EPIDEMIOLOGY OF RESURGENT MALARIA IN EASTERN ZIMBABWE:
RISK FACTORS, SPATIO-TEMPORAL PATTERNS AND PROSPECTS FOR
REGAINING MALARIA CONTROL

by
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ABSTRACT

Despite recent reductions in malaria morbidity and mortality due to the scale up of malaria interventions, malaria remains a public health problem in sub-Saharan Africa. A recent resurgence in malaria, in areas where malaria control was previously successful, has brought to the forefront the importance of research to understand the epidemiology of malaria and the effectiveness of malaria control efforts in resurgent settings. Using cross-sectional surveys, routine data from health-facility based surveillance and publicly available remotely sensed environmental data, this research examined the distribution of malaria and the impact of vector control in Mutasa District, a rural district in Zimbabwe characterized by resurgent malaria.

Firstly, individual- and household level factors independently associated with individual malaria risk were identified using multilevel logistic regression models based on data from cross-sectional surveys conducted between October 2012 and September 2014. Secondly, geostatistical methods and remotely sensed environmental data were used to model the spatial and seasonal distribution of household malaria risk and develop seasonal malaria risk maps with corresponding maps of the prediction uncertainty. Lastly, an evaluation of the effect of introducing an organophosphate for indoor residual spraying was conducted using routine health facility data covering 24 months before and 6 months after the campaign.

The results of the multilevel model suggested that malaria risk was significantly higher among individuals who were younger than 25 years, did not sleep under a bed net, and lived close to the Zimbabwe-Mozambique border. The spatial risk maps depicted relatively increased risk of finding a positive household in low-lying areas along the Mozambique border during the rainy season. Lastly, the introduction of organophosphates to this area with high levels of pyrethroid resistance in the mosquito vector resulted in a
significant reduction in malaria incidence following spraying. These findings elucidate the heterogeneous distribution of malaria, identify risk factors driving malaria transmission and assess the quantitative impact of switching insecticide classes on health outcomes. Collectively, the findings provide evidence to guide country-specific decision making for regaining malaria control and underscore the need for strong between-country initiatives to curb malaria in Eastern Zimbabwe and elsewhere.
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TABLE OF CONTENTS

ABSTRACT ........................................................................................................................... ii
ACKNOWLEDGEMENTS ...................................................................................................... v
TABLE OF CONTENTS ....................................................................................................... vii
LIST OF TABLES .................................................................................................................. ix
LIST OF FIGURES ............................................................................................................... x
LIST OF ABBREVIATIONS .................................................................................................... xi
CHAPTER 1: INTRODUCTION .............................................................................................. 1
  Background and Problem Statement .............................................................................. 2
  Study Objectives ............................................................................................................ 5
  References ....................................................................................................................... 8
  Tables and Figures ......................................................................................................... 11
CHAPTER 2: LITERATURE REVIEW .................................................................................. 12
  Malaria Overview .......................................................................................................... 13
  Malaria Control ............................................................................................................. 15
  Factors Driving Malaria ............................................................................................... 18
  Overview of Analytical Approaches ........................................................................... 23
  Study Setting .................................................................................................................. 28
  References ....................................................................................................................... 32
  Tables and Figures ......................................................................................................... 42
CHAPTER 3: INDIVIDUAL AND HOUSEHOLD LEVEL RISK FACTORS ASSOCIATED WITH
MALARIA IN MUTASA DISTRICT, ZIMBABWE: A SERIAL CROSS-SECTIONAL STUDY ......... 47
  Abstract ......................................................................................................................... 48
  Background ...................................................................................................................... 50
  Methods ........................................................................................................................... 51
  Results .............................................................................................................................. 57
  Discussion ....................................................................................................................... 59
  References ....................................................................................................................... 64
  Tables and Figures ......................................................................................................... 68
CHAPTER 4: HIGH-RESOLUTION MALARIA RISK MAPPING IN MUTASA DISTRICT,
ZIMBABWE: IMPLICATIONS FOR REGAINING CONTROL ............................................. 74
  Abstract ......................................................................................................................... 75
  Background ...................................................................................................................... 77
CHAPTER 5: INITIAL EVIDENCE OF A REDUCTION IN MALARIA INCIDENCE FOLLOWING INDOOR RESIDUAL SPRAYING WITH ACTELlic 300 CS IN A SETTING WITH PYRETHROID RESISTANCE: MUTASA DISTRICT, ZIMBABWE

Abstract .......................................................................................................................97

Introduction .................................................................................................................99

Methods .......................................................................................................................100

Results .........................................................................................................................106

Discussion .....................................................................................................................108

References .....................................................................................................................112

Tables and Figures .......................................................................................................114

CHAPTER 6: CONCLUSION ..........................................................................................119

Discussion of Main Findings .......................................................................................120

Limitations ....................................................................................................................123

Recommendations for Future Research .....................................................................126

Policy Implications .......................................................................................................127

Concluding Remark ....................................................................................................129

References .....................................................................................................................130

BIBLIOGRAPHY ...........................................................................................................132

BRIEF CURRICULUM VITAE .....................................................................................146
LIST OF TABLES

CHAPTER 2

Table 1: Commonly used indices to measure malaria and its intensity ........................................ 42

CHAPTER 3

Table 1: Characteristics of 316 sampled households in Mutasa District (October 2012 – September 2014) ........................................................................................................... 68

Table 2: Characteristics of individuals in Mutasa District at baseline (October 2012 – September 2014) N=1,161 ........................................................................................................... 69

Table 3: Univariate and multivariable multilevel logistic regression analysis of risk factors for malaria RDT positivity (n=1,161) ........................................................................................................... 70

Table 4: Household level random effects summary for the null, individual level and multilevel models .............................................................................................................................................. 71

CHAPTER 4

Table 1: Characteristics of 398 sampled households by RDT status in Mutasa District, October 2012 – April 2015 ........................................................................................................... 93

Table 2: Univariate and multivariable logistic regression models of environmental factors associated with household RDT status in Mutasa District, October 2012 - April 2015 .......... 94

CHAPTER 5

Table 1: Sample characteristics in sprayed and unsprayed wards, pre and post IRS intervention in Mutasa District, Zimbabwe ........................................................................................................... 114

Table 2: Univariate and multivariate incidence rate ratios from negative binomial regression ............................................................................................................................................. 115

Table 3: Summary of prediction accuracy for the 125 week study period for the final model across 42 health facilities ........................................................................................................... 116
### LIST OF FIGURES

**CHAPTER 1**

Figure 1: Map of malaria distribution in Zimbabwe ................................................................. 11

**CHAPTER 2**

Figure 1: Life cycle of the malaria parasite .................................................................................. 43
Figure 2: Map of Africa showing the distribution of pyrethroid resistance ................................. 44
Figure 3: Map of regions of malaria endemicity in Zimbabwe ....................................................... 45
Figure 4: Map of malaria incidence rate per 1,000 for 2012 in Zimbabwe .................................. 46

**CHAPTER 3**

Figure 1: Topographical map of Mutasa District, Zimbabwe and the distribution of sampled households ........................................................................................................................................... 72
Figure 2: Malaria prevalence by age group ..................................................................................... 73

**CHAPTER 4**

Figure 1: Map of Mutasa District, Zimbabwe, indicating positive and negative households .95
Figure 2: Categorical maps of predicted household malaria risk and uncertainty by season for Mutasa District, October 2012 – April 2015 ............................................................................................................................ 96

**CHAPTER 5**

Figure 1: Geographic Distribution of Health Facilities in Mutasa District, Zimbabwe .......... 117
Figure 2: Observed and predicted weekly malaria counts in Mutasa District, 2012-2015 . 118
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based Combination Therapy</td>
</tr>
<tr>
<td>ADDS</td>
<td>Africa Data Dissemination Service</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criteria</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DDT</td>
<td>dichlorodiphenyltrichloroethane</td>
</tr>
<tr>
<td>DEM</td>
<td>Digital elevation model</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Surveys</td>
</tr>
<tr>
<td>EIR</td>
<td>Entomological Inoculation Rate</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalized estimating equation</td>
</tr>
<tr>
<td>GIS</td>
<td>Geographical Information Systems</td>
</tr>
<tr>
<td>GPS</td>
<td>Global Positioning System</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health management information system</td>
</tr>
<tr>
<td>ICEMR</td>
<td>International Centers of Excellence for Malaria Research</td>
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<tr>
<td>IPT</td>
<td>Intermittent preventive treatment</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>ITNs</td>
<td>Insecticide-Treated Nets</td>
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<tr>
<td>IRS</td>
<td>Indoor Residual Spraying</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>LLINs</td>
<td>Long Lasting Insecticide-Treated Nets</td>
</tr>
<tr>
<td>LST</td>
<td>Land Surface Temperature</td>
</tr>
<tr>
<td>MARA</td>
<td>Mapping Malaria Risk in Africa</td>
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<td>MAP</td>
<td>Malaria Atlas Project</td>
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<tr>
<td>MIS</td>
<td>Malaria Indicator Survey</td>
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<tr>
<td>MODIS</td>
<td>Moderate Resolution Imaging Spectroradiometer</td>
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<tr>
<td>MOHCC</td>
<td>Ministry of Health and Child Care</td>
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<tr>
<td>NDVI</td>
<td>Normalized Distance Vegetation Index</td>
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<tr>
<td>NMCP</td>
<td>National Malaria Control Program</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PMI</td>
<td>President’s Malaria Initiative</td>
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<tr>
<td>QIC</td>
<td>Quasi-likelihood under the independence model criterion</td>
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<tr>
<td>RBM</td>
<td>Roll Back Malaria</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>RFE</td>
<td>Rainfall estimate</td>
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<tr>
<td>RMSE</td>
<td>Root mean squared error</td>
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<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
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<tr>
<td>SES</td>
<td>Socio-Economic Status</td>
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<tr>
<td>SRTM</td>
<td>Shuttle Radar Topographic Mission</td>
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<tr>
<td>SSA</td>
<td>sub-Saharan Africa</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>UTM</td>
<td>Universal Transverse Mercator</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1: INTRODUCTION

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Background and Problem Statement

Malaria, a parasitic disease transmitted by female *Anopheles* mosquitoes, remains a public health problem particularly in tropical and subtropical regions. Globally, approximately 3.2 billion people are at risk of malaria [1]. In 2013, malaria caused 198 million cases (uncertainty range 124–283 million) resulting in 584,000 deaths (uncertainty range 367,000–755,000) [1]. While only 13% of the world’s population are found in sub-Saharan Africa (SSA) [2], 80% of global malaria cases and 90% of deaths are concentrated in SSA, with children under five years and pregnant women at greatest risk [1]. Similarly, when the burden is measured by disability-adjusted life years, 93% of the total global burden due to malaria is concentrated in SSA [3]. Conducive climatic conditions, population movement into malaria endemic areas, changing agricultural practices, weak health systems, and changing climatic patterns have contributed to SSA carrying the greatest burden of malaria [4, 5]. Furthermore, the high efficiency of *An. gambiae*, the main malaria vector in SSA and the deadly nature of *Plasmodium falciparum* as a malaria parasite have further contributed to predominance of malaria morbidity and mortality in SSA.

Malaria hinders behavioral and intellectual development, reduces school attendance, and decreases work productivity [6]. In countries with the highest burden, malaria increases household health care expenditures and constitutes 40% of public expenditure [7]. Malaria costs Africa more than US$12 billion every year in lost gross domestic product and inhibits economic growth by 3% every year in malaria-endemic countries [4]. Malaria, therefore, not only affects the health status of Africa’s population but also impedes economic development.

Pronounced reductions in the burden of malaria have recently been reported. An estimated 50% reduction in malaria infection prevalence and 40% reduction in the incidence of clinical disease were achieved between 2000 and 2015 in the Africa region [8].
The reductions have been attributed to economic development, urbanization and an unprecedented increase in financial support in malaria-endemic countries, which led to the massive scale-up of high-impact malaria interventions [9, 10]. Efficacious indoor residual spraying (IRS) and provision of long-lasting insecticide-treated bed nets (LLINs) have been complemented by the introduction of artemisinin-based combination therapy (ACTs) for first-line treatment and improved diagnostic tools [1]. Nevertheless, funding constraints, political instability, climatic changes, human population movement, the rapid spread of insecticide and drug resistance have impeded effective malaria control and elimination, and some regions that have previously controlled malaria have reported increases in the burden of malaria [11]. Over the last two decades, malaria resurgences have been reported across the globe, with over 75 documented instances of malaria resurgence in 61 countries including Zimbabwe [12].

