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Preventive Strategies to Reduce Malaria Burden: Epidemiological Surveillance and Modeling for New Control and Elimination Methodologies

DISSERTATION

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for the degree of

DOCTOR OF PHILOSOPHY

in Social Ecology

by

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DEDICATION

To

My family and friends for listening, supporting, and indulging me
My sister for continuing to inspire me every day
My Bubbles for being mine

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ABSTRACT OF THE DISSERTATION

Preventive Strategies to Reduce Malaria Burden: Epidemiological Surveillance and Modeling for New Control and Elimination Methodologies

By

Amruta Dixit

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Professor Oladele Ogunseitan, Chair

Malaria epidemiology around the world is changing at a rapid pace due to intensive malaria control campaigns in the past decade. In spite of major progress in malaria control, new strategies are needed to reduce the malaria disease burden and reach global eradication goals. Within the framework of translational medicine, this interdisciplinary dissertation used a multilevel approach to describe and evaluate strategies seen as imperative to achieving the goal of malaria elimination set forth by the World Health Organization. We used a combination of field surveys and mathematical modeling methodologies to examine malaria epidemiology from the individual, the community, and the bench-side perspectives in countries aiming at control (Kenya) and elimination (Thailand). In Kenya, the combination of consumer, healthcare provider, and pharmaceutical retailer surveys revealed that the high cost of diagnosis and treatment at a healthcare facility may be inhibiting positive health-seeking behavior and may be incongruent with the goals of

current subsidization policies. In Thailand, field surveys identified cross-border human movement patterns and important migration parameters between Thailand and Myanmar. The multi-node model simulations found an indirect impact of interventions on the side of the border that did not receive the intervention. Sensitivity analyses showed that the indirect impact of vector control was stronger with increased migration rates. Therefore, in this border region that harbors a constant and unmonitored flow of people, the regional malaria elimination strategies need to be accommodative of highly mobile populations. Lastly, we used a combination of field survey data from Kenya and the mathematical model to explore potential added benefits of including a long-lasting microbial larvicide as a supplemental vector control strategy in endemic regions of sub-Saharan Africa where insecticide resistance and changes in vector behavior present significant challenges to control. The model results indicated that larviciding has the potential to provide significant added benefits to malaria control in the context of prevailing pyrethroid resistance and outdoor transmission. In conclusion, parameterizing mathematical models with field-derived entomological and epidemiological data framed within individual, community, and bench-side perspectives, can represent a valuable approach to assist malaria control and elimination efforts.

INTRODUCTION

In 2015, there were approximately 214 million reported cases of malaria around the world, causing more than 438,000 deaths, mostly in children in the World Health Organization (WHO) African Region[1]. Currently, the disease is largely prevalent in the tropical and sub-tropical regions of the world where the climate and other environmental factors are conducive to mosquito breeding and survival; certain countries in those regions have successfully controlled the spread of malaria and are aiming for disease elimination while others remain in the control stage[2].

Ongoing WHO programs to combat malaria include widespread bed-net distribution and vector control, improvement of surveillance and testing methods by encouraging use of rapid diagnostic tests and microscopy where possible, and increasing access to quality-assured anti-malarials[3]. Vector control measures which include bed-net distribution, larviciding, and indoor residual sprays, have been derived from an understanding of known vector behavior patterns. Currently, however, factors such as climate change, political and economic turmoil, and mosquito and parasite evolution are serving to reduce the efficacy of these strategies, consequently slowing down global efforts to eliminate malaria by 2030[2].

In spite of the resources and efforts invested in the control and elimination efforts against malaria, gaps in translation remain and are ever-widening, driven by the acute lack of knowledge of malaria epidemiology in areas of low and unstable transmission. Thus, in my efforts to contribute to bridging the gap between science and policy, I utilize a multidisciplinary approach to acquire critical knowledge of malaria epidemiology in the era of intensive malaria control campaigns. Modeled upon the framework provided by the field

of translational science, my dissertation uses a multilevel approach to describe and evaluate strategies seen as imperative to achieving the goal of malaria elimination set forth by the WHO.

The first chapter considers the individual and how current Kenyan malaria treatment policies, designed to alleviate the financial burden on the patient, may be incongruent with an individual's experience during a malaria episode given that cost is an important component of an individual's decision to seek care; delays associated with seeking treatment for malaria contribute to disease morbidity and mortality[4]. It also seeks to demonstrate how geography can affect an individual's healthcare choices and the implications that may have on malaria transmission in that region. This chapter uses primary data collected from surveys of individuals, hospitals, and local retailers to develop a more comprehensive understanding of the cost of malaria treatment in this area than was previously available.

The second chapter delves into how human movement between communities across the border from each other influences and is influenced by the control and treatment policies that are in place on one side of the border[5,6]. This chapter makes use of field data as well as mathematical modeling to demonstrate the effects of the movement on malaria transmission and presents hypothetical scenarios of what the disease transmission might look like after a shock to the system. The chapter focuses on the movement along the border region of Myanmar and western Thailand, an area that has been particularly prone to political and economic turmoil[7]. While Thailand has achieved control of malaria and is working towards the goal of eliminating from within its borders, Myanmar has high and

uncontrolled malaria transmission[8]. For this reason, this work is especially valuable for it presents some theoretical transmission scenarios that can potentially help Thailand develop policies to mitigate the effects of new infection potential along its borders.

Lastly, the third chapter is based upon the benchside aspect of translational medicine within public health. It employs the same mathematical modeling system used previously to evaluate a new and innovative vector control method in hopes of elucidating the best practices for its use in the field. This chapter combines available field data on climate and mosquitoes with the model to demonstrate how long-lasting microbial larvicides can be best utilized in endemic settings in sub-Saharan Africa. This evaluation is timely because the region is faced with growing threats of insecticide resistance in the mosquitoes and increased outdoor biting and transmission from the mosquitoes[9-11]. Both of these factors mean that the efficacy of the bed-nets and indoor residual sprays is reduced and that humans experience greater exposure to potentially infectious bites despite the presence of these interventions[12].

It is the overall goal of this dissertation to use an interdisciplinary approach to acquire critical knowledge of malaria epidemiology in the era of intensive malaria control campaigns, and to evaluate alternative and innovative strategies for effective malaria control and eventual elimination. I built upon an existing platform of information by incorporating novel modeling techniques to develop and evaluate theoretical predictions of malaria control and elimination efforts in areas of low and unstable transmission.

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CHAPTER 1

Discovering the cost of care: consumer, provider, and retailer surveys shed light on the determinants of malaria health-seeking behaviours

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Abstract

The growing threat of insecticide resistance in mosquitoes and drug resistance in the *Plasmodium* parasites increases the importance of ensuring appropriate malaria case management and enabling positive health-seeking behaviour. Treatment-seeking behaviours are poorly characterized in malaria-endemic regions that have been the focus of intensive control and elimination campaigns. This study uses a comprehensive approach to shed light on the determinants of malaria treatment-seeking behaviours from different perspectives.

We conducted cross-sectional surveys from 832 households, fifteen health centers, and 135 retailers across three sites in the Emuhaya and Kakamega districts of the western Kenyan highlands. Participants were recruited via random sampling and data were collected with the use of a structured questionnaire about malaria treatment-seeking behaviour. All households, healthcare facilities, and retailers were mapped using a handheld GPS and a GIS algorithm was used to calculate "walk distance" based on the Tobler rule; an estimate of this distance was used to calculate the travel time used in the analyses.

Across the three sites, 47.5% - 78.9% of the residents sought diagnosis and treatment at hospitals, clinics, or dispensaries; 6.3%- 26.1% of the residents sought malaria care only at pharmaceutical retailers. Overall, 40.3% to 59.4% of residents reported delaying seeking care for more than 24 hours after fever onset. After adjustment, residents who chose to visit a pharmaceutical retail facility rather than a hospital were 121% and 307% more likely to delay seeking medical care after fever onset than those who reported choosing a healthcare facility for treatment. No significant association was found between travel time and delay in seeking care. The surveys of the healthcare facilities indicated an average total

cost per patient per visit was 112 KES ($1.40 US) for public facilities and 165 KES ($2.06 US) for private facilities.

Understanding the local health behaviours that perpetuate transmission of malaria will help develop targeted preventive measures and educational interventions that can empower the residents with the knowledge needed to combat malaria in a safe and effective manner. Ensuring patient access to health care facilities in countries with high disease burdens has broader implications on measures of equity and on public health prevention methodologies.

Introduction

In spite of intensified malaria control efforts, malaria is a major public health problem, particularly in Africa. Globally, malaria is estimated to affect 200 million people and kill more than 500,000 people per year, mostly children under the age of five[1]. In the past decade, Africa has seen a vast increase in coverage with vector control interventions, with almost half of the susceptible population receiving access to insecticide-treated bed nets[1]. Additionally, indoor residual spraying in Africa protected over 55 million people from malaria[1]. However, with the growing threat of insecticide resistance in mosquitoes[2,3] and drug resistance in the parasites[4,5], ensuring appropriate malaria case management and enabling positive health-seeking behaviour grows in importance.

The health behaviours of the local populace are intrinsically linked to case management policies. Sensitive and accurate diagnosis and timely treatment with effective drugs are key components of the World Health Organization (WHO) malaria treatment guidelines[6]. However, without an understanding of the treatment-seeking behaviours of the susceptible population as well as a careful evaluation of the determining factors of those behaviours, malaria control and elimination programmes may be fragmented from the reality seen in the field, and consequently intervention strategies may not be effective or sustainable.

An important variable in the determination of health-seeking behaviour is access to health care services. According to the WHO, people living within one hour of travel time of a health care facility are generally considered to have access to health care[7]. The inverse relationship between distance to facility and use of health care services has been well

established[8-10]. However, it has largely been based on measures of Euclidean distance[7] even when the topography and transport infrastructure in the area rarely allow for a direct path to the facility. In addition to travel impedances, other factors that can affect health-seeking behaviour include affordability and availability of medicines and medical care[11]**.** Previous studies have shown that in the absence of access to trained medical personnel, people will choose to receive information from untrained sources such as the local chemist or pharmaceutical retailer[12,13]. Self-medication or home treatment of malaria has generally been shown to have a lower cure rate than treatment in an institutional setting[14] and the tendency to self-diagnose malaria and subsequently self-medicate, has been growing in regions of Africa with limited healthcare access[15,16]. These various factors all have an impact on the perpetuation of regional malaria transmission.

In Kenya, 76% of the population is at risk for malaria; in 2013, there were over 2.3 million confirmed cases of malaria in the country[1]. It is crucial to ensure that people are seeking appropriate diagnosis and anti-malarial treatment in a timely manner to reduce malaria mortality, morbidity, and transmission. As treatment-seeking behaviour and healthcare utilization has been shown to be affected by the multitude of factors listed above, we attempted to exact a more comprehensive measure by integrating opinions and habitudes from consumers, health providers, and retailers. The holistic nature of the study is especially appropriate at a time where malaria control efforts such as mass distributions of bed nets and subsidy of artemisinin-based combination therapy (ACT) have intensified, but without a suitable adjustment for health-seeking behaviour patterns of the study population.

The objective of this study was to determine the malaria treatment-seeking behaviour patterns in the western Kenya highlands, and to elucidate some of the major perceived hindrances to healthcare access in that region. The residents' perceptions regarding barriers may impinge upon their ability to seek diagnoses and treatment at a healthcare facility in a timely manner. This discordance between perceptions and reality may serve as a critical target point in an effective malaria control or elimination programme.

Ethical considerations

The project was approved by the Institutional Review Board of UC-Irvine and Ethical Review Committee of Kenya Medical Research Institute.

Methods

Study area and study population

We conducted cross-sectional surveys in three study sites, and collected data from 832 households, fifteen health centres, and 135 retailers in the Emuhaya and Kakamega districts in the western Kenyan highlands (Figure 1A). The study sites included three sub-locations: Iguhu (34˚44′ E, 0˚11′ N, 1,430-1,580 m above sea level) in Kakamega district (Figure 1B); and Emakakha (34˚39′ E, 0˚07′ N, 1,460-1,520 m above sea level) (Figure 1C) and Emutete (34˚38′ E, 0˚02′ N, 1,480-1,640 m above sea level) (Figure 1D) in Emuhaya district. Each site was 3 X 6 km^2 and each was composed of several villages. These sites were used for other vector ecology and malaria epidemiology research by other members of the research team[17-19]. The topography of the study area consists of hills, valleys, and plateaus and a variety of land use and land cover patterns exist. This region generally

experiences two rainy seasons (April–May and October–November) and two dry seasons (January–February and July–August)[13] although during the year the survey was conducted, the rainy season started later than in previous years and lasted well into August 2011[14,6].

Local resident survey

In each of the three study sites, the questionnaire was administered to an adult member of the randomly selected households. Informed consent was obtained from every participant in the study. All households were mapped using handheld global positioning systems (GPS) (Garmin). The predominant tribe in the area is the Luhya tribe and thus, all surveys were translated from English and orally administered in the Luhya language. Survey questions were used to acquire demographic and socioeconomic information and to determine the participants' treatment-seeking behaviour with regards to malaria. The survey also included questions pertaining to treatment facility choices and treatment affordability. All options were read out to the respondents before their answer was recorded. The surveys were conducted by local, trained technicians, over a period of several months, beginning in mid-July and ending in mid-December.

Health facility survey

To assess coverage and utilization of health facilities by local residents, all healthcare facilities within the three study areas were mapped and surveyed by field staff. The initial step was to acquire the complete list of health facilities from KEMRI (Kenya Medical Research Institute). The list contained records of more than 100 facilities in the Western Province with information on services offered, the approximate location, and the second to

fifth administrative level in which each facility was located. Second, each health facility on the topographic map from Kenya Geological Survey was located and health facilities that fell within a ten kilometer radius of the study area and were thus, most likely to serve potential study participants were selected; there were fifteen health facilities on the final list. The team visited each health facility on the final list, recorded the facility's GPS coordinates, and administered the questionnaire to the medical staff member in charge. The information acquired included hours and days of operation, the number and type of medical staff, malaria diagnosis method, any facility-imposed charges associated with a suspected malaria visit, and the storage and supply of anti-malarials.

Pharmaceutical retail facility survey

Given that a considerable proportion of residents purchase anti-malarials from pharmaceutical retail facilities, it is necessary to include such facilities in the surveillance. The team searched for and interviewed all potential outlets along roads and markets where retail facilities are normally located. Pharmaceutical retail facility owners were asked to respond to questions regarding the presence of a licensed pharmacist on site, approximate number of customers served per day, types of anti-malarials in stock, cost for anti-malarials and their supplier for the medication. A total of 135 retailers were surveyed. A small, random sample of these outlets (eight in total) was chosen and one prescription of artemether-lumefantrine (AL, Coartem®) was purchased from each of the chosen outlets in the sample to test for the levels and presence of the pharmacologically relevant active compound by means of ELISA and HPLC[20,21]. The tests were performed according to the protocols described by Wang *et al*[21].

Data analysis

A total of 832 households, fifteen healthcare facilities, and 135 pharmaceutical retail facilities across three study sites participated in the study. All survey responses were entered into MS Excel and the coordinates from the GPS readings were transferred to ArcGIS 10.2 to generate the necessary maps (Figure 1). A GIS algorithm to calculate "walk distance" was created based on the Tobler rule[22]. The estimate of this distance was used to calculate the travel time used in the remaining analyses (Appendix A).

One of the major purposes of the survey was to determine whether or not the participants sought diagnosis and treatment within 24 hours of fever onset. Logistic regression was performed on the survey data using the likelihood of delay as the binary outcome variable. The outcome of a delay in seeking diagnosis and treatment was regressed on key sociodemographic and health-seeking behaviour variables, both individually and in combination. The results of the bivariate analyses (Table 3) and an adjusted multivariate model (Table 4) are included below. When adjusting the multivariate model, both, variables that have been determined as important in the literature as well as variables that measured the participants' perceived barriers were included in the model. Thus, socioeconomic and demographic variables were necessarily included regardless of their significance in the bivariate analyses. The other included variables served as indicators of accessibility, availability of drugs, and affordability.

The missing data were imputed 100 times using the predictive mean matching method using the "mice" package in R 3.1.3. All the regression analyses presented below were performed on the imputed datasets separated by site, rather than as a complete case analysis. Statistical analyses were conducted in R 3.1.3 and MS Excel 2010.

Results

Demographic and socioeconomic characteristics

Among all sites, the majority of households were headed by men (Table 1). Overall, 63% of household heads had only a primary school education or less. At least 91% of the participants across all three sites live in mud homes and approximately 85% of residents in all sites own both furniture and livestock.

Health-seeking behaviours

Although at least 80% of all households surveyed had experienced a malaria infection in the family in the past year, about 10% of the participants indicated that they take no action upon malaria symptom onset (Table 1). In Iguhu and Emutete, approximately 77% of the residents sought diagnosis and treatment at hospitals, clinics, or dispensaries; fewer than 10% of the residents sought malaria care only at pharmaceutical retailers. However, in Emakakha, fewer than 48% of residents sought diagnosis and treatment at a hospital or a clinic and more than 26% of them chose pharmaceutical retailers as their first choice of treatment facility. Overall, a sizeable proportion of residents (40.3% to 59.4%) reported delaying seeking care more than 24 hours after fever onset. The most common reason for the delay was a lack of funds, followed by an expectation of improvement in condition (Table 1).

In spite of long-standing WHO guidelines recommending ACT as the first-line treatment for malaria, only 56% of all participants indicated that they used ACT to treat malaria. More than 29% of all respondents indicated multiple drugs, including quinine, chloroquine, and sulfadoxine-pyrimethamine (SP), as possible options for malaria treatment. This suggests

an overall propensity for choosing treatment based on availability of medication rather than on highest degree of efficacy.

Health access measures

Most participants (84% overall) chose to walk to the treatment facility of their choice (Table 1). All participants were found to be living less than one hour of travel time from a hospital or clinic (maximum calculated time across all sites: 50 minutes) based on our calculations in ArcGIS®. However, patients significantly overestimated the amount of time it would take to walk to the nearest facility (paired t-test, $p<0.001$). For those who reported that the nearest treatment facility was a hospital or clinic, the self-reported travel time to the hospital was overestimated by approximately 22 minutes in Emutete and Iguhu and by over 28 minutes in Emakakha. For those who indicated that the nearest facility was a pharmaceutical retailer, the overestimation of travel time varied by site (18 minutes in Iguhu, 40 minutes in Emutete, and 33 minutes in Emakakha). Of those who sought care exclusively from pharmaceutical retail facilities, 14% did so despite being further away from these facilities than from the nearest hospital or clinic.

