ENVIRONMENTAL AND SOCIO-DEMOGRAPHIC DETERMINANTS OF SEVERE
MALARIA RISK IN URBAN KISUMU, KENYA

by

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To Mom and Papi,
with love and gratitude...

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I come to the end of these credits having taken longer than expected, as has usually been the case. In the words of the late Douglas Adams: "I love deadlines—I like the whooshing sound they make as they fly by." Though I've done my best to credit everyone who helped me, I must emphasize that all mistakes contained in this document are my own. I find, though, that I cannot end quite yet, as I have left the most important acknowledgement for last:

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CHAPTER 1:

INTRODUCTION

Overview

Malaria continues to cause death and disability on a massive scale worldwide, all

efforts to the contrary notwithstanding. Nowhere is the problem more pressing than in

sub-Saharan Africa (SSA), site of the vast majority of malaria cases and casualties. A

century's struggles to understand and combat this scourge have nonetheless left gaps in

our knowledge of the basic epidemiology of malaria, especially with regard to its most

serious manifestations. At the same time, we are faced with an unprecedented

demographic shift as the African population rapidly urbanizes. This dissertation attempts

to address some of the limitations of the current state of knowledge about the

epidemiology of severe malaria in cities of SSA, and to produce knowledge that will

contribute to decision-making for urban planning, delivery of health services, targeted

risk reduction programs and the design of sound environmental management policies, all

urgent priorities in sub-Saharan Africa.

Impact of Malaria

Over a century after Ronald Ross elucidated the *Plasmodium* life cycle, and more

than 50 years after the World Health Assembly's call for the eradication of malaria

worldwide, the global malaria situation remains grim and is worsening. Despite ongoing

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efforts by the international research community and national health programs, malaria remains the world's most important vector-borne disease and one of the leading infectious causes of morbidity and mortality (World Health Organization 2004). Malaria is present in over 100 countries worldwide (Wernsdorfer and Wernsdorfer 1988), with 50% of the world's population at risk—an increase of 10% in the past decade (Hay et al. 2004; Breman, Alilio, and Mills 2004). The situation is particularly pressing in Africa, where estimates of disease burden recognize 1 million deaths and 365 million acute clinical cases each year, the vast majority in SSA among children under five (Snow et al. 1999; Snow et al. 2005). In this region, malaria is responsible for at least 20% of deaths in children under five, 25% of outpatient clinic visits, and 20–50% of hospital admissions (World Health Organization/UNICEF 2003).

Malaria imposes a staggering economic burden for health systems already stretched to their limits by HIV and the many other health concerns faced by the developing world. An estimated U.S.$1.8 billion is spent annually on direct and indirect costs related to malaria, which is responsible for up to 15% of disability-adjusted life years (DALYs) lost in SSA (Foster and Phillips 1998). There is a well-documented and powerful relationship between malaria endemicity and economic performance: average annual growth in per capita GDP is significantly lower in malaria-endemic countries, and it has been estimated that the long-term effect of malaria endemicity is a halving of GNP per capita in malarious countries compared to non-malarious ones (Gallup and Sachs 2001). Malaria endemicity involves debilitating macroeconomic costs, including reduced tourism and direct foreign investment, that are unquantifiable at the level of the

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individual household (Sachs and Malaney 2002). Yet it is the households of the poor that bear the brunt of the malaria problem: 58% of cases occur in the poorest 20% of the world's population (Barat et al. 2004), which may spend as much as 25% of annual income on prevention and treatment (World Health Organization 2000). Malaria engenders social costs as well, including, but not limited to, higher fertility in response to expected childhood mortality and concomitantly lower investment in the education of women, lower household savings, missed schooling and cognitive deficits resulting from the sequelae of severe malaria episodes (Sachs and Malaney 2002).

Burden of Urban Malaria

The increasing mobility of the global population, the growth of urban slums and the continued emergence of treatment-resistant parasite strains and insecticide-resistant vector populations are all potential harbingers of graver problems to come. One setting of particular and growing importance is the urban environment. Africa is currently experiencing the fastest rates of urbanization in the world. As of 1999, 38% of the population lived in urban environments, and the urban African population is projected to grow at 4.4% a year through 2030 (UNFPA 1999), nearly double the world average. Growth in smaller urban areas (i.e., less than one million inhabitants) is projected to account for over 45% of this total. As this population grows, exceeding 50% of the entire African populace by 2015, so will the importance of urban malaria, i.e., malaria arising or presenting in the urban environment. The epidemiology of malaria in this environment is likely to differ substantially from that in the rural areas where malaria has traditionally been studied.

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There is little doubt that malaria is occurring in African cities. In highly endemic areas like Kisumu in western Kenya, malaria represents the primary diagnosis in urban hospitals and the leading cause of death (Kisumu District Ministry of Health 2001). Clinical malaria has been observed in a wide range of urban environments across Africa. Nonetheless, estimates of the current disease burden in urban areas of SSA and of the relative importance of urban—as opposed to rural—malaria, are controversial. This is due in part to the lack of a consistent definition of "urban," forthcoming neither from national governments nor from the international community. In fact, individual countries define urban in a variety of ways, whether through the use of population density thresholds, agglomeration sizes, functional characteristics or administrative boundaries or by *fiat*, so to speak (see, e.g., (Hay et al. 2005). International organizations like the World Health Organization (WHO) accept these definitions at face value, as do the large international health surveys (e.g., Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS)).

The malaria research community has failed to produce a more applicable and consistent classification, almost certainly resulting in inaccurate estimates of the overall burden, and potentially in significant misclassification. By way of illustration, three of the most recent and comprehensive reviews on urban malaria approach the definition of urban in markedly different ways. The first (Robert et al. 2003) assigns central urban,

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peri-urban[1] and rural status according to descriptions of the study area environment in the

literature reviewed, with little discussion of variations in the defining criteria among

studies. The second (Keiser et al. 2004) uses night-time lights (NTL) as measured from

satellite imagery as a proxy for urban environments, while suggesting that these may

consistently *under*estimate urban areas in Africa, since many such areas have no power

grid. The third (Hay et al. 2005), which suggests that NTL consistently *over*estimate

urban areas in Africa as a result of the "bleeding" of light into adjacent rural areas, uses a

population density cutoff of 1,000 people/km^2 for urban and 250 people/km^2 for peri-

urban. A fuller discussion of the merits of various definitions in capturing the important

differences between urban ecological zones in terms of malaria is needed.

With due consideration for definitional difficulties, a major attempt to quantify

the burden of malaria in urban SSA estimates an annual incidence of 24.8–103.2 million

cases of clinical malaria attacks, representing 6 to 28% of the annual global disease

incidence (Keiser et al. 2004). A second review gives a lower estimate of 20.4–49.3

million cases, representing 17.6% of the cases for middle Africa, while again noting

difficulties in defining "urbanicity" (Carneiro, Roca-Feltrer, and Schellenberg 2005).

There is no reason to suppose these figures will not grow in tandem with the urban

African population.

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[1] The term peri-urban is, if anything, more vague than urban. It is used to describe both areas on the
periphery of the urban zone, whether immediately adjacent or at a distance of several kilometers, and areas
with environmental, demographic or economic characteristics intermediate between urban and rural zones.

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Urban Malaria Transmission

A growing body of literature has attempted to characterize transmission of malaria in the urban environment. Virtually all studies in malaria-endemic urban areas have observed local transmission, even in central districts of cities, where transmission levels can be highly heterogeneous (Robert et al. 2003). Despite this, transmission is absolutely and relatively lower in urban areas, for a variety of reasons (Trape and Zoulani 1987). A recent review summarizes the factors involved (Robert et al. 2003). Among these are human ecological and environmental factors including a) land use, b) demography, c) municipal initiatives, and d) individual and household factors, all moderated and modified by climatic and topographical variation. The complex confluence of these features determines vector-human contact and thus, malaria transmission.

Land Use

In general, urban land use has been shown to decrease malaria transmission. Increased concrete, asphalt and other "impervious surfaces" replace vegetation, decreasing the availability of breeding and resting sites for mosquitoes (Robert et al. 2003). At the same time, canalization of streams and surface water produces networks of ditches and gutters that are often highly polluted and unsuitable for anopheline mosquito breeding (Trape and Zoulani 1987). Though adaptation to urban breeding sites has been observed for anophelines in Southeast Asia (particularly *An. stephensi* in India), evidence for this phenomenon in SSA is limited thus far (Khaemba, Mutani, and Bett 1994; Chinery 1990; Jacob et al. 2003).

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The generally lower transmission of malaria in urban areas is in some cases mitigated by environmental and geographic factors. In cities where favorable conditions for mosquitoes exist in close proximity to population clusters, transmission or vector density gradients have been observed, increasing, for example, with proximity to a permanent marsh in Dakar, Senegal (Trape et al. 1992), or in the vicinity of irrigated urban agriculture in Kumasi, Ghana (Afrane et al. 2004). In Kisumu, Kenya, poorly drained areas were associated with anophelines (Keating et al. 2003; Jacob et al. 2003). The factors that tend to decrease transmission in cities, such as high population density, a high proportion of impervious surfaces, pollution and decreased vegetation, are most prevalent in large, well-established cities, whereas smaller, newly-urbanized cities will make up the bulk of the population growth in Africa (UNFPA 1999). This makes it significant, for example, that a study in Brazzaville demonstrated that newly-urbanized areas were more likely to feature high transmission than older city regions (Trape and Zoulani 1987), and in Kisumu, sites changing from nonurban to urban land cover were associated with a higher prevalence of anopheline breeding habitats (Jacob et al. 2003). The deteriorating urban structures so common in large African cities may also promote mosquito breeding. The balance of evidence indicates that focal breeding of mosquitoes will continue in urban SSA as the population continues to concentrate there.

Demography

Human population distribution patterns have been shown to affect the profile of urban malaria transmission. In particular, high population densities associated with cities are theorized to have two important effects. First, the higher ratio of humans to

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mosquitoes tends to dilute the exposure of individuals to potentially infective bites (Trape et al. 1992). Second, the ready availability of human blood meals in cities limits dispersion such that transmission tends to be highly focal (Trape and Zoulani 1987; Sabatinelli, Rossi, and Belli 1986), an observation that may explain the commonly observed heterogeneities in transmission between different districts of the same city.

Urban malaria transmission is affected not only by population distribution but also by population mobility patterns: In Quibdo, Colombia, travel to an endemic area 8–14 days before disease onset was the strongest risk factor for malaria incidence (Osorio, Todd, and Bradley 2004). In the Gambia, travel to rural areas was associated with malaria (Koram et al. 1995b). In Zambia, journeys outside towns were associated with malaria antibodies (Watts et al. 1990). Thus, the presence of urban transmission does not preclude an external origin for many cases: the proportion of malaria cases that originate in urban areas is an unresolved question. This is especially true given the highly mobile nature of new immigrants to urban areas. It is possible that recent immigrant dwellers on the fringes of urban areas act as a continuing source of reinfection for the peri-urban environments that are most likely to present mosquito breeding sites. Further research is needed to quantify the proportion of urban malaria cases that are locally acquired.

Municipal Initiatives

Both concerted control interventions and ordinary municipal maintenance activities can affect transmission. For example, environmental modification was a signal strategy in the elimination of malaria from much of the developed world (Kitron 1987;

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Konradsen et al. 2004). Maintenance of water supplies and waste management can affect the availability of breeding sites, and directed vector control will clearly impact transmission. Zoning can also shape transmission, for example, in central business districts where very few people are around at peak biting hours (Robert et al. 2003).

Individual and Household Factors

While environmental and general demographic factors tend to shape the distribution of transmission within an urban area, individual and household factors are likely to play a greater role in determining individual risk. At the most basic level, socioeconomic status (SES) affects exposure to vectors through a variety of mechanisms. The poor have less access to health care, less resources for preventive and curative activities, and less knowledge about how to avoid and care for disease. They live in areas with inferior sanitation and housing, more crowding, and a greater degree of environmental degradation and pollution. They have poorer nutrition, are more likely to work in hazardous environments, are more likely to harbor preexisting infections, and, in tropical settings, are more at risk for contact with mosquitoes and other disease vectors.

Several studies have identified low SES as a direct or indirect predictor of malaria infection risk. To begin with, 58% of malaria cases occur in the poorest 20% of the world's population (Barat et al. 2004). Socioeconomic status itself, or proxies thereof, has been identified as a predictor of malaria infection in surprisingly few studies in SSA, though there is evidence of this relationship from Asia and South America. In the Gambia, ownership of certain consumer goods was protective for children in the

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household (Koram et al. 1995b), as was knowledge of malaria on the part of the mother (though education of the mother or guardian was not predictive) and features associated with a smaller house. Knowledge was also protective in an urban area of Colombia (Mendez, Carrasquilla, and Munoz 2000). Higher education was indicative of more positive malaria knowledge, attitudes and practices in an urban area in Uganda (Njama et al. 2003).

More commonly, SES is related to malaria transmission through other mechanisms that affect exposure to mosquitoes. For example, a variety of studies have implicated poor housing in malaria transmission in rural areas, identifying specific risk factors, such as the presence of eaves in the Gambia (Lindsay and Snow 1988) and eaves or windows in the Ethiopian highlands (Ghebreyesus et al. 2000). Poor housing and overcrowding were associated with malaria infection in an urban area in the Gambia, as well (Koram et al. 1995b). Low SES has also been related to lower likelihood of purchasing an insecticide-treated bed net (ITN) or pursuing other preventive activities in Kisumu, Kenya (Macintyre et al. 2002). Though evidence exists of a multifactorial relationship between SES and malaria transmission, comprehensive studies of this dynamic in SSA are lacking.

Independently of SES, there is extensive literature on the effects of ITNs on malaria transmission. Bed nets are one of the cornerstones of the current public health effort to combat malaria, and a stated goal of Roll Back Malaria is to increase the proportion of bed net ownership (and usage) among children under five to 60% in SSA.

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ITNs have proven efficacious at interrupting transmission (Gimnig et al. 2003) and

reducing morbidity and mortality (Phillips-Howard et al. 2003) in randomized trials in

Western Kenya. They have also proven effective in a wide variety of real settings,

including some urban environments. In Kisumu, a recent study evaluated the

determinants of bed net usage and other mosquito-avoidance behavior, concluding that

SES was the most important predictor of usage, and that low-SES households tended to

use more expensive, less effective methods (Macintyre et al. 2002). Bed net usage and

use of other preventive methods are very likely to affect patterns of urban malaria

transmission.

Severe Malaria in the Urban Environment

Of the 270 million acute clinical cases of malaria a year, only a small fraction

progress to severe illness and potentially death. Nevertheless, the possible deleterious

outcomes of infection are varied and harsh, with case-fatality rates for the recognized

syndromes of severe malaria hovering around 20% without treatment (Murphy and

Breman 2001) and approaching 50% in some situations (Warrell 1997)[2]. The causal

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[2] The severe consequences of malaria infection can be grouped into a few relatively distinguishable clinical patterns: in particular, cerebral malaria (CM) and severe malarial anemia (SMA) have traditionally been considered the main manifestations of severe malaria. Recently, the additional relevance of respiratory distress (RD), with or without anemia, to the severity of the prognosis has been emphasized (Marsh et al. 1996; English et al. 1996). These entities are not always mutually exclusive, and patients with combined presentations tend to suffer more serious consequences. As a group, they represent the most important complications resulting from infection. A recent study estimated an annual incidence of over half a million cases of CM, 1.42-5.66 million cases of SMA, and 1.12-1.99 million cases of RD, hypoglycemia and related clinical symptoms (Murphy and Breman 2001). The traditional view of malaria pathogenesis has been that CM and SMA represented two well-defined endpoints with simple underlying pathogenic processes (Mackintosh, Beeson, and Marsh 2004; Maitland and Marsh 2004). However, research over the past decade beginning with the affirmation of RD as an important indicator has begun to uncover a more complicated picture, in which multiple pathways produce symptomatically similar syndromes (Clark and Cowden 2003). Severe malaria pathology has come to be seen as a multiple-organ systemic pathology, with metabolic acidosis and concomitant respiratory distress as an important feature (Maitland and Marsh 2004). This finding complicates the search for key mechanisms and risk factors for specific severe malaria

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mechanisms whereby certain individuals get very sick, while much of the population maintains near-constant levels of parasitization with few or no symptoms, are not fully elucidated. If one is interested in examining risk for severe outcomes in the urban environment, another layer of determinants is required to explain the risk of progression to serious outcomes of malaria, including treatment-seeking behavior, other individual and household factors, and specific host and parasite factors.

Treatment-seeking Behavior

Several aspects of treatment-seeking behavior have been implicated as risk factors for severe malaria in the urban environment. In particular, the ability of caretakers to recognize malaria, the propensity to self-treat malaria infection and other sickness, the likelihood of delay before attending a hospital or clinic, and the likelihood that prompt, appropriate treatment are provided to cases have all been investigated for their role in the development of severe disease.

In urban areas of SSA, over 60% of potential malaria cases are self-treated (Brinkmann and Brinkmann 1991). In this context, the ability to recognize malaria and to identify and administer appropriate treatment has important implications for both morbidity and the development of antimalarial resistance. Self-treatment thus constitutes an important pathway in malaria control (Foster 1995). A variety of studies have evaluated the appropriateness, complexity and timeliness of caretakers' responses to child illness. For example: in urban Nigeria, caretakers were found to give treatment

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outcomes. Nonetheless, broad distinctions are apparent in the occurrence and distribution of these syndromes, and a better understanding of the factors contributing to these differences should concurrently advance efforts to elucidate disease mechanisms.

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responsive to their child's specific complaints (Afolabi, Brieger, and Salako 2004). In Ghana, caretaker identification of fever and malaria were found to be fairly sensitive and comparable to diagnosis at a health center (Dunyo et al. 2000). In Bissau, blood levels of chloroquine indicated compliance of caretakers with prescribed regimens over a 6-week period (Kofoed et al. 2003).

Not all is encouraging: a review estimated that underdosing is extremely common, with delays in treatment averaging 3 or more days (McCombie 1996). A study in Blantyre district in Malawi estimated that only slightly more than a third of febrile children received an antimalarial at all (Holtz et al. 2003). In a training intervention for shopkeepers in rural coastal Kenya, sales of drugs to children with fever included an antimalarial in only about one-third of cases, though this proportion rose dramatically with training (Marsh et al. 1999). Moreover, in some situations diagnosis and treatment can be difficult even for trained health workers: in Ibadan, Nigeria, just two-thirds of children diagnosed with malaria had the parasite, and only 56% appropriately prescribed chloroquine for treatment (Fawole and Onadeko 2001).

There is a wide body of literature on treatment seeking, but few definitive answers (McCombie 2002), especially in the urban context. It is clear that urban populations have greater access to health services and facilities, but unclear whether they appropriately utilize these options in the face of severe malaria illness. The provision of prompt, appropriate treatment is the second pillar of the Roll Back Malaria initiative for reducing malaria in SSA; specifically, a goal has been set to ensure that 60% of all malaria cases in

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SSA receive such treatment. Since we don't know which malaria cases are likely to progress to severe illness, a better understanding of the dynamics of self-treatment in the urban environment is a priority.

Individual and Household Factors

In theory, SES should affect both exposure to vectors and the likelihood of developing severe illness once infected. The evidence for a relationship between SES and severe malaria is ambiguous, though. Studies in the Gambia (Koram et al. 1995a) and Gabon (Luckner et al. 1998) found little or no influence of socioeconomic factors on disease, nor did studies in Senegal (Trape et al. 1993) and Kenya (Mbogo et al. 1999), though the latter two were not designed to evaluate this association. However, in the Congo (Carme et al. 1994) households with a case of severe malaria had lower SES than control households, and in Mozambique (Thompson et al. 1997) case status was associated with certain housing characteristics.

Given the strong theoretical reasons for postulating that socioeconomic factors affect severe disease, it is important to clarify their role. Prior studies may have been confounded by study designs that produced systematic differences between hospital cases and community controls and failed to account for spatial autocorrelation (i.e., the likelihood that observations that are closer together are more likely to be similar) in their results.

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Host Factors

The most important host factor associated with severe malaria is immunity. In fact, transmission intensity, endemicity and immunity are interdependently linked as determinants of severe malaria. Transmission affects endemicity and thus immunity, which clearly modifies both the profile of severe disease occurrence and the age profile of individuals experiencing severe outcomes (Molineaux 1997). Specifically, stable transmission leads to a high level of endemicity, a lower mean age of severe complications from malaria, and a high proportion of severe malarial anemia (SMA) relative to cerebral malaria (CM). Where transmission is unstable or intermittent, endemicity is low, severe complications arise in older individuals, on average, and across a wider range of ages, and CM is relatively common compared to SMA (Marsh and Snow 1999; Snow et al. 1994). Whether severe malaria increases linearly with transmission at high levels is less straightforward (Molineaux 1997), but the consensus view is that at low levels, increasing transmission can dramatically increase severe outcomes in populations with low immunity.