In Zimbabwe, the epidemiological pattern of malaria transmission varies by altitude and rainfall patterns [13, 14]. Malaria transmission is marginal along the watershed ridge running from Rusape, near the eastern border with Mozambique, to Gwanda in the southwest. Stable malaria transmission occurs throughout the year in low-lying areas in the north and east of Zimbabwe, bordering Zambia and Mozambique (Figure 1). Half of the population of 13.3 million is at risk of malaria and all malaria cases are due to *P. falciparum* [1]. From 2003 to 2013, the annual reported malaria cases exhibited a drastic decline from ~ 1.5 million to 377,872, with the decline attributed to the scale-up of malaria interventions [15, 16]. Similar pronounced declines were observed in inpatient malaria cases and the case fatality rate [16]. Although declines coincided with the shift from reporting suspected cases to diagnostically confirmed cases in 2009, a rapid impact assessment asserts that the observed declines resulted from the scale up of LLINs and introduction of ACTs [16, 17].
In more recent years, however, surveillance has documented an increase in malaria incidence in areas bordering Zambia and Mozambique [15, 18]. Manicaland Province, which shares a border with Mozambique, is an area hardest hit by malaria. In 2013, Manicaland Province reported more than half of the malaria cases and more than one third of malaria deaths in the country, although it consists of less than 14% of the national population [16, 19]. Furthermore, between 2009 and 2013, the number of confirmed cases of malaria in the province increased from 55,707 to 192,730 [15, 16]. According to the Zimbabwe Demographic and Health Survey (DHS) 2010-11, 41.1% of households in the province owned at least one insecticide treated net (ITN), while only 31.6% of the household population reported sleeping under an ITN the preceding night. Furthermore, only 26% of households surveyed in the province reported receiving IRS in the prior 12 months [20]. Although anti-malaria measures such as IRS, LLINs and case management using ACTs have been implemented since 2007, little progress has been made in regaining full malaria control [21, 22].

Malaria control efforts are particularly difficult in areas along international borders of countries with different malaria intensities. For example, much of South Africa is considered malaria-free, but the success of malaria elimination hinges on successfully controlling malaria in areas in close proximity to higher burden countries [23]. In Botswana, which is now nearing a long-term goal of malaria elimination, malaria hotspots continue to persist in districts sharing borders with Zambia and Zimbabwe [24]. Similarly in Namibia, malaria incidence is highest in the regions along the border with malaria endemic Angola [25]. Outside of southern Africa, similar trends have been observed at the Thai-Myanmar border [26, 27], the Thai-Cambodia border [26, 28], the Myanmar-China border [29], the Bangladesh-India border and the Bangladesh-Myanmar border [30].
Border areas have environmental, administrative and geographic characteristics that uniquely affect the epidemiology and control of malaria. In addition to differences in malaria endemicity, the porosity of borders, frequent human population movement, and suitable climatic conditions for malaria transmission are the major causes of the heavy transmission of malaria along international borders [31, 32]. Political instability, poor collaboration between countries, poor health infrastructures and lack of responsibility of individual countries also play a role in allowing foci of transmission to persist and the reintroduction of malaria into previously malaria-free zones.

With over 75 documented instances of malaria resurgence following a period of successful malaria control in different parts of the world [12], research in resurgent settings, particularly in border areas is required to contribute to the evidence base for regaining malaria control. As malaria goals have shifted from control to elimination and ultimately eradication, understanding malaria transmission in border areas is becoming a key priority. Understanding the epidemiology, vector biology and parasite genomics are important components to guide evidence-based decisions across the range of epidemiological settings: successful malaria control, ineffective malaria control and resurgent malaria. In the hopes of understanding the malaria epidemiology, vector biology and parasite genomics in a setting characterized by resurgent malaria, the Southern Africa International Centers of Excellence for Malaria Research (ICEMR) project purposefully selected Mutasa District, Manicaland Province as a study site [33].

**Study Objectives**

This study was nested within ongoing studies in Mutasa District by the Southern Africa ICEMR with the specific goal of understanding the epidemiology of malaria in a resurgent setting to provide evidence for the implementation of more effective and risk
based malaria control strategies. This dissertation builds upon data collected through community-based surveys, health facility surveillance data and freely available remotely sensed environmental data, and uses sophisticated analytical techniques to achieve this goal. This dissertation addresses the following objectives:

1) Identify individual- and household-level factors associated with malaria risk in Mutasa District, Zimbabwe using a multilevel modeling framework

2) Identify environmental variables driving the spatial heterogeneity of malaria and describe the spatio-temporal distribution of malaria in Mutasa District, Zimbabwe

3) Evaluate the effect of switching from pyrethroids to organophosphates on malaria morbidity reported by health facilities in Mutasa District, Zimbabwe

Understanding the spatial and temporal distribution of malaria, determining the drivers of malaria transmission, and rationalizing the implementation of novel evidence-based strategies are key priorities for malaria epidemiologic research. Chapter 1 introduces the scope of the research. Chapter 2 provides a brief background on malaria, factors known to drive transmission, and a review of the analytical tools used. Research studies addressing each of the three objectives are presented in Chapters 3, 4 and 5. Chapter 3 uses a multilevel framework to identify individual- and household-level factors associated with malaria risk in Mutasa District. The second study, presented in Chapter 4, examines environmental factors as drivers of the spatial and seasonal heterogeneity of malaria risk to construct a spatial prediction model, and develop spatial risk maps by season. Chapter 5 presents an evaluation of the effect of IRS with organophosphates on malaria morbidity reported by health facilities. Chapter 6 concludes the dissertation by providing a discussion of the results and the public health implications with special attention to potential avenues for
future research and policy implications. This dissertation provides quantitative evidence to reduce malaria transmission in Mutasa District and Manicaland Province at large, while underscoring the need for regional collaborations to complement country-specific efforts to curb malaria transmission.
References


Tables and Figures

Figure 1: Map of malaria distribution in Zimbabwe

* Source [34]
CHAPTER 2:
LITERATURE REVIEW

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Malaria Overview

Malaria, a vector-borne disease is caused by five main species of the genus *Plasmodium*: *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. Although *P. vivax* spans the widest geographical area, *P. falciparum*, which is the most life threatening clinically, predominates in Africa and South-East Asia. The other species cause benign or less severe malaria. *P. malariae* is much less frequent while *P. ovale* is similar to *P. vivax* and supersedes it in West Africa. Female *Anopheles* mosquitoes transmit malaria to human hosts. There are over 400 species of *Anopheles* worldwide but only approximately 70 can transmit malaria. The *An. gambiae* complexes are the most efficient vectors and contribute to the severe burden of malaria in SSA. The majority of malaria cases in SSA are transmitted by *An. gambiae* and *An. funestus* mosquitoes [1].

The life cycle of the malaria parasite is depicted in Figure 1 [2]. Briefly, transmission of malaria occurs when an infected female *Anopheles* mosquito injects sporozoites from saliva into an uninfected human. The sporozoites multiply in the liver, rupture the liver cells, and then enter the blood stream as merozoites, which invade erythrocytes and develop into trophozoites. Some merozoites, instead of invading red blood cells, develop into gametocytes that are ingested by female *Anopheles* mosquitoes during a blood meal. Gametocytes, which are released in the mosquito gut, develop into gametes, mature sex cells. Fertilization occurs resulting in diploid zygotes, which form ookinetes that burrow into the mosquito midgut wall and differentiate to oocysts. Oocysts produce large amounts of sporozoites that are released after a few days. Sporozoites rapidly infect the salivary glands of the mosquito. The cycle of human infection begins again when a mosquito bites an uninfected human [1].
The clinical symptoms of malaria, which occur 10-16 days after a mosquito bite, range from asymptomatic to severe. In low transmission areas, most of the population infected by malaria is symptomatic. However, in highly endemic areas, a proportion of the infected population will not exhibit symptomatic disease because of repeated exposure to the parasite. Clinical features of uncomplicated malaria manifest 10-15 days from being bitten. An attack, which typically lasts 6-10 hours, has three stages. The cold stage is characterized by coldness and shivering followed by heat and headache. The final stage is the sweating stage with sweats, tiredness, and joint pain. These attacks alternate with asymptomatic periods every second or third day. Without treatment, infection may last months and could lead to asymptomatic infection that can persist up to a year. The severity and course of malaria infection depends on characteristics of the host and the parasite. For example, in semi-immune individuals, attacks may be less severe and less likely to result in death.

The majority of severe malaria cases and deaths are caused by *P. falciparum* infection. *P.falciparum* causes more severe disease than the other species because of high reproductive capacity, sequestration, and cytoadherence. High parasite burden is associated with *P.falciparum* because of the large number of merozoites produced and the ability of *P. falciparum* to invade erythrocytes of all ages. Other species – *P.vivax* and *P.ovale* prefer young red blood cells and *P.malariae* prefers older erythrocytes. The severity of *P.falciparum* is also due to cytoadherence and sequestration of *P.falciparum*. Only *P. falciparum* causes cytoadherence. Cytoadherence of infected RBCs to the endothelial cells of the capillaries minimizes removal of infected erythrocytes by the spleen, allowing for more efficient erythrocyte invasion. This leads to sequestration of the parasites in various organs. Three severe clinical consequences of *P. falciparum* are cerebral malaria, severe anemia, pulmonary edema and death [3]. Children under five, pregnant women and non-immune
individuals have the highest risk for complicated malaria. During pregnancy, women lose their immunity to malaria. Malaria in pregnancy carries additional risks for the fetus and newborn which can lead to abortions, stillbirths and congenital infection of the fetus; and low birth weight, prematurity, intrauterine growth restriction, malaria disease and death in the newborn [4]. Furthermore the fetus of an infected pregnant woman becomes exposed to \textit{P.falciparum} antigens and may lose the ability to respond to the parasite as a young child [5].

Confirmation of malaria requires evidence of malaria parasites in the peripheral blood or products such as antigens, enzymes or DNA/RNA. The three most common methods to detect malaria parasites are microscopy, polymerase chain reaction (PCR) tests and rapid diagnostic tests (RDT). The diagnosis of malaria by staining thick and thin blood films is generally accepted globally as the gold standard for malaria diagnosis. However, RDTs have increasingly been used since the World Health Organization (WHO) called for simple, quick and low cost diagnostic tests to determine the presence of malaria parasites [6]. RDTs detect specific antigens produced by malaria parasite in the blood of infected individuals. There are a variety of malaria RDTs and most can detect only one species (\textit{P. falciparum}). In places where there is no high quality microscopy, RDTs are an excellent choice as they provide health workers with a diagnosis in real time allowing appropriate and prompt treatment. The value of RDTs is limited by inability to detect infection in those with low malaria parasites and to detect less common species of malaria.

\textbf{Malaria Control}

The potential means of preventing or controlling malaria aim to 1) decrease exposure by implementing IRS and promoting the use of ITNs/LLINs; 2) decrease susceptibility through intermittent preventive treatment (IPT) to ‘at risk’ populations; 3)
treat infected individuals with efficacious drug regimens; and 4) improve the timeliness and appropriateness of case management. According to the 2014 World Malaria Report, 427 million ITNs were distributed to SSA between 2012 and 2014 [7]. Sleeping under an ITN prevents malaria transmission. A mosquito net – treated or untreated, serves as a physical barrier to mosquitoes. The impregnation of a mosquito net with insecticides additionally repels and/or kills mosquitoes [8]. The efficacy and effectiveness of ITNs in reducing disease prevalence, morbidity, and mortality in both high and low transmission settings has been well established in the scientific literature. In areas of stable malaria, ITNs can reduce malaria by 50%, while a reduction of up to 63% can be achieved in areas of unstable malaria [9]. Recent meta-analyses found a 20% protective efficacy of ITNs on reducing all-cause child mortality [10]. There is also evidence suggesting household and community benefits of ITNs beyond the protection afforded at the individual level [11, 12].

