A Temporal-Spatial Analysis of Malaria Transmission in Adama, Ethiopia

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Abstract. Urban malaria is a growing problem in Africa. Small-scale spatial studies are useful in identifying foci of malaria transmission in urban communities. A population-based cohort study comprising 8,088 individuals was conducted in Adama, Ethiopia. During a single malaria season, the Kulldorff scan statistic identified one temporally stable spatial malaria cluster within 350 m of a major *Anopheles* breeding site. Factors associated with malaria incidence were residential proximity to vector breeding site, poor house condition (incidence rate ratio [IRR] = 2.0, 95% confidence interval [CI] = 1.4, 2.9), and a high level of vegetation (IRR = 1.8, 95% CI = 1.0, 3.3). Maximum (IRR = 1.4, 95% CI = 1.1, 1.9) and minimum daily temperatures (°C; IRR = 1.3, 95% CI = 1.2, 1.5) were positively associated with malaria incidence after a 1-month delay. Rainfall was positively associated with malaria incidence after a 10-day delay. Findings support the use of small scale mapping and targeted vector control in urban malaria control programs in Africa.

INTRODUCTION

Urban malaria in Africa is a problem of substantial and growing proportions. Cities currently account for ~45% of the continent’s population and from 18 to 140 million malaria cases annually. Urban centers are rapidly expanding, particularly on their peripheries, where poor-quality housing, lack of drainage, the presence of agriculture, and poverty intensify malaria transmission. Of particular concern is urban malaria in the continent’s densely populated epidemic-prone highland fringe, where increasingly frequent epidemics and rising malaria incidence and mortality form a disturbing trend. Evidence of this trend is the devastating malaria epidemic that occurred in Ethiopia’s central highlands in 2003, causing an estimated 16 million clinical malaria cases and up to 114,000 malaria-attributable deaths.

In highland African cities, there is a need for timely deployment of spatially targeted malaria interventions to curtail malaria epidemics. Although studies have identified important climatic, seasonal, and demographic factors underlying large-scale spatial and temporal patterns of malaria epidemics in African countries, thus far, attempts to develop predictive models of malaria epidemics, which are accurate on the local scale, have not met with success. At present, there are few small-scale temporal-spatial studies of malaria incidence, particularly in urban highland area of Africa. Small-scale temporal-spatial studies of malaria transmission are therefore essential to target interventions toward transmission hot spots, which may shift seasonally within a given locale.

This study sought to describe the temporal and spatial clustering of malaria cases and identify factors associated with malaria clustering in Adama (formerly Nazareth), Ethiopia from August 1 to November 30, 2003, a period in which a massive malaria epidemic occurred throughout Ethiopia, including the study area.

MATERIALS AND METHODS

The data we present here were collected as part of a malaria risk factor study in Adama, Ethiopia, which identified factors associated with malaria risk in individuals. A detailed description of materials and methods for that study has been published elsewhere. This study examines housing quality, household vegetation cover, residential distance to a major *Anopheles* breeding site, weather factors, and *Anopheles* larval density as determinants of household-level malaria incidence in cohort of 1,302 residential compounds (8,697 individuals) in a 1.8-km peri-urban area of the city. A residential compound was defined as one or more households sharing a single yard, usually surrounded by a fence. Most residential compounds (91.6%) contained one household, 6.5% contained two households, and 1.9% contained three to seven households. After exclusion of individuals because of non-continuous residence, age < 1 year, and missing data, the final data set contained 1,187 residential compounds (8,088 individuals).

Data collection. Malaria incidence. Data on the primary outcome of incident clinical malaria infections caused by *Plasmodium falciparum* and *P. vivax* occurring from August 1 to November 30, 2003 in residential compounds were obtained from a patient database at the Adama Malaria Laboratory. Patients records were linked to residential compounds using a unique study identifier, which was assigned to study households in the field and recorded in the patient database each time study area residents visited the laboratory. The Adama Malaria Laboratory is located 2 km from the study site and was the only facility in Adama offering free microscopic diagnosis and treatment of malaria. Thus, inclusion of most cases occurring in the area was warranted.