The relationship between immunity and transmission has implications for severe malaria in the urban context. First, to the extent that exposure to malaria infection in the urban environment is actually decreased, immunity should decrease in city dwellers and produce a profile of disease similar to that for other low-transmission settings. Second, the focal but persistent nature of transmission in urban settings, combined with the reintroduction of malaria into cities following rural journeys, creates a situation where epidemics are possible and likely among less-immune city dwellers. These effects have

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not been observed, perhaps in part because there have been very few studies of severe outcomes in cities, and perhaps because of the dampening effect of readily-available health care facilities and antimalarials. Another possibility is that the failure to accurately define ecological zones or boundaries for high-risk areas within cities has reduced the possibility of observing these effects. We hope to address some of these issues.

In addition to immunity, several host factors have been implicated as protective or risk factors for severe malaria, including, for example, the sickle cell trait, poor nutrition, and HIV co-morbidity. Consideration of these factors is beyond the scope of this project.

Parasite Factors

Among parasite factors known or postulated to modify the risk of severe malaria are strain virulence and resistance to antimalarials such as chloroquine, a severe and growing problem in SSA. Detailed study of parasite factors requires research methods beyond the scope and resources of this dissertation, but we note that strain virulence and antimalarial resistance may be of particular interest in the urban environment: particularly virulent strains could trigger epidemics among non-immune populations despite lower transmission in this environment, and the high availability and inappropriate use of antimalarials is likely to accelerate resistance.

Limitations of the Literature and Research Directions

Several knowledge gaps emerge from this analysis. First, there is no appropriate definition of urban, which limits the generalizability of any findings in this field,

including recommendations for interventions. An appropriate definition must be based on the ecological, social and geographic characteristics that capture important differences among populations with regard to malaria, must be easily applicable in settings where demographic data is often scarce, and must be generalizable to a wide range of urban environments. It should also take advantage of modern technologies such as remote sensing, which can facilitate the process of defining regions, while remaining flexible enough to function where these technologies are unavailable.

Second, although a picture of specific factors that affect risk for malaria infection in cities is emerging, very few studies have evaluated the relative contributions of these factors to the emergence of life-threatening disease in individuals. We also know little about immunity in the urban context and the long-term effects of interventions that decrease exposure. Although a host of candidate malaria vaccines are under investigation, research and development challenges remain (Ballou et al. 2004), and widespread implementation is years away, at best. Thus, the effective use of preventive resources—including mosquito control, personal exposure reduction, prophylaxis of vulnerable groups and environmental modification—remains the best prospect for control. In fact, current policy is moving towards integrated control as the most appropriate method for managing malaria in cities (Donnelly et al. 2005). Our ability to focus resources, target interventions and properly implement control schemes is severely limited by our lack of knowledge about the relative contributions of specific risk factors in generating severe disease.

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The search for risk factors for severe malaria in urban areas is hampered by the lack of studies that have sampled in a manner that is representative of both population and environment, with sufficiently large sample size to evaluate multiple hypotheses. The environmental heterogeneity and rapid population turnover of urban areas require novel approaches to sampling in order to jointly account for socio-demographic and environmental risk factors. Both study design and interpretation should also account for spatial factors related to malaria.

Objectives and Specific Aims

The goal of this dissertation is to examine the effects of environmental and socio-demographic variables on the presentation of severe malaria in an urban area, with regard for spatial interaction between cases. In particular, we aim to:

i)   Improve methods for working in and characterizing the urban environment for epidemiologic research.

ii)   Characterize the spatial and social distribution of severe malaria

iii) Analyze individual-level associations between environmental and socio-demographic factors and severe malaria

iv)   Describe population-level associations between environmental and socio-demographic factors and severe malaria

Clarification of the relative contributions of these factors in urban areas and the ways in which they modify one another should ultimately contribute to better malaria

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prevention and control policies. Ultimately, this knowledge and improved systems for modeling of malaria should have implications for urban planning, delivery of health services, targeted risk reduction programs and the design of sound environmental management policies, all urgent priorities in SSA.

Overview of Research

In order to address these goals, we implemented a project in Kisumu, western Kenya, consisting of three concurrent phases: collection of clinical and laboratory surveillance data for severe malaria cases from Kisumu District Hospital (KDH); completion of a household knowledge, attitudes and practices (KAP) survey encompassing the urban core of Kisumu and collection of maps and geographic information system (GIS) and remote sensing data for Kisumu.

Kisumu is the third-largest city in Kenya, situated in one of the most highly malaria-endemic areas of the world. Within the study area, 202,282 people live in 54,403 households, making it representative of the cities experiencing the fastest population growth in SSA (UNFPA 1999). The presence of a well-equipped and staffed CDC field station in Kisumu and the collection of clinical and lab data at KDH, in tandem with the above factors, made it an ideal location for this study.

At KDH, a team interviewer identified patients presenting with severe malarial anemia, the most common form of severe malaria and the most easily and consistently diagnosed in the clinical setting. All cases were interviewed using an instrument

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developed for the KAP survey and reimbursed for transportation to their home. A field supervisor accompanied them home, marking the household location with a portable Global Positioning System (GPS) unit.

We identified a population-representative sample encompassing all inhabited environments in Kisumu by randomly selecting structures identified from census sublocation maps. Within each census enumeration area, sampling points corresponding to 1-in-10 households were mapped to the selected structures, and an interviewer using a portable GPS unit identified the closest eligible household for interview, for a sample of 4,336. Eligible households had one or more children under 10. The primary caregiver for a randomly selected child in each household was interviewed. The survey instrument included sections on household and individual demographics, health and treatment history of the child, knowledge of malaria, use of malaria prevention, household travel dynamics, and SES, as well as a short environmental assessment filled out by the interviewer. The interviewer used the GPS to establish the exact position of each interviewed household.

A set of aerial photographs and a high-resolution satellite image were obtained for Kisumu and orthorectified. These remote sensing data were used to derive environmental exposure estimates for each point in the study area and to assess the accuracy of census maps and accuracy and the efficiency of the sampling procedure for the KAP survey.

The subsequent chapters of this dissertation comprise analyses related to this project. Chapter 2 describes the novel sampling procedure used to collect exposure information across the urban area of Kisumu. Chapter 3 describes a method for classifying urban areas and shows variations in socio-demographic and environmental factors from the KAP survey across the urban ecotypes thus defined. Chapter 4 presents an unmatched case-control study, comparing cases identified at KDH with a series of controls selected from among the population of the KAP survey. Chapter 5 explores variations in incidence of self-reported malaria and severe malarial anemia and examines neighborhood-level contextual effects within small areas identified from the overall study area. In doing so, it explores potential methods for targeting urban neighborhoods. Finally, Chapter 6 summarizes findings and points out avenues for future research.

Summary

This dissertation attempts to advance methods for studying the epidemiology of severe malaria in urban sub-Saharan Africa. It identifies environmental and socio-demographic risk factors for severe malarial anemia. In doing so, it contributes to existing knowledge on the joint distributions of risk factors in this environment, their relative importance, and the potential efficacy of targeted interventions and integrated malaria control in cities.

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CHAPTER 2:

A NOVEL SAMPLING STRATEGY FOR URBAN MALARIA EPIDEMIOLOGY

Introduction

Malaria remains an acute problem in Sub-Saharan Africa (SSA), with over 1 million deaths and 365 million cases a year, primarily in children under 5 (Snow et al. 1999; Snow et al. 2005). Although estimates differ, a recent review calculates that 6–28% of global malaria arises in urban SSA (Keiser et al. 2004). While most Africans still live in rural areas, the proportion of urban dwellers is significant (38% in 1999), increasing at double the world average (4.4% per annum), and will exceed 50% of the African populace by 2015 (UNFPA 1999). These factors have led to growing recognition of the importance of urban malaria.

Urban malaria is likely to be profoundly different, in epidemiologic terms, from malaria in the rural areas where it has traditionally been studied. Studies attempting to characterize socio-demographic and environmental risk factors for urban malaria face a number of challenges in sampling design, including: the lack of pre-existing sampling frames, heterogeneity of population distribution, and focal nature of malaria transmission in cities. In response to these obstacles, researchers have adopted a variety of strategies.

Many studies have sampled from among patients attending health facilities (e.g., Comoro et al. 2003; Snow et al. 1992; Trape et al. 1987; Koram et al. 1995) or from schools (e.g., Trape 1987; Trape et al. 1992), an approach limited by the catchment areas of the source in physical and sociological space, and potentially not population-representative or generalizable to the urban population as a whole when they fail to encompass particular subpopulations or microenvironmental regimes.

A range of surveys has maximized population-representativeness by enumerating each resident within a limited study area, in rare cases relying on existing census data (though lack of adequate funding throughout SSA and high population turnover in low-income areas often limits the utility of this data (Leete 2001), but more often, undertaking an enumeration as part of the project or piggybacking on an established study (e.g., Mwenesi, Harpham, and Snow 1995; Molyneux et al. 1999; Thompson et al. 1997). In most cases, the study areas in question are either largely rural or cover only small fractions of cities, where this approach is likely to be manageable in terms of cost. Again, the applicability of these results across urban areas in general is unclear.

A variety of cluster sampling approaches have been implemented, requiring population enumeration only in selected areas, again covering a comparatively small portion of the urban landscape (e.g., Holtz et al. 2002; Schultz et al. 1994). Such studies simultaneously increase efficiency and achieve population-representativeness through consideration of design effects for an entire urban population. However, the focal nature of malaria transmission in urban environments due to decreased mosquito dispersal (see,

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e.g., Sabatinelli, Rossi, and Belli 1986; Trape et al. 1992) implies that cluster sampling strategies that fail to encompass significant microecological regimes, either explicitly in sample design or through good fortune in sample selection, will underestimate the importance of urban malaria.

A series of recent studies (Keating et al. 2003; Macintyre et al. 2002) have used a grid-based geographic sampling methodology. This represents an advance in the evaluation of environmental risk factors, since important ecotypes are less likely to be randomly excluded from the sample, yet may not be representative of the population as a whole: the heterogeneous distribution of people within cities implies that sampling strategies based on geography will tend to oversample individuals from sparsely populated areas, which cover a proportionately larger fraction of the study area (i.e., residents of areas with low population densities have a higher probability of representation than residents of high-density zones). The extent of over-sampling should increase with increased clustering of population.

Efficiency questions also limit the scope of population-based sampling strategies for urban malaria. The location and identification of specific individuals in cities requires interviewers with considerable knowledge of the sampling area and may entail an effort that offsets any relative gains in efficiency brought about by proximity to governmental and research institutions. The high mobility and cultural and social diversity of city dwellers requires interviewers with a substantial level of training and flexibility. Interviewer safety may be a real concern. Finally, population turnover is extremely high,

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especially in low-income areas, and can lead to attrition in the selected sample. While many of these factors are not unique to urban areas, the absolute size of the populations and the range of epidemiological and environmental contexts involved are much higher than in rural areas, making this a considerably more complex environment in which to design and implement appropriate research.

In general, new methods are needed that are flexible enough to sample in the urban environment while avoiding the pitfalls of existing strategies. A study that aims to jointly evaluate environmental and socio-demographic factors as they vary across an urban area simultaneously requires population-representativeness and comprehensive coverage of inhabited ecotypes. We describe the application of a novel map-based sampling strategy to select a representative sample for a knowledge, attitudes and practices (KAP) survey on malaria in Kisumu, Kenya. This method approximates a true population-based sample, while eliminating many of the costs of identifying specific sampling units.

Methods

Study Area

Kisumu (pop. 326,407) (Central Bureau of Statistics 2000), on the shores of Lake Victoria in southwestern Kenya, is the third-largest urban area in the country, according to the most recent census (Central Bureau of Statistics 2000). Its size makes it representative of the setting in which most SSA population growth will occur over the next 30 years (UNFPA 1999). The study site was limited to administrative sublocations

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(roughly equivalent to large neighborhoods) of the city, where average population density exceeds 1,000/km^2, although considerable variation exists at smaller scales. This threshold has been used in a recent review of malaria morbidity and mortality across Africa (Hay et al. 2005), and the study area thus defined encompasses a range of urban ecotypes with variation in factors likely to influence malaria risk, including land use/land cover, economic and agricultural activity, distance from urban shops and health facilities and environmental features. The thirteen selected sublocations encompass 202,282 people in 54,403 households (Central Bureau of Statistics 2000), over an area of 62.3 km^2.

Malaria transmission in adjacent rural areas is among the highest in East Africa with 90 to 410 infectious bites per year (Beier et al. 1990; Githeko et al. 1993). Rainfall (1,000–1,500 mm/year) occurs in two seasons (April–June and October–December), and malaria transmission is highest at the end of each rainy season. While vector densities within Kisumu are largely uncharacterized, malaria is consistently the leading cause of outpatient and inpatient morbidity and mortality (Kisumu District Ministry of Health 2001) among children, though HIV is significantly underreported. The majority of malaria infections in Kisumu are due to *P. falciparum* (Githeko et al. 1993).

Sampling Strategy

The basic design strategy for this survey was a 1-in-10 household sample stratified by census enumeration area (EA). The Kenya Central Bureau of Statistics defines EAs during the decennial national census. Each ideally comprises about 100

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households, but this figure varies widely where population density or environmental features require larger or smaller boundaries for convenient enumeration (Central Bureau of Statistics 2000). Each EA represents a geographic stratum in a stratified sampling design. Summary EA-level population data and detailed sublocation maps were obtained from the Kenya Central Bureau of Statistics and used to construct a pseudo-sampling frame, labeled as such because, although no list enumerates every potential sampling unit, a list of structures was available which accurately represent the distribution of the population on the ground, making it possible to sample from among all households with equal probability. Sublocation maps indicated EA boundaries and census-sampled structures (generally houses or apartment complexes) for urban EAs, while census data provided the number of households. Using this information, a 1-in-10 sample was randomly selected from among available census-sampled structures within each of the 535 EAs administratively designated as urban. For 32 EAs designated as rural, maps did not display structures, so a geographically random sample was chosen from a grid of potential sampling points regularly spaced at 100m intervals. Figure 2.1 shows the study area, highlighting urban and rural EA designations (Fig. 2.1b).

The locations of sample structures or points were noted on the sub-location maps, and cross-referenced to a GIS map of the study area developed by the US Centers for Disease Control (CDC) in conjunction with the Kenya Medical Research Institute (KEMRI) (Ombok M, pers. comm.). Each identified location represented a sampling point for the survey. Coordinates for each sampling point were transcribed from the GIS into a handheld Garmin ETrex Global Positioning System (GPS) unit (Garmin, Olathe,

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KS) by trained interviewers. Interviewers used the GPS unit to locate the sampling point, applying a standardized algorithm to identify the closest household with a resident child under 10 years old, and attempted to interview the primary caregiver for that child. Where the caregiver was absent, three attempts, at different times of day, were made to complete an interview before moving on to the next available household. Interviews were conducted during business hours, except where the respondent's schedule dictated otherwise. Where more than one child in a household was eligible for interview, one was randomly selected according to prearranged criteria. A similar process ensured random selection when more than one household was available in a single-structure. Where a single structure contained more than 10 households, extra interviews were conducted to maintain the 1-in-10 sample. All interviews for a specific EA were collected consecutively for logistical reasons. Interviewers were trained to use GPS and tested on their ability to locate specific points prior to the start of data collection. Each was assigned a random sample of EAs to minimize interviewer bias.

KAP Survey Instrument

Interviews were conducted in English, Swahili or Luo, the three most commonly spoken local languages, according to the respondent's preference, and included sections on: demographics, knowledge of the causes and prevention of malaria, use of preventive measures, health and travel history, indicators of socioeconomic status and local environmental characteristics. The content and results of the survey are described fully in Chapter 3.

To minimize non-sampling error related to the survey instrument, a series of preliminary focus group discussions (FGDs) were implemented with caregivers of children up to 10 years of age to gauge comprehension of survey items and estimate probable ranges of response. FGD groups included mothers from the urban center and from peripheral urban and semi-rural zones within the study area. The survey instrument was independently back-translated from Swahili and Luo into English and compared with the original to ensure consistency. Interviewers underwent six weeks of training in quantitative interviewing techniques, mapping and GPS use. Finally, a supervisor randomly accompanied interviewers to monitor equivalence of technique and provide feedback to the primary investigator and separately re-interviewed a subset of households to ensure data completion and assess accuracy. The interviewers, supervisor, and primary investigator met weekly or more frequently as needed, to discuss interviewing problems and review upcoming interview assignments.

Data Processing

Questionnaires were designed using Cardiff Teleforms (Cardiff, Vista, CA) software, allowing completed forms to be scanned directly to a Microsoft ® Access (Microsoft, Redmond, WA) database, thereby minimizing errors in data capture. Three individuals physically examined questionnaires for potential scanning problems and data entry errors prior to scanning. Data analysis was performed in SAS version 9.1 (Cary, NC).

Evaluation of Sample

Sample validity was assessed by quantifying completion and non-response rates, and by comparing the basic demographics of the selected sample with those reported by the 1999 Census (Central Bureau of Statistics 2000) and 1998 Demographic and Health Survey (DHS) (National Council for Population and Development (NCPD) 1999). Sampled EAs were compared to non-sampled EAs on variables of interest, where possible. Accuracy of sampled points was estimated by comparing positions of sampled interviews to the original sampling point coordinates and determining whether interviews were completed within the assigned EA. For all of these analyses, an effort was made to compare the sample selected via the map-based strategy with that selected through a random geographic process.

Protection of Human Subjects

All procedures for this study were supervised by CDC/KEMRI and approved by the institutional review boards of CDC, KEMRI and the University of Michigan. The research protocol and rights and responsibilities of participants were explained to potential respondents by interviewers, and written informed consent was obtained prior to all interviews.

Results

Though all 567 EAs were targeted for sampling, data collection was curtailed for logistical reasons, allowing 473 EAs (83.3%) to be sampled from June 2002 through February 2003, yielding 4,336 valid interviews. Non-sampled EAs were randomly

distributed (Fig. 2.1c). There was no difference in the proportions of sampled urban (83.6%) and rural EAs (84.4%; $\chi^2 = 0.015$, p = 0.9027), and no difference in the mean populations of sampled (353.4) and non-sampled EAs (374.1; t-test, p = 0.27).

Of all sampling points assigned, 96% yielded an interview. Non-response and refusal were minimal: in 357 cases, more than one household had to be approached to obtain an interview. Of these, 270 (75.6%) households were ineligible because there was no child under 10 years old. In 55 cases, no caregiver could be contacted, despite the presence of an eligible child. In 39 eligible households (10.9%), all caregivers refused to participate. The overall non-response rate (i.e., the proportion of identified eligible households where interviews were not completed) was just 2%.

Because the sampling procedure did not specify a particular subject, distance from the assigned sampling point to the sampled household varied. Mean distance to sampling point was 74.6m, but significantly lower in urban EAs (66.6m; 95% CI: 57.6m, 75.6m) than rural EAs (158.6m; 95% CI: 131.0m, 186.1m; t = 5.95, p < 0.0001). This difference remained significant when adjusting for the number of households in the EA (t = 2.22, p = 0.0266). Since distance to sampling point varied, some interviews were performed in EAs other than the one originally assigned. While sampling points were assigned in 473 EAs, interviews were conducted in 511. The mean final sampling fraction was 9.1%. Overall, 55.3% of interviews were performed in the assigned EA, with no significant difference between proportions correctly sampled in urban (55.0%) and rural EAs (57.9%; $\chi^2 = 1.20$, p = .2730).

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The population distribution by age and sex for the sample was compared to that obtained from the 1998 Kenya DHS (Fig. 2.2). For both sexes, the biggest discrepancy was a much higher proportion of the study sample in the lowest two age groups (i.e., 0–10 years old) than observed in the DHS (38.0% versus 24.9%; $\chi^2 = 384.5$, p < 0.0001). Men between 15 and 30 years old were significantly underrepresented in the study sample (10.8%) compared to the DHS (16.5%; $\chi^2 = 118.0$, p < 0.0001), as were women over 35 (4.9% versus 8.5%; $\chi^2 = 178.6$, p < 0.0001), and men over 45 (1.2% versus 5.7%; $\chi^2 = 397.2$, p < 0.0001).

Discussion

The need for data on basic malaria epidemiology in the urban environment demands creative approaches to sampling. Given the marked heterogeneity of urban environments, focal nature of malaria transmission, and lack of pre-existing sampling frames, an ideal sampling approach must be population-representative without relying on strict enumeration, inclusive of important environmental variation, and accurate in terms of the population parameters to be measured, while sufficiently inexpensive and simple for use by local health ministries and researchers. Any potential sampling scheme should be evaluated in terms of each of these factors.