IRS, the other principle strategy for vector control, has been shown to reduce malaria morbidity and mortality by comparable amounts, but estimates of protective efficacy vary by season and transmission level [13]. IRS reduces malaria transmission by reducing mosquito longevity as it repels mosquitoes from entering houses and kills mosquitoes resting indoors after feeding. Malaria vectors, such as An. funestus and An. gambiae that primarily feed on human blood (anthropophagic) and rest indoors after feeding (endophilic) or feed indoors (endophagic) are most vulnerable to IRS [14]. There is some evidence of a community IRS effect as well [15]. Despite the protective efficacy of IRS, ITNs or both [16], recent evidence suggests the reduced efficacy of these two tools due to the development of insecticide resistance to pyrethroids [17, 18]. Insecticide resistance is defined as “the development of an ability in a strain of an organism to tolerate doses of toxicants, which would prove lethal to the majority of individuals in a normal (susceptible) population of the same species” [19]. The development of highly resistant vectors threatens
the sustainability of vector control and subsequently the success of malaria control and elimination.

Although insecticide resistance to almost all four insecticide classes – carbamates, organochlorines, organophosphates and pyrethroids - has been detected in different mosquito vectors, the most worrisome is pyrethroid resistance [20]. According to the 2014 World Malaria Report, out of 63 countries reporting on insecticides used for IRS in 2013, 53 reported using pyrethroids [7]. Currently, pyrethroids are the only class of insecticide approved for use on ITNs and more than 80% of IRS campaigns use pyrethroids [20, 21]. Pyrethroid resistance has been documented across SSA (Figure 2) [20]. As a precaution, many countries opt to switch to an insecticide class with a different mode of action once resistance is detected. However, with growing resistance to multiple insecticides in many locations, this approach is not sustainable. There is need to develop novel insecticide resistance management strategies [22].

Vector control is the cornerstone of many national malaria control programs – however, vector control alone does not eliminate the need for early diagnosis, and prompt treatment. Preventative chemotherapy for at risk populations such as pregnant women has also been used in cases where transmission is very seasonal. Introduction of ACTs to replace monotherapies and the use of RDTs have greatly improved treatment and diagnosis of malaria in endemic countries [23]. The introduction of IPTp and IPTi have also shown positive effects on the burden of malaria in pregnant women and children in a number of areas [24]. Remarkable progress has also been made towards the development of a malaria vaccine and several candidate vaccines are currently undergoing field trials [7, 25]. The development of an effective vaccine would provide another intervention to add to the current arsenal of high impact interventions.
Factors Driving Malaria

*Individual-level factors*

The transmission of malaria is complex and determined by many factors affecting the mosquito vector, human host, *Plasmodium* parasite and the environment. At the level of the individual, factors affecting individual malaria risk include: age, acquired immunity, sex, occupation, recent travel, use of preventative methods, and knowledge of malaria. The effect of age on malaria risk is largely dependent on the level of malaria endemicity and thus the time required to acquire natural immunity to malaria [26]. In areas with high transmission, severe malaria morbidity is restricted to children under five years of age, while malaria disease occurs in all age groups in areas with lower levels of transmission [27]. The relationship between sex and malaria has been less conclusive with some studies finding consistent sex differences in malaria incidence or mortality [28, 29], while others suggest no such relationship [30]. Pregnancy inevitably heightens the susceptibility of women to malaria infection and concurrent complications [4].

It is also possible that the association between age/sex and malaria is confounded by different exposures or behavioral risk factors such as the use of personal protection methods and occupation [28, 31]. Occupation may expose individuals to higher risk of malaria infection [32]. In the Chittagong Hill Districts of southeastern Bangladesh, a recent study found that *jhum* (slash and burn) farmers had significantly higher incidence rates of malaria infection compared with non-cultivators [33]. Higher risk of malaria infection has also been found in gold miners in Venezuela [34]. Historically, large-scale agricultural development and economic growth have fueled the movement of individuals especially migrant laborers [35–37]. For example, in the 1950s as agriculture was booming in malaria-free Swaziland, there was an influx of Mozambican laborers to sugar estates, which catalyzed the reestablishment of malaria in Swaziland in 1970 [35]. More recently, similar
occupational migration from Angola to Namibia [38], Zimbabwe to South Africa [39], Mozambique to Swaziland and South Africa [40] have impeded malaria control and elimination. Movement of individuals between areas of different transmission intensities, whether permanent or seasonal, differentially exposes them to infectious mosquitoes and influences malaria prevention behaviors. Furthermore, the change in living or environmental conditions may be more conducive to malaria infection. Increased malaria risk has been associated with recent travel in Burkina Faso [41], central Ethiopia [42], the highlands of Ethiopia [28], Swaziland [43], Rwanda and Burundi [44].

Evidence is mounting to suggest human population movement has resulted in malaria resurgence [17, 35], malaria epidemics in highland areas [44], the emergence of drug resistance [45], and even the changing spatial distribution of Plasmodium species [46]. Therefore, the movement of individuals in time and space has the potential to challenge national malaria control programs across all ranges of transmission settings. Despite research documenting the association of malaria with human mobility and recent travel in different settings, many gaps remain in understanding the patterns and magnitude of movement especially between countries, demographics characteristics of travelers, differences in individual behaviors especially with regard to use of malaria preventative measures, and the motivations for travel [47]. With recent technological developments such as GPS data loggers and mobile phone call data records, more detailed spatial and temporal information on travel is becoming available[48, 49]. Understanding human movement is critical to the design of appropriate elimination strategies and to avoid resurgence in post-elimination settings.

*Household-level factors*
It has been well established that malaria is not randomly distributed in populations, but often varies between households. Large between-household differentials in malaria risk have been observed over varying distances and can be attributed to risk factors operating at the household level, including socio-economic status (SES), housing type, population density, household use of preventative measures and proximity to conducive environments.

There is evidence, though mixed due to differences in the measures of SES used, that strongly supports the conclusion that malaria infection is associated with household SES [50]. Poorer households may be living in poor quality housing structures, be located nearer vector breeding and generally be more susceptible to malaria infection due to poorer health and diet [51]. Poor housing quality, specifically with open eaves or lack of a roof has been associated with mosquito abundance and malaria [30, 52–54]. Greater exposure to the outdoors may increase human vector contact. Additionally living in a household made of mud or traditional types of housing construction increases the risk of malaria infection [55–57]. The primary pathway through which mud houses increase the risk of malaria is by creating microenvironments conducive for mosquitoes and thus extending their chances of survival and feeding opportunities [55].

Population density may also affect malaria transmission negatively as densely populated areas result in poor habitat conditions that are not conducive environments for *Anopheles* mosquitoes [58, 59]. Densely populated areas tend to have better infrastructure and better access to healthcare [60]. On the other hand, population density may be positively associated with malaria risk as mosquitoes may bite more than one person in a single night [57]. The equivocal findings may be a result of uncontrolled confounding by factors such as vector density and prevalence of ITN use. Poorer households may have less access to preventative measures such as ITNs and health care [50, 61]. In Tanzania and
Uganda, for example, household bed net ownership was lowest among children from the poorest households. The same study however found that in Angola, where there was targeted free bed net distribution to poorer areas, bed net ownership was highest among the poorest [62].

The geographic location of households in relation to vector-breeding sites [54], forests [63], and streams [64–66] has been shown to strongly influence malaria incidence. In southeastern Bangladesh, malaria cases were significantly associated with proximity to water bodies and forests [63]. In northern Angola, malaria cases were significantly associated with proximity to rivers [67]. Studies in Swaziland and Zambia similarly found that households with at least one malaria case tended to be located near bodies of water [64–66]. The distance from households to health facilities has been used as a proxy for access to health care [67, 68], while the distance to international borders has been used as a proxy for cross-border migration [69]. Many household risk factors have been identified, but how these factors interact to expose individuals to malaria infections varies by setting and is largely dependent on environmental factors already at play.

Environmental factors

The importance of climatic factors such as temperature, rainfall and humidity on the distribution, seasonality and transmission intensity of malaria has been well established [70]. Accordingly, climate related covariates are commonly used in the prediction of the burden of malaria, malaria risk mapping, models for outbreak detection and evaluation of vector control interventions. Temperature affects the development, survival and reproduction rates of the parasite within the mosquito, the survival, development and biting rate of the mosquito. Higher temperatures shorten the duration of the sporogony, the
sexual phase of parasite development in the *Anopheles* vector [71], and increase the frequency of blood meals taken thereby accelerating the digestion of blood resulting in more vector-host interactions. Temperatures above 22°C but below 32°C are the most ideal for stable transmission [71]. Elevation is strongly associated with temperature. As elevation increases by 100 meters, temperature decreases by ~ 0.6°C [72]. Typically, elevations greater than 1500 – 2000 meters are considered malaria-free zones, but this limit decreases rapidly with distance from the equator. Rainfall and humidity, on the other hand, influences malaria transmission by creating breeding sites for the aquatic stages of the mosquito life cycle, and favorable humid conditions that promote mosquito growth. While rainfall of at least 80 millimeters for at least three months is necessary for the creation of larval habitats [71], too much rain can destroy larval habitats, greatly limiting transmission.

While climatic factors are integral in defining the spatial and temporal distribution of malaria, other environmental factors can modify the effect of climate. Vegetation, land use and topography are important environmental parameters influencing the availability of shady and humid micro-climates and suitable vector breeding habitats. Factors related to human activities such as urbanization, deforestation, agricultural practices, construction of dams alter the distribution of malaria directly or indirectly.

Several studies have assessed the relationship between malaria and environmental variables in southern Africa. In a study conducted to develop high-resolution maps of malaria risk by transmission season in Swaziland, a logistic regression model indicated that lower elevation, proximity to bodies of water, lower rainfall and warmer temperatures increased the odds of a household having at least one malaria case [65]. A recent study in Zambia showed that households with at least one malaria case tended to be located in close proximity to third order streams and at lower elevations [64]. Using health facility surveillance data for 12 years from 58 districts in Zimbabwe, a national study showed that
warmer temperature, higher rainfall and increased vapor pressure could account for most of the inter-annual variation in malaria case data [73]. Another national study with the goal of developing a reliable habitat model for An. arabiensis found that elevation, isothermality, temperature seasonality, annual precipitation and precipitation of the wettest month were the strongest predictors of potential habitat suitability [74]. In a sub-national study in Masvingo Province, Zimbabwe that also used health facility surveillance data, results from the spatial model indicated that increasing rainfall, warmer temperatures and increasing potential evapo-transpiration increased the risk of malaria [75]. In conclusion, climate and environmental factors define the limits and potential intensity of malaria transmission through their effects on mosquito and parasite life cycles, and are crucial determinants of the effectiveness of various control measures.

**Overview of Analytical Approaches**

*Remote sensing data*

Prior to discussing the analytical tools used in this dissertation, mention should be made of the use of remote sensing data in malaria research. In using environmental data for analysis, there are two main data sources: 1) actual data from weather stations, which is sometimes aggregated to monthly data or interpolated, and 2) remote sensing data, which offers proxy of climate variables. Remote sensing data refers to the collection of information by instruments such as satellites “measuring physical and biological characteristics of some objects without direct contact” [76]. Each data source has strengths and weaknesses related to availability, completeness, spatial and temporal resolution, interpretation and accuracy. Remote sensing data is advantageous over weather station data in that it is available at consistent and frequent time intervals for each grid cell in the set and can easily be linked in geographic information systems as it uses the same map reference system. Additionally, in
rural areas in low-income countries, the distribution of weather stations is sparse and not uniform, and data may be incomplete. Remote sensing data is available for a wide array of indicators including temperature, rainfall, elevation, land use, and greenness of vegetation [76]. With increasing availability of remote sensing data, the use of remote sensing data is becoming more accessible to program managers.

**Malaria risk maps**

One of the goals of epidemiological studies is to understand the geographic patterns of disease by mapping the potential spread of diseases [77]. Global and continental maps of malaria transmission have historically been based on climate suitability for malaria vectors [71, 78]. The Mapping Malaria Risk in Africa (MARA) project was an initiative to map malaria transmission based on climatic data and a more recent initiative, Malaria Atlas Project (MAP), includes high-resolution epidemiological data to produce more precise predictions as well as maps of uncertainty [79, 80]. The proliferation of malaria risk maps in recent years can be attributed to increased availability of data such as entomological and topographical data, availability of environmental covariates from satellites and advances in analytical methods such as model-based geostatistical methods [81].

Geostatistical methods have been used to produce maps of malaria risk at high spatial resolutions [80, 82–84] and applied to large cross-sectional surveys such as the Malaria Indicator Survey (MIS) [83, 85], parasitological data, household surveys [64, 66] and incidence data from malaria surveillance systems[73]. Model-based geostatistical methods allow the estimation of associations between the outcome and covariates. The main advantage is the ability of the resultant model to predict outcome patterns at non-sampled locations and produce smooth risk maps with a measure of uncertainty [86]. Classical statistical methods do not account for spatial dependence whereby observations
closer together in space are more similar than observations further away. Overlooking spatial dependence can lead to biased results. In geostatistical models, the correlation between any pair of locations is considered a function of distance between them and modeled by the covariance matrix of the process.

