*Am. J. Trop. Med. Hyg.*, 82(3), 2010, pp. 391–397
doi:10.4269/ajtmh.2010.09-0047


# Significance of Travel to Rural Areas as a Risk Factor for Malarial Anemia in an Urban Setting

Jose G. Siri, Mark L. Wilson,* Susan Murray, Daniel H. Rosen, John M. Vulule, Laurence Slutsker, and Kim A. Lindblade

*Department of Epidemiology, and Department of Bioststistics, School of Public Health, University of Michigan, Ann Arbor, Michigan; Division of Parasitic Diseases, National Center for Zoonotic, Vector-Borne and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Centre for Vector Biology and Control Research, Kenya Medical Research Institute, Kisumu, Kenya*

*Abstract.* The epidemiology of malaria in urban environments is poorly characterized, yet increasingly problematic. We conducted an unmatched case–control study of risk factors for malarial anemia with high parasitemia in urban Kisumu, Kenya, from June 2002 through February 2003. Cases (n = 80) were hospital patients with a hemoglobin level ≤ 8 g/dL and a *Plasmodium* parasite density ≥ 10,000/μL. Controls (n = 826) were healthy respondents to a concurrent citywide knowledge, attitude, and practice survey. Children who reported spending at least one night per month in a rural area were especially at risk (35% of cases; odds ratio = 9.3, 95% confidence interval [CI] = 4.4–19.7, $P < 0.0001$), and use of mosquito coils, bed net ownership, and house construction were non-significant, potentially indicating that malaria exposure during rural travel comprises an important element of risk. Control of severe malaria in an urban setting may be complicated by *Plasmodium* infections acquired elsewhere. Epidemiologic studies of urban malaria in low transmission settings should take travel history into account.

## INTRODUCTION

Of the estimated 300–500 million annual cases of acute clinical malaria worldwide, only a small fraction progress to severe illness or death.[1] Severe malarial anemia (SMA) is the most frequently observed severe outcome, with an estimated 1.42–5.66 million cases and 0.19–0.97 million fatalities annually in children less than five years of age and a case fatality rate greater than 13%.[2] During the past decade, research has suggested a multi-organ pathology for severe malaria, in which multiple pathways can produce similar syndromes.[3,4] This pathology is much more complex than the view that cerebral malaria (CM) and SMA represent two well-defined severe malaria endpoints with simple underlying pathogenic processes,[5] and complicates the search for severe malaria risk factors. Nonetheless, SMA is recognized as the most important manifestation of severe malaria in highly endemic areas,[6] primarily affecting children six months to three years of age, with increasing transmission leading to earlier encounters with malaria and a higher incidence at younger ages. Where transmission is low, the mean age of clinical cases increases and CM is more frequently observed.[7]

The effects of transmission intensity on community epidemiologic patterns of severe malaria are well-documented.[8,9] However, evidence of socioeconomic and environmental risk factors for specific severe malaria syndromes is inconsistent. Most research has focused on severe malaria in general (i.e., including CM, SMA, and other severe outcomes). In The Gambia, no association was found between severe malaria and household wealth, crowding, educational or occupational characteristics of the parents, or the use of personal protection measures.[10] Two studies in Kenya[11,12] found conflicting results for the effect on severe malaria of presence of domestic animals, house construction, and use of mosquito coils. With regard to SMA specifically, a third study in Kenya found parental education and occupation and use of mosquito coils, but not house construction, to affect risk in univariate, but not multivariate, analysis,[13] whereas a study in Gabon could not identify any effects of socioeconomic status factors.[14] These factors have been linked in various locations to CM[15] and severe anemia.[16] Duration of symptoms and distance to hospital have in several cases been identified as risk factors for severe malaria and severe anemia.[10,16]

Investigations of insecticide-treated bed net (ITN) use and severe malaria are more extensive, but also provide conflicting results. Research in Kenya, The Gambia, and the Congo found no effect of ITN use on severe malaria,[10,12] CM,[15] or malarial anemia.[13] However, bed nets have been shown to reduce mortality and severe morbidity in a variety of contexts.[17,18] Protective effects for bed nets have been observed for anemia in Malawi[19] and severe anemia in Tanzania.[16] Bed nets were shown to increase hemoglobin levels and reduce SMA in western Kenya[20] and to reduce malaria cases in Malawi, where ITNs were socially marketed.[21] Further research is needed to clarify the different effects of socioeconomic and environmental risk factors on severe malaria occurrence.

Severe malaria outcomes have rarely been examined in the context of urban environments, despite rapid urbanization in Africa.[22] This is due, in part, to observed lower transmission in large urban centers relative to rural areas, decreased availability of anopheline vector breeding sites, a lower ratio of vectors to humans, and diminished range of vector dispersion.[23] However, the potential for malaria outbreaks and severe malaria morbidity in sub-Saharan African urban areas is likely increased by high levels of circular rural-urban migration, frequent commerce among peripheral urban and outlying village populations, proximity of low-transmission (low-immunity) areas to high-transmission zones, and the tradition of urban agriculture, which may provide perpetual vector breeding sites and thus chronic sources of infection for urban residents.