The map-based strategy described here was intended to select a sample representative of the target population of households with children under 10 in the selected study area. The age profile of the sample population varies in predictable ways

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from the DHS data for urban areas in Kenya. Since only households with children under 10 are eligible, there is an excess of children in the lowest age groups, and a relative dearth of individuals beyond child-bearing age, relative to the general population. The underrepresentation of adolescent and young-adult males may indicate that men in this age range are less likely to be caregivers of young children, or are more likely to live in households of their own. Since DHS and other data are presented in summary form for all households, not only households with young children, we cannot quantitatively appraise the efficacy of the sampling strategy in capturing the true target population. This is an inherent limitation of the study design. Nonetheless, the observed variation of age distribution in the expected direction is consistent with a representative sample.

There are several other ways in which the study design may have selected for a non-representative sample. First, the sample is not a true population sample, as it is not based on a fully enumerated sampling frame. To the extent that census maps inaccurately portray the relative geographic locations of inhabited buildings, or that map-identified structures do not represent inhabited buildings, whether because of initial misclassification or abandonment in the period between ascertainment and sampling, or that inhabited structures are not represented on the maps, there will be inaccuracies in the way the true population is rendered. This is most true in places with rapid urbanization or a substantial influx or outflow of residents, where census maps may rapidly become inaccurate. However, from the production of census maps in 1999 to study sampling in 2002, it is unlikely that any areas changed substantially enough to seriously affect population representativeness. This assertion is borne out by a comparison of the census

maps with aerial photographs of Kisumu from 1996 and high-resolution satellite images from 2003. Conversely, since individual residential changes are likely to occur at a much higher rate than the pace of wholesale urbanization, the use of sampling points that reflect the geographic distribution of residents rather than identifying an individual sampling unit is likely to represent a gain in efficiency, since the sample will not suffer attrition due to persons or households that are no longer present. Second, since one eligible child was identified for each household, households with fewer children under 10 will be oversampled relative to larger households.

In addition to design factors, aspects of the implementation of the sampling strategy may have affected the representativeness of the sample. In particular, though response rates were very high and a sample was obtained from nearly every sampling point, the proportion of houses that were recorded as ineligible because there was no eligible child was lower than expected, less than 6% of all attempted interviews. This is inconsistent with observations that 11.3% of all households in Nyanza province, where Kisumu is situated, are single-member (this figure rises to 26.3% in urban areas country-wide, but likely reflects the very high rate in Nairobi) (National Council for Population and Development (NCPD) 1999). Some proportion of multi-member households will also lack eligible children. One of two explanations may account for this discrepancy: either interviewers tended to approach households that were more likely to have eligible children or interviewers, despite standardized algorithms for selecting the household closest to the sampling point, or not every sampling effort was recorded. It is likely that the reality is a combination of these factors. In itself, this should not bias results, unless it

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is also true that interviewers selected for households that were more likely to agree to participate, the differences between volunteers and 'refusers' having been documented for a wide variety of studies. As there was no information obtained from refusers, this possibility cannot be evaluated with the current data, although there was no apparent spatial pattern among these cases.

The final inclusion of just a portion (83%) of the total EAs could affect either the internal or external validity of the sample: we have stressed the importance of population-representativeness and environmental exhaustiveness in obtaining valid estimates and extrapolating results. However, although the lack of sampling in certain EAs precludes estimation of population parameters for these areas, the lack of observable differences between sampled and non-sampled EAs, and the still-broad coverage of the study area lead us to believe that this sample retains its internal validity. Moreover, given the geographically random distribution of non-sampled EAs and ground knowledge of the study area, we do not expect that there are any significant urban ecotypes that were not covered. Thus, these results can cautiously be inferred to be applicable to similar urban environments across SSA.

We observed geographic variation between actually sampled points and assigned sampling points, likely arising from several sources of error: GPS inaccuracy, variability in the precise placement of the GPS mark for an interview in relation to the structure being sampled, failure to find an eligible household at the precise sample point and vagaries of local neighborhood structure that may have forced interviewers to travel

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further to find an eligible house. To the extent that this variability created undersampling or oversampling in particular geographic strata, it also affects the precision of parameter estimates in those areas. It should be noted that misclassification error, in terms of interviews conducted in an EA other than the assigned EA, increased in poor urban and peri-urban areas. This increase may be related to the small size of EAs in these areas. Nonetheless, significantly shorter distances between assigned and sampled points in administratively urban areas, where the map-based sampling strategy was used, compared with administratively rural areas, where geographically-random sampling was necessary, demonstrates a correspondence between the actual distribution of population and the distribution of sampling points used in the sampling process. Moreover, while at finer scales this method does not have the accuracy that would be obtained by a population-based sample founded on a complete census, aggregation of EAs into larger areas for analysis removes the positional and demographic uncertainty associated with geographic deviations, restoring the precision of parameter estimates for those areas.

In addition to geographic error introduced by sampling, we observed inaccuracies in the census maps that were most pronounced for poor urban and peri-urban areas. To the extent that these inaccuracies led to errors in mapping EA boundaries to the GIS and ground coordinates, the precision of parameter estimates will be diminished, and potentially biased in either direction, depending on whether the 'true' EA encompasses a larger or smaller population than the map-identified EA. However, this type of misclassification should be non-differential and should diminish with aggregation of EAs for analysis.

Cost and efficiency represent important benchmarks beyond simple accuracy and validity for any sampling strategy to be applied in SSA, where local resources for research and data collection are frequently scarce. The present system includes several features that may be viewed as improvements over traditional sampling methods for urban areas and may be of particular use where rapid sampling is a priority. The use of pre-programmed handheld GPS units decreases interviewer training costs and interviewing time, as interviewers are guided to the appropriate sampling point, even with no prior knowledge of the study area. Retraining costs are obviated in part, as interviewers do not need to be familiarized with new areas or study sites to nearly the extent necessary if individual sampling units are to be identified. The costs of complete enumeration for the study area or for specified clusters are avoided, contingent on the availability of reasonably accurate summary population figures. It should be noted that the current study made use of both pre-existing population summary figures and census maps, elements that normally constitute a large proportion of the expenditures of a population enumeration (MacIntyre 1999). Nonetheless, data of this sort should be available for most cities in some format, and it may be possible to adapt other types of data (e.g., land tenancy maps or remote sensing images) to the identification of sampling points for map-based sampling.

A final issue that bears mentioning in the evaluation of this sample is the definition of 'urbanicity' used to designate the study area. There is no standard definition for urban: national guidelines variously draw on population density thresholds, absolute

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population sizes, proportions of residents in various occupations and other functional characteristics, or, tautologically, on administrative boundaries (see, e.g., Hay et al. 2005). We used population density to define boundaries for the purposes of this study, as the most widely available and generally applicable of these measures, while recognizing that a suite of other factors are jointly and interactively responsible for determining what is 'urban.' The specific cutoff of $1,000/km^2$ was determined to be intermediate between published national guidelines for several countries (e.g., USA: $1,000/km^2$, India: $390/km^2$; Philippines: $500/km^2$) and the few population densities reported for urban areas in the malaria literature (e.g., Maputo, Mozambique: $2,000–18,000/km^2$ (Thompson et al. 1997); Brazzaville, Congo: $5,000–25,000/km^2$ (Trape and Zoulani 1987); Bakau, The Gambia: $\sim 2,000/km^2$ (Lindsay et al. 1990)). A recent review of urbanization and malaria uses this threshold in estimating malaria morbidity and mortality across Africa (Hay et al. 2005). Clearly, different valuations of the variables used to define urbanicity would have led to different study areas and overall parameter estimates for this urban area. In the absence of a standard definition, equally valid studies of the same city are likely to yield different and irreconcilable parameter estimates. The same holds true for intra-urban classification schemes that use terms such as peri-urban, semi-urban or even suburban without specifying what is meant by these terms. Further research is needed into the salient characteristics of urban versus rural malaria and the factors that should determine urban boundaries in the context of malaria research in order to maximize the utility of results. We will evaluate the implications of various urban/rural classifications *within* the urban environment in Chapter 3.

In summary, a novel map-based strategy was used to identify and survey a sample of caregivers of children under 10 in urban Kisumu, Kenya as a preliminary step towards characterizing risk factors for malaria in the urban environment of SSA. This strategy, based on the use of handheld GPS to identify sampling points selected from census maps of the study area, addresses some of the observed deficiencies in sampling strategies used previously in this milieu and offers improvements in terms of representativeness and cost-efficiency over traditional sampling methods for urban areas.
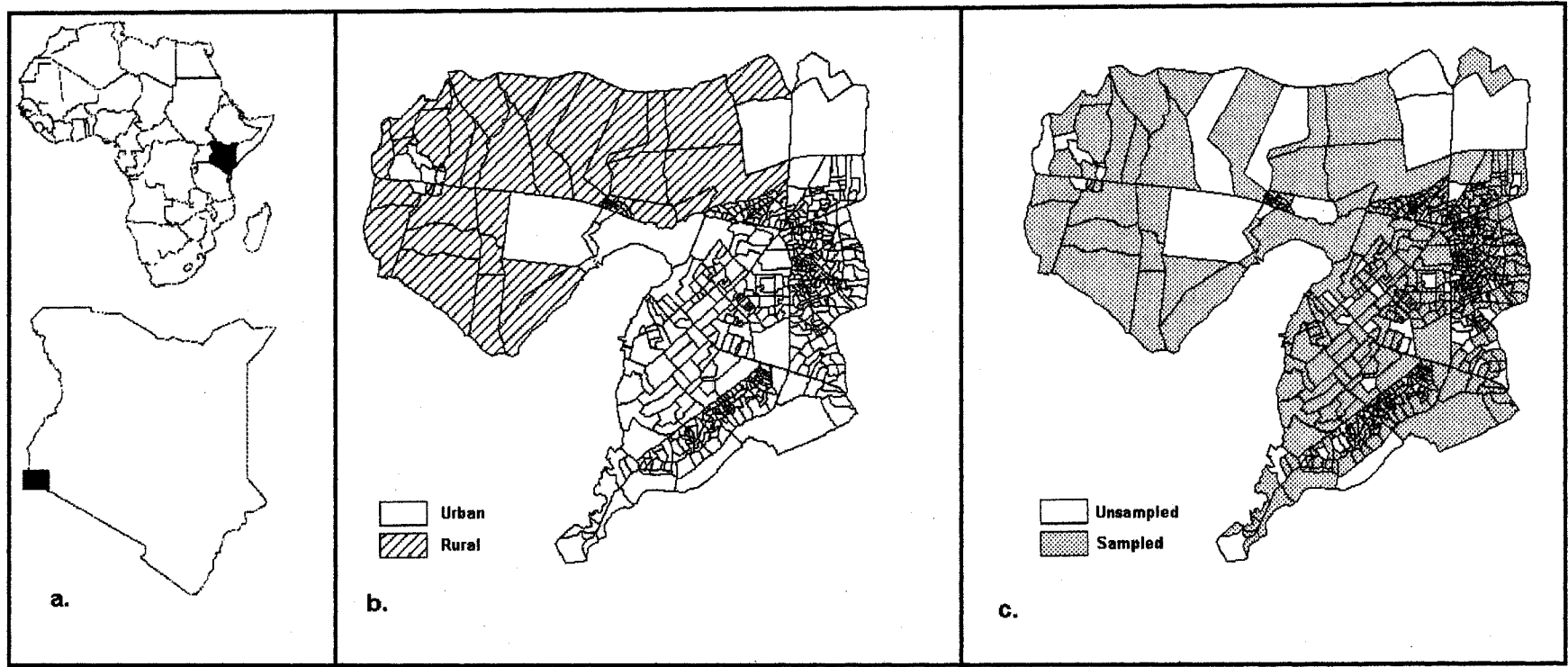
Figure 2.1: Study Area; a) Area of detail; b) Urban/rural designation of census enumeration areas (EAs) within study area; c) Sampled and unsampled EAs
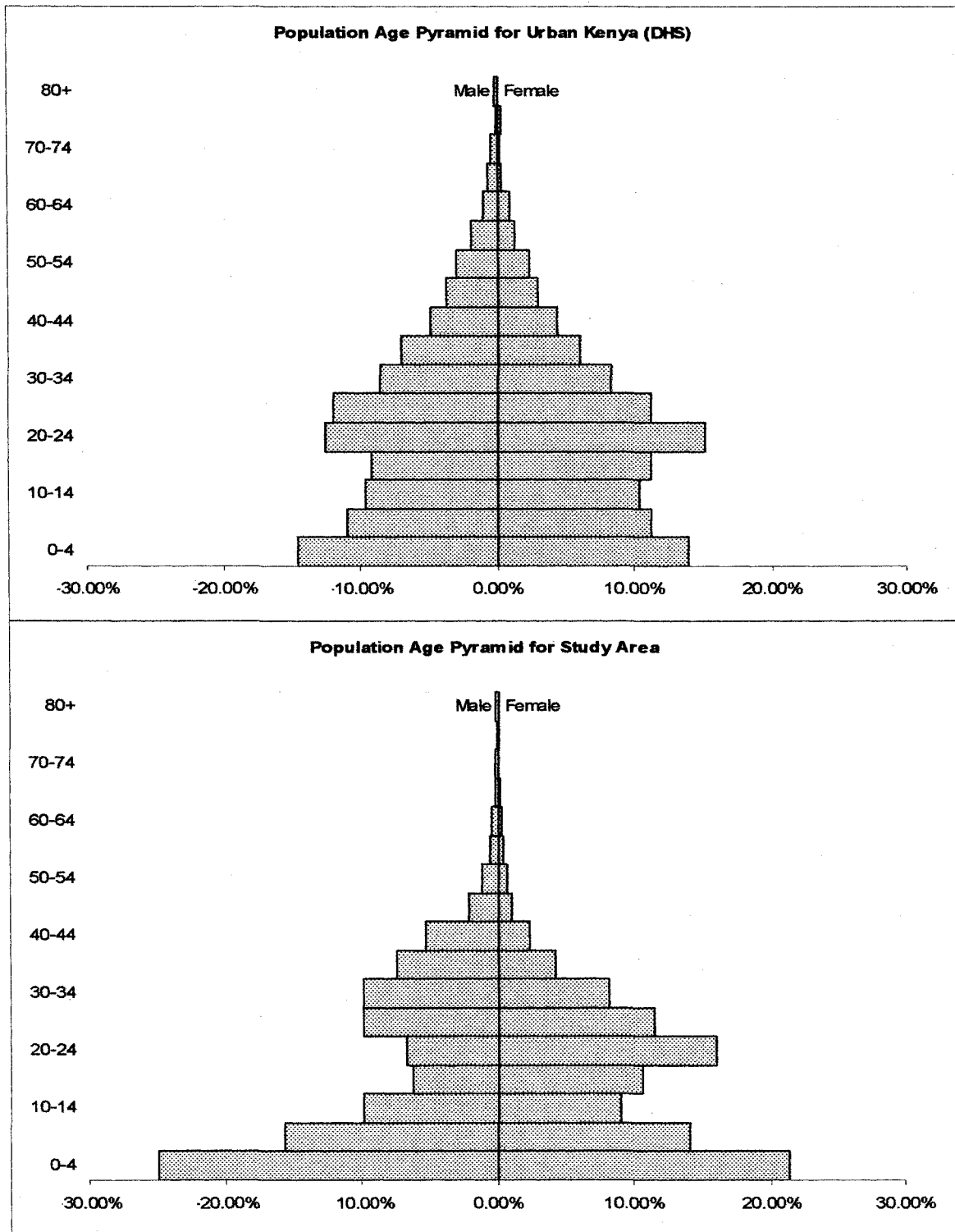
Figure 2.2: Comparison of Study Area Population with Population of Urban Kenya; Population Age Pyramid for a) Study Area and b) Urban Kenya (from DHS)

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CHAPTER 3:

MALARIA PREVENTION AND TREATMENT PRACTICES VARY BY LEVEL OF URBANIZATION IN KISUMU, KENYA

Introduction

The increasing urbanization of sub-Saharan Africa (SSA) is likely to profoundly alter the epidemiology of malaria on the continent. Transmission rates are generally lower in urban than rural areas due to the lower availability of mosquito breeding sites (Trape and Zoulani 1987b); higher socioeconomic status and better access to diagnosis and treatment may reduce the level of clinical disease. Nonetheless, several characteristics of African cities amplify transmission in ways unlikely to be observed in the rural areas where malaria has traditionally been studied. Among these are the presence of household farms in areas of high population density (Afrane et al. 2004), broken water pipes or poor drainage systems that create pools of water in slums (Keating et al. 2003), wetland breeding sites in close proximity to peri-urban areas (Thompson et al. 1997), rapid changes in land use (Jacob et al. 2003), and high rates of travel between urban and rural areas (Osorio, Todd, and Bradley 2004). The combination of spatially focal transmission (Trape and Zoulani 1987a) and high population density creates both opportunities for targeted control (Carter, Mendis, and Roberts 2000) and greater potential for outbreaks. Moreover, there is evidence that despite advantages with respect to access, treatment is often inappropriate and/or inadequate in cities (Donnelly et al.

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2005) and the formal health sector is often bypassed in favor of self-treatment (McCombie 2002).

Urban SSA is now estimated to account for 6–28% of the global malaria burden (Keiser et al. 2004), a result of the large and rapidly increasing proportion of Africans living in cities, projected to reach 50% by 2015 (UNFPA 1999). The wide range of uncertainty in this figure reflects a lack of knowledge of risk factors operating in this environment, as well as definitional difficulties with respect to urbanization, discussed below. As the proportion of city dwellers increases, current understanding of environmental risk factors for malaria transmission and knowledge patterns that influence malaria treatment and prevention behaviors must be adjusted to an urban context. Moreover, the extreme heterogeneity of urban areas with regard to housing standards, educational levels, household wealth, access to treatment, community resources and proximity to potential mosquito breeding sites implies that malaria interventions applied wholesale across these areas will not have an ideal impact. Rather, homogeneous intra-urban zones with consistent malaria epidemiologic profiles must be identified to permit targeting of prevention, control and treatment programs. While a few quantitative studies have explicitly considered urban-rural differences in social and behavioral factors related to malaria (e.g., Gardiner et al. 1984;Holtz et al. 2002), little research has centered on intra-urban differences to allow proper focusing of interventions. Furthermore, the lack of accepted terminology for urban ecotypes limits the generalizablity of results from individual studies: the terms "urban," "peri-urban," "semi-urban" and "suburban" have no standard definition in the malaria literature. Detailed classifications have been

proposed for slums, based on household resources and relative deprivation (UN-HABITAT 2003), but similarly universal and quantitative designations are needed for urban areas as a whole.

The goal of this study was to develop a data-based methodology for subdividing urban areas into more homogenous units using variables readily available to city health officials and researchers. We have attempted to describe these units in terms of levels of urbanization, socio-demographic characteristics, indicators of malaria transmission, and knowledge, attitudes and practices (KAP) related to malaria. The methods detailed in this report will help establish a more uniform process for continent-wide classification of urban areas according to level of urbanization and will help focus malaria interventions within urban areas.

Methods

Study Area and Sampling

The study was conducted in Kisumu (pop. 326,407) (Central Bureau of Statistics 2000) located along the shores of Lake Victoria in western Kenya. Kisumu represents the demographic setting within which most SSA population growth will occur over the next 30 years (UNFPA 1999), i.e., cities under 1 million inhabitants. Malaria transmission in adjacent rural areas is among the highest in East Africa with from 90 to 410 infectious bites per year (Beier et al. 1990; Githeko et al. 1993). Rainfall (1,000–1,500 mm/year) occurs in two seasons (April–June and October–December) and malaria transmission is highest at the end of each rainy season.

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The sampling methods are described in detail in Chapter 2. Briefly, 13

administrative sublocations (roughly equivalent to large neighborhoods) with overall

population densities greater than 1,000/km^2 were selected from within the Kisumu

municipal boundaries (although considerable variation in population density by census

enumeration area (EA) exists within each sublocation). A recent review of urbanization

and malaria uses this threshold in estimating urban malaria morbidity and mortality

across Africa (Hay et al. 2005), and the study area thus defined encompasses a range of

urban ecotypes with variation in factors likely to influence malaria risk. The selected

area contained 202,282 people in 54,403 households (Central Bureau of Statistics 2000).

A map-based sampling scheme was used to select 4,550 sampling points—corresponding

to households—in 473 of 567 EAs, a 10% sample, with probability of selection

proportional to population density. Within each household, a child (hereafter, the

'selected child') was randomly designated as a participant from among eligible

individuals (i.e., children under 10 years of age), and the primary caregiver interviewed.