Risk factor analysis for delay in seeking care

Overwhelmingly, participants who chose to delay seeking medical care for more than 24 hours after fever onset were more likely to visit the pharmaceutical retailer to purchase medication rather than visit the hospital to seek diagnostic workup and treatment. This association was significant and strongly pronounced across all three sites (Table 3). It was reflected in the bivariate analyses and stayed significant even after adjustment for other

variables. When all other potentially influential variables were accounted for, residents who chose to visit a pharmaceutical retail facility rather than a hospital were more likely to delay seeking medical care after the onset of malaria by between 121% and 307% than those who reported choosing a healthcare facility for malaria treatment (Table 4).

Healthcare facility characteristics

There were fifteen healthcare facilities that served the study population. Of the fifteen, eleven were publicly administered by the Kenya Ministry of Health and four were privately owned and operated (Table 2). It was found that 40% of them exhausted their stores of artemisinin-based malaria treatment at least one or more times per month; six out of the fifteen encountered a shortage more frequently. Furthermore, the average cost to patients per visit for malaria treatment at a public facility was 72 KES (equivalent to $0.90 US at the time) and 125 KES ($1.56 US) at a private facility. The costs were reflective of the admission or registration fees, diagnosis fees, and other miscellaneous charges. These charges did not include the cost of the subsidized ACT drugs (40 KES, $0.50 US, to be paid for by the patient) bringing the average total cost per patient per visit up to 112 KES ($1.40 US) for public facilities that did not have ACT in stock and 165 KES ($2.06 US) for private facilities.

Most of the facilities (twelve) used microscopy in combination with other diagnosing methods to determine infection status as recommended by the WHO; however, three of the health facilities treated patients based on clinical presentation only. Of the fifteen clinics and hospitals, eleven (ten public and one private) received their drug supply directly from Kenya Medical Supplies Authority, the medical logistics provider for all Ministry of Medical

Services/Public Health supported healthcare facilities in the country. Two private facilities purchased directly from the manufacturer and two others (one private and one public) purchased their ACT stock from local retailers.

Pharmaceutical retail facility characteristics

Of the 135 pharmaceutical retail facilities interviewed for the study, only nineteen were operated by a licensed chemist or pharmacist. The remaining facilities were operated by small business owners who ran shops in the local markets or along the roadsides. All nineteen licensed chemists or pharmacists had anti-malarials available for sale in their facility on the day of the interview. However, only 49 of the 116 non-licensed retailers were found to sell any kind of anti-malarial therapy. Of those 49, only sixteen reported the presence of ACT in stock. The remainder sold SP drugs, amodiaquine, quinine, and pain medications. The most commonly stocked antimalarial among the non-licensed retailers were SP drugs; twenty-two shops carried a variety of SP brands. Nine sold amodiaquine and five stocked quinine, either individually or in combination with other therapies. Of all 135 retailers, 38% served 100 or more customers per day.

The surveys of retailers also served as an opportunity to test for the presence of counterfeit or substandard artemisinin-based anti-malarial drugs in the study sites. Survey staff purchased and tested samples of AL-Coartem® from a random selection of eight retailers and pharmacies associated with healthcare facilities and further testing found that all samples contained the manufacturer-labelled amount of the artemisinin-derived active compound (Appendix B), suggesting the quality of ACT being sold met the standard requirements.

Discussion

Timely and appropriate case management of malaria is integral to the reduction of disease-associated morbidity and mortality. An improvement in the understanding of treatment-seeking behaviours in the susceptible populations can enable the development of targeted interventions that are designed in a manner that is feasible and sustainable within individual communities. However, in spite of intensive interventions in the area, the determinants of treatment-seeking behaviours in our study population have been poorly described.

The results of the current study concur with existing literature to show that medical facilities are largely the primary source of malaria care after fever onset[13]. However, the pharmaceutical retailers are a dominant player in the system and need to be considered as an important variable in any future interventions. Furthermore, the subsidies for ACT provided by the government may be masking the high cost of care imposed by medical facilities, thus driving patients towards cheaper alternatives or to delay seeking care altogether.

The results show a strong association between treatment-seeking delay and choosing to seek treatment at a pharmaceutical retailer rather than visiting a health care facility. This association is significant and present in all sites and holds even after adjustment for other variables. This may be reflective of a reduced perception of severity of malaria that has been shown to occur in areas of medium to high malaria endemicity[23]. Combined with other barriers such as availability of drugs and costs associated with a hospital visit, the low level of perceived severity may be a strong contributor to delaying care.

It was expected that travel time would be a strong barrier of access to medical care in the study population. However, among the participants who responded to the survey regarding their reasons for delaying treatment, a lack of funds stood out as the primary response. Yet, the regression analyses did not show a clear association between delaying treatment and self-reported affordability across the three sites. This may be due to a discrepancy in the participants' interpretation of affordability based on our survey and the intention of the survey question. Participants may have delayed seeking care at the time of malaria symptom onset because they did not have sufficient funds. However, at the time when they chose to seek treatment, they may have procured the necessary funds and thus, their perception of affordability would have shifted.

Furthermore, the travel time derived for this study, though an improvement upon measures using Euclidean distance, cannot account for the variety of factors that may influence a person's estimation of the travel time from their home to the nearest healthcare facility. These factors may include road conditions (which vary with the seasons), the ability to gather sufficient funds, preparing oneself or child for travel, and procuring transportation. These estimates, along with other self-reported variables were also susceptible to recall bias, as is the case with many survey-based studies. However, a diligent attempt was made to glean a representative sample of the area by using an appropriate sample size in each site and by randomizing the selection of participants from within the pre-defined areas.

Since surveys of the healthcare facilities indicated that the average cost of a malaria-related visit is between 112 and 165 KES (including the cost of medication), it is clear that is there is discordance in the original intention of the subsidization policy and its implementation.

While ACT at government-run facilities was meant to be provided for free to the patient, the frequent stock-outs led the facilities surveyed to refer patients elsewhere, including to private retailers, where the patients may face a greater likelihood of receiving a less effective anti-malarial. Private retailers are not always bound by the subsidization policy and charge for ACT at a higher rate than 40 KES[24]. The ubiquity of various anti-malarial drugs in the market combined with the high charges associated with a hospital or clinic visit may also serve to reduce a patient's perceived need for a full diagnostic workup. Accessibility is an important determinant of treatment-seeking behaviour and has implications for the continued transmission of malaria. Some of the variation in health-seeking behaviours between the three study sites may be attributed to the lack of paved roads in the area and the hilly terrain, neither of which are conducive to motor access (see Figure 1). Most of the participants did not live along major roads. The perceived benefits of receiving a proper malaria diagnosis from a healthcare facility may not be sufficient to outweigh the perceived cost of travel, in terms of both time and effort. Finally, there is a stark difference between the low number of healthcare facilities located in Emakakha and how many more are located in the other two study sites; there is one dispensary and one health centre located within the boundaries of Emakakha and another health centre that lies between the boundaries of Emakakha and Emutete. However, there are several retailers lining the major road that bisects the Emakakha study area, which may help explain why more than one third of the residents in the site reported a retailer as the nearest treatment facility.

As was observed in the study by Sumba *et al*, the participants' decision to seek treatment at a healthcare facility within 24 hours of fever onset was not significantly correlated with

their socioeconomic status, education level, or proximity to the facility[13]. The strongest determining factor of delay was the decision to choose to seek treatment at a pharmaceutical retailer rather than a medical facility. As such, the observed propensity of the pharmaceutical retailers as seen in other studies to sell medication without appropriate anti-malarial properties has serious negative implications for malaria control and the potential for the spread of artemisinin resistance[11,25]. A previous experience of being referred to a pharmaceutical retailer when the healthcare facility had depleted its ACT stock may also deter patients from making future visits to the healthcare facility; they may choose to go directly to the retailer, seeing it as a cheaper, faster, and quicker alternative. Future interventions must recognize and include retailers as key players in any control or elimination programme that is to be implemented.

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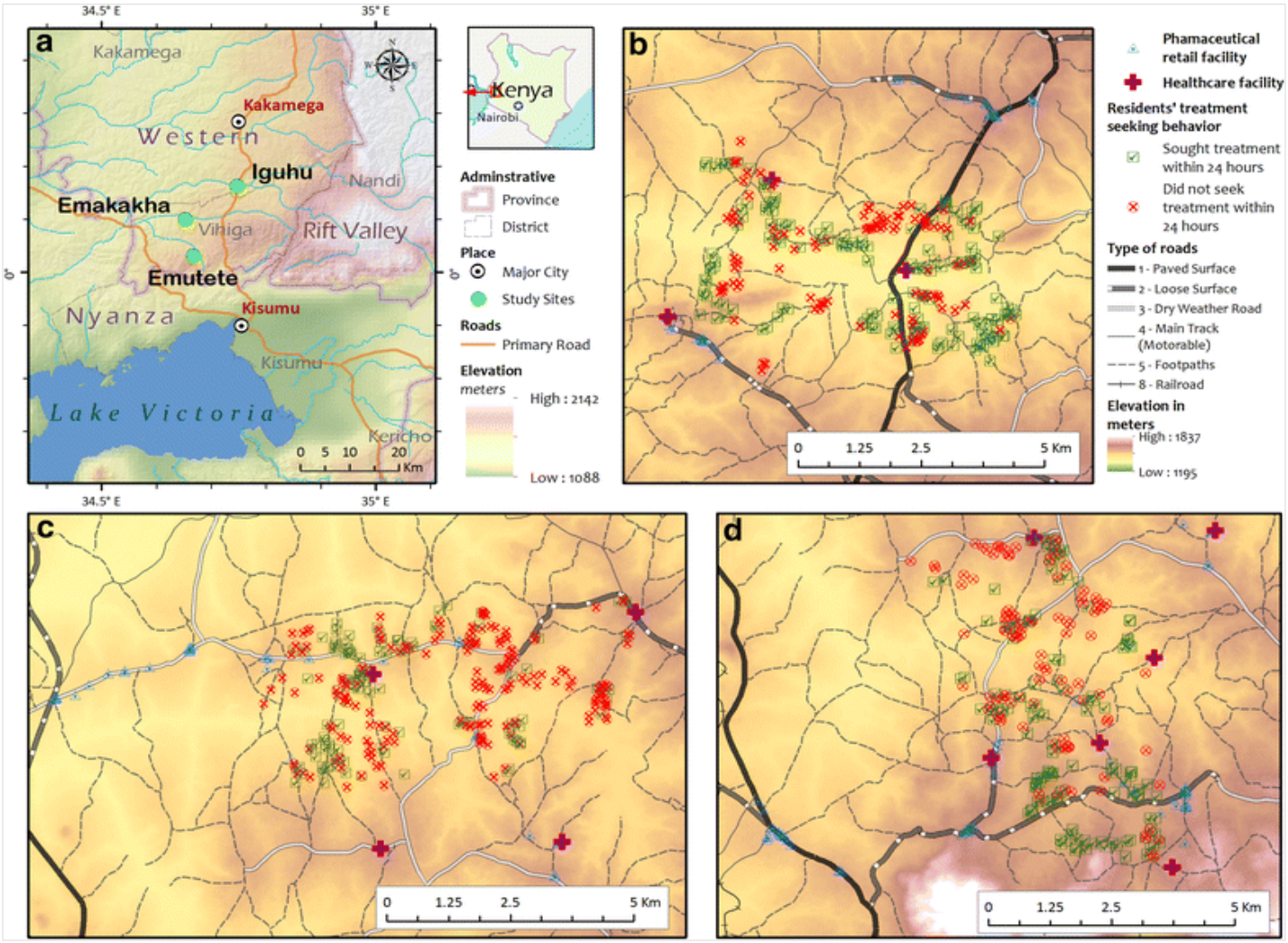

Figure 1A. Overview of all study sites. Location of study sites within Kenya. **Figure 1B, IC, ID. Iguhu, Emakakha, and Emutete study areas.** Each map focuses on the individual study area and shows the distribution of residents' healthcare seeking patterns. The individual study area's healthcare facilities and retail outlets are also shown along with its roads and access paths.

Table 1. Socioeconomic and demographic characteristics of study participants in western Kenya highlands

Variable	Emakakha (N= 303)	Emutete (N= 256)	Iguhu (N= 273)	*Total (N= 832)*
Demographic variables				
Primary income earner education				
Did not finish primary	42 (13.9%)	62 (24.2%)	75 (27.5%)	*179 (21.5%)*
Primary school	137 (45.2%)	114 (44.5%)	97 (35.5%)	*348 (41.8%)*
Secondary school and beyond	123 (40.6%)	79 (30.9%)	101 (37.0%)	*303 (36.4%)*
Missing	1 (0.3%)	1 (0.4%)	0	*2 (0.2%)*
Sex of primary income earner				
Male	236 (77.89%)	144 (55.9%)	196 (71.8%)	*576 (69.2%)*
Female	66 (21.8%)	107 (41.8%)	75 (27.5%)	*248 (29.8%)*
Both sexes	0	2 (0.8%)	2 (0.7%)	*4 (0.5%)*
Missing	1 (0.3%)	5 (3.5%)	0	*6 (0.7%)*
Socioeconomic indicators				
Possessions				
Ownership of both furniture and livestock	268 (88.4%)	238 (93.0%)	204 (74.7%)	*710 (85.3%)*
Ownership of furniture only	29 (9.5%)	15 (5.8%)	48 (17.5%)	*92 (11.1%)*
Ownership of livestock only	2 (0.7%)	3 (1.2%)	19 (7.0%)	*24 (2.9%)*
None	2 (0.7%)	0	0	*2 (0.2%)*
Missing	2 (0.7%)	0	2 (0.8%)	*4 (0.5%)*
Home construction				
Mud	276 (91.0%)	235 (91.8%)	253 (92.7%)	*764 (91.8%)*
Cement/Brick	22 (7.3%)	17 (6.6%)	17 (6.2%)	*56 (6.7%)*
Missing	5 (1.7%)	4 (1.6%)	3 (1.1%)	*12 (1.4%)*

Malaria status				
No malaria infection in family in past year	3 (1.0%)	0	4 (1.5%)	*7 (0.8%)*
At least one victim in family in past year	291 (96.0%)	205 (80.1%)	242(88.6%)	*738 (88.7%)*
Missing	9 (3.0%)	51 (19.9%)	27 (9.9%)	*87 (10.5%)*
Health-seeking behaviours				
Action taken upon suspicion of malaria				
Treatment sought at hospitals, clinics, and dispensaries exclusively	144 (47.5%)	202 (78.9%)	204 (74.7%)	*550 (66.1%)*
Treatment sought at pharmaceutical retail facilities exclusively	79 (26.1%)	16 (6.3%)	25 (9.2%)	*120 (14.4%)*
Treatment sought at traditional healers exclusively	1 (0.3%)	0	0	*1 (0.1%)*
No treatment facility preference indicated	42 (13.9%)	9 (3.5%)	25 (9.2%)	*76 (9.1%)*
No action taken	37 (12.2%)	24 (9.4%)	18 (6.6%)	*79 (9.5%)*
Missing	0	5 (1.9%)	1 (0.3%)	*6 (0.7%)*
Treatment seeking timeline				
Delay treatment for > 24 hours after fever onset	180 (59.4%)	117 (45.7%)	110 (40.3%)	*407 (48.9%)*
Seek treatment within 24 hours after fever onset	119 (39.3%)	135 (52.7%)	160 (58.6%)	*414 (49.8%)*
Missing	4 (1.3%)	4 (1.6%)	3 (1.1%)	*11 (1.3%)*
Medicine				
Artemisinin combination therapy (ACT) exclusively	172 (56.8%)	149 (58.2%)	147 (53.9%)	*468 (56.3%)*
Non- ACT exclusively: quinine, SP, Fansidar	46 (15.2%)	16 (6.3%)	25 (9.2%)	*87 (10.5%)*
Painkillers exclusively	10 (3.3%)	6 (2.3%)	2 (0.7%)	*18 (2.2%)*
Combination of ACTs, non-ACT, and painkillers	71 (23.4%)	80 (31.3%)	94 (34.4%)	*245 (29.4%)*
Missing	4 (1.3%)	5 (1.9%)	5 (1.8%)	*14 (1.7%)*

Facility where pharmaceutical treatment is purchased				
Hospitals, clinics, and dispensaries exclusively	153 (50.5%)	188 (73.4%)	174 (63.7%)	*515 (61.9%)*
Shopkeepers and chemists exclusively	110 (36.3%)	24 (9.4%)	56 (20.5%)	*190 (22.8%)*
No preference indicated	37 (12.2%)	41 (16.0%)	43 (15.8%)	*121 (14.5%)*
Missing	3 (1.0%)	3 (1.2%)	0	*6 (0.7%)*
Health access measures				
Self-reported nearest facility				
Hospitals, clinics, and dispensaries exclusively	180 (59.4%)	227 (88.7%)	243 (89.0%)	*650 (78.1%)*
Shopkeepers and chemists exclusively	109 (36.0%)	16 (6.2%)	25 (9.1%)	*150 (18.0%)*
Comparable distance to hospitals/clinics/dispensaries and pharmaceutical retail facilities	12 (3.9%)	12 (4.7%)	4 (1.5%)	*28 (3.4%)*
Missing	2 (0.7%)	1 (0.4%)	1 (0.4%)	*4 (0.5%)*
GIS-calculated nearest facility				
Health care center exclusively	93 (30.7%)	158 (61.7%)	248 (90.8%)	*499 (60.0%)*
Pharmaceutical retailer exclusively	209 (69.0%)	95 (37.1%)	17 (6.2%)	*321 (38.6%)*
Equidistant	1 (0.3%)	3 (1.2%)	8 (3.0%)	*12 (1.4%)*
Travel time				
Mean self-reported travel time to nearest facility	54.9 mins (95.4%)	55.1 mins (98.0%)	47.1 mins (96.0%)	*52.4 mins (96.5%)*
Missing	14 (4.6%)	5 (2.0%)	11 (4.0%)	*30 (3.6%)*
Average GIS-calculated travel time				
Health care center	32.5 mins	25.5 mins	27.6 mins	*85.6 (28.5%)*
Retailer	21.9 mins	27.0 mins	57.6 mins	*106.5 (35.5%)*
Method of travel				
Walk exclusively	260 (85.8%)	200 (78.1%)	240 (87.9%)	*700 (84.1%)*
Bicycle	30 (9.9%)	16 (6.2%)	10 (3.7%)	*56 (6.7%)*

Car or other motorized transport	8 (2.6%)	25 (9.8%)	10 (3.7%)	*43 (5.2%)*
Mix of walking, biking, and motorized transport	3 (1.0%)	12 (4.7%)	11 (4.0%)	*26 (3.1%)*
Missing	2 (0.7%)	3 (1.2%)	2 (0.7%)	*7 (0.8%)*
Reason for delay (if any)				
Do not delay	2 (0.7%)	0	1 (0.4%)	*3 (0.4%)*
Money	182 (60.0%)	98 (38.3%)	89 (32.6%)	*369 (44.4%)*
Distance	2 (0.7%)	2 (0.8%)	1 (0.4%)	*5 (0.6%)*
Expect improvement of condition	46 (15.2%)	50 (19.5%)	33 (12.1%)	*129 (15.5%)*
Transportation	1 (0.3%)	0	1 (0.4%)	*2 (0.2%)*
Mix	15 (4.9%)	1 (0.4%)	5 (2.1%)	*21 (2.5%)*
Other	0	0	1 (0.4%)	*1 (0.1%)*
Missing	55 (18.2%)	105 (41.0%)	142 (52.0%)	*302 (36.3%)*
Affordability of treament				
Found treatment unaffordable	43 (14.2%)	85 (33.2%)	99 (36.3%)	*227 (27.3%)*
Found treatment affordable	245 (80.8%)	169 (66.0%)	174 (63.7%)	*588 (70.7%)*
Missing	15 (5.0%)	2 (7.8%)	0	*17 (2.0%)*

Table 2. Summary of health care facility (hospitals, clinics, and dispensaries) surveyed.