A few studies have examined the epidemiologic profile of severe malaria and anemia in urban areas,[24–28] and there is substantial research on urban behavioral factors related to malaria,[29–31] on urban entomologic patterns,[23,32] and on the distribution of prevalent infection in urban areas.[33,34] However, few studies have attempted to quantify risk factors for severe malaria outcomes among urban residents.[19,28,35] To address this need, we investigated the epidemiology of malarial anemia in the

*Address correspondence to Mark L. Wilson, Department of Epidemiology, School of Public Health, University of Michigan, 109 Observatory, Ann Arbor, MI 48109-2029. E-mail: wilsonml@umich.edu

city of Kisumu, Kenya, a hyperendemic region representative of rapidly growing urban environments in SSA.[22] In particular, we implemented an unmatched case–control study aimed at understanding risk factors for malaria in this urban setting.

## METHODS

**Study area.** This study was conducted in Kisumu, western Kenya (population = 326,407)[36] on the shores of Lake Victoria. The proximity of the lake, extensive swamps, abundant rainfall (1,000–1,500 mm/year) and a year-round warm climate combine to make this region one of the most favorable for malaria transmission in east Africa.[37] Transmission is highest in several months after the rainy seasons, which occur during April–June and October–December. In rural areas near Kisumu, exposure to infective mosquito bites is estimated to be 90–410 per year.[37,38] The study site was limited to the urban core of Kisumu and partitioned into three eco-epidemiologic zones (urban, peri-urban, and semi-rural) as described fully elsewhere.[39] Briefly, seven variables related to malaria and urbanization were summarized at the geographic scale of the national census enumeration area (EA) (encompassing, on average, approximately 100 households), and three factors accounting for a large proportion of the variation in this data identified through principal components analysis. This analysis is a mathematical procedure that takes a number of potentially correlated variables and transforms them into a smaller number of uncorrelated variables that account for much or most of the variation in the data. A clustering algorithm was applied to these EA-level factor scores to assign each EA to an urbanization zone.

Kisumu District Hospital (KDH) is a government-run facility in central Kisumu that accounts for 13% of district hospital beds and is among the most important regional centers for treatment of severe malaria arising in the urban area. Data from a concurrent knowledge, attitudes, and practices (KAP) survey[40] indicates that approximately half the population would go to KDH in a health emergency, more than any other local facility. The U.S. Centers for Disease Control and Prevention (CDC), in conjunction with the Kenya Medical Research Institute (KEMRI), maintained a continuous surveillance system for malaria at KDH from 1996 through 2005, with ongoing collection of clinical and laboratory data during and prior to our study period.

**Study design and participants.** This case–control study involved cases with malarial anemia and high parasitemia identified from among patients coming to the pediatric inpatient ward of KDH from June 2002 through February 2003. Cases were initially defined as children less than 10 years of age with a hemoglobin level ≤ 8 g/dL and parasite density ≥ 10,000/μL who were normally resident within the study area. However, all observed cases were ≤ 7 years of age. This definition differs from the standard World Health Organization definition for SMA, which specifies a hemoglobin threshold of ≤ 5 g/dL. Our higher cutoff value was chosen to enhance comparability with other studies on anemia conducted in the same area and to ensure sufficient availability of cases for analysis. Cases for which informed consent was obtained were accompanied to their home by a study interviewer who made local environmental and household observations and recorded the geographic coordinates of the house using a handheld global positioning system. Control children were chosen from among respondents to a concurrent citywide KAP survey.[40] To ensure comparability of case and control children, eligibility for controls was restricted to children within the observed case age range (i.e., ≤ 7 years of age). The criteria for inclusion as a control included residing within the study area, no history of malaria or serious illness within the previous 30 days, and indicating KDH as the first choice for treatment in the event of severe illness in the household.

Clinical data for cases were obtained from the CDC surveillance group during the course of treatment and during the interview at KDH. Trained CDC staff performed all laboratory procedures. A hemoglobin test device (HemoCue Inc., Lake Forest, CA) was used to measure hemoglobin levels. *Plasmodium* parasitemia was determined by using standard methods of microscopic examination of blood smears.[41] Clinical data were not available for controls.

**Survey instrument and ancillary data.** The KAP survey instrument was administered at the hospital to caregivers of cases by a study interviewer. A trained supervisor accompanied field and hospital interviewers on randomly selected occasions to ensure consistency. The survey instrument consisted of eight sections: basic demographics, knowledge of malaria, health and treatment history, malaria treatment-seeking behavior, use of malaria prevention, travel history, socioeconomic status, and environmental characteristics of the home and surroundings. Wealth was assessed by constructing an index based on ownership of specific household items using principal components analysis.[42] The distribution of the first component resulting from this analysis was divided into percentiles. An index variable was created for housing quality, measuring whether houses had either open eaves or windows with low-quality covering, potentially enabling mosquitoes access to the household.

Population data and maps were obtained from the Kenya Central Bureau of Statistics. Locations of survey households were determined using a handheld Garmin Etrex global positioning unit (Garmin, Olathe, KS). Geographic data were processed with geographic information system software (ArcGIS version 9.0; Environmental Systems Research Institute, Redlands CA), which was also used to estimate population density from digitized street maps and enumeration area boundaries. A Quickbird high-resolution multispectral satellite image (DigitalGlobe, Longmont, CO) was used to derive normalized difference vegetation index (NDVI) values for the entire study area using PCI Geomatica (PCI Geomatics, Richmond Hill, Ontario, Canada). The NDVI, which ranges from –1 to 1, was transformed to a 200-point scale by adding 1 to the value and multiplying by 200, to create a more interpretable index and to enhance comparability with other studies.[43]

**Statistical analysis.** Observed distributions for 32 potential risk factors and confounders were compared by case status using SAS version 9.1 (SAS Institute, Cary, NC). Significant associations were identified by using chi-square[44] or Fisher's exact[45] tests for categorical and Student's t tests[46] or Wilcoxon's rank-sum[47] tests for continuous variables. All significant predictors of case status were entered singly into logistic regression[48] models for malarial anemia to produce odds ratios (ORs).