Compound distance to the vector breeding site. From August 1 to 3, 2003, two experienced vector control technicians surveyed the study area to identify seasonally permanent *Anopheles* vector breeding sites. A single site was identified; this was a 0.50-km² flood plain bordering the study area that was used as a watering hole for cattle during the heavy rains, which occur from July to October, and for agriculture from January to October. Over study follow-up, water temperature and larva samples were taken every 2 weeks from the periphery of the site closest to the study area (~0.10 km in length). The median larva/pupae count was 124 per 100 dips (interquartile range [IQR] = 150.5); median water temperature was 22.3°C. Using a hand-held Global Positioning System (GPS), the geographic coordinates of all residential compounds were measured to a horizontal accuracy of < 10 m. Continuous
variables were created to define the distance of each compound to the vector breeding site.

Residential compound factors. Study interviewers used exemplary photographs to visually assess housing quality, compound tidiness, and vegetation cover near homes and rate these factors on a three-point scale as low, medium, or high. Household heads were asked the total number of residents in the residential compound. To control for potential confounding by insecticide treated nets (ITNs) obtained after study follow-up was completed, study households were revisited in December 2003 and asked about the number and date of acquisition of ITNs in the household. (ITNs were promoted and sold by local government in the study area starting in September 2003 in an attempt to halt the ongoing malaria epidemic.)

Weather factors. Data on daily high and low temperatures and rainfall in the study area during 2003 were obtained from the Adama weather station (latitude 8°33′, longitude: 39°17′) of the National Meteorological Agency of Ethiopia. This station is located in Adama and records daily maximum and minimum dry bulb temperature (°C) and total 24-hour rainfall measured using a rain gauge. Semi-monthly mean values for daily low and high temperatures and rainfall were calculated from the daily data.

Mapping and statistical analysis. Analyses were conducted to assess temporal-spatial clustering of malaria in the study area and to identify factors associated with malaria. These analyses describe the number of incident malaria infections occurring in residential compounds each day of study follow-up. Temporal trends in malaria incidence were examined by plotting the total number of malaria cases from the study area by week of study follow-up. Temporal weather trends were examined by plotting semi-monthly mean values for weather factors by time for the period of May 15 to November 30, 2003. A visual assessment of spatial clustering of malaria was made by developing a smoothed map of malaria risk in the study area, using the Kernel method, an interpolating and smoothing technique for individual point location data. ArcGIS 9.3 Spatial Analyst was used to generate two smoothed surfaces representing population density and malaria cases with a smoothing bandwidth of 100 m. A map was created by dividing the malaria case surface by the population density surface.19

Statistically significant temporal-spatial malaria clusters in the study area were identified by a Kulldorff scan statistic (SaTScan v6.1.3.). This statistic uses a large number of two-dimensional scanning windows of varying sizes that center on geographical points throughout the study area, each of which reflects a possible malaria cluster. P values for a Poisson-based likelihood ratio are obtained in each scanning window through Monte Carlo simulation. Under the null hypothesis, malaria risk is constant over time and space. Under the alternative hypothesis, risk is greater inside compared with outside the scanning window; if the null hypothesis is rejected, the area inside the scanning window is identified as belonging to a malaria cluster.20

Univariate and multivariable analysis. Study data comprise a panel time series, in which each residential compound contributes eight panels of semi-monthly malaria incidence data over 16 weeks of follow-up. A generalized estimating equation (GEE) model was used to examine the effect of explanatory factors on semi-monthly malaria incidence in residential compounds. Several explanatory factors were constructed from the primary data for use in analysis. The factor poor house quality equaled 1 for compounds with housing quality scored as poor; the reference category was moderate or good. The factor high vegetation cover was defined as 1 for compounds scored as high; the reference category was moderate or low. The factor tidy compound was set to one for compounds scored as very tidy; the reference category was somewhat tidy or not tidy, which referred to compounds with visible vegetative or household litter, open pits, or piles of construction material. The factor had ITN equaled 1 for each compound and 2-week panel combination in which ITNs were owned. Four dummy variables were developed for the continuous variables residential distance from the breeding site; these were 150–350, 351–650, 651–950, and 951–1,250 m (which was the referent category). No residential compounds were found at distances < 150 m from the breeding site. For the purpose of visualizing the relationship between residential distance and malaria risk, linear splines were constructed for residential distance from the breeding site by identifying breakpoints (knots) where the slope of the regression line of malaria incidence on distance was thought to change. Knots were placed at 450, 650, 950 and 1,250 m. The continuous variable larva/pupa count (weighted by 100 dips) was transformed into two dummy variables for each 2-week panel as high or medium (155–503 counts) compared with the referent category of low or none (0–88 counts). Cutoff points for linear splines and dichotomized factors were determined by comparing Aikake information criteria (AIC) values in univariate models, which regressed malaria counts on the factor of interest using different breakpoints. Semi-monthly mean values for daily high and low temperatures and rainfall were calculated from the daily data.

