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Lack of Consistent Malaria Incidence Hotspots in a Highland Kenyan Area During a 10-Year Period of Very Low and Unstable Transmission

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Abstract. The use of spatial data in malaria elimination strategies is important to understand whether targeted interventions against malaria can be used, particularly in areas with limited resources. We previously documented consistent areas of increased malaria incidence in the epidemic-prone area of Kipsamoite in highland Kenya from 2001 to 2004. In this area and a neighboring subcounty (Kapsisiywa), malaria incidence decreased substantially in 2005, going from peak incidence of 31.7 per 1,000 persons in June 2004 to peak incidence of 7.4 per 1,000 persons in May 2005. Subsequently, the use of indoor residual spraying and artemisinin combination therapy malaria treatment led to a possible interruption of malaria transmission for a 13-month period from 2007 to 2008, after which the incidence returned to very low levels until an epidemic in April–July 2013. In the present study, we used novel kernel density estimation methods to determine whether areas of increased malaria incidence were consistent in six periods of peak incidence from 2003 to 2013, and to assess patterns of incidence in the period before versus. after the period of possible interruption. Areas of highest incidence differed during peak malaria transmission periods over the years 2003–2013, and differed before and after the potential malaria interruption. In this epidemic-prone region with very low malaria transmission, consistent malaria "hotspots" identified in a time of higher transmission are no longer present. Ongoing assessment of spatial malaria epidemiology to identify and target current areas of elevated malaria risk may be important in campaigns to control or eliminate malaria in epidemic-prone areas.

INTRODUCTION

The value of maps to inform intervention strategies was established during the first epidemiologic investigation linking cholera to the Broad Street pump in London, by John Snow in 1854.[1] With advances in technology, collection of spatial data has become an integral piece of current malaria elimination strategies, in which cases, vectors, parasite isolates, and interventions are all mapped.[2] The Roll Back Malaria partnership recognized the importance of spatial data in malaria elimination strategies and specifically called for shrinking the malaria map from the endemic margins inward in its Global Malaria Action Plan.[3,4] This practical strategy builds on the successes of the past century as evidenced by the global distribution of malaria from 1900 to 2002.[5] A blanket approach to interventions is not sustainable, and incorporating spatial data into investigations can inform targeted prevention and control strategies to maximize effectiveness with limited financial resources.

Local interruption is the first step toward elimination. As reported, the study area of Kipsamoite and Kapsisiywa experienced a period of possible local interruption in transmission from April 2007–April 2008 after the Ministry of Health (MOH), in 2005, switched to artemisinin combination therapies for first-line treatment of uncomplicated malaria and introduced indoor residual spraying (IRS) in the study area that increased to widespread (> 85%) coverage in 2007.[6] An important concern in malaria programs is preventing reintroduction of disease after interruption has been achieved. Identifying and then targeting clusters of malaria transmission when incidence reaches low levels are strategies used as programs transition toward elimination.[4,7] These targeted interventions are continued as elimination is sought. We previously documented consistent areas of increased malaria risk in the area of Kipsamoite from 2001 to 2004, but malaria incidence in this area after 2005, and particularly after the period of possible malaria interruption from 2007 to 2008, has remained 3- to 10-fold lower than in the 2001–2004 period. Thus, it was unclear if the consistent "hotspots" identified previously would remain in a period of much lower transmission. A strategy that uses interventions repeatedly targeted to specific areas assumes that malaria will reemerge in the specific locations where it faded. In the present study, we had the opportunity to test this assumption by exploring whether cases reemerged in the same locations where they were reported during periods of higher transmission, and to evaluate whether regions of increased malaria incidence were consistent in the periods before and after potential malaria interruption.

MATERIALS AND METHODS

Study population, location, and data sources. The study population consists of all occupants of the study area of Kipsamoite and Kapsisiywa, in Nandi County, western highland Kenya. The study population grew from 6,752 in April 2003 to 9,186 in December 2013. At the time of initial enrollment, field assistants used global positioning system (GPS) to map household coordinates. The study area's health Ccenters, forest edge, and swamps were also mapped using GPS.[8] The study sites are located approximately 20 km apart and share similar ranges of altitudes (Kip: 1,941–2,108 m; Kap: 1,887–2,065 m).[8,9] The western edge of Kip borders the Nandi North forest, and the large Kimondi swamp borders the eastern edge of Kip and the western edge of Kap.[8,9] Both sites experience unstable highly seasonal malaria transmission

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patterns. Figure 1 details the study area, including the locations of the households and health centers.

In general, the area experiences two rainy seasons described as the long rains from April to June and the short rains from October to December. During demography surveillance, field assistants enumerated all households in the entire study area and recorded data on births, deaths, and migrations of occupants. Starting in 2005, an indicator for household treatment by IRS, an annual intervention led by the MOH from 2005 to 2010 in the study area, was captured. The class of insecticides used in the IRS campaigns was pyrethroids, which have residual effects typically lasting 2–3 months.[10,11] These data were collected every 3–4 months (2003–2005), every 4–6 months (2006–2008), or annually (2009–2013). During the study period, passive surveillance of men, women, and children of all ages who presented to either of the two study area health dispensaries (Kipsamoite Health Center or Kapsisiywa Health Center) with symptoms of malaria were evaluated for clinical malaria by microscopy. Microscopy was performed independently by two trained microscopists, with a third and final assessment by a third microscopist if the first two results were discordant. Free diagnosis and treatment of malaria were provided as per MOH guidelines. Detailed descriptions of the study cohort were published in a prior manuscript (Hamre et al.,[12] A mass insecticide-treated bed net distribution campaign reduced malaria risk on an individual but not population level in a highland epidemic-prone area of Kenya, AJTMH, in press).

Study ethical review. Written consent was obtained from the heads of households during initial enrollment for participation in demography and passive clinical malaria surveillance, and from individual participants presenting to the health centers with symptoms of malaria for blood collection. The studies were approved by the Institutional Review Boards of Case Western Reserve University and the University of Minnesota, and by the Kenya Medical Research Institute Ethical Review Committee.