A total of 4,336 interviews were completed between July 2002 and January 2003.

Urban Classification

Urban EAs were classified into one of three ecotypes (urban, peri-urban or semi-

rural) based on a set of variables reported in the literature as indicators of urbanization or

of malaria transmission within urban areas, and considered accessible to health officials.

Selected indicators included: household access to electricity and piped water, ownership

of the dwelling, education levels (UN-HABITAT 2003), distance from the city center

(Schellenberg et al. 1998), population density (Snow et al. 1998), and normalized difference vegetation index (NDVI) (Eisele et al. 2003). Access to electricity and piped water, household ownership and education levels were assessed in the KAP survey and summary measures computed for each EA[1]. NDVI was derived from a high-resolution multispectral Quickbird satellite image (DigitalGlobe, Longmont, CO) of the study area in February 2003. Household coordinates were ascertained using handheld Garmin Etrex Global Positioning System (GPS) units (Garmin, Olathe, KS), and distance from the city center calculated using ArcGIS v. 9.0 (ESRI, Redlands, CA). Population density was computed in ArcGIS using census data and maps.

A principal components analysis (PCA) was performed, using the PRINCOMP procedure in SAS v. 9.1 (Cary, NC) to identify linear combinations of the original variables explaining a greater proportion of the variation in the data. The FASTCLUS procedure in SAS was used to implement a k-means clustering algorithm to assign EAs to one of the three ecotypes on the basis of the factor loadings obtained through PCA. Since the results of k-means clustering are sensitive to the initial seed, the algorithm was replicated 100 times with different random seeds, and the solution chosen that maximized the cubic clustering criterion (CCC), which compares clusters identified by the algorithm to hypothetical clusters arising through sampling from a uniform distribution on a hyperbox (Sarle 1983).

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[1] These and other socio-demographic variables are often available from census data, but lack of adequate funding throughout SSA and high population turnover in low-income areas in many cases limits the utility of this data (Leete 2001).

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The geographic properties of the classification produced by this method were compared to alternate classifications based on administrative designation of urban versus rural (Central Bureau of Statistics 2000) and population density thresholds (urban $\geq$ 1,000/km^2; peri-urban $\geq$ 500/km^2) (see, e.g., Hay et al. 2005). Additionally, we compared the distribution of several variables clearly related to urbanization (use of gas for cooking, presence of earth floors in the dwelling and car ownership) but not used in the classification process, across levels of urbanization as determined by the three classification schemes (clustering, administrative and population density).

KAP Survey Instrument

The survey instrument was comprised 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. Some items referred to the household or to the selected child rather than the caregiver.

Three variables were derived from original survey items, the first two of which represent primary indicators established for RBM by the Abuja Declaration of 2000 (World Health Organization 2000): whether a household owned an ITN; whether sulfadoxine-pyrimethamine (SP), the first-line antimalarial in Kenya, was provided within one day of onset of symptoms for emergent cases of self-reported malaria (i.e., prompt, appropriate treatment (PAT)); and whether the caregiver exhibited good general

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knowledge of malaria (i.e., identified mosquitoes as the cause of malaria, fever as a primary symptom, and bednets as a preventive method).

Several continuous variables were transformed and/or categorized in order to simplify analysis and display important relationships more clearly. A PCA was used to produce a wealth index based on ownership of specific household items, and the resulting distribution divided into quintiles (Filmer and Pritchett 2001). Educational attainment was classified into three categories: no formal education, some primary, and completed primary (i.e., eight years of formal schooling). Three age categories were recognized for caregivers: under 20, 20 to 50, and over 50.

Statistical Analysis

Univariate distributions were produced for the three variables of interest, and stratified by socio-demographic factors, including level of urbanization, wealth, household size and characteristics of the caregiver (age, marital status, educational attainment, and whether or not household head). Categorical data were analyzed using the chi-square statistic or Fisher's exact test where data were sparse. Student's T-test was used to identify differences in means for continuous variables. P-values under 0.01 were considered statistically significant.

Data processing is described more fully in Chapter 2. Briefly, survey forms were checked for data entry problems, then scanned directly into a Microsoft ® Access

(Microsoft, Redmond, WA) database using Cardiff Teleforms (Cardiff, Vista, CA) software. General statistical analyses were performed using SAS.

Protection of Human Subjects

The protocol for this study was reviewed and approved by the institutional review boards of the Centers for Disease Control and Prevention (Atlanta, GA), the Kenya Medical Research Institute (Nairobi, Kenya) and the University of Michigan (Ann Arbor, MI). Written informed consent from participants was obtained prior to all interviews.

Results

Level of Urbanization

The PCA identifies three factors accounting for about 70% of the variation in the original set of variables (Table 3.1). Factor loadings greater than 0.4 are considered significant. Factor I loads strongly on house ownership and NDVI, and has a strong negative relationship with population density. Factor II loads strongly on access to piped water and decreased distance to the town center. Factor III loads strongly on completion of primary school and access to electricity. Maps of factor distributions show distinctive and distinct patterns for the three (Fig. 3.1).

Applied to these factors, the clustering algorithm produces zones that are more continuous and homogeneous than those identified through the use of population density thresholds (Fig. 3.2). The clustering method also distributes population more evenly and produces zones that are more strongly predictive of variation in other urban variables

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than either of the other methods examined (Table 3.2). Unlike the classification based on population density thresholds, it retains all EAs administratively classified as rural within the semi-rural category.

Demographics

The mean ages of caregivers and children selected for the survey were 28.1 and 4.1 years, respectively. Respondents were predominantly female and married (Table 3.3), and were culturally homogeneous: of the 4,336 survey subjects, a large majority (75.4%) were members of the Luo tribe, and almost all (86.2%) identified themselves as Christians. Most completed at least some secondary schooling, while a negligible proportion reported no schooling. The mean household size was 4.8, and approximately a third of respondents (32.1%) identified themselves as the head of their household.

Of all respondents, 15.8% lived in EAs identified by the clustering algorithm as urban, 54.6% in peri-urban, and 29.6% in semi-rural, reflecting the distribution of the general population by level of urbanization. Socio-demographic characteristics varied significantly across residential strata (Table 3.3). Urban households were wealthier and larger than non-urban households, while peri-urban households were the least wealthy. Among respondents, urban caregivers were most likely to be single, peri-urban youngest and most often female, and semi-rural oldest, most often male and most likely to be head of their household. Education decreased from urban to peri-urban to semi-rural EAs.

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Knowledge of Malaria

Knowledge of malaria causes, symptoms and prevention was generally high (Table 3.4). Ninety-six percent of respondents identified mosquitoes as a cause of malaria, 98.6% named at least one hallmark symptom (i.e., fever, chills, head or body aches, loss of appetite, lethargy), and 94.1% described at least one method of malaria prevention (e.g., use of bednets, burning of mosquito coils, wearing of protective clothing). Identification of symptoms associated with severe malaria episodes was low, although nausea or vomiting was mentioned by nearly half of respondents. Respondents that were wealthy, highly educated or middle-aged (i.e., 20–50) were more likely to provide correct answers for all categories. Urban respondents were more likely to correctly name a cause of malaria, and peri-urban respondents less likely to describe the use of bednets as a preventive measure.

Most respondents had good general knowledge of malaria: 68.0% volunteered the best answer for each category: i.e., mosquitoes as a cause, fever, chills or shaking as a symptom and bednets as a preventive measure. This was significantly more common in urban areas than peri-urban (74.1% versus 65.4%, p < 0.0001), among the wealthiest quintile compared to the least wealthy (77.8% versus 54.7%, p < 0.0001), among those with secondary schooling compared to those with no schooling (79.5% versus 37.9%, p < 0.0001), and among caregivers between 20 and 50 years old compared with younger or older caregivers (70.9% versus 55.5%, p < 0.0001).

Preventive Measures

Overall, 57.7% of respondents reported at least one bednet in their household (Table 3.5). Respondents were asked how many of these had been treated with insecticide in the previous year, yielding an estimate of 30.0% of households with ITNs. In households with bednets, four of five household members, on average, had slept under a net the previous night, and the selected child averaged 5.9 nights under a net the previous week. Mosquito coils and insecticides were also commonly used to prevent malaria; coils were the most common preventive method overall. Use of other measures, such as insect repellent, protective clothing, or smoke, was negligible. Nearly 1 in 10 (8.6%) households did not practice any type of mosquito prevention.

Urban residence was a strong predictor of all aspects of net usage (Table 3.5): urban residents were more likely to own nets (74.2%, versus 55.7% for peri-urban ($p <$ 0.0001) and 52.5% for semi-rural ($p < 0.0001$)) and owned more nets per household (mean 1.7, versus 1.0 for peri-urban ($p < 0.0001$) and 0.9 for semi-rural ($p < 0.0001$)). Urban residents were more likely than non-urban to have treated their nets within the past year (53.9% versus 48.1%; non-significant, $p = 0.0160$), were more likely to own an ITN (42.5% versus 27.6%; $p < 0.0001$), had a higher proportion of household members sleeping under nets (84.9% versus 79.7%; $p < 0.0001$); and averaged more nights sleeping under the net by the selected child (mean 6.4 versus 5.7; $p < 0.0001$) during the previous week than non-urban residents. Wealth and education were also strongly predictive of use of preventive measures: 85.8% of respondents in the highest wealth

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quintile owned bednets (mean 2.2 per household), compared with just 34.9% in the lowest (mean 0.4 per household) $(p(\chi^2) < 0.0001$ and $p(t) < 0.0001$ respectively).

The patterns of use of preventive measures for peri-urban and semi-rural residents were similar and contrasted strongly with those for urban residents (Table 3.5). In particular, urban residents were more likely to use bednets in conjunction with some other method of prevention (52.6% versus 36.4%; $p < 0.0001$), and less likely to rely exclusively on methods other than bednets (21.7% versus 35.9%; $p < 0.0001$). In contrast, mosquito coils were more often used by non-urban, less wealthy and less educated respondents (e.g., 65.1% of respondents in the lowest wealth quintile used coils, compared with just 42.7% in the highest, $p < 0.0001$).

Health History

Overall, 38.5% of respondents reported malaria in their child, and 54.3% in at least one member of the household during the previous month. Very few reported unconsciousness or convulsions. The proportion of children and number of days with malaria or fever decreased with increasing wealth and education, was lowest for middle-aged respondents, and decreased from semi-rural to peri-urban to urban zones. The proportion of households reporting malaria also decreased with caregiver educational attainment, but increased with wealth, though the increase was small, 49.3% for the lowest quintile versus 54.9% for the highest (non-significant, $p = 0.0158$).

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Treatment-seeking

Among respondents that reported at least one day of malaria, fever, convulsions or unconsciousness (n = 1,893, 43.7%) in their selected child during the previous month, those from wealthy households were significantly more likely to have sought treatment: 90.2% for the highest quintile versus 79.0% for the lowest (p < 0.0001). Overall, 18.3% claimed not to have sought treatment from any source. The formal sector (e.g., hospitals, health centers, private physicians) was used exclusively by 71.1% of respondents, while 20.1% indicated self-treatment (e.g., using shops, pharmacies, consulting with family or friends) exclusively, and 6.6% combined these two modalities. Use of traditional medical options (e.g., traditional healers) was infrequent, less than 2% alone or in any combination. Choice of treatment options varied according to level of urbanization and age of respondent, with urban and younger caregivers more likely to have chosen the formal sector. Peri-urban residents took slightly longer, on average, before seeking treatment (2.12 days) than semi-rural (1.92 days) or urban (1.95 days) residents (p(t) = 0.0421).

Nearly all caregivers (95.4%) gave medicine to their sick children (Table 3.6). The first- and second-line antimalarials for Kenya, SP and amodiaquine, respectively, rank second and third among the most commonly given medicines, behind analgesics, which are often prescribed in combination with other medications. Most caregivers who gave medicine gave at least one antimalarial (67.8%), though this was less likely among young or old caregivers than those between 20 and 50 (55.4% versus 70.8%, p < 0.0001), those without less schooling (p = 0.0040), and the less wealthy (non-significant, p =

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0.0738). The mean time between onset of sickness and medication was 1.48 days, and slightly shorter among peri-urban residents (1.39) than semi-rural (1.58 days, p = 0.007) or urban (1.61 days, non-significant, p = 0.0190).

Just 20.7% of sick children received the first-line antimalarial (SP) within 1 day of onset of illness (PAT). There were no significant differences in the proportion receiving PAT among peri-urban (21.7%), urban (21.2%) and semi-rural (19.1%) areas. However, substantial differences were observed among the highest wealth quintile (31.0%) versus the lowest (13.9%, p < 0.0001), among those with some secondary school (27.3%) compared to those with no schooling (12.0%, p = 0.0172), and among caregivers between 20 and 50 (22.4%) versus younger (12.8%; non-significant, p = 0.1566) or older (14.4%, p = 0.0018) ones. Caregivers who demonstrated strong general knowledge of malaria were significantly more likely to provide appropriate treatment (23.6%) as those who did not (15.3%, p < 0.0001).

Discussion

The clustering algorithm employed here in several ways extends or improves upon methods consistent with prior research and national guidelines for defining urban areas (see, e.g., (Hay et al. 2005) for a discussion of various usages). First, it produces continuous zones that are both homogeneous for variables of interest and inclusive of significant portions of the urban population. These factors should improve the feasibility and relevance of targeted interventions for malaria control. Second, it makes use of indicator variables that are likely to exist and to be readily available for the majority of

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African cities, an important consideration where resources are scarce. Third, though ground-truthing is problematic in the absence of well-articulated definitions for urbanization, clustering more accurately identifies and delineates outlying urban pockets and peri-urban slum areas than the other methods considered (data not shown). Finally, this classification is more strongly associated with other variables clearly related to urbanization than are the other arrangements[2]. In sum, the current method is more geographically coherent and effective at highlighting differences in urbanization-related variables across urban ecotypes than prior methods.

Urbanization-related differences were observed in socio-demographic variables and malaria KAP: household size and wealth; educational attainment; age and marital status of caregivers; age distribution of children; extent of malaria knowledge; reported malaria morbidity; choice of treatment modality; likelihood and timing of treatment; and use of malaria prevention were all significantly related to urbanization. Though the magnitude of the difference was small for many of these variables, the cumulative effect implies quite different epidemiological contexts.

This analysis confirmed that residents of the most highly urbanized zones are best equipped to cope with malaria. They are wealthier and better educated than residents of other zones and have better general knowledge of malaria. They are more likely to own

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[2] Since the variables used to validate this classification are gathered from the same region and are to some extent correlated with the classification variables, some caution is warranted in interpreting these results, though the ability to predict variation in factors not used in the clustering algorithm is clearly a positive outcome. One potential test of this method would be to derive a clustering solution in another city in SSA using only a random selection of half of the available EAs. The ability to accurately predict variation in factors not used for classification in EAs not used to derive the clustering solution would strongly support the utility of this method.

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and use ITNs and to supplement them with other preventive behaviors. Their children experience the least illness and are most likely to be exposed to the formal health sector during a malaria episode, though they are not more likely to receive PAT.

A less-expected result is the congruence of the peri-urban and semi-rural zones. Some clear differences exist between these groups: semi-rural residents are the least educated and most likely to have experienced a recent malaria episode; peri-urban residents are the least wealthy, display the lowest level of general malaria knowledge, and are slowest to seek treatment. For malaria morbidity and a variety of socio-demographic indicators, peri-urban residents are intermediate between urban and semi-rural. However, peri-urban and semi-rural dwellers are much more similar to each other than to urban residents in terms of preventive and, to a lesser extent, treatment-seeking behaviors. This resemblance is somewhat counterintuitive, since the variables known to mitigate transmission in urban areas (e.g., high population density, low availability of breeding sites, high pollution) (Trape and Zoulani 1987b) are most pronounced in slum-like peri-urban zones, and since the physical access to social, economic and civic institutions of peri-urban dwellers more closely mirrors urban than rural inhabitants. There is a sense that peri-urban areas should be intermediate, geographically and epidemiologically, between urban and rural, and without strict definitions, it is unsurprising that this assumption is reflected in most summary measures of malaria across these zones. The similarity of peri-urban to rural areas has been observed in other contexts (see, e.g., Robert et al. 2003) and implies that rural interventions may in some cases be more effective in peri-urban areas than those developed for cities as a whole.

The Abuja Declaration of 2000 established 60% goals for ownership of ITNs and provision of PAT for malaria (World Health Organization 2000), goals that remain distant for many Kisumu residents. The observed figure of 57.7% ownership of bednets (treated or not) for the study area matches the proportion (56%) noted by a recent study of preventive behaviors in Kisumu (Macintyre et al. 2002). Ownership of ITNs is moderately high (43%) in the urban zone, as is general knowledge of malaria (74.1%). Since the ITN rate is based on recall of treatment within the past year, this figure is likely an underestimate, as some nets must have been bought pre-treated in the year prior to the survey. In this context, provision of partially or wholly subsidized retreatment for currently owned bednets could boost the proportion of ITNs close to the RBM goal. The comparatively high wealth and education of urban residents implies that partial subsidization may provide a low-cost yet effective intervention in these areas, while allowing for cost recovery at some level.

The high level of use of mosquito coils, especially by the poor and the less educated, tallies with evidence of similar patterns from Kisumu and other urban areas (see, e.g., Macintyre et al. 2002; Njama et al. 2003). Reliance on mosquito coils for prevention, despite higher long-term costs and lower efficacy, is a problem that must be addressed. In non-urban areas, ITN ownership is much lower, as is knowledge of malaria, such that subsidies for retreatment are unlikely to form effective strategies. Interventions should focus on subsidization of new net purchases, particularly for long-lasting ITNs, and on education programs emphasizing the relative benefits of ITNs versus

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mosquito coils. ITN promotion and/or distribution may be particularly important where peri-urban zones adjoin major mosquito breeding sites, as very high population densities in these areas imply risk for large numbers of residents, and create the potential for highly cost-efficient interventions.

Patterns of treatment-seeking behavior are more complicated. The overall proportion of PAT is very low; just 20.8% of ill children receive SP within a day of falling ill, with an average delay of 1.5 days before medication. This delay may reflect the familiarity of Kisumu residents with malaria and/or the non-specific nature of symptoms. Residents may wait to be sure that a specific case needs treatment before providing medication and expending limited resources. It is significant that, while SP was the first-line antimalarial for Kenya during the study period, amodiaquine was also a commonly prescribed and effective treatment. If the latter is included in the definition, the proportion receiving PAT rises to 30.8%. Thus, the proportion of ill children that received an effective antimalarial in the critical time period is likely higher than the official figure according to the WHO definition, a fact tempered by the lack of dosage information in this study and the low likelihood of correct dosage given self-treatment (Marsh et al. 1999; Nyamongo 1999; Hamel et al. 2001). We observed a very low level of reported self-treatment in our sample compared with other studies in urban SSA, but this is likely an artifact of the survey questionnaire, given the very high level of medication of ill children, and the shorter average time between onset of illness and medication than between onset of illness and reported treatment-seeking.

Though there were no significant differences in the proportions of residents providing PAT across urban zones, urban caregivers wait longer than others before providing medicine to their ill children. Peri-urban residents report more illness than urban, and wait the longest of all groups before seeking treatment, while providing medication the soonest[3]. The pattern for urban residents may reflect a high level of confidence in the availability of emergency health services or a reluctance to medicate without medical advice, given that such advice is easier to obtain. The close correspondence of time to treatment with time to medication may also imply that urban dwellers are waiting for diagnosis in the formal health sector before medicating. If this is true, any intervention that increases the efficiency and turnover rate for local hospitals and clinics should raise the proportion of PAT. Clearly, education on appropriate drug choice and dosage is also needed.

Although distance from health facilities was not evaluated statistically, it does not appear to be a major factor in timing of treatment or medication; semi-rural residents, who are generally live at a greater distance from the urban center than urban and peri-urban residents, fall between the latter two in terms of timing. Since peri-urban dwellers tend to medicate more quickly than others, an extra effort should be made to provide education on correct drug choice and dosage, especially in the context of the Kenyan government's recent decision to shift the first-line antimalarial from SP to artemisinin-based combination therapy (ACT). This effort should be aimed at both caregivers and shopkeepers, given the high level of utilization of self-treatment options.

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[3] It seems likely that caregivers did not usually interpret self-treatment (i.e., giving medicine to their sick children) as "treatment-seeking," for the purposes of their responses to the KAP survey.