The GEE model used the negative binomial distribution for malaria counts and an unstructured autocorrelation structure between time panels. The negative binomial overdispersion level was determined by comparing AIC values and residuals between models with different overdispersion levels. The autocorrelation structure was determined through an assessment of de-trended time series plots of malaria counts. Time varying explanatory factors were treated with time lags to account for delays in their effects on malaria incidence. The lag size was determined by comparing AIC values in models with different lag sizes. Temperature and rainfall factors had 4- and 10-week lags, respectively; ITN ownership and larva factors had a 2-week lag. To adjust for within-compound correlation, Huber-White sandwich estimators were used to calculate coefficient SEs.

Crude associations between explanatory factors and malaria were estimated by regressing a single factor against semi-monthly malaria counts in residential compound. A multivariable model was developed to examine the effects of household, weather, and larvae/pupa factors on malaria incidence. Candidate factors for the multivariable model were selected based on hypothesized relationships, the statistical performance of factors in univariate analysis, and correlations among the factors. Candidate factors were entered into the model in their presumed order of importance; non-statistically significant factors were removed unless deemed important for theoretical reasons. Interaction terms were assessed by adding one interaction term at a time to the final model.

RESULTS

Temporal and spatial trends in malaria incidence. Malaria incidence over study follow-up was 110.64 per 1,000 popu-
lation, a rate higher than any recorded in any Adama neighborhood in the previous 10 years (Oromiya Regional Health Office, unpublished data). Overall, 886 malaria cases arose in 671 individuals; 27.7% of residential compounds had at least one case. Incidence rose sharply from August to mid-September, remained high throughout October, and declined sharply in November (Figure 1). Larvae/pupae counts per 100 dips ranged from 0 to 503 over study follow-up (Figure 1).

Only one seasonally permanent *Anopheles* vector breeding site was identified in the study area; malaria incidence was spatially concentrated within the 350 m of this site (Figure 2). Malaria cases occurred throughout the study area; however, incidence was focused in the area adjacent to the site in each month of follow-up (Figure 3). The Kulldorff scan statistic identified a single statistically significant cluster ($P = 0.001$) of 502 malaria cases, from 149 residential compounds (population 886 people) in a 0.31-km$^2$ area within 400 m of the major seasonal breeding site (data not shown).

**Residential compound factors.** The average size of residential compounds was 6.7 individuals. Most residential compounds were of poor condition (69.8%), and few (3.5%) owned an ITN at study baseline. In the multivariable model, both poor house condition and high level of vegetation were significantly associated with approximately a doubling of malaria incidence in residential compounds; ITN use in the previous 2 weeks was not significant in the model (Table 1).

**Vector breeding site factors.** In multivariable modeling, high or medium larvae/pupae counts were associated with a significant increase in malaria incidence in the subsequent 2 weeks (IRR = 2.9; 95% CI = 2.3, 3.6). Moreover, residential proximity to the vector breeding site was strongly associated with malaria risk; households living 150–250 m from the site had 22 times higher malaria risk compared with those 950 m or greater from the site (Table 1). Figure 4 shows crude and adjusted malaria incidence by residential distance from the major vector-breeding site increased, particularly over the first 350 m. Compounds within 350 m of the site were estimated to have >10 times the malaria incidence over study follow-up (adjusted incidence = 684.8 per 1,000 population) compared with compounds >350 m from the site (adjusted incidence = 65.7 per 1,000 population; analysis not shown).