Malaria risk maps can be used to identify residual transmission foci to target vector control, detect cases in high risk areas, and manage the risk of importation. Nevertheless, an important gap to date has been that many malaria risk maps have been constructed at large spatial scales (global, regional and national). Substantially fewer maps have been developed at finer spatial scales such as district level, the level at which many malaria control programs are implemented. Another limitation has been that until very recently, many malaria maps did not estimate the level of uncertainty in predicted risk.

If the associated uncertainty is ignored, results can be misleading. Maps of uncertainty may be useful in helping to prioritize areas where further information needs to be collected. Malaria risk maps at finer spatial scales will allow the identification of groups of households where malaria is most likely to occur and consequently, the efficient deployment of malaria interventions.

Multilevel Modeling of Malaria

Another goal of epidemiological studies is to determine risk factors associated with disease. Malaria is influenced by various determinants and risk factors defined at different levels justifying the multilevel approach. As previously outlined, at the individual level, malaria infection is associated with age, sex, immunity, occupation, travel; and knowledge, beliefs and perceptions of malaria. Heterogeneity of malaria transmission and disease at the household level is driven by household size, type of house, proximity to vector breeding sites, socioeconomic status, sleeping arrangements, presence of domestic animals near the
home, migration, and the use of preventive methods. Therefore, individuals with similar individual level risk may exhibit different levels of malaria risk as they belong to different households. If a three-level hierarchy were considered, insecticide and drug resistance, social norms, cultural values, beliefs, and practices might be malaria risk factors that are important at the community level.

Multilevel modeling is a statistical approach to analyze the influence of a succession of nested levels on disease simultaneously while accounting for clustering. The data have an inherent multilevel structure, for example: individuals in a household, households in a village and villages in a district. The outcome, which can be continuous or discrete, is then modeled as a function of variables characterizing the different levels. These models must take into account the dependency in the outcome and correlation among individuals in the same household, arising from the nested data structure.

Until recently, most of the malaria research has focused on either using the household or individual as the unit of analysis, or considering in isolation only the effect of ecological factors on malaria risk. Multilevel analysis allows the effects at the individual level to be examined in conjunction with household level and ecological level factors, thereby providing a more complete picture. This type of analysis can aid the formulation and delivery of integrated control strategies targeting ‘at risk’ individuals and high-risk households.

**Evaluation of vector control interventions**

There are five aspects of malaria interventions that have frequently been evaluated: vaccine trials, case management, diagnostic techniques, cost effectiveness and vector control [24]. The third objective of this dissertation focuses on the effect of the latter. Several epidemiological metrics can be used to monitor and evaluate vector control
including: parasite rate as determined by cross-sectional surveys, entomological inoculation rate through entomology surveys and malaria morbidity and mortality determined through health facility based surveillance (Table 1). The use of each metric and corresponding data source has strengths and weaknesses.

The potential of routine entomological surveillance data to measure the effect of IRS has not been fully exploited due to huge cost and labor needs. The reported number of malaria cases and deaths to the HMIS are commonly used core indicators to track the progress of malaria control programs [7]. If reasonably good population data are available, parasitologically confirmed malaria incidence is a good proxy of transmission intensity. Using HMIS is advantageous as many low and middle-income countries have such a system, and minimal additional investment is needed to acquire data to assess the effect of IRS and other population level interventions.

Several studies across SSA have documented the effect of IRS on health outcomes using routine HMIS data. In Kanungu District, Uganda, 16 months after the introduction of IRS, there was a decrease from 52% to 26% in the proportion of patients under five years diagnosed with clinical malaria [87]. In Zanzibar, four years after the scale up of IRS, ITNs and ACTs as first line treatment, routine data from 6 inpatient health facilities found a decrease in malaria deaths of 90% and reductions of 78% in inpatient cases and 99.5% in malaria outpatient cases [88]. In Zambia, one year after the introduction of IRS to urban districts, mortality in health centers in 15 sampled urban districts fell by 63% in children under five, but the number of malaria cases remained stable [89].

Despite the ability of longitudinal data from HMIS to reflect changes related to the implementation of interventions, there are several caveats to using these data to evaluate malaria programs. Changes observed in malaria morbidity and mortality may not
necessarily reflect changes in incidence of disease in the population due to quality of reporting, changes in health seeking behaviors, and changes in testing [90]. Additionally, failure to account for potential confounders and contextual factors – such as the scale up of other interventions, changing diagnostic confirmation practices and climatic variables - make it impossible to rule out the possibility that changes observed were caused by factors other than the intervention; thus observed results may not adequately represent the true effect of interventions.

Despite concerns about the biases of HMIS, there have been recent calls to utilize these data to provide evidence for program effectiveness. The challenges of using HMIS data are not unique to malaria, but the quality of malaria indicators lags behind that of other diseases because of difficulties with diagnosis and also unlinked data systems (laboratory vs. clinical diagnosis for malaria) [91]. For the HMIS data to be useful in monitoring malaria trends, there is urgent need to increase the proportion of malaria diagnoses reported based on laboratory confirmation and to link laboratory results to reported malaria cases [92].

As countries move towards malaria elimination, the utility of national household surveys such as the DHS and MIS, will decline due to the impractical sample sizes that will be needed to detect changes at low parasite prevalences and at smaller spatial scales [93]. In addition, such surveys are intermittent, costly and heavily dependent on external organizations for sustainability. As such, the use of HMIS data on malaria cases and deaths will become increasingly important for evaluation of malaria programs [91].

**Study Setting**

*Zimbabwe*
Zimbabwe is a land-locked country bordered by Mozambique to the east, Zambia to the north, Botswana to the west and South Africa to the South. It covers an area of 390,757 km$^2$, which stretches from 15° to 22° S latitude and from 25° to 33° E longitude. The population according to the 2012 Census was 12.9 million, comprising of approximately 52% women and 15% children under 5 years of age [94]. Although the country has undergone some development, it is still predominantly rural with only 39% urban residents [95].

Zimbabwe has a diverse elevation ranging from 500 meters in Beitbridge on the southern border with South Africa; to above 2,000 meters in the eastern highlands. This influences both the intensity and distribution of rainfall and temperature range. The rainy season typically runs from November to April, with the average annual rainfall ranging from 1500 – 2000 mm in the eastern highlands to less than 400 mm in the southern lowveld [96]. Based on location and elevation, Zimbabwe has historically been divided into three malaria zones. Malaria endemicity ranges from hypoendemic in areas >1200 meters in the north and >900 meters in the south, to hyperendemic in areas <600 meters in the south and <900 meters in the north (Figure 3) [97].

According to the World Malaria Report of 2014, half of the Zimbabwean population was at risk of malaria, and all malaria cases were due to *P. falciparum*, the most virulent malaria parasite [7]. From 2000 to 2013, the annual reported malaria cases exhibited a drastic reduction from 1,533,960 to 377,872, with the decline attributed to the scale-up of malaria-related interventions [98, 99]. In 2009, malaria diagnosis and ACTs became free in the public health sector, and free mass distribution of ITNs targeting all age groups was initiated [7]. In 2013, more than 75% of the population at risk was protected by either ITNs or IRS [7]. Although the scale up of interventions likely contributed to the declines observed, decreases also coincided with improved diagnostic capabilities resulting from the use of
confirmed diagnosis from 2009 [98]. As RDTs increasingly replaced microscopy and clinical diagnosis, the number of diagnostic tests performed more than quadrupled between 2004 and 2013 [100]. In spite of these external contextual factors, both a rapid assessment and a sub-national study showed trends in malaria cases and mortality were at least in part related to the introduction and scale-up of interventions [101, 102].

Despite significant declines in the burden of malaria, the development and spread of insecticide resistance has been documented across Zimbabwe and has adversely affected vector control. The first report of insecticide resistance was in Chiredzi District in 1974, where benzene hexachloride (BHC) resistance was detected in An. arabiensis, the main malaria vector [103]. In 2006, a population of An. arabiensis resistant to DDT was discovered in Gokwe Distrist [103]. More recently (2013-14), An. funestus, which dominates in Mutasa District, exhibited resistance to pyrethroids and carbamates but remained susceptible to organochlorines and organophosphates [18]. These findings necessitated a shift to a long lasting organophosphate formulation, pirimiphos-methyl in four high transmission districts in Manicaland Province in November - December 2014 [104]. Based on the success of the 2014 campaign, this year PMI and the Zimbabwe NMCP intends to support the scale up of pirimiphos-methyl to all seven districts in Manicaland [98].

Due to insecticide resistance, drug resistance and limited funding, persistent hotspots remain in districts along the Zambia border and Mozambique border despite the decline in reported cases nationally (Figure 4) [17, 18, 102, 105]. Mozambique has a stable epidemiological pattern of malaria all year with a peak in the rainy season [106]. Zambia, on the other hand, is malaria endemic but has been targeting to create malaria free zones in the southern province [107]. Manicaland province was noted to be the largest contributor of high malaria incidence. In 2012, the highest malaria incidence was reported in Nyanga (200/1,000), Mutasa (141/1000) and Mbire (124/1,000) districts [99].
**Mutasa District**

Mutasa District, one of 56 districts in Zimbabwe, is located in Manicaland East Province. It is situated between latitudes 18°00 S and 19°00 S and longitudes 32°00 E and 33°00 E. The elevation is undulating with elevation averaging 900 meters above sea level in the valleys and rising above 1600 meters in the mountains. The district is drained by the Pungwe and Honde rivers. The major rain fall season is November – April, annual rainfall averages 1,340 millimeters, and the highest monthly rainfall occurs in January or February. The highest temperatures occur in August-October with high relative humidity between November - February. The district has an estimated population of 180,454 and has an agro-based economy. Crops cultivated in the district include maize, bananas, coffee and tea.

**Aims of the dissertation**

The research described in this dissertation was possible due to the research infrastructure and experience of the Southern Africa ICEMR, which established Mutasa District as a research site in October 2011. This dissertation includes three studies that collectively seek to describe the epidemiology of malaria in Mutasa District. Additionally, this dissertation seeks to understand the effect of current malaria control interventions with the goal of informing the optimization of malaria control in Eastern Zimbabwe. The first paper (Chapter 3) describes a cross-sectional study that identified individual and household level factors associated with RDT positivity in sample households. The second paper (Chapter 4) describes a cross-sectional study that identified environmental factors associated with malaria risk and assessed the seasonal and spatial distribution of household malaria risk. The third paper (Chapter 5) describes a quasi-experimental study that evaluated a recent indoor residual spraying campaign.
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Tables and Figures

Table 1: Commonly used indices to measure malaria and its intensity

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Definition</th>
<th>Advantages and disadvantages</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entomological inoculation rate (EIR)</td>
<td>Expected number of infectious bites received per person per unit time</td>
<td>• Difficult and labor intensive to obtain</td>
<td>Entomological surveys</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gold standard measure of transmission</td>
<td></td>
</tr>
<tr>
<td>Parasite rate</td>
<td>Proportion of population with parasites in their blood</td>
<td>• Varies by age, season and species of parasite</td>
<td>Cross-sectional surveys</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Proportion of infections will be missed by RDTs and microscopy</td>
<td></td>
</tr>
<tr>
<td>Force of infection</td>
<td>Number of new infections per person per unit time</td>
<td>• Difficult to measure accurately</td>
<td>Cohort studies or repeated cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limited precision</td>
<td></td>
</tr>
<tr>
<td>Vectorial capacity</td>
<td>Expected number of infectious bites which arise from all of the mosquitoes that bite an individual on a single day</td>
<td>• Difficult to measure all components needed to calculate</td>
<td></td>
</tr>
<tr>
<td>Annual parasite index</td>
<td>Total number of confirmed cases per year divided by the total population</td>
<td>• Dependent on age and diagnostic method</td>
<td>Cohort studies</td>
</tr>
</tbody>
</table>

Source: Adapted from [108]
Figure 2: Life cycle of the malaria parasite

Source [2]
Figure 3: Map of Africa showing the distribution of pyrethroid resistance

Source: [20]
Figure 3: Map of regions of malaria endemicity in Zimbabwe

Source: [109]
Figure 4: Map of malaria incidence rate per 1,000 for 2012 in Zimbabwe

Source: [99]
CHAPTER 3:
INDIVIDUAL AND HOUSEHOLD LEVEL RISK FACTORS ASSOCIATED WITH MALARIA IN MUTASA DISTRICT, ZIMBABWE: A SERIAL CROSS-SECTIONAL STUDY

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Abstract

Background: Malaria constitutes a major public health problem in Zimbabwe, particularly in the north and east bordering Zambia and Mozambique. In Manicaland Province in eastern Zimbabwe, malaria transmission is seasonal and unstable. As a result of intensive scale up of malaria interventions, malaria control was successful in Manicaland Province. However, over the past decade, Manicaland Province has reported increased malaria transmission, and the resurgence of malaria in this region has been attributed to limited funding, drug resistance and insecticide resistance. One of the worst affected districts is Mutasa District. The aim of the study was to identify malaria risk factors at the individual and household levels to better understand what is driving factors associated with malaria and consequently enhance malaria control in eastern Zimbabwe.