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The classification of urban areas is a non-trivial exercise in the description of urban malaria. At a minimum, the different results obtained using the clustering algorithm illustrate the risks of generalizing results from studies where "urban," "peri-urban," and/or "rural" are undefined. Moreover, the earlier methods often produce zones encompassing very small populations, which are of little use when attempting to target local interventions or identify community deficits in knowledge or malaria prevention behavior. This is likely to be even truer in more densely populated and/or larger urban areas throughout Africa than in Kisumu. It is worth noting that using much higher population density thresholds produces urbanization maps that superficially resemble that obtained through clustering (results not shown). However, the highest-density areas, rather than being the most urban, correspond to the peri-urban areas in the cluster solution. Population density is fundamentally incapable of defining urbanization, a multi-factorial concept, on its own, as the most highly populated areas are not usually the most 'urban.'

Apart from national guidelines, a large amount of research has gone into defining urban extents and classifying urban areas using remote sensing. Most notably, the Global Rural-Urban Mapping Project (GRUMP) has used nighttime lights (NTL) in conjunction with local lists of settled areas to construct a worldwide mask of urban extents (Hay et al. 2005). This has been combined in various ways with the Gridded Population of the World (GPW) maps to derive estimates of urban populations. In addition, several authors have described algorithms for using remotely sensed data to classify urban areas for

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malaria research (see, e.g., Tatem and Hay 2004). These efforts are essential to the construction of continental risk maps and the estimation of the overall burden of malaria attributable to urban areas, but both skirt the fundamental issue of defining urban for use in malaria epidemiology. Nighttime lights are a proxy for population density, which, as discussed above, is an inadequate measure of urbanization. It is unlikely that remote sensing alone can resolve this issue; rather, it should be one component of a classification method that includes socio-demographic data.

We attempted to choose a minimum set of indicator variables that captures important variation in urbanization yet is available to researchers and public health ministries *a priori* or with a minimum of field research. In doing so, we identified three factors that explain a large amount of the variation in the original variables. While these factors, *per se*, are unmeasurable, we can interpret their meanings based on factor loadings (Table 3.1) and distributions (Fig. 3.1). These suggest that Factor I relates to agriculture, or more generally vegetation, since population density is low and home ownership and NDVI high both in areas with rural character and in wealthy urban neighborhoods Factor II is likely a proxy for infrastructure, associated with access to piped water and proximity to the town center. Strong loadings on use of electricity and completion of primary school may indicate that Factor III is related to wealth, though this interpretation is less straightforward.

It is clear that these three fundamental elements (i.e., vegetation, infrastructure and wealth) better describe urbanization than do simple characterizations based on single

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variables. Nonetheless, this study has likely overlooked variables and combinations thereof that would produce better solutions. We believe the debate over a widely-applicable solution is vital, and must address the following:

- Necessary and sufficient classification variables

- Optimal number of classification levels

- Optimal scale of classification units

- Standardization of methods to maximize speed and cost-efficiency

- Integration of modern technology (e.g. remote sensing)

- Statistical methods for meta-analysis, given varying solutions for different cities

A key point arising from this analysis is that cities can be classified into levels of urbanization using a standard, repeatable and unbiased process, based on variables that should be readily available to local health ministries and researchers alike, and incorporating both remotely-sensed data and socio-demographic information. This process should permit more relevant comparisons between and within urban areas and should inform targeted urban malaria interventions, the definition and mapping of urban boundaries and ecotypes as relevant to malaria, and estimates of urban malaria morbidity.

There are several limitations to this study. Only a subset of EAs in the study area was sampled due to resource limitations. It is possible that environmental or socio-demographic variation in unsampled EAs could shift some of the conclusions, though we expect any bias to be towards the null, since unsampled EAs are randomly distributed.

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The small number of samples in some EAs decreased the accuracy of proportions for the EA-level summary variables in those areas, though the classification map appears coherent. A different choice of study area, or of units of analysis, might have yielded different answers. We have not attempted to define risk factors for malaria in this paper, but Chapter 4 examines these in detail for severe malarial anemia.

It is clear that malaria plays an ongoing role in the lives of residents of Kisumu, and moreover that they are conversant with the causation and natural history of the disease. Nonetheless, prevention and treatment activities remain well short of their targets. Further research is needed on the causes of delay in treatment and medication, on dosage patterns and how these all vary by level of urbanization, and on the response of intra-urban communities to specific interventions. Perhaps most importantly, a consensus is needed within the malaria epidemiologic community on what constitutes urban, in order to allow for mutually complementary research programs.

Table 3.1: Principal Component Analysis Factor Loadings for Enumeration Area-Level Urbanization Variables

Variable	Factor I	Factor II	Factor III
Proportion of caregivers completing primary school	0.00098	-0.04665	**0.89380**
Proportion of households with access to electricity	-0.03707	0.39822	**0.72166**
Proportion of households that own their dwelling	**0.67133**	-0.16530	-0.22856
Proportion of households with piped water	0.11341	**0.86257**	0.21333
Population density	**-0.71133**	-0.17275	-0.19904
Distance from center of town	0.32208	**-0.80290**	0.00288
Mean NDVI*	**0.82191**	-0.18915	-0.01660

* NDVI = Normalized Difference Vegetation Index

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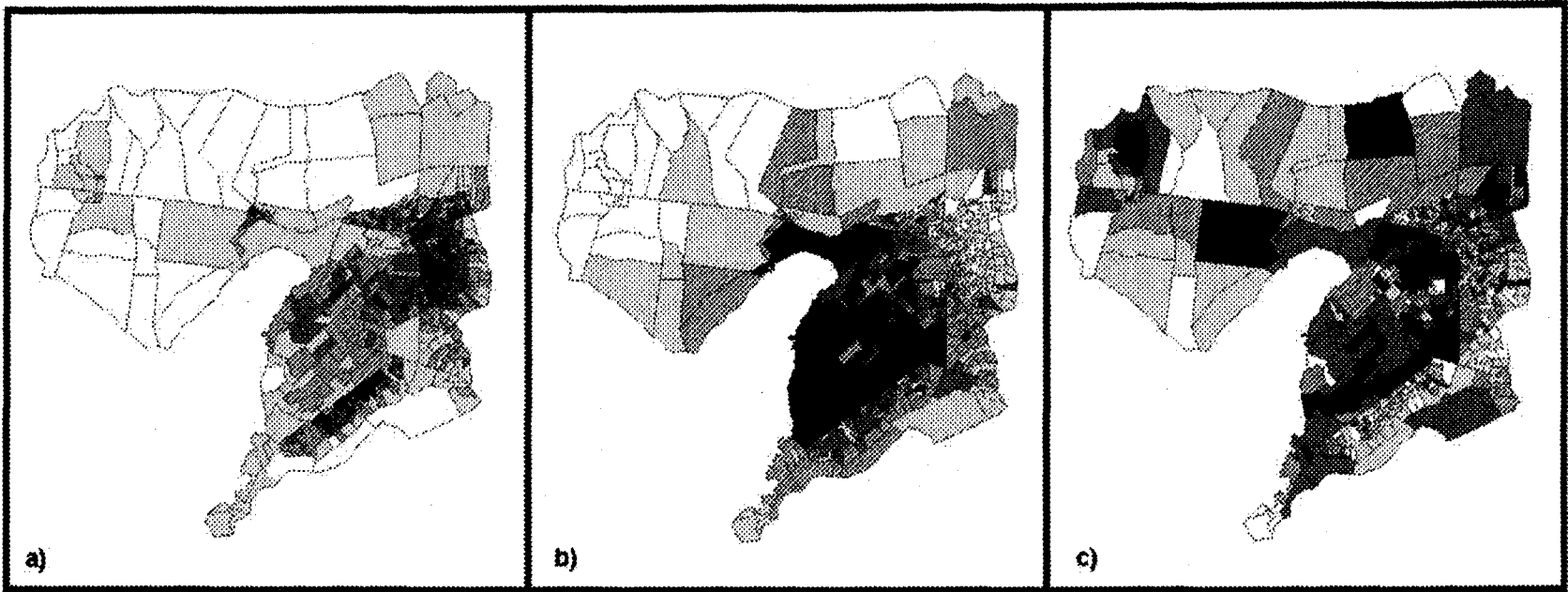
Figure 3.1: Spatial Distribution of Principal Component Factors for Urbanization-Related Variables: a) Factor 1: Agriculture/Vegetation; b) Factor 2: Infrastructure; c) Factor 3: Wealth

Figure 3.2: Classification of Level of Urbanization in Kisumu, Kenya Using Three Methods
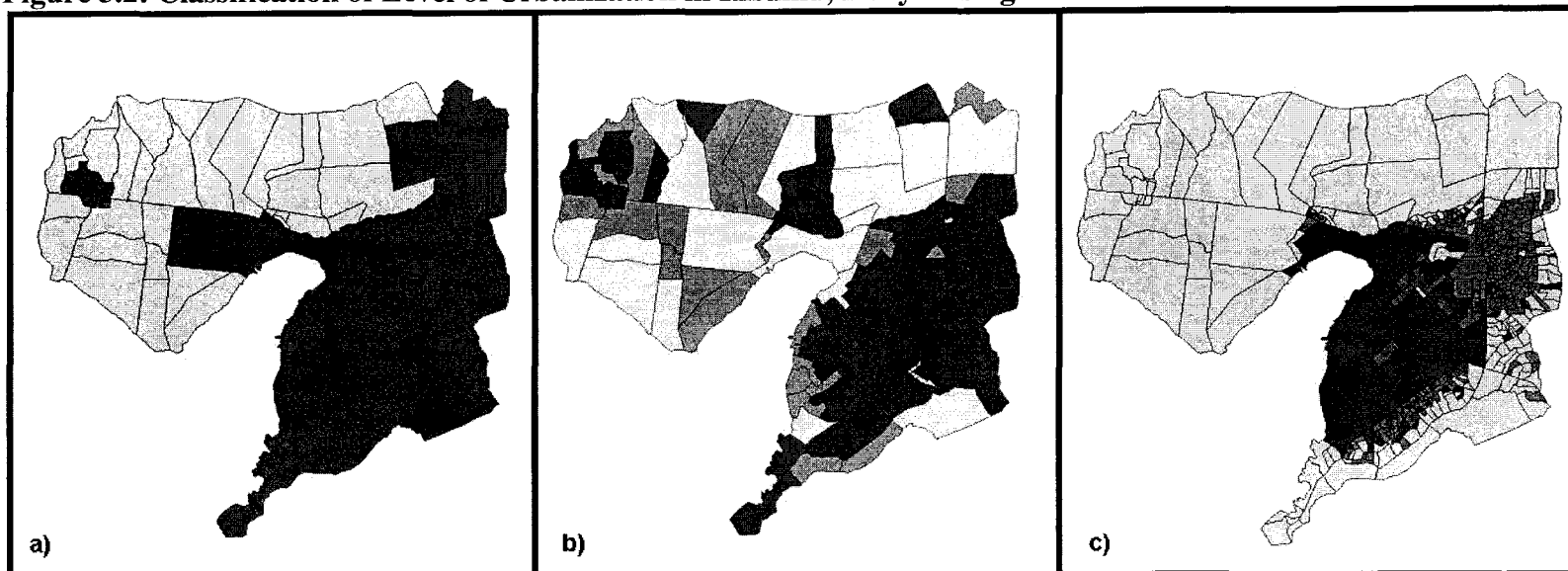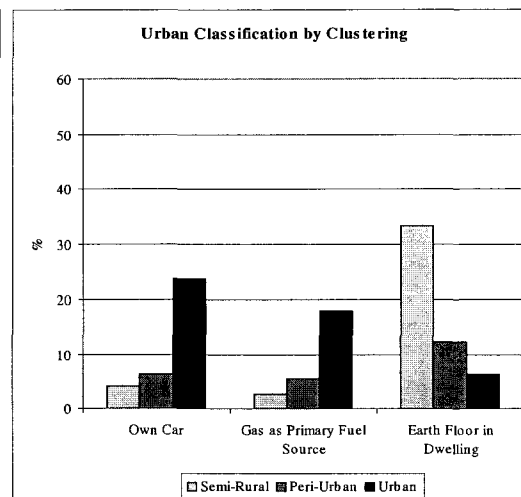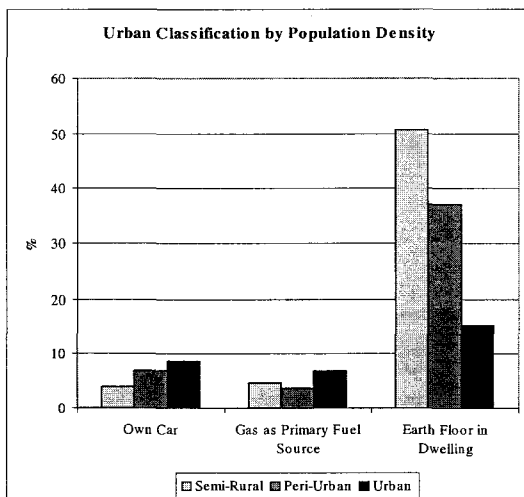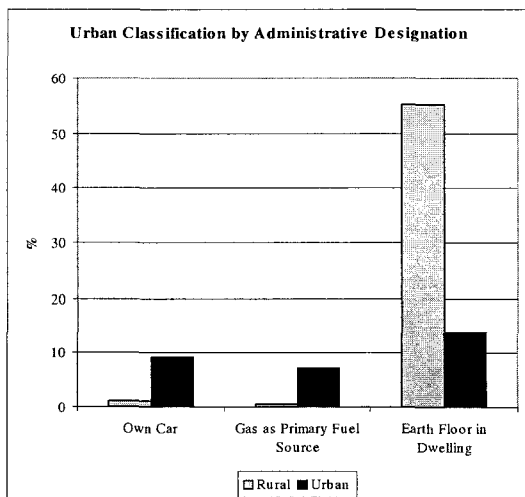
Table 3.2: Urbanization Indicators and Population in Relation to Three Urban Classification Systems

Classification System:	Administrative Designation				Population Density Thresholds					Clustering				
Variable	Semi-Rural	Urban	Test Statistic	P-value	Semi-Rural	Peri-Urban	Urban	Test Statistic	P-value	Semi-Rural	Peri-Urban	Urban	Test Statistic	P-value
Car ownership	1.1%	9.2%	29.4	< 0.0001	4%	7%	8.7%	4.7	0.094	4.2%	6.4%	23.8%	251.2	< 0.0001
Gas as primary fuel source	0.5%	7.3%	25.3	< 0.0001	4.7%	3.8%	6.9%	3.9	0.143	2.8%	5.5%	18.1%	178.6	< 0.0001
Earth floor in dwelling	55.3%	13.9%	411.3	< 0.0001	50.7%	37.1%	15.3%	177.5	< 0.0001	33.2%	12.2%	6.4%	322.4	< 0.0001
Proportion of population	8.7%	91.3%			3.5%	4.3%	92.3%			29.6%	54.6%	15.8%		

Table 3.3: Survey Demographics by Level of Urbanization

Variable	Overall % (N=4,336)	Urban % (N = 684)	Peri-Urban % (N = 2,369)	Semi-Rural % (N = 1,283)
Size of Household				
2-4	51.1	45.9	52.9	50.7
5-7	40.9	43.4	39..8	41.5
8+	8.0	10.7	7.3	7.8
Education of Caregiver (yrs)				
None	2.0	1.2	1.9	2.7
Primary	44.4	37.4	43.5	49.9
Some secondary +	53.6	61.4	54.7	47.4
Age of Caregiver (yrs)				
< 20	16.7	17.5	16.9	15.9
21–30	51.9	48.3	53.7	50.4
31–40	24.6	27.8	23.5	25.1
41–50	5.1	5.3	4.4	6.1
> 50	1.7	1.2	1.4	2.6
Sex of Caregiver				
F	85.4	83.2	87.3	83.0
M	14.6	16.8	12.7	17.0
Marital Status of Caregiver				
Married	74.8	71.9	75.6	75.0
Single	25.2	28.2	24.4	25.0
Age of Child (yrs)				
0–6 months	6.3	6.6	6.3	6.2
6 months–1 year	6.9	5.6	7.0	7.4
1–2 years	13.5	13.2	14.9	11.2
2–3 years	16.2	15.8	16.3	16.4
3–4 years	12.5	13.2	12.7	11.7
4–5 years	10.1	11.8	9.8	9.8
5–10 years	34.5	33.9	33..0	37.3
Wealth Index (quintiles)				
I (Poorest))	19.9	10.6	22.5	20.0
II	19.3	16.8	20.9	17.5
III	20.7	17.5	21.3	21.5
IV	20.1	20.9	18.5	22.6
V (Wealthiest)	20.0	34.1	16.9	18.4

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Table 3.4: Causes, Methods of Prevention and Symptoms of Malaria Identified by Caregivers (N = 4,336)*

Causes of Malaria	%
Mosquitoes	94.1
Presence of mosquito habitats	22.5
Heat/Cold/Temperature change	19.3
Bad food or water	13
Personal exposure to mosquitoes	4.7
Caused by other disease	0.2
Get it from animals	0.1
Don't know	1.7
Methods of Malaria Prevention	
Bednets	77.1
Control of mosquito habitats	38.1
Malaria prophylaxis	30.8
Coils and similar measures	18.3
Killing adult mosquitoes	11
Repellent and other personal protection	9.7
Prayer/Ritual	0.1
Don't know	5
Symptoms of Malaria	
Fever/Chills/Shivering	87.8
Vomiting/Nausea	49.4
Headache	45.2
General pain/Joint pain/Aching	41.5
Loss of appetite	36.4
Tiredness/Lethargy/Malaise	17.9
Gas/Diarrhea/Stomachache	16
Dizziness	6.4
Jaundice/Pallor/Color change	5.4
Convulsions/Unconsciousness	3.8
Cough	3.6
Sore/Rash	1.4
Bleeding	0.4
Sore throat	0.3
Swelling	0.1
Don't know	0.4

Table 3.5: Use of Malaria-Preventive Measures *

Variable	Overall % (N=4,336)	Urban % (N = 684)	Peri-Urban % (N = 2,369)	Semi-Rural % (N = 1,283)
Preventive Measure				
Mosquito coils	59.8	50.0	59.8	64.9
Bednets	57.7	74.2	55.7	52.5
Insecticide/Spray	17.0	30.3	16.0	12.0
Insect Repellent/Lotion	1.3	1.6	1.3	1.0
Fire/Smoke	0.7	0.3	0.4	1.4
Protective clothing	0.4	0.2	0.4	0.3
Prayer/Ritual	0.0	0.0	0.0	0.0
No preventive measures	8.6	4.1	8.7	10.9
Only bednets	18.7	21.7	19.0	16.6
Only measures other than bednets	33.7	21.7	35.6	36.5
Bednets and other measures	39.0	52.6	36.6	36.0

*Reported percentages may not sum to 100%, as multiple responses were allowed.

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Table 3.6: Medicine Recently Provided for Malaria Treatment by Caregivers *

Medicine Provided	Percent receiving medication of those reporting illness during prior month (N = 1,893):
Analgesic	55.9
Sulfadoxine/Pyrimethamine	31.9
Amodiaquine	20.8
Antibiotics	15.9
Quinine	9.4
Chloroquine	8.8
Traditional medicine	0.2
Artemisinin	0.1
Don't know	6.0

*Reported percentages may not sum to 100%, as multiple responses were allowed.

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CHAPTER 4:

ENVIRONMENTAL AND SOCIO-DEMOGRAPHIC DETERMINANTS OF SEVERE MALARIAL ANEMIA IN AN URBAN SETTING: A CASE-CONTROL STUDY IN KISUMU, KENYA

Introduction

Only a small fraction of the 365 million annual cases of acute clinical malaria

progress to severe illness or death (Snow et al. 2005), though it is not fully understood

why many remain free of dangerous complications despite near-constant parasitization.

The most important manifestation of severe malaria is severe malarial anemia (SMA),

with an estimated 1.42–5.66 million cases and 0.19–0.97 million fatalities annually in

children under five, a case fatality rate over 13% (Murphy and Breman 2001). Over the

past decade, research has suggested a multiple-organ systemic pathology for malaria, in

which multiple pathways produce symptomatically similar syndromes (Maitland and

Marsh 2004; Clark and Cowden 2003), a much more complex picture than the traditional

view in which cerebral malaria (CM) and SMA represent two well-defined endpoints

with simple underlying pathogenic processes (Mackintosh, Beeson, and Marsh 2004).

This complicates the search for risk factors for specific severe malaria outcomes.

Nonetheless, broad distinctions are apparent in the distribution of these syndromes. SMA

tends to be the most important manifestation of severe malaria in highly endemic areas

(Marsh and Snow 1999), primarily affecting children aged six months to three years, with

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increasing transmission leading to earlier incidence. Where endemicity is low, SMA tends to occur in older children and assumes a less important role relative to CM.