Variable	**Public**	**Private**
Number of facilities surveyed	*11 (73.3%)*	*4 (26.7%)*
# of hospitals	3 (20.0%)	1 (6.7%)
# of health centres	5 (33.3%)	2 (13.3%)
# of dispensaries/clinics	3 (20.0%)	1 (6.7%)
***Hours of operation**:*		
9 hours or fewer	7 (46.6%)	4 (26.7%)
24 hours	4 (26.7%)	0
***Days of operation**:*		
5 days/ week	5 (33.3%)	1 (7.0%)
7 days/week	6 (40.0%)	3 (20.0%)
Median population served [range]	13,885 [1,310-164,951]	11,189 [2,683-20,000]
Staffing		
# of facilities with doctors [range]	2 (13.3%) [0-8]	1 (7.0%) [0-3]
Median number of clinical officers [range]	2 [0-18]	1.5 [0-4]
Median number of nurses [range]	8 [2-53]	7 [2-20]
Median number of microscopists [range]	2 [0-4]	2 [2-4]
Malaria		
Median # of microscopy confirmed cases in 3 mos. preceding survey [range]	222	189
Diagnostic method: Microscopy exclusively	5 (33.3%)	2 (13.3%)
Diagnostic method: Microscopy + RDT	3 (20.0%)	2 (13.3%)
Diagnostic method: Symptoms exclusively	3 (20.0%)	0
ACT stocking		
Facilities stocked with ACT at time of survey	11 (73.3%)	4 (26.7%)
Experienced shortage of ACT in 3 months preceding survey [range]	4 (26.7%)	2 (13.3%)
# of facilities that had to wait >24 hours before ACT was restocked	4 (26.7%)	2 (13.3%)
# of facilities that either substitute another anti-malarial or	5 (33.3%)	2 (13.3%)

refer patient to nearest retailer		
Charges [in Kenyan shillings]		
# of facilities that charged registration fees [average fee]	11 (73.3%) [19 KSH]	3 (20.0%) [55 KSH]
# of facilities that charged diagnosis fees [average fee]	8 (53.3%) [46 KSH]	4 (26.6%) [70 KSH]
# of facilities that charged other miscellaneous fees per patient per visit [average fee]	8 (53.3%) [26 KSH]	0
# of facilities that charged for medication [average fee]	1 (6.7%) [40 KSH]	3 (20.0%) [73 KSH]
Overall average costs per patient of health care facility visit (not including cost of medication) [range]	72 KSH [30 KSH- 90 KSH]	125 KSH [50 KSH-250 KSH]

Table 3: Bivariate analyses of risk factors for odds of delaying treatment >24 hours by study site.

Variable	***Emakakha OR [95% CI]***	***Emutete OR [95% CI]***	***Iguhu OR [95% CI]***
Lived in mud home	**4.21 [1.60, 11.04]**	3.02 [0.96, 9.52]	3.42 [0.95, 12.2]
Ref: Lives in cement/brick home	*1*	*1*	*1*
Owned either furniture or livestock or neither	0.77 [0.37, 1.60]	0.81 [0.30, 2.21]	0.79 [0.45, 1.41]
Ref: Owns both furniture and livestock	*1*	*1*	*1*
Wage head has a primary school education	0.98 [0.59, 1.63]	**1.89 [1.04, 3.42]**	1.03 [0.58, 1.83]
Wage head did not finish primary school	0.63 [0.31, 1.27]	1.65 [0.83, 3.26]	1.45 [0.79, 2.67]
Ref: Wage head finished secondary school or beyond	*1*	*1*	*1*
Female wage head of household	1.34 [0.76, 2.36]	1.63 [0.98, 2.72]	**3.41 [1.96, 5.94]**
Ref: Male wage head of household	*1*	*1*	*1*
Chose pharmaceutical retailers for treatment	**3.86 [2.36, 6.30]**	**2.79 [1.42, 5.50]**	**1.86 [1.06, 3.28]**
Ref: Chose healthcare facility for treatment	*1*	*1*	*1*
Self-reported nearest facility was a pharmaceutical retailer	**2.12 [1.30, 3.45]**	**5.05 [1.97, 12.93]**	***0.20 [0.07, 0.59]***
Ref: Self-reported nearest facility was a healthcare facility	*1*	*1*	*1*
Walked to facility when seeking treatment	1.11 [0.57, 2.18]	0.59 [0.32, 1.08]	2.24 [0.96, 5.21]
Ref: Took a car or other motorized transport to facility when seeking treatment	*1*	*1*	*1*
Found treatment to be unaffordable	**2.64 [1.31, 5.31]**	1.28 [0.76, 2.16]	***0.56 [0.33, 0.95]***
Did not find treatment to be	*1*	*1*	*1*

unaffordable			

(OR: odds ratio, CI: confidence interval; ***significant at α < 0.05****)*

Table 4: Multivariate (adjusted) model of relevant risk factors for odds of delaying treatment > 24 hours by study site.

Variables	***Emakakha OR [95% CI]***	***Emutete OR [95% CI]***	***Iguhu OR [95% CI]***
Lived in mud home	**8.32 [2.58, 26.90]**	2.75 [0.78, 9.74]	2.39 [0.60, 9.61]
Ref: Lives in cement/brick home	*1*	*1*	*1*
Owned either furniture or livestock or neither	0.98 [0.42, 2.27]	0.88 [0.31, 2.55]	0.65 [0.34, 1.26]
Ref: Owns both furniture and livestock	*1*	*1*	*1*
Wage head has a primary school education	0.82 [0.46, 1.47]	1.60 [0.82, 3.14]	0.94 [0.49, 1.79]
Wage head did not finish primary school	0.45 [0.20, 1.03]	1.46 [0.67, 3.21]	0.99 [0.49, 1.99]
Ref: Wage head finished secondary school or beyond	*1*	*1*	*1*
Female wage head of household	1.29 [0.68, 2.45]	1.69 [0.96, 3.0]	**3.13 [1.72, 5.69]**
Ref: Male wage head of household	*1*	*1*	*1*
Chose pharmaceutical retailers for treatment	**4.07 [2.31,7.21]**	**2.21 [1.07, 4.61]**	**2.60 [1.35, 4.99]**
Ref: Chose healthcare facility for treatment	*1*	*1*	*1*
Self-reported nearest treatment facility is pharmaceutical retailer	1.37 [0.76, 2.49]	**4.23 [1.55, 11.53]**	***0.15 [0.04, 0.48]***
Ref: Self-reported nearest facility was a healthcare facility	*1*	*1*	*1*
Walked to facility when seeking treatment	1.10 [0.5, 2.42]	***0.48 [0.24, 0.95]***	1.91 [0.76, 4.81]
Ref: Took a car or other motorized transport to facility when seeking treatment	1	1	1

Found treatment to be unaffordable	**5.36 [2.24, 12.81]**	1.15 [0.64, 2.06]	0.59 [0.33, 1.06]
Did not find treatment to be unaffordable	*1*	*1*	*1*

(OR: odds ratio, CI: confidence interval; ***significant at α < 0.05****)*

Chapter 2

Exploring the effects of human movement on malaria epidemiology: modeling the impact on elimination strategies

Abstract

Human movement across porous borders has been connected with perpetuating the transmission of malaria. It has been suggested that it is this type of movement along its shared border with Myanmar that has contributed to keeping Thailand from reaching its goal of eliminating malaria from the country. The objective of this study is to describe the patterns of movement and to use them to determine the impact of human movement between these areas of unequal malaria transmission on malaria epidemiology and elimination strategies.

The study used an integrative approach that involved the incorporation of mathematical modelling strategies with empirical field data collected from 599 individuals across four villages and one hospital. The survey results show that in the villages along the border, the majority ethnic Karen peoples retain deep ties to their communities in Myanmar with between 48.7% and 89.9% of them frequently crossing the border for various reasons. The results suggest that the beneficial impact of a bednet intervention would be sensitive to the size of the population in which it is deployed as well as to the migration rates between countries. The model results also indicate that such an intervention can elicit an indirect beneficial effect of reducing prevalence in Myanmar even when it is only deployed in Thailand. This suggests that such an intervention could be highly cost-effective in terms of cases averted per dollar spent. Following more rigorous testing of these scenarios, it would be worth conducting a field test to validate the model results.

Introduction

In order to improve our understanding of malaria dynamics in the Greater Mekong Subregion, a critical evaluation of the contribution of human movement to the perpetuation of the disease is warranted[1]. The phenomenon of human movement has long been suspected to affect the success of elimination strategies in malaria-endemic countries[2-5]. Efforts toward malaria elimination consist of intervention strategies that include, but are not limited to: vector control, early diagnosis and treatment, and bednet distribution[6]. Over the past several decades, Thailand has made significant strides towards achieving malaria elimination[7-10]. However, in spite of its concerted efforts, patches of transmission remain, lying predominantly along the border shared with Myanmar[11]. The objective of this study is to describe the patterns of migration and to determine the impact of human movement between these areas of unequal malaria transmission on malaria epidemiology and elimination strategies using an integrative approach, incorporating mathematical modelling strategies with empirical field data.

It has been shown by Adams *et al* that hubs and reservoirs of infection can be places visited frequently and are highly dependent on the distribution of mosquito populations and variability in human travel patterns[4]. Emerging evidence points to the central role of movement in the perpetuation of resistant malaria and the undermining of successful interruption of transmission[12]. The number of infected travelers entering an area in a given time period indicates the vulnerability borne by an area and the high vulnerability exhibited by labor migrants, suggests that a “transborder” approach to elimination would have higher efficacy[2,13]. The border regions between Thailand and Myanmar were chosen because these are usually the regions of countries where policies, currencies, and

capabilities become more fluid, leading to situations where the needs of the citizens can fall through the cracks, creating the ideal environment for disease transmission[14].

The largely unmonitored flow of humans between Myanmar, which is still in the control stage, into Thailand, which has reached the pre-elimination stage, can be understood to have deleterious effects on Thailand's progress towards elimination[15]. However, the effect of this flow on Thai elimination strategies is as yet undetermined. This study will aim to shed light on the human movement patterns within a relatively understudied area and attempt to model potentially disruptive scenarios that can help guide policies focused on malaria elimination.

Ethical considerations

The surveys were approved by the institutional review boards at UC Irvine in the US and Mahidol University in Thailand.

Methods

The study area containing the sentinel sites is based in Tak Province in western Thailand (Figure 1), which borders the Karen State in Myanmar. The border between Tak Province in Thailand and Myanmar is over 500 km long, encompassing several districts on the Thai side. The study area is situated in Tha Song Yang district, which experiences a tropical climate with a 6-mo rainy season spanning from May to early October[16,17]. Mean annual rainfall varies between 1,400 mm and 2,300 mm across the district; the mean annual temperature ranges between 20°C and 29°C. The population in the area consists of Thai

citizens, foreign nationals (including migrant workers), and refugees residing in camps as well as in certain villages[17].

Surveillance is conducted for both active and passive malaria cases in Thailand where a cross-sectional survey of households in the community is conducted twice a year during the high and low transmission seasons to detect asymptomatic infections. Bednets are widely distributed in the area and free treatment is available for those with confirmed malaria infections. The surveys were conducted between June and July of 2014 and during the course of that year, there were 1,193 confirmed malaria cases reported by the Thai sentinel sites. However, due to a lack of consistent and timely reporting by all affiliated institutions, it is expected that the reported numbers of malaria cases underrepresent the actual prevalence of the disease in the area.

Survey Methodology

Surveys to determine migration patterns were conducted in four border villages and a district hospital in Thailand. Each survey respondent gave their full consent before being questioned. The households and patients were surveyed using a weighted sample size approach with a randomized selection method. Each survey was orally administered in the language of the respondent's preference (either in Karen or in Thai). The surveys were designed to gather data on a number of demographic and socioeconomic variables and solicited responses that would best elucidate the movement patterns that are most commonly used in the regions of interest. Participants were asked to recall details of their most recent malaria infection episode as well as the particulars of their most recent trip across the border, if applicable. The surveys included questions on: use of malaria

prophylaxis, frequency of travel, duration of trip, and the purpose of cross-border travel. Responses were initially separated by type of location in which the survey was administered (hospital or village). Responses from the villages were further pooled based on geographic, demographic, and socioeconomic similarity between adjacent villages. Hence, survey results have been presented in three categories: hospital, northern villages, and southern villages.

Model Parameterization

The data collected from the survey was used to inform the parameter settings for the Epidemiological MODeling (EMOD v. 2.8) provided by the Institute for Disease Modeling; EMOD is an agent-based mechanistic model of malaria transmission[18]. The specific equations, time-steps, parameter fits, and parameter estimates not specific to the current study are described elsewhere[18-21]. The climate data required for the model included precipitation, temperature, and relative humidity. These data were acquired from the IDM's COMputational Platform Service (COMPS) database which provides the spatial interpolation of the historical meteorological observations of World Meteorological Organization identified weather stations from National Oceanic and Atmospheric Administration's National Centers for Environmental Information[22].

With the use of this software, we have created a multi-node simulation to further examine the effect of migration between adjacent areas. The nodes were created using climate, vector, and geographical settings specific to the study sites in Thailand. The surveys administered in each of the sites, combined with previous work in the area, informed the

parameter settings that pertained to human populations and the migration parameters (Table 1 and 2).

Two types of movement were set within the model: local and regional. Local migration rates were also included in the model settings to represent movement between adjacent villages on the same side of the border from each other; these rates were kept constant throughout all simulations (Table 2). The regional migration rates were determined by dividing the reported number of cross-border trips per day by the pooled sample populations of the villages or hospital surveyed. The survey-derived rate was set as the current regional migration rate for each set of nodes and is represented in the model as the proportion of the population who cross the border per day. It was multiplied by four to represent the possibility of more open borders between Myanmar and Thailand. A virtual closure of the border was also represented with the same regional migration rate being applied to all the nodes for all cross-border travel; in this scenario, the regional migration rate was reduced to 1 person per 1000 people. In addition, the model included within-country regional migration rates between large population centers on the same side of the border that were outside of walking distance from each other.

A conceptual model of the scenarios is outlined in Figure 2. The conceptual model also includes an additional pair of nodes (Tha Song Yang and Tha Song Yang_Myanmar) that are situated to the north of the villages of Suan Oi and Suan Oi_Myanmar. While Tha Song Yang was not surveyed during the study period, it and its Myanmese counterpart was utilized in the model to represent the reservoirs of infection that often reside in larger populations and thus, the results of the model output for Tha Song Yang are not included in every relevant set of figures.

For each modeling scenario, a burn-in period of three years was applied to ensure the steady-state dynamics could be observed within the simulation. Thus, the nodes on the Thai side of the border receive an intervention of a bednet at Day 1095 of the simulation. The killing rates per indoor resting post-feed encounter (KR) for the bednets were simulated at 70% KR and at 10% KR in order to mimic the current efficacy as well as potential effects of insecticide resistance. Demographic coverage of the bednets was set at 50% so that usage, as well as ownership could be taken into account within the model. The change in disease prevalence is shown for the duration of 360 days, starting 105 days after the application of a bednet intervention. Since the same regional migration rate was applied to the two northern villages and their Myanmese counterparts, their model output is shown together in Figure 3. The two southern villages also shared migration rates and thus, their model results are shown together with their corresponding villages in Myanmar in Figure 4. Figure 5 shows the region containing the hospital in Thailand as well as the corresponding region across the border, in Myanmar.

Data Analysis

A total of 398 households in four villages and 201 hospital patients participated in the study. All survey responses were entered into MS Excel 2010 and the aggregated data on important variables are presented in Table 2. Statistical analyses were conducted in R 3.2.0 while the model output was converted from a binary format to CSV files and subsequently transferred to MS Excel 2010 in order to generate the figures.

Results

Survey Results

In total, 599 surveys were administered between the four Thai villages and the hospital. The respondents were mostly ethnic Karen, female, had a primary school education or less, and tended to work outdoors (Table 2). More than 88% of all respondents reported owning bednets in their homes. The malaria rates varied between the sites with only 1.7% of the southern villagers versus 19.8% of the northern villagers reporting a malaria infection in the past year.

Though the study participants shared similar demographic characteristics across all sites, the migration patterns from area to area varied. All of the sites had significantly different proportions of cross-border travelers ($\chi 2$ test, p-value <0.001). The highest proportion of cross-border travelers was seen in the southern villages (89.9%). The most common methods of crossing the border were walking and using a boat. The average duration of the visit across the border was used as an indicator of exposure to malaria infection. Between 42.6% and 59.7% of all respondents returned home within 24 hours. Tourism and shopping were the most commonly listed reasons for crossing to Myanmar, followed by professional or family reasons. At the Thai hospital, 9.6% of the respondents who reported crossing the border to seek care at the hospital during the survey period were Myanmese patients who were surveyed in Thailand. More than 92% of all respondents stated that they crossed the border with their family or friends.

Model Results

The model ran cross-sweeps on the migration parameters along with the intervention efficacy on all five pairs of nodes representing the study sites as well as the pair of nodes that represented a population reservoir in each country. The disease prevalence in each node pairing for three different migration rates (1X, 4X, and no migration) and two different bednet efficacies (10% KR and 70% KR) are shown in Figures 3-5. The absolute differences in disease prevalence for the time period shown in those figures are listed out in Table 4.

Figure 3A and 4A are a representation of the current situation. With bednets at 70% KR distributed to the Thai nodes, the results show that under the current, survey-based regional migration rates, the prevalence on both sides of the border decreases approximately 50% on both sides, with the Myanmese side of the border showing slightly higher overall prevalence than the villages on the Thai side (Table 4). Figure 5A shows the current situation in the region of the Thai hospital which is located in the town of Mae Tan. Here, the difference in prevalence approximately 15 months after the bednet intervention is 58.4% on the Thai side and 24.1% on the Myanmese side. Figures 3B and 4B show that if bednet efficacies were to drop to 10% KR under current migration rates, the prevalence in Thailand would drop between 25.8% and 27.7% in the northern Thai villages and approximately 22% in their Myanmese counterparts. In Figure 5B, the reduction in prevalence on the Myanmese side is roughly half what is experienced on the Thai side (18.9% in MT_M versus 37.4% in MT).