Methods: Between October 2012 and September 2014, individual demographic data and household characteristics were collected from cross-sectional surveys of 1,116 individuals residing in 316 households in Mutasa District. Factors characterizing the surrounding environment were obtained from remote sensing data. Factors associated with malaria (measured by rapid diagnostic test [RDT]) were identified through univariate and multivariate multilevel logistic regression models.

Results: A total of 74 (6.4%) participants were RDT positive. Parasite prevalence differed by season (10.4% rainy and 2.9% dry, OR 4.52, 95% CI 2.11-9.69). Sleeping under a bed net showed a protective effect against malaria (OR 0.54, 95% CI 0.29-1.00) despite pyrethroid resistance. The household level risk factors protective against malaria were household density (OR 0.89, 95% CI 0.87-0.97) and increasing distance from the border with Mozambique (OR 0.86, 95% CI 0.76-0.97). Increased malaria risk was associated with recent indoor residual spraying (OR 2.30, 95% CI 1.16-4.56).
Conclusions: Malaria risk was concentrated in areas located at a lower household density and in closer proximity to the Mozambique border. Malaria control in these “high risk” areas may need to be enhanced. These findings underscore the need for strong cross-border malaria control initiatives to complement country specific interventions.
Background

Zimbabwe lies in the southern fringe of malaria transmission in sub-Saharan Africa [1]. Approximately half of the population of 12.9 million live in malarious areas and malaria transmission occurs in 47 of the 65 districts in the country [2, 3]. Annually, malaria causes an estimated 380,000 reported cases and 350 deaths [3]. The epidemiology of malaria varies in different regions of the country, ranging from year-round transmission in the low-lying areas of the Zambezi and Limpopo valleys, to epidemic-prone areas along the watershed ridge running from the east to southwest of the country [4]. Malaria transmission in Manicaland Province, on the border with Mozambique is unstable with seasonal epidemics. In 2009, 55,707 confirmed cases of malaria were observed in Manicaland Province, which increased to 192,730 in 2013 [3]. Manicaland Province, an area hardest hit by malaria, reported more than half of the malaria cases and more than one third of malaria deaths in the country [5].

Nationally, the annual number of cases of malaria reported has dramatically declined from 1.5 million in 2000 to just over 370,000 in 2013 [3, 5]. This has not been the case for Manicaland Province however. Within Manicaland Province, the Districts of Nyanga and Mutasa are ranked nationally as the Districts with the highest incidence of clinical malaria, based on passive case-finding data from health centers [5]. Considering the previous intensive control measures, and relatively low incidence of malaria, the sharp increase in malaria morbidity and mortality most likely represents a resurgence of malaria in an area where malaria control was previously successful. This apparent increased burden has been attributed to a combination of insecticide resistance, drug resistance and limited funding, which disrupted malaria control programs that had been effective for more than 50 years [6–8].
Given limited resources, better understanding of the epidemiology of malaria transmission in the context of resurgent malaria would support local malaria control strategies and maximize the impact on reducing malaria morbidity and mortality. In order to provide more reliable active case-finding data, serial cross-sectional surveys were conducted from 2012 to 2014 to identify individual- and household-level risk factors for malaria in Mutasa District.

**Methods**

*Study setting and procedures*

Mutasa District has an elevation ranging from 900 meters in the Honde valley to over 1,500 meters in the mountains (Figure 4). Rainfall patterns in Zimbabwe are highly seasonal with a rainy season from November to April and dry season with little to no rainfall from May to October. Mutasa District received 2,352 millimeters of rainfall during the 2013-2014 rainy season and 96 millimeters during the dry season as measured in Hauna, the main town in the Honde valley. The district had an estimated 169,756 residents representing 42,479 households at the time of the 2012 census [2], and the population depends heavily on agriculture for its livelihood. Malaria transmission in the study area is characterized as seasonal and unstable with major outbreaks during the rainy season [9]. *Plasmodium falciparum* is the main malaria species and *Anopheles funestus* the dominant malaria vector [10], with high levels of resistance to pyrethroid and carbamate insecticides [8]. Indoor residual spraying (IRS) and mass distribution of insecticide treated nets (ITNs) are the main vector control interventions implemented in the study area by the National Malaria Control Programme (NMCP) and partners. The population covered by pyrethroid-based IRS in Mutasa District was 88% in 2012 and 91% in 2013. In 2014, an orgaphosphate, pirimiphos-methyl was used and covered 92% of the population. ITNs were distributed to
the general population in 2013 and limited to boarding schools in 2014.

A high-resolution satellite image of the study area obtained in 2011 from DigitalGlobe Services, Inc. (Denver, Colorado) was imported into ArcGIS 10.2 (Environmental Systems Research Institute, Redlands, California), and the locations of households were identified manually and digitized. A grid containing 1x1 kilometer cells was overlaid onto the image and the first stage of sampling involved selection of grid cells. This selection process ensured adequate geographic distribution of the sample while considering logistical challenges in reaching remote areas where transport is difficult especially during the rainy season. In the second stage of sampling, households were randomly selected from within the selected grid cells and assigned to one of two study cohorts: longitudinal and cross-sectional. Households in the prospective longitudinal cohort were surveyed every other month while households in the cross-sectional study were surveyed only once during the entire study period. The process of creating a sampling frame by digitizing households from a high-resolution satellite image has been implemented and validated [11–13].

Trained interviewers followed standardized operating procedures that had been developed and piloted in the field to ensure reliability. After obtaining written informed consent for study participation from adults and caregivers as well as assent from children older than 7 years, interviewers administered a questionnaire to the head of the household that was used to list all household members and collect basic demographic information. Household members were eligible for inclusion in the study if they were a resident of the selected household regardless of age and pregnancy status. A questionnaire was used to collect data on socio-demographic characteristics, malaria-related knowledge, malaria history, and use of malaria preventative measures. A finger-prick blood sample was obtained for malaria parasite testing using a rapid diagnostic test (RDT) (SD BIOLINE,
Malaria Ag P.f., Standard Diagnostic Inc). Those with positive test results were offered treatment with artemisinin-combination therapy (ACT) according to national guidelines. Responses to the questionnaires and RDT results were recorded and stored electronically on Android tablets using Open Data Kit (ODK) software, then transferred to REDCap 4.1, a secure, web-based application designed to support data capture for research studies [14].

**Study Measures and Instruments**

The outcome of interest was whether an individual tested positive or negative for malaria by RDT on the day of enrolment. Supporting data were collected describing features at the individual and household level as well as of characteristics of the surrounding environment. Individual-level characteristics included age, sex, history of malaria-related symptoms, malaria knowledge and use of bed net and other preventive measures. Age was grouped into five categories: <5, 5-14, 15-24, 25-49 and 50 or more years. A composite malaria knowledge score was created using responses to survey questions evaluating knowledge of symptoms, causes and prevention of malaria. Use of a bed net was determined by asking respondents “Do you sleep under a bed net?” and responses were dichotomized into yes/no categories.

Potential household-level risk factors obtained from questionnaires administered to the heads of the households included: education level of household head, household size, and indoor residual spraying in the past six months. A household wealth index was constructed using a principal components analysis of household characteristics (housing floor material, primary cooking fuel used and water source) and asset ownership (radio, television, refrigerator, bicycle, motorbike and car)[15, 16]. The first principal component accounted for 21% of the variability. Greatest weight was given to ownership of a television (0.72), use of electricity as the primary cooking fuel (0.69) and ownership of a refrigerator
(0.68). A proxy for household socio-economic status (SES) was created by dividing the wealth index into tertiles defining the poorest, middle, and richest households.

Several variables characterizing the environment surrounding households were obtained. As proximity to certain environmental and social features can play an important role in understanding spatial disease patterns, the Euclidean distances from each household to the nearest health facility, the nearest main road, the Zimbabwe-Mozambique border, and to different categories of streams were calculated in ArcGIS 10.2 using the “Near” tool. The nearest health facility to each surveyed household was used as a proxy for access to health services. The distance to nearest nth order stream, distance to the nearest road and distance to the Zimbabwe-Mozambique border were proxies for proximity to vector breeding sites, accessibility to transportation and cross-border migration, respectively.

Construction of a stream network was based on hydrological models from a 90-meter resolution digital elevation model (DEM) of the study area from the Shuttle Radar Topographic Mission (SRTM) [17]. While lower order streams typically flow during the rainy season only, higher order streams have greater peak flows, are found at low elevations and flow throughout the year. Within the study area, the highest stream order was four; therefore, distance from a surveyed house to first-, second-, third- and fourth-order streams were determined. Topographical attributes are potentially relevant for habitat suitability of malaria vectors, thus aspect, slope, and elevation were extracted from the DEM [13, 18]. The aspect, which ranges from 0 to 360 degrees, was categorized into three topographically important slope orientations: northern-facing, southern-facing and all other slope orientations. In the southern hemisphere, northern facing slopes tend to be warmer and less humid because of more direct sunlight [13, 19].

Using buffering techniques and the global positioning system (GPS) location of all houses, the number of houses within circular buffers of radii 250, 500 and 1,000 meters
were calculated to give the local house density. A LANDSAT™ 8 image from July 2014 with a spatial resolution of 30 meters and eleven spectral bands was downloaded from the United States Geological Survey Land Processes Distributed Active Archive Center [20]. The Normalized Difference Vegetation Index (NDVI) ranges from -1 to 1, with higher values indicating denser vegetation. NDVI was calculated as the ratio of near infrared (NIR) and red spectral bands \[ \text{NDVI} = \frac{\text{NIR} - \text{red}}{\text{NIR} + \text{red}} \]. Land use for the study area was generated by unsupervised land cover classification using LANDSAT™ 8 image bands 2, 3, 4, 5, 6 and 7; and classified into six groups: water, crop, bare land, impervious, grass and forest.

**Statistical Analysis**

The analysis was based on the single visit conducted at cross-sectional households and the initial visit to longitudinal households, subsequent visits to these households were excluded, as repeated testing and treating can alter the natural history of malaria transmission within households [21]. Descriptive analyses were performed to explore the characteristics of both the outcome and supporting variables using chi-square tests for categorical variables and t-tests for continuous variables. The outcome variable, RDT positivity for each individual, was dichotomous for which logistic regression was the appropriate method for analysis. As individuals were nested within households and individuals within a particular household may have been more similar to one another than to individuals in other households, the assumption of independence in standard logistic regression methods is likely to be violated. To account for the hierarchical structure of the data and potential clustering effect of RDT outcomes within households, multilevel logistic regression analysis was used to model RDT positivity as a function of individual and household-level factors. Environmental variables were obtained per household and were considered household-level variables for analysis.
Three consecutive models were fitted to the data. In Model 1 (null model), the probability of an individual testing RDT positive was only a function of the individual’s household and modeled by a random intercept allowing estimation of the overall between household variance for the outcome measure, RDT positivity. Model 2 (individual level model) included individual level variables associated with malaria risk. Initially, Model 2 contained all individual-level variables significantly associated with RDT positivity (p<0.2) in univariate regressions (each variable tested one at a time) and several variables (age, sex, and bed net use) deemed important a priori. Variables not significant at the p < 0.05 level were eliminated one by one in order of least significance. Potential explanatory variables that were not found to be significant in the univariate models were evaluated one by one for inclusion in the model. Model 3 (multilevel model) added household-level variables to Model 2 using the same manual model selection. Within- and cross-level interactions were assessed and variables were tested for multicollinearity. The association of explanatory variables with RDT positivity was quantified by odds ratios (OR) and 95% confidence intervals (CI). Environmental data processing and maps were made in ArcGIS version 10.2. Environmental data were linked to parasitological data according to GPS location. Non-spatial data analysis was conducted using STATA 12.0 (StataCorp, College Station, Texas) while spatial analyses were performed in R development software using geoR package [22].

