Applications of GIS and Spatial Statistics for Malaria Research in Rural Zambia: Evaluation of Risk Factors and Risk Mapping in Nchelenge District and Elimination Strategies in Macha

By
Jessie Pinchoff, MPH

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ABSTRACT

Objective: The goals of this dissertation project were to understand malaria transmission dynamics in two different settings in Zambia. The specific aims in Nchelenge District, an uncontrolled transmission setting, were to describe the individual-, household- and environmental-level risk factors for malaria (Paper 1); and to generate and validate seasonal malaria risk maps (Paper 2). The specific aims in Macha District, a low transmission setting, were to describe factors associated with sustained bednet use (Paper 3), and determine the efficiency of reactive case detection and focal drug administration in treating infections missed by passive surveillance (Paper 4).

Methods: Both sites are part of the International Center for Excellence in Malaria Research (ICEMR) for southern Africa. Satellite images are used to generate sampling frames, and households randomly selected for enrollment. Questionnaires, blood samples, mosquitoes and GPS coordinates are collected. Multilevel models with random effects were built for the odds of RDT positivity in Nchelenge District (Paper 1). Logistic regression and prediction models were used to create seasonal malaria risk maps and validated using RMSE in Nchelenge District (Paper 2). A multi-level longitudinal model with random intercepts was generated to determine factors associated with bednet use in Macha District (Paper 3). A simulation model was constructed to predict the distribution of RDT and PCR cases of malaria, to determine the efficiency of reactive case detection and focal drug administration in Macha District (Paper 4).

Results: Age, report of symptoms, and proximity to certain ecological features increased risk of malaria infection, and varied by season (Paper 1). Risk maps

accurately predicted household malaria risk; prediction was best in the rainy season and for smaller households (<4 members) (Paper 2). Several factors including presence of nuisance mosquitoes and distance to healthcare facilities affected reported bednet use (Paper 3). Reactive case detection identified and treated RDT positive cases that cluster around index households; focal drug administration would treat PCR positive RDT negative cases missed otherwise (Paper 4).

Conclusions: In high transmission settings, spatial targeting of high-risk areas and populations is necessary to reduce malaria transmission; risk maps and school-based interventions may be suggested. In a low transmission setting, sustained use of personal protective measures and implementation of active case detection strategies to treat every remaining case is necessary for elimination.

COMMITTEE OF FINAL THESIS READERS

William J. Moss, MD
Professor and Thesis Advisor
Department of International Health

Frank C. Curriero, PhD
Associate Professor
Department of Epidemiology

Douglas E. Norris, PhD
Professor
Department of Molecular and Microbiology and Immunology

Kawsar R. Talaat, MD
Assistant Scientist
Department of International Health

ALTERNATE THESIS READERS

Margaret Kosek, MD
Professor
Department of International Health

Christopher D. Heaney, PhD
Assistant Professor
Environmental Health Sciences

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATONS AND ACRONYMS

ACT	Artemisinin combination therapy
DALY	Disability Adjusted Life Year
EIR	Entomological inoculation rate
GEE	Generalized Estimating Equations
GIS	Geographic Information System
GMAP	Global Malaria Action Plan
GPS	Global Positioning System
ICEMR	International Center for Excellence in Malaria Research
IEC	Information, education, communication
IPC	Intermittent Parasite Clearance
IPT	Intermittent Preventive Therapy
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Net
LLIN	Long lasting insecticide treated Net
MACEPA	Malaria Control and Evaluation Partnership in Africa
MIS	Malaria Indicator Survey
MDA	Mass Drug Administration
MDG	Millennium Development Goal
NMCC	National Malaria Control Center
NMCP	National Malaria Control Program
PCR	Polymerase Chained Reaction
PECM	Prompt and Effective Case Management

PMI	Presidential Malaria Initiative
RACD	Reactive Case Detection
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
RMSE	Root Mean Square Error
SMC	Seasonal Malaria Chemoprophylaxis
USAID	United States Agency for International Development
WHO	World Health Organization

1. Introduction

1.1 Global Malaria Control Strategy

Malaria is a parasitic infectious disease responsible for an estimated 655,000 deaths in 2010, 91% of which were in Africa (1). Transmission has declined globally; 59 out of 103 countries with ongoing transmission in 2000 are projected to meet the Millennium Development Goal (MDG) target of reversing the incidence of malaria (2). With these successes, a renewed call for global malaria eradication has been supported by the Bill and Melinda Gates Foundation, World Health Organization (WHO), and, more recently, the Roll Back Malaria (RBM) Partnership (3). Effective prevention and control measures include distribution of insecticide treated nets (ITNs), indoor residual spraying (IRS), prompt treatment of confirmed cases with rapid diagnostic tests (RDT) or microscopy and artemisinin combination therapies (ACT), and intermittent preventive therapy (IPT) for pregnant women and infants (4). The widespread implementation of these interventions has coincided with a decline in malaria transmission in some regions.

ITN distribution is a cornerstone of malaria control efforts and one of the least expensive interventions available for malaria control. ITNs are nets hung over the sleeping area to create a barrier between the sleeping individual and biting mosquitoes; they are treated with insecticides to additionally kill or repel mosquitoes that come into contact with them. A recent meta-analysis concluded that in endemic areas, ITN use was associated with a reduction in all-cause mortality among children under five years old by a mean of 17% in the first two years after their introduction (5). The Global Malaria Action Plan (GMAP) has

called for universal coverage with ITNs, defined as 100% coverage among at risk populations (6), prompting increased distribution through various mechanisms such as government distribution or subsidies. Starting in 2008, the ITNs that have been distributed are Long Lasting Insecticide Treated Nets (LLINs). LLINs have insecticide embedded in the net and are designed to retain insecticidal efficacy through at least 20 WHO standard washes and last an estimated 3 years (7). Between 2008 and 2010, a total of 254 million LLINs were delivered to sub-Saharan Africa, enough to cover two-thirds of the 765 million persons at risk in the region (8).

After ITNs, and more recently LLINs, the most common vector control intervention is indoor residual spraying (IRS). Scale up of IRS has increased the number of people protected by IRS in Africa from 10 million to 78 million in 2010 (9). IRS is the application of a long-lasting, residual insecticide to the surfaces inside structures (walls, eaves, ceilings) that might be malaria vector resting surfaces (9). Thus IRS is most effective against indoor feeding (endophagic) and especially indoor resting (endophilic) vectors. IRS reduces the vector's lifespan, vector density, and human-vector contact, leading to reduced malaria transmission (9). The cost of IRS is high and targeted interventions with high coverage would be most cost-effective and have the strongest impact on transmission (9). Targeted IRS also has a community-wide benefit, protecting sprayed households and nearby households (10).

In addition to vector control activities, prompt diagnosis and treatment of malaria are critical to reducing transmission and pursuing elimination. Passive

case detection requires the least resources; it involves testing and treating individuals seeking care for malaria at a health facility. However, this method misses individuals who are asymptomatic and those who do not or cannot seek treatment. In low- to moderate-transmission settings, active case detection methods will be necessary, such as the implementation of reactive test and treat or reactive case detection (RACD). This method screens and treats individuals within a defined radius of a passively detected index case for malaria parasites (11). This method is based on the observation that infections tend to cluster spatially; a previous study in Zambia found that the prevalence of malaria among household members of passively detected cases was eight times higher than randomly selected control households (12).

Current testing is done with RDTs; they are inexpensive, provide results in 15 to 20 minutes, and do not require any electricity or other equipment (13). However, in low-transmission settings RDTs do not reliably detect low-density parasitemia (≤200 parasites/μL); these infections can only be detected by PCR with a limit for detection of parasitemia of 0.02 p/μL (13, 14). A potential strategy for treating these last remaining infections is focal mass drug administration (MDA), which presumptively treats all persons within a certain radius of the passively detected index cases without testing.

Malaria transmission varies regionally in intensity. In some settings, malaria is uncontrolled with perennial transmission, or high morbidity and mortality year round. As transmission declines, in large part due to the implementation of the above interventions, malaria becomes more focal (15).

These residual foci of transmission can then be targeted to further reduce transmission. Recent successes in controlling malaria related morbidity and mortality have prompted an optimistic call for a renewed effort to eradicate the disease. However, it is unlikely these interventions alone will be able to eliminate malaria in areas with high transmission potential.

1.2 Study objectives and rationale

1.2.1 Overall goals and specific aims

The overall goal of this dissertation project was to analyze factors associated with malaria transmission in two settings of rural Zambia. In a high transmission region with ineffectual malaria control, the goals were to assess factors associated with continued transmission, and develop a risk map to highlight high-risk areas for targeted intervention and surveillance. In a low transmission setting of southern Zambia, the goal was to identify characteristics associated with sustained use of ITNs and to explore a simulation model to evaluate the efficiency of active case detection strategies and focal drug administration for malaria elimination.

The following specific aims were addressed:

- Specific Aim 1: Implement generalized estimating equations (GEE) to assess individual, household and environmental factors associated with RDT positivity in a cross-sectional cohort of households in Nchelenge District from 2012-2014.

- Specific Aim 2: To generate and validate a predictive seasonal risk map of malaria and a map of model uncertainty based on a cross-sectional cohort of households in Nchelenge District from 2012-2014.

- Specific Aim 3: To explore individual, household and environmental factors associated with sustained ITN use in a longitudinal cohort of households in Macha from 2008-2014.

- Specific Aim 4: To examine the efficiency of reactive case detection for identifying and testing asymptomatic or sub-patent infections, and to determine the added impact of a focal drug administration on missed infections that are RDT negative but PCR positive in Macha from 2009-2012.

1.2.2 Rationale for specific aim 1

Malaria transmission in some areas remains high despite the scale-up of malaria control activities. Malaria transmission in Zambia varies from low in Lusaka Province to perennial transmission in Luapula Province (56% positive by RDT), illustrating high variation within this single country (16). Research is necessary to determine why transmission is not declining in some areas as it has in other regions where the same control interventions have been implemented. This aim will examine individual, household and environmental factors from a prospective cohort study to identify high-risk populations or areas that are sustaining high transmission in this region. These findings may guide the

development of malaria control program policy to target those at highest risk and modify the current strategy to substantially reduce transmission.

1.2.3 Rationale for specific aim 2

Malaria is heterogeneous in its distribution across time and space, reducing the effectiveness of blanket disease control strategies (17). Advances in remote sensing and satellite imagery allow for highly accurate characterization of environmental and ecological features that are predictive of mosquito breeding sites (18). Mosquito breeding sites may be found in close proximity to certain environmental features leading to spatial variation in malaria transmission risk. Spatial and seasonal heterogeneity of malaria transmission remain poorly characterized, and many existing risk maps have limited operational use to malaria control activities because they are at coarse spatial resolution (national level or higher), based on historical data, or based on national level surveys with large unsampled areas (19-21). The aim for this project will be to generate and validate a high-resolution, seasonal risk map and uncertainty map based on prospective cohort data and environmental features derived from satellite imagery and remotely sensed data.

1.2.3 Rationale for specific aim 3

Malaria elimination refers to the interruption of malaria transmission within a given geographic area (22). As transmission declines, there is concern that perceived risk also declines, coinciding with failure to sustain high coverage and use of personal preventive measures. Resurgence of malaria is often attributed to a weakening of control measures (23). As transmission falls, it is crucial to

maintain high coverage of vector control measures such as LLINs and promote their continued use (24). This study will combine longitudinal survey data with qualitative data regarding LLIN use and entomological data to understand factors associated with LLIN use over time. The results can be used to inform malaria control program activities and messages in areas with low transmission to ensure sustained use of LLINs.

1.2.4 Rationale for specific aim 4

Data suggest that continued use of current interventions may not be sufficient to eliminate malaria. This will require shifting the focus on treating illnesses to clearing infections (14, 25). Asymptomatic malaria infections are increasingly problematic in low transmission settings because they go undiagnosed and untreated. As malaria transmission declines and is spatially clustered (15), active case detection strategies are often targeted to households near a known case. Active case detection can involve screening and treating of nearby persons, or potentially a targeted drug administration in which all nearby persons are treated. While it is clear that RDTs lose specificity in low transmission settings and fail to detect low-density parasitemia (≤200 parasites/μL), the impact of sub-patent infections on transmission is not known (13, 14, 26). The Malaria Eradication Research Agenda Consultative Group suggests that any parasitemia, no matter how low, represents a potential for transmission and therefore should be targeted for elimination (27). In regions where PCR is not feasible, mass drug administrations may be effective for reducing transmission but is not currently recommended because of the potential

for drug resistance or adverse events (28). This aim will determine the proportion of RDT positive asymptomatic persons who would be identified through reactive case detection and the remaining PCR positive, RDT negative persons who would only be impacted through focal mass drug administration.

2. Review of the Literature

2.1 Malaria Burden in Africa

Malaria presents a major health problem globally; in 2010 it was responsible for an estimated 216 million episodes of illness, 86% of which occurred in children under 5 years of age, and resulted in 655,000 malaria related deaths (1). 81% (174 million) of these infections occurred in Africa, representing 91% of the total deaths (1). Malaria is not only a leading direct cause of death, it is also associated with a high rate of disability adjusted life years (DALYs) which represent years of life lost to morbidity (29).

Declines in malaria cases and malaria related deaths by up to 50% have been measured in 11 countries, including Zambia (1, 30). According to the World Health Organization (WHO), global malaria incidence has dropped 17% since 2000 and malaria-specific mortality rates have fallen by 26% (1). These improvements have been ascribed to myriad factors, including changes in climate, improvements in the quality of health systems, improved access to diagnostics and highly effective drugs, and large scale prevention campaigns. Countries reporting decreases in incidence and mortality are those that have implemented intense malaria control interventions; however, there is evidence of increasing severity of morbidity and mortality associated with declining transmission (8, 31).

In regions with high intensity of malaria transmission, the environment is suitable for mosquito development and the number of cases is stable each year; commonly, high transmission or endemic malaria is defined as clinical incidence of greater than 1 per 10,000 population per year in an administrative unit (32). In high transmission settings, children under five years old are the most severely affected by malaria related mortality and morbidity, specifically severe anemia. With near-constant exposure to the parasite, relative immunity is often acquired in children during their first 5 years (33). Wernsdorfer *et al* found that malaria specific mortality rates were lower among infants born into the malaria transmission season due to the acquisition of passive transmission of antibodies from the mother (33). However, in low transmission settings, where the population may be exposed during short, seasonal patterns of malaria or not at all for several seasons, the case fatality rate sharply increases (5). These populations are at high risk for epidemic outbreaks of malaria, which are associated with increased rates of severe and cerebral malaria and a 25-50% increase in case fatality rates (34).

Low or unstable transmission areas are defined as those in which malaria transmission is plausible biologically but limited due to environmental factors; the clinical incidence is defined as less than one case per 10,000 population per year (32). Communities in low transmission settings may experience a shift to more severe disease, higher rates of cerebral malaria in children, and a shift in cases from younger to older individuals because they become immunologically naïve with decreased exposure to malaria (1, 5, 30, 34, 35). Cerebral malaria in

particular is less common at higher transmission, suggesting frequent exposure to *P. falciparum* in infancy and early childhood allows the development of protective immune mechanisms prior to the onset of physiological susceptibility to cerebral complications of malaria (5, 36). In low transmission settings, older age groups are predicted to be more important to malaria transmission than young children, while in high transmission settings children bear a higher proportion of the burden (35). Low transmission settings may be prone to epidemics or outbreaks of malaria, situations in which facilities are more likely to be under equipped, over used, under staffed, and often run out of diagnostic tests and drugs (34). Thus, maintaining high rates of ITN use in low transmission areas is essential to prevent severe disease and potential resurgence of infections if control measures break down.

2.2 Malaria Transmission Cycle

2.2.1 Malaria Transmission: *Plasmodium* Parasite

Malaria is transmitted by to humans by five different species of the *Plasmodium* parasite: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* (1, 37). *P. falciparum* is responsible for the most cases, and is associated with mortality rates up to 30% in non-immune populations in the absence of treatment (1, 38).

2.2.2 Malaria Transmission: Mosquito Vector

Over 70 species of anopheline mosquito are capable of transmitting malaria, but only 40 are considered important vectors, and only the female mosquito transmits disease (38). There is significant variation in host feeding preferences,

biting, and resting behavior, as well as in the selection of breeding sites by mosquito species. Understanding mosquito behavior and factors that influence where mosquitoes oviposit is essential for creating efficient and successful intervention programs. Climate and weather may play a large part in the density of mosquitoes in a local area, as they are key factors in determining breeding sites. Seasonal climate change is known to be an important determinant of malaria incidence since it affects both mosquito vector dynamics and parasite development rates (39). Precipitation and humidity are regarded as the primary determinants of variation in anopheline population size and mosquito survival (30). Studies indicate that rainfall of about 80 mm per month for at least five months can result in stable malaria transmission (40).

Temperature is associated with mosquito development; warm temperatures, ideally between 18 and 22 degrees Celsius, in addition to the presence of water at vector breeding sites (many formed by rainfall) are necessary for malaria to be transmitted (40). In many studies, the number of malaria cases was found to increase after approximately six weeks under these conditions. Higher temperatures can influence vector abundance and infectivity; temperature can impact pathogen replication, maturation, and the period of infectivity (41). Malaria incidence is usually low during the dry-hot season when vector populations are reduced and spatially confined, and most studies focus on the peak transmission in the rainy season (39).

Extreme heat or sudden climate changes can decrease vector survival time or disturb pathogen development. Climate change leading to the disruption of

stable seasonal rainfall in a geographic location may impact vector population dynamics and increase the possibility of mosquito mortality (30). Studies conducted in rural high transmission areas have noted instances where in the absence of organized prevention efforts, a dramatic temporal decline in the density of malaria mosquito vectors occurred despite a history of high *P. falciparum* endemicity (30). This has been attributed to a natural decline in the vector population due to sudden decreases in rainfall (30, 42-46). There may also be differences in mosquito ecology in high as compared with low transmission areas; in low endemicity and epidemic prone areas, *Anopheles* density and malaria transmission were found to be more clustered around breeding sites than in high transmission areas (47).

Implementing effective vector control interventions can also be improved by understanding general anopheline behavior and differences between the species, which may necessitate targeted interventions. There is significant variation in the anthropophilic index (a measure of a vectors preference for human blood), breeding site preferences, endophagy (feeding indoors) and endophily (resting indoors) (33).

For most anophelines, the usual flight range between breeding grounds and blood sources is 1.6 km (33) (maximal flight range however can be over 10km), meaning residents of households closer to breeding sites are often at increased risk of being bitten. However, breeding sites may vary by mosquito species; for example, *An. gambiae* prefer shallow and small water collections while *An. funestus* breeds in small permanent water bodies. Mosquitoes such as

An. gambiae and *An. funestus* that are endophagic and endophilic put humans at increased risk. However, they are targeted more efficiently by vector control activities such as ITNs use that protect humans in their homes when these mosquitoes are likely to be biting in that habitat.

However, a third significant malaria vector in sub-Saharan Africa, *An. arabiensis*, displays a larger degree of variation in foraging behavior (48, 49). *An. arabiensis* will readily feed upon cattle (50), and this species is favored by drier environments and has adapted to peri-urban environments (51). However, other studies have suggested cattle and domestic animals attract larger populations of mosquitoes, potentially increasing local risk of transmission for humans (52).

These examples indicate variation in the efficiency of the malaria vector between different species, many of which may co-exist. This may lead to dynamics between the vectors, and the possibility of interventions inducing replacement of one species with another. For example, a study conducted in Benin found that *An. funestus* partially replaces the main vector, *An. gambiae*, in the dry season (33), a behavior that has been documented elsewhere in Africa (53, 54). This emphasizes the importance of year round vector control activities as compared with seasonal interventions when risk of malaria infection is highest.

Understanding mosquito behavior and how shifts in disease ecology may impact malaria transmission are essential to designing successful vector control strategies. Tailored control efforts have been suggested based on the ecological

distribution of malaria, as the current global trend is the pursuit of malaria elimination.

2.2.3 Malaria Transmission: Human Hosts

Transmission risk may be modified by individual- and household-level factors such as genetics, use of personal protective measures, care seeking behavior, and composition of the household walls and roof. Use of personal protective measures, such as LLINs, are effective at reducing childhood morbidity and mortality from malaria, and may reduce transmission intensity (55). LLINs may be more likely to be used in the cool-dry season when the temperature is not too high, and often infants and pregnant women are prioritized if few nets are available leaving school aged children vulnerable (56-58). Household features such as having open eaves or using window screens may also impact malaria transmission in the household (59).

Age is strongly associated with malaria infection for several reasons. First, school-aged children are the least likely to use personal protective measures; an analysis of school-age children in 18 African countries found that between 38-42% of school-age children were unprotected (32). There is also a clear association between age and report of symptoms in high transmission settings. With frequent exposure, partial immunity develops, leading to a reduction in the acute clinical symptoms of malaria (14). Asymptomatic malaria does not have a standard definition but may be based on parasite density thresholds, report of symptoms such as fever, and presence of gametocytes which do not cause disease symptoms (14). Asymptomatic cases with low parasite density may not

be detectable via RDT, and if left untreated, the infection may persist for up to a year (14). School-age children are likely to be asymptomatic after acquiring partial immunity and are the least likely to be protected; school-based interventions including intermittent preventive chemoprophylaxis (IPC) or seasonal malaria chemoprophylaxis (SMC) may substantially reduce transmission in these areas.

2.3 Malaria Goals: Strategies for Malaria Control, Elimination, and Eradication

2.3.1 Goals and Targets

The key strategies to support eventual eradication of malaria have been outlined by the Roll Back Malaria (RBM) Global Malaria Action Plan (GMAP) and focus on three major approaches: aggressive and sustained malaria control in highly endemic countries, progressive malaria elimination from the endemic margins inward (shrinking the malaria map), and continued research into new tools, approaches and strategies (60).

2.3.2 Malaria Control

Despite the progress in scaling up malaria control interventions, some regions continue to experience high, perennial transmission of malaria. Malaria control efforts are largely ineffective in these areas, for a variety of reasons. Increased insecticide resistance, human population movement across borders or internally, or increased use of RDTs for confirmation may identify less severe cases previously missed (61). Some areas also have high transmission potential, meaning that without active suppression of malaria, transmission will return to its intrinsically high prevalence (as measured by the R_0) (23). If control activities are

interrupted, resurgence of malaria will occur; it will return to the state of equilibrium from which it has been reduced by malaria control efforts (23, 62). Challenges for malaria control are related to distribution of malaria prevention efforts, vector control activities, improving access to care, maintaining high coverage of control activities and evaluating progress (2).

2.3.3 Malaria Elimination

The African continent supports wide variation in risk of malaria, ranging from less than one new infection per year to over three new infections per day (29). Transmission intensity can be measured in different ways, such as calculation of the entomologic inoculation rate (EIR) or prevalence of parasitemia. EIR is the number of mosquito bites per night multiplied by the proportion of those mosquitoes positive for malaria sporozoites; they range from less than 5 to over 500, and give a relative estimate of transmission intensity. However, EIR estimates are often not reliable, particularly in low endemicity settings. Parasite prevalence is therefore commonly used, with an estimated 80% of Africa's population residing in areas with a parasite prevalence in 2-10 year olds of over 5%, and 50% with a parasite prevalence over 40% (63). Parasite prevalence less than 10% is defined as hypoendemic, 11-50% is considered mesoendemic, >50% constant prevalence is hyperendemic and >75% is holoendemic (64).

According to the WHO, the objectives of malaria control programs range from reducing the disease burden to eliminating the disease from a defined geographical region based on transmission intensity (Figure 2.8) (22). Partly due

to climate changes and partly due to human interventions, the landscape of malaria transmission has been significantly changing over the past several decades. In high transmission areas, the widespread application of interventions has led to successful decreases in malaria prevalence. After only three years of high ITN coverage in a region of Zambia, ITN use correlated with decreased seropositivity for *P. falciparum* (65). Once malaria has been controlled in high transmission settings (defined as <5% slide positivity rate), the WHO recommends a transition phase be introduced. There are three recommendations to sustain reductions of malaria incidence: 1) sustain control interventions, 2) adapt health services to lower case load and reduced levels of immunity, and 3) strengthen surveillance systems to allow rapid response to new cases (1). Neglect or breakdown of control activities may result in a re-emergence of malaria in the region, leading to a subsequent increase in transmission (34). There are several countries with successful malaria control programs that experienced a dramatic resurgence of malaria cases when control measures ceased (32).

If malaria is to be eliminated, it is essential to maintain high levels of vector control activities throughout the year, including the dry season when vector density is low and risk may be perceived as low (39). Elimination may be the goal in areas where malaria transmission has been reduced substantially, or in areas with low transmission. However, as malaria transmission decreases, the risk of epidemic outbreaks of malaria increases. Epidemic malaria has been defined as “a periodic sharp increase in incidence that is clearly in excess of the

usual" (42). Long intervals of very low or no transmission result in little effective immunity acquired by the population; this increases the risk for severe malaria epidemics when the disease resurfaces (37, 42).

For example, several formerly malaria-free regions of the African highlands have become epidemic prone (47). Malaria outbreaks have been reported in these highland areas, potentially as a result of climatic anomaly, land-use changes, drug resistance, population migration, and breakdown of both the local health system and vector control activities (47). To avoid this resurgence of disease, the WHO recommends that countries shift from control activities to malaria elimination strategies that include detection of all malaria cases, prevention of onward transmission, management of malaria foci, and management of importation of malaria parasites (22).

Challenges for malaria elimination persist, and more research is necessary but difficult. Low sample sizes are an obstacle to properly power studies in these regions (66). Broadening the definition of malaria infections to include asymptomatic infections and sub-patent infections can pose diagnostic challenges, but these remaining infections are part of the human parasite reservoir (14). Determining the prevalence of asymptomatic infections, how long asymptomatic infections last, how much asymptomatic and sub-patent infections contribute to transmission, the association between gametocyte carriage and asymptomatic infection, and the efficiency of mass drug administration or mass screen and treat for elimination should be investigated in future research (14).

2.4 Applications of GIS and Spatial Statistics

2.4.1 Malaria Control

High-resolution satellite imagery and remotely sensed data are becoming increasingly accurate and available, with implications for infectious disease control. Remotely sensed data have been found to accurately characterize ecological features that are predictive of mosquito breeding sites (18). Features such as proximity to streams, topography, urbanization, and others have been found to be associated with malaria transmission. These data can be used to generate risk maps of transmission, which have several uses for malaria control. First, they can be used to target malaria control activities, particularly vector control interventions, to high-risk areas. This may increase the efficiency and cost-effectiveness of targeting interventions. They can also be used for the planning, implementation and evaluation of vector control interventions such as IRS. These data can also be used to model the effects of varying coverage levels of interventions and their spatial distribution. These methods have growing implications for guiding and improving malaria control activities to reduce transmission to manageable levels.

2.4.2 Malaria Elimination

In low transmission settings that are approaching malaria elimination, GPS and spatial analysis have additional use. They can be used for hotspot analysis, to detect residual foci of transmission (15, 22). As in moderate- and high-transmission settings, they can be used to direct targeting of interventions to areas of continued transmission. Real-time mapping of GPS coordinates of cases can identify resurgence of transmission from residual foci of transmission

or importation of cases leading to local transmission (22). GPS spatial analysis can be used for improved surveillance and implementation of active case detection methods. As malaria has been found to cluster as transmission declines, targeting of interventions can be directed to these hotspots (15, 67). For example, to implement reactive test and treat methods, the GPS coordinate of an index household identified via passive case detection can be used to direct community health workers to test and treat index household members and additional households within a radius of the index.

2.5 Country Background: Zambia

2.5.1 Zambia

Zambia is a landlocked country located in southern Africa. It experiences three distinct seasons: a hot, dry season from late August to October; a warm, rainy season from approximately November to April; and a cool, dry season from May to early August (19, 68). Traditionally, malaria transmission is highest in the first and fourth quarters, peaking in March towards the end of the warm, rainy season (68). Most parts of the country are high plateau areas with some rivers, valleys and mountains (19). While infant, child and under-five mortality rates have been declining in the past several years, they remain high from a global perspective (Zambia is ranked 13th in the world for highest under-five mortality) (69). Mortality rates also fall well below the Millennium Development Goals (MDGs) target to reduce by two thirds the number of under-five deaths by 2015 (70).

Zambia has 72 districts, with health facilities ranging from widely dispersed small health posts staffed by a single nurse up to hospitals (located in 60 of the 72 districts)(68, 71). In 2006, user fees in rural Zambia were abolished, resulting in increased accessibility of the healthcare system (68). However, there is still evidence of difficulty accessing healthcare; for example in Macha, Southern Province, Zambia patients must purchase and provide a notebook used to maintain their medical records, the cost of which may be prohibitive.

The Zambian government is committed to preventing and treating malaria. In 2010, 73% of all households owned at least 1 ITN or reported IRS within the last twelve months. Additionally, 52% of children under five and 46% of pregnant women reported sleeping under an ITN the previous night (32). There have also been significant improvements in treatment, despite insufficient availability of RDTs to confirm malaria diagnosis, and occasional stock outs of ACT medications (72).

2.5.2 Disease Burden in Zambia

Malaria remains a leading cause of death in Zambia, comprising about 50% of the disease burden among children under five (73). All nine provinces of Zambia are endemic for malaria and 90-100% of the population is considered at risk (72). According to the WHO, malaria is the 3rd leading cause of death among children under 5 in Zambia (Figure 2.1). Recent estimates indicate approximately 4.5 million episodes of malaria and 7,737 malaria-associated deaths in 2011 (4, 74).

In the current Zambian environment, disease vectors remain present and a significant number of humans remain infected or are asymptomatic carriers. This means that despite progress in reducing the incidence of malaria, there is always the potential for a rapid resurgence, which could be disproportionately severe as cohorts with lower acquired immunity age through the population (68). It has been noted that in regions of high transmission, the burden of disease rests on very young children and the main effect is severe malarial anemia (31).