Figures 3, 4, and 5C & D show a situation in which there is four times as much cross-border movement than was determined from the survey. In Figure 3, 4, and 5C, all the villages on

both sides of the border experience, on average, a 51% decrease in disease prevalence, with the lowest reduction seen in MT_M (46.1%) and the highest seen in MSN_M (55.8%). In Figure 3D, the northern villages on both sides of the border see an approximately 30% reduction in prevalence over the course of one year. In Figure 4D, the southern villages experience a slightly higher reduction (an average of 36% across all four nodes). The hospital region indicated in Figure 5D experiences a reduction of 33.9% on the Thai side but only a reduction of 25.1% on the Myanmese side of the border.

In Figs 3, 4 and 5E, the virtual elimination of cross-border migration, combined with an efficacious bednet intervention in Thailand, brings the prevalence down 59% to 66% in the Thai regions. However, the largest reduction in prevalence on the Myanmese side of the border is seen in TO_M (38.5%) and the smallest is in SO_M (11.5%). Figure 3, 4, and 5F describe a situation in which there is virtually no cross-border migration and the bednet intervention is not very effective. The northern villages, seen in Figure 3F, indicate a vast discrepancy in how the intervention affects the prevalence over a year. MSN_M shows a difference of 30.7% in prevalence, with a last known prevalence rate of 39.6%. This is higher than the last known prevalence rate in MSN of 55.5%, reflecting a 23.3% difference since the start of the year. The village of SO, however, experienced a 51% decrease in prevalence whereas SO_M only saw a 6.4% decrease. In Figure 4F, while the absolute reduction in prevalence is very similar, if not identical, across both sets of villages in the south (27.4% in TO & TO_M, 29.1% in NB, and 29.7% in NB_M), the overall prevalence on the Thai side of the border is still higher than on the Myanmese side of the border.

Discussion

In spite of the recent reduction in malaria transmission in regions with the highest disease burdens, Thailand has yet to reach the elimination stage of malaria control[23]. In the face of growing political and economic turmoil and the emergence of drug resistance in malaria parasites, an improvement in the understanding of human movement patterns in the Greater Mekong Subregion along porous borders is needed to inform intervention policy and generate change. The results of this study shed light on the movement patterns and their resulting impact on elimination strategies along the border region between Thailand and Myanmar.

The survey indicated that most of the residents of these border regions were ethnic Karen who migrated to Thailand in previous years and have assumed permanent residences. The high proportion of cross-border travelers as well as the most common purposes listed for travel, suggest that in spite of now living in Thailand, the residents of these regions retain deep ties to their community across the border. The frequency with which they cross, their relatively short durations of stay, and the ease of crossing demonstrated by the availability of walking points and boats (especially in the southern villages), all confirm that this particular region of the border is highly susceptible to unofficial and unrecorded movement. This reiterates the need for a pragmatic approach to elimination strategies whose efficacies are not dependent on being administered to more stationary populations.

One of the underlying objectives of this study was to determine malaria acquisition risk for travelers in this region. However, the low number of reported malaria cases in all the sites made it difficult to assert significant association between this type of movement and malaria infection in this region with any degree of significance (Appendix C). Baum *et al*

have shown that up to 92% of the infections seen in this area are submicroscopic and asymptomatic[23]. Recent studies have also highlighted the strength of the contribution of asymptomatic carriers as transmission reservoirs and of submicroscopic malaria on disease transmission[24,25]. In order to be able to determine association between travel and malaria infection with confidence, a more rigorous diagnostic approach would need to be deployed along with survey mechanisms.

The survey results indicate that modelling the current scenario as well as potentially disruptive scenarios, is a valuable exercise in determining the best approach with regards to more efficacious elimination strategies. Though the situation in the field is inherently complex, the model is designed in a way that allows the user to simplify the situation and focus on certain parameters of interest. Since bednets are the most commonly deployed intervention, the model was used to display the trends in disease prevalence that could be expected if mosquitoes were to develop resistance to the insecticides commonly used to treat the nets. What we saw in the results for the northern and the southern villages was that reduced bednet efficacy seemed to have a noticeable impact when the cross-border migration rates were low. While panels A- E of Figures 3 and 4 all followed the general pattern of having higher prevalence on the non-intervention (Myanmar) side of the border, Figures 3F showed a higher prevalence in MSN rather than MSN_M. Figure 4F showed a higher prevalence in both NB and TO rather than in TO_M and NB_M.

We believe that this is due to three different factors that should be considered when interpreting these results. One, the population of the village is crucial to the sensitivity of the impact of migration (Table 1). Two, the village's proximity to a population center will contribute to and will be impacted by the within-country movement it experiences to and

from that population center during the simulation (Figure 2). Finally, the population ratio of the village on the intervention side as compared to its counterpart on the non-intervention side will also dictate the extent of the decrease observed in the prevalence rate.

It is also interesting to note that in the face of a 400% increase in migration between countries, the disease prevalence begins to converge between the Thai villages and their Myanmese counterparts. The intervention continues to decrease the prevalence on both sides, as it did under current migration rates. However, with many more people crossing the border every day, the impact of the intervention is felt more deeply even in the non-intervention areas. The decrease in prevalence may be occurring because the bednet intervention is designed to kill mosquitoes at a specific but exponentially decaying rate after contact is made with the insect. This may result in fewer vectors being capable of transmitting malaria in the region and would also explain why the intervention has an indirect effect of at least marginally reducing prevalence in Myanmar regardless of the migration rate or bednet efficacy. More likely, however, the increased travel between countries may mean that more people are exposed to a protective intervention more frequently and this may reduce the transmission that could be occurring due to asymptomatic carriers or those who were infected with submicroscopic infections.

Finally, we see that regardless of the scenario, the prevalence in the Thai region containing the hospital, MT, does not overlap the prevalence see in its Myanmese counterpart. We posit that part of this has to do with combination of the region's relatively large population as compared to its relatively low current regional migration rate, which keeps the two

populations largely separated. However, it is a promising sign that the indirect effect of the intervention in Thailand can still be seen to a small extent on the Myanmese side.

This work is exploratory in nature and thus has a number of limitations. The malaria dynamics within the model have been validated by previous work[26-28]. However, each new set of variables, including a new geography and a new climate, can introduce more uncertainty into the model output. The issue of uncertainty can and will be addressed in later work which will focus on running multiple simulations with different random seeds of the same scenario so that we can obtain simulation intervals and relay our results with a degree of confidence. Calibrating the model so as to reflect the situation in the field as accurately as possible has also proven to be a challenge. The surveys that were administered in Thailand were also administered in China and Myanmar along their shared border region (Appendix D). However, the difficulty of calibrating the vector population in those countries prevented us from successfully developing a reasonable model of transmission in that region in time.

Barring calibration difficulties, employing a modelling approach to evaluate potential elimination strategies is very valuable in this region. Deploying effective intervention strategies in areas with border region embroiled in political or economic turmoil can be very labor intensive, especially along resource-deficient areas that harbor patches of transmission[8,11]. This exploratory analysis can help to guide the direction of development of new elimination strategies by informing stakeholders of the frequency of cross-border movement and the importance of continuing with interventions even when prevalence is low. Especially in regions with low and inconsistent malaria transmission, there are

generally insufficient resources to conduct the early diagnosis and treatment programs that can help target asymptomatic or submicroscopic malaria cases.

The results of the model can help us determine the appropriate interventions that can help reduce transmission through other means. Furthermore, the exploration of modeling scenarios can help determine optimal intervention deployment strategies. In the case of this work, it appears that bednets appear to have indirect effects on the non-intervention area as well, suggesting that this intervention would be highly cost-effective in terms of cases averted per dollar spent. Following more rigorous testing of these scenarios, it would be worth conducting a field test to validate the model results. The current intervention strategy of bednet distribution may be one of the more potent strategies to deploy in this area because it can help kill the vectors that would freely cross the border even when humans are immobile. Additional vector control interventions such as indoor residual sprays and larviciding should also be considered if the interventions are to have a significant and longer-term effect.

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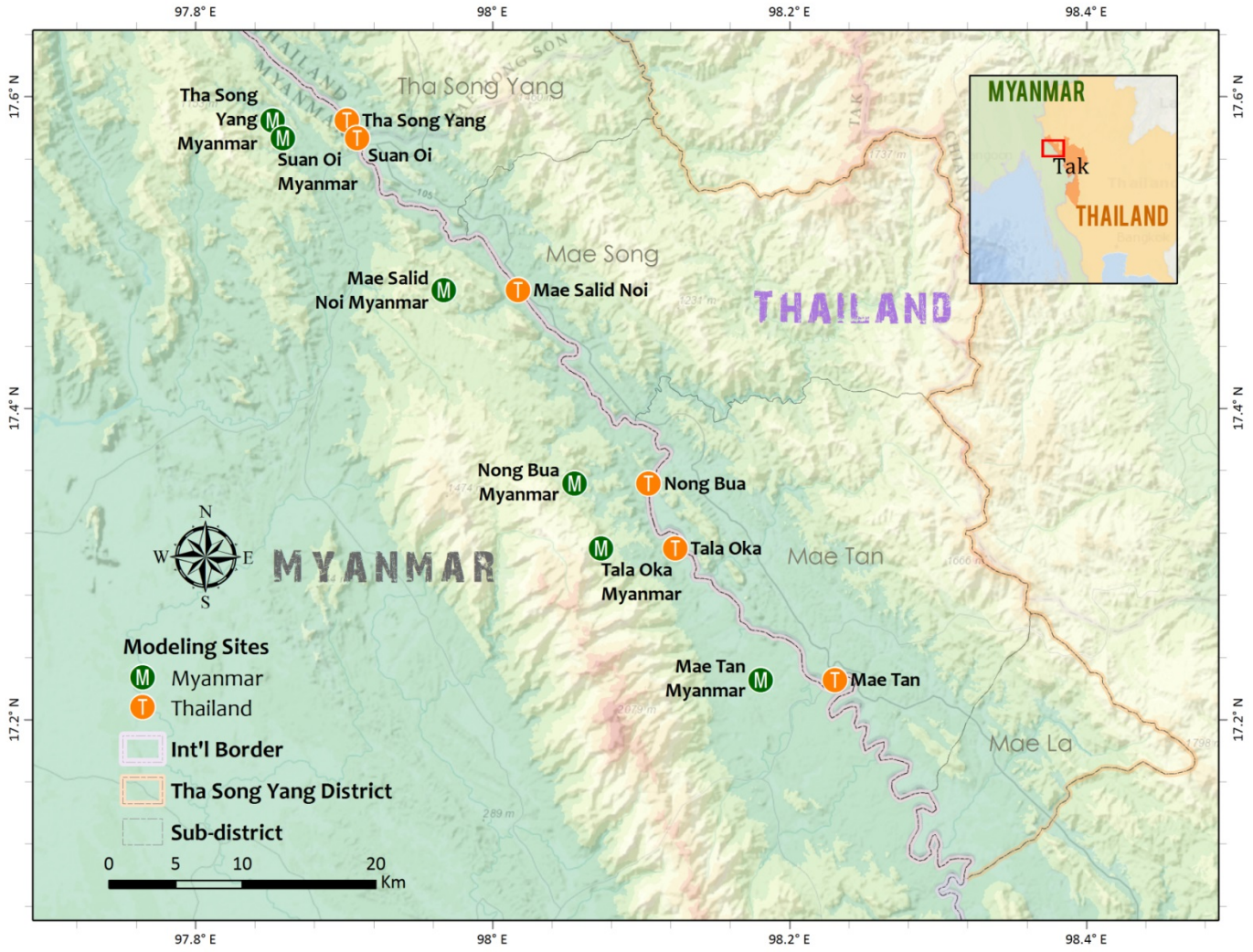

Figure 1: Modelling and survey sites in the border region between Thailand and Myanmar.

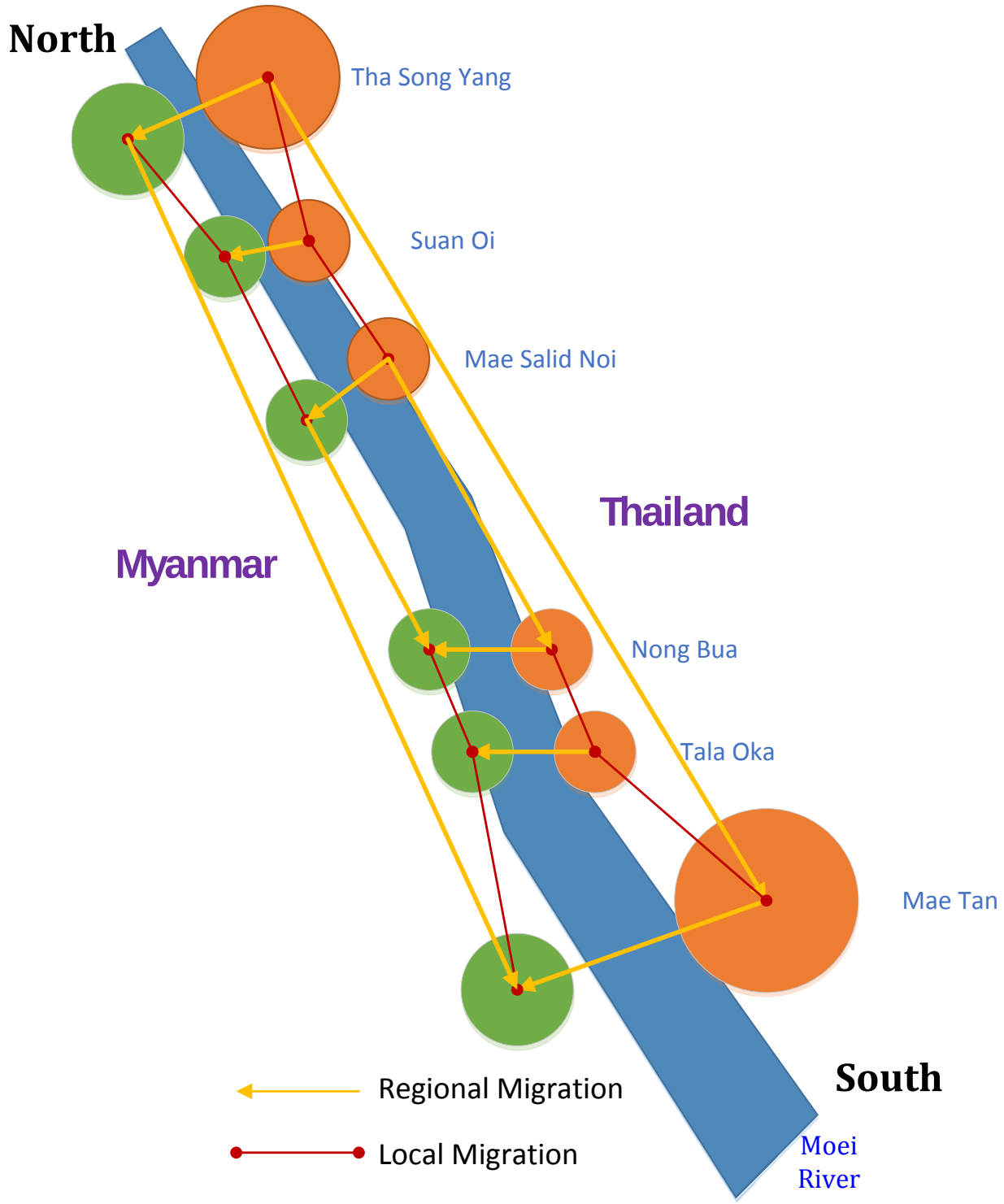

Figure 2: Conceptual rendering of the Thailand-Myanmar study sites within the EMOD model.

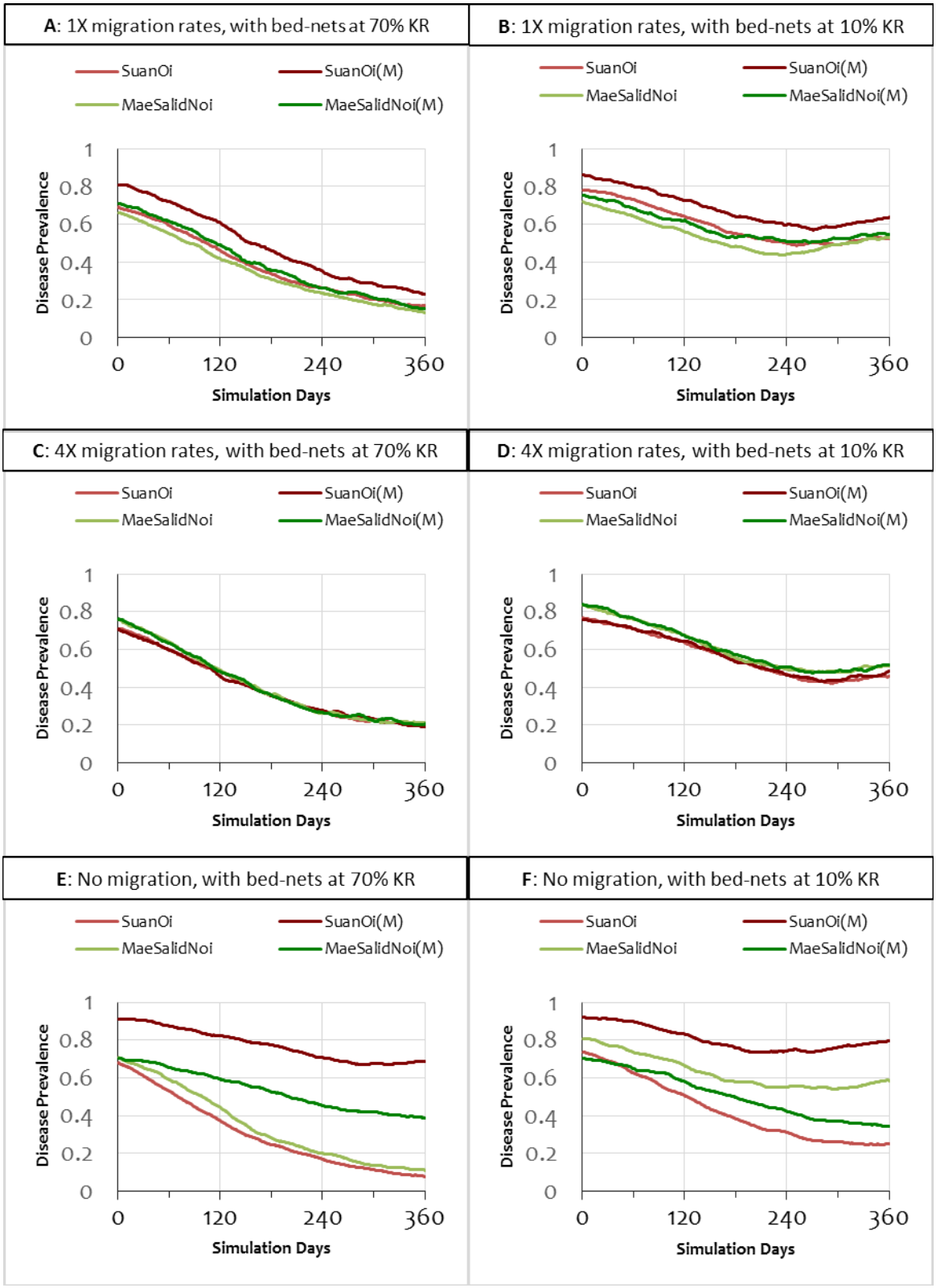

Figure 3: Disease prevalence for a year in the northern Thai villages and their Myanmese counterpart areas beginning 105 days post-bednet intervention applied on the Thai side of the border only.