**Weather factors.** Figure 5 shows mean semi-monthly temperature and rainfall in Adama from mid-May to the end of November 2003. Rainfall was heavy from mid-June to mid-September, after which it declined rapidly. Daily maximum temperatures declined from mid-May to the end of July and slowly rose to a peak in October; daily minimum temperatures remained fairly steady from mid-May through mid-September, after which they declined. Multivariable modeling showed that both higher mean maximum daily and minimum daily temperatures were significantly associated with increased malaria incidence after a 4-week lag. Each 1°C increase in semi-monthly mean daily temperature was associated with a 40% and 30% increase in malaria incidence for daily maximum and minimum temperature, respectively. Rainfall levels also affected malaria incidence; each millimeter increase in semimonthly rainfall was associated with a 7% increase in malaria after a 10-week delay (Table 1). No interaction terms were significant in the multivariable model.
DISCUSSION

In this urban setting of highland Ethiopia, a single, temporally stable spatial cluster of malaria located within 400 m of the seasonally permanent breeding site was identified. Multiple regression modeling confirmed that proximity to this site strongly influenced malaria risk over distances as small as 100 m. The finding that malaria transmission is highly focal in low transmission areas is consistent with other local scale spatial studies of malaria transmission carried out under both epidemic and non-epidemic conditions.21–23

In this study, increases in maximum and minimum daily temperatures were both associated with moderate increases in malaria incidence after a 1-month delay. The IRRs reported here for weather factors are independent of larvae/pupae factors, because the latter were also included in the model. This analysis thus shows weather-related increases in malaria risk unrelated to larval production most likely because of increased adult mosquito longevity and fitness associated with warmer and moister conditions. Much of the literature on weather factors and malaria risk omits Anopheles factors in their models, with some reporting IRRs for daily temperatures and rainfall higher than were reported here. In this analysis, if larvae/pupae densities are excluded from the final multivariable model, the IRRs and 95% CIs associated with minimum and maximum daily temperature and rainfall are 1.0 (referent) and 1.1 (referent), respectively. Considered in this light, this study’s findings are largely consistent with those of another

Table 1
Crude and adjusted estimates of malaria risk factors in residential compounds in Adama, Ethiopia August 1 to November 30, 2003

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) or mean (SD)</th>
<th>Crude IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>House characteristics</strong></td>
<td></td>
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<tr>
<td>Owned bed net at baseline</td>
<td>43 (3.55)*</td>
<td>1.0 (0.7, 1.6)</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>High level of vegetation in compound</td>
<td>33 (2.78)*</td>
<td>2.1 (1.0, 4.6)</td>
<td>1.8 (1.0, 3.3)</td>
</tr>
<tr>
<td>Poor house condition</td>
<td>832 (69.74)*</td>
<td>4.8 (3.1, 7.3)</td>
<td>2.0 (1.4, 2.9)</td>
</tr>
<tr>
<td><strong>Distance to vector breeding site (m)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150–350</td>
<td>136 (11.23)*</td>
<td>30.2 (19.8, 45.8)</td>
<td>22.6 (14.9, 34.3)</td>
</tr>
<tr>
<td>351–650</td>
<td>364 (30.06)*</td>
<td>5.6 (3.6, 8.5)</td>
<td>4.9 (3.2, 7.3)</td>
</tr>
<tr>
<td>651–950</td>
<td>445 (36.75)*</td>
<td>2.0 (1.3, 3.2)</td>
<td>1.9 (1.2, 3.0)</td>
</tr>
<tr>
<td>950–1,250</td>
<td>266 (21.97)*</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td><strong>Weather and Anopheles factors</strong></td>
<td></td>
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</tr>
<tr>
<td>Maximum temperature (°C) (1-month lag)</td>
<td>26.71 (1.27)†</td>
<td>1.0 (0.9, 1.1)</td>
<td>1.4 (1.1, 1.9)</td>
</tr>
<tr>
<td>Minimum temperature (°C) (1-month lag)</td>
<td>15.14 (1.10)†</td>
<td>1.3 (1.1, 1.4)</td>
<td>1.3 (1.2, 1.5)</td>
</tr>
<tr>
<td>Rainfall (mm) (10-week lag)</td>
<td>5.43 (4.20)†</td>
<td>1.0 (1.0, 1.1)</td>
<td>1.0 (1.0, 1.1)</td>
</tr>
<tr>
<td>Number of Anopheles larvae and pupae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High or medium larvae/pupae (2-week lag)</td>
<td>4 (57.1)§</td>
<td>2.9 (2.3, 3.6)</td>
<td>2.3 (1.6, 3.3)</td>
</tr>
<tr>
<td>Low or no larvae/pupae (2-week lag)</td>
<td>3 (42.9)§</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
</tbody>
</table>