Descriptive analysis. Spatial data previously collected were imported into ArcGIS version 10.1 and projected to the World Geodetic System 84/Universal Transverse Mercator zone 36N coordinate system.[8,13] Household coordinates for the last 10 reported clinical malaria cases detected at the health centers by passive surveillance preceding the period of possible interruption and first 10 cases after this period were mapped along with characteristics of the study area, including the locations of the health centers and forest and swamp borders. A shapefile of the polygonal boundaries of the study area was created in ArcGIS and exported for use in R.[13,14]

Statistical analysis. Kernel density estimation (KDE) methods for analyzing spatial point patterns were used to evaluate the spatial variation of clinical malaria and routine IRS campaign coverage.[15–17] Kernel density estimation is a smoothing technique applied to spatial point data where a moving three-dimensional function of a given bandwidth visits each location and weights events within the area defined by the bandwidth according to their distance from the location being considered.[18] The size of the bandwidth strongly influences KDE. A bigger bandwidth produces more smoothing and tends to be more biased, whereas a smaller bandwidth tends to be less biased but more noisy, with more peaks, most of which are spurious. Adaptive smoothing techniques have been developed to allow the bandwidth to be different in different parts of the map depending on the amount of information available at each

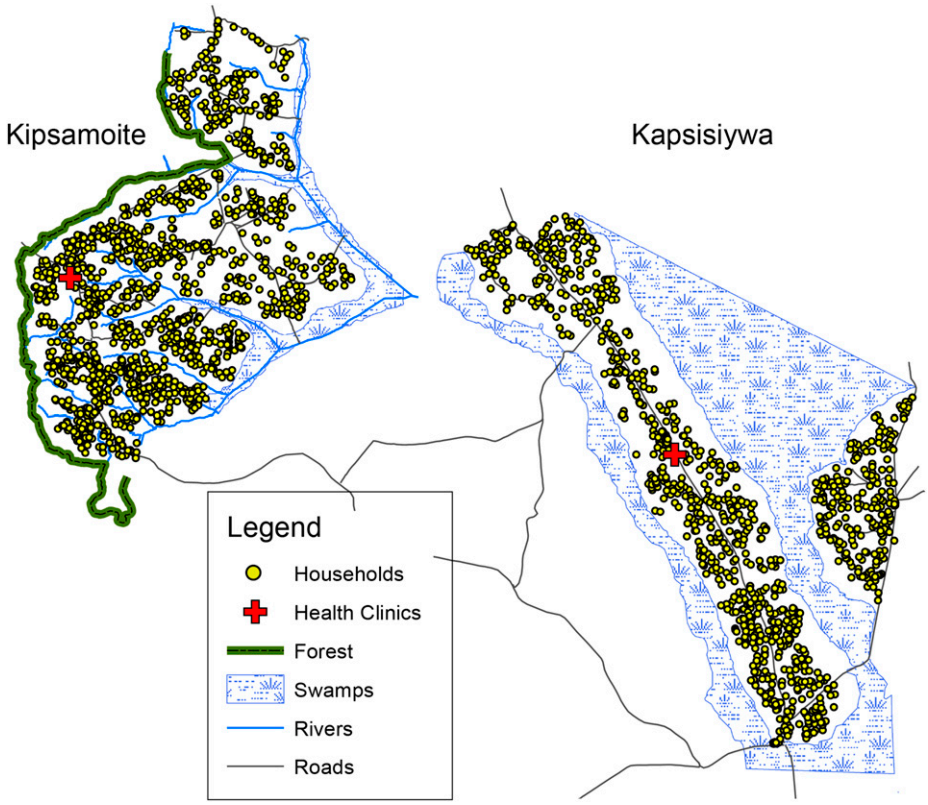

FIGURE 1. Detailed map of the study area, Kipsamoite and Kapsisiywa, Nandi County, Kenya. This figure appears in color at www.ajtmh.org.

TABLE 1

Overall cases of clinical malaria from the number of unique individuals residing in the number of unique households, by time period

Time period	Cases	Individuals	Households
Before interruption (April 2003–March 2007)	956	833	498
After interruption (May 2008–December 2013)	281	277	234
Peak 2004 (May–July)	319	311	231
Peak 2005 (April–June)	85	84	73
Peak 2007 (January–March)	51	51	45
Peak 2009 (April–June)	42	42	36
Peak 2011 (April–June)	60	59	58
Peak 2013 (June–July)	71	71	67

Peak periods for 2003, 2006, 2008, 2010, and 2012 are not reported. In 2003, data collection commenced during the period of peak incidence. In 2006, a gap in data collection occurred because of study and staff transitions. In 2008, a total of 14 clinical malaria cases were reported and none before May. In 2010 and 2012, no distinguishable peak periods were observed, with total annual cases of 27 and 17 reported, respectively.

location. In low-density areas, the bandwidth is larger to allow greater smoothing, whereas areas with more densely packed events have smaller bandwidths. This allows greater sensitivity to these events and ultimately avoids smoothing out important detail in areas with enough information to support more detailed estimates.[18,19] Edge correction methods have also been developed so that bias is not introduced into the density estimates for locations near the study area's borders.[20] The pieces of the standardized KDE equation are presented in Equation (1) (see citation for a graphic illustration of how KDE works).[18]

$$\hat{\lambda}_{\tau}(s) = \sum_{i=1}^{n} \frac{1}{\tau^2} k\left(\frac{s - s_i}{\tau}\right) \quad (1)$$

where $\hat{\lambda}_{\tau}(s)$ is the estimated probability density at location s, s is a location in the study area, s_i is the location of the ith event, n is the number of locations, τ is the bandwidth smoothing parameter, and $k()$ is the kernel weighting function in standardized form.