The prevalence of malaria parasitemia in children under five years of age was 16% in 2010, with a slightly higher rate in children in rural areas (20.4%) as compared with urban areas (5.2%) (72, 75). The parasite prevalence measured at 109 locations across the provinces of Zambia in 2011 highlights variation throughout the country (Figure 2.2). Luapula Province reports the highest malaria parasitemia prevalence, measured as 56% (by RDT) in the 2012 Malaria Indicator Survey (MIS) (16). Southern Province reported the 2nd lowest parasitemia of the 9 provinces, reported as 10% in 2012 (16). Parasitemia nationally peaked among children 4 years of age, and was higher among the lowest wealth quintile and in rural areas (16).

Particularly at risk are individuals living in epidemic, unstable transmission regions. In Zambia, this represents about 48% of the population, with another 34% of the population living in endemic, stable transmission areas (18). The distribution of endemic and epidemic malaria in Zambia is depicted (Figure 2.3). It is recommended that individuals in areas that have experienced a sharp

decline in malaria incidence maintain successful control efforts to avoid disease resurgence (31).

2.5.3 Zambian National Malaria Control Initiative

Despite relatively successful control efforts, Zambia experienced resurgent malaria transmission between 1976 and 2000. Zambia's Gross Domestic Product (GDP) had been steadily increasing, but declined in 1976 following the fall of the copper industry (68). Factors attributed to this decline in malaria control activities included political turmoil caused by the struggle against apartheid, international constraints regarding the use of DDT, and the country's broader economic decline (68).

In addition to these broader political, economic, and social issues, other factors driving malaria resurgence included the removal of DDT from the market, rapid increase in drug resistance to chloroquine (the firstline malaria treatment), and the HIV epidemic (76). The launch of the Roll Back Malaria (RBM) Partnership in 1998, coupled with the development of new technologies and an agreement of priorities within the development community, marked a global commitment to halve the burden of malaria, with a focus on Africa (73). This led to the selection of Zambia as a case study of the benefits of rapidly scaled up malaria control. Resources were concentrated and focused on Zambia with the goal of producing a success story as a model for southern Africa. Zambia was chosen because it was perceived as having the institutional capacity and political will to successfully undertake such a program (68). Zambia's National Malaria

Control Program (NMCP) is considered one of the most successful malaria prevention initiatives.

Since the late 1990s, Zambia has revitalized its malaria control program, with dramatic declines in malaria incidence in many parts of the country. Since 2003, Zambia has been engaged in a large-scale, centrally coordinated national anti-malaria campaign that has become a model in sub-Saharan Africa (68). The goals of Zambia's NMCP are to achieve a 75% reduction in malaria incidence and a 20% decrease in under-five mortality by 2011, through several evidence-based interventions (68). The interventions advocated for malaria control are: widespread distribution of ITNs, application of insecticides in homes using IRS, preventive treatment for pregnant women and effective treatment of infected persons (19, 76, 77).

The NMCP budget includes significant aid from the Global Fund to Fight HIV/AIDS, Tuberculosis, and Malaria (GFATM), the United States Agency for International development (USAID), the World Bank, the President's Malaria Initiative (PMI), the WHO, and the Bill and Melinda Gates Foundation (through the Malaria Control and Evaluation Partnership in Africa-MACEPA) (19, 72). The Government of Zambia budgeted $25.4 million for the Department of Public Health's Malaria Control and Management activities in 2008, amounting to 61% of the department's budget (13). The President's Malaria Initiative (PMI) budgeted $24 million for malaria control activities in 2011, supporting prevention and treatment efforts, including the procurement and distribution of ITNs (72).

Zambia's government also eliminated taxation on malaria-control tools, including mosquito nets and relevant insecticides (73).

Although the incidence of malaria remains high, there were promising declines in incidence and mortality up until 2009. In 2009, however, there was evidence of a resurgence of malaria despite significant progress in scaling up of prevention efforts (68). The reasons for this resurgence are not known with certainty, but highlight the need to maintain control programs in order to successfully control malaria, even when the number of cases have been substantially reduced (8). Until the goal of malaria elimination is actualized, the sustainability of gains achieved is at risk, and would continue to be at risk after due to importation of cases from neighboring regions.

Today, Zambia's integrated malaria control program is one of the world's largest national treatment and prevention plans. The program is led by the National Malaria Control Centre (NMCC), a sub-division of the Department of Public Health and Research within Zambia's Ministry of Health. The national secretariat is responsible for overall program administration throughout the country and disburses funds to districts on a programmatic basis. The NMCC works in partnership with Medical Stores (a quasi-private national distribution program for all drugs and medical supplies in the public sector) to ensure that each district and referral hospital receives adequate supplies of drugs and diagnostic tools. Seventy-two District Medical Offices (previously "District Health Offices") directly implement most national malaria prevention and treatment

programs. The districts are grouped into nine provinces, each with a Provincial Health Office responsible for supervising district health programs.

The NMCC's primary intervention is distribution of LLINs, but it has also set targets to achieve "Prompt and Effective Case Management" (PECM), with a goal of ensuring that at least 80% of malaria patients receive effective treatment within 24 hours of the onset of symptoms. Zambia became one of the first countries to introduce ACTs (artemisin combination therapy, specifically artemether plus lumefantrine, with the brand name Coartem®). ACTs are free in the public sector, and became the first-line treatment for all malaria cases during the 2002 to 2003 malaria transmission season (although it was not widely available until 2005-2006). Despite these strong, concerted efforts to reduce malaria burden, Zambia is one of three countries in the world that has reported a recent an increase in malaria burden (8).

Zambia currently has two active GFATM malaria grants, focused on the scale-up of LLINs, the scale-up of ACTs, and the re-introduction of IRS (72). A Malaria Indicator Survey (MIS) conducted in 2012 concluded that 72% of households in Zambia owned at least one LLIN, and 60% of children under five years old reported sleeping under it the night before (16). LLINs are distributed for free through mass distribution campaigns, antenatal care services, and Expanded Program on Immunization (EPI) clinics, as well as through smaller distributions that target vulnerable groups. The Zambian Ministry of Health calculates that with new cohorts of pregnant women, and ITN damage and replacement needs, that in 2012 about 3 million nets will be needed to ensure

universal coverage (72). Ensuring that prevention and treatment efforts are continued is necessary to avoid resurgence of disease and to expand the geographical boundaries in which malaria is successfully controlled.

2.6 Overview: Study Sites

This study will be conducted at two sites: Macha in Choma District, Southern Province, Zambia, and Nchelenge District in Luapula Province, Zambia. The two study sites represent different phases of malaria control; Macha, Southern Province, Zambia is considered an example of successful malaria control, while Nchelenge District, Luapula Province is considered an example of ineffective malaria control. The locations of the sites in Zambia are depicted in the map of Zambia (Figure 2.4).

2.6.1 Macha, Choma District, Southern Province, Zambia

Macha, in Choma District, is located at 16.39292°S, 26.79061° E, at an elevation of approximately 1,100 meters above sea level (65), and with a population of approximately 204,898 individuals (78). The habitat around the Malaria Research Trust (MRT) field station in Choma District, southern Zambia, is characterized as Miombo woodland, and experiences the lowest mean annual rainfall (650-800 mm) in the country (79). Choma District inhabitants are primarily subsistence farmers living in village areas under a local headman. Households in the Choma area typically consist of several dwelling structures made from mud and grass, a central wall-less cooking structure, and several domestic animal enclosures. Animal enclosures are usually within 20 m of human dwellings.

These individuals are in the catchment area for Macha Hospital, which is located at the center of MRT.

The prevalence of parasitemia in children under five in Southern Province was 13.7% in 2006, and decreased to 5.7% in 2010 (78). Southern Province of Zambia has historically experienced hyperendemic *P. falciparum* transmission vectored primarily by *An. arabiensis*, with *An. funestus* as a secondary vector (80). Since this drought, few specimens of *An. funestus* have been captured, pointing to the sensitivity of *An. funestus* to drought and changing environmental conditions (48, 49). 92% of blood meals identified from *An. arabiensis* collected in Macha came from human hosts, indicating that this population of *An. arabiensis* is highly anthropophilic compared with similar collections of indoor-resting *An. arabiensis* in other parts of Africa (48). *An. arabiensis* in the area had an EIR of 1.6-18.3 infective bits per person per season from 2004-2006(49), and an even lower EIR now. There are also high numbers of "nuisance" mosquitoes, specifically culicines, which do not transmit malaria but may influence ITN use in the area.

Free mass distribution of ITNs by the Zambian government provided 4,800 LLINs to Macha in 2007 (80). In Choma District, where Macha is located, 61-80% of households have target coverage of 3 ITNs per household (65, 76). Despite this high distribution, there is heterogeneity in the ages not protected by an ITN (Figure 2.6), and of the *An. Arabiensis* that had taken a blood meal, almost all were from humans (65). This indicates they are either feeding before 10 pm (14% of *An. arabiensis* in Macha forage during this time), feeding on the

individuals not protected by ITNs, or that ITNs are not highly effective potentially due to loss of insecticide on the net due to age, and high number of holes in the nets (65).

Pediatric hospitalizations due to malaria reported at Macha Hospital decreased from approximately 1,400 admissions per malaria season in 2000-2001 to 41 in 2008 (Figure 2.5) (54). If prevention efforts are maintained, then Macha may be a candidate for malaria elimination.

2.6.2 Nchelenge District, Luapula Province, Zambia

The second site is Nchelenge District, Zambia, in Luapula Province. It lies in a high rainfall belt of the Central African plateau, and this district has a population of 137,000 individuals (78). Nchelenge is located in the marshlands of the Luapula River near Lake Mweru, and individuals in the area are mainly fisherman and farmers (78). This site is also near the Zambian border with the Democratic Republic of the Congo (DRC), and maintains an alarmingly high parasite prevalence, perhaps due to migration from DRC (81) or residents traveling to high risk areas to work as farmers. Vectors in this region are *An. funestus* and *An. gambiae* (78). The prevalence of parasitemia in children younger than 5 years of age in Luapula Province was 32.9% in 2006 and increased to 50.5% in 2010, making it the province with the highest prevalence in the country (75). Nchelenge District experiences year round transmission of malaria. Despite malaria control efforts including distribution of ITNs, deployment of IRS and use of ACT treatment, malaria cases have not declined. There is a

high incidence of cases of malaria per 1000 persons, and disproportionate burden on children under 5 years of age (Figure 2.7).

Figure 2.1

World Health Organization: Top 5 causes of death in Zambia among children under 5 years of age, 2008 (82)

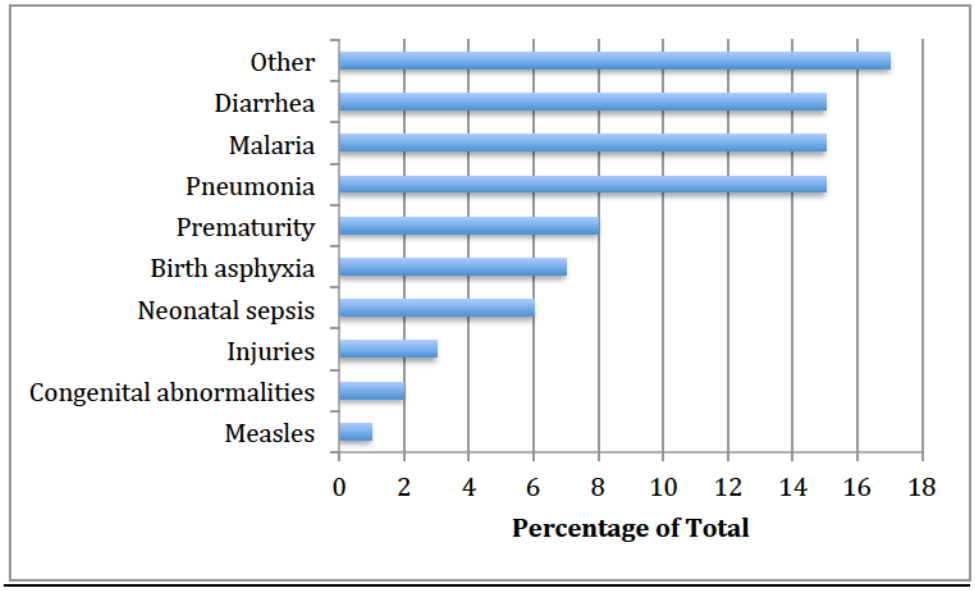


Figure 2.2

Parasite prevalence at 109 cluster locations in provinces across Zambia, 2011 (65)

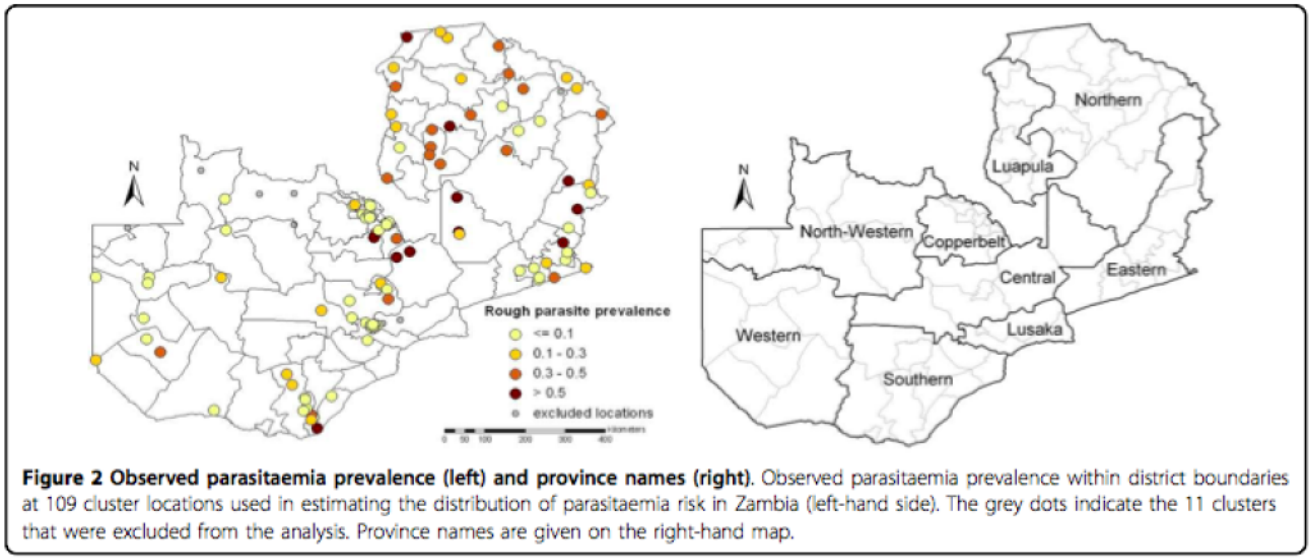
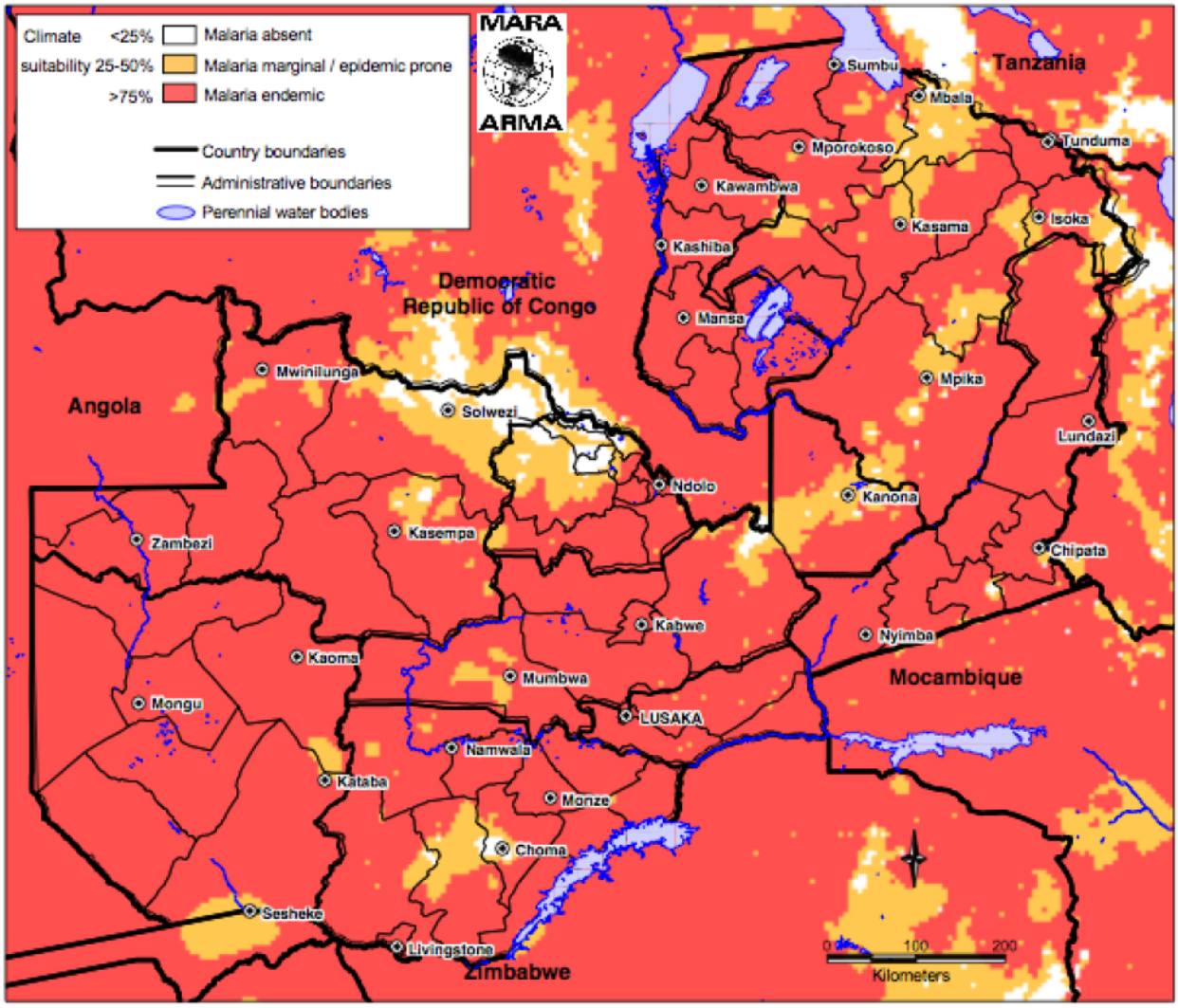


Figure 2 Observed parasitaemia prevalence (left) and province names (right). Observed parasitaemia prevalence within district boundaries at 109 cluster locations used in estimating the distribution of parasitaemia risk in Zambia (left-hand side). The grey dots indicate the 11 clusters that were excluded from the analysis. Province names are given on the right-hand map.

Figure 2.3

Distribution of Endemic and Epidemic Malaria in Zambia, 2005 (83)



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2005, Medical Research Council, PO Box 70380, Overport, 4067, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute, Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR), Roll Back Malaria (RBM).
Malaria distribution model: Craig, M.H. et al. 1999. Parasitology Today 15: 105-111. Topographical data: African Data Sampler, WRI, http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm.

Figure 2.4

The two study sites, Macha (Choma District) and Nchelenge District, on a map of Zambia's nine provinces

Figure 2.5

Decline in pediatric hospitalizations at Macha Hospital between 2000 and 2010 (78)

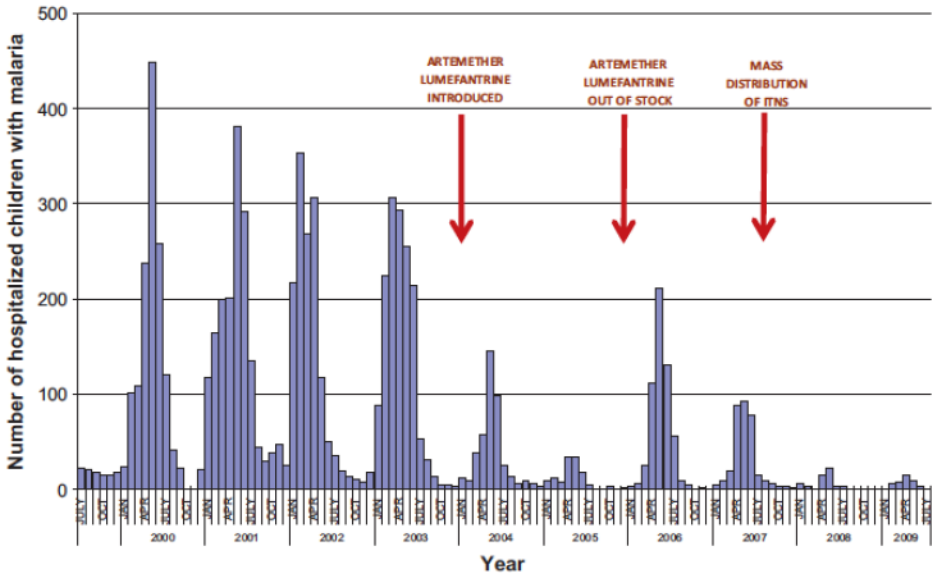


Figure 2.6

Ages of individuals **not** protected by an ITN during the 2008-2009 season in Macha, Zambia (84)

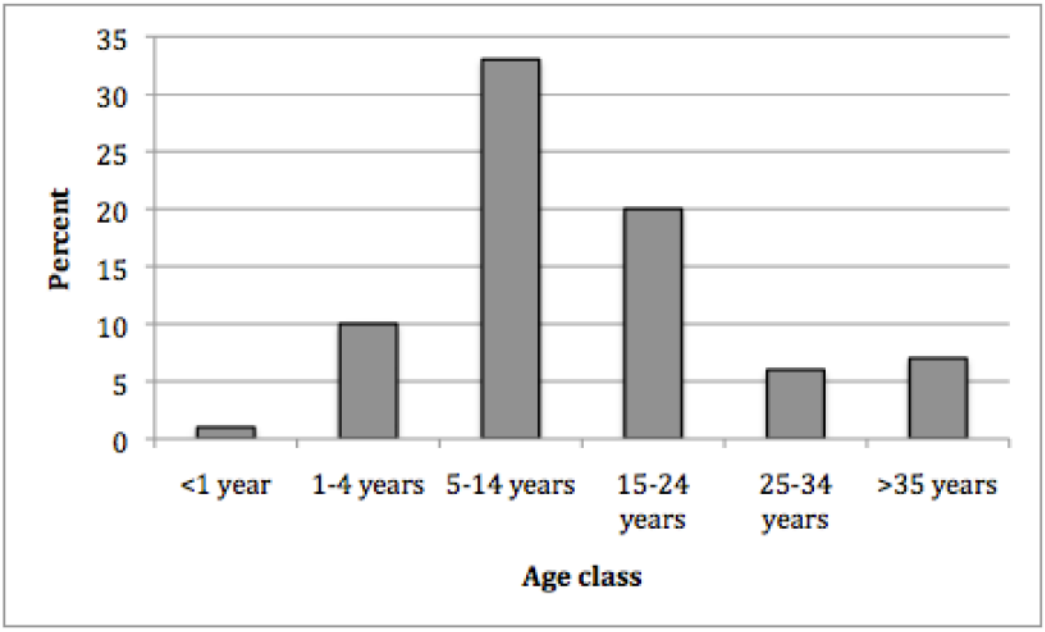


Figure 2.7

Malaria incidence in Nchelenge District between 2005 and 2009.

Data courtesy of the Nchelenge District Health Office, Ministry of Health, Zambia

(78)

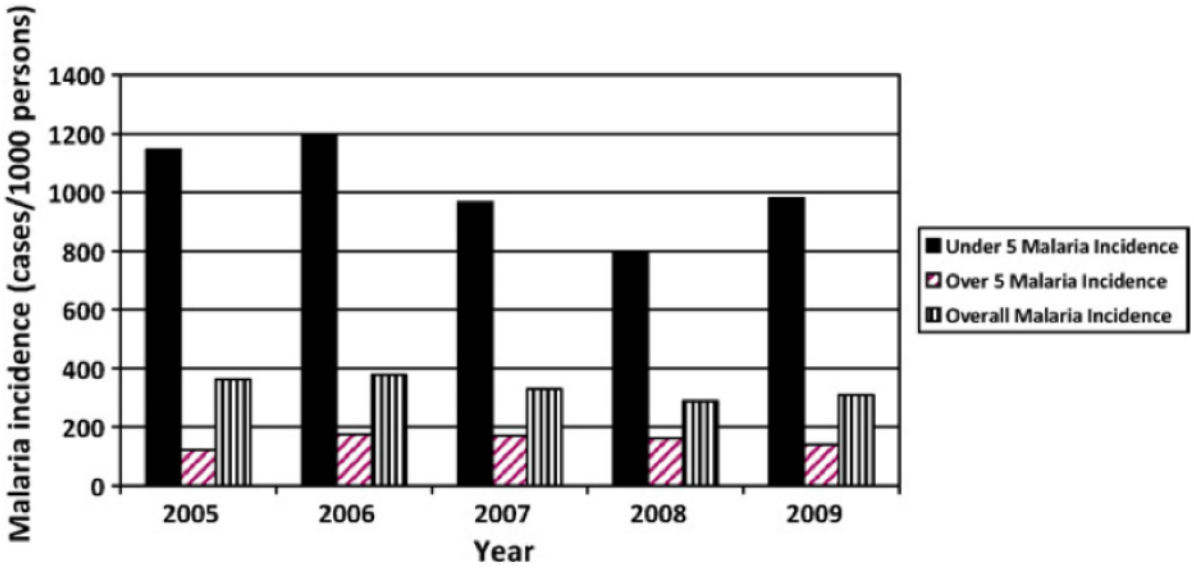
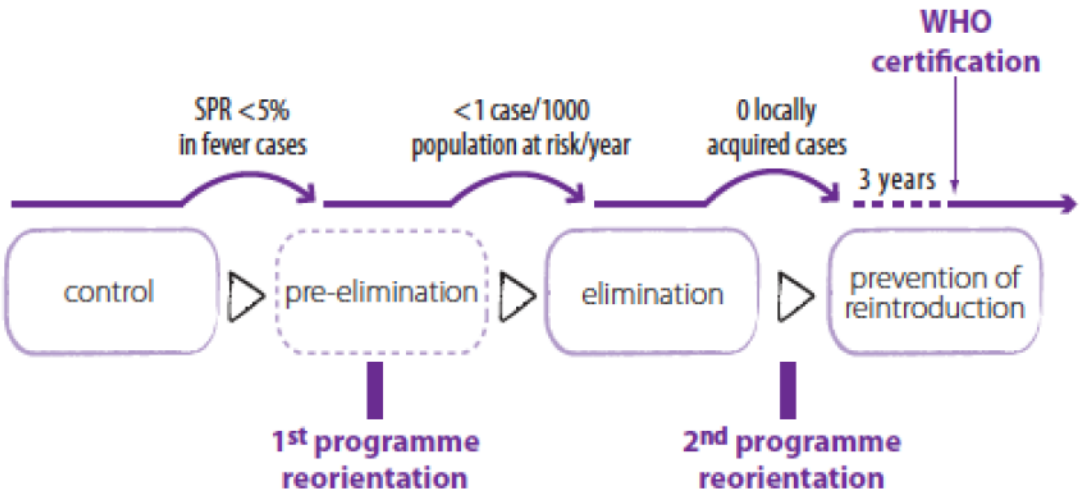


Figure 2.8

Malaria program phases towards successful elimination (22)



SPR: slide or rapid diagnostic test positivity rate.

[a] These milestones are indicative only: in practice, the transitions will depend on the malaria burden that a programme can realistically handle (including case notification, case investigation, etc.).

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Chapter 3: Seasonal malaria risk factors in a region with perennial transmission: multi-level characteristics associated with RDT-positivity in northern Zambia, 2012 – 2014

Authors: Jessie Pinchoff, Mike Chaponda, Tim Shields, James Lupiya, Mbanga Muleba, Modest Mulenga Frank C. Curriero and William J. Moss for the Southern Africa International Centers of Excellence for Malaria Research

Abstract

Background: The scale up of malaria control efforts has resulted in substantial declines in transmission in some but not all regions of sub-Saharan Africa. Understanding factors associated with ongoing malaria transmission in these areas may guide targeted interventions to high-risk areas and populations.

Methods: Household malaria surveys were conducted in Nchelenge District, Luapula Province in northern Zambia. Household structures were enumerated within selected 1 x 1 km grid cells overlaid on a satellite image of the study area. Households within these grid cells were randomly selected for enrollment. Households were enrolled into cross-sectional (single visit) or longitudinal (visits every other month) cohorts but analyses were restricted to cross-sectional visits and the first visit to longitudinal households. During study visits, adults and caretakers of children were administered a questionnaire and a blood sample was collected for a malaria rapid diagnostic test (RDT). Environmental features in proximity to each household were characterized based on satellite imagery and digital elevation models. Characteristics associated with RDT positivity were analyzed using GEE models. Two-way interactions with season were explored.

Results: A total of 1,362 individuals residing within 367 households were enrolled between 2012 and 2014. Over the study period, 49% of study

participants were RDT positive. Despite high malaria transmission throughout the year, rainfall was highly seasonal. Half of all RDT positive individuals were between the ages of 5 and 17 years although this age group comprised only 34% of study participants. In a multivariable GEE model, the odds of an individual being RDT positive was associated with age. Compared with adults over the age of 18 years, children 0 to 4 had over 2.5 times higher odds of a positive RDT (OR=2.5; confidence interval [CI] 1.6, 3.9) and children 5 to 17 years had almost 6 times higher odds of being RDT positive (OR=5.7; CI 4.2, 7.7). Report of fever was also associated with RDT positivity although the association decreased with age: for each increasing age category the odds of fever decreased 29% among RDT positive participants (OR=0.7; CI=0.5, 1.0). Several environmental features were associated with the risk of malaria. The odds of a positive RDT increased by 20% (OR=1.2; CI 1.0, 1.3) for every 10 meter decrease in elevation; by 9% (OR=1.1; CI 1.0, 1.2) for every 250 meter decrease in distance from a category 1 stream; by 46% (OR=1.5; CI 1.3, 1.7) for every 250 meter decrease in the distance to a road; and decreased 2% (OR=1.0, CI 1.0, 1.0) for every additional 10 households within 500 meters of an enrolled house. The odds of a positive RDT were almost twice as high in the rainy season (OR=1.9 CI: 1.2, 2.9). In the rainy season, the odds of a positive RDT increased 6% (OR=1.1, CI: 1.0, 1.1) for every 250-meter decrease in the distance from a category 3 stream. Proximity to an open well was associated with 30% higher odds of malaria and this approached statistical significance (OR=1.3 CI: 0.9, 2.9).