A multivariate logistic model was constructed using the LOGISTIC procedure in SAS. Variable selection for this model was guided by results of the bivariate analysis and the known epidemiology of malarial anemia. However, the limited number

of cases (n = 80) constrained the number of variables that could be considered. Although logistic models with less than 10 events per variable should be interpreted with caution,[49] excluding important variables can bias or invalidate results. Based on previous studies, seven variables were included in the multivariate model *a priori*: child age, bed net ownership (independent of whether nets were treated), mosquito coil use, housing quality, regular travel to rural area by the child (i.e., at least one night per month), household wealth, and level of urbanization. Level of urbanization comprised an index encompassing a wide range of other socioeconomic and environmental variables, including NDVI, distance to town, population density, ownership of transportation and luxury items.[39] In addition, variables that met the Bonferroni significance criteria for multiple testing (i.e., $P < 0.0016$ for 32 individual risk factors) in bivariate analysis were included as potential risk factors in the multivariate model. Interaction terms were not considered because of the small sample size.

The final logistic model was produced using a forward selection method, beginning with the seven initial variables, and including other variables that again met criteria for multiple testing during multivariate analysis. Multicollinearity among predictor variables was assessed using variance inflation factors.[50] Continuous variables were examined for nonlinearity with respect to the logit of the dependent. Multiple imputation was used to compensate for small amounts (< 5%) of missing data in some variables; three imputations were considered adequate based on guidelines in the literature.[51] The Hosmer-Lemeshow goodness-of-fit test[52] was used to assess adequacy of model fit. Residual diagnostics were used to identify significant outliers, and the model was rerun with those observations removed to test the stability of parameter estimates. A variogram of the model residuals measuring the similarity between pairs of point measurements at different geographic distances was constructed using PROC VARIOGRAM in SAS.

**Protection of human subjects.** Written informed consent from parents or caretakers of participants was obtained prior to all interviews. The protocol for this study was reviewed and approved by the institutional review boards of The University of Michigan (Ann Arbor, MI), CDC (Atlanta, GA), and the Kenya Medical Research Institute (Nairobi, Kenya).

## RESULTS

From July 2002 through February 2003, 141 children less than 10 years of age had malarial anemia and high *Plasmodium* parasitemia at KDH. Of these children, 80 (57%) were identified and interviewed for this study. Captured cases were slightly younger, smaller, and lighter in weight than uninterviewed cases, although no differences were statistically significant. Symptoms were comparable in captured and missed cases, except that the latter had significantly lower parasitemia (mean = 35,218/μL versus 48,061/μL; t = 2.75, $P = 0.007$). Over the same period, 826 controls were identified from among 4,336 interviews conducted in the KAP survey.

Not surprisingly, age was found to be a strong predictor of case status, with cases much more likely to be between six months and three years old than controls, and few cases greater than five years of age (Table 1). Various characteristics of the structure, environment and behavioral patterns of

TABLE 1
Bivariate analysis of categorical variables investigated as potential risk factors for severe malarial anemia in Kisumu, Kenya*