Kernel density estimation requires no event or one event per spatial location; so we created an indicator variable to identify whether a household had at least one case of clinical malaria reported during the time period being considered in any given analysis. We then used KDE to estimate the density, as a function of location, of developing clinical malaria in our study area. More specifically, we estimated and mapped the natural logarithm of the spatial relative risk functions (sRRFs), the ratio of the density of households with cases over the density of households without cases.[21,22] To evaluate whether peaks in the estimated surface identify regions in the study area with significantly elevated risk of malaria, we computed one-sided asymptotic tolerance contours (i.e., P-value contours at a significance level of 0.05) and overlaid these on the maps.[23]

We applied the KDE approach using adaptive bandwidths and edge correction methods during the periods before interruption (April 2003–March 2007) and after interruption (May 2008–December 2013). Similarly, we computed sRRFs and performed associated tests for the periods of peak incidence in 2004 (May–July), 2005 (April–June), 2007 (January–March), 2009 (April–June), 2011 (April–June), and 2013 (June–July). Peak periods for 2003, 2006, 2008, 2010, and 2012 were not evaluated for various reasons. In 2003, data collection commenced during the period of peak incidence. In 2006, a gap in data collection occurred because of study and staff transitions. No distinguishable peak periods were observed in 2008,

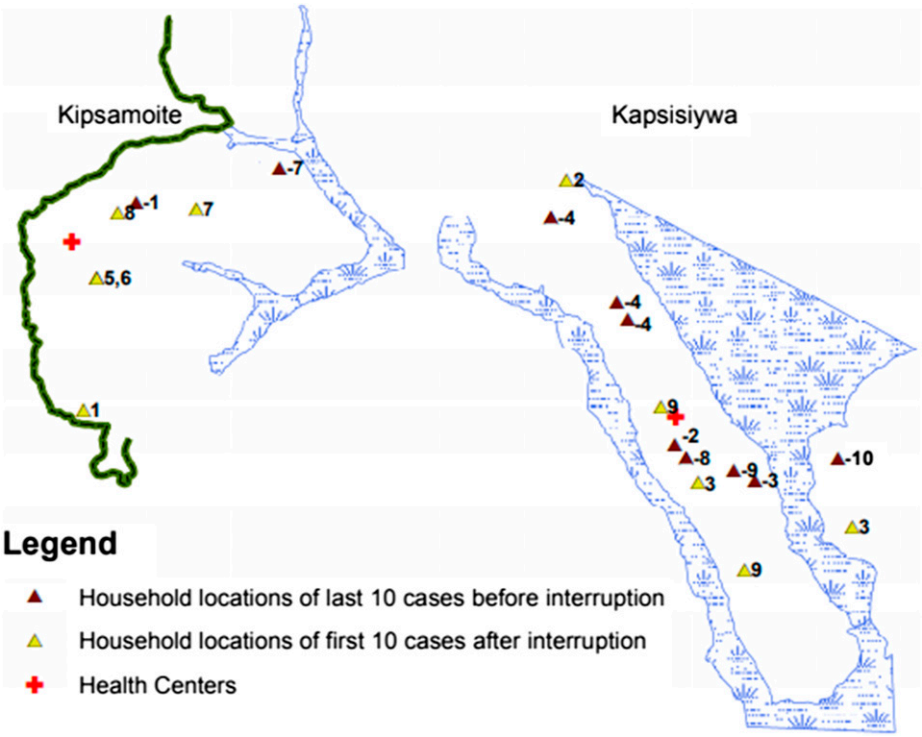

FIGURE 2. Household locations of the last 10 cases before and first 10 cases after a period of possible interruption of malaria transmission in the Kipsamoite and Kapsisiywa study area. Negative values indicate the order the cases were reported for the last cases before interruption, with increasing values nearer to this period. Positive values indicate the order the cases were reported after the period of interruption, with increasing values further from this period. Cases reported on the same day share values. This figure appears in color at www.ajtmh.org.

2010, or 2012, where 14, 27, and 17 annual cases were reported, respectively.

Using the same household-level KDE approach, we estimated sRRFs for the MOH-led annual IRS campaigns that took place in the study area from 2005 to 2010. To evaluate whether valleys in the estimated surface identify regions with significantly lower IRS coverage, we computed one-sided asymptotic tolerance contours at alpha = 0.05 and overlaid these on the maps.

Many epidemiologic studies do not enumerate every person in every household in a given study area so that a sample-level analysis like the household one described previously is the only option available to researchers. However, we did enumerate every person so that the underlying population can be truly well estimated. Table 1 summarizes the number of overall cases of clinical malaria from the number of unique individuals residing in the number of unique households for each period of analysis.

To enable us to use this individual-level information (instead of reducing it to a household-level summary), we repeated the spatial point pattern analysis for cases of clinical malaria using jittered household coordinates for individuals who shared the same household so that no two individuals shared exact coordinates (i.e., instead of using identical coordinates for all individuals in a household, we added a small amount of random noise to each individual's coordinates to spread them out a bit). This allowed each individual to contribute to the analysis using their respective case status during the period of analysis. No individual had a jittered coordinate more than 10 m in either latitude or longitude from the initial household coordinate recorded during demography surveillance.

All analyses excluded potential recrudescent cases in individuals, defined as a case occurring within 30 days of another case without a negative blood smear in between visits. Transmigration information captured during demography surveys was evaluated to account for individuals who moved households within the study area after initial enrollment. The sparr version 0.3-6 package in R version 3.2.1 was used to do all computations presented here (The R Foundation for Statistical Computing, Vienna, Austria).[14,21]

RESULTS

Descriptive spatial analysis. Figure 2 displays the locations of the households corresponding to the last 10 cases before the period of possible interruption and the first 10 cases after interruption. Households labeled with negative values represent cases before the period of interruption, increasing in order from the tenth-to-last case (–10) to the last case (–1) identified at the health centers. Households labeled with positive values represent cases after the period of interruption, increasing in order from the first case (1) to the 10th case (10) identified at the health centers. Households that share values on the map had cases of clinical malaria reported on the same day. Although both the last and first cases adjacent to the period of interruption were reported in Kipsamoite, these 20 mapped cases show no clear spatial pattern of disease. Eight of the last 10 cases before interruption were reported in Kapsisiywa, including three reported on the same day, whereas half of the first 10 cases after interruption were experienced in each of Kipsamoite and Kapsisiywa. Two cases in Kipsamoite after the period of interruption were from members of the same household.