Conclusions: Environmental risk factors for malaria suggest that mosquito breeding sites along category 1 streams, roads and open wells may be sufficient to support perennial transmission, increasing in the rainy season as category 3 streams flood. Children and adolescents between the ages of 5 and 17 were at the highest risk of malaria infection throughout the year. School-based programs may be effective at targeting this high-risk group.

Background

During the past two decades, malaria control has been a focus for the international public health community. Support for malaria has increased from approximately US$100 million in 2000 to nearly $2 billion in 2013 (1). In 2007, malaria eradication was endorsed by the Bill & Melinda Gates Foundation and supported by the World Health Organization (WHO) and Roll Back Malaria (RBM) Partnership as a worldwide goal (2, 3). Zambia is a malaria-endemic country that rapidly scaled-up malaria control activities from 2006 to 2011, including case management with rapid diagnostic tests (RDTs) and artemisinin-combination therapy (ACT), distribution of long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), and intermittent preventive therapy (IPT) for pregnant women (4). Reductions in malaria burden following scale-up of similar malaria control interventions were identified in Rwanda but were not sustained in parts of Kenya, and resurgence of malaria throughout regions in Africa (including Zambia) has been documented (5-7). These mixed results highlight the heterogeneity of malaria transmission and the challenges to control.

Malaria transmission varies across climatic seasons, ecological zones, neighboring villages, and even within households (8-11). Environmental exposures such as land cover, soil moisture, streams, elevation, and topography can modulate malaria risk because they are predictive of vector breeding sites (12). Households in close proximity to breeding sites have higher mosquito densities and are at increased risk of transmission (8). These environmental risk factors may interact with socio-cultural factors at the household; socioeconomic

status, who within the household uses bed nets, and the construction of human dwellings are associated with malaria risk (11, 12).

As recommended by the Malaria Eradication (MalERA) Consultative Group on Modelling, there is a need to better understand the effects of seasonality on aspects of malaria transmission (13). For example, the rainy season is associated with increased numbers of anopheline breeding sites and increased parasite development rates (14). However, irrigation, roads and urbanization may create breeding sites that persist throughout the year, diminishing the seasonal effect (12, 15-17). Season may also be associated with malaria morbidity. At high transmission levels malaria prevalence is not seasonal, although clinical malaria may be (15). In the dry season, non-febrile, low level parasitemia may be widespread (18). These findings suggest that despite high transmission year round, there may be important seasonal differences in risk factors and clinical manifestations for malaria.

Despite recent reductions in malaria infection, illness, severe disease and death recorded across Zambia (19-21), malaria transmission remains high in some geographic areas. Malaria transmission in Zambia varies from low in Lusaka Province to perennial transmission in Luapula Province, suggesting high variation within a single country (22). Nchelenge District is located within Luapula Province where, despite increased coverage with IRS and the distribution of 429,753 LLINs between 2006 and 2011, the parasite prevalence increased from 38% in 2006 to 53% in 2012, although this may be due in part to increased use of RDTs for confirmation (5). The Zambian 2011-2015 National Malaria Strategic

Plan recommends targeting limited resources to the highest risk areas based on epidemiological trends (23).

Understanding individual, household and environmental factors associated with increased malaria risk is necessary to inform and optimize control strategies. Multi-level statistical techniques and spatial analysis are increasingly used to describe and assess risk factors for malaria (12). This study analyzed a series of cross-sectional household surveys in Nchelenge District between 2012 and 2014 to identify characteristics associated with RDT positivity. Targeting control activities and distribution of preventive measures to groups or areas identified as high-risk may reduce malaria transmission in this region.

Methods

Nchelenge District is located in northern Zambia in the marshlands of Luapula Province along Lake Mweru, and shares an international border with the Democratic Republic of the Congo. Luapula Province has the highest prevalence of malaria in Zambia (24). *Anopheles gambiae s.s.* and *Anopheles funestus* are the primary vectors in the area (20). Nchelenge District has a tropical climate with a distinct dry season (May-October) and rainy season (November-April). In 2010, an estimated 147,927 people lived in Nchelenge District (5). The population is mobile, traveling between the lake for the fishing season and inland for farming as a fishing ban is in effect from December 1st to March 1st.

A satellite image of the district was used to construct a sampling frame. A QuickbirdTM satellite image was obtained from Digital Globe Services, Inc.

(Denver, Colorado) and imported into ArcGIS 9.2 (ESRI, ArcGIS, Redlands, CA). One-kilometer square grid cells were overlaid on the image and cells were selected based on distance to Lake Mweru. Within the selected grid cells, structures of appropriate size and shape were identified as potential households and were enumerated manually. Simple random sampling was used to select households within the grid cells that were eligible for surveys conducted throughout the year. Households were enrolled into either prospective longitudinal (visited every other month) or cross-sectional (visited once). This analysis was restricted to cross-sectional surveys and the first visit to longitudinal households because of the reduction in malaria risk following repeated study visits (25).

Study procedures began with community mobilization activities, including approvals from local chiefs and headmen (25). Households consisted of one or more domestic structures where members of a family resided. All individuals living at that residence were eligible to participate. Informed consent was obtained from adults over the age of 16 years and parents or guardians of children under the age of 16 years. A questionnaire was administered to collect demographic information, knowledge and beliefs regarding malaria transmission and prevention, history of recent malaria and anti-malarial treatment, care-seeking behavior, and the use of insecticide-treated nets (ITNs). Answers to questions regarding where the household got their water, such as an open well or a borehole were also recorded. A blood sample was collected by finger prick for a malaria rapid diagnostic test (RDT) (ICT Diagnostics, Cape Town, South

Africa). Individuals that tested positive were offered treatment with artemether-lumefantrine (Coartem®). The study was approved by the Institutional Review Boards of the Tropical Diseases Research Centre in Ndola, Zambia and the Johns Hopkins Bloomberg School of Public Health.

Environmental Characterization

Environmental covariates were generated based on proximity to each household's coordinates and were analyzed using ArcGIS version 9.2 (ESRI ArcGIS, Redlands, CA). A handheld Android tablet was used to record each household's coordinates. A digital elevation model (DEM) for the area with 90 m resolution was obtained from the Shuttle Radar Topography Mission (SRTM) version 3. Elevation values correspond to the reflective surface on the earth and represent soil surface, vegetation and man-made features such as asphalt roads. The SRTM imagery was collected during a 2001 space shuttle mission using a multi-frequency, multi-polarization radar system. Each pixel represents a 90 m average elevation around each pixel's center. The DEM was processed in ERDAS Imagine 2011 and imported into ArcGIS 10.1. The ArcHydro Tools module of ArcGIS was used to develop a stream network and classification. This module uses elevation values to determine water flow direction and accumulation to build a stream network, which is assigned to a stream order based on the Strahler classification. The Strahler classification assigns an order value of 1, 2, 3, etc. based upon the hierarchy of tributaries. Each beginning segment of a stream or river within a stream network is a first-order or category 1, and where two first-order streams come together they form a second-order stream. When

two second-order or category 2 streams meet they form a third-order stream. The degree of slope was also derived from the SRTM image.

All structures that appeared to be households in the study area were enumerated based on satellite imagery. The sum of these structures located within 500 meters of a study household was calculated as a measure of population density. The distance from each enrolled household to the nearest road, nearest health facility and Lake Mweru were also calculated using the near tool in ArcGIS. A binary variable denoting households near the lake or interior was generated based on spatial location, with households less than 3 km from the lake considered near. The distance from Lake Mweru to the most distant site within the study area was 17 km.

The Normalized Difference Vegetation Index (NDVI) was calculated using LandSat 5 data and is calculated as: (near infrared – visible infrared) divided by (near infrared+visible infrared) (μm). Values range from -1 to +1, with negatives representing bodies of water, low values representing asphalt or sand, and high values correlated with dense vegetation. NDVI was explored as a continuous variable but a binary NDVI variable was used for the statistical models due to lack of variation in the study area. Distances to the nearest road, health facility, and to Lake Mweru were calculated for each household.

Rainfall data from a weather-monitoring tool was used to generate a variable for season. The HOBO Micro Station (Onset Computer Corporation, Bourne, MA) is a four-sensor data logger designed to measure rainfall, temperature, and relative humidity at hourly intervals.

Statistical Analyses

RDT positive individuals were compared to RDT negative individuals for individual level characteristics. Household and environmental level characteristics were explored comparing households with no RDT positive residents to those with any RDT positive residents. Proportions were tested using the chi-square test and means were compared using Student's t-test. Individual, household and environmental level characteristics were analyzed using generalized estimating equations (GEE) to account for intra-household clustering. Two-way interaction terms were generated to assess seasonal variation in the effects of each environmental risk factor. Variables with p values ≤0.1 in univariate models were eligible for inclusion in the final model. A multi-variable GEE model was constructed to account for intra-household clustering and non-significant covariates in the GEE model were removed to generate a parsimonious final model. Statistical analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

A total of 1,366 individuals residing in 353 households were visited between April 2012 and May 2014 (Figure 3.1). Parasite prevalence was 38% in 2012 and increased to 49% in 2013 (Figure 3.2). Despite seasonal rainfall, RDT positivity remained higher than 20% every month (Figure 3.2).

Several individual level factors were associated with RDT positivity in univariate analyses. Of those that were RDT positive, most were 5 to 17 year old

children (50%) compared to children younger than 5 years (25%) and adults older than 18 years (25%) (Table 3.1). RDT positivity was associated with reported symptoms, specifically for individuals reporting chills (41% vs. 34%), fever (46% vs. 37%), and headache (48% vs. 41%) within the prior 2 weeks (Table 3.1). Reported use of an ITN the night before was lower for RDT positive individuals (52%) compared to RDT negative individuals (73%), consistent with a protective effect (Table 3.1).

Several household level factors were associated with having at least one RDT positive resident compared to households with no RDT positive residents. Households comprised of a higher number of residents were more likely to have at least one RDT positive resident (median 4 vs. 2 household members), reflecting the higher number of individuals in the household at risk (Table 3.2). Reported use of an open well as the main source for household drinking water was higher among households with any RDT positive residents (42% vs. 32%). Households in areas with lower population density and in the interior away from Lake Mweru were more likely to have an RDT positive resident (median 141 structures within 500 m of the household vs. 210) (Table 3.2).

In a multi-variable GEE analysis, several individual, household, and environmental characteristics were associated with RDT positivity. Compared to adults over the age of 18 years, children younger than five years had 3.6 higher odds (OR=3.6; CI 2.5, 5.1) of being RDT positive, and children 5 to 17 years of age had a 6.8 higher odds (OR=6.8; CI 4.8, 9.6) of being RDT positive (Table 3.3). As expected, history of fever was significantly associated with RDT

positivity and approached significance in a two-way interaction with age: as the age category increased a history of fever decreased 26% (OR=0.7; CI 0.5, 1.0). Individuals residing within the same household were twice as likely to be RDT positive compared to individuals in other households (OR=2.0; CI 1.3, 2.9) (Table 3.3). Other individual level variables, such as receiving malaria medications in the past 2 weeks or using an ITN, that were significant in the univariate analyses, were not significantly associated with RDT positivity in the full GEE model.

Several environmental factors were associated with RDT positivity in the multivariable GEE model. Odds of a positive RDT were 90% higher during the rainy season than the dry season (OR=1.9; CI: 1.2, 2.9) (Table 3.3). The median elevation in the study area was 951 meters (minimum 877 meters, maximum 1049 meters). As household elevation decreased by 10 meters, the odds of RDT positivity increased 20% (OR=0.1.2; CI 1.1, 1.3) (Table 3.3). As the distance of the household to a category 1 stream decreased 250 meters, the odds of RDT positivity increased 9% (OR=1.1; CI 1.0, 1.2) (Table 3.3). Category 2 and 3 streams were not associated with malaria; however, the interaction term for category 3 streams and season was significant. In a two-way interaction between distance to a category 3 stream and season, the odds of RDT positivity increased 6% per 250 meters as distance to a category 3 stream decreased during the rainy season (OR=1.1; CI 1.0, 1.1) (Table 3.3).

Households with a higher proportion of RDT positive residents appeared to be located along some of the inland category 1 streams, with variation along the lake (Figure 3). Open wells were more commonly reported as a source for

household water inland from Lake Mweru, and were potential breeding sites for anopheline mosquitoes (Appendix 1). A higher proportion of RDT positive residents resided in households along category 3 streams during the rainy season (Figure 3.4).

Discussion

Despite the rollout of malaria control interventions, Nchelenge District experiences intense perennial transmission of malaria. This study identified school-age children as a high-risk population in the area, and identified several household- and environmental-level factors that may increase transmission risk at the household. School-age children were the most likely to have malaria, but also less likely than young children to experience symptoms due to the acquisition of partial immunity. Proximity to certain environmental features, such as category 1 streams, roads, and lower elevation areas may increase household malaria risk because they are generally predictive of anopheline mosquito breeding sites. Household features such as the use of an open well may increase household risk for similar reasons. The risk of malaria also doubled in the rainy season, which may be related to proximity to category 3 streams due to the observed model interaction. These individual and household level risk factors may explain some variation in malaria risk, but Nchelenge District as a whole experiences very high parasitemia year round.

There are several reasons malaria control efforts may be ineffectual in this setting. The recent rise in reported cases could be attributed to increasing

insecticide resistance, population movement across borders from high transmission areas, shifts in biting behavior of mosquitoes to outdoors or earlier times, or increased use of RDTs for parasitological confirmation (5, 20, 26). Additionally, while delivery of health services and key interventions has increased, coverage levels may be too low to have a measurable impact (5, 13). For example, according to the 2012 National Malaria Indicator Survey (MIS), Luapula Province reported low rates of IRS (16%), and the lowest levels of IPT use in pregnancy (58%) (22). Importantly, LLIN use in Luapula Province increased from 34% in 2010 to 78% in 2012 (22, 24).

The significant association between environmental factors such as proximity to streams and elevation with RDT positivity is not surprising, as these predict the presence of anopheline breeding sites and are indicative of malaria transmission potential (16, 27, 28). Anopheline breeding sites range from foot prints, puddles, ponds, and shallow moving streams (27). In Nchelenge District, category 1 streams may provide sufficient breeding sites for year round transmission. In the rainy season, category 3 streams previously too large or fast moving for mosquito breeding sites may flood and create marsh-like wetlands on the riverbanks. This may be reflected in the nearly two-fold increased odds of a positive RDT in the rainy season.

Interestingly, the odds of a positive RDT were higher closer to roads. This may be because erosion along dirt roads created puddles that are ideal for breeding sites. A study in Kenya found that water pooled along roads, creating potential breeding sites (16). Similarly, the use of open wells for household

drinking water may create small bodies of water that persist through the dry season, providing breeding sites in close proximity to households. Open wells suggest a high water table in Nchelenge District and a high water table has previously been linked with malaria transmission (29). Testing for anopheline mosquito larvae along roads and in open wells may identify opportunities for targeted vector control interventions.

In addition to environmental factors associated with RDT positivity, some individual and household level characteristics were also significant. Age of the participant was highly associated with RDT positivity, in particular among children aged 5 and 15 years. Children in this age category are at increased risk of malaria and are least likely to use interventions such as LLINs (1, 9). Priority for LLINs is often given to very young children and women of child bearing age, leaving school-aged children vulnerable. Age was also found to interact with reported fever. As age increased, report of fever as a symptom decreased. Previous studies have identified an interaction between age, report of fever, lower parasitemia and season (30). A high prevalence of asymptomatic parasitemia may be critical in maintaining transmission (31-33). School-aged children who have acquired partial immunity may be asymptomatic carriers of both asexual parasites and gametocytes, and may be reservoirs for the parasite through the dry season (34). School based test and treat interventions and/or seasonal malaria chemoprophylaxis (SMC) may be particularly effective in reducing transmission in Nchelenge District.

This analysis has some limitations, mainly that it is reliant on RDTs to detect infection with *P. falciparum*. In such a high transmission setting, some people may be antigenemic for a long time after parasite clearance, leading to over-estimation of parasitemia by RDT (35) . According to the Malaria Indicator Survey, 32% of children had malaria parasites by microscopy and 56% had malaria by RDT (22). Lastly, it is likely that travel occurs in this area, for migrant work or social functions such as weddings and funerals, which may present opportunity for malaria infection not related to the participants' household.

Despite seasonal rainfall, perennial transmission of malaria continues in Nchelenge District. Despite some seasonality, environmental features likely offer sufficient breeding sites for high year round vector population and transmission. Targeted control interventions and novel strategies are necessary to reduce transmission. First, malaria risk maps may be useful in targeting vector control activities to high-risk geographic areas. Second, school-based interventions should be explored to target this high-risk population. The epidemiology and management of malaria in school-age children has received little attention but has consequences on educational attainment and transmission (36). IPT is now being studied in school-age children in the form of intermittent parasite clearance in schools (IPC), seasonal malaria chemoprevention (SMC), and test and treat programs administered by schools (36). Targeting high-risk geographic areas and populations may be cost effective and efficient for reducing malaria transmission.

Table 3.1

Individual characteristics associated with RDT positivity in Nchelenge District, 2012-2014

	RDT Negative		RDT Positive	Univariate unadjusted p-value
Number of individuals	700		662	
Female	388 (56%)		340 (52%)	0.16
Age category				<0.0001
< 5 years	132 (19%)		168 (25%)	
5 to 17 years	141 (20%)		332 (50%)	
≥18 years	427 (61%)		162 (25%)	
Last time visited health facility for malaria				0.001
1 month ago	158 (23%)		189 (29%)	
2-6 months ago	176 (25%)		147 (22%)	
> 7 months ago	212 (30%)		152 (23%)	
Never	113 (16%)		132 (20%)	
Experienced following symptoms in the past 2 weeks				
Chills	239 (34%)		272 (41%)	0.009
Fever	259 (37%)		300 (46%)	0.002
Headache	287 (41%)		316 (48%)	0.009
Took malaria medications in past month	142 (20%)		185 (28%)	0.001
Own ITN	510 (73%)		460 (69%)	0.17
Use ITN	431 (73%)		308 (52%)	<0.0001

Table 3.2

Household characteristics with and without RDT positive residents in Nchelenge District, 2012-2014

	No RDT+ household members		**At least 1 RDT+ household member**	**Univariate unadjusted p-value**
	N (%)		N (%)	
Households	100		267	
Median number household members (IQR)	2 (1, 8)		4 (1, 13)	<0.0001
Maximum household education level				0.03
Primary	54 (54%)		182 (68%)	
Secondary	43 (43%)		82 (31%)	
Higher	3 (3%)		3 (1%)	
Open well main source of household drinking water	32 (32%)		112 (42%)	0.08
Ever received IRS	29 (30%)		83 (31%)	0.78
Median elevation in meters (IQR)	959 (921, 1006)		960 (928, 1028)	0.99
Median distance in meters to category 1 stream (IQR)	715 (354, 1082)		723 (341, 1150)	0.52
Median distance in meters to category 2 stream (IQR)	2172 (470, 3105)		1969 (510, 2857)	0.6
Median distance meters to category 3 stream (IQR)	1644 (427, 2197)		1365 (311, 2130)	0.71
Median distance in meters to nearest health care facility (IQR)	3172 (792, 6163)		4074 (1809, 6092)	0.29
Median distance in meters to road (IQR)	88 (28, 176)		69 (34, 126)	0.13
Percent inland (3 km from Lake Mweru)	63 (63%)		151 (57%)	0.28
Median degree of slope (IQR)	1.7 (0.9, 2.0)		1.6 (1.0, 2.5)	0.76
NDVI value ≥ 0.5	44%		56%	0.04
Number of other households within 500 m of each household	201 (83, 613)		141 (64, 447)	0.002
Study visit in rainy season	48 (48%)		150 (56%)	0.16

Table 3.3

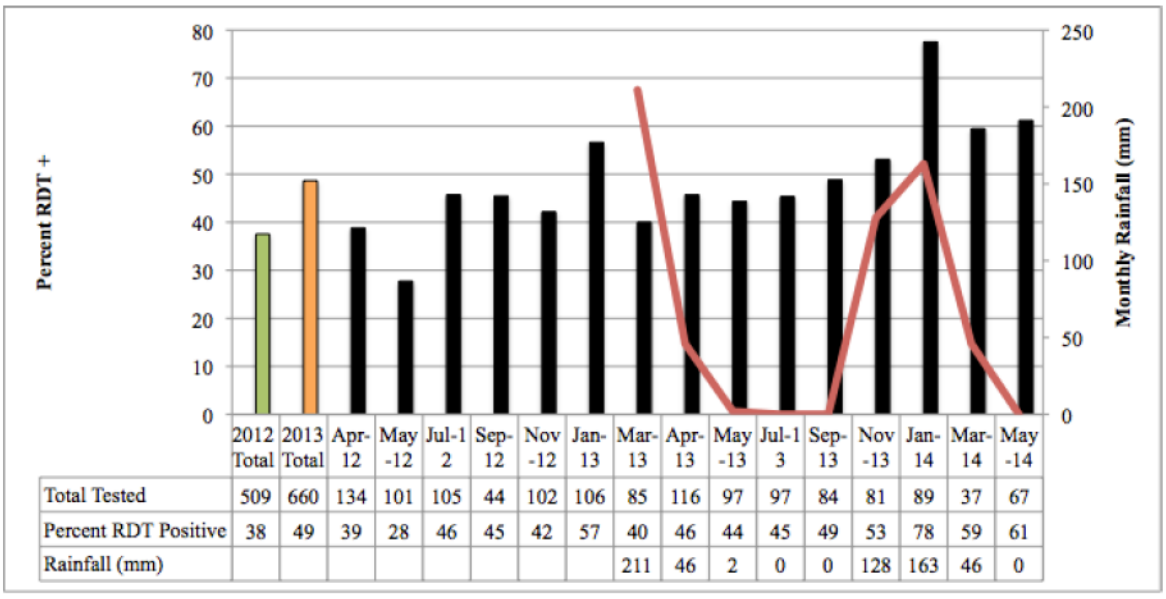
Factors associated with RDT positivity in Nchelenge District, 2012-2014

Factors	Univariate	Multivariable
Fixed Effects	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Individual Level Factors		
Sex	0.84 (0.68, 1.02)	0.96 (0.76, 1.2)
Age Category		
0 to 4 years	3.3 (2.5, 4.4)	2.5 (1.6, 3.9)
5 to 17 years	5.7 (4.4, 7.5)	5.7 (4.2, 7.7)
Older than 18 years	REF	REF
Fever	1.4 (1.1, .8)	2.3 (1.1, 4.7)
Age fever interaction	0.71 (0.53, 0.96)	0.74 (0.54, 1.0)
Sought care for malaria	0.98 (0.91, 1.06)	-
Taken antimalarials past 4 weeks	1.5 (1.1, 2.0)	-
Use ITN night before	0.38 (0.29, .51)	-
Household and Environmental Level Factors		
Water source: open well	1.4 (1.0, 1.8)	1.3 (0.94, 2.9)
IRS, ever	0.91 (0.70, 1.2)	-
Elevation (per 10 m)	1.06 (0.99, 1.13)	1.20 (1.10, 1.30)
Degree of slope	1.0 (0.97, 1.1)	-
Distance to nearest road*	1.36 (1.17, 1.59)	1.46 (1.26, 1.71)
Within 3 km of Lake Mweru	0.85 (0.65, 1.1)	-
Number of structures within 500 m	0.99 (0.98, 0.99)	0.98 (0.98, 0.99)
Rainy season	1.33 (1.02, 1.73)	1.9 (1.2, 2.9)
NDVI value ≥ 0.5	1.32 (1.01, 1.72)	-
Distance to category 1 stream*	1.06 (.99, 1.14)	1.09 (1.00, 1.18)
Distance to category 2 stream*	1.01 (0.99, 1.04)	-
Distance to category 3 stream*	1.00 (0.97, 1.02)	0.96 (0.93, 1.00)
Interaction: season-category 3 stream	1.05 (0.99, 1.11)	1.06 (1.00, 1.11)
Random Effects	OR (95% CI)	OR (95% CI)
Household random effect	-	2.0 (1.4, 2.8)

*per 250 meters

Figure 3.1

Percent of enrolled participants RDT positive per month in Nchelenge District, 2012-2014



	2012 Total	2013 Total	Apr-12	May-12	Jul-12	Sep-12	Nov-12	Jan-13	Mar-13	Apr-13	May-13	Jul-13	Sep-13	Nov-13	Jan-14	Mar-14	May-14
Total Tested	509	660	134	101	105	44	102	106	85	116	97	97	84	81	89	37	67
Percent RDT Positive	38	49	39	28	46	45	42	57	40	46	44	45	49	53	78	59	61
Rainfall (mm)									211	46	2	0	0	128	163	46	0

Figure 3.2

Map of 1 km grid cells, enumerated structures and enrolled households in Nchelenge District, 2012-2014

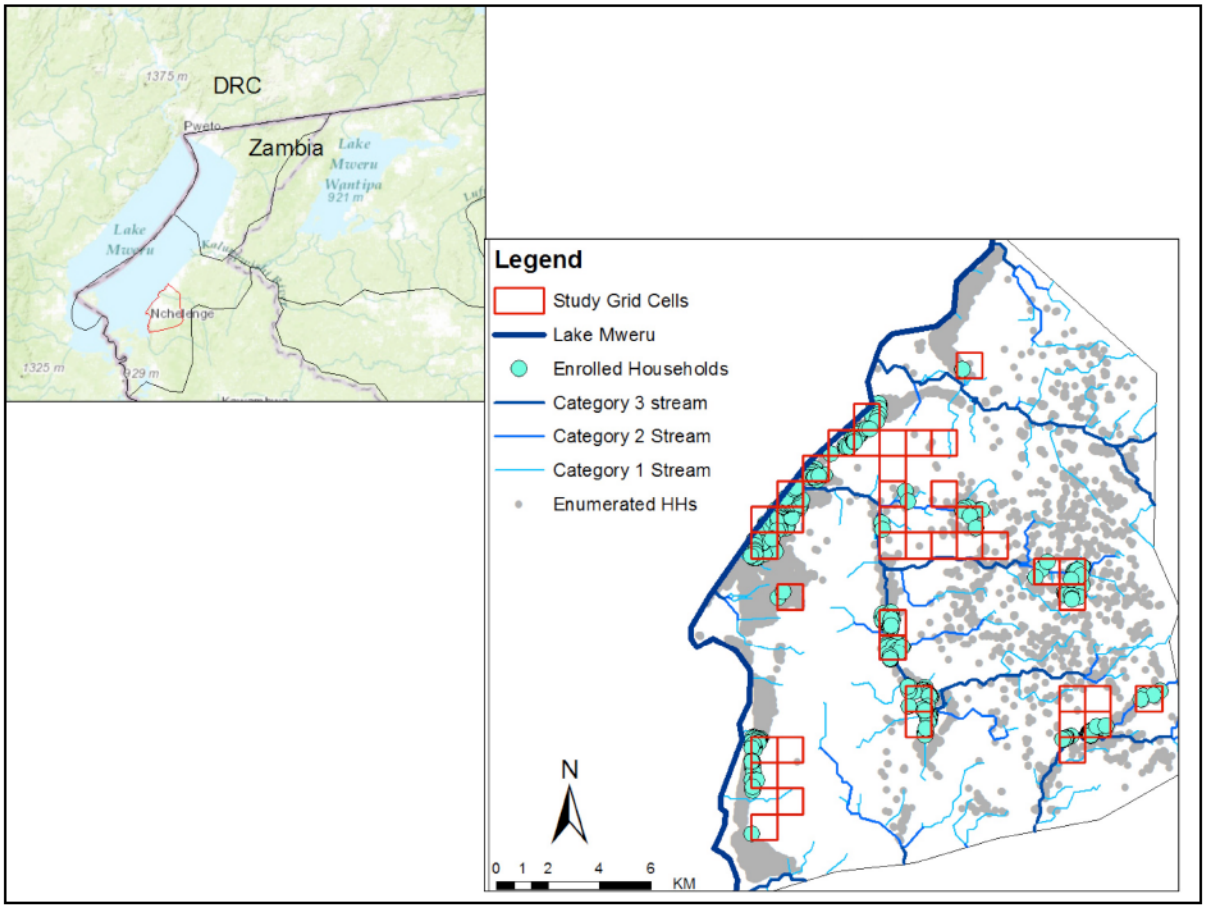


Figure 3.3

Map of the proportions of RDT positive residents within surveyed households in Nchelenge District, 2012-2014