*Ethical considerations*

The study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB), the Biomedical Research and Training Institute IRB and the Medical Research Council of Zimbabwe. Discussions were held with chiefs and other community leaders about the study purpose and conduct, and permission was given to visit households in their area. Informed consent was obtained from the head of household before
enrollment and written informed consent was obtained from all of the eligible adult
participants and caregivers. Assent was obtained from children from children 7 to 15 years
old.

Results

Descriptive analysis

A total of 1,187 individuals from 319 households were visited between October
2012 and September 2014. Two households with missing geographical coordinates and 22
individuals with missing RDT results were excluded from the analysis, giving a final sample
of 1,161 individuals residing within 316 households. Of the 316 households, only a small
proportion used electricity to cook (8.2%), had piped water (34.5%), were situated on
northern facing slopes (6.7%) or were located at elevations ≥820 meters (25.0%).
Households were on average 1.7 (interquartile range (IQR): 0.6–5.0) kilometers from the
nearest health facility and 1.3 (IQR: 0.8–3.3) kilometers from the nearest main road. About
two thirds of respondents (61%) reported their household ever having been sprayed with
insecticide, with just over half (57%) of these households reporting that spraying had
occurred within the previous 6 months (Table 1).

Of the 1,161 individuals, 189 (16%) were children under 5 years of age and 648
(56%) were females. The rate of bed net ownership was 82%, and the most cited barriers to
bed net ownership were cost, heat, and the perception that there were no mosquitoes. Of
those with access to a bed net, 52% self-reported actually sleeping under a bed net. Use of
bed nets varied by season with 60% of participants sleeping under a bed net during the
rainy season compared to 46% during the dry season.

During the study period, 74 individuals from 50 households tested positive for
malaria by RDT and 16 of the households included more than one RDT-positive household
member at the time of enrolment. The overall crude parasite prevalence by RDT was 6.4% (95% CI 5.0 – 7.8%), and was higher during the rainy season compared with the dry season (10% vs. 3%, p<0.05). The highest prevalence in RDT positivity was in young adults 15 to 24 years of age. There was a sharp decline in RDT positivity between young adults 15 to 24 years of age and adults 25 to 49 years of age (Figure 5). Of the RDT positive individuals, 16% and 23% reported a fever in the prior 48 hours and in the previous two weeks, respectively (Table 2).

Multivariate analysis

Multilevel, multivariate, logistic regression showed that RDT positivity was associated with age (p value = 0.05) (Table 3). Compared to the reference group (age ≥50 years), individuals <5, 5-14, and 15-24 years had approximately 2.7 times the odds of RDT positivity (OR 2.67, 95% CI 0.94-7.56; OR 2.61; 95% CI 0.97-7.06; OR 2.70; 95% CI 1.00-7.29). Individuals 25-49 years were not found to have a significantly different risk of RDT positivity than the reference age ≥50 category (OR 0.94; 95% CI 0.33- 2.70). Sleeping under a bed net decreased the odds of a positive malaria RDT (OR 0.5; 95% CI 0.3- 1.0) despite pyrethroid resistance in An. funestus.

At the household level, for every 1 kilometer increase in distance from the Zimbabwe-Mozambique border, the odds of RDT positivity decreased by 14% (OR 0.86; 95% CI 0.76-0.97). The cumulative effect of distance to the Zimbabwe-Mozambique border was substantial, as half of study households were located six or more kilometers away from the border; the odds of malaria in individuals from these distant households were 65% lower (OR 0.35, 95% CI: 0.18 – 0.65) than among individuals in households close to the border. Furthermore, for every additional 10 houses within 250 meters, the odds of RDT positivity decreased by 11% (OR 0.89; 95% CI 0.87- 0.97). Elevation was associated with
lower risk of malaria although it did not reach statistical significance (p=0.1). Residing in a household ≥850 meters above sea level reduced the odds of malaria compared to a household <800 meters (OR 0.32; 95% CI 0.09-1.09). Individuals in households surveyed during the rainy season were 4.52 times more likely to test positive for malaria (OR 4.52; 95% CI 2.11-9.69) than those in households surveyed during the dry season.

The household random effect for the null model (CI = Confidence Interval, IRS = Indoor residual spraying, OR = Odds ratio, RDT= rapid diagnostic test)

Table 4, Model 1) showed that RDT positivity was clustered at the household-level, confirming the need for a multilevel approach instead of conventional logistic regression. After adding individual-level and household level variables, the random effect variance decreased from 2.24 (CI = Confidence Interval, IRS = Indoor residual spraying, OR = Odds ratio, RDT= rapid diagnostic test)

Table 4, Model 1) to 0.69 (CI = Confidence Interval, IRS = Indoor residual spraying, OR = Odds ratio, RDT= rapid diagnostic test)

Table 4, Model 3). However, the variance of the random intercept remained significant (p=0.04), suggesting that there are unobserved variables that may further explain heterogeneity across households (CI = Confidence Interval, IRS = Indoor residual spraying, OR = Odds ratio, RDT= rapid diagnostic test)

Table 4, Model 3).

Discussion

After many years of apparently effective control, the Manicaland Province of Zimbabwe has experience resurgence of malaria in recent years and has now become one of the most affected Provinces in the country. This study identified individual- and household-level factors associated with malaria identified based on cross-sectional surveys involving
active case detection in Mutasa District, one of the Districts most affected by malaria in Manicaland. The study highlights the importance of both individual- and household-level factors in determining malaria risk. Malaria risk was significantly higher among individuals who: (1) were younger than 25 years; (2) did not sleep under a bed net; (3) were sampled during the rainy season; (4) lived in sparsely populated areas; and (5) lived close to the Zimbabwe-Mozambique border. Several of the findings have clear implications for malaria control in this District that may also be applicable to other settings with similar epidemiology.

Of particular significance is the finding that the closer individuals live to the Zimbabwe-Mozambique border, the higher their risk of malaria. Several regional studies have found higher risk of malaria closer to international borders. In Mpumalanga Province, South Africa, individuals living within 5 kilometers of the Mozambique border had 4 times the risk of malaria compared to individuals residing further from the border [23]. Similarly in Namibia, the highest risk of malaria was found along the border with Angola, which is considered malaria endemic [24, 25]. There are three mechanisms by which distance to the Zimbabwe-Mozambique border may affect malaria transmission in Mutasa District: lower elevation closer to the border, cross-border migration by residents on both sides of the border or movement of infected mosquitoes into the area [26, 27]. The elevation in Mutasa District generally slopes from west to east, with low-lying areas near the border with Mozambique (Figure 4), and the risk of malaria is higher at lower elevations. Mutasa District has experienced considerable human population movement to and from Mozambique, for example, during the Mozambican civil war and more recently, during the economic crisis in Zimbabwe [16]. The border with Mozambique is porous and individuals move between countries for employment, to access health care and to visit relatives. These migrants may serve as a human reservoir of malaria parasites [28, 29]. Malaria control in
western Mozambique is largely dependent on case management, with limited IRS and distribution of ITNs only in peri-urban areas [30]. The movement of parasite-carrying individuals from the higher transmission setting of Mozambique may be undermining malaria control as has been suggested from studies in other countries where malaria resurgence has been attributed in part to frequent human population movement across international borders [24, 31].

Regionally, several inter-country collaborations have been developed to address cross-border malaria, including the Lubombo Spatial Development Initiative between Mozambique, South Africa, and Swaziland [32], the Trans-Kunene Malaria Initiative between Namibia and Angola [25], and the Trans-Zambezi Malaria Initiative between Angola, Botswana, Namibia, Zambia, and Zimbabwe [24]. The success of these regional initiatives has been hampered, however, by lack of political will, limited funding, slow mobilization of resources and poor coordination [25, 33]. The strong relationship between malaria and proximity to the Zimbabwe-Mozambique border provides yet another argument for the importance of not only individual country strategies but also regional collaborations in controlling malaria. Stronger inter-country collaborations will be especially important as malaria goals shift from control to elimination.

Malaria RDT positivity was associated with younger age. Compared to the reference group (age 50 and older), individuals <25 years were significantly more likely to be RDT positive and the risk of malaria infection was highest for adolescents and young adults. This might be a result of different exposure rates, and other behavioral risk factors in the younger population [8-10]. In fact, individuals 15-24 years old reported the lowest usage of bed nets, followed by 5-14 year olds. Sleeping under a bed net was associated with a lower risk of malaria, which is consistent with evidence from randomized controlled trials [34]. This reduced risk is in spite of the high levels of pyrethroid resistance in Mutasa District [8],
and so is presumably due to the physical barrier effect of ITNs rather than their insecticidal properties. Approximately 58% of individuals did not have access to or did not use a bed net, increasing their odds of acquiring malaria by 46%. Malaria interventions including ITN distribution need to target younger populations, perhaps through school-based interventions to achieve higher ITN coverage and contribute more effectively to reductions in malaria transmission.

IRS reduces malaria transmission by reducing the life span of mosquitoes and by reducing the density of mosquitoes in sprayed households [35, 36]. Recent IRS of a house was expected to be associated with a significant protective effect against malaria infection. However, IRS within the previous 6 months was in fact associated with increased odds of malaria. One plausible explanation for this seemingly paradoxical result is that indoor residual spraying was more likely applied where the risk for malaria was greater. In a resource limited setting, targeting higher prevalence areas can maximize impact [37].

According to Zimbabwe's Malaria Strategic Plan, only some districts are targeted for IRS based on previous transmission patterns and incidence data [3]. Another likely explanation is that insecticide resistance that has been reported nationally may be undermining IRS efficacy. Results of insecticide susceptibility tests in 2013 and 2014 showed that the main malaria vector in Mutasa District, *An. funestus* was resistant in bioassays to both pyrethroids and carbamates [8]. Lastly, recent IRS was self-reported, and may have been misclassified. It is likely that misclassification would be non-differential with respect to the outcome, RDT positivity, thus biasing the results towards the null.

The results presented here should be interpreted in light of several limitations. Given that the use of bed nets and recent residual spraying of household were self-reported, these exposure variables may be subject to social desirability bias and recall bias. In the case of use of bed nets, any bias may be minimal as interviewers requested to see the bed
nets in households reporting ownership of at least one bed net – though it was noted that physical presence was not necessarily related to effective use.

Although data on a variety of potential confounding factors was collected, the final model only explained 69% of the between household variance. There may be other factors not measured in this study that contribute towards the understanding of malaria transmission in an area such as Mutasa District. For example, agriculture is the main activity in this District and engaging in agriculture related activities has been associated with increased malaria risk, particularly among migrant laborers [38, 39]. Understanding the movement of individuals, not just at large spatial scales like across international borders, but locally, may also be important to understanding the epidemiology of malaria. The association of recent travel with malaria has been explored and more recent research has attempted to more finely define travel by including time of travel, transmission intensity at origin and destination and duration of travel [40]. Simple Euclidean distance to the Zimbabwe-Mozambique border, which was used as a proxy for cross-border migration, does not account for the actual physical travel path used, access to transportation and the time of travel and so these data may underestimate actual distance and time applicable to migration. However, in the absence of digital data on road network for the study area and actual travel paths, the distance to the border was taken to be a reasonable proxy for cross-border migration, and has previously been used as a surrogate measure for migration and importation of malaria cases [26].