Kernel density estimation: Household level and clinical malaria. After excluding potential recrudescent cases, from April 2003 to March 2007 before the period of possible interruption, clinical malarial cases were reported among individuals from 498 households as compared with 234 households from May 2008 to December 2013 after the period of possible interruption. Figure 3 shows heat maps of the estimated sRRFs of clinical malaria before and after interruption. Darker shades represent regions with higher sRRFs of malaria. In this household-level analysis, before interruption, significantly elevated sRRF was primarily seen in Kapsisiywa, with a few small regions of significantly elevated sRRFs in northern Kipsamoite. After interruption, significantly elevated sRRF was again more prominent in Kapsisiywa, especially eastern Kapsisiywa, but more and different areas in Kipsamoite also experienced significantly elevated sRRFs of clinical malaria.

During the peak period of malaria transmission from May to July 2004, clinical malaria was identified at the health centers

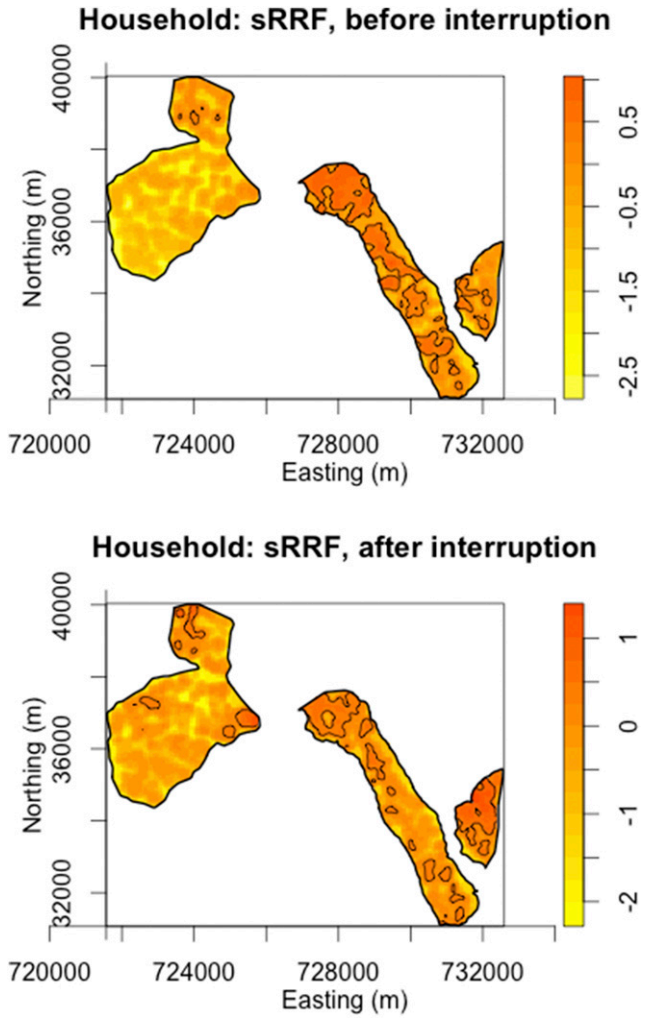

FIGURE 3. Estimated natural log of the spatial relative risk functions (sRRFs) of clinical malaria among households before and after a period of possible interruption of clinical malaria. Areas with a significantly elevated risk as compared with other areas during the same time period are indicated by overlaid black tolerance contours ($P < 0.05$). This figure appears in color at www.ajtmh.org.

among study area individuals from 231 households. After IRS commenced in the area in 2005, incidence was reduced (see incidence figure from Supplemental Figure 1).[12] During the peak April–June 2005 and January–February 2007 transmission seasons, cases were reported among individuals from 73 and 45 households, respectively. After interruption, cases among individuals from 36, 58, and 67 households were reported during the peak April–June 2009, April–June 2011, and June–July 2013 transmission seasons, respectively. Figure 4 shows the estimated sRRFs of clinical malaria during these peak periods before and after interruption in the study area, and the distribution of these sRRFs is displayed as histograms in Supplemental Figure 3. During the peak 2004 transmission season, significantly elevated sRRF was predominant in Kapsisiywa and northern Kipsamoite. In 2005, significantly elevated sRRF of clinical malaria was reported in fewer areas than in 2004, primarily in northern Kapsisiywa and eastern and north-central Kipsamoite. During the nearest peak before interruption in 2007, the only region with significantly elevated sRRF was a central area close to the Kapsisiywa Health Center. During the nearest peak after interruption in 2009, no areas of significantly elevated sRRF were reported. During the 2011 peak transmission season, significantly elevated areas of sRRF were again reported, primarily in northern Kapsisiywa, whereas in 2013, the areas of significantly elevated sRRF differed from those in 2011, with the exception of one small area in eastern Kapsisiywa. Instead, areas in southern and eastern Kapsisiywa and areas of north-central Kipsamoite had significantly elevated sRRFs of clinical malaria. To aid in the comparison of significantly elevated sRRFs of malaria across peak periods, we overlaid the tolerance contours for each peak period onto the same map (see Figure 5).