| Variable | No. (%) cases, n = 80 | No. (%) controls, n = 826 | Odds ratio (95% CI) | *P* |
|---|---|---|---|---|
| Household head is male | 70 (87.5) | 565 (68.4) | **3.2 (1.6–6.3)** | **0.0004** |
| Presence of wage earner other than caregiver | 41 (51.3) | 365 (44.2) | 1.3 (0.8–2.1) | 0.2253 |
| At least one self-reported household malaria case during previous month | 25 (31.3) | 340 (41.2) | 0.7 (0.4–1.1) | 0.0829 |
| Child's age | | | | < **0.0001** |
| < 6 months | 8 (10.0) | 86 (10.4) | 1.0 (0.5–2.1) | 0.9082 |
| 6 months–3 years | 61 (76.3) | 338 (40.9) | **4.6 (2.7–7.9)** | < **0.0001** |
| 3–5 years | 8 (10.0) | 212 (25.7) | **0.3 (0.2–0.7)** | **0.0018** |
| > 5 years | 3 (3.8) | 190 (23.0) | **0.1 (0.0–0.4)** | < **0.0001** |
| Child regularly spends ≥ 1 night/month in rural area | 28 (35.0) | 34 (4.1) | **12.5 (7.1–22.2)** | < **0.0001** |
| Child slept under a bed net during previous week | 41 (51.3) | 374 (45.3) | 1.3 (0.8–2.0) | 0.3152 |
| Child shares a sleeping room | 79 (98.8) | 800 (96.9) | NA | NA |
| Child was born in a rural area | 11 (13.8) | 86 (10.4) | 1.4 (0.7–2.7) | 0.3586 |
| Prior household residence was rural | 32 (40.0) | 128 (15.5) | **3.7 (2.3–6.1)** | < **0.0001** |
| Ownership of current residence | 21 (26.3) | 207 (25.1) | 1.1 (0.6–1.8) | 0.8434 |
| Ownership of land other than residence | 62 (77.5) | 406 (49.2) | **3.5 (2.1–6.1)** | < **0.0001** |
| Ownership of rural land | 49 (61.3) | 267 (32.3) | **3.3 (2.1–5.3)** | < **0.0001** |
| Bed net ownership | 45 (56.3) | 431 (52.2) | 1.2 (0.7–1.9) | 0.4863 |
| ITN ownership | 20 (25.0) | 220 (26.6) | 0.9 (0.5–1.6) | 0.7518 |
| Use mosquito coils for malaria prevention | 42 (52.5) | 555 (67.2) | **0.5 (0.3–0.9)** | **0.0074** |
| House has open eaves or poorly covered windows | 58 (72.5) | 539 (65.2) | **2.0 (1.1–3.6)** | **0.0164** |
| House wall materials (stone or brick) | 28 (35.0) | 314 (38.0) | 1.0 (0.6–1.7) | 0.954 |
| House floor not earthen | 61 (76.3) | 665 (80.5) | 1.2 (0.7–2.3) | 0.5259 |
| Presence of windows | 70 (87.5) | 800 (96.9) | 0.8 (0.2–2.6) | 0.7244 |
| Standing or running water within 10 meters | 32 (40.0) | 149 (18.0) | **3.9 (2.4–6.5)** | < **0.0001** |
| Primary source of washing water is natural | 16 (20.0) | 63 (7.6) | **3.0 (1.7–5.6)** | **0.0002** |
| Domestic animals kept overnight at residence | 22 (27.5) | 103 (12.5) | **2.7 (1.6–4.5)** | **0.0002** |
| Level of urbanization | | | | 0.3323 |
| Semi-rural | 30 (37.5) | 291 (35.2) | 1.1 (0.7–1.8) | 0.6852 |
| Peri-urban | 41 (51.3) | 388 (47.0) | 1.2 (0.7–1.9) | 0.4645 |
| Urban | 9 (11.3) | 147 (17.8) | 0.6 (0.3–1.2) | 0.1386 |

* CI = confidence interval; NA = not available; ITN = insecticide-treated bed net. Statistically significant values are shown in **bold**.

TABLE 2
Bivariate analysis of continuous variables investigated as potential risk factors for severe malarial anemia in Kisumu, Kenya*

| Variable | Cases mean (95% CI), n = 80 | Controls mean (95% CI), n = 826 | Odds ratio (95% CI) | *P* |
|---|---|---|---|---|
| No. persons in household | 5.09 (4.69–5.48) | 4.32 (4.21–4.43) | **1.3 (1.1–1.4)** | **0.0001** |
| Length of time in current residence, years | 5.78 (4.13–7.43) | 4.11 (3.74–4.49) | **1.2 (1.0–1.4) (5-year increase)** | **0.0165** |
| Wealth percentile | 45.9 (40.1–51.8) | 49.8 (47.8–51.8) | 1.0 (0.9–1.0) (10% increase) | 0.2492 |
| Proportion of household members sleeping under net during previous night | 0.78 (0.68–0.88) | 0.83 (0.81–0.86) | 0.5 (0.2–1.4) | 0.3161 |
| Number of nights/month child sleeps outside Kisumu | 0.8 (0.37–1.23) | 0.34 (0.18–0.50) | 1.1 (1.0–1.1) | 0.1113 |
| NDVI (within 25 meters of household) (scale = 0–200) | 124.9 (121.9–128.0) | 129.5 (128.5–130.4) | **0.8 (0.7–0.9) (increase of 10 units)** | **0.0068** |
| Distance to lakeshore, km | 2.01 (1.78–2.24) | 2.08 (2.02–2.14) | 0.9 (0.7–1.2) | 0.5176 |
| EA population density, 1,000/km$^2$ | 16 (12.2, 19.9) | 18.8 (17.3, 20.3) | 1.0 (0.9–1.0) (increase of 5,000/km$^2$) | 0.1914 |
| Distance to hospital, km | 2.84 (2.57, 3.12) | 2.58 (2.50, 2.66) | 1.2 (1.0–1.4) | 0.0526 |

* CI = confidence interval; NDVI = normalized difference vegetation index; EA = enumeration area. Statistically significant values are shown in **bold**.

the household were significantly related to malarial anemia in bivariate analysis (Tables 1 and 2). In addition to the seven variables selected *a priori* for multivariate analysis, eight others met the significance criteria for multiple testing, and were included as candidate variables in the forward-selected logistic model including sex of household head, land ownership other than residence, rural land ownership, prior residence in rural area, close proximity to standing/running water, washing with natural water sources, domestic animals present overnight, and household size.

Despite a relatively low number of events per variable (6.7), regression diagnostics indicated a good fit to the data, no significant problems with outliers or autocorrelation (variance inflation factors for predictor variables were uniformly low, ranging from 1.03 to 1.38), and moderate predictive ability (max-rescaled $r^2 \approx 45\%$). The resulting multivariate logistic model showed that age was a strong predictor of case status when adjusting for other factors (Table 3). Bed net ownership or use of mosquito coils were not statistically protective after multivariate adjustment. Relative to those living in an urban EA, children in semi-rural and peri-urban areas were more likely to be cases, though neither association was significant, nor was there significant increased risk from poor housing quality. Other variables found to be significant risk factors in the final model included ownership of land other than the residence (OR = 4.0, 95% confidence interval [CI] = 2.1–7.6, $P < 0.0001$), presence of standing or running water within 10 meters of the household (OR = 4.8, 95% CI = 2.5–9.3, $P < 0.0001$), presence of domestic animals overnight at the household (OR = 3.9, 95% CI = 1.8–8.1, $P = 0.0004$), and number of people in the household (OR = 1.4, 95% CI = 1.2–1.6, $P = 0.0002$). Most significantly, the odds of being a case were more than nine times greater (OR = 9.3, 95% CI = 4.4–19.7, $P < 0.0001$) for children who reported typically spending at least one night per month in a rural area.