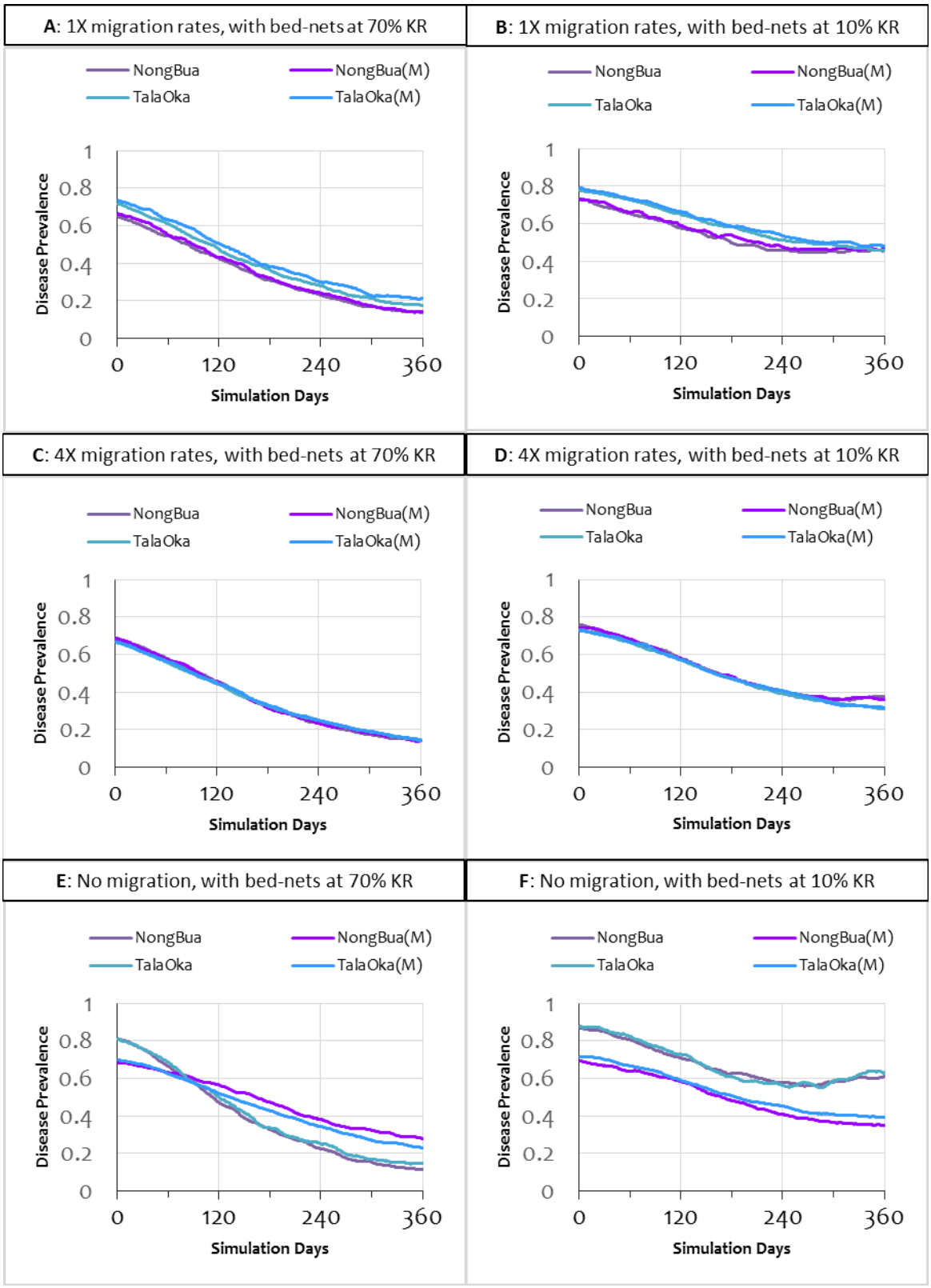

Figure 4: Disease prevalence for a year in the southern Thai villages and their Myanmese counterparts areas beginning 105 days post-bednet intervention applied on the Thai side of the border only.

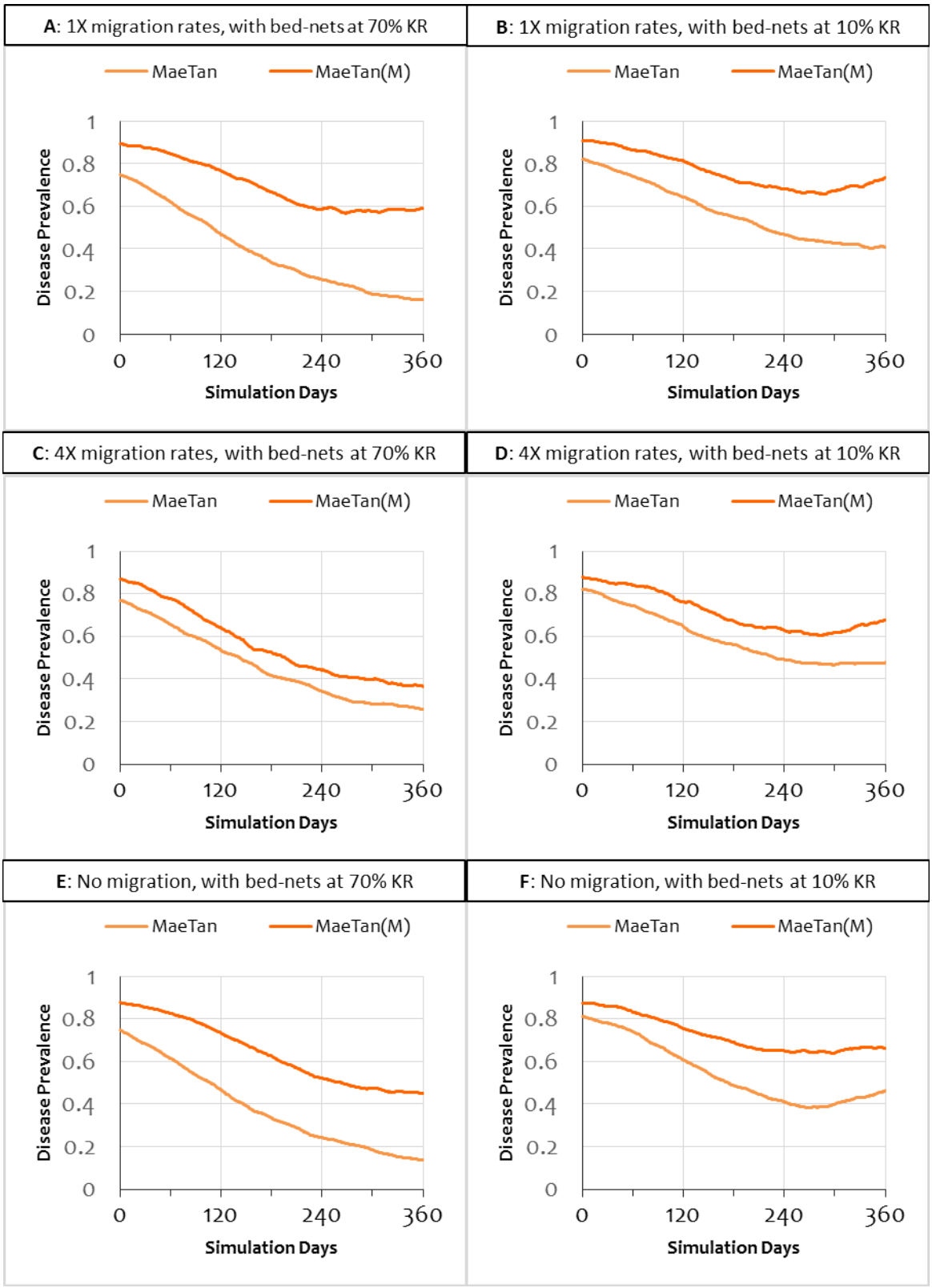

Figure 5: Disease prevalence for a year in the Thai hospital region and its Myanmese counterpart area beginning 105 days post-bednet intervention applied on the Thai side of the border only.

Table 1: Legend of study sites and corresponding population settings used in the model

Node Name	**Village Name/Country**	**Population**
TSY	Tha Song Yang/Thailand	3000
TSY_M	Corresponding village/Myanmar	1500
SO	Suan Oi/Thailand	800
SO_M	Corresponding village /Myanmar	800
MSN	Mae Salid Noi/Thailand	1000
MSN_M	Corresponding village /Myanmar	1000
TO	Tala Oka/Thailand	1000
TO_M	Corresponding village/Myanmar	800
NB	Nong Bua/Thailand	2500
NB_M	Corresponding village/Myanmar	1000
MT	Mae Tan/Thailand	5000
MT_M	Corresponding village/Myanmar	1500

Table 2: Listing of all rates used in EMOD settings for the migration parameters (rate is shown as proportion of population travelling per day).

Origin	Destination	Local Migration Rate	Regional Migration Rate: 1X	Regional Migration Rate: 4X	Regional Migration Rate: Negligible Migration
TSY	SO	0.1			
TSY_M	SO_M	0.1			
SO	TSY	0.1			
SO	MSN	0.02			
SO_M	TSY_M	0.1			
SO_M	MSN_M	0.02			
NB	TO	0.1			
NB_M	TO_M	0.1			
TO	NB	0.1			
TO	MT	0.05			
TO_M	NB_M	0.1			
TO_M	MT_M	0.05			
MT	TO	0.05			
MT_M	TO_M	0.05			
TSY	TSY_M		0.036	0.144	0.001
TSY	MT		0.02	0.02	0.02
TSY_M	TSY		0.072	0.288	0.001
TSY_M	MT_M		0.02	0.02	0.02
SO	SO_M		0.036	0.144	0.001
SO_M	SO		0.076	0.304	0.001
MSN	MSN_M		0.036	0.144	0.001
MSN	NB		0.05	0.05	0.05
MSN_M	MSN		0.076	0.304	0.001
MSN_M	NB_M		0.05	0.05	0.05
NB	NB_M		0.108	0.432	0.001
NB	MSN		0.05	0.05	0.05
NB_M	NB		0.216	0.864	0.001
NB_M	MSN_M		0.05	0.05	0.05
TO	TO_M		0.108	0.432	0.001
TO_M	TO		0.216	0.864	0.001
MT	MT_M		0.006	0.024	0.001
MT	TSY		0.02	0.02	0.02
MT_M	MT		0.012	0.048	0.001
MT_M	TSY_M		0.02	0.02	0.02

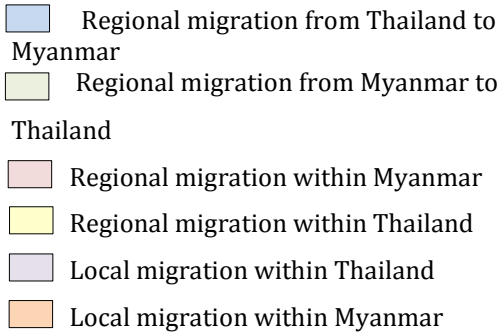

Table 3: Demographic and migration characteristics of study participants across sentinel sites in Thailand.

	Thailand northern villages (n=111)	**Thailand southern villages** (n=287)	**Thailand Tha Song Yang Hospital** (n=201)
Demographic variables			
Ethnicity			
Thai	0	0	139
Karen	111	287	57
Missing	0	0	4
Sex			
Male	43 (38.7%)	124 (43.2%)	89 (44.3%)
Female	67 (60.4%)	162 (56.4%)	111 (55.2%)
Missing	1 (0.9%)	1 (0.4%)	1 (0.5%)
Occupation of respondent			
Outdoor worker (e.g., farmer, plantation worker, day laborer, etc.)	59 (53.1%)	231 (80.5%)	139 (69.1%)
Indoor worker (e.g., factory worker, teacher, housewife)	51 (46.0%)	56 (19.5%)	62 (30.9%)
Unspecified or missing	1 (0.9%)	0	0
Highest education level completed			
Did not finish primary	83 (74.8%)	190 (66.2%)	116 (57.7%)
Primary school	21 (18.9%)	54 (18.8%)	39 (19.4%)
Secondary school and beyond	7 (6.3%)	39 (13.6%)	44 (21.9%)
Unspecified or missing	0	4 (1.4%)	2 (1.0%)
Type of mosquito control used in the past month			
None	6 (5.4%)	10 (3.4%)	17 (8.5%)
Bednet	98 (88.3%)	272 (94.8%)	183 (91.0%)
Repellent	0	1 (0.4%)	0
Multiple methods	7 (6.3%)	2 (0.7%)	0
Missing	0	2 (0.7%)	1 (0.5%)
Did you have a malaria infection in the past year?			
Yes	22 (19.8%)	5 (1.7%)	34 (16.9%)
No	84 (75.7%)	282 (98.3%)	153 (76.1%)
Missing	5 (4.5%)	0	14 (7.0%)

Migration variables			
Have you ever crossed the border for any reason?			
Yes	54 (48.7%)	258 (89.9%)	52 (25.8%)
No	57 (51.3%)	27 (9.4%)	144 (71.6%)
Missing	0	2 (0.7%)	4 (2.0%)
The following variables were recorded as a percentage of all travelers	(N=54)	(N=258)	(N=52)
Method of crossing the border			
Walk	2 (3.7%)	37 (14.3%)	5 (9.6%)
Motorized public transport	2 (3.7%)	4 (1.6%)	4 (7.7%)
Boat	5 (9.3%)	136 (52.7%)	7 (13.5%)
Motorized private transport	0	1 (0.4%)	0
Swim	0	2 (0.8%)	0
Multiple	45 (83.3%)	78 (30.2%)	27 (51.9%)
Missing	0	0	9 (17.3%)
Average duration of visit			
≤24 hours	23 (42.6%)	154 (59.7%)	24 (46.2%)
>24 hours	23 (42.6%)	50 (19.4%)	26 (50.0%)
Missing	8 (14.8%)	54 (20.9%)	2 (3.8%)
Purpose of visit			
Job	18 (33.4%)	91 (35.3%)	9 (17.3%)
Visit family	11 (20.4%)	33 (12.8%)	11 (21.2%)
To receive medical care	1 (1.8%)	0	5 (9.6%)
For tourism or shopping	23 (42.6%)	134 (51.9%)	21 (40.4%)
Multiple reasons	0	0	1 (1.9%)
Unspecified or missing	1 (1.8%)	0	5 (9.6%)
Do you cross the border with friends or family?			
Yes	50 (92.6%)	246 (95.4%)	49 (94.2%)
No	4 (7.4%)	12 (4.6%)	3 (5.8%)
Missing	0	0	0
Total number of trips by season (per 4 months)			
Monsoon	624	4136	148
Winter	512	3769	132
Summer	380	3416.5	158

Table 4: Absolute difference in prevalence in each node over the course of 1 year, starting 105 days after the application of a bednet intervention.

Scenario	Suan Oi (M)	Suan Oi	Mae Salid Noi (M)	Mae Salid Noi	Tala Oka (M)	Tala Oka	Nong Bua (M)	Nong Bua	Mae Tan (M)	Mae Tan
1X mig, 70%KR	49.2%	51.1%	49.8%	51.1%	47.0%	51.5%	50.6%	51.3%	27.1%	58.4%
1X mig, 10%KR	22.2%	25.8%	22.1%	27.7%	23.8%	26.3%	26.3%	27.3%	18.9%	37.4%
4X mig, 70%KR	47.6%	50.0%	55.8%	54.2%	49.2%	50.4%	54.3%	53.9%	46.1%	50.0%
4X mig, 10%KR	28.9%	30.9%	32.2%	30.8%	33.5%	36.0%	37.7%	36.5%	25.1%	33.9%
No mig, 70%KR	11.5%	64.1%	26.7%	60.1%	38.5%	62.6%	33.4%	66.0%	30.9%	59.0%
No mig, 10%KR	6.4%	51.0%	30.7%	23.3%	27.4%	27.4%	29.7%	29.1%	15.8%	42.5%

Chapter 3

Modeling the Added Benefits of Long-lasting Microbial Larviciding on Malaria Transmission in Endemic Settings in Sub-Saharan Africa

Abstract

Recent studies show that increases in insecticide resistance and in outdoor transmission hamper the efficacy of the first-line malaria intervention tools: long-lasting insecticidal nets (LLIN) and indoor residual spraying (IRS). Long-lasting microbial larvicides (LLML) may be a useful supplement to current intervention strategies.

Using EMOD v1.8.1 developed by the Institute for Disease Modeling, we simulated malaria transmission under three scenarios using parameter estimates from study sites in western Kenya: 1) varied efficacy of LLML, 2) application of LLML during different seasons, and 3) modeled LLML as a supplemental tool under different levels of insecticide resistance and outdoor transmission.

The results show that without supplemental interventions, the impact of LLINs and IRS on malaria transmission and prevalence gradually decline due to increasing insecticide resistance and outdoor transmission. The results indicate that supplementing a LLIN-only intervention with LLML in an area with high insecticide resistance and increased outdoor transmission could reduce the prevalence by 35.2%. Adding LLML to LLIN interventions in areas with little to medium levels of insecticide resistance and increased outdoor transmission could reduce prevalence to 28.5% and 32.5% respectively within 3 years of the initial LLML application. The optimal application time for the LLML intervention is at the start of the dry season when habitats are at their lowest capacity.

These results suggest that LLML has the potential to provide significant added benefits to malaria control in the context of prevailing pyrethroid resistance and outdoor transmission.