Kernel density estimation: Household level and IRS. The annual MOH-led IRS campaigns from 2005 to 2010 had

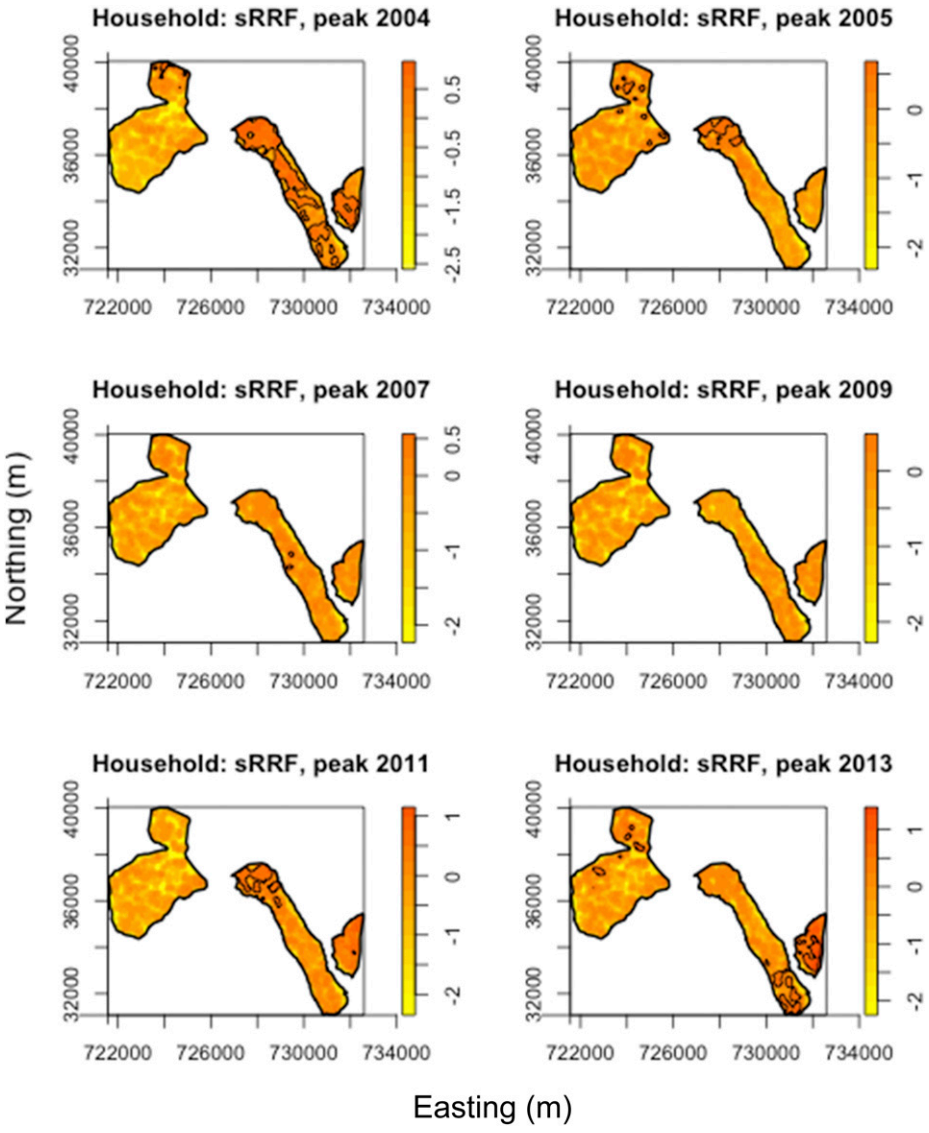

FIGURE 4. Estimated natural log of the spatial relative risk functions (sRRFs) of clinical malaria among households during peak periods of malaria transmission in 2004, 2005, 2007, 2009, 2011, and 2013. Areas with significantly elevated risk as compared with other areas during the same time period are indicated by overlaid black tolerance contours ($P < 0.05$). This figure appears in color at www.ajtmh.org.

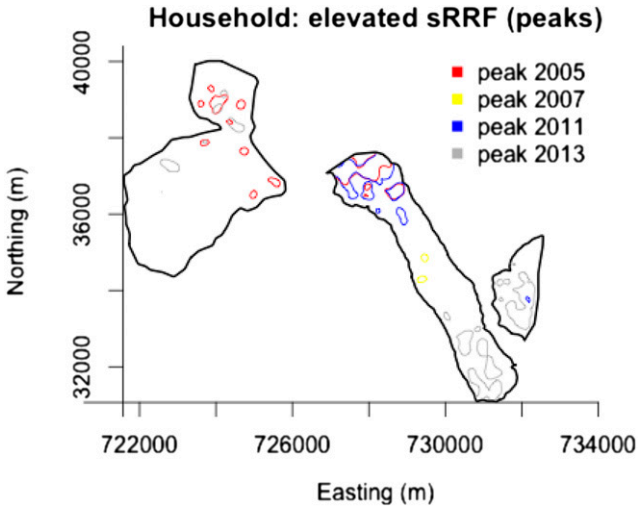

FIGURE 5. Overlaid areas of elevated spatial relative risk functions (sRRFs) of clinical malaria ($P < 0.05$) during peak periods of transmission. (Peak 2005 in red, peak 2007 in yellow, peak 2009 had no areas of elevated risk, peak 2011 in blue, and peak 2013 in gray. Peak 2004 is not shown for comparison because of it being a period of higher transmission with many more areas of elevated risk.) This figure appears in color at www.ajtmh.org.

varying coverage, which ranged from 29.5% to 88.8% of households (see IRS coverage from Supplemental Figure 3).[12] Figure 6 shows the estimated sRRFs of IRS coverage from 2005 to 2010. During the 2005 IRS campaign when 35.2% of households were sprayed, significantly lower sRRF was found in Kipsamoite and a small part of northern Kapsisiywa. In 2006, the areas of significantly lower sRRFs were in northern and south-central Kipsamoite (outside the area surrounding the health center) and northern and eastern Kapsisiywa. In 2007 and 2008, the areas of significantly lower sRRFs spanned Kipsamoite. In 2009 and 2010, similar areas in Kipsamoite showed significantly lower sRRFs, with southern and eastern Kapsisiywa in 2009 but northern and central Kapsisiywa in 2010. Indoor residual spraying has not been conducted in the study area since 2010.