TABLE 3
Multivariate logistic regression of potential risk factors for severe malarial anemia in Kisumu, Kenya*

| Variable | Adjusted odds ratio (95% CI) | *P* |
|---|---|---|
| Use mosquito coils for malaria prevention | 0.6 (0.3–1.1) | 0.0853 |
| Bed net ownership | 0.9 (0.5–1.7) | 0.8334 |
| House has open eaves or poorly covered windows | 1.8 (0.8–4.1) | 0.1297 |
| Child regularly spends ≥ 1 night/month in rural area | **9.3 (4.4–19.7)** | **< 0.0001** |
| Wealth percentile (increase of 10%) | **0.8 (0.7–0.9)** | **0.0004** |
| Household head is male | **3.6 (1.6–8.1)** | **0.0017** |
| Ownership of land other than household | **4.0 (2.1–7.6)** | **< 0.0001** |
| Standing or running water within 10 meters | **4.8 (2.5–9.3)** | **< 0.0001** |
| Domestic animals kept overnight at residence | **3.9 (1.8–8.1)** | **0.0004** |
| No. persons in household | **1.4 (1.2–1.6)** | **0.0002** |
| Level of urbanization | | |
| Semi-rural | 1.7 (0.7–4.6) | 0.2756 |
| Peri-urban | 2.0 (0.8–5.1) | 0.1415 |
| Urban | Reference | Reference |
| Child's age | | |
| < 6 months | **6.7 (1.5, 30.8)** | **0.0143** |
| 6 months–3 years | **18.9 (5.0, 70.9)** | **< 0.0001** |
| 3–5 years | 3.3 (0.8, 14.5) | 0.1100 |
| > 5 years | Reference | Reference |

* CI = confidence interval. Statistically significant values are shown in **bold**.

## DISCUSSION

This study characterized risk factors for malarial anemia in an urban setting surrounded by an area of high endemicity in western Kenya. The observed age range of cases was consistent with that observed for severe malaria outcomes in other highly endemic areas, as was the failure to observe any CM among admissions to KDH during the study period.[8] Although the latter may be caused by difficulty in diagnosing CM,[53,54] the age profile for cases of malarial anemia was more like that observed in rural settings than in typically lower-transmission urban contexts. We found that regular overnight travel to rural areas was a strong risk factor after adjusting for other factors in the multivariate analysis, which suggested that frequent exposure to infected mosquitoes during rural travel significantly increased risk among urban residents. Although prior residence in a rural area did not meet the Bonferroni criteria for inclusion in the multivariate model, it was a risk factor in bivariate analysis. This finding may further substantiate the idea that chronic rural exposure contributes to incidence of malarial anemia, such that children from high-exposure rural areas experience higher risk even after migrating to cities, although this was difficult to evaluate in our study. In bivariate analysis, we did not find an effect for increasing length of time spent in rural areas. However, this finding may reflect recall difficulty in accurately reporting duration of travel or monthly or seasonal variations in travel patterns.

The current data do not enable us to establish a causal link between exposure during rural travel and acute presentation with malarial anemia. Investigating such a link would have

required details of recent trips (often multiple trips per household) with respect to timing, location, and participation by individual household members, adding considerable complexity to the survey process for interviewers and respondents. However, there was a significant correlation between reporting typical travel to rural areas and spending at least one night outside Kisumu in the previous month. This link needs to be explored in more detail.

Two-thirds of cases occurred in households where the child did not typically travel to rural areas, indicating some level of intra-urban transmission. The magnitude of this is unclear for various reasons: for example, some children for whom regular travel was not reported might nevertheless have spent a recent night in a rural area. Further research is needed to clarify the roles of travel, rural exposure, chronic and acute infection, and intra-urban transmission in determining severe malaria risk in sub-Saharan African urban settings.

The effects of bed net ownership, mosquito coil use, and house construction were all in the expected direction, but not statistically significant. Bed nets or ITNs have been found not to reduce SMA in some contexts,[10,12,15] although it is generally accepted that they reduce *Plasmodium* infection and mortality. In urban Kisumu, increased risk of malarial anemia may have resulted if a significant fraction of exposure subsequently occurred during travel when nets were not being used. Mosquito coils were found to be preventive in bivariate analysis, but had a non-significant effect after multivariate adjustment. Good house construction, as characterized in this study, normally is considered to be another barrier to transmission, and was similarly related to malarial anemia in bivariate analysis, but non-significant in the multivariate model. As with nets, good house construction would not have prevented increased exposure during travel.

Household size was found to represent a risk factor in the final model. However, this result is potentially an artifact of the different sampling schemes for cases and controls. To the extent that household size is associated with other risk factors, this finding could bias results in either direction. Although we were unable to include interaction terms in the final model, the inclusion of household size should have controlled for this effect. Moreover, we did not observe inordinately high correlations between household size and other variables in the data.