While the effects of age and endemicity on SMA presentation are well-documented (Reyburn et al. 2005; Snow et al. 1997), the evidence for socioeconomic and environmental risk factors for SMA is often conflicting. In the Gambia, no association was found between severe malaria and house construction, wealth, crowding or educational characteristics of the mother (Koram et al. 1995); in Gabon, no SES factors were associated with SMA (Luckner et al. 1998). However, in Tanzania, higher quality of housing construction and educational level of the parents were significant protective factors (Kahigwa et al. 2002). The presence of domestic animals (Mbogo et al. 1999a; Snow et al. 1998), house ownership (Koram et al. 1995; Kahigwa et al. 2002; Snow et al. 1998), and use of mosquito coils (Snow et al. 1998; Carme et al. 1994; Koram et al. 1995) have also been identified as either risk or protective factors by various studies. The data on bednet usage is more complete, but no less convoluted: studies in Kenya, the Gambia and Gabon found no effect of bednet usage on SMA, severe malaria, and CM, respectively (Snow et al. 1998; Koram et al. 1995; Carme et al. 1994), whereas a number of studies have demonstrated protective effects (Holtz et al. 2002; Kahigwa et al. 2002), bednets were shown to beneficially impact hemoglobin levels in a long-term study in Western Kenya (ter Kuile et al. 2003) and a project in Malawi demonstrated a significant reduction in malaria cases resulting from an ITN social marketing program (Mathanga et al. 2005). A study on the Kenyan coast found no difference in the number of anopheline vectors between malaria case and control households, yet found the presence of small,

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temporary pools of water to be a risk factor (Mbogo et al. 1999b). Duration of symptoms and distance to hospital are among the few consistently identified risk factors (Koram et al. 1995; Kahigwa et al. 2002). More data needs to be gathered to identify the contexts in which these factors take on different effects.

One context in which SMA has rarely been examined is the urban environment. Compared with malaria in traditional environments, urban malaria has received little attention until recently, despite the accelerating urbanization of Africa, with the highest urban growth rates in the world (UNFPA 1999). In part, this is due to the observation that transmission is almost inevitably lower in large urban centers relative to rural areas, due to the lower availability of breeding sites, ratio of vectors to humans, and range of vector dispersion (Trape et al. 1992). However, a number of factors suggest the potential for malaria outbreaks and severe malaria morbidity in urban areas in Africa, including: high levels of rural-urban migration; frequent commerce and travel between and among peripheral urban populations and outlying villages; the close proximity of low-transmission areas, and presumably low-immunity populations, to high-transmission zones; and the tradition of urban agriculture (UA), which may provide stable sources of infection for urban residents. A few studies have examined the epidemiological profile of SMA in urban areas (Afolabi et al. 2001; Modiano et al. 1998; Trape 1997; Gay-Andrieu et al. 2005; Klinkenberg et al. 2006), and there is substantial research on urban behavioral factors related to malaria (e.g., Nieto, Mendez, and Carrasquilla 1999; Snow et al. 1992; Molyneux et al. 1999), on urban entomological patterns (e.g., Olano, Carrasquilla, and Mendez 1997; Trape et al. 1992), and on the distribution of prevalent infection in urban

areas, generally in relation to proxies for transmission intensity, such as proximity to potential breeding sites (e.g., El Sayed et al. 2000; Thompson et al. 1997). Very few studies, however, have attempted strictly to identify risk factors specific to urban residents, suggesting that urban SMA morbidity has not been adequately investigated.

We conducted an unmatched case-control study to identify socio-demographic and environmental risk factors for SMA in Kisumu, Kenya, a city with high malaria endemicity. This city represents the most rapidly growing urban environment in Africa, i.e., cities under one million inhabitants (UNFPA 1999).

Methods

Study Area

This study was conducted in Kisumu (pop. 326,407) (Central Bureau of Statistics 2000) in western Kenya on the shores of Lake Victoria (Fig 4.1). 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. Transmission is highest after rainfall peaks during April–June and October–December. In rural areas near Kisumu, exposure to infective mosquito bites is estimated at 90–410 per year (Beier et al. 1990; Githeko et al. 1993). The study site was limited to the 'urban' core of Kisumu, and partitioned into three eco-epidemiological zones—urban, peri-urban and semi-rural—as described fully in Chapter 2.

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Kisumu District Hospital (KDH) is a government-run facility in central Kisumu, accounting for 13% of hospital beds in the district. It is one of the most important centers for the treatment of severe malaria arising in the urban area, along with Nyanza Provincial Hospital, the major referral center for the province. Data from a concurrent knowledge, attitudes and practices (KAP) survey (see Chapter 3) indicates that about half the population would go to KDH in a health emergency, more than any other health facility in the city. The United States Centers for Disease Control (CDC), in conjunction with the Kenya Medical Research Institute (KEMRI) maintained a continuous surveillance system for malaria at KDH, with ongoing collection of clinical and lab data, during and prior to the study period.

Study Design

This unmatched case-control study involved cases with SMA identified from among patients presenting at the pediatric inpatient ward of KDH from June 2002 to February 2003. Cases were defined as patients under 10 years of age presenting with hemoglobin $\leq$ 8 g/dL and parasite density $\geq$ 10,000/μL, that were resident within the study area. Cases that provided informed consent to participate in the study were accompanied to their home by a study interviewer who made local environmental and household observations and geolocated the case household. Controls were chosen from among respondents to the citywide KAP survey described in detail in Chapter 3. The criteria for inclusion as a control were 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.

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Clinical data for all 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 from HemoCue (HemoCue Inc., Lake Forest, CA) was used to measure hemoglobin levels. *Plasmodium* parasitemia was determined via standard methods of microscopic examination of Giemsa-stained blood smears.

Although the cross-sectional survey (Chapter 3) involved children under 10 years of age, controls in this case-control study were limited to age 7 or below, to better reflect the age distribution among cases[1]. The KAP survey was administered to cases at the hospital. A trained supervisor accompanied KAP survey and hospital interviewers on randomly selected occasions to ensure consistency. Data were processed using Cardiff Teleforms (Cardiff, Vista, CA) software and scanned directly into a Microsoft ® Access (Microsoft, Redmond, WA) database.

Survey Instrument and Ancillary Data

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. Some items referred to the household or to the selected child rather than the caregiver. In addition, wealth was assessed by constructing an index based on ownership of specific household items using principal

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[1] All identified cases were seven years of age or younger (see Results).

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components analysis (PCA) (Filmer and Pritchett 2001). The resulting distribution was divided into percentiles.

Population data were obtained from the Central Bureau of Statistics, and locations of survey households were determined using a handheld Garmin Etrex Global Positioning System (GPS) unit (Garmin, Olathe, KS). Geographic data were processed with Geographic Information System (GIS) software (ArcGIS, ESRI). Population density estimates were made using areas calculated in the GIS from regions digitized from detailed 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). NDVI, which ranges from −1 to 1, was transformed to a 200-point scale by adding 1 to the value and multiplying by 200, in order to create a more interpretable index and to enhance comparability with other studies (Eisele et al. 2003).

Statistical Analysis

Basic univariate distributions were produced for 32 potential risk factors and confounders and compared with case status using SAS v 9.1 (Cary, NC). Significant predictors were identified using chi-square tests for categorical and student's t-test or Wilcoxon's test for continuous variables. Fisher's exact test was used where necessary for sparse data. Caregiver characteristics were not considered as predictors because the different selection methods for cases and controls may have produced bias in those

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variables. All significant predictors were entered singly into logistic regression models for SMA to produce odds ratios (ORs).

A multivariate logistic model for SMA was constructed using the LOGISTIC procedure in SAS. In part, variable selection for this model was guided by the results of the bivariate analysis, but theoretical considerations were of primary interest. The limited number of cases (n = 80) constrained the number of variables that could be considered; on the one hand, research has shown that logistic models with less than 10 events per variable must be interpreted with caution (Peduzzi et al. 1996). On the other hand, the exclusion of important variables from a model can bias or invalidate results—as can the inclusion of extraneous variables.

Based on the known epidemiology of SMA, seven variables were included in the multivariate model *a priori*. These included: age of the child; ownership of bednets and use of mosquito coils, representing the most important preventive methods in terms of prevalence and effect; house construction, often cited as a potential risk factor for malaria[2]; recent travel by the selected child to a rural area, rarely investigated as a malaria risk factor in Africa; and wealth and level of urbanization, both indices that encompass a wide range of other socio-economic and environmental variables, including NDVI, distance to town, population density, ownership of transportation and luxury items etc. (see Chapter 2 for a description of level of urbanization).

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[2] An index variable was created measuring whether houses had open eaves or windows with inadequate (i.e., non-glass) covering, potentially allowing mosquitoes access to the household

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In addition, variables that met the Bonferroni significance criteria for multiple

testing (i.e., $p < 0.0016$) in bivariate analysis were included as potential risk factors in the

multivariate model. Interaction terms were not considered, due to the small sample size.

The final model was produced using a forward selection method, beginning with the

seven required variables, and including other variables that met criteria for multiple

testing during multivariate analysis. Multicollinearity among predictor variables was

assessed using variance inflation factors (VIFs), which are based on the extent of multiple

correlation between variables—low VIFs indicate low levels of multicollinearity.

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 (Schafer 1999). The Hosmer-Lemeshow goodness-of-fit test

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 in order 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. A sharp rise in the variogram at short distances indicates spatial

autocorrelation. We assessed the extent of autocorrelation in order to determine whether

parameter estimates needed adjustment for a correlated covariance structure.

Protection of Human Subjects

The protocol for this study was reviewed and approved by the institutional review boards of the University of Michigan (Ann Arbor, MI), the Centers for Disease Control and Prevention (Atlanta, GA), and the Kenya Medical Research Institute (Nairobi, Kenya). Written informed consent from participants was obtained prior to all interviews.

Results

From July 2002 to January 2003, 80 of 141 (57%) cases of SMA were identified and interviewed at KDH. More than half of those cases that were missed (i.e., not identified and interviewed) clustered in the first and last months of recruitment. Captured cases were slightly younger, smaller and weighed less than missed cases, though these relationships were non-significant (data not shown). Symptoms were comparable in actual and missed cases, except that the latter had significantly lower parasitemia (mean 35,218/μL versus mean 48,061/μL; t = 2.75, p = 0.0068). Captured cases were attended to and blood slides completed more quickly than for missed cases, though the differences were non-significant. Over the study period, 826 potential controls were identified for inclusion in the study from among 4,336 interviews conducted in the KAP survey.

As expected, age was found to be a very strong predictor of case status, with cases much more likely to be between six months and three years old than controls, and very few cases over five. All cases were seven years of age or younger. A number of characteristics of the caregiver and of the structure, environment and behavioral patterns of the household were found to be significantly ($\alpha = 0.05$) related to SMA in bivariate

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analysis, and are listed in Table 4.1. Variables found to be non-significant are listed in Table 4.2. Over and above the seven variables designated a priori for inclusion in the final model, eight variables met the Bonferroni criteria for multiple testing, and were included as candidate variables in the forward-selected multivariate model. These included: gender of the household head, ownership of land other than the residence, ownership of rural land, prior residence in a rural area, standing or running water in close proximity to the home, use of natural water sources (i.e., streams, ponds, etc.) for washing water, overnight presence of domestic animals at the household, and household size.

Table 4.3 shows effects obtained for risk factors through multivariate logistic regression modelling. Candidate variables were screened for multicollinearity: among the twelve variables in the final model, no VIF was greater than 1.4, and correlations were generally low, always below 0.35, indicating no significant multicollinearity. A Box-Tidwell transformation of the wealth index did not indicate a nonlinear relationship between wealth and the logit of case status, so wealth was treated as a continuous variable. Age category was a strong predictor of case status, as expected. Net ownership had no effect on case status; use of mosquito coils was protective, but non-significant. Relative to living in an urban enumeration area (EA), children in semi-rural and peri-urban areas were more likely to be cases, though neither association was significant, nor was increased risk from open house construction. Other variables found to be significant risk factors in the final model included ownership of land other than the residence (OR = 3.99), presence of standing or running water within 10m of the household (OR = 4.83),

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presence of domestic animals overnight at the household (OR = 3.86), and number of people in the household (OR = 1.37). Most significantly, the odds of being a case were over nine times higher for children from households where the child had spent at least night in a rural area during the previous month.

The max-rescaled-r-square for the model was approximately 45%, indicating moderate predictive ability. The Hosmer-Lemeshow goodness-of-fit test was non-significant, suggesting a decent fit to the data. Residuals for the logistic model were examined to assess model fit. Though several outliers were observed, few observations had exceptionally high influence. Deletion of the most extreme outliers did not seriously affect parameter estimates. The deviance residuals for the initial multivariate model were used to fit a variogram, which did not indicate spatial autocorrelation in the results (data not shown).

Discussion

This study illustrates the significance of SMA in an urban setting of high endemicity. The age range for cases more closely approximates the age distribution commonly seen in rural high-transmission areas than the older distribution that has occasionally been observed in African cities or other regions with intermittent or low-level transmission (Reyburn et al. 2005). We did not observe any cerebral malaria among admissions to KDH during this time period, though a major reason for this may be the difficulty of diagnosis for this syndrome; there is considerable interobserver variation in assessing cerebral malaria and it is often misdiagnosed in clinic and hospital settings (Makani et al. 2003; Newton et al. 1990). Nonetheless, the distinctively 'rural' profile of

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severe malaria observed is consistent with the finding that recent travel to rural areas was an extremely strong risk factor for SMA. Though not included in multivariate analysis, prior residence in a rural area was likewise a strong risk factor for SMA, and may also imply closer ties to rural areas and increased travel frequency.

On the one hand, these observations suggest that, in hyperendemic areas such as Kisumu, immunity, and therefore the profile of severe disease, may depend more upon contact with the rural periphery than on intra-urban transmission. In fact, children who travel regularly to rural areas are likely to come into frequent contact with much higher transmission rates than they experience in the city. On the other hand, the fact that nearly half of SMA cases arose in households where there is no evidence of travel to rural areas indicates that at least some transmission must be occurring within the city. Nonetheless, the very high risk observed for recent travelers demands attention and further research to clarify the role of specific travel patterns in determining risk.

The failure of bednets to show any significant effect on SMA was unexpected, though not unprecedented (Snow et al. 1998). A possible explanation for this finding is that, as indicated above, a large proportion of exposure leading to SMA may occur during excursions from the urban area. If this were true, then use of bednets or ITNs during time in the city would have little effect on risk, as observed. House construction, as parameterized in this study, constitutes another level of barrier protection, and was similarly non-significant in multivariate analysis, perhaps for the same reasons. Mosquito coils, protective in this context, were close to being significant; this is difficult

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to explain, but not unprecedented (Snow et al. 1998). We did not examine household bednets, and cannot be sure of their condition or physical integrity—it may be that area methods such as mosquito coils or other repellents are more effective than nets in poor repair. It is also possible that the effect of coils is related to differential use and effect among residents at different levels of urbanization. Though we were not able to evaluate interaction terms, it is possible that coils and repellents, utilized disproportionately by poorer and less urban residents, have a greater effect where mosquitoes are more abundant. Larger studies should consider interactions of preventive methods with level of urbanization.

The overall effect of level of urbanization on risk for SMA was non-significant, though residence in particular zones had marginally significant effects, and a number of the individual variables that go into estimating level of urbanization were associated with disease at a significance level which suggested a strong relationship, but did not meet stringent criteria for inclusion in the multivariate analysis . Among these were distance to the hospital, population density, source of water and NDVI. Distance has been implicated in the development of severe malaria (e.g., Schellenberg et al. 1998) as has population density, either directly (Snow et al. 1997) or by implication in studies of urban versus rural environments. Exposure to breeding sites is commonly noted as a risk factor for malaria (Staedke et al. 2003; Trape and Zoulani 1987); in this case, both the presence of water near the house and the use of water from natural sources (i.e., streams, ponds, rivers) were identified as risk factors for SMA. It is unclear why level of urbanization as a whole was non-significant, but it may have to do with the unexpected effect of NDVI, which acted in a manner opposite to that anticipated. Higher NDVI, indicating higher

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vegetation, was associated with lower risk for SMA. This relationship held true at multiple scales; i.e., whether NDVI was assessed within 25m of the household, 50m, 100m or 200m, though effects were only significant for the first two distances, and decreased monotonically (data not shown). This effect of NDVI is probably related to at least two factors. First, the lowest NDVIs are found in peri-urban areas, whose residents are most likely to travel to rural areas outside the city. Second, high NDVIs are often observed in areas with very high socioeconomic standards, where access to prevention and treatment are much higher.

This study has several limitations that arose during implementation or analysis. The most important is the limited sample size, which dramatically limits our ability to make inferences about potential risk factors. Accurate parameter estimates for logistic regressions depend in part on the inclusion of all relevant variables, and it is likely that some important variables were not included in this study, as evidenced by the risk factors that were significant on bivariate analysis, but not included in the multivariate model. Conversely, accurate models also depend on the exclusion of irrelevant factors and on avoiding overfitting of the model by limiting the number of variables considered in relation to the number of events (Peduzzi et al. 1996). The final model in this instance had 6.7 events per variable, lower than the recommended level, so specific risk estimates should be treated with caution. 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 good compromise under

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the circumstances, though a larger study over a longer period of time would be better suited to evaluate the multifactorial nature of SMA risk.

A major limitation was the failure to capture about 40% of cases at KDH. It is unclear why the study failed to capture certain cases, but differences between identified and missed cases are minimal, and not expected to bias the analysis. The cases that were captured were, in general, sicker than the missed cases, such that results from this study may only be applicable to more severe cases of SMA. Also, 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 been some combination of inability to handle the caseload with interviewer inexperience or fatigue.

Two methodological limitations also affected the results. Although the controls were selected to be population-representative and to reflect the catchment area of KDH, estimates may be biased to the extent that individuals inaccurately reported their hospital preference, or that sick cases fail to report to the hospital at all. In addition, the different selection procedures for cases and controls make it impossible to estimate the effect of caregiver characteristics on presentation with SMA, which in other settings have proved to be important risk factors. Though we observed strong effects for caregiver gender, status, schooling and age (data not shown), it is unclear whether these reflect actual risk factors for SMA, or simply which member of the household is likely to be available to bring a child to the hospital during working hours. Given the limitation of needing to conduct interviews in the hospital, this may be a difficult obstacle to overcome, but future studies would benefit from an attempt to conduct all interviews (i.e., case and control

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interviews) at the family residence, and to more strictly define "primary caregiver" during the recruitment process.

The different origins for SMA cases implicit in these data suggest that different prevention and control strategies may be necessary for urban residents who travel frequently to rural areas, a large and growing class. In some cases, traditional strategies may be ineffective for this group, as when families that use bednets at home fail to do so when traveling. In particular, travel histories and their impact on severe malaria need to be more carefully described in Africa, where studies have so far been very limited on this topic. At the same time, both the presentation of these cases within urban areas and the limited window within which they seem to experience exposure (i.e., during travel to rural areas) present opportunities for effective and efficient control that are often unavailable in remote areas where access to health facilities is limited. A better understanding of risk factors should allow for effective targeting of control strategies in this group.

Likewise, we need a clearer picture of risk factors for severe malaria for those urban residents who do not travel, about half the sample in this study. A major component of this research should focus on describing the urban environment and delineating the specific elements of urbanization that may increase risk. The method for describing urbanization described in Chapter 3 is a step toward this goal, but the failure of this characterization to fully capture significant risk for severe malaria implies the need for further research.