Introduction

Despite increased control efforts, malaria remains a major public health problem, especially in Africa. The World Health Organization estimates that the African region experiences over 188 million cases and approximately 394,200 deaths due to malaria annually[1]. In the past decade, vector control interventions in Africa have intensified and almost half of the susceptible population has been provided with access to insecticide-treated bednets[1]. Malaria morbidity and mortality are particularly severe in epidemic-prone regions such as highlands where human populations have little immunity to malaria [2-4].

Recently, a massive scale-up of long lasting insecticidal nets and indoor residual spraying, together with the introduction of artemisinin-combination treatments, have led to substantial reductions in malaria prevalence and incidence in Africa [1,5,6]. However, increases in insecticide resistance in mosquitoes and drug resistance in malaria parasites have changed malaria epidemiology around the world and have necessitated a re-evaluation of existing vector control methods [7-11]. Emerging insecticide resistance in adult mosquitoes and an uptick in the levels of outdoor transmission further limit the efficacy of insecticide-treated nets and shift the burden of control to larval control methods that prevent the emergence of adult mosquitoes[12-14]. Therefore, new supplemental interventions that can tackle outdoor transmission and insecticide resistance are urgently needed.

Microbial larvicides have a long history of efficacious use in vector control strategies implemented around the world[7-9]. They have been suggested as a supplemental intervention tool to tackle outdoor transmission and mitigate the effects of insecticide

resistance[15-17]. Currently available larval control methods are limited in their duration of efficacy and the frequency of reapplication required by these larvicides impose high material and operational costs on the consumer. Recently, slow-release microbial larvicide formulations that can provide long-lasting larviciding effect have become available[18,19]. These slow-release formulations use *Bacillus thuringiensis israelensis*/*Bacillus sphaericus* that only kill mosquito larvae and are approved by the US Environmental Protection Agency. They can be effective over a period of several months and thus, do not require the weekly re-treatment of habitats that traditional larvicides require [18,19]. These LLML formulations may be potentially cost-effective; however, their contribution to malaria reduction and the optimal application strategies are yet unknown.

The objective of this study is to model the efficacy and the appropriate field application strategy of LLML in reducing malaria transmission and malaria incidence in Africa. The modeling results are needed to determine whether LLML are valuable as a supplemental malaria control tool to further reduce malaria and whether they can contribute to the design of highly efficacious intervention strategies.

Methods

Malaria Vector Transmission Model

All simulations were conducted with the Epidemiological MODeling (EMOD) software v1.8.1, an agent-based mechanistic model of malaria transmission[20]. The vector transmission model of EMOD was used in this study as it has been used to successfully model malaria dynamics elsewhere[21,22]. The model included input parameters critical to malaria transmission such as vector species, habitat availability, rainfall, temperature, and

vector interventions. The specific equations, time-steps, and parameter estimates that are not specific to this study are described elsewhere[23-25]. The simulation used relevant parameter estimates from well-characterized field sites in the Kakamega region in western Kenya where malaria is epidemic[26].

Entomological survey

The model was calibrated using data gathered from field sites in the Kenyan highlands. All the surveyed aquatic habitats were aggregated into three categories based on their size, shape, larval carrying capacity, and structural dependence on rainfall: permanent, semi-permanent, and temporary, and the larval density was estimated based on the larval count per dip, number of dips, habitat dimensions, and survey radius by species and habitat type (Table 1). The larval counts for each habitat type and each vector species were then calculated and prepared for EMOD configurations. Table 2 lists the common life span and intervention durability parameters for this study.

Climate Data

EMOD climate input files required precipitation, temperature, and relative humidity data for simulating vector transmission. The data were acquired from the nearest World Meteorological Organization (WMO) station at Kakamega, Western Kenya. Daily mean temperature, dew point temperature, and precipitation were acquired from January 1st, 1985 to December 31st, 2014 for a total of 10,950 data points. Relative humidity was then calculated from mean temperature and dew point temperature based on August-Roche-Magnus approximation[27]. Missing data from original WMO records were filled by

calculating the 30 years daily average with 15 days simple moving average function available in MS Excel.

Model Calibration

The model was calibrated to the historical case data collected from the Iguhu District Hospital located in Iguhu, Kakamega County[28]. Clinical malaria infections were confirmed by microscopy and the parasite species specific to the patient's infection was recorded. Historical malaria epidemic data also collected from literature reviews and previous work in Kakamega County[29,30]. The average pre- intervention malaria prevalence prior to 2004 was around 600 cases per thousand person-years. The historical average clinical malaria prevalence after LLIN and IRS intervention was approximately 250 cases per thousand person-years[29,30]. Vector data gathered from the Kakamega area during the corresponding time periods served to parameterize the model's vector settings[31,32].

Model Simulation

Vector transmission dynamics were simulated with specific parameters and three major scenarios were created in order to answer the following questions:

1. How does LLML, LLIN, and IRS efficacy affect the entomological inoculation rate (EIR)?
2. What are the effects of varying seasonal application on the effective period of larviciding?
3. How does LLML perform as a supplemental tool in the context of varying levels of insecticide resistance?

Each scenario that was designed to address the outlined questions was repeated 500 times with different random seeds and allowed for both climate and rainfall stochasticity (Appendix F). For each modeling scenario, a burn-in period of three years was applied to ensure the steady-state dynamics could be observed within the simulation. The first day after the end of the three year burn-in period was considered to be January 1, 1988 and all scenarios designated to receive an intervention, started the intervention campaign from January 1, 1989. All scenarios were set to continue the simulation for fifteen years. The outputs for each repetition of all designed scenarios included the daily EIR (infectious bites/day) and malaria infected ratio (total population infected fraction).

We simulated multiple scenarios with intervention campaigns of both LLIN and IRS administered at different levels of insecticide resistance. The killing rates per indoor resting post-feed encounter (KR) for both LLIN and IRS were simulated from 0% to 50% in 10% increments to mimic insecticide resistance. Demographic coverage for LLINs was set at 50% based on literature estimates of bednet usage from the area[33]. Based on field observations and existing literature, we selected three levels of killing rates to explore in greater detail[34,35]. Scenarios with 10% KR represented a high level of insecticide resistance, medium insecticide resistance level was represented at 30% KR, and those with 50% KR were set to represent an average of the current intervention efficacy of LLIN and IRS in the study site. The efficacy of LLML as an individual intervention in permanent habitats was also tested; we applied LLML at a 10%, 30%, and 50% KR with reapplications in the targeted habitats at 4 month intervals for 5 years.

Malaria transmission is significantly affected by spatial and temporal heterogeneity[28]. Climatic and seasonal variability can greatly affect the efficacy of larviciding efforts. Four separate intervention scenarios were designed to evaluate the efficacy of the initial application of LLML during each season in the study area. Each simulation received LLIN campaigns every 5 years with 30% KR, 50% physical blocking rate, and 50% demographic coverage. Additionally, a LLML campaign with 50% KR was applied every 120 days with start days corresponding to approximate start days of the four different seasons experienced in this area. Although they had different start days in one calendar year, the outputs were aligned to show the impact since initial application.

In order to simulate the efficacy of LLML as a supplemental tool under different levels of resistance, we used 10% KR to represent a high level of larvicidal resistance, 30% KR as the medium resistance, and 50% KR as the low level or no resistance. To simulate outdoor transmission, we ran scenarios that included a variety of indoor feeding fractions for the mosquito species included in our simulations. Simulations distributed LLINs with 50% blocking rate every five years to 50% of the population. One outdoor transmission scenario included the addition of an IRS intervention with 20% physical blocking rate to 80% of the population. A LLML campaign was added as a supplemental intervention tool in all scenarios. LLML was reapplied every 120 days with 50% KR on permanent habitats starting at the start of the dry season and the results were compared to the baseline.

Data Analysis

The daily EIR and malaria infected ratio of the 500 repetitions from each scenario were aggregated and the mean, along with other descriptive statistics were computed using

statistical software JMP 12 (SAS Corporate, Cary, NC, USA). For improved data visualization, the 15-day simple moving average filter was also applied onto the output dataset to smooth the curves.

To compare the efficacy of the malaria intervention, we calculated either the normalized daily EIR difference (N-DEIR diff) or the reduction in percentage of infected population for all the scenarios. The N-DEIR diff was calculated using Equation 2 below. Here, the daily EIR of the treatment (T) scenario is subtracted from that of the baseline control (C) scenario and the difference is then divided by the daily EIR of the baseline control (C) scenario.

$$\text{N-DEIR diff} = \frac{DEIR_C - DEIR_T}{DEIR_C} \times 100\% \qquad Eq.2$$

We used the 95% simulation intervals to indicate significance in differences between treatments.

Results

Modeling Insecticide Resistance with Individual Interventions

Insecticide resistance demonstrated by the malaria vectors was found to have a significant negative impact on the efficacy of the LLIN and IRS interventions programs (Figs 1 & 2). Although the overall transmission of malaria was significantly reduced from the baseline by the presence of the LLIN and IRS interventions, the annual EIR halfway through the life of the bednet intervention was 1.387 at the lowest resistance level (50% KR), above the desired rate of <1 that would be needed to halt the spread of disease. Six months after the initial IRS campaign, the annual EIR was 2.482 when the IRS efficacy was set at the lowest

resistance level. Two months after the initial LLML application, the annual EIR was seen to be 4.38 with LLML functioning at 50% killing rate.

Spatial & Temporal Effects of LLML

Seasonality continues to play a role in the efficacy of all interventions used in the model. Peaks and valleys are seen in scenarios with frequent reapplications of interventions. Figure 4 demonstrates the efficacies of four different LLML intervention scenarios; the settings for all four are the same but for the start time of the initial application. Figure 4A shows that when the initial LLML application is made at the start of the dry season, it can help attain the greatest percentage reduction in prevalence as compared to the baseline prevalence. Figure 4B presents the same data but framed in relation to the start of the rainy season as the baseline, thus highlighting the strength of the impact that a dry season LLML intervention start would have on overall prevalence.

Added benefits of LLML

The added benefit of LLML is large only when resistance to pyrethroids is high, but not evident when resistance is low (Figure 5). For example, under low or no insecticide resistance conditions, the reduction in infection prevalence varied between 2.8% and 8.3% within approximately three years of the LLML application. In Figure 6, the lines represent the total reduction in the percentage of infected population in each treatment scenario as compared to the baseline scenario. These results demonstrate that the overall reduction in the infected fraction could reach 35.2% after interventions under high resistance situations with reduced indoor feeding conditions. In low or no insecticide resistance conditions and

fewer mosquitoes feeding indoors, the reduction in prevalence could reach between 28.5% and 32.5% within 3 years of the first LLML application. Figure 7 shows the total number of new malaria cases that can be averted with the application of LLML in two settings: where indoor feeding fractions are high (*An. gambiae* and *An. funestus* feeding indoors 95% of the time and *An. arabiensis* feeding indoors 30% of the time) and where outdoor transmission is high (*An. gambiae* and *An. funestus* feeding indoors 50% of the time, and *An. arabiensis* feeding indoors 15% of the time). The results show that under high resistance and high indoor feeding conditions, a total of 313 new infections are prevented over the course of 3 years. Under high resistance and high outdoor feeding conditions, a total of 339 new infections are prevented over 3 years.

Discussion

Despite very high bednet coverage, malaria incidence in many African areas is increasing after a short-lived reduction that coincided with the LLIN and IRS scale-up. This resurgence is attributed to rising rates of insecticide resistance and outdoor transmission because the current first-line malaria vector control methods do not target outdoor transmission and do not work efficiently with insecticide resistant mosquitoes[30]. Therefore, new interventions that can both suppress outdoor transmission and are not contingent on the use of insecticides are urgently needed. LLML represent a highly promising and potentially cost-effective supplemental intervention[19,36].

The results indicate that in the presence of insecticide resistance, IRS and LLINs retain the ability to reduce transmission significantly below baseline levels, although they perform differently based on the level of resistance. Over the span of the 1081-day simulation, in

low and medium resistance settings, LLINs and IRS (Figure 1 and 2) individually reduce the population infected fraction lower than is achieved at equivalent levels of resistance by LLML alone (Figure 3). This indicates that while LLML could be a useful supplemental tool, it may not be a good stand-alone method, especially in areas with low to medium levels of insecticide resistance without significant outdoor transmission. However, Figure 3 shows us that the additive effect of LLML is not sensitive to potential emergence of resistance in the mosquito larvae.

Our results shown in Figure 4 demonstrate that applying LLML in the dry season when larval habitats are limited is more beneficial than when it is applied during the rainy season. Stable weather conditions during the dry season could also contribute to keeping the LLML briquette in place. Applying LLML later in the wet season still results in significant reduction of the daily EIR but will not match the efficacy of the dry season application. Repeated applications of LLML on targeted habitats will cause the efficacy of the intervention to converge over time and eliminate the difference seen between seasonal applications. Logistically, a dry season start is also optimal in the field because improved weather and road conditions allow for greater access into areas that could harbor larval habitats. However, while the model enabled decay of the LLML briquette in the habitat, the decay rate was constant and free from climatic fluctuations. The decay of the briquette under field conditions is likely to differ between habitats depending on a variety of factors that could not be accommodated for in the model.

Importantly for public health, adding LLML to the repertoire of LLIN interventions in areas with high insecticide resistance and high outdoor transmission, is seen to eliminate 389 new malaria cases over 3 years as compared to using LLINs alone. Within the model

settings, that translates to a reduction of 35.2% in disease prevalence. If this precipitous reduction in new cases is seen in more densely populated or areas of higher transmission, it has the potential to save several hundred lives over the course of a year.

Outdoor malaria transmission and insecticide resistance are two of the most important challenges in malaria control in Africa. Long-lasting microbial larvicides represent a promising new tool that can target both indoor and outdoor transmission and help to mitigate the problem of insecticide resistance. Our modeling results show that using LLML as supplemental tool could provide 28.5% to 35.2% more reduction in infections. Based on our results, supplementing with LLML in areas with high insecticide resistance provides an opportunity to bridge the gap between malaria transmission and current interventions and increase their ability to regain control of transmission in a non-invasive and potentially more cost-effective manner.

Under the simulated conditions, LLML has strong potential to revolutionize malaria vector control in Africa. However, comprehensive field evaluations of LLML will be needed to provide critical validation for whether LLML can be used as a supplemental malaria control tool for further reducing malaria incidence in Africa.

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Figure 1: LLIN Campaign Scenarios

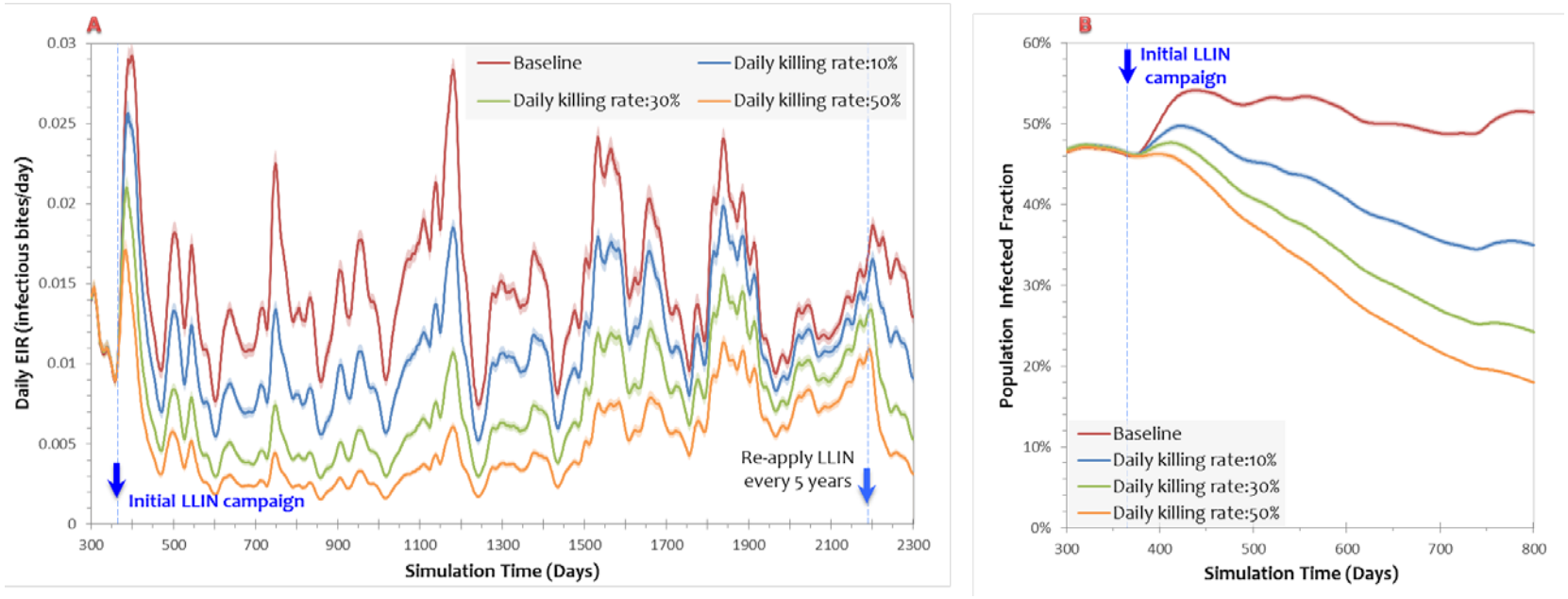

Figure 1A shows the average daily EIRs (solid lines) and the 95% simulation intervals (shaded areas) from the simulations where LLINs were the only intervention administered. Figure 1B shows the average proportions of the simulated population with a malaria infection (solid lines) and their accompanying 95% simulation intervals (shaded areas) under the same conditions as 1a. It is clear that growing insecticide resistance poses a threat to the overall efficacy of the LLIN intervention though they remain a useful tool in reducing malaria transmission and decreasing prevalence.