The overall effect of level of urbanization on malarial anemia risk was non-significant, although some individual variables comprising this index (e.g., distance to the hospital, population density, source of water, and NDVI) were significantly associated with disease in bivariate analysis. These relationships were in the directions expected, except that higher NDVI, indicating more nearby vegetation, was associated with lower risk for malarial anemia. This unexpected relationship may possibly have resulted from the low NDVIs that are found in peri-urban zones (where residents are most likely to travel to rural areas), or from higher socioeconomic levels that enable greater access to malaria prevention in highly urban zones where houses have gardens. The unexpected association with NDVI may explain why the urbanization index was not a significant predictor. Inclusion of interaction terms in a larger dataset would help clarify these relationships.

The limited sample size reduced the statistical power of this study to identify some risk factors. Nonetheless, the strict requirements for inclusion in the final model, the consistent direction and magnitude of observed relationships in comparison with bivariate results, and the robustness of the model to deletion of outliers and exclusion of specific variables indicate that it represents a solid and conservative compromise. A larger study over a longer period of time is needed to further explore the multifactorial nature of risk for severe malaria outcomes. We failed to recruit ≈40% of cases meeting our case definition at KDH, but differences between identified and missed cases were minimal and should not have biased the analysis. Captured cases were generally sicker than those that were missed, indicating that our results may only be applicable to more severe cases. The reasons why cases were missed are not clear. However, missed cases tended to cluster near the beginning and end of the study period and during times when caseload was high, indicating that failure to capture may have resulted from some combination of an inability to handle the caseload with interviewer inexperience or fatigue. We were also unable to evaluate the effects of caregiver characteristics because of the different methods for recruitment of cases and controls.

These results imply that different prevention and control strategies may be necessary for the large and growing group of urban residents, many of whom frequently travel to rural areas. Traditional prevention strategies may be ineffective for urban families who use bed nets at home but fail to do so when traveling. In particular, travel histories and their impact on severe malaria need to be more carefully described in sub-Saharan Africa because studies have so far been limited on this count. At the same time, the presentation of these cases within urban areas and the limited timeframe within which some may experience exposure (i.e., during travel to rural areas) present opportunities for effective and efficient prevention that are often unavailable in remote areas where access to health facilities is limited and exposure is protracted. A better understanding of the link between travel and severe malaria could have direct practical benefits for public heath by helping to direct the allocation of resources among and within cities, effectively targeting and focusing education and intervention programs, and producing clear and informed policies for urban public health. Likewise, a clearer picture is needed of risk factors for severe malaria for those urban residents who do not travel. A major component of this research should focus on describing the urban environment and delineating the specific elements of urbanization that may increase risk. Such efforts should produce a better understanding of urban malaria risk factors, thus enabling effective targeting of control strategies to those at greatest risk of severe malaria.

Received January 25, 2009. Accepted for publication October 25, 2009.

Acknowledgments: We are indebted to the parents and caregivers who agreed to participate in this project and to Kisumu government officials who provided permission and support for the research. The Kenya Central Bureau of Statistics and Maurice Ombok provided census data and maps. Amos Odhacha and Frank Odhiambo contributed to the implementation of focus group discussions and coordination with local officials. The KDH staff and CDC/KEMRI workers at KDH were instrumental in identifying and recruiting cases. The CDC/KEMRI staff at the Kisian field station facilitated the day-to-day functioning of the project. We also thank CDC/KEMRI interviewers, including Betty Odidi, Dinah Wambua, Lillian Omollo, Modrine Alumasa, Paul Oluru, Dominic M'Njeru, Rose Ouma, and Tereza Achieng for their participation in the study.

Financial support: This research was supported by CDC/KEMRI and by the University of Michigan through the Rackham Graduate

School, the Center for Research on Ethnicity, Culture and Health, and the Global Health Program.

Disclaimer: This manuscript was published with the approval of the Director of the Kenya Medical Research Institute. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Authors' addresses: Jose G. Siri, Health and Global Change Project, International Institute for Systems Analysis, Laxenburg, Austria. Mark L. Wilson, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI. Susan Murray, Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI. Daniel H. Rosen and Laurence Slutsker, Division of Parasitic Diseases, National Center for Zoonotic, Vector-Borne and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, GA. John M. Vulule, Centre for Vector Biology and Control Research, Kenya Medical Research Institute, Kisumu, Kenya. Kim A. Lindblade, Centers for Diseases Control and Prevention Regional Office for Central America and Panama, Unit 3190, DPO AA.