* N (%) of study area residential compounds with house characteristic.
† Mean (SD) for temperature refers to July 1 to October 15, 2003; for rainfall refers to May 1 to September 15, 2003.
‡ Taken to two decimal places, the IRR for rainfall was 1.07 (95% CI = 1.03, 1.10).
§ N (%) of 2-week periods (August 1 to November 15).
|| In a model which excludes the factors “Number of Anopheles larvae and pupae,” “High or medium larvae/pupae” and “Low or no larvae/pupae,” weather factors have the following adjusted IRRs and 95% CIs. Maximum temperature: 1.6 (1.4, 1.9). Minimum temperature: 2.5 (2.1, 3.0). Rainfall: 1.1 (1.1, 1.2).
This study found that higher Anopheles larva/pupae densities were positively associated with malaria incidence after a 2-week delay. In theory, this association should require a lag of 3–7 weeks to allow time for larval development, sporogony, and the incubation period to clinical disease in human hosts. However, time estimates for these processes are based on laboratory findings, whereas substantial variation may exist under real life conditions. For example, the pace of larval development depends on water temperature and food availability, whereas clinical incubation periods vary by human immune response and the number of parasites in the infecting dose and parasite characteristics. In addition, larvae/pupae counts from this study contained few pupae, which are more mobile than larvae and may have escaped collection. Because pupae develop in 3–4 days, their under-representation in larvae/pupae counts may account for the shorter than expected lag time between larva/pupae densities and malaria incidence.

In addition to weather and vector breeding site factors, this study examined the association between malaria incidence and residential compound factors. The moderate increase in malaria risk associated with poor housing quality and high vegetation coverage in the residential compound observed in this study are consistent with findings in the literature. It is noteworthy that the area of high malaria transmission adjacent to the major vector breeding site contained predominately poor-quality housing, making it difficult to isolate the effect of housing on malaria risk in the study population. This study found no association between malaria risk and recent use of ITNs, a factor for which there is substantial evidence of a protective effect against malaria infection. It is likely that there was insufficient statistical power to detect the effect of ITNs on malaria incidence in the study area. Only 196 compounds owned an ITN at the study's conclusion, among which 71% had acquired the ITN after mid-October, by which time malaria transmission was already subsiding. Furthermore, ITN acquisition was more common in residential compounds with good housing quality where malaria incidence was lower.

This study is one of only a few to examine small-scale spatial and temporal malaria clustering in an urban African setting and therefore makes an important contribution to literature on malaria epidemiology. Study strengths include the use of a well-defined population cohort from which we obtained covariate information on 93% of residential compounds. In addition, malaria cases were microscopically diagnosed by experienced technicians and are likely to represent most cases occurring in study area. This is because the study area is located in a malaria epidemic-prone region where most malaria infections are symptomatic and result in treatment seeking. Furthermore, it is likely that study area residents primarily sought treatment at the Adama Laboratory, which was well known in the community and was the only facility providing free microscopic diagnosis and treatment of malaria. Nevertheless, it is possible that some malaria infections arising in the study area were treated at home or at private clinical facilities and were therefore excluded from this analysis. Other methodologic limitations of study data should also be considered in interpreting study findings. Data on adult mosquito densities were not collected; the correlation of adult vector densities with other explanatory factors would have strengthened study findings. Data were also not collected on temporary vector breeding site, and we were therefore unable to estimate the importance of these sites on malaria transmission.

This study has important implications for malaria control in urban Africa, showing that residential proximity to vector breeding sites, type and status of residential compound, temperature, and rain patterns were all important factors shaping malaria risk. The study's finding of a single, large, stable malaria cluster located near a productive Anopheles vector breeding suggests that targeted vector control interventions will greatly reduce the malaria burden in urban communities of Africa. Research has shown that targeted larviciding and focal use of outdoor and indoor residual spraying with insecticides can achieve a high level of coverage, greatly reducing adult vector populations. These interventions are cost effective, particularly when malaria clusters are focal and relatively stable over the malaria transmission season, which is common in urban areas of Africa. This study highlights the utility of small-scale malaria mapping to identify transmission hot spots within communities, a method that has been successfully used in at least two urban malaria control programs in Africa. Further studies should assess how small-scale malaria mapping can be used in conjunction with targeted vector control interventions to enhance the effectiveness of urban malaria control in Africa.

Received December 19, 2008. Accepted for publication July 2, 2009.

Acknowledgments: The authors acknowledge all the community members and patients who participated in the study, as well as the laboratory staff, vector control technicians, and data collectors whose diligence made this study possible. The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

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