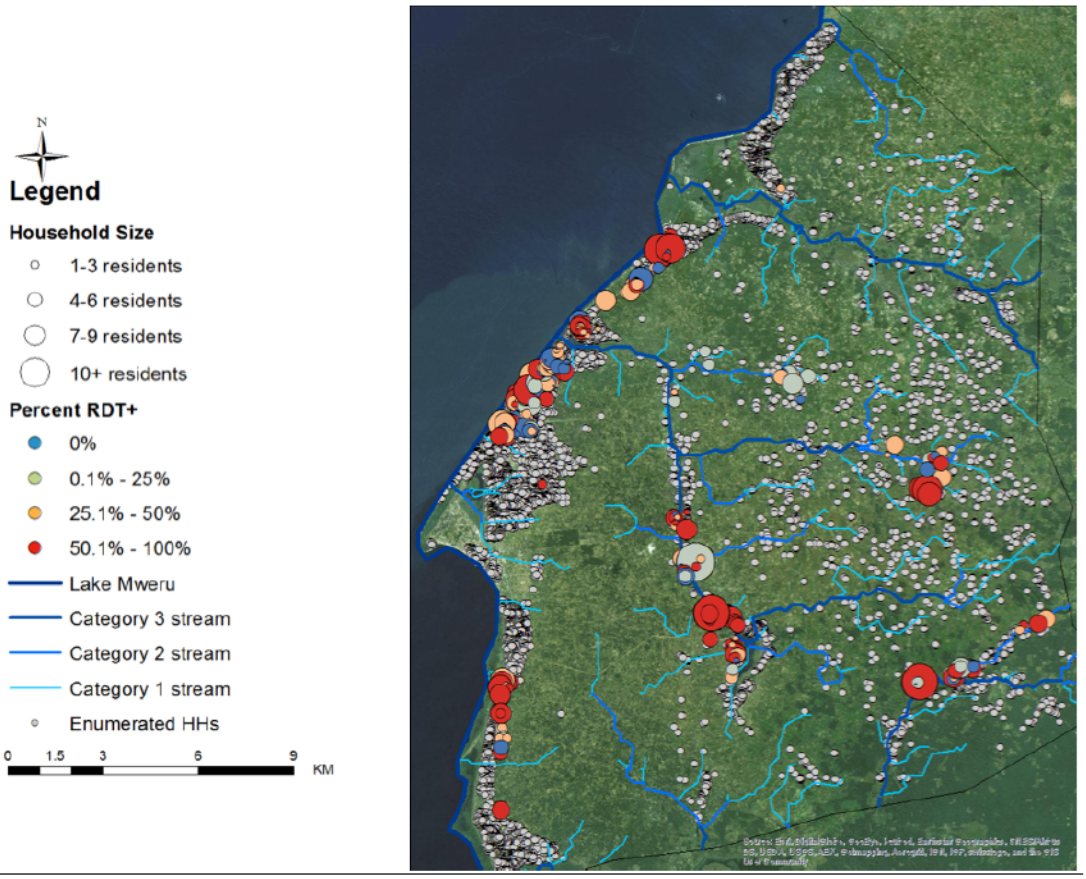
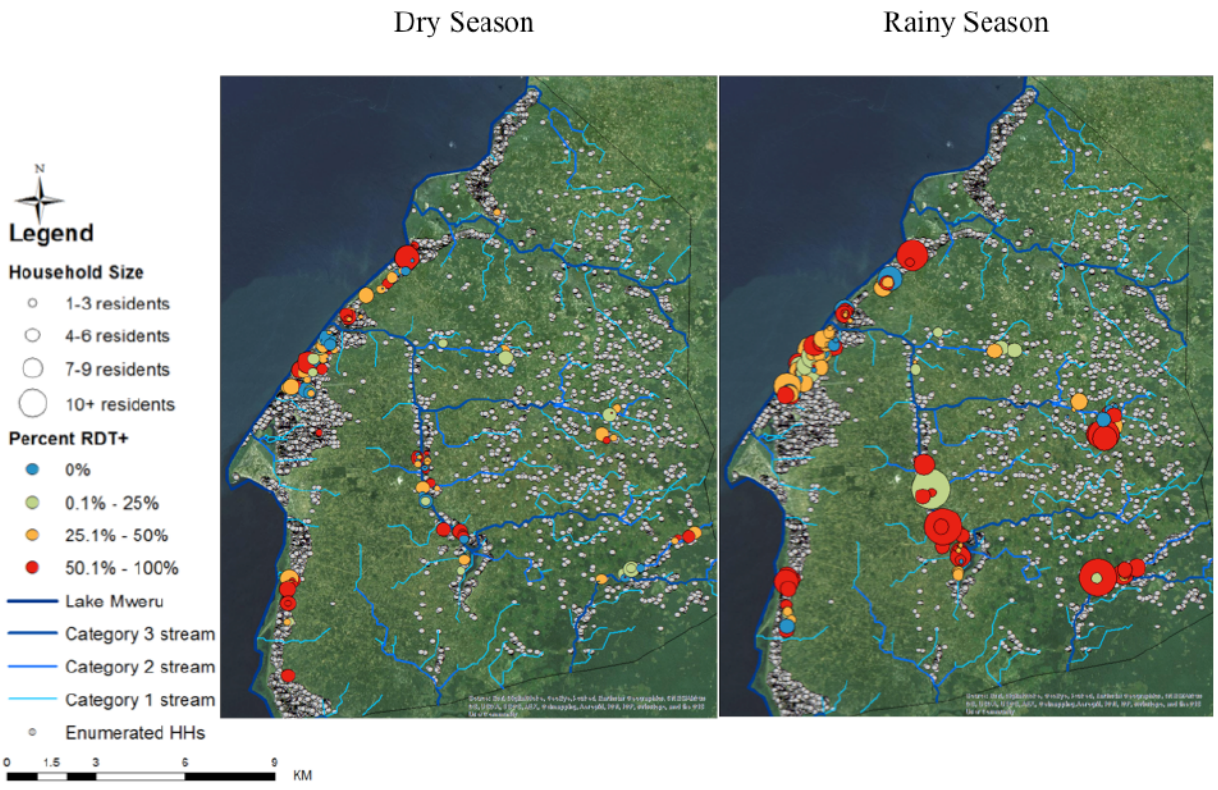


Figure 3.4

Map of the proportions of RDT positive residents within surveyed households by season in Nchelenge District, 2012-2014



Appendix 1

Three examples of open wells used by households in the study area.

Photos courtesy of Mbanga Muleba.

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Chapter 4: Spatial Prediction of Seasonal Malaria Risk in a Setting with Perennial Transmission: Setting of Nchelenge District, in Northern Zambia, 2012-2014

Authors: Jessie Pinchoff, Timothy Shields, Mike Chaponda, Mbanga Muleba, Modest Mulenga, William J. Moss and Frank C. Curriero for the Southern Africa International Centers of Excellence for Malaria Research

Abstract

Background: Despite scale-up of malaria control activities in Zambia, transmission remains high in some areas. Proximity to environmental features indicative of vector breeding sites may modulate household malaria risk. Malaria risk maps may be used to target vector control interventions to high-risk populations.

Methods: Household malaria surveys were conducted in Nchelenge District, Luapula Province in northern Zambia from February 2012 through December 2013. Households were enumerated based on satellite imagery and randomly selected for study enrollment. At each visit, adults and caretakers of children were administered a questionnaire and a malaria rapid diagnostic test (RDT) was performed. Data on the spatial distribution of malaria cases were used to generate a risk map based on demographic and environmental features, including population density, vegetation index, slope, and proximity to category 1, 2, and 3 streams, Lake Mweru, health facilities and roads. Streams were categorized using hydrological models based on a digital elevation model (DEM) derived from the Shuttle Radar Topography Mission version 3. Logistic regression models based on environmental variables were used to construct spatial prediction risk maps using R statistical software packages and ArcGIS

v10.2.

Results: A total of 351 households were visited, comprising 1,362 participants, of whom 48% were RDT positive. Several environmental features were associated with increased household malaria risk in a multivariable logistic regression model. The rainy season nearly doubled household malaria risk (OR=1.9, 95% confidence interval [CI]: 1.3, 2.9). For every 250-meter decrease in distance from a category 1 stream, households had a 10% increased risk of malaria (OR=1.1, CI: 1.0, 1.2). This relationship was also observed for category 3 streams but only during the rainy season: for every 250-meter decrease in distance from a category 3 stream malaria risk increased 5% (OR=1.1, CI: 1.0, 1.1). For every 250-meter decrease in distance from a road, households had a 44% increased risk of malaria (OR=1.4, CI: 1.2, 1.8). Increased degree of slope and lower altitude were also associated with a higher household malaria risk. The model was validated using both internal and external evaluation measures to generate and assess root means square error (RMSE). The final, validated model was used to predict and map malaria risk with a measure of risk uncertainty.

Conclusions: Malaria risk in a high, perennial transmission setting is heterogeneous at a local scale, with variation by season. Prediction maps based on proximity to environmental features may be useful to target vector control interventions to the highest risk geographic areas.

Background

Zambia is a malaria endemic country in sub-Saharan Africa that has historically experienced high burden of malaria morbidity and mortality. Between 2006 and 2011, several national malaria control interventions were scaled-up, including case management with rapid diagnostic tests (RDTs) and artemisinin-combination therapy (ACT), distribution of long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), and intermittent preventive therapy (IPT) for pregnant women (1). Despite substantial progress, malaria transmission remains high northern Zambia. In regions experiencing high, perennial transmission, the goal is malaria control: to reduce the burden of malaria to a manageable level (2). New or enhanced methods are necessary to achieve malaria control in resource-constrained areas with persistently high malaria transmission. Generating maps of variation in malaria risk can be used to target control interventions for maximal impact. However, uptake of mapped malaria epidemiology remains poor; only 5 countries used mapped malaria data to define their national strategic plans or applications to the Global Fund (3).

One obstacle to control is that malaria transmission is heterogeneous in its distribution across time and space (4). Mathematical models predict that heterogeneity of transmission reduces the efficacy of disease control strategies (5). Advances in remote sensing and satellite imagery allow for highly accurate characterization of environmental and ecological features that may be associated with mosquito breeding sites (6), such as proximity to water (7, 8), topography (9), vegetation (10, 11) and anthropogenic features such as roads or irrigation systems (12, 13). These features alter the geographical distribution of malaria by

directly or indirectly influencing the development, density and location of mosquito vectors and their breeding sites (14). The ability to predict spatial variation in malaria risk has improved with these advanced technologies.

Malaria risk maps need to be at a sufficiently fine scale of spatial resolution and accuracy to be useful as spatial decision support tools for targeted malaria control, as incidence can vary significantly across small geographic areas (15, 16). Spatial and seasonal heterogeneity of malaria transmission remain poorly characterized and many existing risk maps have limited operational use for malaria control activities because they are at coarse spatial resolution (national level or higher), based on historical data, or on national level surveys with large unsampled areas (17-19). Few malaria risk maps are associated with measures of spatial uncertainty, which may provide valuable information on model fit and accuracy (20). High-resolution maps may be useful for efficient and cost-effective targeting of interventions to the highest risk areas (3, 10, 14, 16, 20-22).

The study aim was to generate and validate a high-resolution empirical risk map for household malaria risk in Nchelenge District, Luapula Province, Zambia. This is a region with inadequate malaria control. According to the National Malaria Indicator Survey (MIS) in 2012, Luapula Province had the highest malaria prevalence in the country (23). In Nchelenge District specifically, malaria parasitemia increased from 38% to 56% between 2006 and 2012 (24). The risk map determined environmental features predictive of malaria risk, information that can be used for targeting of malaria control activities.

Methods

Study Participants and Procedures

Satellite images were used to generate a sampling frame for the random selection of households to enroll in a prospective community cohort study. Longitudinal (households visited repeatedly) and cross-sectional (households visited once) surveys were conducted, alternating by month. A grid with 1x1 km^2 cells was drawn over the satellite image of Nchelenge District, Luapula Province, and grid cells were selected based on geographic location; households within each selected grid cell were enumerated and assigned a GPS coordinate. Satellite imagery was obtained from DigitalGlobes Services, Inc (Denver, Colorado). The image was imported into ArcGIS 10.2 (ESRI, ArcGIS, Redlands, California) and locations of households were identified and enumerated manually.

A field team was provided coordinates of the randomly selected households to contact for enrollment. If a household was not found or refused participation, a household was selected from a back-up list of randomly selected households. After obtaining permission from the local chief and head of household, as well as individual informed consent, a questionnaire was administered to each participant residing within the household and a blood sample was collected by finger prick. For children under the age of 16 years, the questionnaire was directed to their caregiver who provided consent. Rapid diagnostic tests (RDT) were used to detect *P. falciparum* histidine-rich protein 2 (ICT Diagnostics, Cape Town, South Africa). The RDT was shown to detect 82%

of test samples with wild-type *P. falciparum* at a concentration of 200 parasites/μL and 98% of test samples with a concentration of 2000 parasites/μL, with false positives in 0.6% of negative samples (25). All individuals with positive RDTs were offered treatment with artemether-lumefantrine (Coartem®).

Landscape characterization

Environmental covariates were generated for each study household and analyzed using ArcGIS version 9.2 (ESRI ArcGIS, Redlands, CA). A handheld Android tablet was used to record the household coordinates. A digital elevation model (DEM) for the area with 90-meter resolution was obtained from the Shuttle Radar Topography Mission (SRTM) version 3. Elevation values correspond to the reflective surface on the earth and represent soil surface, vegetation or man-made features such as asphalt roads. The SRTM imagery was collected during a 2001 space shuttle mission using a multi-frequency, multi-polarization radar system. Each pixel represents a 90-meter average elevation around each pixel's center. The DEM was processed in ERDAS Imagine 2011 and imported into ArcGIS 10.1. The ArcHydro Tools module of ArcGIS was used to develop a stream network and classification. This module uses elevation to determine water flow direction and accumulation to build a stream network, which is assigned to a stream order based on the Strahler classification. The Strahler classification assigns an order value of 1, 2, 3, etc. based upon the hierarchy of tributaries. Each beginning segment of a stream or river within a stream network is a first-order or category 1 stream. A second-order stream is formed when two first-order streams come together. When two second-order or category 2 streams meet

they form a third-order stream. The degree of slope was also derived from the SRTM image.

All structures that appeared to be households were enumerated based on satellite imagery. The sum of these structures located within 500 meters of a study household was calculated as a measure of population density. The distance from each enrolled household to the nearest road, nearest health facility and Lake Mweru were also calculated using the near tool in ArcGIS. A binary variable denoting households near the lake or interior was generated based on spatial location, with households less than 3 km from the lake considered near.

The normalized difference vegetation index (NDVI) was used to assess ground cover. NDVI is derived from LandSat 5 Moderate Resolution Imaging Spectroradiometer (MODIS) from the US Geological Survey (USGS) Land Processes Distributed Active Archive Center (LP DAAC). NDVI is the ratio of (near infrared – visible infrared) divided by (near infrared + visible infrared) in μm, with 30-meter resolution. Values for NDVI range from -1 to +1: negative values represent bodies of water, values near zero represent asphalt, and increasing values correspond to increasing abundance of actively photosynthesizing vegetation or “greenness” (11).

Rainfall data from a weather-monitoring tool was used to generate a variable for season. The HOBO Micro Station (Onset Computer Corporation, Bourne, MA) is a four-sensor data logger designed to take measurements of rainfall, temperature and relative humidity at hourly intervals.

Statistical analyses

We identified prevalent malaria infections by RDT using data from the cross-sectional surveys and first visit to the longitudinal survey households. Logistic regression was used to identify environmental features associated with the proportion of individuals in a household who were RDT positive. Variables including all two-way interactions with season were explored in univariate models and those with p-values ≤0.1 were considered for inclusion in the final model. Logistic regression inference was based on the quasi-binomial distribution to account for overdispersion. Semivariogram plots based on regression standardized residuals were used to assess residual spatial variation (spatial variation in the proportion of RDT positive individuals per household not accounted for by the regression variables).

Model fit was evaluated using the Hosmer-Lemeshow goodness of fit test. Prediction performance of the final model was evaluated internally and with an external data set. For internal evaluation, a Monte-Carlo scheme was designed as follows: for each 1,000 iterations, the data were randomly split into a training data set and a prediction data set, with the prediction set being 10% (n=35) of the total 351 sampled households from 2012-2014. The final regression model was refit in each iteration and used to predict the number of RDT positive household members in the prediction data set. Root mean squared error (RMSE) comparing the predicted to the true number of RDT positives per household was the performance metric used. Results were summarized by the average RMSE and corresponding 95% prediction interval (taken as the 2.5^{th} and 97.5^{th}

percentiles) from the 1,000 Monte Carlo RMSEs. For external evaluation, the final regression model was run for the data restricted to 2012-2013 and used to predict the number of RDT positive household members for the 2014 sampled households (n=57) with RMSE used to evaluate prediction performance. In both the internal and external evaluation of the model's predictive performance, RMSE was calculated for all the predictions and also stratified for larger versus smaller households, defined by using the median threshold of 4 household members, and those prediction households sampled in the rainy versus dry seasons. Statistical analyses were conducted using R statistical software packages (version 3.1.1) (26).

As a final step in the analysis, a grid of 500 m^2 cells was drawn over the study site in ArcGIS. Environmental covariates matching those in the final model were generated for the centroid of each grid cell. The final model fit using the full 2012-2014 data was used to predict the risk of RDT household positivity at each grid cell and then mapped onto the grid. Inverse distance weighting (IDW) was implemented in ArcGIS to smooth risk values. A map of prediction uncertainties was also produced based on the standard error from the prediction model, using the same methods as for the prediction risk values for the grid. A final map of the difference in prediction values by season was created to highlight areas where there was more change between seasons. Only environmental variables were included in the model because these values are obtainable at un-surveyed locations and can be used in the model to predict malaria risk beyond the study area.

Results

A total of 353 households comprising 1,366 individuals were sampled between April 2012 and June 2014. Households had an average of 4 household members (minimum of 1 and maximum of 13 individuals). The median proportion of RDT positive individuals in a household was 50% (IQR 15%, 67%.) (Table 4.1). Fifty-four percent of study visits occurred during the rainy season.

In the final multivariate logistic regression model, several environmental features were associated with the proportion of individuals testing RDT positive within households. Malaria increased with proximity to streams and during the rainy season. Household malaria risk was almost double during the rainy season compared to the dry season (OR=1.9, CI: 1.3, 2.9) (Table 4.2). Household risk of malaria increased 10% (OR=1.1, CI: 1.0, 1.2) for every 250-meter decrease in distance from a category 1 stream. Although proximity to a category 3-stream was not associated with RDT positivity, a significant interaction was identified between proximity to category 3 streams and season. In the rainy season, household risk of malaria increased 5% (OR=1.1, CI: 1.0, 1.1) for every 250-meter decrease in distance from a category 3 stream (Table 4.2). Household malaria risk was also associated with terrain, as measured by elevation and slope. The range of elevation in the study area was 877 to 1049 meters. For every 50-meter decrease in elevation, household risk of malaria increased 61% (OR=1.6, CI: 1.2, 2.2) (Table 4.2). The degree of slope is the angle at which the terrain lies. The range for the entire study area was between 0 and 30 degrees and the range for sampled households was between 0 and 10 degrees. For each increase in the degree of slope, household risk of malaria increased 7%

(OR=1.1, CI: 1.0, 1.2) (Table 4.2). Household risk of malaria increased by 44% (OR=1.4, CI: 0.1.2, 1.8) for every 250-meter distance closer to the nearest road (Table 4.2).

Residual semivariograms based on Pearson standardized regression residuals and maximum likelihood fitted spherical semivariogram models were calculated for both the null (intercept only) and final regression models (Appendix 2). Comparing the null model to the final regression model revealed that the included regression covariates substantially accounted for spatial variation in the regression outcome. However, regression inference and prediction variances were still adjusted for over-dispersion to provide more conservative estimates.

To validate the predictive performance of the final multivariable model, both internal and external evaluations were implemented. For the internal evaluation based on the 2012-2014 data, the average RMSE was 1.2, suggesting that on average, when applied to the total number of household members, the model prediction was within 1.2 individuals (95% prediction interval: 0.8, 1.6) of predicting the correct number of RDT positive household members (Table 4.3). Model prediction was better in the dry season; the average ratio of the rainy season RMSE to dry season RMSE was 1.1 (95% prediction interval: 0.6, 1.9) (Table 4.3). Model prediction was better in houses with 4 or fewer residents; the average ratio of the RMSE for large houses (>4 members) to small houses (≤4 members) was 1.8 (95% prediction interval: 1.0, 2.9) (Table 4.3).

In the external validation, the model was generated using 2012-2013 data to assess model fit withholding the 57 households visit during 2014. The external validation produced an RMSE of 1.4, indicating that on average the model predicted risk when applied to the total number of household members was within 1.4 individuals of predicting the correct number of RDT positive household members, slightly higher than for the internal validation (Table 4.3). The ratio for rainy to dry season RMSE was 1.3, and for large to small households was 2.4 (Table 4.3). The 2012-2013 and 2014 household locations with observed versus predicted plots based on the 2014 households for all predictions and for predictions stratified by season and household size are depicted (Figure 4.3).

After validation of the final model, a predictive malaria risk map was generated for the rainy and dry seasons based on the full 2012-2014 data set. The maps indicate increased household malaria risk near roads and category 1 streams, and in proximity to category 3 streams during the rainy season only (Figure 4.1). The standard errors from the prediction map were mapped to identify areas of higher uncertainty of model predictions (Figure 4.1). The difference in predictions between rainy and dry season highlights the seasonal increase in risk along category 3 streams (Figure 4.2).

Discussion

Malaria risk maps for Nchelenge District, Zambia identified significant spatial and seasonal variation in malaria risk within a small geographic area in a region with high, perennial malaria transmission. To date, ecological analyses to

guide malaria control have been limited. Overall models are complex, there is variation in the effects of the same ecological features in different areas or times, and marked residual variation of malaria continues to be detected, signifying that models are not controlling for all aspects of malaria transmission (10). This inconsistency and high level of complexity make ecological models and maps often not readily available to malaria control programs. Even if they are available, most countries fail to use them in planning their national malaria control strategies (3).

This model was constructed based on high-resolution satellite imagery and malaria prevalence data collected between 2012 and 2014 in a cohort of randomly selected households. The model accurately identified environmental features associated with increased household malaria risk and also characterized variation in prediction uncertainty. The inclusion of an uncertainty map is important yet unusual in spatial analyses of malaria transmission and risk maps. It is critical to show spatial variation in prediction uncertainty to highlight areas for additional surveillance, ensure appropriate use of risk maps and address ways to improve model predictions.

The risk map identified several high-risk areas based on proximity to environmental features. Streams and marshlands are highly associated with vector breeding sites. Category 1 streams are small and the water is not fast moving; these may provide ideal breeding sites for anopheline mosquitoes year round in Nchelenge District. Category 2 and 3 streams may be too large and fast moving to provide vector-breeding sites. However, in the rainy season, category

3 streams may flood, creating marsh-like conditions ideal for anopheline breeding sites. This may increase the abundance of anopheline vectors in the rainy season. Additional potential sources of year round breeding sites are highlighted by the increased risk of malaria along roads and in households that use open wells as the main source of water. Previous studies have found that satellite images and remotely sensed data accurately predict breeding sites, which is useful since ground testing can be expensive and time intensive (6, 27). However, it is important to continue assessing the accuracy of these data.

The risk maps generated in this analysis have some limitations. The semivariogram, a measure of residual spatial variation, indicates that the model accounts for most but not all spatial variation. Unexplained spatial variation may be from individual and household level factors such as age, use of protective measures, and roof material of the household (10). These variables cannot be included in models predicting from sampled to unsampled areas because household data in unsampled areas is not known, although environmental data can be derived in unsampled areas from satellite imagery and remotely sensed data and used to predict the outcome of malaria risk. The risk maps are also based on RDT positivity of individuals within enrolled households; in such a high transmission setting, it is possible that some people may be antigenemic for several weeks after parasite clearance, leading to over-estimation of parasitemia by RDT.

In Nchelenge District, the prevalence of malaria remains high, and improved techniques are necessary to reduce the burden of disease. The malaria

risk map generated in this study accurately characterized the heterogeneity of malaria transmission and identified high-risk areas. There are many uses for malaria risk maps such as this one by national malaria control programs if they can be generated at the appropriate level of spatial resolution. Generating high-resolution, predictive risk maps that highlight heterogeneity of malaria can help limited resources be more efficiently spatially targeted according to local needs (14, 19). Risk maps may aid in the prioritization of high-risk areas, and in guiding the implementation of focused, intense interventions (4). Using risk maps to guide targeting may be particularly applicable to IRS, which is an expensive yet effective method of vector control that is increasing in use despite few recommendations for where and how to target. For risk maps to be useful spatial decision support tools for targeted malaria surveillance and intervention delivery, the maps must be at high spatial resolution but must also be based on data and models accessible to national malaria control programs. These findings may be expanded and used to build improved risk maps for Zambia.

Table 4.1
Characteristics of sampled households and environmental variables in Nchelenge District, 2012-2014

	Households with ≥ 1 RDT-positive resident	Households with no RDT positive residents	All households
Median number of household members (IQR)	4 (3, 5)	2 (1, 4)	4 (2, 5)
Median distance to nearest category 1 stream in meters (IQR)	723 (341, 1150)	715 (354, 1082)	717 (345, 1113)
Median distance to nearest category 2 stream in meters (IQR)	1969 (510, 2857)	2172 (470, 3105)	2139 (510, 2898)
Median distance to nearest category 3 stream in meters (IQR)	1365 (311, 2130)	1644 (427, 2197)	1442 (338, 2138)
Median number of structures within 500 meters (IQR)	141 (64, 447)	210 (83, 613)	145 (71, 479)
Median distance to nearest road in meters (IQR)	69 (34, 126)	88 (55, 176)	74 (39, 139)
Median degree of slope (IQR)	1.6 (1.0, 2.5)	1.5 (0.9, 2.0)	1.6 (1.0, 2.3)
Median elevation in meters (IQR)	950 (939, 966)	953 (940, 970)	951 (939, 967)
Median normalized difference vegetation index (IQR)	0.5 (0.5, 0.6)	0.5 (0.4, 0.5)	0.5 (0.5, 0.6)
Median distance to nearest health facility in meters (IQR)	4075 (1809, 6092)	3172 (792, 6163)	3987 (1526, 6104)
Median distance to Lake Mweru in meters (IQR)	747 (449, 6895)	723 (516, 6284)	725 (462, 6881)

Table 4.2
Univariate and multivariable logistic regression models of environmental factors associated with RDT positivity in Nchelenge District, 2012-2014

	Univariate Models*			Multivariable Model	
	OR	95% CI		OR	95% CI
Distance to category 1 stream (per 250 m)	1.1	1.0, 1.1		1.1	1.0, 1.2
Distance to category 2 stream (per 250 m)	1.0	1.0, 1.0		-	-
Distance to category 3 stream (per 250 m)	1.0	1.0, 1.0		1.0	0.9, 1.0
Rainy season	1.4	1.1, 1.8		1.9	1.3, 2.9
Interaction: Category 3 stream and rainy season	1.1	1.0, 1.1		1.1	1.0, 1.1
Number of structures within 500 m	0.9	0.9, 1.0		0.9	0.9, 1.0
Distance to nearest road (per 250 m)	1.4	1.2, 1.6		1.4	1.2, 1.8
Degree of slope	1.0	1.0, 1.1		1.1	1.0, 1.2
Elevation (per 10 m)	1.3	1.0, 1.6		1.6	1.2, 2.2
NDVI value ≥0.5	1.3	1.1, 1.6		-	-
Distance to health facility (per 250 m)	1.0	1.0, 1.0		-	-
Distance to Lake Mweru (per 250m)	1.0	1.0, 1.0		-	-
Lake vs. interior	0.8	0.7, 1.0		-	-

*Univariate variables with p values ≤0.1 eligible for inclusion in multivariable model

Table 4.3
RMSE values and ratios calculated for an internal and external validation of final multivariable models for malaria risk in Nchelenge District, 2012-2014

	RMSE Values from Internal Validation (95% confidence interval)	RMSE Values from External Validation Using Data Collected in 2014
Characteristic		
RMSE	1.2 (0.8, 2.6)	1.4
RMSE ratio rainy vs. dry	1.1 (0.6, 1.9)	1.3
RMSE ratio large vs Households with >4 residents	1.8 (1.0, 2.9)	2.4

Figure 4.1
Predictive malaria risk map and uncertainty maps by season for Nchelenge District, 2012-2014

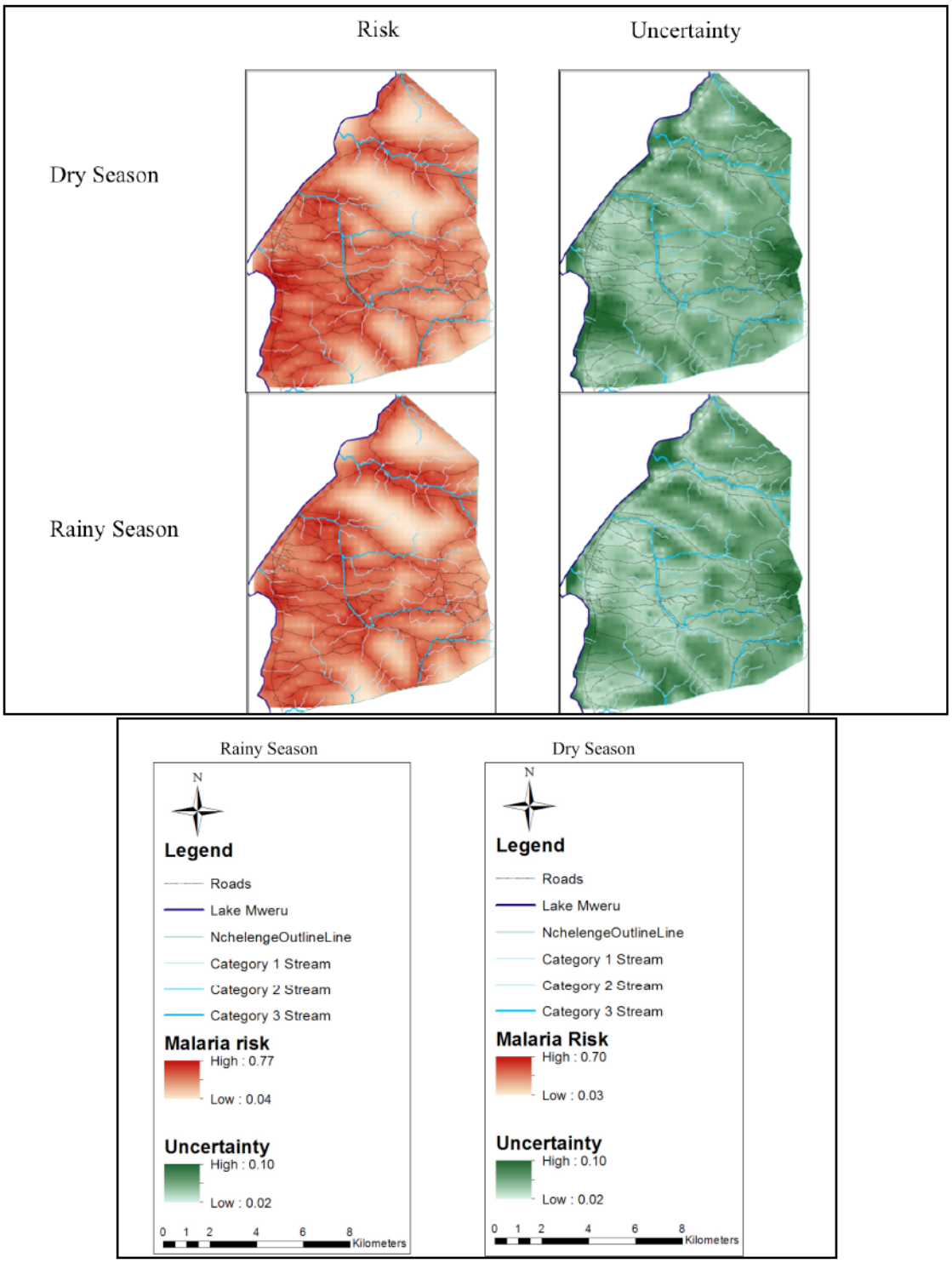


Figure 4.2

Map of difference in risk (rainy minus dry risk values) between seasons for Nchelenge District, 2012-2014 to identify areas of increased change between seasons