## REFERENCES

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI, 2005. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature 434:* 214–217.
2. Murphy SC, Breman JG, 2001. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. *Am J Trop Med Hyg 64:* 57–67.
3. Maitland K, Marsh K, 2004. Pathophysiology of severe malaria in children. *Acta Trop 90:* 131–140.
4. Clark IA, Cowden WB, 2003. The pathophysiology of falciparum malaria. *Pharmacol Ther 99:* 221–260.
5. Mackintosh CL, Beeson JG, Marsh K, 2004. Clinical features and pathogenesis of severe malaria. *Trends Parasitol 20:* 597–603.
6. Marsh K, Snow RW, 1999. Malaria transmission and morbidity. *Parassitologia 41:* 241–246.
7. Greenwood BM, 1997. The epidemiology of malaria. *Ann Trop Med Parasitol 91:* 763–769.
8. Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, Olomi R, Cox J, Nkya WM, Lemnge M, Greenwood BM, Riley EM, 2005. Association of transmission intensity and age with clinical manifestations and case fatality of severe *Plasmodium falciparum* malaria. *JAMA 293:* 1461–1470.
9. Snow RW, Omumbo JA, Lowe B, Molyneux CS, Obiero JO, Palmer A, Weber MW, Pinder M, Nahlen B, Obonyo C, Newbold C, Gupta S, Marsh K, 1997. Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa. *Lancet 349:* 1650–1654.
10. Koram KA, Bennett S, Adiamah JH, Greenwood BM, 1995. Socioeconomic determinants are not major risk factors for severe malaria in Gambian children. *Trans R Soc Trop Med Hyg 89:* 151–154.
11. Mbogo CN, Kabiru EW, Glass GE, Forster D, Snow RW, Khamala CP, Ouma JH, Githure JI, Marsh K, Beier JC, 1999. Vector-related case-control study of severe malaria in Kilifi District, Kenya. *Am J Trop Med Hyg 60:* 781–785.
12. Snow RW, Peshu N, Forster D, Bomu G, Mitsanze E, Ngumbao E, Chisengwa R, Schellenberg JR, Hayes RJ, Newbold CI, Marsh K, 1998. Environmental and entomological risk factors for the development of clinical malaria among children on the Kenyan coast. *Trans R Soc Trop Med Hyg 92:* 381–385.
13. Ong'echa JM, Keller CC, Were T, Ouma C, Otieno RO, Landis-Lewis Z, Ochiel D, Slingluff JL, Mogere S, Ogonji GA, Orago AS, Vulule JM, Kaplan SS, Day RD, Perkins DJ, 2006. Parasitemia, anemia, and malarial anemia in infants and young children in a rural holoendemic *Plasmodium falciparum* transmission area. *Am J Trop Med Hyg 74:* 376–385.
14. Luckner D, Lell B, Greve B, Lehman LG, Schmidt-Ott RJ, Matousek P, Herbich K, Schmid D, Mba R, Kremsner PG, 1998. No influence of socioeconomic factors on severe malarial anaemia, hyperparasitaemia or reinfection. *Trans R Soc Trop Med Hyg 92:* 478–481.
15. Carme B, Plassart H, Senga P, Nzingoula S, 1994. Cerebral malaria in African children: socioeconomic risk factors in Brazzaville, Congo. *Am J Trop Med Hyg 50:* 131–136.
16. Kahigwa E, Schellenberg D, Sanz S, Aponte JJ, Wigayi J, Mshinda H, Alonso P, Menendez C, 2002. Risk factors for presentation to hospital with severe anaemia in Tanzanian children: a case-control study. *Trop Med Int Health 7:* 823–830.
17. D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK, Thomson MC, Cham MK, Cham BA, Greenwood BM, 1995. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet 345:* 479–483.
18. Nevill CG, Some ES, Mung'ala VO, Mutemi W, New L, Marsh K, Lengeler C, Snow RW, 1996. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Trop Med Int Health 1:* 139–146.
19. Holtz TH, Marum LH, Mkandala C, Chizani N, Roberts JM, Macheso A, Parise ME, Kachur SP, 2002. Insecticide-treated bednet use, anaemia, and malaria parasitaemia in Blantyre District, Malawi. *Trop Med Int Health 7:* 220–230.
20. ter Kuile FO, Terlouw DJ, Kariuki SK, Phillips-Howard PA, Mirel LB, Hawley WA, Friedman JF, Shi YP, Kolczak MS, Lal AA, Vulule JM, Nahlen BL, 2003. Impact of permethrin-treated bed nets on malaria, anemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. *Am J Trop Med Hyg 68:* 68–77.
21. Mathanga DP, Campbell CH, Taylor TE, Barlow R, Wilson ML, 2005. Reduction of childhood malaria by social marketing of insecticide-treated nets: a case-control study of effectiveness in Malawi. *Am J Trop Med Hyg 73:* 622–625.
22. UNFPA, 2008. *World Urbanization Prospects: The 2007 Revision*. United Nations Population Division. Available at: http://esa.un.org/unup/.
23. Trape JF, Lefebvre-Zante E, Legros F, Ndiaye G, Bouganali H, Druilhe P, Salem G, 1992. Vector density gradients and the epidemiology of urban malaria in Dakar, Senegal. *Am J Trop Med Hyg 47:* 181–189.
24. Afolabi BM, Salako LA, Mafe AG, Ovwigho UB, Rabiu KA, Sanyaolu NO, Ibrahim MM, 2001. Malaria in the first 6 months of life in urban African infants with anemia. *Am J Trop Med Hyg 65:* 822–827.
25. Modiano D, Sirima BS, Sawadogo A, Sanou I, Pare J, Konate A, Pagnoni F, 1998. Severe malaria in Burkina Faso: influence of age and transmission level on clinical presentation. *Am J Trop Med Hyg 59:* 539–542.
26. Trape JF, 1997. Which strategy for malaria control in Africa? *Parasitol Today 13:* 125–126.
27. Gay-Andrieu F, Adehossi E, Lacroix V, Gagara M, Ibrahim ML, Kourna H, Boureima H, 2005. Epidemiological, clinical and biological features of malaria among children in Niamey, Niger. *Malar J 4:* 10.
28. Klinkenberg E, McCall PJ, Wilson MD, Akoto AO, Amerasinghe FP, Bates I, Verhoeff FH, Barnish G, Donnelly MJ, 2006. Urban malaria and anaemia in children: a cross-sectional survey in two cities of Ghana. *Trop Med Int Health 11:* 578–588.
29. Nieto T, Mendez F, Carrasquilla G, 1999. Knowledge, beliefs and practices relevant for malaria control in an endemic urban area of the Colombian Pacific. *Soc Sci Med 49:* 601–609.
30. Snow RW, Peshu N, Forster D, Mwenesi H, Marsh K, 1992. The role of shops in the treatment and prevention of childhood malaria on the coast of Kenya. *Trans R Soc Trop Med Hyg 86:* 237–239.
31. Molyneux CS, Mung'ala-Odera V, Harpham T, Snow RW, 1999. Maternal responses to childhood fevers: a comparison of rural and urban residents in coastal Kenya. *Trop Med Int Health 4:* 836–845.
32. Olano V, Carrasquilla G, Mendez F, 1997. Transmission of urban malaria in Buenaventrua, Colombia: entomological features [in Spanish]. *Rev Panam Salud Publica 1:* 287–294.
33. El Sayed BB, Arnot DE, Mukhtar MM, Baraka OZ, Dafalla AA, Elnaiem DE, Nugud AH, 2000. A study of the urban malaria transmission problem in Khartoum. *Acta Trop 75:* 163–171.
34. Thompson R, Begtrup K, Cuamba N, Dgedge M, Mendis C, Gamage-Mendis A, Enosse SM, Barreto J, Sinden RE, Hogh B, 1997. The Matola malaria project: a temporal and spatial study