Using multilevel modeling, individual and household characteristics were identified that were predictive of malaria risk, implying that combined interventions targeting “at risk” individuals and “high risk” areas may effectively reduce malaria. This study underscores the need for strong regional initiatives to control malaria. Results from this study can be used by malaria control managers to define priority populations and areas for
intensified efforts. Increasing coverage of malaria interventions and undertaking inter-
country programs will be key to regaining malaria control in Mutasa and other Districts in
Zimbabwe.
References


34. Lengeler C: Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane database Syst Rev* 2004:CD000363.


Tables and Figures

Table 1: Characteristics of 316 sampled households in Mutasa District (October 2012 – September 2014)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest education level of head of household</td>
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<td></td>
</tr>
<tr>
<td>None or primary</td>
<td>129</td>
<td>44.0</td>
</tr>
<tr>
<td>Secondary or higher</td>
<td>164</td>
<td>56.0</td>
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<tr>
<td>Land use</td>
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<td></td>
</tr>
<tr>
<td>Crop</td>
<td>180</td>
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</tr>
<tr>
<td>Bare land</td>
<td>29</td>
<td>9.2</td>
</tr>
<tr>
<td>Impervious</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Grass</td>
<td>89</td>
<td>28.2</td>
</tr>
<tr>
<td>Forest</td>
<td>14</td>
<td>4.4</td>
</tr>
<tr>
<td>Aspect of slope</td>
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</tr>
<tr>
<td>Northern</td>
<td>21</td>
<td>6.7</td>
</tr>
<tr>
<td>Southern</td>
<td>51</td>
<td>16.1</td>
</tr>
<tr>
<td>All other orientations</td>
<td>244</td>
<td>77.2</td>
</tr>
<tr>
<td>Piped water is main source of water</td>
<td>104</td>
<td>34.5</td>
</tr>
<tr>
<td>Electricity is main source of cooking energy</td>
<td>26</td>
<td>8.2</td>
</tr>
<tr>
<td>Household ever sprayed</td>
<td>187</td>
<td>61.1</td>
</tr>
<tr>
<td>Household sprayed in the past six months</td>
<td>95</td>
<td>29.8</td>
</tr>
<tr>
<td>Median IQR</td>
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<td></td>
</tr>
<tr>
<td>Elevation (m)</td>
<td>786</td>
<td>757,819</td>
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<tr>
<td>Household size</td>
<td>5</td>
<td>3.8</td>
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<tr>
<td>Distance to first order stream (m)</td>
<td>578</td>
<td>370,747</td>
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<tr>
<td>Distance to second order stream (m)</td>
<td>1300</td>
<td>1044,1578</td>
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<tr>
<td>Distance to third order stream (m)</td>
<td>1579</td>
<td>575,2274</td>
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<tr>
<td>Distance to forth order stream (m)</td>
<td>1885</td>
<td>1118,3760</td>
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<tr>
<td>Distance to nearest health facility (m)</td>
<td>1687</td>
<td>568,5016</td>
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<tr>
<td>Distance to main road (m)</td>
<td>1307</td>
<td>752,3336</td>
</tr>
<tr>
<td>Distance to Zimbabwe-Mozambique border (m)</td>
<td>6040</td>
<td>4526,8899</td>
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<tr>
<td>Number of households within 250m buffer</td>
<td>16</td>
<td>8.42</td>
</tr>
<tr>
<td>Number of households within 500m buffer</td>
<td>51</td>
<td>31,104</td>
</tr>
<tr>
<td>Number of households within 1000m buffer</td>
<td>174</td>
<td>137,242</td>
</tr>
<tr>
<td>NDVI</td>
<td>0.22</td>
<td>0.18,0.27</td>
</tr>
</tbody>
</table>

NDVI = Normalized Difference Vegetation Index, IQR = Interquartile range
Table 2: Characteristics of individuals in Mutasa District at baseline (October 2012 – September 2014) N=1,161

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total study population N = 1,161</th>
<th>RDT positive N=74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt;5</td>
<td>189</td>
<td>16.3</td>
</tr>
<tr>
<td>5-14</td>
<td>255</td>
<td>22</td>
</tr>
<tr>
<td>15-24</td>
<td>220</td>
<td>18.9</td>
</tr>
<tr>
<td>25+</td>
<td>497</td>
<td>42.8</td>
</tr>
<tr>
<td>Sex</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>513</td>
<td>44.2</td>
</tr>
<tr>
<td>Female</td>
<td>648</td>
<td>55.8</td>
</tr>
<tr>
<td>Fever on the previous day</td>
<td>65</td>
<td>5.6</td>
</tr>
<tr>
<td>Fever in past two weeks</td>
<td>118</td>
<td>10.2</td>
</tr>
<tr>
<td>Nausea/vomiting on the previous day</td>
<td>25</td>
<td>2.2</td>
</tr>
<tr>
<td>Nausea/vomiting in past two weeks</td>
<td>59</td>
<td>5.1</td>
</tr>
<tr>
<td>Chills on the previous day</td>
<td>62</td>
<td>5.3</td>
</tr>
<tr>
<td>Chills in past two weeks</td>
<td>105</td>
<td>9.0</td>
</tr>
<tr>
<td>Visited health facility/post in past month for malaria</td>
<td>166</td>
<td>14.3</td>
</tr>
<tr>
<td>Visited health facility/post in past 6 months for malaria</td>
<td>413</td>
<td>35.6</td>
</tr>
<tr>
<td>Owns a bed net</td>
<td>948</td>
<td>81.7</td>
</tr>
<tr>
<td>Slept under bed net</td>
<td>493</td>
<td>52.1</td>
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RDT = rapid diagnostic test
Table 3: Univariate and multivariable multilevel logistic regression analysis of risk factors for malaria RDT positivity (n=1,161)

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR</th>
<th>Univariate 95% CI</th>
<th>P</th>
<th>Multivariate OR</th>
<th>Multivariate 95% CI</th>
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<td><strong>Individual level factors:</strong></td>
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<tr>
<td>Age categories (years)</td>
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<tr>
<td>&lt;5</td>
<td>2.64</td>
<td>0.92, 7.56</td>
<td>0.03</td>
<td>2.67</td>
<td>0.94, 7.5</td>
<td>0.05</td>
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<tr>
<td>5-14</td>
<td>2.84</td>
<td>1.03, 7.84</td>
<td>0.05</td>
<td>2.61</td>
<td>0.97, 7.0</td>
<td>0.06</td>
</tr>
<tr>
<td>15-24</td>
<td>2.54</td>
<td>0.93, 6.96</td>
<td>0.06</td>
<td>2.70</td>
<td>1.00, 7.2</td>
<td>0.09</td>
</tr>
<tr>
<td>25-49</td>
<td>0.91</td>
<td>0.31, 2.69</td>
<td>0.07</td>
<td>0.94</td>
<td>0.33, 2.7</td>
<td>0.00</td>
</tr>
<tr>
<td>≥ 50</td>
<td>Reference</td>
<td></td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.91</td>
<td>0.53, 1.54</td>
<td>0.7</td>
<td>0.97</td>
<td>0.33, 2.70</td>
<td>0.91</td>
</tr>
<tr>
<td>Sleep under bed net</td>
<td>0.65</td>
<td>0.35, 1.19</td>
<td>0.1</td>
<td>0.54</td>
<td>0.29, 1.00</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Household level factors:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevation categories (m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;800</td>
<td>Ref</td>
<td>0.12</td>
<td></td>
<td>Ref</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>800 – 849</td>
<td>0.78</td>
<td>0.35, 1.74</td>
<td>0.03</td>
<td>1.16</td>
<td>0.55, 2.45</td>
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<tr>
<td>≥850</td>
<td>0.31</td>
<td>0.08, 1.12</td>
<td>0.03</td>
<td>0.32</td>
<td>0.09, 1.09</td>
<td></td>
</tr>
<tr>
<td>Number of houses within 250 m (per 10 houses)</td>
<td>0.89</td>
<td>0.80, 0.99</td>
<td>0.03</td>
<td>0.89</td>
<td>0.87, 0.97</td>
<td>0.01</td>
</tr>
<tr>
<td>House sprayed with IRS in past 6 months</td>
<td>3.87</td>
<td>2.08, 7.18</td>
<td>&lt;0.01</td>
<td>2.30</td>
<td>1.16, 4.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak season (December – May)</td>
<td>5.40</td>
<td>2.52, 11.4</td>
<td>&lt;0.01</td>
<td>4.52</td>
<td>2.11, 9.69</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Distance to Mozambique border (per km)</td>
<td>0.92</td>
<td>0.82, 1.02</td>
<td>0.01</td>
<td>0.86</td>
<td>0.76, 0.97</td>
<td>0.01</td>
</tr>
<tr>
<td>Distance to second order stream (per km)</td>
<td>2.37</td>
<td>1.25, 4.49</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Distance to main road (per km)</td>
<td>1.18</td>
<td>0.99, 1.42</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Northern facing slope (aspect)</td>
<td>3.00</td>
<td>0.97, 9.25</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Electricity is main source of cooking energy</td>
<td>0.11</td>
<td>0.01, 1.10</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI = Confidence Interval, IRS = Indoor residual spraying, OR = Odds ratio, RDT= rapid diagnostic test
Table 4: Household level random effects summary for the null, individual level and multilevel models

<table>
<thead>
<tr>
<th>Household random effect</th>
<th>Estimate</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Null model</td>
<td>2.24</td>
<td>0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2: Best individual level model</td>
<td>2.41</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3: Best multilevel model</td>
<td>0.69</td>
<td>0.52</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Figure 4: Topographical map of Mutasa District, Zimbabwe and the distribution of sampled households
Figure 5: RDT positivity by age group

![Bar chart showing RDT positivity by age group.](chart)

- <5 years: 8% (±2%)
- 5-14 years: 8% (±2%)
- 15-24 years: 12% (±2%)
- 25-49 years: 4% (±2%)
- 50+ years: 6% (±2%)
- All ages: 7% (±2%)

Percent RDT positive vs. Age group (years)
CHAPTER 4:
HIGH-RESOLUTION MALARIA RISK MAPPING IN MUTASA DISTRICT, ZIMBABWE:
IMPLICATIONS FOR REGAINING CONTROL

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Abstract

Background: In Zimbabwe, more than half of malaria cases are concentrated in Manicaland Province, where seasonal malaria epidemics occur despite intensified control strategies. The objectives of this study were to develop a prediction model based on high-resolution environmental risk factors and obtain seasonal malaria risk maps for Mutasa District, one of the worst affected districts in Manicaland Province.

Methods: Household RDT status was obtained from ongoing community-based surveys in Mutasa District from October 2012 through April 2015. Environmental variables were extracted from remote sensing data sources and linked to household RDT status. Logistic regression was used to model the probability of household positivity as a function of the environmental covariates. Model prediction performance and overall model fit were examined. Model predictions and prediction standard errors were generated and inverse distance weighting was used to generate smoothed maps of malaria risk and prediction uncertainty by season.

Results: Between October 2012 and April 2015, 398 households participated in the household surveys. Ninety-six individuals representing 66 households tested RDT positive. Household malaria risk was significantly higher among households sampled during the rainy season and further from the Mozambique border, while malaria risk was lower in sparsely populated areas as well as households located at higher elevations during the rainy season. The resulting maps predicted elevated risk during the rainy season particularly in low-lying areas bordering with Mozambique. In contrast, the risk of malaria was low across the study area during the dry season with foci of malaria scattered along the northern, western and south-eastern peripheries of the study area.

Conclusion: This study demonstrates significant heterogeneity of malaria transmission within Mutasa District, which was strongly linked to elevation, house density and proximity
to the Mozambique border. These findings underscore the need for strong cross-border malaria control initiatives to complement country-specific interventions.
Background

Since the 1950s, Zimbabwe dramatically reduced the national burden of malaria, largely through diagnosis and treatment and indoor residual spraying (IRS), and more recently, distribution of insecticide-treated bed nets (ITNs) [1]. Despite this, malaria has re-emerged as a public health problem in the past decade and this resurgence has been attributed to limited funding for control, drug resistance by *Plasmodium* parasites and insecticide resistance by major *Anopheline* vectors [2–5]. The re-emergence of malaria in areas with previously successful control poses a challenge to the sustainability of gains made in reducing malaria and current efforts to reduce the burden of malaria to achieve elimination. More than half of malaria cases reported in Zimbabwe in recent years occur in Manicaland Province, where malaria continues to rebound despite intensified control strategies [6–8]. In 2009, Manicaland province reported 55,707 confirmed cases of malaria, but by 2013, the number of reported cases had more than tripled to 192,730, despite a significant reduction in the national burden of malaria during the same period [8, 9].

Manicaland Province continues to experience unstable malaria transmission and is vulnerable to epidemics and research is needed to understand the reasons for this.