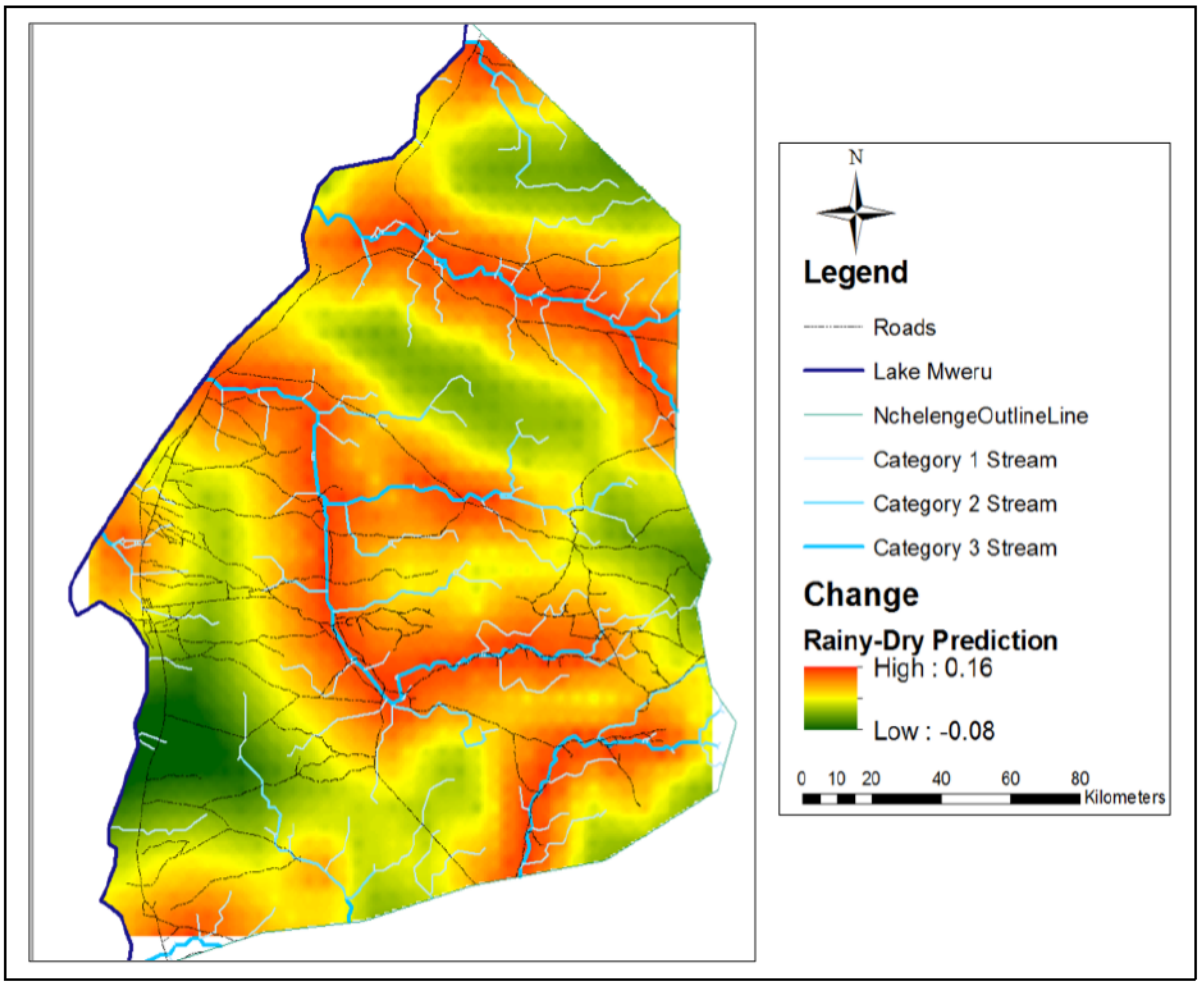
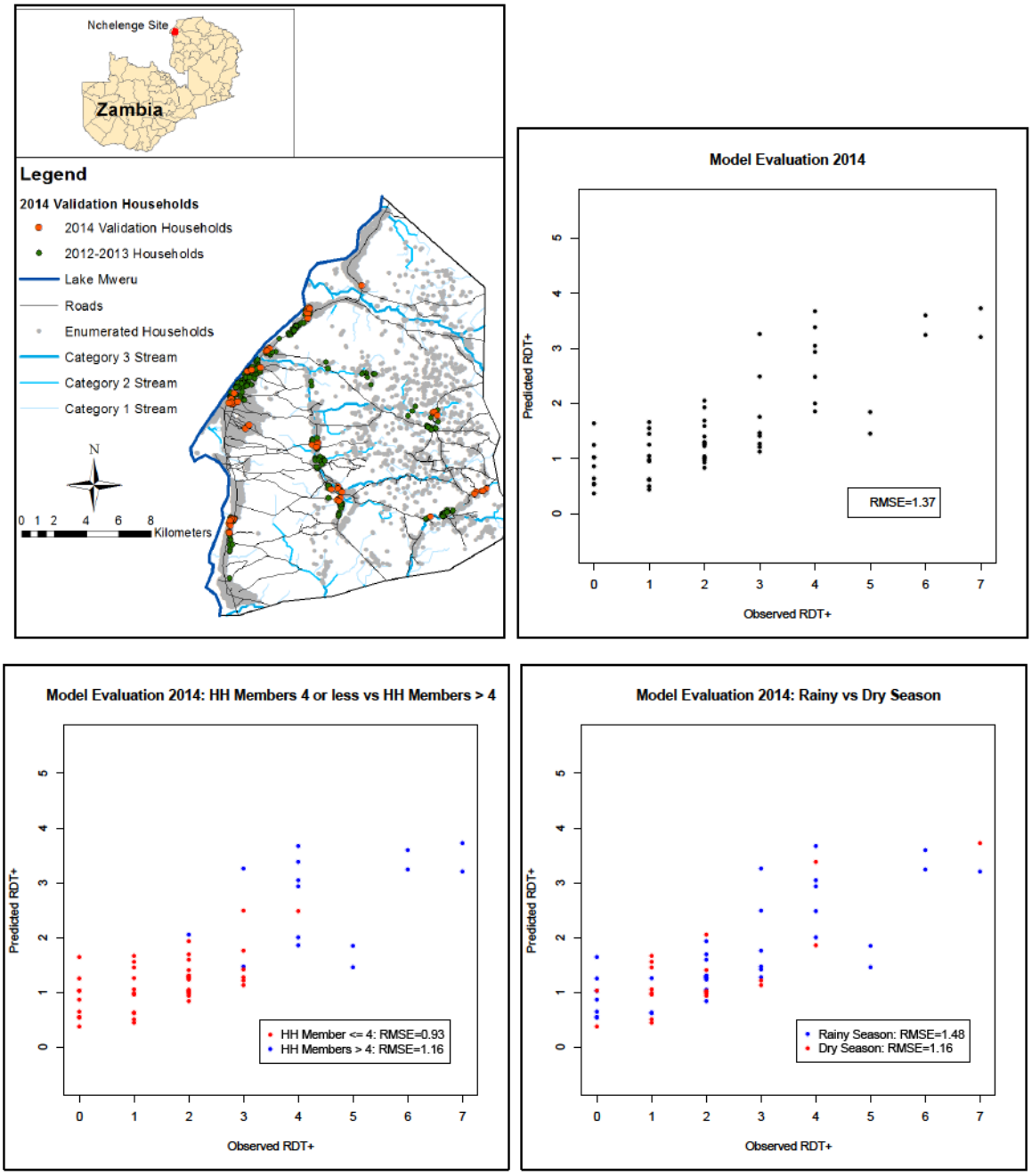


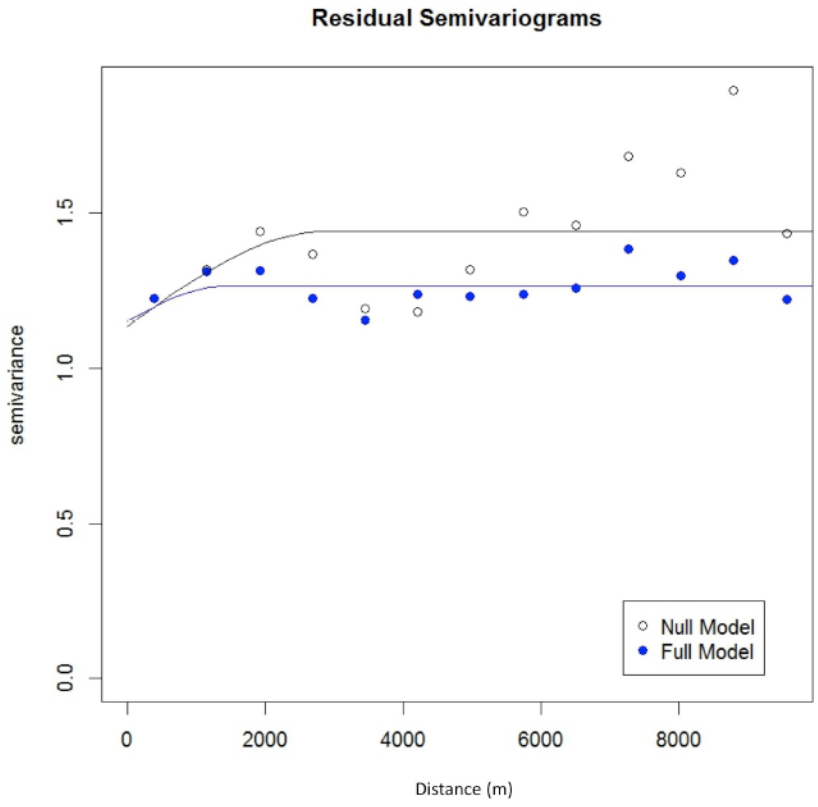
Figure 4.3

External evaluation results: map of Nchelenge District study area indicating the 2012-2013 and 2014 households (upper left), observed vs. predicted plots for all households (upper right), stratified by season (bottom left), and stratified by household size (bottom right).



Appendix 2

Residual semivariograms based on Pearson standardized regression residuals of null model (intercept only) and full model (multivariable model). The fitted semivariogram lines represent maximum likelihood fitted spherical semivariogram models.



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Chapter 5: Individual- and Household-Level Factors Associated With Sustained ITN Use Following a Reduction in Malaria Transmission in Southern Zambia

Authors: Jessie Pinchoff, Harry Hamapumbu, Tamaki Kobayashi, Limonty Simubali, Jennifer Stevenson, Douglas E. Norris, Elizabeth Colantuoni, Philip E. Thuma and William J. Moss for the Southern Africa International Centers of Excellence for Malaria Research

Abstract

Background: The prevalence of malaria has declined in parts of sub-Saharan Africa. As the perceived risk of malaria decreases, the use of personal protective measures may also decline. Understanding factors that influence insecticide-treated net (ITN) ownership and use in areas of declining transmission is critical to promote continued use and thus achieve and sustain malaria elimination.

Methods: Households in the catchment area of Macha Hospital in Choma District, Southern Province, Zambia were enumerated using satellite imagery and randomly selected for enrollment. Households were either visited once (cross-sectional) or every other month (longitudinal). A questionnaire was administered to adults and caretakers of children to collect information on malaria-related beliefs and behaviors, and a malaria rapid diagnostic test (RDT) was performed. Mosquitoes were collected concurrently using light traps.

Results: The prevalence of malaria as measured by RDT at cross-sectional and first visit to longitudinal households decreased from 8.4% in 2008 to 2.1% in 2013. ITN ownership at the cross-sectional and first visit to longitudinal households increased from 77% in 2008 to 83% in 2013. Overall, ITN use was higher at follow-up visits (77%) compared to first visits (62%) in the longitudinal

cohort ($p<0.0001$). Individual and household level factors associated with ITN use were assessed using longitudinal, multi-level regression models. In the multi-level model, ITN use was 80% higher during the rainy season compared with the dry season (OR=1.8; 95% confidence interval [CI]=1.5, 2.2), and 50% higher among participants who learned about malaria from a community health worker as opposed to not learning or learning from another source (OR=1.5; CI 1.2, 2.0). Residents of households with three or more nets were more than twice as likely to use an ITN (OR=2.1; CI 1.4, 3.1). For every increase in 500 meters from the nearest health center, the odds of ITN use decreased 7% (OR=0.9; CI 0.9, 1.0). For 2012 and 2013, the association between total (anopheles and culicine) mosquitoes and ITN use was assessed. A total of 9, 265 mosquitoes were caught; 2,728 (29.4%) anophelines and 6,537 (69.6%) culicines. In a multi-level logistic regression model, the odds of ITN use were more than twice as high if more than five mosquitoes were captured in the house as compared to 0 mosquitoes, after adjusting for season and whether it was the first or a follow up visit (OR=2.1; CI 1.1, 3.9). Lastly, responses to qualitative questions were tabulated to identify reasons for not owning or using an ITN. Absence of mosquitoes and difficulty hanging ITNs in the household were deterrents to ITN use.

Conclusions: ITN use can be sustained in low transmission settings with continued education and distributions, and may be driven in part by the presence of nuisance mosquitoes.

Background

The Bill and Melinda Gates Foundation, World Health Organization (WHO), and, later, the Roll Back Malaria (RBM) Partnership are all supporting malaria elimination (1). Several tools are widely used for malaria control and elimination, including artemisinin combination therapies (ACTs) for treatment of infection confirmed by rapid diagnostic tests (RDT) or microscopy, indoor residual spraying (IRS), intermittent preventive therapy for pregnant women (IPTp), seasonal malaria chemoprophylaxis, and long-lasting insecticide treated nets (LLINs). Substantial increases in funding for malaria control and the procurement and distribution of these tools for prevention and treatment are associated with declines in malaria burden (2). Some formerly high and medium endemic countries have reduced malaria prevalence to low levels (1% or lower community parasite prevalence for *Plasmodium falciparum*) (3, 4).

Unfortunately, these gains may be followed by resurgence of malaria in regions with high transmission potential if control efforts are not sustained (4-10). A recent review identified 75 resurgence events in 61 countries since the 1930s and 91% of these were attributed at least in part to the weakening of malaria control programs, such as complacency following successful malaria control (11). Despite renewed funding and a global effort to eliminate malaria in some countries, recent increases in malaria incidence in countries such as Rwanda and Zambia have generated concern that control efforts may not be sustainable (11, 12). Ensuring the continued use of LLINs as a major component of vector control in low transmission settings is necessary to achieve and sustain malaria control and elimination.

LLINs are one of the most cost-effective, widely distributed interventions to prevent malaria. The WHO strongly recommends behavior change interventions including information, education, communication (IEC) campaigns and post-distribution “hang-up campaigns” to ensure continued, proper use of LLINs (13). Between 2008 and 2010, 254 million nets were delivered throughout sub-Saharan Africa, sufficient to cover 66% of the 765 million persons at risk (14). The number of nets distributed in 2010 decreased but the 3-year total of nets available in 2014 (distributed 2011-2013) is estimated to be more than 400 million (15). A Cochrane review of 22 randomized trials confirmed the efficacy of bed nets in preventing malaria in children and communities (16-19). As transmission falls, it is crucial to maintain high coverage of vector control measures such as LLINs and promote their continued use (20). This entails a better understanding of LLIN user preferences, use patterns, alternative uses for LLINs, and factors influencing LLIN use (21-23), particularly in regions with declining transmission.

Little data exist on the sustained use of ITNs, including LLINs, in regions of declining malaria transmission. Understanding trends in ITN use over time in these settings and identifying factors associated with their continued use are critical to achieving and sustaining malaria elimination. This study assessed ITN use over a six-year period in a region of declining malaria transmission in southern Zambia.

Methods

Study site and population

The study was conducted in the catchment area of Macha Hospital in Choma District, Southern Province, Zambia between February 2008 and December 2013. The single rainy season lasts from December through April, followed by a cool dry season from April until August and a hot dry season through November. Malaria transmission peaks during the rainy season (24). The hospital catchment area is populated by villagers living in small, scattered homesteads. The prevalence of malaria has declined in this area since 2004. ACTs were introduced as first-line anti-malarial therapy in Zambia in 2002 (25) and into the study area in 2004. ITNs were widely distributed in the study area in 2007 (26) and more recently, 11,543 ITNs were distributed from nine health posts around the Macha Hospital in June 2012 (Phil Thuma, personal communication).

The development of the sampling frame and enumeration of households were reported elsewhere (26). Briefly, satellite images were used to construct a sampling frame from which households were selected by simple random sampling for enrollment into prospective longitudinal and cross-sectional surveys of malaria. Cross-sectional households were visited once and longitudinal households were visited every other month and replaced if residents declined further participation. Coordinates of households were recorded using GPS, and Euclidean distance to the nearest health facility was calculated using ArcGIS v9.2. Households enrolled in the longitudinal cohort were repeatedly surveyed every other month, while households enrolled in the cross-sectional cohort were

surveyed once. Households could enter or exit the longitudinal cohort at any time; the number of follow up visits ranged from 2 to 35 visits. After comparing ITN use at longitudinal follow-up visits with ITN use at cross-sectional and the first longitudinal household visit, the analyses were restricted to households enrolled in the longitudinal cohort that reported owning at least one ITN.

The study was approved by the University of Zambia Research Ethics Committee, the Institutional Review Board of the Tropical Diseases Research Centre and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. Informed consent was translated into local languages and obtained from adult participants and the parents or guardians of children.

Sample survey data

During each study visit, a questionnaire was administered to consenting participants over 16 years of age and to the guardians of participants younger than 16 years of age. Data collected included demographic information, history of recent malaria and antimalarial treatment, reported health seeking behavior, knowledge of malaria transmission and prevention, and ownership, care and use of ITNs the night prior to the visit. A blood sample was collected by finger prick for malaria rapid diagnostic test (RDT) (ICT Diagnostics, Cape Town, South Africa). Participants who were RDT positive were offered treatment with artemether-lumefantrine (Coartem®). In a subset of households visited during 2012 and 2013, overnight mosquito collections were conducted using Centers for Disease Control and Prevention (CDC) light traps and both anopheline and culicine mosquitoes were enumerated.

Statistical analysis

Reported ITN use was compared between first visits (cross-sectional households and first visit to longitudinal households) and follow-up visits (longitudinal households only). ITN ownership and use over time were analyzed by month and season. Among longitudinal participants who reported owning an ITN, demographic and household level variables were compared between those who reported sleeping under an ITN and those who reported not sleeping under an ITN using the chi square test for proportions and the t-test for differences in means. A multi-level longitudinal model was constructed to assess factors associated with ITN use adjusting for individual and household clusters via random intercepts. Variables associated with ITN use in univariate models were included in the multi-level longitudinal model using a p-value cut off of 0.1. Study time was modeled as a quadratic function of time and the main effect of season was included using an indicator variable (rainy season vs. dry season). Model fit was assessed using the ROC Area C-Statistic. An LLIN distribution occurred in Southern Province in June 2012, therefore a binary variable was constructed to examine ITN ownership and use before and after June 2012. Qualitative questions regarding ITN ownership and use were tabulated. A multi-level logistic regression model was used to investigate the association between total (nuisance) mosquito density and ITN use among a subset of households.

Results

Temporal trends and descriptive factors associated with ITN use

A total of 585 cross-sectional and 70 longitudinal households were enrolled between February 2008 and December 2013. The parasite prevalence as measured by RDT was 8.4% in 2008 but subsequently declined to 2.1% in 2013 (Table 5.1). The proportion of participants in the cross-sectional and first longitudinal surveys who reported owning an ITN was 77% in 2008, 64% in 2009, 54% in 2010, 52% in 2011, 52% in 2012 and 83% in 2013 (Figure 15.). Of the participants who reported owning an ITN, the proportion who reported using an ITN the night before was 56% in 2008, 58% in 2009, 49% in 2010, 56% in 2011, 51% in 2012, and 73% in 2013 (Figure 5.1).

The longitudinal surveys included 399 individuals residing in 66 households that reported owning an ITN, and followed for an average of 6 visits (minimum of two and maximum of 36 visits) for a total of 3,689 observations. ITN ownership was consistently higher during follow-up visits of the longitudinal households (58% use at cross-sectional and first visits as compared with 77% during follow up) (unadjusted p-value=0.01). The proportion of ITN use reported each year was higher at follow-up visits compared with initial visits for each year of the study, except for 2013 (Figure 5.1). ITN ownership and use followed a seasonal trend, with a slight but statistically significant higher use during the rainy season from November to April (72%) compared to the dry season (65.7%; $p<0.0001$) (Figure 5.2). Both ITN ownership and use were significantly higher after ITN distribution in June 2012 for first visits (58% ownership and 52% use pre-distribution compared with 75% ownership and 70% use post distribution)

and longitudinal follow-up visits (80% ownership and 78% use pre-distribution compared with 86% ownership and 71% use post distribution) (Table 5.2).

Individual and household level characteristics were compared in univariate analyses between those who reported using an ITN and those who did not among participants in the longitudinal surveys. Among households that own an ITN, 40% of ITN users were over 18 years of age, 37% were between 5 and 17 years of age, and 23% were under the age of 4 years. In univariate analyses, ITN users were more likely to be over the age of 18 years as compared with younger than 5 years (40% vs. 23%). ITN users were more likely to report using their ITN during the rainy season (86% vs. 73%), report more than three ITNs owned by the household (36% vs. 0%) and live closer to a health facility (median distance of 7.1 meters vs. 13.8 meters) (Table 5.3).

Factors associated with ITN use

In a multi-level longitudinal model that adjusted for individual and household level clustering, several individual and household level factors were associated with ITN use among residents of longitudinal households that own at least one ITN. Compared to adults older than 18 years, children younger than five years of age were 35% less likely to sleep under an ITN ($p<0.0001$) and children and adolescents 5 to 17 years of age were 55% less likely to sleep under an ITN ($p<0.01$) (Table 5.4). Participants who reported learning about malaria from a CHW were 50% more likely to use their ITN compared to those who learned from a different source such as radio or at school (<0.01) (Table 5.4). Residents of households with more than three ITNs were twice as likely to

use an ITN than residents of households with fewer than 3 ITNs ($p<0.01$). Individuals had 80% higher odds of using an ITN during the rainy season than the dry season ($p<0.0001$). Although ITN use was significantly higher after the 2012 ITN distribution, this association was not significant after controlling for distance to the nearest facility. Since the household level random intercept variance estimate was larger than the individual level random intercept variance estimate, greater differences between households were observed than the variation between individuals within a household. ITN use increased slightly over time (about 9% per 6 months) despite the low parasite prevalence (Table 5.4). The model was considered a strong fit for the data (ROC Area C-statistic of 0.82).

Mosquitoes and ITN use

The association between ITN use and the total number of mosquitoes (anophelines and culicines) captured in the household was measured in all cross-sectional and longitudinal households visited during 2012 and 2013. A total of 9,265 mosquitoes were captured; 2,728 anophelines and 6,537 culicines (Table 5.5). Controlling for season and whether the visit was a follow-up or baseline visit, the odds of using an ITN increased with increasing number of total mosquitoes caught. As compared to households with no mosquitoes, the odds of ITN use increased 19% where 1 to 4 mosquitoes were captured (OR=1.2; [0.8, 1.9]), and more than doubled in households with five or more mosquitoes (OR=2.1 [1.1, 3.9]) (Table 5.6).

Qualitative survey and ITN use

Qualitative questions were tabulated for the cross-sectional and first visit to each longitudinal house. Almost half of participants who did not own an ITN reported they were too expensive (42%) despite the history of free ITN distribution in the community (Table 5.7). Of the 1,654 participants who owned an ITN, 250 (16%) did not use an ITN because there were no mosquitoes, 76 (4%) reported ITNs did not protect against mosquitoes, 139 (7%) reported they were unable to hang the net over their sleeping space and 100 (5%) reported their net was too old to use (Table 5.7).

Discussion

Overall, ITN use in the study area was high over the six-year study period, during which the prevalence of malaria fell to 2%. While Malaria Indicator Surveys measure malaria prevalence and ITN ownership and use with cross-sectional surveys, this study was able to identify individual and household level factors influencing ITN use over time and included data on the number of mosquitoes within study households. Maintaining high ITN use is a key driver for keeping malaria prevalence low and reducing risk of resurgence; however, this will not be possible unless high ownership is maintained through frequent ITN distributions (27). Understanding factors that influence ITN use in low transmission settings is crucial but these areas tend to not be a priority since disease burden is low (28).

Several individual and household level variables were associated with sustained ITN use in this region of declining malaria transmission in southern Zambia. Individuals reporting that they learned about malaria from a CHW were more likely to use their ITN. Being enrolled in our longitudinal cohort appears to have also contributed to increased ITN use, likely because frequent visits from the field team increased awareness and education about malaria, and served as a reminder to use personal protective measures. Households that reported owning three or more nets also reported they were more likely to sleep under an ITN. Additionally, a substantial increase in both ITN ownership and use was recorded after a mass ITN distribution campaign in the province that included household visits and assistance hanging the nets. Distance to the nearest health facility was also strongly associated with ITN use, suggesting that distributions may reach nearby households but not achieve universal coverage (15, 29, 30). Many distribution campaigns originate at healthcare facilities, suggesting households closer to clinics or hospitals may potentially have higher ITN ownership and use (15). While ITN use increased despite declining malaria transmission, our findings suggest that without continued ITN distributions and educational campaigns, ITN use may decrease over time.

Children and adolescents 5-17 years old were the least likely to sleep under an ITN. Similarly, in Kenya, children aged 5 to 14 years reported significantly lower ITN usage (31). School-based ITN distributions and educational campaigns may help target this high-risk age bracket; traditionally targets of interventions are children under 5 years and pregnant women, often

excluding older children. A second factor associated with lower ITN use was season. In response to qualitative questions, participants reported that deterrents to ITN use were that it was too hot or there were few mosquitoes during the dry season. Recent studies in Kenya and Tanzania also identified strong seasonality to ITN use (31-33).

ITN use also was associated with the number of mosquitoes collected in the household. Previous studies also found the presence of culicine mosquitoes to be associated with ITN use (20, 33, 34). Potentially, promoting the protection ITNs afford against nuisance mosquitoes in public health messages to the community may increase ITN use. A recent study in Zanzibar concluded that future behavior change communications should expand current messages of the potential benefits of net use other than protection against malaria (35).

Quantitative and qualitative studies suggest a range of factors associated with sleeping under an LLIN; however, these studies were mainly conducted in areas where the malaria burden was high (32, 33, 36-40). In low transmission regions in Uganda, Swaziland and Zambia, reasons for not using an LLIN included the low density of mosquitoes and the infrequency of malaria (41-43). In contrast, a recent qualitative study in Zanzibar, where malaria prevalence decreased from 50% to less than 2% in 15 years, found that caretakers strongly believed in the protection afforded by LLINs despite the reduction of malaria risk (7, 20, 44). Although malaria was no longer considered a common disease, caretakers associated high mosquito density with increased risk of malaria (20). Other factors associated with bed net use in Zanzibar were instructions from

healthcare workers or hearing about malaria in the media (20). Attrition in LLIN ownership and use also is associated with the aging and breakdown of nets. Nets will be discarded or used for other activities more commonly in areas where perceived risk is low (10, 22). These findings suggest that if malaria transmission is reduced, personal protective measures such as ITNs may no longer be used.

There were some limitations to these data, mainly, that ITN use was self-reported. Measuring actual use of ITNs is difficult as they must not only be properly hung, have few or no holes, and be treated with insecticide, but they must also be used consistently during hours that mosquitoes are biting. We were unable to account for the physical integrity of the nets; even though ownership and use were high, ITNs may not have adequately provided protection. A recent study in the area identified significant degradation of ITNs (45). Because few cases of malaria were identified in this cohort, ITN effectiveness at reducing parasitemia could not be measured.

As transmission declines, the goal of malaria elimination may be pursued. Threats to the effectiveness of ITNs for malaria elimination include insecticide resistance, damage to the ITNs, and inconsistent funding. Field studies have concluded that the lifespan of an ITN is shorter than expected and many areas report high attrition rates (22, 45-47). Participants reported they stopped using their ITNs as they became old, had holes or were dirty, as supported by other study findings (22). While distribution campaigns are considered both effective and cost-effective (15, 48), these activities must occur often enough to avoid gaps in ITN coverage and use. Additional cost-effectiveness studies are

necessary in low transmission settings(49). A sensitivity analysis found that if transmission decreased from an incidence of 1,209 per 1,000 to 237 per 1,000 was associated with an increase in net cost/savings per malaria case averted from 3.26 USD to 21.29 USD (48). With constrained resources and funding, other methods of targeting ITN distributions may become necessary as transmission declines. Targeting education campaigns and distributions to 5-17 year olds and promoting ITN use during the low transmission season may lead to increased, year round use by the community.