of malaria transmission and disease in a suburban area of Maputo, Mozambique. *Am J Trop Med Hyg 57:* 550–559.
35. Ronald LA, Kenny SL, Klinkenberg E, Akoto AO, Boakye I, Barnish G, Donnelly MJ, 2006. Malaria and anaemia among children in two communities of Kumasi, Ghana: a cross-sectional survey. *Malar J 5:* 105.
36. Central Bureau of Statistics, Ministry of Finance and Planning, 2000. *1999 Population and Housing Census*, *Volume I*. Nairobi: Kenya.
37. Githeko AK, Service MW, Mbogo CM, Atieli FK, Juma FO, 1993. *Plasmodium falciparum* sporozoite and entomological inoculation rates at the Ahero rice irrigation scheme and the Miwani sugar-belt in western Kenya. *Ann Trop Med Parasitol 87:* 379–391.
38. Beier JC, Perkins PV, Onyango FK, Gargan TP, Oster CN, Whitmire RE, Koech DK, Roberts CR, 1990. Characterization of malaria transmission by *Anopheles* (Diptera: Culicidae) in western Kenya in preparation for malaria vaccine trials. *J Med Entomol 27:* 570–577.
39. Siri JG, Lindblade KA, Rosen DH, Onyango B, Vulule J, Slutsker L, Wilson ML, 2008. Quantitative urban classification for malaria epidemiology in sub-Saharan Africa. *Malar J 7:* 34.
40. Siri JG, Lindblade KA, Rosen DH, Onyango B, Vulule JM, Slutsker L, Wilson ML, 2008. A census-weighted, spatially-stratified household sampling strategy for urban malaria epidemiology. *Malar J 7:* 39.
41. Alonso PL, Smith T, Schellenberg JR, Masanja H, Mwankusye S, Urassa H, Bastos de Azevedo I, Chongela J, Kobero S, Menendez C, 1994. Randomised trial of efficacy of SPf66 vaccine against *Plasmodium falciparum* malaria in children in southern Tanzania. *Lancet 344:* 1175–1181.
42. Filmer D, Pritchett LH, 2001. Estimating wealth effects without expenditure data–or tears: an application to educational enrollments in states of India. *Demography 38:* 115–132.
43. Eisele TP, Keating J, Swalm C, Mbogo CM, Githeko AK, Regens JL, Githure JI, Andrews L, Beier JC, 2003. Linking field-based ecological data with remotely sensed data using a geographic information system in two malaria endemic urban areas of Kenya. *Malar J 2:* 44.
44. Pearson K, 1900. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *Philosophical Magazine Series 5:* 157–175.
45. Fisher RA, 1935. The logic of inductive inference. *J R Stat Soc Series A 98:* 39–54.
46. Gosset WS, 1908. The probable error of a mean. *Biometrika 6:* 1–25.
47. Wilcoxon F, 1945. Individual comparisons by ranking methods. *Biometrics 1:* 80–83.
48. Aldrich JH, Nelson FD, *Linear Probability, Logit and Probit Models*. Newbury Park, CA: Sage Publications; 1984.
49. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR, 1996. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol 49:* 1373–1379.
50. Velleman P, Welsch R, 1981. Efficient computing of regression diagnostics. *Am Stat 35:* 234–242.
51. Schafer JL, 1999. Multiple imputation: a primer. *Stat Methods Med Res 8:* 3–15.
52. Hosmer DW, Lemeshow S, 1980. A goodness-of-fit test for the multiple logistic regression model. *Communications in Statistics A-10:* 1043–1069.
53. Makani J, Matuja W, Liyombo E, Snow RW, Marsh K, Warrell DA, 2003. Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description. *QJM 96:* 355–362.
54. Newton CR, Pasvol G, Winstanley PA, Warrell DA, 1990. Cerebral malaria: what is unarousable coma? *Lancet 335:* 472.