Figure 2: IRS Campaign Scenarios

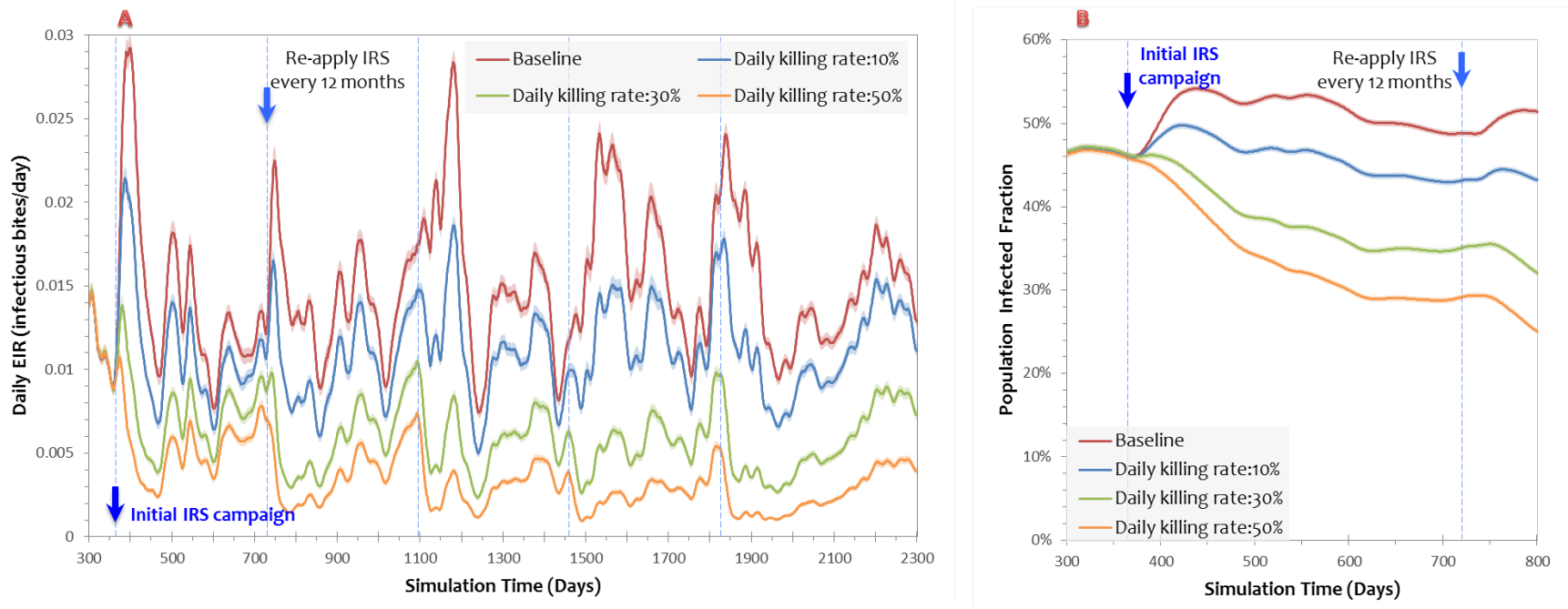

Figure 2A shows the average daily EIRs (solid lines) and the 95% simulation intervals (shaded areas) from the simulations where IRS was the only intervention administered. Figure 2B shows the average proportions of the simulated population with a malaria infection (solid lines) and their accompanying 95% simulation intervals (shaded areas) under the same conditions as 2a. In general, IRS is seen to be a less effective intervention than LLIN, given that even under low resistance conditions (orange), the lowest population infected fraction is still 25% as compared to the population infected fraction of 18% with a LLIN-only intervention.

Figure 3: LLML Campaign Scenarios

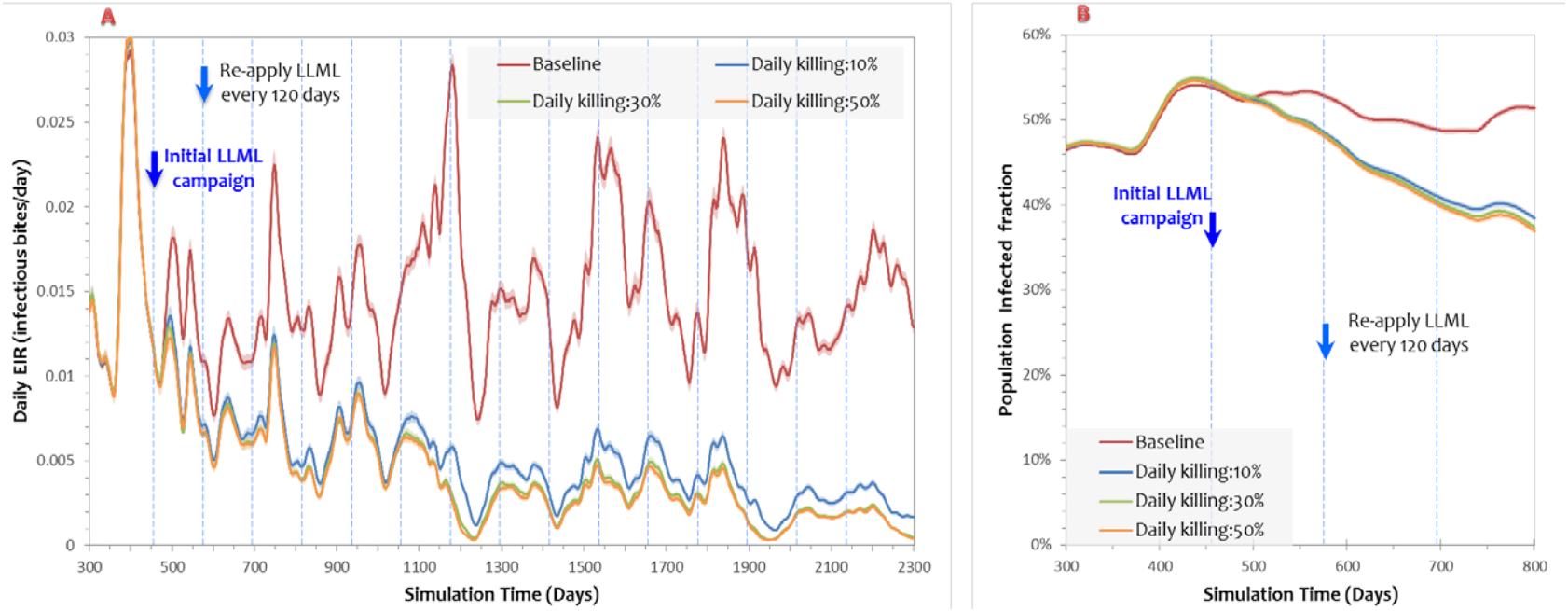

Figure 3A shows the average daily EIRs (solid lines) and the 95% simulation intervals (shaded areas) from the simulations where LLML was the only intervention administered. Figure 3B shows the average proportions of the simulated population with a malaria infection (solid lines) and their accompanying 95% simulation intervals (shaded areas) under the same conditions as 3a. Although LLML is not as efficacious as a stand-alone intervention as either LLINs or IRS, it is important to note that its efficacy also does not seem to be as sensitive to resistance as the other interventions. Fig 3A shows that the variation in the daily EIR does not begin to differ significantly for a prolonged length of time between the various killing rates of LLML until Day 1061, almost 2 years after the initial application.

Figure 4: Seasonal Application of LLML

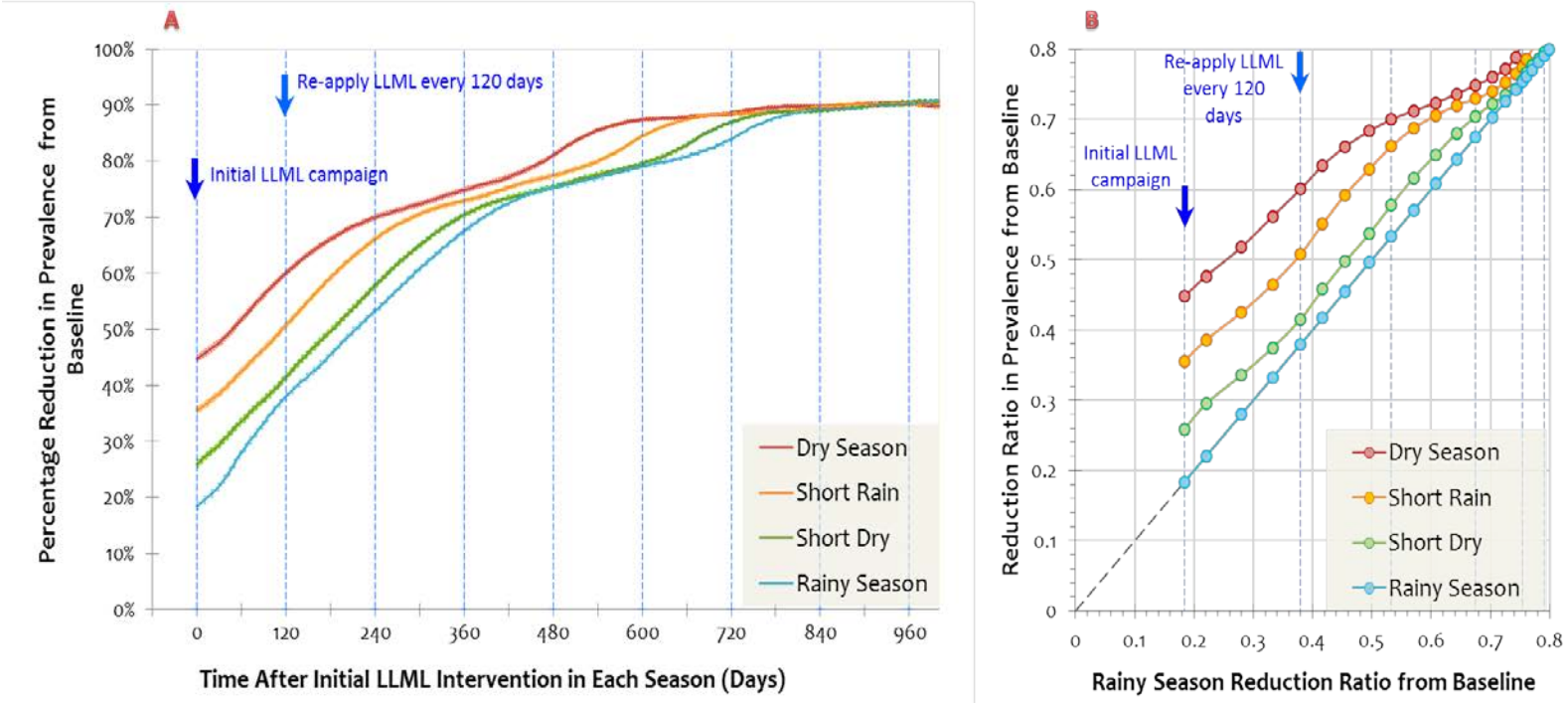

Figure 4A shows the reduction in prevalence from the baseline (solid lines) and the 95% simulation intervals (shaded areas within dotted lines) as normalized from the baseline (not shown) in the simulations where LLML was administered in conjunction with LLINs. Figure 4B shows that the optimal season in which LLML distribution should begin is the long dry season (red line) because it has the greatest reduction in prevalence from baseline.

Figure 5: Additional Benefits of LLML with LLIN & IRS, Current Levels of Indoor Feeding

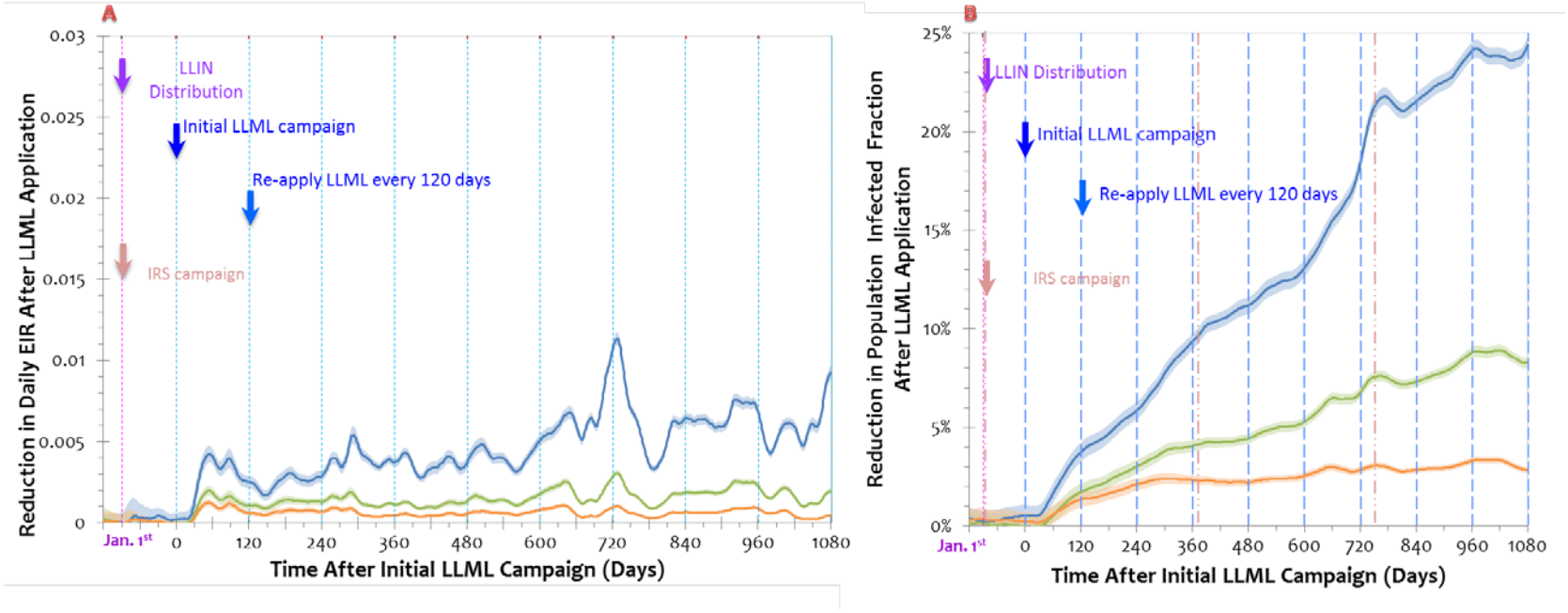

Figure 5A shows the average daily EIRs (solid lines) and the 95% simulation intervals (shaded areas) from the simulations where LLML was first administered during the dry season in conjunction with LLINs and IRS. Figure 5B shows the reduction in the proportion of infected population (solid lines) and the 95% simulation intervals (shaded areas) as normalized from the baseline (not shown) in the simulations where LLML was first administered during the dry season in conjunction with LLINs and IRS. With both IRS and ITN interventions working at low resistance and high fractions of indoor feeding (95% for *An. gambiae* and *An. funestus*, 15% for *An. arabiensis*), LLML does not have a strong impact on transmission or on prevalence though it is still significantly greater than the baseline.

Figure 6: Additional Benefits of LLML with LLIN, Reduced Levels of Indoor Feeding

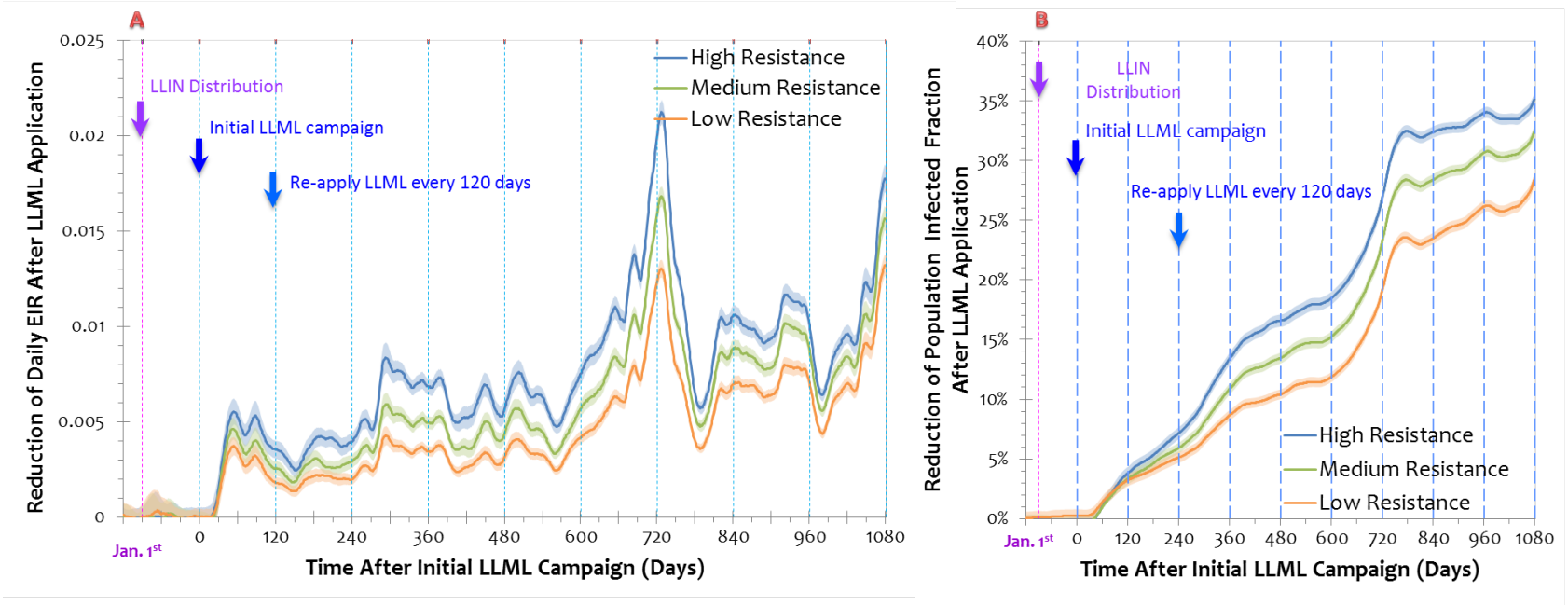

Figure 6A shows the average daily EIRs (solid lines) and the 95% simulation intervals (shaded areas) from the simulations where LLML was first administered during the dry season in conjunction with LLIN. Figure 6B shows the reduction in the proportion of infected population (solid lines) and the 95% simulation intervals (shaded areas) as normalized from the baseline (not shown) in the simulations where LLML was first administered during the dry season in conjunction with LLIN. In this scenario, the increased outdoor feeding (50% for *An. gambiae* and *An. funestus*, 30% for *An. arabiensis*), has improved the additional benefit conferred by a LLML intervention.