These study findings support others in the literature that concluded free universal distribution, ongoing education and hang up campaigns are successful in increasing ITN use, at least within the 6 months following the distribution (32). As transmission in this area continues to decline, ensuring the continued use of LLINs will be necessary. Future research should more thoroughly examine the effective lifespan of LLINs, and if funding is reduced as transmission declines, then research regarding the effectiveness and costs of focalized LLIN distributions and targeting of high-risk groups should be explored.

Table 5.1

RDT positivity in cross-sectional and longitudinal households at baseline visit, 2008-2013

Visit Year	Total		
	RDT+	Observations	Percent
2008	32	380	8.4%
2009	11	703	2%
2010	2	899	0.2%
2011	3	775	0.4%
2012	1	396	0.13%
2013	6	288	2.1%

Table 5.2

Number and percentage of participants reporting ITN ownership and use before and after ITN distribution in June 2012

	Pre Distribution N (%)	**Post Distribution N (%)**
Baseline visits, only*		
Own ITN	1794 (58%)	853 (75%)
Use ITN	974 (52%)	680 (70%)
Follow-up visits to longitudinal households, only		
Own ITN	3157 (80%)	593 (86%)
Use ITN	2442 (77.6%)	373 (71%)

*Baseline visits include cross-sectional visits and first visit to longitudinal households only; no follow up visits

Table 5.3

Individual and household level factors of reported ITN use among longitudinal households that own an ITN at baseline visit, 2008-2013

Individual level variables				
		Don't use ITN	Use ITN	Unadjusted P Value
Number of individuals		113	275	
Age Category				
0 to 4 years		24 (21%)	64 (23%)	0.25
5 to 17 years		52 (46%)	102 (37%)	
≥18 years		37 (33%)	109 (40%)	
Male		51 (45%)	137 (50%)	0.4
RDT positive		4 (2%)	5 (1%)	0.66
Peak season		82 (73%)	237 (86%)	0.001
Learned about malaria from CHW		47 (42%)	111 (40%)	0.82
Household level variables				
		No ITN users in household	Any ITN users in household	
Number of households		18	48	
Number of children under 5 in the household				0.02
0		2 (11%)	20 (42%)	
1 or more		16 (89%)	28 (58%)	
Household Education				0.03
Primary		4 (22%)	26 (54%)	
Secondary or higher		14 (78%)	22 (45%)	
Own more than 3 ITNs		0 (0%)	17 (36%)	0.003
Distance to clinic per 500 meters (median (min, max))		13.8 (3.3, 25.8)	7.1 (0.17, 26.1)	0.01

Table 5.4

Multi-level model of individual and household level factors associated with reported ITN use over time, 2008-2013

Factors	Odds Ratio* (95% Confidence Interval)
Fixed Effects:	
Household Level	
Distance to nearest facility (per 500 m)	0.93 (0.88, 0.98)
Own more than 3 ITNs	2.1 (1.4, 3.1)
Post 2012 ITN distribution	1.7 (0.94, 3.2)
Rainy season	1.8 (1.5, 2.2)
Number of children under 5 in the household	1.0 (0.89, 1.2)
Individual Level	
Gender	0.98 (0.78, 1.2)
Age Category	
Over 18 years	REF
0 to 4 years	0.66 (0.48, 0.90)
5 to 17 years	0.45 (0.35, 0.58)
Learned about malaria from a CHW	1.5 (1.2, 2.0)
Random Effects:	Variance (SE[+])
Household random effect	1.2 (0.17)
Individual random effect	0.35 (0.11)

[+] SE: standard error

* The model results are adjusted for a quadratic function of time to account for variation in the odds of ITN use during follow-up at the individual level. The estimated time effects are: time (per 6 months): 1.1 (1.1, 1.2), time^2 (per 6 months^2): 0.99 (0.99, 0.99).

Table 5.5

Number and distribution of mosquitoes caught in cross-sectional and longitudinal households, subset between 2012 and 2013

	Total Caught	Minimum (per house)	Median (per house)	Mean (per house)	Maximum (per house)
Anophelines	2,728	0	0	2	180
Culicines	6,537	0	1	4	463
Total	9,265	0	1	5	463

Table 5.6

GEE model of the association between total number of mosquitoes and ITN use in a subset of surveyed households between 2012 and 2013

Fixed Effects:	**OR**	**95% CI**	**P Value**
0 mosquitoes	REF		
1 to 4 mosquitoes	1.19	(0.75, 1.89)	0.46
5+ mosquitoes	2.11	(1.14, 3.93)	0.02
Rainy season	0.83	(0.56, 1.24)	0.36
Follow up visit vs baseline visit	2.76	(1.57, 4.85)	0.001
Random Effects:	Estimate (SE)		
Household Random Effect	3.73 (0.39)		

Table 5.7

Qualitative responses for reasons not owning or using an ITN at baseline visit (includes among cross-sectional households) in Macha, 2008-2013

What is the reason you do not OWN a bednet in your house?	
N	2,647
It is too expensive	1073 (42.1%)
No mosquitoes around	58 (2.3%)
Bednets not available	52 (2%)
Change my sleeping space too often	30 (1.2%)
Not enough nets for everyone in the house in the house	28 (1.1%)
Don't know where to buy one	27 (1.1%)
It does not protect against mosquitoes/insects	23 (0.9%)
It is too hot under the net	10 (0.39%)
What is the reason you do not USE a bednet?	
N	1,654
No mosquitoes around	250 (16.2%)
Cannot hang it over my sleeping space	139 (6.5%)
The net I have is too old	100 (4.6%)
Doesn't protect against mosquitoes/insects	76 (3.5%)
Chang my sleeping space too often	53 (2.5%)
There is not enough space under the net/I feel closed in	26 (1.2%)
It is not the rainy/malaria season	24 (1.1%)
The net is itchy	17 (0.8%)
It's too hot under the net	13 (1%)

Figure 5.1

Reported ITN use at cross-sectional and the first visit to longitudinal households, compared to reported use during follow-up visits to longitudinal households: 2008 to 2013.

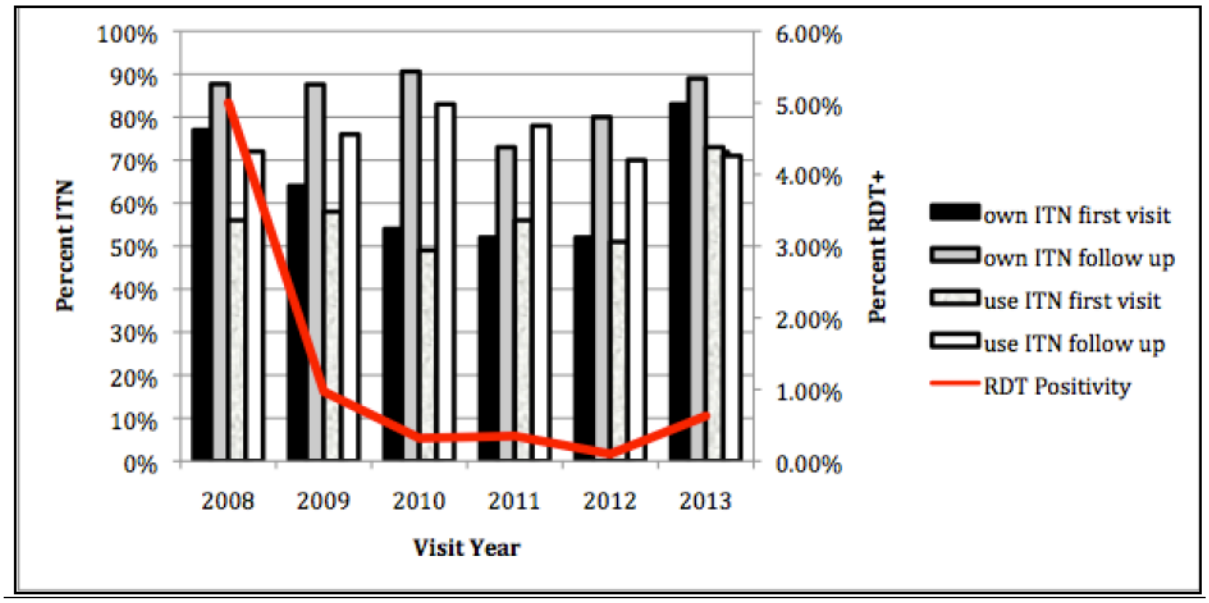


Figure 5.2

Reported bednet ownership and use among longitudinal households per month from 2008-2013 (grey areas indicate rainy season)

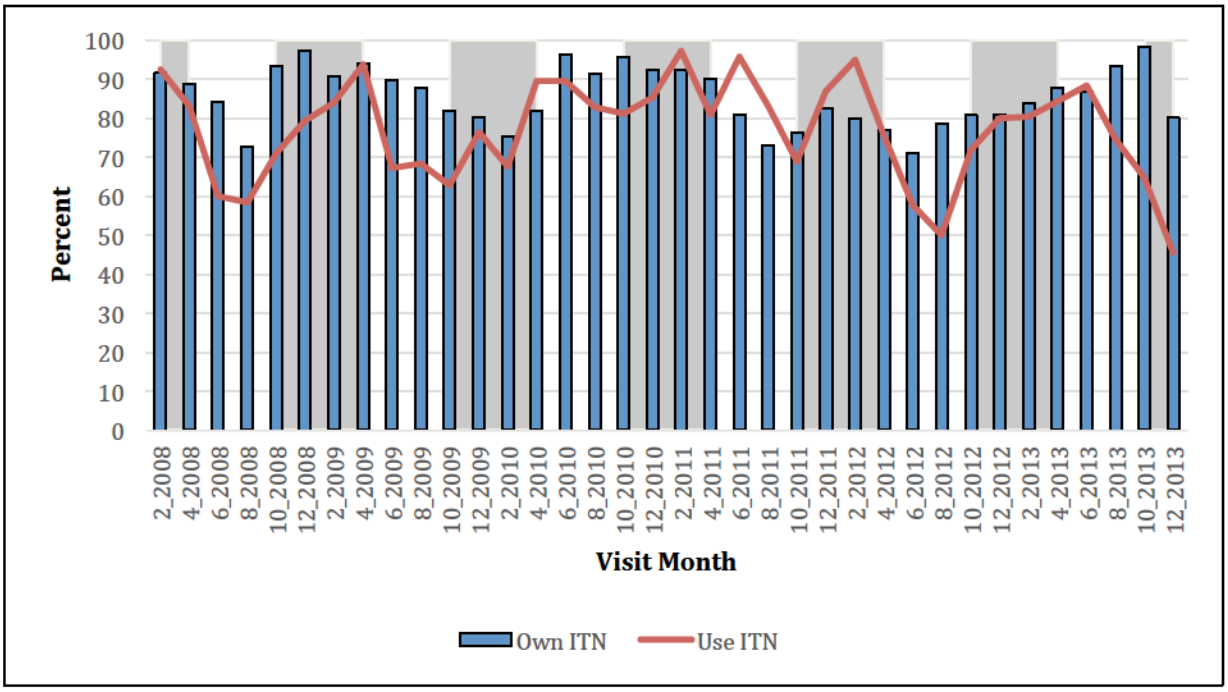
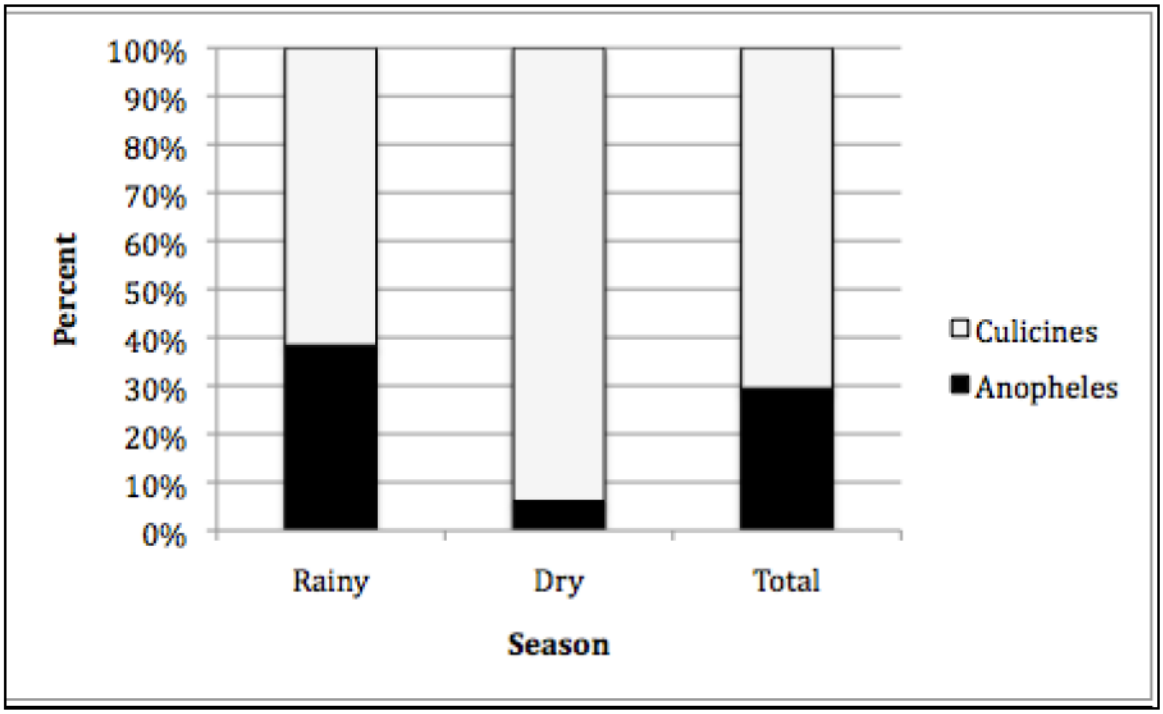


Figure 5.3

Seasonality and mosquito species caught in households in Macha, 2012-2013



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Chapter 6: Efficiency of reactive case detection with focal drug administration for malaria elimination: simulations based on cross-sectional surveys in rural southern Zambia

Authors: Jessie Pinchoff, Kelly Searle, Tim Shields, Harry Hamapumbu, Tamaki Kobayashi, Natasha M. Laban, Sungano Mharakurwa, Philip E. Thuma, Frank Curriero, William J. Moss for the Southern Africa International Centers of Excellence for Malaria Research

Abstract

Background: As malaria transmission declines and elimination is pursued, identifying and treating the remaining few infected individuals will be critical. Passive or reactive case detection with rapid diagnostic tests (RDTs) may not identify individuals with sub-patent or asymptomatic infection who serve as persistent reservoirs. Reactive case detection with focal mass drug administration may be a strategy to eliminate parasite reservoirs in low transmission settings.

Methods: Household malaria surveys were conducted within Southern Province, Zambia between 2009 and 2012. During study visits, questionnaires were administered to adults and caretakers of children and a blood sample was collected to detect *Plasmodium falciparum* by RDT and polymerase chain reaction (PCR). All household structures within the study area were enumerated using satellite imagery. Simulations were performed to extrapolate data from surveyed to simulated households. Residents classified as RDT-positive, that reported seeking care at health facilities, experienced symptoms of malaria, or reported taking antimalarials were considered index cases detected through passive surveillance. Radii of increasing size around each index household were examined to determine the proportion of households with an infected individual

detected through reactive case detection and targeted through test-and-treat or focal drug administration.

Results: The parasite prevalence in surveyed households at baseline visits declined from 2% in 2009 to 0.1% in 2012. Based on simulated data, a cross-K function identified spatial clustering of missed RDT-positive and PCR-positive, RDT-negative residents in households around index houses. RACD testing and treating residents of neighboring households within 500 meters using RDT would have identified only 56% of all households with an RDT-positive resident. Furthermore, only 54% of the PCR-positive, RDT-negative individuals would be identified within 500 meters of the index case household and these individuals would be missed using RDT. Although logistically difficult, screening within 1,000 meters of the index case household using RDT would have identified 84% of all households with an RDT-positive resident but still would fail to identify 81% of all households with a PCR-positive, RDT-negative resident.

Discussion: Reactive case detection will identify asymptomatic individuals that do not seek care, but will not be sufficient to eliminate malaria. Sub-patent infections undetectable by RDT will be missed, and PCR is too expensive for routine diagnostic use. Focal mass drug administration may be necessary to treat these remaining infections.

Background

A renewed call for global malaria eradication has been supported by the Bill and Melinda Gates Foundation, World Health Organization (WHO), and, more recently, the Roll Back Malaria (RBM) Partnership (1). Targets were set to reduce the burden of malaria by 75% by 2015 and eliminate malaria in 8-10 countries by 2015 (2). Scale-up of prevention and control measures, such as distribution of long-lasting insecticide treated nets (LLINs), indoor residual spraying (IRS), prompt treatment of confirmed cases with rapid diagnostic tests (RDT) and artemisinin combination therapies (ACT), and intermittent preventive therapy (IPT) among pregnant women and infants, have proven effective (3). Declines in malaria cases and malaria-related deaths by up to 50% have been measured in 11 countries, including Zambia (4, 5).

Case detection and treatment are critical for malaria control but as elimination is pursued a broader definition of malaria infection will need to include asymptomatic and sub-patent infections. These remaining infections are part of the human parasite reservoir but pose diagnostic challenges (6). Passive case detection involves identification of symptomatic persons seeking care at health facilities and testing via RDT or microscopy (7). Passive case detection requires the least resources but fails to identify sub-patent infections, asymptomatic infections or infections in persons who do not seek medical care at health facilities. The proportion of all infected individuals who are asymptomatic or have sub-patent infection is often substantially higher than symptomatic infections, suggesting a majority of infected individuals will be missed with passive case

detection alone (7-10). Thus, several active case detection strategies have been developed to target these remaining infections.

Reactive case detection (RACD) is an active surveillance strategy based on the observation that malaria cases are spatially and temporally clustered as transmission declines and the assumption that passively detected index cases represent foci of infection (7, 11). With RACD, all persons within a defined radius of the index case are screened using RDTs and treated with ACTs. In a study of RACD in southern Zambia, the prevalence of malaria was 8% within index households compared to 0.7% in a random sample of control households (12). However, RACD relies on RDTs to guide treatment, and in low transmission settings, they may not reliably detect all infections. A recent study in southern Zambia found that the sensitivity of the *P. falciparum* histidine-rich protein 2 (*Pf*hrp2)-based RDT compared to nested PCR was only 17%, missing sub-patent infections (10). More sensitive diagnostics that can be used in the field are necessary, as currently available PCR technologies are not feasible for field use. If RACD is not able to identify all remaining infections, another strategy such as focal mass drug administration (MDA) may be considered. Focal MDA does not rely on a diagnostic but treats all individuals within a targeted area.

Little data exist on the appropriate radius from an index household that should be screened with RACD or targeted with a focal MDA. Using a series of cross-sectional household surveys and model simulations in a low transmission setting in southern Zambia, the efficiency of these two different strategies was quantified. Specifically, the radius around an index house necessary to achieve

different levels of treatment coverage was estimated. RACD with test-and-treat, in which only RDT positive individuals receive treatment, was compared to focal MDA, in which all individuals within a defined radius are presumptively treated.

Methods

Study Site and Procedures

The study was conducted in a low transmission setting within the catchment area of Macha Hospital in Choma District, Southern Province, Zambia between January 2009 and December 2012. Macha Hospital is approximately 70-kilometers from the town of Choma, and lies on a plateau 1,100-meters above sea level (7). The single rainy season lasts from December through April when malaria transmission peaks, followed by a cool dry season from April until August, and a hot dry season through November. The primary malaria vector is *Anopheles arabiensis* (13). The prevalence of malaria in this region has declined substantially over the past decade (14). The study was approved by the University of Zambia Research Ethics Committee and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

The development of the sampling frame and enumeration of households have been reported elsewhere (15). Briefly, all household structures were enumerated based on satellite images and used to construct a sampling frame. Households were selected by simple random sampling for enrollment into prospective longitudinal (visited every other month) or cross-sectional (visited once) surveys of malaria parasitemia. This analysis was restricted to households enrolled in the cross-sectional surveys and the first visit to longitudinal

households because of the reduction in malaria risk following repeated study visits (16). Households surveyed between January 2009 and December 2012 were included in this analysis.

All individuals residing in selected households were eligible to participate. Informed consent was obtained from adult participants and from caregivers of children. A questionnaire was administered to collect demographic information, current signs and symptoms of malaria, history of recent malaria and antimalarial treatment, reported health seeking behavior, knowledge of malaria transmission and prevention, and use of personal protective measures. A blood sample was collected by finger prick for malaria RDT, preparation of thin and thick blood smear slides for microscopy, and preparation of a dried blood spot (DBS). The RDT (ICT Diagnostics, Cape Town, South Africa) detected *Pf*hrp2 and was shown to detect 82% of test samples with wild-type *P. falciparum* at a concentration of 200 parasites/μL (17). Participants who were RDT positive were offered treatment with artemether-lumefantrine (Coartem®). The DBS were collected on filter paper (Whatman, Protein Saver card 903, Piscateway, New Jersey), dried overnight and stored individually with desiccant in a sealed plastic bag at -20°C.

PCR Methods

A Chelex© extraction method was used to recover parasite DNA from the DBS (18) [15]. Positive and negative control samples spotted as dried blood on filter paper were included in each extraction experiment. Positive controls consisted of parasitized blood from laboratory cultures at 1,000 parasites/μL.

Negative controls consisted of blood from individuals with no travel history to malaria endemic areas. Extracted DNA was stored at -20ºC until PCR was conducted.

A *Plasmodium* nested PCR assay was used to detect asexual stage parasite DNA using two sets of primers targeting a segment of the mitochondrial cytochrome b gene (cytb) conserved in all four human *Plasmodium* parasites (19). No-template controls were included in each experiment and reactions were run in a Techne™ TC-412 thermo cycler. Amplified product was detected by electrophoresis on 1% agarose gel and viewed under UV light as an 815 base pair DNA band.

Spatial Risk Map

A spatial risk map was developed previously using survey data collected in 2007 and 2008 (15). Logistic regression was used to identify environmental features associated with the odds of a household having an RDT positive resident. Each enumerated household was assigned a malaria risk according to its location on the spatial risk map ranging from 0.07 to 0.797 referred to as the ecological risk and included in the simulation model.

Population Level Simulation

Simulations were performed using multiple imputation based on predictive models to extrapolate from surveyed to simulated households. The steps used in the simulation were described previously (7). Briefly, a household level dataset with covariates of interest was compiled for the development of predictive models. Dichotomous covariates of interest were predicted using logistic

regression and continuous covariates of interest were predicted using linear regression. Each of the following variables was predicted at the household level, extrapolating from surveyed to simulated households: RDT status (at least one RDT positive resident), PCR status (at least one PCR positive resident), antimalarial treatment status, at least one symptomatic household resident, at least one care seeking resident, at least one symptomatic and care seeking RDT positive resident, and residents treated for malaria who sought care. For the predictive models, geographic coordinates, ecological risk based on the spatial risk model, mean age of the household residents and number of household residents were used as initial predictive covariates.

Logistic regression models were evaluated using the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver-operating curve (AUC). Linear regression models were evaluated using the R^2. The p-values for the Hosmer-Lemeshow goodness-of-fit test and the AUC measurements for dichotomous variables were greater than 0.05. The R^2 values for continuous models were greater than 0.05. The models were validated using a random selection of 100 households to ensure model fit.

The simulation was performed using multiple imputation chained equations (MICE) method in STATA version 12.1 (StataCorps, College Station, TX), also referred to as fully conditional specification or sequential regression multivariate imputation (20, 21). Surveyed household values were observed while simulated households had full data only for geographic coordinates and ecological risk of malaria. The MICE model imputes values for non-surveyed

households and enables incorporation of multiple predictive covariates to simulate the population, allowing use of outcome values imputed for a household to be used in the prediction of outcomes imputed in each subsequent chain. The simulated data were assessed to ensure these data did not differ significantly from observed data.

Classification of Households

Households were classified as having a member passively detected (index cases) if they had an RDT positive resident who reported having symptoms and displayed care seeking behavior. Care-seeking behavior was determined if the individual reported visiting a health post or clinic for their most recent febrile illness or reported receiving antimalarial medication from a health facility at the time of the survey. Malaria specific symptoms consisted of having a fever with either headache or chills in the prior two weeks.

Households were classified as having infected residents not detected by passive surveillance if they had one or more RDT-positive residents who would not have sought care or had one or more RDT-negative PCR-positive residents. Individuals were classified as detected through RACD if they were RDT-positive but asymptomatic or minimally symptomatic, did not display care seeking behavior, or both. Individuals were classified as treated through MDA alone if they had a sub-patent infection that was RDT-negative but PCR-positive.

Spatial Analysis of Population Level Simulated Data

Positive households were mapped using ArcGIS version 10.2 (ESRI, Redlands, California). Households identified by passive case detection, RACD,

and focal MDA were added as data layers geo-referenced to Universal Transverse Mercator (UTM) Southern Hemisphere, Zone 35, WGS1984 coordinate system. Distance-based buffers were created surrounding index households (identified via passive case detection) representing varying distances surrounding identified households that would be screened for malaria. Buffers from 140 to 3,000 meters were evaluated to determine the buffer size needed to identify maximum proportions of households with individuals who would be missed by RACD: RDT positive, asymptomatic and non care seeking individuals missed by RACD, and RDT negative PCR positive individuals only treated by focal MDA. A radius of 140-meters is currently being used by programs in parts of Southern Province (Personal communication, Anna Winters). The buffers were dissolved to ensure that a household could only be counted once in the event that a missed household was located within the buffer of more than one index household. Each buffer layer was spatially joined to the households missed by RACD and only treated by focal MDA. The sum of all missed households within each buffer layer, the proportion of households identified by RACD, and the proportion of households missed unless targeted for MDA were calculated. The sum of all negative households also was calculated for each buffer.

Results

A total of 6,210 households were enumerated based on high-resolution satellite imagery of the Macha Hospital catchment area. Of those, 531 households were surveyed between 2009 and 2012 and the remaining 5,679

households were simulated (Figure 1). Of the surveyed households, the mean household size was 5.7 individuals (standard deviation=3.6). The proportion of surveyed households with an individual who reported seeking care for a recent febrile illness was 0.80 and the proportion of surveyed households with an individual taking antimalarials was 0.09. The proportion of surveyed households with an individual experiencing malaria-like symptoms and seeking care was 0.06. The proportion of surveyed households identified as having an RDT-positive individual was 0.03, and the proportion having a PCR-positive but RDT-negative individual was 0.11 (Table 1), reflecting the greater sensitivity of PCR compared with RDT.

Characteristics of simulated households from the model resembled surveyed households. There were no statistically significant differences between surveyed and simulated households; however, the proportion of households with an individual seeking care for malaria was slightly lower in the simulated households as compared with the surveyed households (0.80 vs. 0.77, p=0.1) (Table 1). The spatial intensity and spatial clustering of surveyed and simulated households were not statistically different as assessed by K function and spatial intensity ratios, i.e. the model maintained the spatial pattern of sampled households (not shown).

Three cross-K functions identified significant spatial clustering of missed households with RDT-positive residents, missed households with PCR-positive RDT-negative residents, and all missed households around index case households (Appendix 1, Appendix 2, Figure 2). A difference in K function

showed that missed households with RDT-positive residents were significantly more clustered than households with PCR-positive RDT-negative residents (Appendix 3), implying greater effectiveness of a test-and-treat strategy using RDTs for RACD, in regions where transmission is high enough that most infections are detectable by RDT. The spatial intensity of missed households with RDT-positive residents and PCR-positive RDT-negative residents, and the difference between these spatial intensities, identified areas where there were significantly different intensities of these missed households (Appendix 3, Appendix 4). The region where the intensity of households with RDT-positive residents was stronger corresponded to higher risk areas determined by a previously constructed risk map; the mean risk value for missed households with RDT-positive residents was 0.50 as compared with the mean risk value for households without an RDT-positive resident was 0.32 ($p<0.0001$) (Figure 4). This finding suggests risk maps can be used to identify areas where RACD using a test-and-treat strategy may be more effective.

The proportion of all missed households with an RDT positive resident or PCR positive RDT negative resident increased from 15% and 11% at a 140 meter radius to 100% and 99% at a 2000 meter radius (Figure 5). Within a 140-meter radius, a total of 647 (11%) of non-index households were identified: 5 (11%) of all missed households with an RDT-positive resident and 108 (15%) of all missed households with PCR-positive RDT-negative residents (Table 2, Figure 3). Within a 300-meter radius, a total of 1,797 (31%) of non-index households were identified: 18 (40%) of missed households with an RDT-positive

resident, and 236 (34%) of missed households with an RDT-negative PCR-positive resident. Within a 500-meter radius, a total of 2,976 (52%) of non-index households were identified: 25 (56%) of all missed households with an RDT-positive resident and 381 (54%) of all missed households with PCR-positive RDT-negative residents (Table 2, Figure 3). Within a 1,000-meter radius, a total of 4,640 (81%) of non-index households were identified: 38 (84%) of all missed households with an RDT-positive resident and 560 (80%) of all missed households with PCR-positive RDT-negative residents (Table 2, Figure 3).

Discussion

In areas where malaria transmission has been controlled, additional strategies will be necessary to treat remaining infections that are not identified by passive case detection. This study identified significant spatial clustering of missed individuals in households around index households identified through passive case detection. This spatial clustering suggests that surveillance methods such as RACD, in which passively detected index cases trigger the testing and treatment of residents in neighboring households, may identify a proportion of remaining infections. However, sub-patent infections, which also cluster around index households, would be missed if a positive RDT test were a prerequisite for treatment. To target these infections, focal MDA may be a more effective strategy to eliminate the parasite reservoir.