Kernel density estimation: Individual level and clinical malaria. The population-level analysis of individuals with jittered household coordinates provided more detailed maps of the sRRF of clinical malaria in the study area than the sample-level analysis using households. This is not surprising because the power of the analysis comes from events, and the individual-level analysis has more events to consider. Clinical malaria cases were reported from 833 and 277 individuals before and after the period of interruption, respectively. The health centers identified 311, 84, 51, 42, 59, and 71 individuals with clinical malaria during the defined peak periods in 2004, 2005, 2007, 2009, 2011, and 2013. Figures 7 and 8 replace the household-level analysis in Figures 3 and 4 with an individual-level approach.

Similar to the household-level analysis, significantly elevated sRRFs of clinical malaria was predominant in Kapsisiywa before interruption, although many more areas in Kipsamoite experienced elevated sRRFs than the small regions in Kipsamoite identified in the household-level analysis. The overall sRRF of malaria was lower throughout the study area when the individual-level analysis was considered (i.e., there are more areas with lighter shades in the individual-level analysis than in the household-level analysis). This was also true for the period after interruption.

During the 2004 peak transmission period, significantly elevated sRRF was experienced in multiple regions scattered throughout the study area. During the 2005 peak period, significantly elevated sRRF was seen predominantly in eastern and northern Kipsamoite. More areas in Kapsisiywa experienced significantly elevated sRRFs during the peak 2007 period, primarily centrally located near the health center. Also, like the 2005 peak period, eastern and northern Kipsamoite had significantly elevated sRRFs in 2007, but in fewer areas. Only one small area of significantly elevated sRRF was identified in northern Kipsamoite during the nearest peak period after interruption in 2009. During the 2011 peak period after interruption, significantly elevated sRRF was identified in northern and eastern Kapsisiywa, and in 2013, more areas of significantly elevated sRRFs were identified, including in southern Kapsisiywa and central Kipsamoite.

DISCUSSION

Areas of consistently increased malaria risk have been identified in areas of high[24,25] and low[26,27] malaria transmission. Previously, in the highland area of Kipsamoite assessed in the present study, stable hotspots were identified from 2001 to 2004 during epidemic and non-epidemic years.[8] However, the present study showed that even in Kipsamoite, once lower transmission conditions prevailed, the "hotspots" of increased transmission varied greatly from year to year. In almost all periods, there were areas of significantly elevated sRRFs of clinical malaria in both Kipsamoite and Kapsisiywa, and these were present before and after a 13-month period in which clinical malaria was absent in the study area. However, the regions of elevated sRRFs differed during the periods before and after interruption of clinical malaria cases. In particular, during peak periods after interruption (2009–2013), the sites of elevated incidence were not the same as those with elevated incidence during peak periods before this period of possible interruption (2003–2007). Hence, no patterns were identified that would warrant consistently targeting intervention and control strategies to specific sites within the study areas.

Variable patterns of spatial transmission have been found in areas of low transmission, with some studies supporting consistent hotspots as aforementioned and others suggesting greater variability.[28–30] Among those reporting spatial heterogeneity of malaria over time, incidence in the article by Platt et al.[28] in the Webuye division of Bongoma East district, western Kenya, ranged from 1.8 to 3.6 per 100 persons and covered an area of 115 km^2. Ihantamalala et al.[29] illustrated the spatial heterogeneity of malaria incidence for the entire country of Madagascar by classifying incidence based on its National Malaria Control Program elimination phases of < 1 per 1,000 (pre-elimination), 1 to < 10 per 1,000 (moderate transmission), 10 to < 50 per 1,000 and 50+ per 1,000 (combined as high transmission). In the Loreto region of Peru, annual incidence from 2006 to 2010 reduced from 48.9 to 11.6 per 1,000 persons before increasing again to 42.7 per 1,000 in 2013 as reported by Soto-Calle et al.[30] Even in areas of high malaria transmission like coastal Kenya, "hotspots" may not

be consistent over time.[31] Factors that affect the presence of these areas, including population density and age, proximity to vector breeding sites, and housing characteristics (e.g., distance to road, swamp, or river; roof material; and presence of window eaves or screens) may change over time or change with new human interventions that affect these factors.[8,28,32–34] Few studies of spatial malaria risk over time have been conducted in areas of extremely low transmission like Kipsamoite and Kapsisiywa, where monthly incidence was consistently low from 2005 to 2013, peaking at 7.1 per 1,000 persons in May 2005 before interruption and 5.6 per 1,000 persons in June 2013 after interruption. Thus, the present article provides new data for subnational areas in which malaria incidence is extremely low but not yet zero. Yet, with improved malaria control and elimination campaigns, more and more areas may come down to similarly low levels of transmission. The present study demonstrates that spatial analysis of malaria risk needs to be consistently reevaluated in areas of low transmission when targeted interventions are planned.

Evaluation of the spatial distribution of cases to potentially detect clusters (i.e., elevated risk regions) of disease is of primary interest, but solely considering case locations, as in alternative methods, may only reflect the distribution of the population.[15] Kernel density estimation is thus superior to alternative cluster detection methods that only consider cases and do not take into consideration the underlying population distribution of the study area and that use traditional shape boundaries to identify regions of elevated risk.[35] Major strengths of the KDE approach are the adaptive bandwidth technique, which provides flexibility in modeling heterogeneous spatial distributions, and edge-correction methods, which account for the portion of the