Figure 7: Cumulative Number of Additional New Infections Prevented with LLML Supplemental Intervention Under Varied Outdoor Transmission Conditions

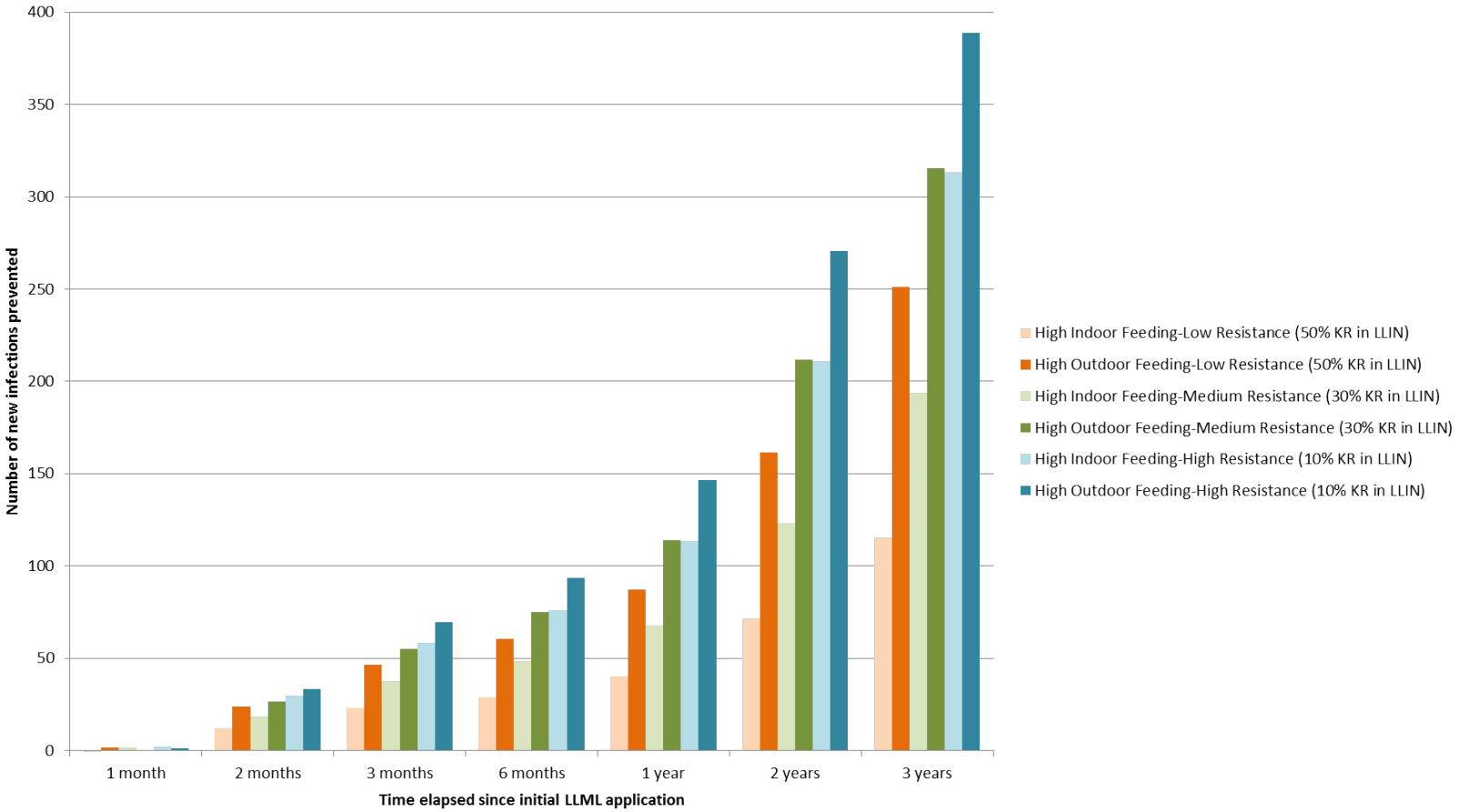

Table 1: Survey larval density and counts were aggregated by vector species and habitat type used in the EMOD configurations: (a) estimated larval density per square meter in study area; (b) estimated larval counts by habitat enumerations and vector species in 1 by 1 degree area.

(a)	Larval Density (larvae/m^2)					
Habitat Type	**Modeling Habitat**	**Est. Area Occupied in 1x1 Deg**	***An. gambiae s.l.***	***An. funestus***	**Other Anophelines**	***Culicines***
Permanent	CONSTANT	0.60%	0.174	0.035	0.031	0.568
Semi-Permanent	WATER_VEGETATION	0.71%	0.042	0.012	0.005	0.432
Temporary	TEMPORARY_RAINFALL	0.19%	6.836	0.319	0.138	6.721

(b)	EMOD Habitat Larval Counts in 1x1 Degree Area				
Habitat Type	***An. gambiae s.s.***	***An. arabiensis***	***An. funestus***	**Other Anophelines**	***Culicines***
Permanent	12.1×10^6	7.62×10^6	2.58×10^6	2.32×10^6	42.4×10^6
Semi-Permanent	22.8×10^6	1.43×10^6	1.01×10^6	0.48×10^6	37.9×10^6
Temporary	100.1×10^6	62.7×10^6	7.61×10^6	3.29×10^6	160×10^6

Table 2: General life span and durability settings for intervention campaigns.

Model Parameter	LLIN	IRS	LLML
Durability_Time_Profile	BOXDECAYDURABILITY	DECAYDURABILITY	BOXDECAYDURABILITY
Start_Day	January 1st	January 1st	April 1st
Primary_Decay_Time_Constant	1 Year	3 Months	2 Months
Secondary_Decay_Time_Constant	2 Years	0.5 Month	3 Months
Timesteps_Between_Repetitions	5 Years	1 Year	4 Months
Number_Repetitions	2	5	10

CONCLUSION

This dissertation employed an interdisciplinary and multilevel approach to acquire critical knowledge of malaria epidemiology in the era of intensive malaria control campaigns, and to evaluate alternative and innovative strategies for effective malaria control and eventual elimination within the framework of translational science. Over the course of this research, I explored: a) how health policies regarding malaria treatment are not always well-matched to an individual's particular health-seeking behavior patterns, b) how human movement across porous borders can impact intervention strategies aimed at eliminating malaria, and c) how new vector control methods such as long-lasting microbial larvicides can be used to combat the growing threat of insecticide resistance and outdoor transmission in endemic areas.

Understanding the local health behaviours, including the human movement patterns that perpetuate transmission of malaria will help develop targeted preventive measures, as well as to develop educational interventions that can empower the residents with the knowledge needed to combat malaria in a safe and effective manner. Ensuring patient access to health care facilities in countries with high disease burdens has broader implications on measures of equity and on public health prevention methodologies. Implementing interventions in the border regions with unstable transmission can have beneficial effects on both sides of the border and thus, potentially become more cost-effective with regards to infections prevented. Finally, where insecticide resistance increases and outdoor feeding behavior is unpredictable, the application of novel vector control methods such as LLML can be an important supplemental tool.

It is hoped that the results of this study begin to fill in the gaps in knowledge that would be required to implement policy changes and improve access to appropriate health care facilities and can begin to direct the development of targeted intervention measures.

Appendix A-Chapter 1: Summary of the estimated average travelling speed and cost-weighted factor for potential terrain conditions in western Kenya.

Our surveys of area hospitals and clinics, local chemists, and neighborhood retail outlets were designed to shed light on the availability and supply of recommended anti-malarials in our study area of interest. Our field surveys of the residents of the area provided insight into local health-seeking behaviors. In order to best describe and evaluate our measures of accessibility, we employed certain GIS-based methodologies in our analyses. We collected and digitized the detailed spatial information on the population, health facilities, pharmacies, road network, and topographic features influencing the access-time. These were used to develop a geospatial accessibility model based on Tobler's (1993) equation to estimate travel speeds and subsequent access-time to the nearest health facility and pharmaceutical retailer. The model took into account different topography and transport types and was calibrated using data from actual field survey and observation made by patients seeking treatment.

We assembled all the geo-referenced data, including base map, health facilities, pharmacy, transport network (roads, tracks and barriers), and other topographic features into a geodatabase. We then established our geospatial accessibility model by implementing Tobler's (1993) equation with the "cost-weighted distance" algorithm within a geographical information system (GIS), ArcGIS Desktop 10.1 (ESRI Inc), to estimate access-time from every 30 x 30 meters grid square to the nearest health facility or pharmaceutical retailer. Separate models were developed for mobilized versus non-mobilized forms of transport and for scenarios with and without access barriers, such as

rivers; the likely proportion of residents using each transport type to access facilities in different locations was also estimated. To maximize the realistic estimation in our models, we carried out several calibrations in which survey data on actual access-time reported by survey cases were used to find the optimum model parameters in either mobilized versus non-mobilized forms of transport (Table 3). By combining our estimations and topographic features, we generated several high resolution surfaces under several practical transportation or destination scenarios by 10 minutes access-time intervals.

Walk distance is based on the "Path Distance" tool found in the software. It calculates, for each cell, the least accumulative cost distance to the nearest source, while accounting for surface distance and horizontal and vertical cost factors and weights the speed deduction with the slope change.

$$w = 6 \times EXP(-3.5 \times |S + 0.05|)$$

$$w = 6 \times EXP\left(-3.5 \times \left|\tan\frac{Slp}{57.29578} + 0.05\right|\right)$$

-- Tobler (1993)

Here, w is the walking velocity, S is dH/dX = tan (θ), the dimensionless slope; Slp is the degree of slope; the value 57.29578 shown here is a truncated version of the result from 180/π. The unit of velocity w is given in km/hr. This algorithm was created to better estimate pedestrian travelling times. To estimate the travel speeds for crossing different flat terrain, we assumed adults in our study communities could walk at a speed of 5 km/h on field foot path; for off-path travel, we multiplied by a factor of 0.6 to get a walking speed of 3 km/h; for specific land-cover impediments, we used 2.5 km/h to estimate people walking through forested areas and assumed they could maintain a speed of 1 km/h to

cross a swampy area. We also assumed people could not cross rivers or water bodies unless there was a bridge.

The traveling speeds for people with vehicle (mainly by car, minibus, or motorcycle) are estimated to be 50 km/h on primary roads (tarmac roads), 30 km/h on secondary roads (gravel roads), and 20 km/h on dry weather road (dirt roads). When traveling on the small, narrow track with bicycle or tricycle, 10 km/h is held as the maximum speed[17]. This was applied to our data from households, retailers, and hospitals and walking times were calculated based on terrain maps used by others within the project. The application of this particular rule is prudent in this case given that a large majority of our participants in all surveyed areas used walking as their primary mode of transportation to reach the health facility (Table 2).

Based on the estimation of travel speeds for each terrain condition, we calculated the cost-weighted factors. The cost-weighted factor represents the potential impedance or the "resistance" in the distance calculation while simulating the difficulty of passing through a specific terrain condition. The higher the value of cost-weighted factor, the higher the impedance of movement on the ground, and the greater the amount of time that is needed to travel an equivalent distance as compared to a cell with lower impedance. Low cost-weighted factors (impedance values) could be assigned to high-speed terrain conditions such as bound surface road, with much larger values for loose surface road or rough terrain. Barriers such as a wide river or a big water body were designated as an inaccessible area, and swamps or forests could be assigned very large impedance values. For instance, if the cost-weighted factor for traveling on a primary road (bound surface) at the speed of 50 km/hr is defined as 1, the factor for traveling on dry weather road (dirt

surface- which has lower traveling speeds of 20 km/hr), can be defined at 2.5. Table S1 shows the summary of the estimated average traveling speed and cost-weighted factors for potential terrain conditions that might be observed in our study area. While the cost-weighted factor represents the impedance which is inversely proportional to the average travel speed of each terrain type, a relative 'time-cost' surface or 'equivalent distance' surface can be produced for further modeling simulation.

Table S1. Summary of the estimated average traveling speed and cost-weighted factor for potential terrain conditions in western Kenya

Terrain Condition	**Average Traveling Speed (km/hr.)**	**Cost-Weighted (Impedance) Factors**
Primary Road (Bound Surface) (motorized transport)	50	1
Secondary Road (Loose Surface) (motorized transport)	30	1.667
Dry Weather Road (earth surface) (motorized transport)	20	2.5
Main Track (motorized transport)	10	5
Footpath (by foot)	5	10
Off Road/path (by foot)	3	16.667
Forest (by foot)	2.5	20
Swamp (by foot)	1	50
River (inaccessible)	0	-1

Appendix B- Chapter 1: Comparison between values measured by ELISA and HPLC in the commercial artemisinin-based drugs. The labeled value of active ingredients (a.i.) was all 2.0

Drug names	Lot No.	Site obtained	Measured content [a] (mg/mL)	
			ELISA	HPLC
Artefan 20/120	P0251C	Kakamega, Kenya	2.16 ± 0.03	2.33 ± 0.18
	BNP0501D	Emuhaya, Kenya	2.38 ± 0.11	2.21 ± 0.01
	BNP0031D	Emuhaya, Kenya	2.21 ± 0.23	2.22 ± 0.01
CO-FALCINUM	B/NK 01885	Vihiga, Kenya	2.23 ± 0.21	2.17 ± 0.04
	B/NK 0C32	Vihiga, Kenya	2.16 ± 0.15	2.21 ± 0.01
	B/NK 01646	Vihiga, Kenya	2.38 ± 0.11	2.22 ± 0.12
	N/A b	Vihiga, Kenya	2.39 ± 0.33	2.11 ± 0.02
	B/NK 10489	Vihiga, Kenya	2.22 ± 0.10	2.28 ± 0.03

Appendix C- Chapter 2: Fisher test to determine correlation between malaria and travel

Study Site	Travel Status	Reported malaria infection	Did not report malaria infection	Fishers Test Results
Northern Thai villages	Cross-border travelers	14	35	Odds ratio: 1.5 p-value: 0.38
	Did not cross the border	13	49	
Southern Thai villages	Cross-border travelers	5	208	Odds ratio: NA p-value: 0.32
	Did not cross the border	0	74	
Thai Hospital	Cross-border travelers	12	45	Odds ratio: 1.48 p-value: 0.40
	Did not cross the border	22	122	

Northern villages: Suan Oi, Mae Salid Noi
Southern villages: Tala Oka, Nong Bua
Hospital: Tha Song Yang Hospital

Appendix D- Chapter 2: Demographic and migration characteristics of study participants across sentinel sites in China, Thailand, and Myanmar.

	China (n= 278)	**Myanmar** (n=367)	**Thailand northern villages** (n=111)	**Thailand southern villages** (n=287)	**Thailand Tha Song Yang Hospital** (n=201)
Demographic variables					
Sex					
Male	174 (62.6%)	148 (40.3%)	43 (38.7%)	124 (43.2%)	89 (44.3%)
Female	102 (36.7%)	215 (58.6%)	67 (60.4%)	162 (56.4%)	111 (55.2%)
Missing	2 (0.7%)	4 (1.1%)	1 (0.9%)	1 (0.4%)	1 (0.5%)
Occupation of respondent					
Outdoor worker (e.g., farmer, plantation worker, day laborer, etc.)	202 (72.7%)	198 (54.0%)	59 (53.1%)	231 (80.5%)	139 (69.1%)
Indoor worker (e.g., factory worker, teacher, housewife)	67 (24.1%)	167 (45.5%)	51 (46.0%)	56 (19.5%)	62 (30.9%)
Unspecified or missing	9 (3.2%)	2 (0.5%)	1 (0.9%)	0	0
Highest education level completed					
Did not finish primary	32 (11.5%)	27 (7.4%)	83 (74.8%)	190 (66.2%)	116 (57.7%)
Primary school	179 (64.4%)	267 (72.7%)	21 (18.9%)	54 (18.8%)	39 (19.4%)
Secondary school and beyond	58 (20.9%)	58 (15.8%)	7 (6.3%)	39 (13.6%)	44 (21.9%)
Unspecified or missing	9 (3.2%)	15 (4.1%)	0	4 (1.4%)	2 (1.0%)
Type of mosquito control used in the past month					
None	41 (14.7%)	14 (3.8%)	6 (5.4%)	10 (3.4%)	17 (8.5%)
Bednet	190 (68.3%)	290 (79.0%)	98 (88.3%)	272 (94.8%)	183 (91.0%)
Indoor residual spray	4 (1.4%)	34 (9.3%)	0	0	0

Repellent	25 (9.0%)	21 (5.7%)	0	1 (0.4%)	0
Multiple methods	15 (5.4%)	5 (1.4%)	7 (6.3%)	2 (0.7%)	0
Missing	3 (1.1%)	3 (0.8%)	0	2 (0.7%)	1 (0.5%)
Did you have a malaria infection in the past year?					
Yes	22 (7.9%)	19 (5.2%)	22 (19.8%)	5 (1.7%)	34 (16.9%)
No	253 (91.0%)	347 (94.5%)	84 (75.7%)	282 (98.3%)	153 (76.1%)
Missing	3 (1.1%)	1 (0.3%)	5 (4.5%)	0	14 (7.0%)
Migration variables					
Have you ever crossed the border for any reason?					
Yes	162 (58.3%)	182 (49.6%)	54 (48.7%)	258 (89.9%)	52 (25.8%)
No	115 (41.4%)	182 (49.6%)	57 (51.3%)	27 (9.4%)	144 (71.6%)
Missing	1 (0.3%)	3 (0.8%)	0	2 (0.7%)	4 (2.0%)
The following variables were recorded as a percentage of all travelers	(N=162)	(N=182)	(N=54)	(N=258)	(N=52)
Method of crossing the border					
Walk	73 (45.1%)	33 (18.1%)	2 (3.7%)	37 (14.3%)	5 (9.6%)
Motorized public transport	10 (6.2%)	16 (8.8%)	2 (3.7%)	4 (1.6%)	4 (7.7%)
Boat	2 (1.2%)	1 (0.5%)	5 (9.3%)	136 (52.7%)	7 (13.5%)
Motorized private transport	64 (39.5%)	81 (44.5%)	0	1 (0.4%)	0
Swim	1 (0.6%)	0	0	2 (0.8%)	0
Multiple	5 (3.1%)	26 (14.3%)	45 (83.3%)	78 (30.2%)	27 (51.9%)
Missing	7 (3.1%)	25 (13.7%)	0	0	9 (17.3%)
Average duration of visit					
≤24 hours	105 (64.8%)	113 (62.1%)	23 (42.6%)	154 (59.7%)	24 (46.2%)
>24 hours	50 (30.9%)	54 (29.7%)	23 (42.6%)	50 (19.4%)	26 (50.0%)

Missing	7 (4.3%)	15 (8.2%)	8 (14.8%)	54 (20.9%)	2 (3.8%)
Purpose of visit					
Job	56 (34.6%)	31 (17.0%)	18 (33.4%)	91 (35.3%)	9 (17.3%)
Visit family	43 (26.5%)	46 (25.3%)	11 (20.4%)	33 (12.8%)	11 (21.2%)
To claim IDP/refugee status	0	3 (1.6%)	0	0	0
To receive medical care	0	21 (11.6%)	1 (1.8%)	0	5 (9.6%)
For tourism or shopping	43 (26.5%)	50 (27.5%)	23 (42.6%)	134 (51.9%)	21 (40.4%)
Multiple reasons	12 (7.4%)	3 (1.6%)	0	0	1 (1.9%)
Unspecified or missing	8 (4.9%)	28 (15.4%)	1 (1.8%)	0	5 (9.6%)
Do you cross the border with friends or family?					
Yes	102 (63.0%)	100 (55.0%)	50 (92.6%)	246 (95.4%)	49 (94.2%)
No	55 (33.9%)	67 (36.8%)	4 (7.4%)	12 (4.6%)	3 (5.8%)
Missing	5 (3.1%)	15 (8.2%)	0	0	0
Total number of trips by season (per 4 months)					
Monsoon	2576	749	624	4136	148
Winter	3254	777	512	3769	132
Summer	2006	854	380	3416.5	158