This study identified two challenges for active case detection in a low transmission setting pursuing malaria elimination: asymptomatic infections and

sub-patent infections. The proportion of asymptomatic cases is high in many formerly malaria endemic regions. The number of asymptomatic infections is often higher than symptomatic infections, and can be as high as 96%, suggesting a majority of these cases will be missed with passive case detection alone (7-9). There are indications that asymptomatic individuals have higher gametocyte carriage (6). Many remaining infections are missed by passive surveillance since they are less likely to seek care. RACD is a form of active case detection that would identify and treat these asymptomatic cases as long as they are RDT positive and clustered around index case households. Asymptomatic cases were located in the higher risk areas as determined by a malaria risk map, suggesting ongoing transmission in this region. However, some proportion of these missed infections will be sub-patent with low levels of parasitemia.

Sub-patent or low parasitemia infections create diagnostic problems in low transmission settings. Sub-patent malaria infections are below a density than the threshold necessary for detection by microscopy or RDT (22). Of concern is that sub-patent, asymptomatic infections can still transmit malaria and make up a large proportion of infections in low transmission settings (6, 22). Sub-patent infections in low transmission settings are estimated to result in 20-50% of all transmission episodes (23). Further research is necessary, but some findings suggest sub-patent infections are still transmissible and may be an obstacle to malaria elimination (6, 24). RDTs lose their specificity in pre-elimination settings because they do not reliably detect low-density parasitemia (≤200 parasites/μL).

PCR is considered the gold standard and is capable of detecting low-level parasitemia (6, 24). However, it is too expensive for field use.

If a better diagnostic tool is not available, another option is to presumptively treat using forms of focal MDA. MDA is a method for the control and elimination of many parasitic infectious diseases, including schistosomiasis and lymphatic filariasis, in which treatment is given presumptively without prior screening (22, 25). Although a recent Cochrane Review found MDA to be effective at reducing transmission for up to 6 months (26), this method is not widely used for malaria. Some issues including the optimal drug combination to use, the number of rounds of MDA per year, and duration of MDA are yet to be determined (22). Securing adequate resources and funding to implement MDA, determining target high-risk areas and/or populations, population acceptability, and to monitor carefully for adverse events and drug resistance will also be critical (22).

There were some limitations to this study. First, the models were based on several assumptions, mainly that the data represent one transmission season and complete coverage is achieved of all individuals in all households within the screening radii of identified households shortly after an index case is identified (7). By assuming that the data represent one transmission season, seasonality or temporal trends are not captured by this analysis. In support of this assumption, malaria clusters are found to be quite stable over time, specifically clusters of asymptomatic parasitemia (25). However, the efficiency of RACD would likely vary by season and over time, and the implementation of RACD itself

would impact transmission; future studies should assess the impact of seasonal malaria transmission on optimal RACD strategies. The assumption of full coverage of all households and all household residents located within each screening radii represents a best-case scenario of efficiency of RACD and focal MDA (7). In practice, coverage would not be 100% due to logistics and feasibility; specifically, the cost of the resources necessary to test and treat all residents of households surrounding index households may be limiting. Lastly, assumptions were made in extrapolating from surveyed to simulated households; no differences were detected between these two groups suggesting the model fit the data well and the simulation was accurate. However the simulated data may not fully account for heterogeneity between surveyed and simulated households (7). External validation methods should be explored for future simulation models. Another major limitation is that report of travel was not included in the analysis; a recent study in Senegal found during RACD that the primary risk factor for transmission was travel (27).

RACD and focal MDA are two methods that may be considered to target remaining malaria infections missed by passive surveillance methods. The optimal radius for RACD is unclear, although programs in Southern Province are currently employing a 140-meter radius. Based on our findings, this radius would miss a substantial proportion of remaining infections. In Macha, for 80% of missed infections to be identified and treated, the radius would have to be 1,000 meters. However, a recent study conducted in Swaziland found that 1,000 meter radius was not logistically feasible for RACD (28). The cost-effectiveness and

logistical feasibility will decrease as transmission declines and the necessary screening radius becomes large. Since RDT positive missed cases were found to cluster, and were located in high geographic risk areas, further research could determine if there is a transmission level threshold below which RACD becomes less efficient. If sub-patent infections contribute to transmission, then RACD may not be effective, and focal MDA may be considered to treat these remaining infections. However, the 1,000-meter radius may not be feasible for focal MDA. Further research is also necessary to determine the efficacy, safety and feasibility of a focal MDA strategy to treat sub-patent infections.

Identifying and treating malaria-infected individuals who do not seek care, experience symptoms or have low parasitemia are essential to achieving malaria elimination. RACD and focal MDA may be considered as a method to achieve this goal. However, further research is necessary to determine the optimal radius to implement and whether it is efficient or logistically feasible. Variations in the optimal radius by season should also be explored. This will be critical in guiding policy decisions regarding use of RACD or focal MDA for malaria elimination.

Table 6.1

Characteristics of surveyed and simulated households

	Surveyed Households	Simulated Households	P Value
Number of households	531	5,679	
Residents per household (mean,SD)	5.7 (3.6)	5.7 (3.6)	0.48
Mean age (mean, SD)	24.8 (13.8)	24.5 (13.3)	0.3
Households with an RDT positive individual (%)	0.03	0.03	0.68
Households with a PCR positive individual (%)	0.11	0.12	0.38
Households with an individual taking antimalarials (%)	0.09	0.08	0.21
Households with an individual seeking care (%)	0.80	0.77	0.10
Households with an individual with malaria-like symptoms (%)	0.63	0.63	0.87
Households with an individual with malaria-like symptoms and seeking care (%)	0.53	0.53	0.47
Households with an individual taking antimalarials with care seeking behavior (%)	0.06	0.06	0.47

Table 6.2

Number and proportion of total households with non-index, RDT positive residents identified in reactive case detection, and households with RDT negative/PCR positive residents identified in mass drug administration at various screening radii

Screening radius (meters)	Total households with non-index residents tested	Number of households with RDT positive residents missed by passive case detection	Number of households with RDT-/PCR+ residents missed by passive case detection and RACD	Percent of households with non-index residents tested	Percent of households with RDT positive residents missed by passive case detection	Percent of households with RDT-/PCR+ residents missed by passive case detection and RACD
140	647	5	108	11%	11%	15%
300	1797	18	236	31%	40%	34%
500	2976	25	381	52%	56%	54%
1000	4640	38	560	81%	84%	80%
1500	5394	45	647	94%	100%	92%
2000	5655	45	695	99%	100%	99%
2500	5716	45	702	99%	100%	99%
3000	5728	45	704	99%	100%	100%
Total:	5740	45	704	-	-	-

Figure 6.1

Map of surveyed and simulated households in Macha catchment area, 2009-2012

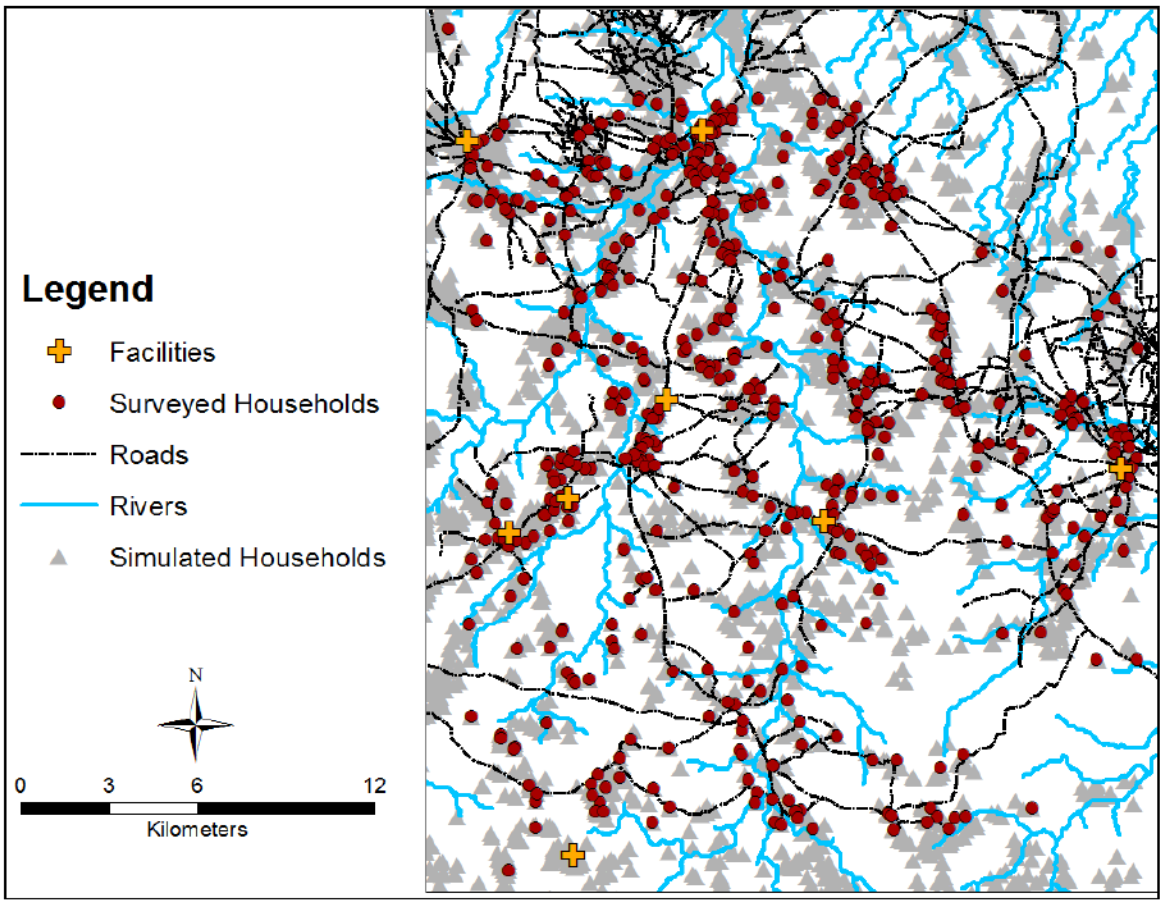


Figure 6.2

Cross K function of all missed households

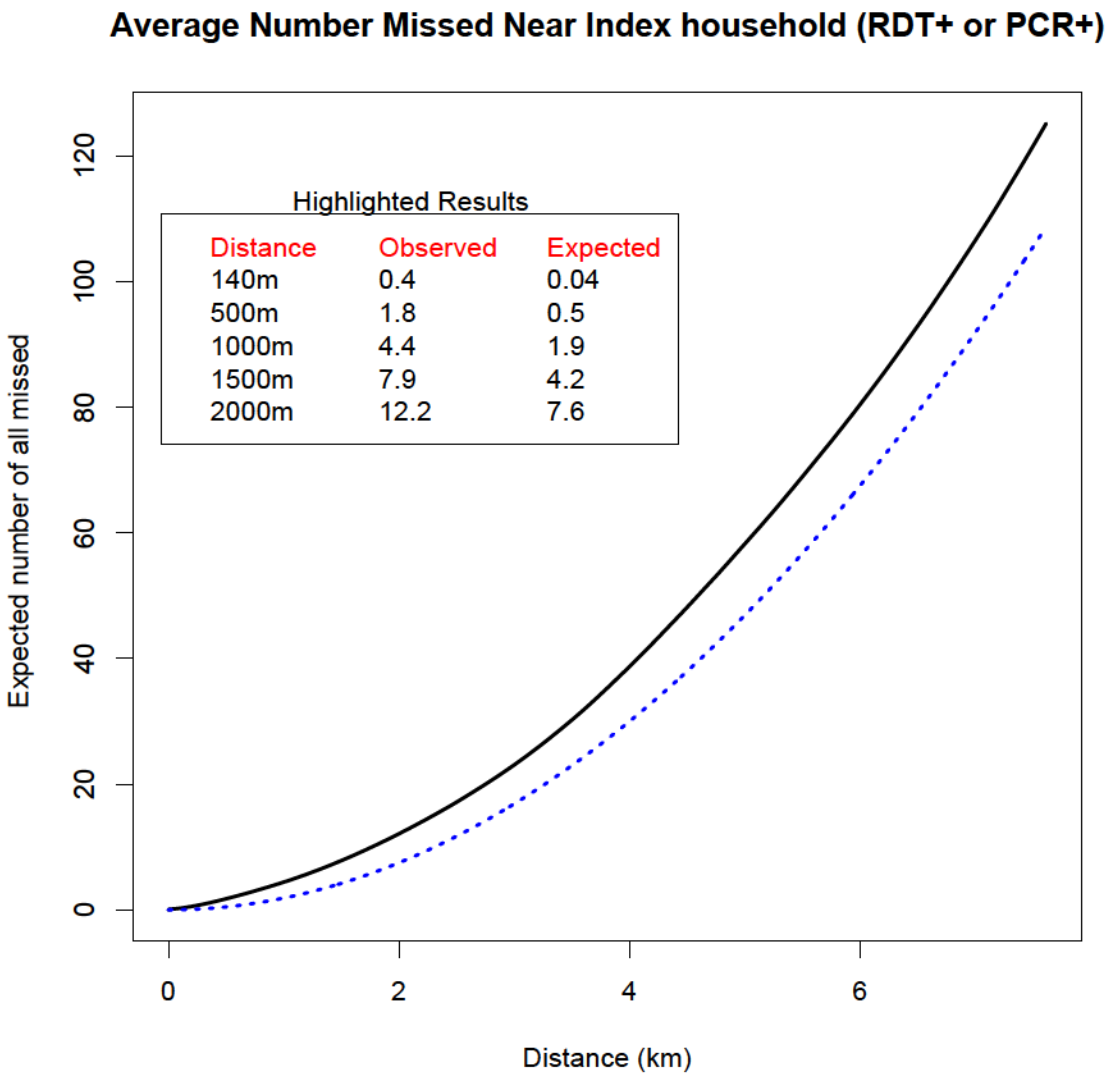


Figure 6.3

Map of screening radii surrounding RDT positive identified and missed households

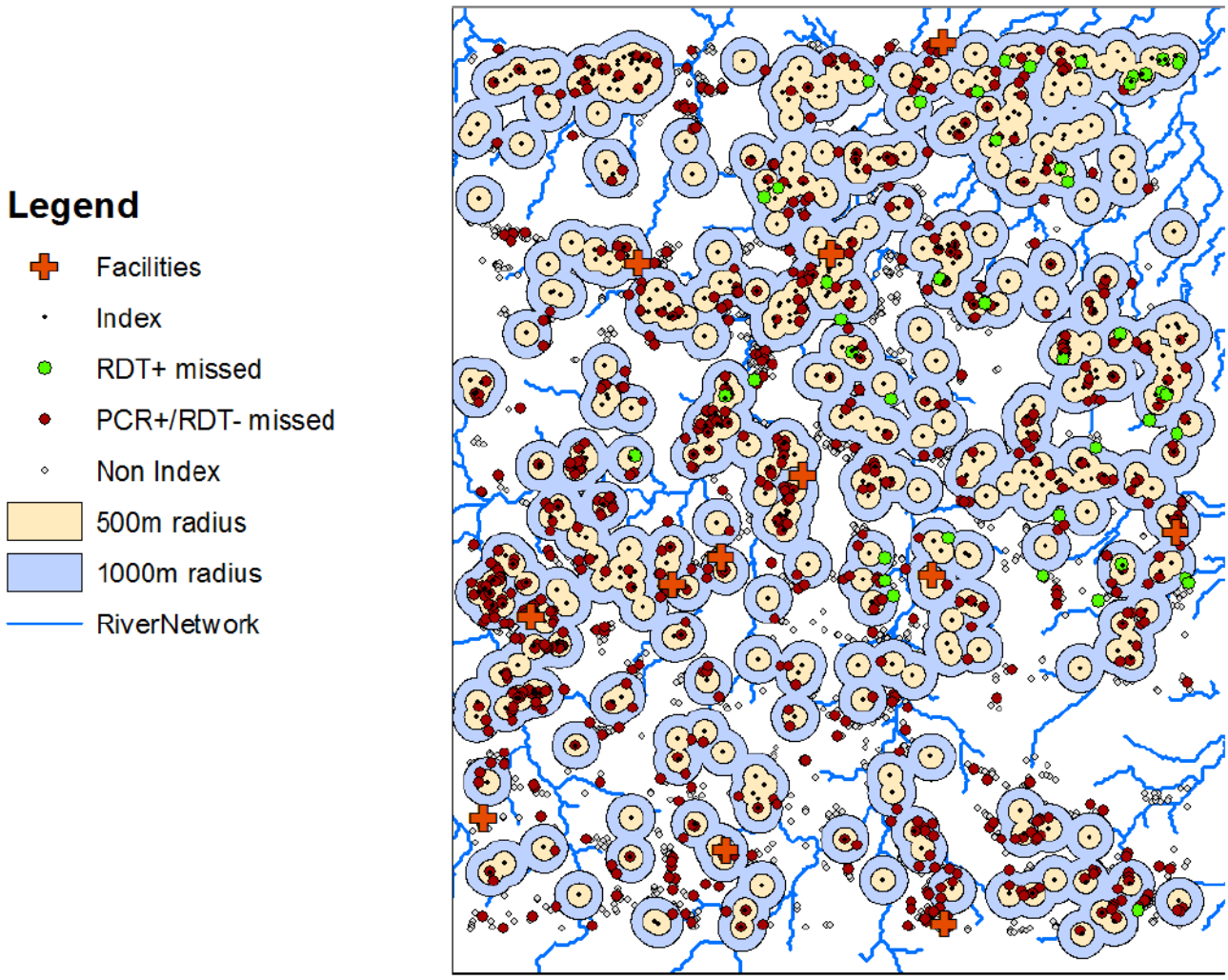


Figure 6.4

Percentage of all missed households (RDT positive asymptomatics that did not seek care, sub-patent PCR positive/RDT negative) at increasing screening radii surrounding index households

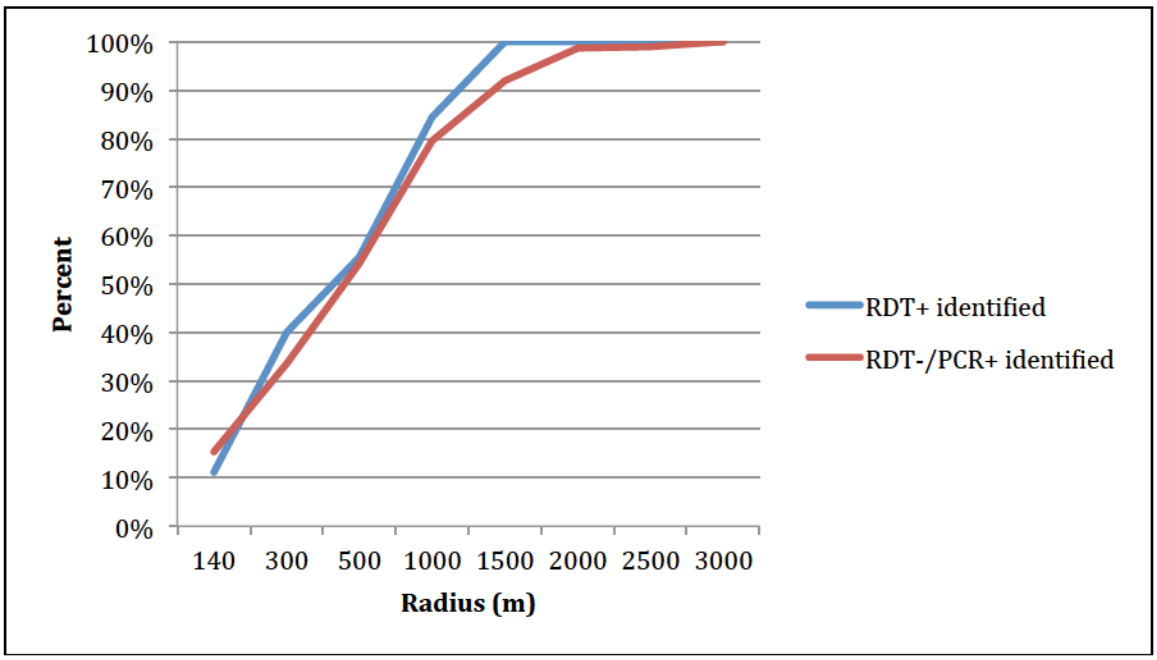
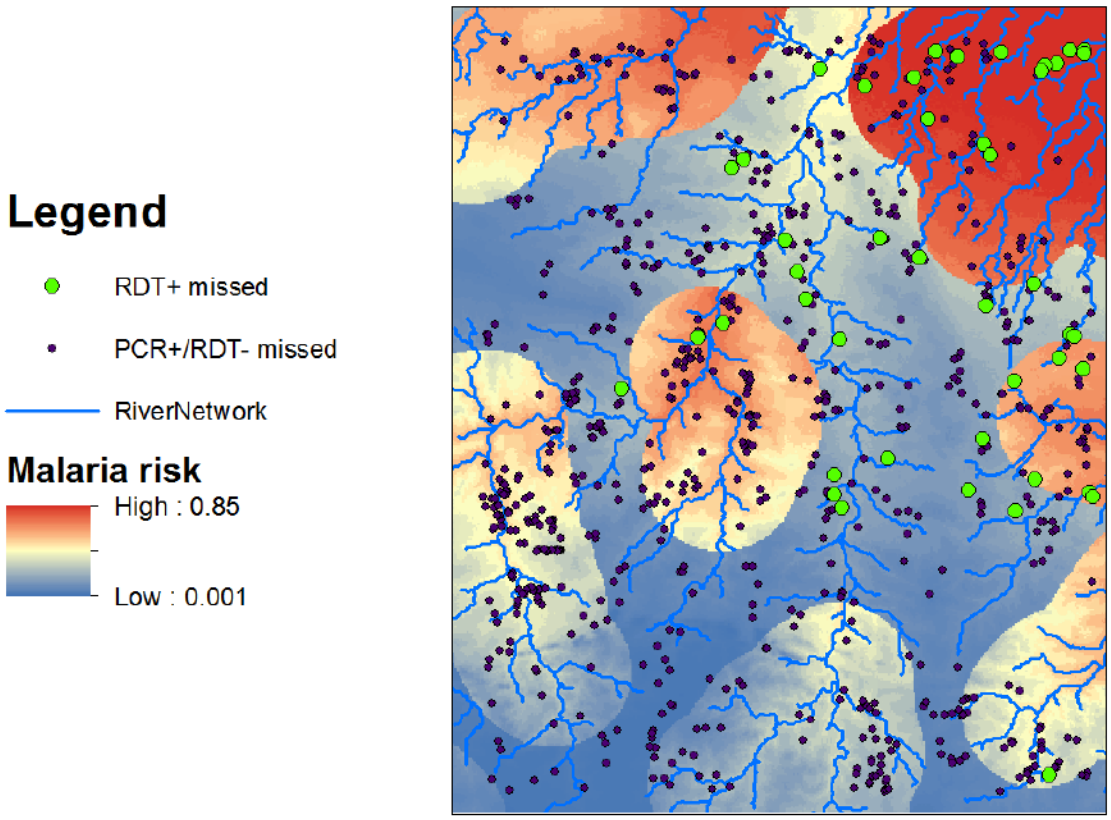


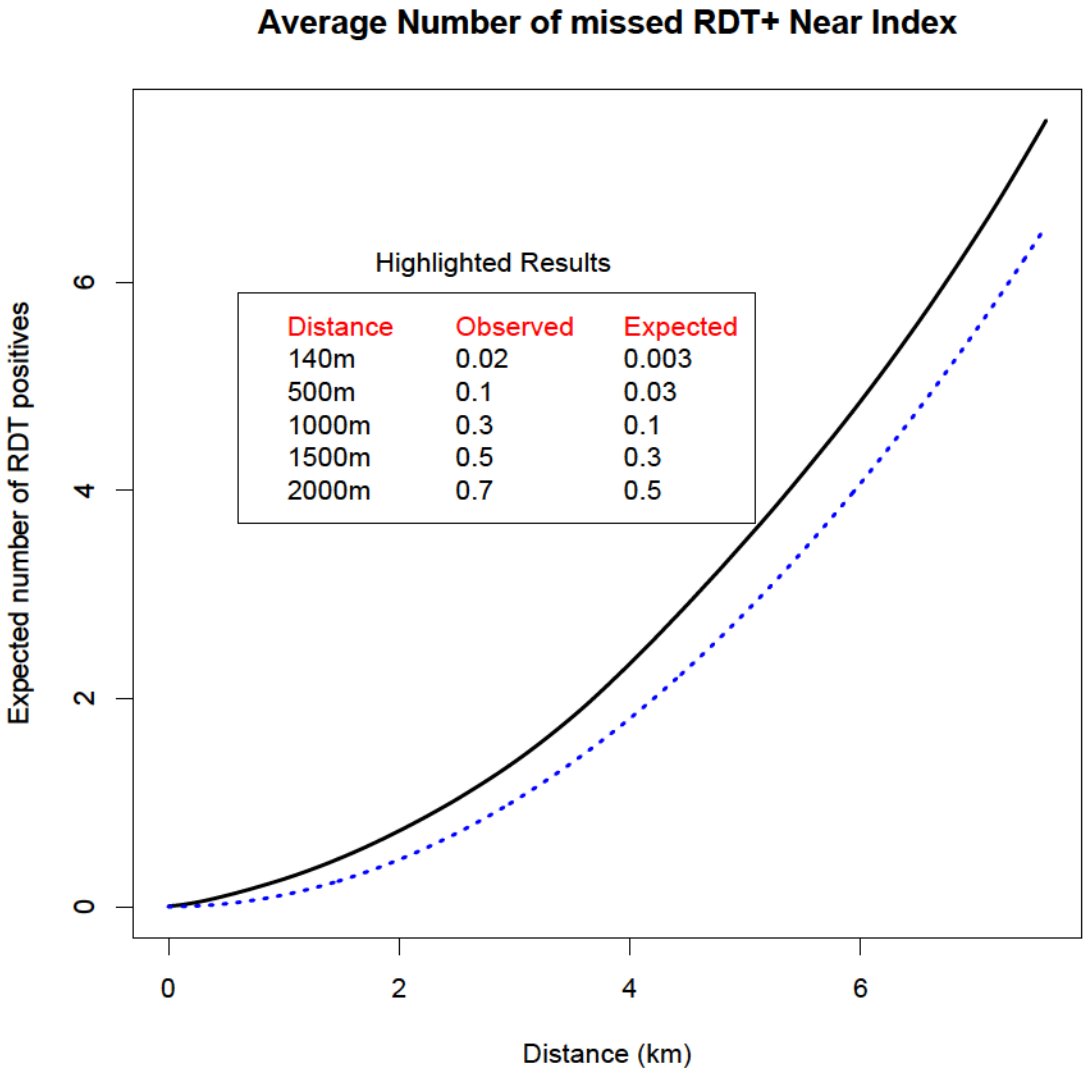
Figure 6.5

Missed households overlaid on risk map generated from 2008 cohort data



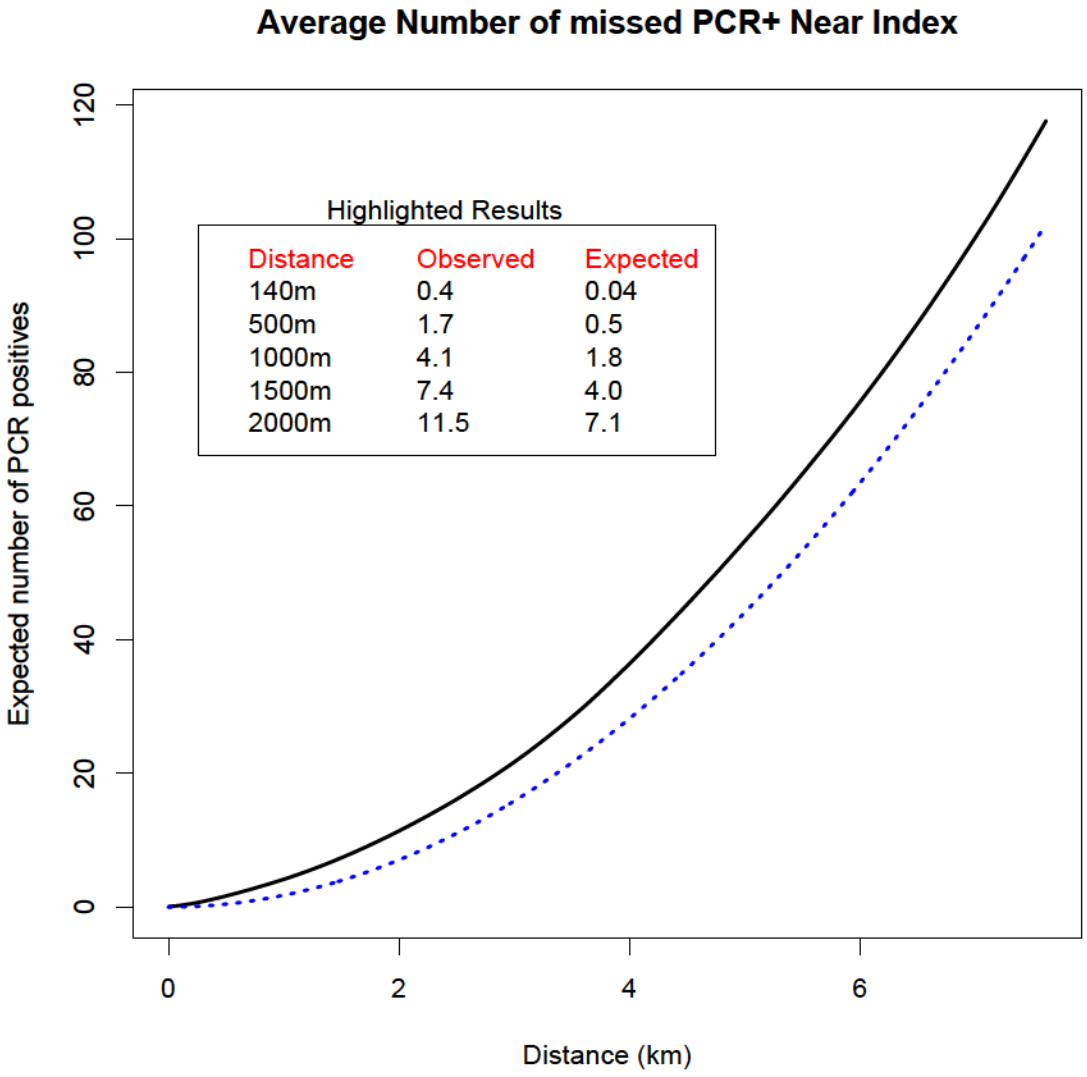
Appendix 3

Cross K function of households with missed RDT-positive residents within varying radii of an index household



