	12.60 [7.17, 22.15]	<0.0001
	2014	4.91	23.26 [12.24, 44.21]	<0.0001
	Total	3.63	12.30 [8.56, 17.66]	<0.0001
China				
	2011	8.00	64.00 [3.38, 1210.61]	0.0034
	2012	5.00	25.00 [4.33, 144.31]	<0.0001
	2013	2.88	8.27 [2.65, 25.79]	0.0001
	2014	4.10	16.81 [6.32, 44.68]	<0.0001
	Total	3.95	15.64 [8.07, 30.30]	<0.0001