Table 4.1: Study factors associated with severe malarial anemia in bivariate analysis in Kisumu, Kenya (n = 906)

Categorical Variable	Cases (n = 80)	Controls (n = 826)	Odds Ratio	p-value
Household head is male	70 (87.5%)	565 (68.6%)	3.21 (1.63, 6.33)	0.0004
Ownership of land other than residence	62 (77.5%)	406 (49.4%)	3.53 (2.05, 6.07)	<0.0001
Ownership of rural land	49 (61.3%)	267 (32.5%)	3.29 (2.05, 5.27)	<0.0001
Prior residence was rural	32 (41.6%)	128 (16.0%)	3.74 (2.29, 6.11)	<0.0001
Standing or running water w/in 10m	32 (46.4%)	149 (18.1%)	3.92 (2.37, 6.50)	<0.0001
Primary source of washing water is natural	16 (20.0%)	63 (7.6%)	3.03 (1.65, 5.55)	0.0002
House has open eaves or poorly covered windows	58 (79.5%)	539 (65.7%)	2.02 (1.13, 3,63)	0.0164
Domestic animals kept overnight at residence	22 (27.5%)	103 (12.5%)	2.66 (1.56, 4.53)	0.0002
Child spent at least one night in a rural area in previous month	36 (46.2%)	111 (13.8%)	12.53 (7.05, 22.23)	<0.0001
Use mosquito coils for malaria prevention	42 (52.5%)	555 (67.4%)	0.54 (0.34, 0.85)	0.0074
Child's age				<0.0001
< 6 months	8 (10.0%)	86 (10.4%)	5.89 (1.53, 22.73)	0.0101
6 months - 3 years	61 (76.3%)	338 (40.9%)	11.42(3.53, 36.88)	<0.0001
3 - 5 years	8 (10.0%)	212 (25.7%)	2.39 (0.63, 9.13)	0.2032
> 5 years	3 (3.8%)	190 (23.0%)	REF	REF

Continuous Variable	Case Mean	Control Mean	Odds Ratio	p
Number of people in household	5.09 (4.69, 5.48)	4.32 (4.21, 4.43)	1.26 (1.12, 1.42)	0.0001
NDVI (within 25m of household)	124.9 (121.9, 128.0)	129.5 (128.5, 130.4)	0.98 (0.96, 0.99)	0.0068
Length of time in current residence (years)	5.78 (4.13, 7.43)	4.11 (3.74, 4.49)	1.04 (1.01, 1.07)	0.0165

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Table 4.2: Study factors not associated with severe malarial anemia in bivariate analysis in Kisumu, Kenya (n = 906)

Variable	Cases (n = 80)	Controls (n = 826)	Odds Ratio (95% CI)	p-value
House wall materials (stone or brick)	28 (38.4%)	314 (38.1%)	1.01 (0.62, 1.66)	0.9540
House floor not earthen	61 (83.6%)	665 (80.5%)	1.23 (0.65, 2.34)	0.5259
Presence of windows	70 (95.9%)	800 (96.9%)	0.76 (0.22, 2.57)	0.7244
Bednet ownership	45 (56.3%)	431 (52.2%)	1.18 (0.74, 1.87)	0.4863
ITN ownership	20 (25.0%)	220 (26.6%)	0.92 (0.54, 1.56)	0.7518
Ownership of current residence	21 (26.3%)	207 (25.2%)	1.05 (0.63, 1.78)	0.8434
Presence of wage-earner other than caregiver	41 (51.3%)	365 (44.2%)	1.33 (0.84, 2.10)	0.2253
At least one self-reported household case of malaria during previous month	25 (31.3%)	340 (41.2%)	0.65 (0.40, 1.06)	0.0829
Child slept under a bednet during previous week	41 (51.3%)	374 (45.4%)	1.26 (0.80, 2.0)	0.3152
Child shares a sleeping room	79 (100.0%)	800 (97.2%)	n.a.*	n.a.
Child was born in a rural area	11 (13.8%)	86 (10.4%)	1.37 (0.70, 2.69)	0.3586
Level of urbanization				0.3323
Semi-Rural	30 (37.5%)	291 (35.2%)	1.68 (0.78, 3.64)	0.3583
Peri-Urban	41 (51.3%)	388 (47.0%)	1.73 (0.82, 3.64)	0.2656
Urban	9 (11.3%)	147 (17.8%)	Reference	
Continuous Variable	**Case Mean**	**Control Mean**	**Odds Ratio**	**p-value**
Distance to lakeshore (km)	2.01 (1.78, 2.24)	2.08 (2.02, 2.14)	0.92 (0.72, 1.18)	0.5176
EA Population Density (/1,000)	16.0 (12.2, 19.9)	18.8 (17.3, 20.3)	0.99 (0.98, 1.00)	0.1914
Distance to hospital (km)	2.84 (2.57, 3.12)	2.58 (2.50, 2.66)	1.19 (1.00, 1.43)	0.0526
Proportion of household members sleeping under net during previous night	0.78 (0.68, 0.88)	0.83 (0.81, 0.86)	0.49 (0.17, 1.43)	0.3161
Wealth percentile	45.9 (40.1, 51.8)	49.8 (47.8, 51.8)	1.00 (0.99, 1.00)	0.2492
Number of nights child slept out of Kisumu during previous month	0.80 (0.37, 1.23)	0.34 (0.18, 0.50)	1.06 (0.99, 1.13)	0.1113

Table 4.3: Multivariate logistic regression of potential risk factors for severe malarial anemia in Kisumu, Kenya (n = 906)

Variable	Odds Ratio (95% CI)	p-value
Use mosquito coils for malaria prevention	0.58 (0.31, 1.08)	0.0853
Bednet ownership	0.94 (0.51, 1.73)	0.8334
House has open eaves or poorly covered windows	1.84 (0.83, 4.07)	0.1297
Child spent at least one night in a rural area in previous month	9.33 (4.42, 19.69)	**<0.0001**
Wealth percentile	0.98 (0.97, 0.99)	**0.0004**
Household head is male	3.63 (1.63, 8.12)	**0.0017**
Ownership of land other than household	3.99 (2.09, 7.64)	**<0.0001**
Standing or running water w/in 10m	4.83 (2.51, 9.28)	**<0.0001**
Domestic animals kept overnight at residence	3.86 (1.83, 8.12)	**0.0004**
Number of people in household	1.37 (1.16, 1.62)	**0.0002**
Level of urbanization		
Semi-rural	1.73 (0.65, 4.63)	0.2756
Peri-urban	2.01 (0.79, 5.09)	0.1415
Urban	Reference	
Child's age		
< 6 months	6.71 (1.46, 30.75)	**0.0143**
6 months - 3 years	18.86 (5.02, 70.88)	**<0.0001**
3 - 5 years	3.33 (0.76, 14.54)	0.1100
> 5 years	Reference	

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CHAPTER 5:

URBAN NEIGHBORHOOD-LEVEL VARIATION IN SELF-REPORTED AND SEVERE MALARIA INCIDENCE IN KISUMU, KENYA

Introduction

There is a strong spatial component to malaria transmission and morbidity. Cases

are more likely to occur near mosquito breeding sites (Carter, Mendis, and Roberts 2000)

and where human activities promote transmission or fail to prevent it. Clustering of cases

is likely to be more pronounced in urban areas, where mosquito breeding opportunities

are diminished and transmission is more highly focal than in rural zones (Trape and

Zoulani 1987). Considerable spatial variation in vector density has been observed even

in smaller villages (Smith et al. 1995). Immune exposure to malaria increased in relation

to vector density gradients in Dakar, Senegal (Trape et al. 1992), and urban malaria risk

has been related to proximity to breeding sites in Mozambique (Thompson et al. 1997)

and urban agriculture in Ghana (Afrane et al. 2004).

Clustering of severe malaria cases has been evaluated less frequently, but a study

on the Kenyan coast observed space-time clustering of severe cases in a rural

environment (Schellenberg et al. 1998), and a study in two cities in Ghana identified

marked heterogeneity in the distribution of malaria and severe anemia and stressed the

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importance of identifying and targeting specific areas for integrated malaria control (Klinkenberg et al. 2006).

The focal nature of malaria in cities presents opportunities for targeted intervention and control, yet there are difficulties in appropriately identifying target zones for intervention. Administrative districts often cross ecological and sociological boundaries and do not always comprise homogeneous epidemiologic regimes. A recent conference on urban malaria noted the importance of characterizing urban environments in such a way as to accurately identify environmental and other risk factors (Donnelly et al. 2005). Chapter 3 of this dissertation describes a method for categorizing cities into levels of urbanization. However, ideal targeting of malaria interventions requires classification on a finer scale, with regard for spatial context. Moreover, in the smaller, denser neighborhoods of cities, the community-level effects of risk factors may be as significant in determining individual risk as individual-level factors. Community-level effects have been observed for ITN usage (Hawley et al. 2003) in the context of malaria, and for a wide variety of other factors in the literature of ecologic studies.

For this analysis, we use a spatially-constrained clustering algorithm to identify homogeneous neighborhoods within an urban area and compare neighborhood-level variation in incidence of self-reported malaria and clinically confirmed severe malarial anemia (SMA). We examine evidence for spatial autocorrelation of malaria rates between neighborhoods and describe correlations between malaria outcomes and neighborhood-level environmental and socio-demographic variables.

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Methods

Study Area and Sampling

The study was conducted in Kisumu (pop. 326,407) (Central Bureau of Statistics 2000) located along the shores of Lake Victoria in southwestern Kenya. Kisumu represents the demographic setting within which most SSA population growth will occur over the next 30 years (UNFPA 1999), i.e., cities under 1 million inhabitants. Malaria transmission in adjacent rural areas is among the highest in East Africa with from 90 to 410 infectious bites per year (Beier et al. 1990; Githeko et al. 1993). Rainfall (1,000–1,500 mm/year) occurs in two seasons (April–June and October–December) and malaria transmission is highest at the end of each rainy season.

A citywide knowledge, attitudes and practices (KAP) survey was used to quantify socio-demographic factors related to malaria. Sampling methods for this survey are described in detail in Chapter 2. Briefly, 13 administrative sublocations with overall population densities greater than $1,000/km^2$ were selected from within the Kisumu municipal boundaries. The selected area contained 202,282 people in 54,403 households (Central Bureau of Statistics 2000). A map-based sampling scheme was used to select 4,550 sampling points—corresponding to households—in 473 of 567 enumeration areas (EAs), a 10% sample, with probability of selection proportional to population density. Within each household, a child was randomly designated as a participant from among all children under 10, and the primary caregiver interviewed. A total of 4,336 interviews were completed between July 2002 and January 2003.

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Concurrently, cases of SMA were identified at Kisumu District Hospital (KDH), a government-run facility in central Kisumu. The case identification process is described fully in Chapter 4. Briefly, the US Centers for Disease Control (CDC), in conjunction with the Kenya Medical Research Institute (KEMRI) maintained a continuous surveillance system for malaria at KDH, with ongoing collection of clinical and lab data, during and prior to the study period. Cases were defined as patients presenting at the inpatient ward with hemoglobin $\leq$ 8 g/dl and parasite density $\geq$ 10,000/μL, who were resident within the study area. Clinical data were obtained from the CDC/KEMRI surveillance group during the course of treatment and during the interview at KDH. Cases that provided informed consent to participate in the study were administered the KAP survey and accompanied to their homes by a study interviewer, who made local environmental and household observations and geolocated the case household. Of 141 cases presenting at KDH over the study period, 80 were interviewed and geolocated. Basic clinical and location information was available for all (i.e., 141) cases.

Survey Instrument and Ancillary Data

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

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analysis (PCA) (Filmer and Pritchett 2001). The resulting distribution was divided into percentiles.

Population data were obtained from the Central Bureau of Statistics (Central Bureau of Statistics 2000) and locations of survey households were determined using a handheld Garmin Etrex Global Positioning System (GPS) unit (Garmin, Olathe, KS). Geographic data were processed with Geographic Information System (GIS) software (ArcGIS, ESRI). Population density estimates were made using areas calculated in the GIS from regions digitized from detailed street maps and EA 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). NDVI, which ranges from -1 to 1 and represents surface vegetation level, was transformed to a 200-point scale by adding 1 to the value and multiplying by 200, in order to create a more interpretable index and to enhance comparability with other studies (Eisele et al. 2003).

Neighborhood Classification

BoundarySeer (Biomedware, Ann Arbor, MI) software was used to divide the study area into neighborhoods using a spatially-constrained agglomerative clustering algorithm. The clustering criteria included three factors related to urbanization identified by PCA and tentatively identified with a) presence of agriculture/vegetation; b) level of infrastructure; and c) wealth (see Chapter 3). In addition, likelihood of attendance at KDH was included as a factor relevant to targeting of health interventions. All factors

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were standardized by Z-score scaling prior to clustering, such that each variable had mean equal to 0 and standard deviation equal to 1, but different ranges. During the clustering process, each EA is initially considered a unique cluster. A proximity measure is calculated for each pair of spatially adjacent clusters, in this case the Euclidean distance between median values of the factors of interest. The most similar clusters are merged and the process is reiterated until a pre-specified cluster number is reached. To allow for ground knowledge to supplement the purely mathematical clustering algorithm, a cluster number higher than the one associated with maximum goodness-of-fit (i.e., maximum between-cluster sum of squares versus within-cluster sum of squares) was specified, and final aggregation into neighborhoods was accomplished manually. Singleton clusters were merged into the cluster with which they shared the largest boundary.

A set of variables potentially related to malaria at the community level were identified from the KAP survey and summarized for each of the defined neighborhoods. These included wealth, years of education, years of residence in the current dwelling, house construction, use of natural water sources, presence of standing or running water near the household, travel by household members to rural areas, ownership of domestic animals, ownership of bednets, use of mosquito coils and basic knowledge of malaria. Neighborhood-level NDVI and population density were abstracted from satellite and census data, respectively. Each of these variables was compared with incidence rates for self-reported malaria and SMA.

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Incidence Rate Calculation

Incidence of self-reported malaria in children under 10 years old was estimated from a KAP survey item asking whether the selected child had experienced an episode of malaria in the previous month. Each child thus contributed one person-month of risk, such that the overall proportion of children reporting recent malaria for the KAP survey is an expression of the monthly incidence rate, averaged over the 7 months of the study. This number was standardized to express incidence in episodes per 1,000 child-months, both overall and for each neighborhood individually[1].

Incidence of SMA was estimated from cases observed at KDH. For 80 interviewed cases, precise locations were available; for the remaining 61, each case was assigned to a neighborhood using self-reported location data collected during the course of normal surveillance by CDC/KEMRI. Where self-reported location data was ambiguous, but could be narrowed down to two or three neighborhoods, a fraction of a case was assigned to each candidate neighborhood. To find the population-at-risk, the population of each neighborhood was multiplied by the fraction under 10 years old estimated for urban areas by the Kenya DHS (i.e., 25.2%) (National Council for Population and Development (NCPD) 1999). The resulting figure was multiplied by the fraction of survey respondents that indicated KDH as their first-choice hospital in an emergency, in order to eliminate the population unlikely to present at KDH from

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[1] The estimation of an annual rate in this highly endemic area would, on average, imply multiple infections for each individual in the study area. However, the current study design does not permit the identification of recurrent malaria episodes in a single individual. Since it is impossible to estimate the effect of increasing immunity or changed preventive or treatment behavior after an initial episode, incidence for self-reported malaria has been preserved as a monthly rate.

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incidence calculations. The calculated rate was standardized to express incidence in episodes per 1,000 child-years for each neighborhood and overall.

Spatial Autocorrelation

In order to test for spatial autocorrelation in malaria incidence rates, Moran's I was calculated for distributions of self-reported malaria and SMA using GeoDa 0.9.5 (University of Illinois, Urbana-Champaign, IL). Moran's I tests whether the proportion of adjacent areas that have similarly high or low rates exceeds that expected if rates were distributed at random.

Statistical Analysis

We compared the incidence of self-reported malaria and SMA, and relationships between incidence of each and neighborhood-level independent variables, using the Spearman correlation coefficient, a non-parametric measure of comparative rank orders for two sets of observations. All calculations were performed in SAS v 9.1 (Cary, NC)

Protection of Human Subjects

The protocol for this study was reviewed and approved by the institutional review boards of the Centers for Disease Control and Prevention (Atlanta, GA), the Kenya Medical Research Institute (Nairobi, Kenya) and the University of Michigan (Ann Arbor, MI). Written informed consent from participants was obtained prior to all interviews.

Results

Neighborhood Identification

The clustering algorithm identified a set of eleven neighborhoods (Fig. 5.1), with a mean population of 18,389 (range: 830–92,668), mean area of 5.75 km^2 (range: 0.12 km^2–25.51 km^2) and mean population density of 6,156/km^2 (range: 198/km^2–23,997/km^2). An overlay of neighborhood boundaries with urban classification (Fig. 5.1) indicates that two neighborhoods consist mostly of urban EAs, four of peri-urban, and five of semi-rural; neighborhoods are labeled accordingly as U1–U2, PU1–PU4, and SR1–SR5. Two neighborhoods are substantially mixed (U2, PU4) and are categorized according to the provenance of the majority of their populations. Neighborhood boundaries differ substantially from boundaries of the nearest administrative equivalent, i.e., sublocations (Fig. 5.2).

Malaria Incidence and Spatial Autocorrelation

The mean incidence rates by neighborhood for self-reported malaria and SMA are 446.8 cases/1,000 children/month (range: 257.1–632.4 cases/1,000/month) and 16.3 cases/1,000 children/year (range: 5.2–38.8 cases/1,000/year), respectively (Table 5.1). There is no significant tendency for rates in adjacent neighborhoods to correlate for either self-reported malaria (Moran's I = -0.31, p = 0.20) or for SMA (Moran's I = -0.08, p = 0.54). Rates of self-reported malaria and SMA are uncorrelated at the neighborhood level (Spearman's R = -0.03, p = 0.94).

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Neighborhood-Level Correlations

Table 5.2 shows Spearman correlation factors and single linear regression coefficients for neighborhood-level factors with respect to self-reported malaria and SMA. A number of factors are strongly correlated with incidence of self-reported malaria, including wealth, length of schooling, household bednet ownership, and strong knowledge of malaria, each of which are associated with decreased incidence, and open household construction and use of a natural water source (e.g., pond, stream), which are associated with increased risk. None of the factors are strongly associated with incidence of SMA, though travel to a rural area by the caregiver, household head or child in the previous month approaches significance ($R = 0.51$, $p = 0.1$).

Discussion

The clustering algorithm described here attempts to identify neighborhoods that are epidemiologically homogeneous for factors related to malaria. The areas defined by this data-based method differ substantially from neighborhoods defined by administrative sublocation boundaries, in terms of the environments and populations they encompass. By implication, malaria interventions that are targeted at existing administrative units will prove inefficient in cases where these units encompass multiple epidemiologic regimes. For example, neighborhood PU3, with the highest rate of self-reported malaria and second-highest rate of SMA, is included entirely within a sublocation which is substantially semi-rural, with lower overall malaria rates (Fig 5.2). A sublocation-level analysis would fail to note this high-risk area, and intervention at the sublocation scale

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would be wasteful of effort, since the highest risk is bounded within a much smaller area than the sublocation itself.

The current method has limitations: the use of different proximity metrics leads to slightly different neighborhood categorizations (data not shown), and sensitivity analysis of the stability of neighborhood boundaries would be an appropriate further step. Furthermore, existing administrative and social structures must be involved in the management of interventions, and the practical experience of local health workers and ministries must guide neighborhood definitions to a certain extent.

Incidence rates for self-reported malaria and SMA were within expected ranges, though the former was quite high. The overall mean of 446.8 cases of malaria per 1,000 per month is substantially higher than the mean incidence rate (717/1,000/year, or 59.8/1,000/month) predicted for high-transmission urban settings by a recent effort to model malaria morbidity in Africa (Carneiro, Roca-Feltrer, and Schellenberg 2005). However, it is within the 95% uncertainty ranges estimated by the same review for two supplemental models with relaxed assumptions, including studies that examined older children and with shorter overall duration. The overall mean of 16.3 cases of SMA per 1,000 per year is near the high end of the inter-quartile range (2.5–18.9) estimated by the same review, while significantly lower than the 88.7 observed in a community-based study in nearby Asembo Bay (McElroy et al. 2000). However, the Asembo Bay study was restricted to 0–3 year-olds, in whom SMA rates would be expected to be higher. Though the SMA rate also reflects the use of an Hb cutoff of 8g/dL, as opposed to the 5

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g/dL cutoff used in some studies (definitions of SMA in the epidemiologic literature are rarely standardized, despite WHO guidelines), it remains a high incidence for an urban area in SSA.

We interpret these rates with some caution, for four reasons. First, it was not possible to obtain EA-level estimates of the under-10 population, so the populations-at-risk were estimated using the overall proportion of the population under 10 years old. To the extent that this proportion varies among EAs and neighborhoods, incidence rates will be inaccurate. Second, data was collected over a seven-month period, including the end of the first rainy season and entirety of the second. With a full year of data, incidence rates could have increased or decreased relative to those observed. Third, incidence rates for SMA are derived from just one hospital. We were able to define the catchment area for KDH by identifying the hospital of choice for survey respondents, and incidence rates for attendees at KDH should be accurate. Nonetheless, to the extent that attendees of other hospitals experience different rates of SMA, our results will be inaccurate. There are two other major hospitals in the study area. For one, Nyanza Provincial Hospital, we have no reason to believe that attendees differ in any substantial way from KDH attendees. The other, Aga Khan Hospital, serves a wealthier population, in which SMA rates might be expected to be lower. Attendees of Aga Khan hospital would come primarily from neighborhood U1, such that the rate of SMA in this neighborhood is likely to be an overestimate. Finally, there is a substantial degree of uncertainty in self-reporting of illness, though in high-malaria-transmission settings of SSA, diagnosis of malaria is presumptive when presenting with fever.