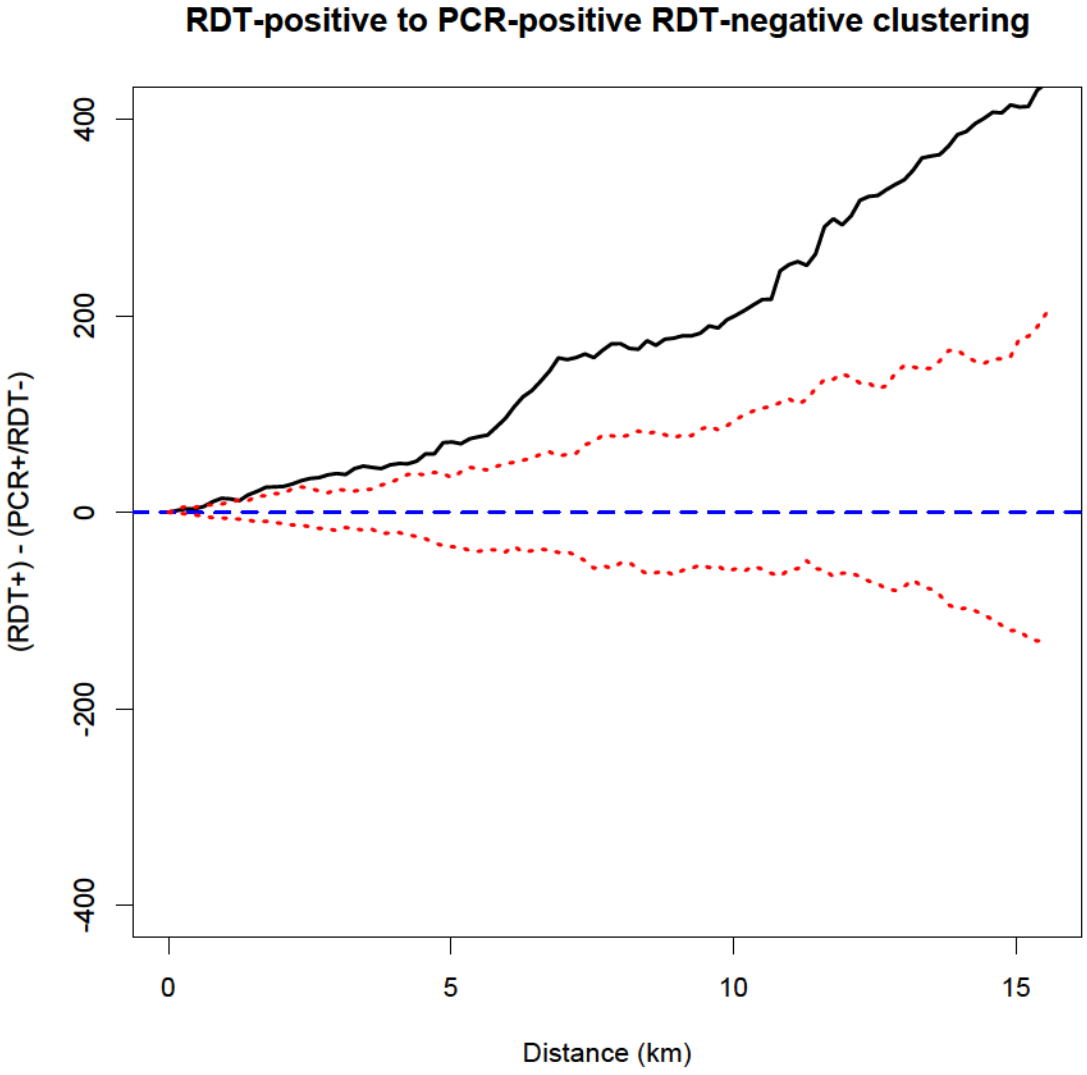
Appendix 4

Cross K function of households with missed PCR-positive RDT-negative residents within varying radii of an index household



Appendix 5

Difference in K Function comparing spatial clustering of missed households with an RDT-positive resident to missed households with an RDT-negative PCR-positive resident

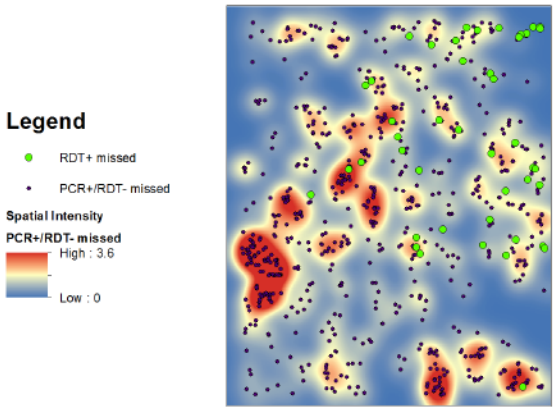


Appendix 6

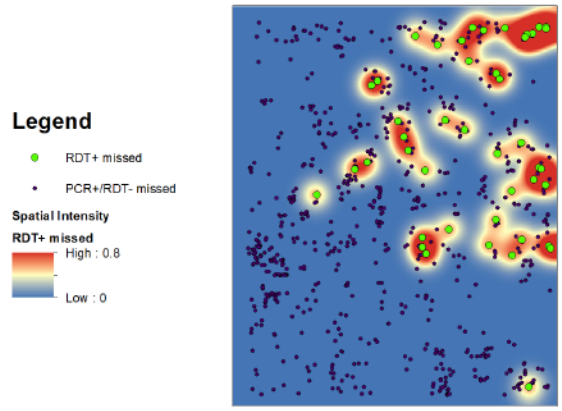
Comparison of spatial intensity of missed households with an RDT-positive resident to missed households with an RDT-negative PCR-positive resident, and absolute difference of spatial intensities

Spatial Intensity:

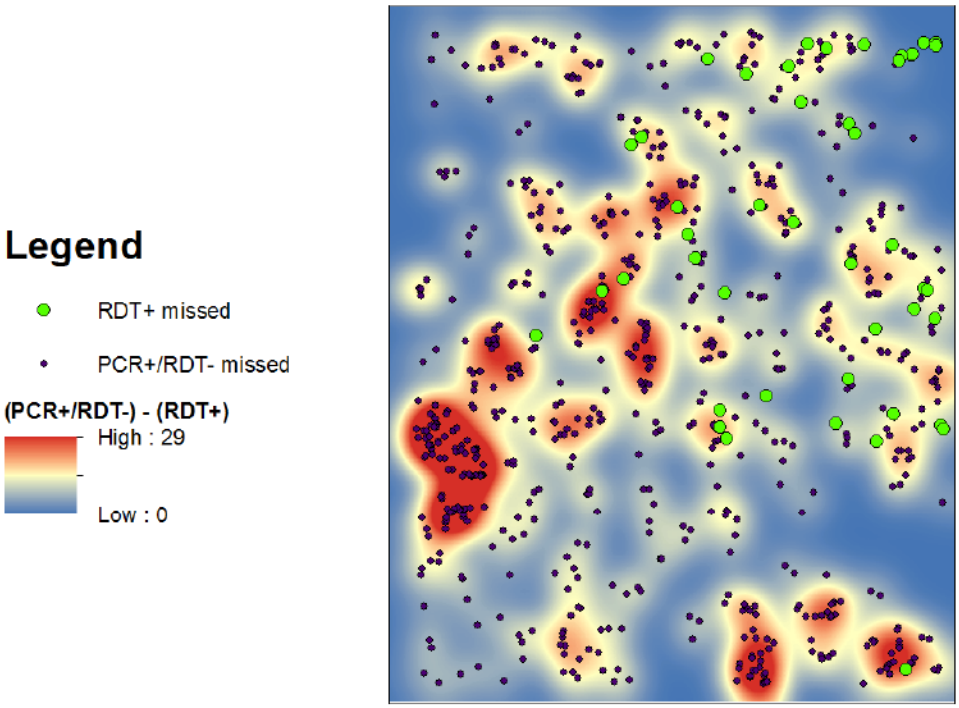
PCR+/RDT- missed houses



RDT+ missed houses



Difference in spatial intensities: (PCR+/RDT- houses) – (RDT+ houses)



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Chapter 7:

Conclusions and Recommendations

7.1 Summary of Major Findings

The findings of this dissertation highlight critical factors and strategies for malaria control and elimination in two different transmission settings in Zambia. Historically, malaria transmission in Zambia was high and endemic, with varying levels of malaria control over the past 50 years. Despite the widespread implementation of the malaria control interventions recommended by the WHO, malaria transmission remains high in some areas of Zambia. Advances in high-resolution satellite and remote sensing technology allow for accurate spatial analyses that have many applications for understanding malaria transmission dynamics and guiding policy.

In the high transmission setting, Nchelenge District, this dissertation aimed to identify risk factors for malaria infection and to use environmental data to generate and validate a predictive risk map for malaria. Paper 1 identified individual, household and environmental factors associated with malaria as determined by RDT positivity in a cross-sectional cohort of households in Nchelenge District between 2012-2014. The results highlight the importance of age in the distribution of malaria, the high proportion of asymptomatic cases, and the impact of a household's geographic location and proximity to environmental features. Paper 1 identified 5 to 17 year olds as the highest risk age category of malaria infection as measured by RDT. Paper 1 also found that report of symptoms decreased with increasing age category, and this interaction was

statistically significant in the full multi-level model. Lastly, the model identified environmental features that increase household risk of malaria. These environmental features are likely predictive of malaria vector breeding sites, thus proximity to these features increases risk of malaria transmission.

Paper 2 expands upon the findings related to the proximity of households to environmental features in order to generate and validate a predictive seasonal risk map of malaria and a map of model uncertainty. There are many potential uses for predictive risk maps for malaria control and elimination; however, they are difficult to generate at appropriate spatial resolution and with representative case data. Maps that are generated are often not validated and are at coarse spatial resolution. Paper 2 illustrates potential validation techniques, implementing both internal and external evaluation methods. It also highlights the importance of presenting uncertainty values and maps in addition to predictive risk maps to ensure appropriate use and interpretation. The results of paper 2 illustrate the highly seasonal transmission patterns, and increased risk of transmission in proximity to category 1 streams, roads, category 3 streams (in the rainy season only), lower elevation, and in less population dense areas.

Paper 1 and 2 explored similar data but with different aims and modeling objectives. Paper 1 takes a more inference focused approach, identifying and quantifying risk factors for RDT positivity in individuals within households in Nchelenge. Findings highlight important individual level characteristics such as age and household level characteristics such as proximity to environmental features, to characterize the distribution of malaria. The modeling objective in

Paper 2 is focused on prediction, predicting household malaria risk at unsampled locations and mapping this risk. Environmental and ecological variables were derived from satellite imagery and remotely sensed data to all points in the region, and these variables were considered for inclusion in the risk model for predicting and mapping malaria risk. An ecological prediction map for malaria risk from the model derived in paper 2 cannot include individual and household level variables because they are unknown at unsampled locations. However, the importance of individual level variables in characterizing malaria risk as was shown in paper 1, and may explain some of the residual spatial variation unexplained by the ecological model.

Paper 3 and 4 explored strategies for pursuing elimination in a low transmission setting in Southern Province. Paper 3 determined individual, household and environmental factors associated with sustained ITN use in a longitudinal cohort of households visited between 2008 and 2013. ITN ownership and use remained high throughout the study period despite the declining transmission (from 8% to 2% between 2008 and 2013). Reported ITN use was higher in the rainy season, among participants who learned about malaria from a community health worker as opposed to not learning or learning from another source, in households that owned 3 or more nets, and ITN use decreased farther from health facilities (Paper 3). A sub-analysis of households visited between 2012 and 2013 found that nuisance mosquitoes also impacted ITN use. The total number of mosquitoes caught in the household, regardless of the genus, increased the report of ITN use. This was supported by the tabulation

of qualitative questions that ITN use was less likely if respondents reported few or no mosquitoes around (Paper 3). These findings can guide malaria control programs, specifically ITN distribution campaigns, to improve ITN coverage and use in areas where transmission risk has declined.

Paper 4 evaluated active case detection methods for malaria elimination in a low transmission setting. Current interventions will not be sufficient to eliminate malaria; additional strategies may be necessary. The simulation of cross-sectional cohort data in this area determined the efficiency of RACD and focal MDA in a low transmission setting. The results of Paper 4 found that a substantial proportion of infections are missed by passive surveillance; RACD would identify many additional asymptomatic infections and/or individuals that do not seek care, that test RDT positive first. However, some remaining infections will be sub-patent and not detected via RDT. Although controversial, recent findings suggest sub-patent infections are still capable of transmitting malaria and will need to be targeted to achieve elimination. To treat these last remaining cases, a better diagnostic test is necessary, or focal MDA may be implemented. Focal MDA would presumptively treat all individuals who reside within a given radius of a passively detected index household. Paper 4 underscores that current methods will not be sufficient to eliminate malaria in most regions. Additional active surveillance methods and treatment options are critical for the elimination of malaria.

7.2 Recommendations for Future Research

Future research should be conducted to expand upon the findings of this dissertation. The analyses presented in Paper 1 should be re-run to compare

results using PCR instead of RDT to determine malaria infection. Potentially, RDT results are overestimating malaria prevalence; in high transmission settings, individuals may be antigenemic for up to two weeks after treatment, leading to a positive RDT result after parasite clearance. The analyses conducted in paper 1 can be expanded to the longitudinal households; trends in the risk factors of malaria transmission over time will aid in the understanding of transmission dynamics in such an endemic setting. A question regarding recent travel history was added to the survey used in this study in 2013; future analyses of malaria transmission in Nchelenge District should investigate the impact of recent travel on malaria infection. Overnight travel is often reported for migrant work as well as for social functions such as funerals in this region, and may contribute to spreading of malaria. Open wells and roads may be tested for anopheline mosquito larvae to determine if they are contributing to vector density in the area and may provide a target for vector control activities.

The risk maps generated in Paper 2 provide a useful first step and baseline comparison for future research regarding risk mapping in this region. Malaria risk maps can be used for several activities, including targeting of IRS, targeting of vector control management, and identification of hot spots of transmission. A critical expansion of the methods and findings of Paper 2 would be to generate risk maps that can be available to national malaria control programs and based on free environmental data. Exploring methods to expand the findings from this risk map to incorporate surveillance data and free spatial data would make these findings generalizable and useful for guiding malaria

control activities to the highest risk areas. Another area for future research is to generate risk maps using entomological data collected at this site. If certain environmental features predict vector-breeding sites, then these findings may provide better targets for vector control activities. Lastly, risk maps may be used in simulation models to determine the impact of spatially targeted interventions. Since the current risk map only reflects variation by environmental features, future simulation models of household coverage of interventions may further explain variation in transmission at the individual or household level.

In the low transmission setting, additional research is necessary on the best strategies to pursue malaria elimination. Paper 3 identified key factors that should be highlighted in ITN distribution campaigns in pre-elimination settings. For example, future research should examine the message of ITN campaigns and potentially alter the message to promote 'a good nights sleep' and protection from nuisance mosquitoes, in addition to preventing malaria transmission. Additional research is necessary to determine the effective life span of an ITN in field settings, and ensure that new nets are distributed at appropriate intervals to maximize impact and minimize costs. Lastly, research is necessary to determine if ITN campaigns should be modified in extremely low transmission settings; some concern regarding insecticide resistance and changes in mosquito behavior due to ITNs should be explored further.

Paper 4 was limited because the analysis is based on simulated findings with certain assumptions. Future research using simulation models should include seasonal components, in order determine the impact of seasonality on

active case detection. Active surveillance methods should also include questions regarding recent overnight travel that may lead to importation of cases. Additional research should highlight the impact of RACD and/or targeted MDA under field conditions; likely, follow up will not be perfect, there may be a lag between the detection of a case passively and the reaction at the household, there may be diagnostic or drug stock outs, and all individuals may not be home at the time of the reaction visit. Access may be impaired during the rainy season, limiting home visits. Additional research is necessary to determine the impact of sub-patent infections and the best method to treat them. A diagnostic tool that can detect very low parasitemia, or a vaccine, would be best; until then, the impact of targeted MDA should be explored. The exact anti-malarial (ideally one with gametocidal properties) to use and what dosage remains undecided; future research in this area should also determine the potential for adverse events and the acceptance of this practice by the community. Additional research is being focused on how to target and treat every remaining infection in order to pursue the goal of malaria elimination.

7.3 Policy Implications

This dissertation has several policy implications for malaria control and elimination. Findings from paper 1 and 2 can guide targeting of interventions to the highest risk populations and geographic areas. The finding in paper 1 that school age children are at highest risk of malaria may suggest the exploration of school-based interventions or school-based MDA. The findings from paper 2 may be expanded to generate large-scale, high-resolution risk maps for regional use. Risk maps are recommended by the WHO for the targeting of vector control

activities such as IRS, because targeting these activities to high-risk areas is significantly more cost-effective with maximal impact. Overall policy implications for Nchelenge District are the targeting of interventions to the highest risk population and geographic areas to control the burden of malaria.

Findings from paper 3 and 4 have policy implications for pursuing the goal of malaria elimination. The finding that ITN use remains high in a low transmission setting is promising. Despite reduced perceived risk, individuals in the region continue to report high ITN use. Findings from paper 3 suggest that current education campaigns and distributions are achieving high coverage and encouraging sustained use of ITNs. The finding that nuisance mosquitoes increase ITN use may be integrated into current education campaigns. The findings from paper 4 that both asymptomatic, RDT-positive infections and RDT-negative, PCR-positive sub-patent infections cluster around passively detected, index cases is critical in guiding research on active surveillance and elimination strategies. The presence of sub-patent infections in the study area suggest RACD will not treat every last infection and additional research regarding focal MDA is necessary. The WHO recommends pursuing active case detection strategies that target asymptomatic and sub-patent infections, as these are able to contribute to transmission and are missed by passive surveillance.

CURRICULUM VITAE

JESSIE PINCHOFF, MPH

Email: jpincho1@jhu.edu
Phone: 646 416 2388
Permanent Address: 370 Central Park West #501, New York, NY 10025

EDUCATION

PhD	2010 – 2015	**Johns Hopkins University,** Baltimore, MD Bloomberg School of Public Health Department of International Health Global Disease Epidemiology and Control Certificate: Vaccine development and policy Johns Hopkins Malaria Research Institute Fellow
MPH	2010	**Columbia University,** New York, NY Mailman School of Public Health Department of Epidemiology
BA	2007	**Northwestern University**, Evanston, IL Department of Anthropology Minor Global Health

RESEARCH EXPERIENCE

Spatial Epidemiology Consultant
Center for Infectious Disease Research Zambia, Lusaka, Zambia, Jan 2014-present

- Led and coordinated analysis of completed research study including revisiting sites, data cleaning, and development of analysis plan for two manuscripts.
- Implemented statistical analyses using SAS, ArcGIS, and SaTScan. Analyses describe reactive case detection strategy implications for malaria control, and a spatial analysis of the distribution of incident malaria cases in a peri-urban moderate transmission setting.

Research Assistant/Data Analyst
Akros Global Health, Lusaka, Zambia, Fall 2013 - present

- Assisted with planning and trainings in collaboration with the Zambian National Malaria Control Center on the use of DHIS2 for district and regional health officers to plan and track malaria surveillance data in Zambia.
- Developed and assisted with planning the 2014-2015 indoor residual spraying campaign conducted across 15 districts in northern Zambia. Developed implementation plan and protocol to enumerate all structures in selected districts using QGIS and Google Earth imagery, and strategy for targeting households for spraying.
- Designed and implemented data collection and analysis to determine accuracy of Google Earth imagery to enumerate structures, and compare to output from mSPRAY a tablet based tool to collect data on indoor residual spraying.

Research Analyst/Consultant
NYC Dept of Health and Mental Hygiene, New York. NY, Fall 2014-present

- Generated and executed analysis plan regarding trends in mortality associated with HIV and viral Hepatitis co-infection.
- Data cleaning, management and analysis using large relational dataset comprised of surveillance data from 2000-2010 matched between HIV, communicable disease, and vital statistics registries.

Epi Scholars Fellow
NYC Dept of Health and Mental Hygiene, New York. NY, Summer 2012-2013

- Led and organized data cleaning and management of a relational dataset comprised of HIV, STD, Hepatitis B, Hepatitis C, and Tuberculosis surveillance data collected from 2000 to 2010 in NYC.
- Collaborated with epidemiologists and program managers from various bureaus within the NYC Department of Health, specifically Bureau of HIV/AIDS research and Communicable Disease.
- Generated and executed data analyses in SAS, SaTScan, and ArcGIS software.
- Developed and generated internal presentations, conference presentations and internal documents regarding deterministic match methodology and initial findings.

Research Assistant/Data Analyst
Johns Hopkins University, Baltimore, MD, Spring 2011-2013

- Developed and implemented of analysis of spatial data regarding eye disease (glaucoma, macular degeneration) and distances individuals travel from their home, supervised by Dr. Frank Curriero. Analyses and data cleaning in R software and ArcGIS.

Research Assistant/Data Analyst
Earth Institute. New York, NY, Fall 2009-2010

- Managed, cleaned and analyzed data from the Millennium Villages Project relating to tuberculosis control at each of twelve sites across Africa.
- Compiled, generated and edited presentations, internal reports, and annual report of initial findings from findings from each site.

Field Researcher
University of Buenos Aires. Buenos Aires, Argentina, Summer 2009

- Assisted with parasitological analyses and PCR assays on projects regarding Chagas disease transmission.
- Conducted fieldwork to capture sylvatic mammals; assisted with collection and testing of samples for Chagas disease, leishmaniasis, and rabies.
- Developed and initiated an analysis plan regarding factors associated with congenital Chagas transmission.

Data Analyst
Feinberg School of Medicine, Chicago, IL Fall 2007- 2008

- Data analyst for the national coronary artery risk development in young adults (CARDIA) study Chicago site.

- Tabulated and analyzed data, created powerpoint presentations for internal and external reports on incoming data.
- Assisted with generating analysis plans and conducting statistical analyses for reports and presentations using CARDIA data.
- Developed and carried out original research analysis regarding fitness and bone density

Field Epidemiologist
Nelson Mandela Metropolitan University, Port Elizabeth, South Africa
- Implemented original research to determine how nutrition, specifically vitamin supplementation, interacts with anti-retrovial therapy among HIV positive individuals living in Port Elizabeth, South Africa.
- Developed data collection and analysis methods; collected and cleaned data in the field, conducted interviews, generated analysis plan carried out using STATA software.

GRANTS AND AWARDS

Special Projects Grant (2014)
- $25,000 awarded by the International Center for Excellence in Malaria Research (ICEMR) for southern Africa to carry out research regarding risk mapping for targeted indoor residual spraying.

Johns Hopkins Malaria Research Institute Pre-doctoral Fellowship (2013).
- Awarded by the Johns Hopkins Malaria Research Institute for two years of pre-doctoral research.

Epi Scholars Fellowship (2012).
- Awarded by the New York City Department of Health to work with the Program for Collaboration and Service Integration (PCSI) project in the Division of Disease Control at the NYC Department of Health.

Field Placement Grant (2011).
- Awarded by the Center for Global Health at Johns Hopkins University for independent research in Zambia.

Maternal Infant Health Predoctoral Fellowship (2011).
- NIH Fellowship awarded for relevant coursework and research.

Global Health Research Grant (2009)
- Awarded by Columbia University for independent summer research project.

Undergraduate Research Grant (2006).
- Grant awarded by Northwestern University to conduct independent research.

PUBLICATIONS

Peer Reviewed Publications

1. **J. Pinchoff,** J Chipeta, GC Banda, S Miti, TM Shields, FC Curriero, WJ Moss. Spatial Clustering of Measles Cases During Endemic (1998-2002) and Epidemic (2010) Periods in Lusaka, Zambia. *BMC Infectious Diseases (*revise and resubmit).

2. C Prussing, C Chan, **J Pinchoff**, L Kersanke, K Bornschlegel, S Balter, A Drobnik, J Fuld. HIV and Viral Hepatitis Co-infection in New York City, 2000-2010: Prevalence and Case Characteristics. Accepted at *Epidemiology and Infection.*

3. **J. Pinchoff,** A Drobnik, K Bornschlegel, S Braunstein, C Chan, JK Varma, J Fuld (2014). Deaths Among People with Hepatitis C in New York City, 2000-2011. *Clinical Infectious Diseases*. 58: 8

4. A Drobnik, **J Pinchoff**, G Bushnell, S Ly, J Yuan, JK Varma, J Fuld (2014). Matching HIV, Tuberculosis, Viral Hepatitis, and Sexually Transmitted Diseases Surveillance Data, 2000-2010: Identification of Infectious Disease Syndemics in New York City. *Journal of Public Health and Management*. 20(5), 506-512

5. F. Curriero, **J.Pinchoff,** SW van Landingham, L Ferucci, DS Friedman, P Ramulu. Alteration of travel patterns with vision loss from glaucoma and macular degeneration. *JAMA Ophthalmology*.

6. **J. Pinchoff**, M. Carnethon, T. Church, A. Hankinson, D.R. Jacobs, Jr., C.E. Lewis, P.J. Schreiner, B. Sternfeld, O.D.Williams, S. Sidney. (2008) The association of physical activity and fitness levels with bone density: CARDIA Fitness Study. *American Journal of Epidemiology*. Vol 167 supplement 11. (Abstract)

7. Ravosa Matthew, Kunwar Ravinder, Nicholson Elisabeth, Klopp Emily, **Pinchoff Jessie**, et al (2006). Adaptive Plasticity in Mammalian Masticatory Joints. *Proc of SPIE.* 6318

8. Ravosa, Matthew, Klopp Emily, **Pinchoff Jessie**, et al (2007). Plasticity of Mandibular Biomineralization in Myostatin Deficient Mice. *Journal of Morphology* 268:275-282

REPORTS

1. Matching New York City Viral Hepatitis, Tuberculosis, Sexually Transmitted Diseases and HIV Surveillance Data, 2000-2010. Epi Research Report, October 2013. http://www.nyc.gov/html/doh/downloads/pdf/epi/epiresearch-PCSI.pdf

POSTERS AND PRESENTATIONS

1. Spatial patterns of malaria transmission over one year in a clinic catchment area of Chongwe District, Zambia
   Oral Presentation at American Society for Tropical Medicine and Hygiene Conference
   New Orleans, LA 2014

2. Individual and Household Level Factors Associated with RDT-Positivity in a High Malaria Transmission Setting of Northern Zambia, 2012- 2013
   Poster Presentation at American Society for Tropical Medicine and Hygiene Conference
   New Orleans, LA 2014

3. Spatial Prediction of Malaria Risk in a High Transmission Area of Nchelenge District in Northern Zambia, 2012-2014
   Poster Presentation at American Society for Tropical Medicine and Hygiene Conference
   New Orleans, LA 2014

4. Individual and Household Level Factors Associated With Insecticide Treated Bednet (ITN) Use Between 2008 and 2013 in a Low Malaria Transmission Setting of Southern Zambia
   Poster Presentation at American Society for Tropical Medicine and Hygiene Conference
   New Orleans, LA 2014

5. Factors associated with sustained use of bed nets in a region of declining malaria transmission in southern Zambia: A longitudinal study 2008-2012
   Oral presentation at the Zambian National Health Research Conference
   Lusaka, Zambia 2013

6. Spatial clustering of measles cases during the 2010 outbreak in Lusaka, Zambia
   Poster presentation at the Zambian National Health Research Conference
   Lusaka, Zambia
   2013

7. Using cross- matched surveillance data to describe persons with HIV-Hepatitis C (HCV) co-infection and persons with HIV-Hepatitis B (HBV) co-infection in New York City, 2000-2010
   Oral presentation at the Council for State and Territorial Epidemiologists Annual Research Meeting
   Pasadena, CA 2013

8. Reportable infectious diseases among people with tuberculosis in New York City, 2000-2010
   Poster presentation at the Council for State and Territorial Epidemiologists Annual Research Meeting
   Pasadena, CA 2013

9. Mortality among people with Hepatitis C And HCV/HIV co-infection in New York City, 2000-2011
   Poster presentation at the American Public Health Association Annual Research Meeting
   Boston, MA 2013

10. Trends in HIV/Hepatitis C co-infection among men who have sex with men (MSM) in New York City (NYC), 2000-2010
    Poster Presentation at the ID Week Annual Research Meeting
    San Francisco, CA 2013

11. Causes of death among people with Hepatitis C in NYC, 2000-2011
    Poster presentation at the ID Week Annual Research Meeting
    San Francisco, CA 2013

12. Trends in Hepatitis C and liver related causes of death among people with Hepatitis C infection in NYC, 2000 to 2010
    Poster presentation at the ID Week Annual Research Meeting
    San Francisco, CA 2013

13. Do Individuals With Glaucoma And/or Macular Degeneration Restrict Their Travel Outside The Home To More Nearby Locations?
    Poster presentation at the Association for Research in Vision and Ophthalomology Annual Research Meeting
    Fort Lauderdale, FL 2012

14. The association of physical activity and fitness levels with bone density: CARDIA Fitness Study.
    Poster at the American Hearth Association Annual Research Meeting
    Chicago, IL 2008

TEACHING SKILLS

Teaching Assistant, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, 2010-2013

Global Disease Control Policies and Programs (classroom)
Global Disease Control Policies and Programs (online)
Spatial Analysis and GIS

SKILLS AND INTERESTS

- Speak fluent Spanish.
- Skilled in STATA, R, SAS, SaTScan statistical analysis software
- Skilled in ArcGIS, Microsoft Office (Powerpoint, Excel, Word, Access), Endnote reference software.

Interest in spatial epidemiology, multi-level modeling, time series analysis and infectious diseases