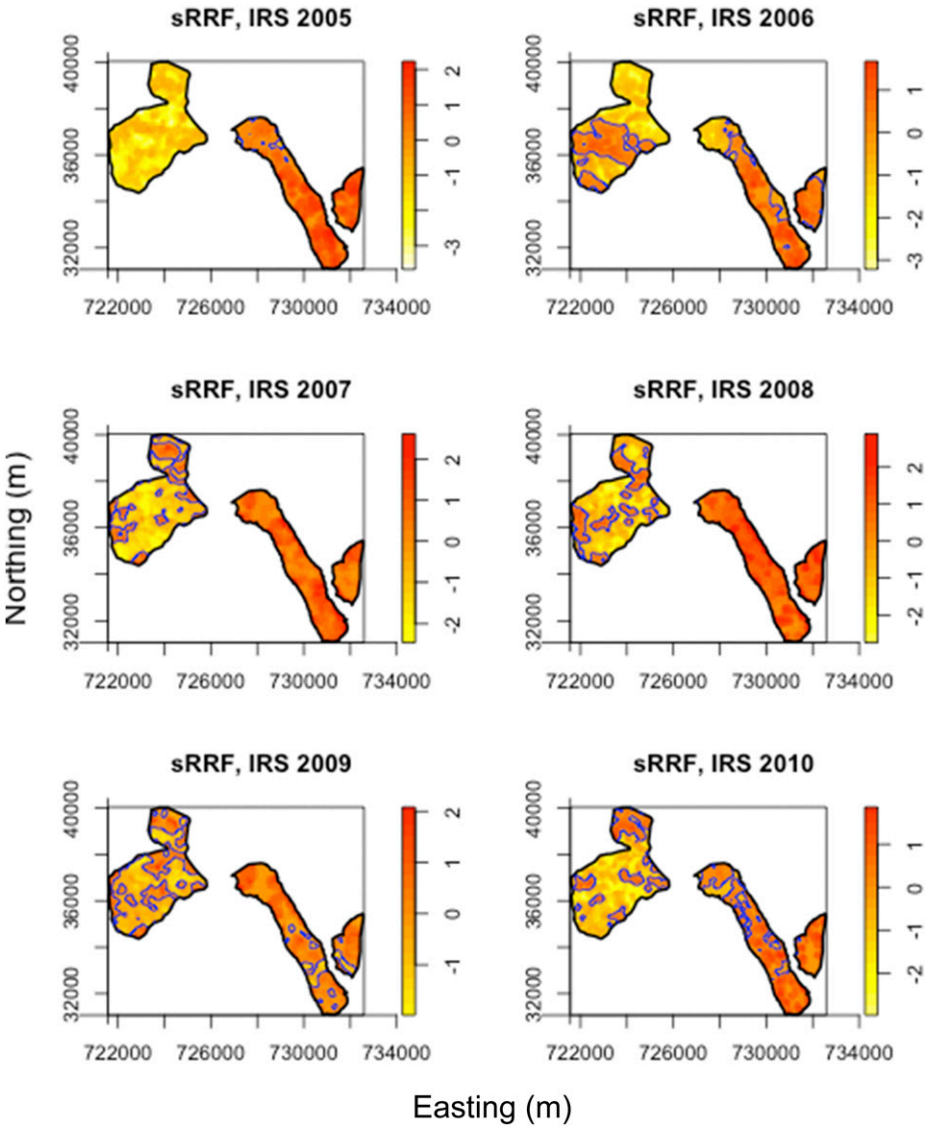

FIGURE 6. Estimated natural log of the spatial relative risk functions (sRRFs) of indoor residual spraying among households during the annual Ministry of Health indoor residual spraying (IRS) campaigns during 2005–2010. Areas with significantly lower coverage as compared with other areas during the same time period are indicated in overlaid blue tolerance contours ($P < 0.05$). This figure appears in color at www.ajtmh.org.

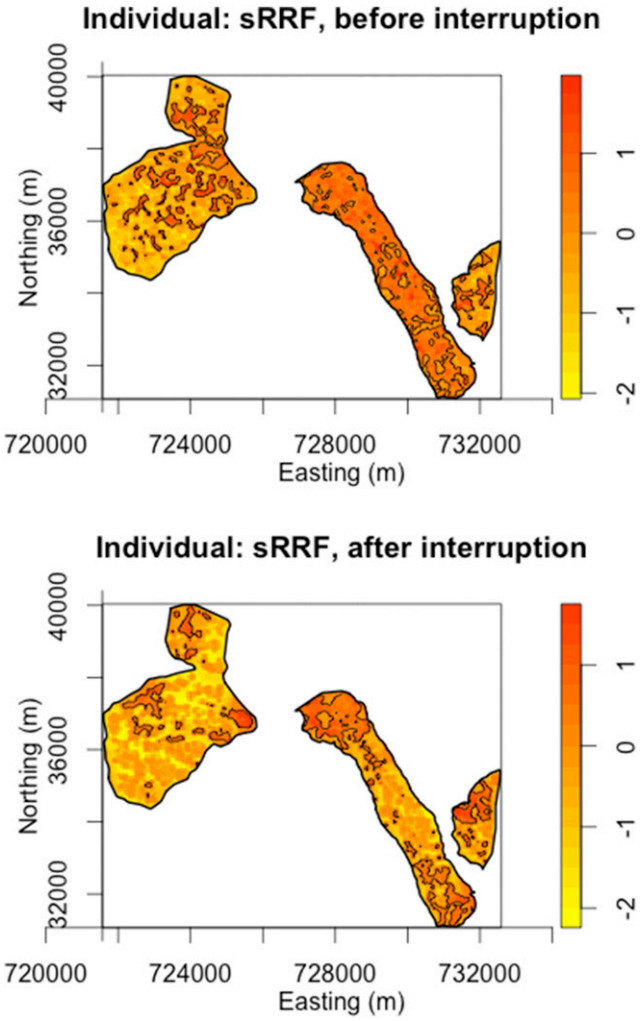

FIGURE 7. Estimated natural log of the spatial relative risk functions (sRRFs) of clinical malaria among individuals before and after a period of interruption of clinical malaria. Areas with significantly elevated risk as compared with other areas during the same time period are indicated by overlaid black tolerance contours ($P < 0.05$). This figure appears in color at www.ajtmh.org.

kernel lying outside the study boundary, and thus avoid a negative bias. Limitations of this study include the ability to detect only cases of malaria that attended the health centers (although prior studies have shown that this population largely relies on these dispensaries for primary care of malaria),[36] gaps in data collection during brief periods of 2005 and 2006, and the requirement for zero or one events at a given spatial location for KDE techniques. To address the latter method issue while using individual-level rather than strictly household-level case data, we jittered the coordinates for members of shared households so that each had a unique location, and we repeated the spatial point pattern analysis for cases of clinical malaria. Information was still lost for individuals with multiple cases during a specified time period, but this alternative analysis did provide more data for analysis than simply evaluating case status at the household level.