The lack of clustering among rates for self-reported malaria or SMA implies sharp boundaries for epidemiologic regimes in this urban context. In fact, the presence of high-incidence areas adjacent to low-incidence neighborhoods confirms the highly focal nature of transmission in this context, and strengthens the case for targeting of interventions. An unexpected finding was the lack of correlation between rates of severe and uncomplicated malaria. If severe episodes of malaria arise out of initially uncomplicated infections, there should be a degree of correlation between the observed neighborhood rates, all else being equal. These data suggest the presence of strong mechanisms affecting the development of severe disease in some communities.

Six factors were strongly correlated with incidence of self-reported malaria at the community level: wealth, schooling, house construction, use of natural water sources, ownership of bednets, and basic knowledge of malaria. Though it is not possible to infer causal relationships from this ecologic data, all of the associations are in the expected direction, and community-level effects are plausible. There are some inconsistencies in the data; for example, it is unclear why use of natural water sources should present as a risk factor, while both presence of water in proximity to the household and NDVI fail to do so. In some cases, neighborhoods may encompass such large areas that focal environmental risk factors are 'averaged out,' thus failing to show an association.

No factor was closely associated with incidence of SMA. This was unexpected, as 10 of 13 potential explanatory variables (excluding net ownership, population density

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and knowledge of malaria) were very strongly associated with SMA at the individual level (see Chapter 4). Travel to a rural area by a member of a household approaches significance in this context, and was a very strong risk factor at the individual level, which may imply that severe cases are often acquired on trips out of the city.

An important next step, for both self-reported malaria and SMA, will be to examine individual and community-level factors jointly in a multi-level model. The current study is limited by the small number of units of analysis, which limits analysis to non-parametric tests of association and precludes calculation of effect estimates or evaluation of interaction between risk factors. The addition of community-level data to individual-level models with higher sample sizes is likely to improve these models and to provide more detailed and accurate information on the effects of particular risk factors.

In summary, a spatially-constrained clustering algorithm was used to identify eleven neighborhoods in Kisumu, Kenya, which effectively captured differences in incidence of severe and uncomplicated malaria. Incidence of self-reported malaria was very high for high-transmission urban areas in SSA, while incidence of SMA was somewhat high. Severe and uncomplicated malaria exhibited markedly different distributions, and were uncorrelated at the neighborhood level. Further research is needed on community-level risk factors for malaria.

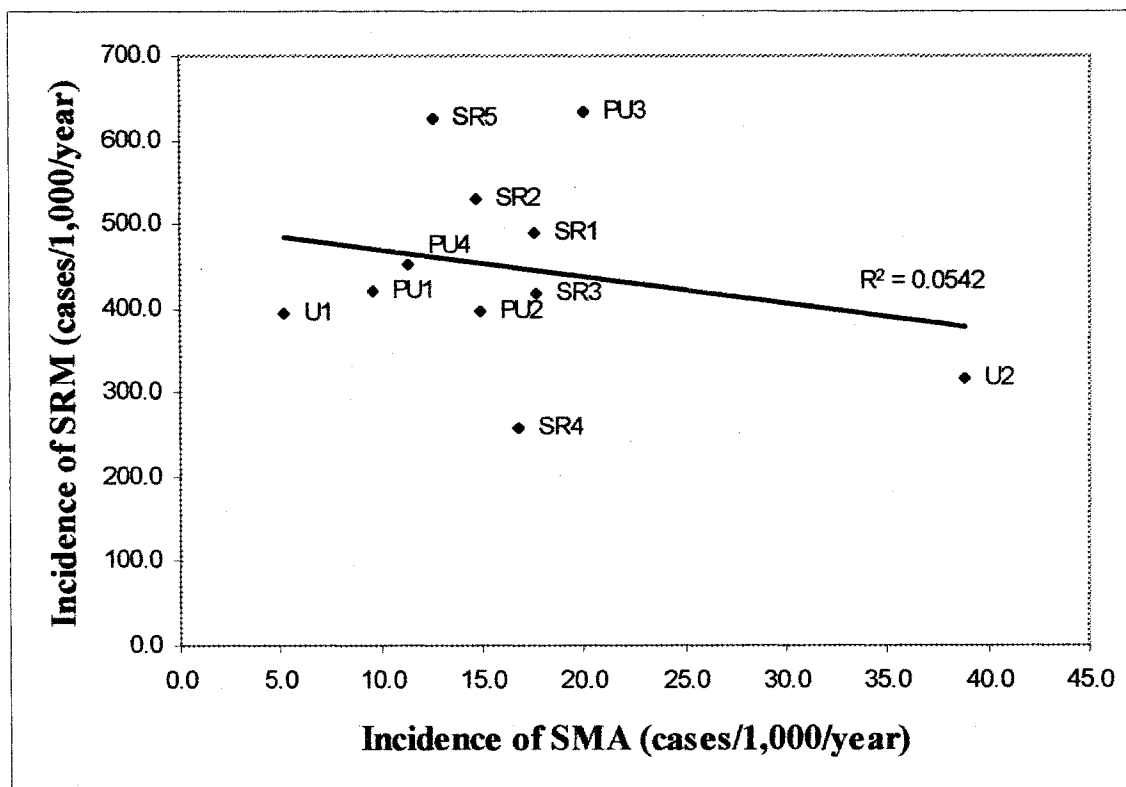121

Urbanization

- Semi-rural
- Peri-Urban
- Urban
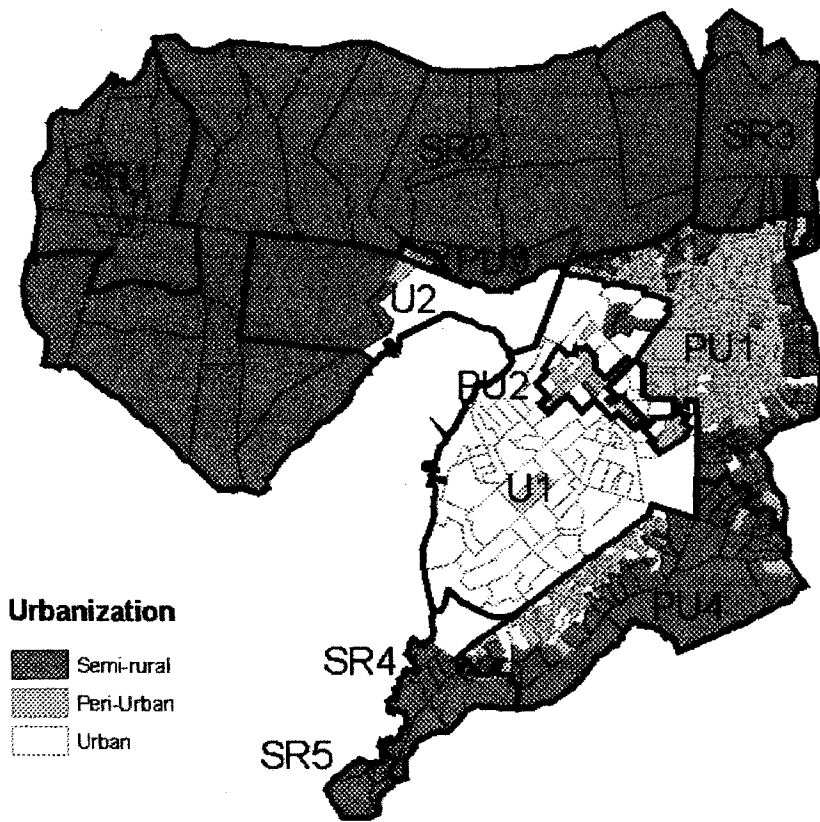
Figure 5.1: Kisumu Neighborhoods Identified by Clustering Compared with Urban Classification of Enumeration Areas

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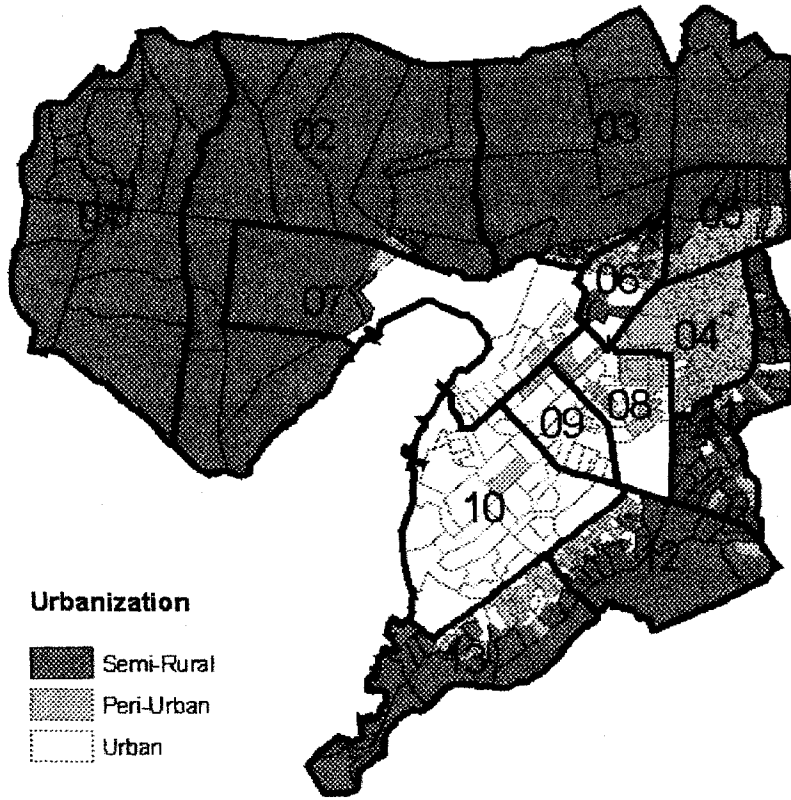
Figure 5.2: Kisumu Sublocations Compared with Urban Classification of Enumeration Areas

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Table 5.1: Incidence of Self-Reported Malaria and Severe Malarial Anemia in Kisumu Neighborhoods

Neighborhood	Self-Reported Malaria (cases/1,000 children/month)	Severe Malarial Anemia (cases/1,000 children/year)
Urban		
1	392.9	5.2
2	315.8	38.8
Peri-Urban		
1	421.2	9.6
2	395.4	14.9
3	632.4	20.0
4	452.3	11.4
Semi-Rural		
1	490.6	17.5
2	529.4	14.7
3	418.6	17.6
4	257.1	16.8
5	625.0	12.6

Figure 5.3: Scatter Plot of Neighborhood Incidence of Self-reported Malaria versus Severe Malarial Anemia

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Table 5.2: Association Between Rates of Self-Reported Malaria and Severe Malarial Anemia and Selected Neighborhood-level Socio-demographic and Environmental Variables

Variable	Self-Reported Malaria		Severe Malarial Anemia	
	Spearman Correlation Coefficient	p-value*	Spearman Correlation Coefficient	p-value*
Mean wealth percentile	-0.75	**0.0073**	0.13	0.7092
Mean length of schooling (yrs)	-0.85	**0.0008**	0.23	0.5015
Mean length of residence (yrs)	-0.01	0.9788	0.02	0.9577
House has open eaves or poorly covered windows (%)	0.65	**0.0320**	0.01	0.9788
Household uses natural water source for washing (%)	0.63	**0.0366**	0.06	0.8723
Standing or running water within 10m of household (%)	0.08	0.8110	-0.22	0.5192
Caregiver, household head or child spent at least one night in a rural area in previous month (%)	0.3	0.3775	0.51	0.1051
Domestic animals kept overnight at residence (%)	0.56	0.0730	-0.19	0.573
Household owns at least one bednet (%)	-0.79	**0.0037**	-0.05	0.87
Household uses mosquito coils for malaria prevention (%)	0.34	0.3118	0.02	0.9577
Survey respondent shows good basic knowledge of malaria (%)	-0.87	**0.0005**	0.35	0.2847
Mean NDVI	0.3	0.3701	0.11	0.7495
Population density	0.34	0.3118	-0.35	0.28

* Values in bold significant at $p < 0.05$

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CHAPTER 6:

CONCLUSION

Overview

Despite all efforts to the contrary, malaria continues to be a tremendous public health issue for sub-Saharan Africa. Though the players in malaria relief have changed, and Roll Back Malaria (RBM)—sponsored by the World Health Organization (WHO)—has taken the place of the World Health Assembly of a half-century previous, the song remains the same: over a quarter of a billion cases and a million deaths a year. Efforts to combat malaria are hampered by a lack of understanding of some of the basic epidemiologic parameters of the disease, such as why certain children develop serious or fatal illness while others survive frequent infection with only mild disease, or whether interventions like insecticide-treated nets (ITNs) that reduce exposure over the long-term are likely to increase the risk of certain forms of severe illness like cerebral malaria.

While rapid progress is being made on many fronts, our knowledge of malaria in the urban environment, and especially of the epidemiology of severe disease, is limited at best. Moreover, the lack of consistent definitions for "urban" on the part of the research community has led to a situation in which it is impossible to tell whether conflicting assessments of the effects of particular risk factors represent truly different results, flaws in study design, or simply semantic artifacts. Similarly, the effort to quantify the malaria

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burden in terms of urbanization remains crude at best, when we have not decided what "urban" is. These problems are especially troubling in light of the tremendous rate of urbanization in SSA, faster by far than anywhere else on Earth. As more of Africa's population concentrates in cities, it will become increasingly more important to understand malaria in this relatively new epidemiologic context.

The goal of this study was to assess risk factors for one syndrome of severe malaria (i.e., severe malarial anemia (SMA)) in the urban context. In doing so, we aimed to jointly assess environmental and socio-demographic factors in a manner that was both representative and easily applicable for different cities in SSA. We intended to define the urban environment through quantitative means that would allow for meaningful comparisons between studies in different cities. Finally, we hoped to identify simple targets for effective malaria interventions in cities and to clarify the relative contributions of different variables. We have accomplished all three goals to some extent, though there is substantial work left to do. We discuss each in turn.

Sampling for Urban Areas

Epidemiologic research in cities in SSA is hampered by the lack of pre-existing sampling frames, which leads either to great expense in fully enumerating the populations of small intra-urban zones, or to sampling schemes that are not population-representative. Research on risk factors for malaria is further constrained by the need to sample the environment, as well as the population, in a representative fashion.

Chapter 2 of this study discusses a novel sampling strategy for urban areas that is capable of jointly assessing environment and population in a representative way, using census maps to approximate a sampling frame and handheld Global Positioning System (GPS) units to locate identified sampling points. Over a seven-month period, seven interviewers conducted a knowledge, attitudes and practices (KAP) survey related to malaria, yielding 4,336 valid interviews with probability proportional to population over a broad geographic range and sampling 9.1% of households and 83.3% of census enumeration areas (EAs) in Kisumu. Of all identified sampling points, 96% yielded a valid interview. Unsampled EAs and sampling points were randomly distributed. We demonstrate that the sample selected by this method differs demographically in predictable ways from that of the general population, and show that the sampling distribution more closely approximates the distribution of population than a geographically random sampling distribution. We maintain that the use of a pseudo-sampling frame reduces attrition in the sample due to rapid population turnover, and that the use of handheld GPS represents a dramatic increase in cost-efficiency of sampling, since far less *a priori* knowledge of the study area is required for interviewers to locate sampling units and retraining costs are therefore reduced or obviated. We also note that the current method allows far larger regions to be studied than where complete enumeration is necessary.

We noted several disadvantages to the proposed method. First, the use of GPS with some spatial inaccuracy, along with the need to identify an eligible household, leads to a lower proportion of interviews conducted in the assigned EA than expected. Census

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maps are not always accurate, and it is likely that this also contributes to the low rate. Finally, since the sampling frame is not completely enumerated, we also rely on census figures to produce sampling fractions and incidence rates. It is likely that these figures contain some degree of inaccuracy as well. Nonetheless, we believe this method represents an improvement over current sampling methods for urban areas, when the goal is to evaluate both environmental and social risk factors.

We were unable to precisely gauge the accuracy of the sampling method in capturing the population of interest because of the lack of specific demographic data on households with children under 10. We believe an important step in validating this strategy is to compare the sample obtained via this method to a sample obtained via complete population enumeration, in terms both of demographics and response levels. More specific data is also needed on the costs of sample collection for this method versus other methods.

Urban Classification

As discussed above, the lack of consistent classifications for urban areas is a major impediment to research on urban malaria or, for that matter, any urban public health issue. Progress is being made on one front; a consistent and clear definition of slums has been proposed by the United Nations. A more comprehensive approach to quantitative classification of urban areas is necessary.

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In Chapter 3, we discuss the use of principal components analysis and a k-means clustering algorithm to produce a data-based classification of urban areas. We incorporate some of the variables used to define slums and others that are both relevant to urbanization in the context of malaria and readily available to researchers and health officers in SSA. We demonstrate that this classification is superior to classifications based on administrative designation and on population density in terms of homogeneity of the regions produced and population coverage, and that it better captures variation in other variables related to urbanization than do the other systems. We also illustrate dramatic intra-urban differences in knowledge about malaria, in the use of preventive measures and in health and treatment-seeking history. In particular, we show that peri-urban areas are in many ways more like rural than urban environments and maintain that malaria interventions targeted toward these areas should reflect that similarity. We observe serious shortfalls in meeting the goals set forth for ITN usage and prompt, appropriate treatment with antimalarials in the Abuja Declaration, and also see a high level of usage of inappropriate or less effective preventive measures, such as mosquito coils, by the less wealthy and less educated.

Further research and particularly discussion is needed on the classification of urban areas. Consistent definitions are vital to producing research on the epidemiology of malaria in this context. While the current method provides a quantitative definition, it is only one of many that are possible, varying in which variables and the number of ecotypes to be identified, in methods for choosing boundaries, in proximity metrics and in clustering methodologies, to name a few options.

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Moreover, while a simple classification is a great stride in the right direction, and sufficient for many applications, including continent-wide estimates of malaria burden and cross-city comparisons of malaria risk factors, other needs require further classification. For example, targeting malaria interventions within a specific city requires the identification of epidemiologically homogeneous neighborhoods. In Chapter 5, we use our urban classification in conjunction with estimates of a hospital catchment zone to identify 11 neighborhoods in Kisumu. We demonstrate variation in the risk of self-reported malaria and SMA across these neighborhoods. This method could be used to identify very specific target zones for malaria interventions, but further work is needed. The identification of neighborhoods is sensitive to the choice of proximity metric, and a sensitivity analysis of different methods would help clarify the important factors in setting boundaries. We hope to use the current data to accomplish this in the future.

Risk Factors

Though a fair amount of work has been done on the effect of environmental risk factors for malaria in urban areas, this has been less true for severe malaria, and evaluations of socio-demographic risk factors are conflicting. Also, almost no studies have attempted to examine the community-level effects of either type of risk factor on severe malaria in the urban context.

We assessed individual-level environmental and socio-demographic risk factors for severe malarial anemia (SMA) through a case-control study with hospital-identified

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cases and community controls, identified through the KAP survey. Eighty cases and 826 controls were included in the study, which is discussed in Chapter 4. A wide range of socio-demographic and environmental risk factors were found to significantly affect individual risk in univariate analysis. Though further analysis was limited by sample size, a multivariate logistic regression identified recent travel to rural areas by the child as a very serious risk factor for SMA, while finding no effect for use of ITNs. This is a highly significant result, as there are few estimates of the effect of urban-rural travel on severe malaria rates in Africa. If most severe malaria is acquired outside cities, ITNs, which are currently considered the most effective form of malaria prevention, may be less useful in urban areas.

Further research is needed on the effects of urban-rural travel in African cities, including a classification of the type and number of trips made, and to what extent these factors affect risk. In addition, this study was limited by small sample size and a high proportion of uninterviewed cases. More research into risk factors for SMA is needed.

We briefly considered community-level risk factors for SMA and for self-reported malaria in Chapter 5. With just 11 sampling units, we were limited to non-parametric analyses of correlation. We found that a number of socio-demographic factors were highly correlated with self-reported malaria, including bednet use, while the only factor that approached significance in predicting SMA was travel by a member of the household to a rural area—bednet use was completely uncorrelated with incidence of SMA. The latter are consistent with our results for individual-level risk factors, yet it is unclear why

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the distributions of self-reported malaria and SMA would be as different as observed. Further research is necessary on the differences between uncomplicated and severe malaria risk factors in the urban context. We plan to use the current data to fit a multi-level model jointly examining individual and community-level risk factors for severe and self-reported disease.

Summary

In summary, this dissertation contributes to the current understanding of severe malaria in the urban context, a large and growing public health issue. It outlines a new methodology for simultaneous sampling of population and environment and applies statistical methods to the classification of urban areas for research. It examines individual- and community-level risk factors for severe malaria, and comprises one of the few estimates of the effect of travel to rural areas on severe malaria risk in sub-Saharan Africa. Finally, it outlines plans for future research in this area.