Interruption of malaria could not be transformed into malaria elimination at these sites because there was no plan for elimination at the time of interruption, and any such plan would have required substantial ongoing resources. Maintaining interruption of transmission will require significant operational and financial commitment, and its likelihood of success will need to be evaluated before resources are committed to that goal.[7,37–39]

With consideration of subnational malaria elimination campaigns, assessment of the micro-epidemiology of malaria hotspots in areas approaching elimination levels becomes increasingly important. The present article provides new data for areas of very low and unstable transmission. Such areas may increase over time if malaria control campaigns continue to have success, and therefore understanding how transmission and incidence vary in these areas is of increasing importance to eventual malaria elimination campaigns. When elimination does become the goal in epidemic-prone highland Kenya, we know that our study area can achieve levels of transmission below current standard means of detection. Performing spatial epidemiology in near real time with intervention implementation may increase the effectiveness of a planned intervention strategy as well such that current areas of elevated risk can be identified and specifically targeted. Spatial methods can be applied at different resolutions, and exploring these may be beneficial to planning as a spatial pattern could be present and detectable at one level of resolution but not at a finer resolution (e.g., a spatial pattern might be evident for villages within a district but not households within a village). The study area may also benefit from additional active case detection methods, where persons with asymptomatic infections are targeted for testing and treatment.[40] Under these conditions, targeted interventions may be most appropriate. A combination of strategies is likely required to achieve interruption and eventual elimination of malaria in our study area and other highland areas of very low malaria transmission.

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Note: Supplemental figures appear at www.ajtmh.org.

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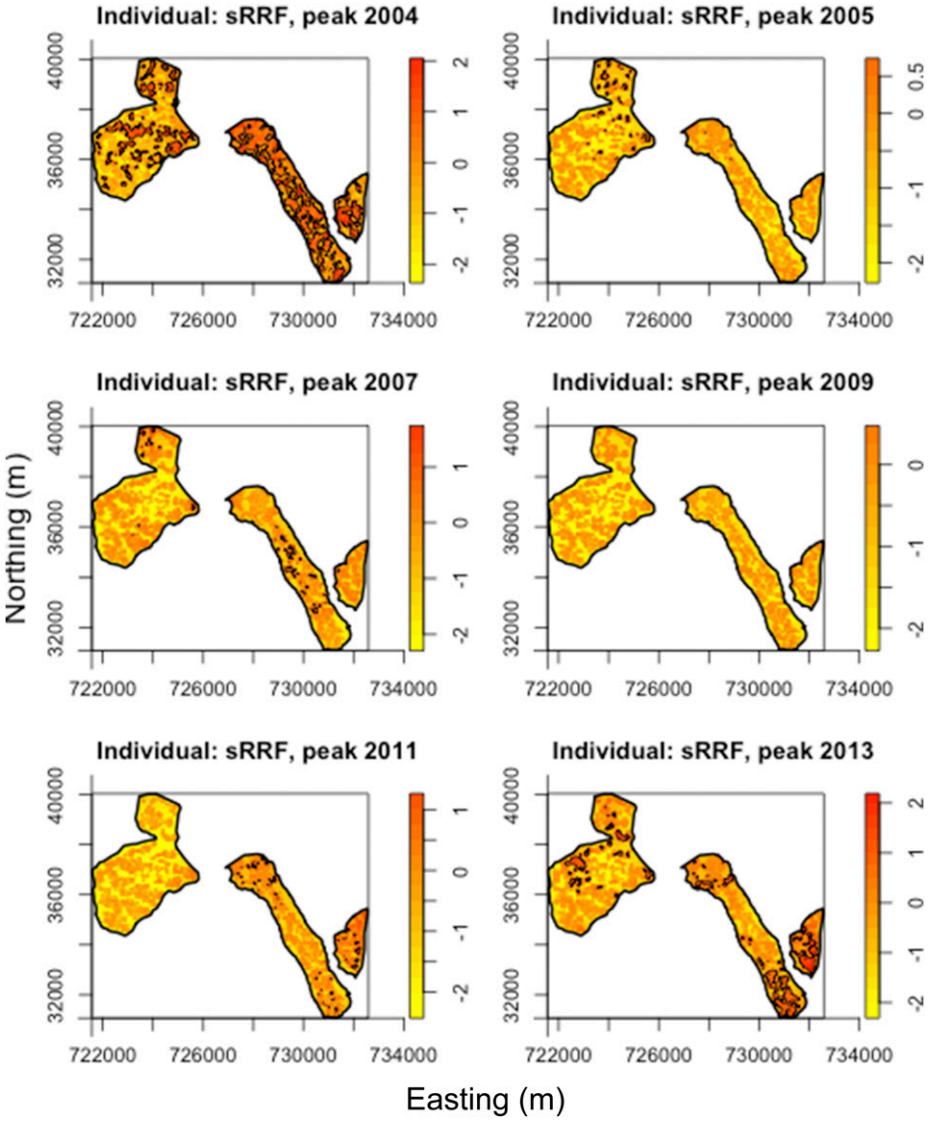

FIGURE 8. Estimated natural log of the spatial relative risk functions (sRRFs) of clinical malaria among individuals during peak periods of malaria transmission in 2004, 2005, 2007, 2009, 2011, and 2013. Areas of significantly elevated risk as compared with other areas during the same time period are indicated by overlaid black tolerance contours ($P < 0.05$). This figure appears in color at www.ajtmh.org.

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