Understanding the local epidemiology of malaria, particularly the heterogeneity across time and space is critical to achieving control and elimination. Remote sensing data and geographic information systems (GIS) have been used widely to describe spatial and temporal variations of malaria at macro and micro scales [10–14]. A national level malaria risk model using district level monthly malaria data from health facilities across Zimbabwe found that annual and seasonal variations in malaria incidence were explained by rainfall, vapor pressure and temperature [16]. Malaria risk zones have also been described in Masvingo Province, Zimbabwe on the basis of eight environmental factors affecting vector
reproduction, development and survival, showing that southern districts in the Province had the highest risk of malaria [17]. These data, however, rely on passive case finding, and there is a paucity of malaria risk maps and models describing the spatial distribution of malaria in Zimbabwe that are based on more reliable active case finding data [15–18].

The aim of this study was to develop a prediction model based on high resolution environmental risk factors and to construct seasonal malaria risk maps for Mutasa District, one of the worst affected districts in the worse affected Province in Zimbabwe. In contrast to previous malaria risk maps and models, spatial and seasonal variation of malaria in relation to environmental factors in Zimbabwe are described at the finer geographic scale of a district. Additionally, malaria prevalence data were based on active case detection through household surveys, whereas other risk maps and models in Zimbabwe were based on malaria case data available from health facilities [16, 17]. Describing the spatial patterns of malaria transmission and identifying environmental factors driving spatial and seasonal variation of malaria provide an understanding of local malaria epidemiology and can inform the planning and implementation of malaria control at the spatial scale most malaria control programs operate.

**Methods**

**Study area**

This study was conducted in Mutasa District, Manicaland province between October 2012 and April 2015. Mutasa District is situated in the north-east of Zimbabwe, bordering Maniça Province of Mozambique (Figure 6). Mutasa District stretches from 18.20° to 18.58°S latitude and from 32.71° to 33.06° E longitude, and covers an area of 622 km², with an estimated population of 170,000 mostly agricultural persons. Elevation varies from 600 meters in the river valleys to 2,500 meters in the mountain areas inland. The average daily
temperature is 21.5°C, varying from 24.5°C in November and 16.3°C in July. Transmission of *Plasmodium falciparum* malaria is highly seasonal, with peaks during the rainy season (November – April). *Anopheles funestus* is the major malaria vector.

**Parasitological data**

Parasite prevalence was obtained from ongoing community-based surveys in Mutasa District as part of Southern Africa International Centers of Excellence for Malaria Research (ICEMR) program. Details of the sampling and study procedures have been described elsewhere [19]. In brief, a sampling frame was generated using a high-resolution satellite image of the study area obtained from DigitalGlobe Services, Inc (Denver, Colorado) [20]. Grids 1 x 1 kilometer comprised the sampling frame and were purposefully selected to ensure geographic variation while minimizing logistical challenges. A random sample of households from each of the selected grids was generated, and the latitude and longitude of each selected household were confirmed by trained interviewers using a handheld Global Positioning System (GPS). All household members, and caregivers in the case of minors, were informed of the study purpose and procedures and were invited to participate. Demographic and socio-economic information at the individual and household level was obtained using previously pilot-tested questionnaires administered by research staff to household members and heads of households, respectively. As part of the survey, participants were asked to give a finger prick blood sample that was tested for histidine-rich protein 2 antigen of *P. falciparum* using rapid diagnostic tests (RDT)(SD-Bioline Malaria Antigen P.f; Standard Diagnostics, Inc). RDT positive participants were offered treatment with artemisinin-based combination therapy (ACT) in accordance with national policies. Household RDT status, defined as positive for any household having at least one RDT positive resident, was the outcome of interest.
Environmental data

The environment is an important driver in the development and survival of malaria parasites and mosquito vector. Using a variety of sources, sets of environmental variables including elevation, slope, aspect, vegetation cover, land use, distances to streams of different categories, distance to the main road, distance to the nearest health facility, distance to the Mozambique border and household density were compiled and linked to household RDT status. Elevation was extracted from a 90 meter, high-resolution Shuttle Radar Topography Mission (SRTM) digital elevation model (DEM) [21]. DEM-derived raster maps were used to obtain slope and aspect in degrees for each participating household. The Normalized Difference Vegetation Index (NDVI), available from the United States Geological Survey (USGS) Land Processes Distributed Active Archive Center (LP DAAC), was used as a proxy for vegetation cover. Using bands 4 and 5, corresponding to the red and near-infrared spectral bands from a multispectral Landsat 8™ image from July 2014, an NDVI raster layer was calculated: \[ \text{NDVI} = \frac{(\text{Band 5} - \text{Band 4})}{(\text{Band 5} + \text{Band 4})} \]. Using the same Landsat 8™ image, a land use raster layer was created by performing unsupervised land use classification [22]. Land use classes included: water, impervious, bare land, grass, crop, and forest.

Hydrologic analysis was performed using the DEM to create a stream network layer, containing attribute information expressing the classifications of streams using Strahler's method [23]. In this classification, a stream of order 2 is formed when two streams of order 1 join. Stream classifications ranged from 1 indicating low volume streams typically present only during the rainy season, to 4 indicating high volume, year-round streams usually found at lower elevations. The two major rivers in Mutasa District, the Pungwe and Honde, had a stream order of 4. The Euclidean distance from each household to the nearest stream in each of the 4 classes was calculated in ArcGIS 10.2 (ESRI, Redlands, California). Similar
processes were used to identify the distance from each participating household to the nearest road, health facility and the Mozambique border. Using the geographic coordinates of all enumerated households in the study area, a measure of household density was computed as the number of structures within 250 meters of a participating residence. A binary variable denoting the rainy season, defined as the period between November and April, was generated based on rainfall data from the Southern Africa ICEMR station in Hauna, a commercial center in Mutasa District. All images and features were projected into Universal Transverse Mercator (UTM) Zone 36 S coordinate system to allow the calculation of distances in meters.

Statistical analysis

The outcome of interest was whether or not a household had at least one member test positive by RDT for malaria parasites. Exploratory data analysis comparing environmental variables between positive and negative households was conducted using chi-square tests for categorical variables and t-test for continuous variables. Logistic regression was used to model the probability of household positivity as a function of the environmental covariates. An initial multivariate logistic regression model included all environmental variables found to be significant (p<0.1) in univariate analyses. An indicator variable for the rainy season (November to April) was also considered in the model both as a main effect and as an interaction to allow for effect modification due to season. A manual stepwise variable selection procedure was used and overall model fit examined by the Akaike Information Criterion (AIC) and Hosmer-Lemeshow goodness of fit test. A p-value greater than 0.05 for the Hosmer-Lemeshow test statistic and a lower value of AIC indicate a better fitting model. To assess residual spatial variation, semivariograms of the standardized residuals from the logistic regression model residuals were used [24].
Internal prediction performance of the final multivariate model was evaluated using Monte Carlo cross-validation with 1,000 iterations. The total number of households sampled between October 2012 and April 2015 was randomly split; one third of sampled households were assigned to the test set and the remaining to the training set. The final multivariate logistic regression model was then fit to the training set and predictions made over the test set. The observed values and the predicted logistic regression probability of household positivity at ‘test’ locations were compared using the root mean squared error (RMSE) of prediction. After implementing 1,000 iterations of this process, the RMSE was averaged and the corresponding 95% prediction intervals computed. The RMSE and prediction intervals were also calculated by season to assess seasonal variation in prediction performance. Smaller values of RMSE indicate better prediction performance of the model and provide an average measure of prediction error.

Sensitivity, specificity and the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve were also used as additional tools to assess model performance in both the internal and an external evaluation. The sensitivity was defined as the proportion of true positives the model predicted as being positive, while the specificity was defined as the proportion of true negatives the model classified as being negative. To classify a household as positive or negative, a cutoff was applied to the predicted probabilities. The whole range of cut-offs (0 to 1) was examined and results plotted on an ROC curve. A cut-off was chosen to maximize both sensitivity and specificity. The greater the AUC, the closer the predictions are to the observed data, indicating a more discriminatory model.

External evaluation of the model prediction performance was assessed by fitting the final model to a training set based on data from October 2012 to April 2014 and predicting on to a validation set comprised of the households enrolled in the most recent 12 months
(May 1, 2014 to April 30, 2015). The RMSE between the observed and predicted presence of at least one malaria case in a household was calculated as the index of accuracy. Sensitivity, specificity and AUC were computed and reported.

The final multivariate logistic regression model built on data from October 2012 and April 2015 was used to predict and map the probability of household RDT positivity. A fine grid of 100x100m cells covering Mutasa District was created within ArcGIS 10.2 and values of environmental determinants were extracted to the centroid of each grid cell. Model predictions and prediction standard errors were generated for each grid cell and stratified by season via the rainy/dry season variable included in the final model.

All spatial data manipulations, processing of environmental data and distance calculations were performed in ArcGIS 10.2. All statistical and spatial statistical analyses were carried out in R statistical software version 3.1.0.

**Ethical considerations**

The Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health, the Biomedical Research and Training Institute and the Medical Research Council of Zimbabwe approved this research. Permission was sought from local chiefs for conduct of the study in their area of control, and written informed consent from all participants. Consent was obtained from caregivers or legal guardians of minors, with assent for those aged 7-16 years.

**Results**

A total of 20,247 structures were identified in Mutasa District from the manual digitization of households. Between October 2012 and April 2015, 398 households participated in the household surveys. The total number of individuals per household
varied from 1 to 25, with the typical family averaging 3.7 household members. Of the 1,480 individuals in the sampled households, 249 (17%) were children under five years and 824 (56%) were female. Ninety-six individuals representing 66 households tested RDT positive, giving a malaria prevalence of 96/1480 (7%) for individuals and 66/398 (14%) for households. Most of the participating households were located in the Honde valley running through the center of the District (Figure 6). The median elevation of participating households was 787 meters compared to a median elevation of 828 meters for all enumerated households. Overall, households with at least one RDT positive resident tended to be located at lower elevations, further from the main road, closer to the Mozambique border and in more sparsely populated areas (Table 5).

The final model indicated that households sampled during the rainy season were three times more likely to be positive than households sampled in the dry season (aOR 2.97, 95% CI 1.61 – 5.69, p<0.001). Distance to the Mozambique border was strongly associated with household RDT status. Specifically, for every 1,000 meter increase in distance from the Mozambique border, the odds of a household having at least one RDT positive resident decreased 16% (aOR 0.84, 95% CI 0.75 – 0.93, p=0.002). Although the main effect of elevation was not significant (aOR 1.03, 95% CI 0.98 – 1.08, p=0.15, per 10 meter increase in elevation), there was evidence that the effect of elevation was modified by season (i.e. significant season by elevation interaction) and hence elevation was retained as a main effect. In the rainy season, for every 10 meter increase in elevation, there was an 11% decrease in the household risk of malaria (aOR 0.89, 95% CI 0.82-0.96, p=0.003). There was borderline evidence to suggest that the probability a household had at least one RDT positive resident decreased by 29% for every additional 10 structures within a 250 meter buffer (aOR 0.71, 95% CI 0.48-0.99, p=0.06) (Table 2)
The Hosmer-Lemeshow goodness of fit statistic for the final model was 14.2 with a p-value of 0.18, indicating the model was a good fit for the data. There was little indication of residual spatial variation (spatial dependence in the regression model residuals) as evidenced by comparing the estimated semivariograms of Pearson standardized residuals from the null and final model (results not shown). AIC results showed that the final model offered a better fit than the null intercept model (AIC for null model = 360, AIC for full model= 326).

The predictive performance of the model on the full sample of households was assessed by considering the AUC of the ROC. The model adequately discriminated positive households from negative households as the predicted risk was higher in positive households than negative households 78% of the time (AUC = 0.78). From the possible range of predicted probabilities (0 to 1), a cut-off probability of 0.21 for classifying a household as positive provided the optimal diagnostic efficiency with sensitivity and specificity of 56% and 86% respectively.

Using 133 households as training locations (33.3%) for internal evaluation, the model’s prediction had an RMSE of 0.36, indicating that the model prediction had an average error of 0.36 when predicting the binary RDT status (0 or 1) of a household. The prediction model also showed better performance in the dry season than in the rainy season, as indicated by a relative RMSE of 1.34 (95% prediction interval 1.01 - 1.80). In the training locations, the model had an overall specificity and sensitivity of 88% and 54% respectively. For the rainy season, the sensitivity and specificity of the model were 61% and 80% respectively. The model performance during the dry season had better specificity (96%) but far worse sensitivity (42%). When the model was validated prospectively by holding out the last 12 months of data (external evaluation), the RMSE was 0.68. Similar to the results in the internal evaluation, there was an improvement in prediction accuracy
During the dry season relative to the rainy season (relative RMSE 1.43). For model performance, the specificity was higher than the sensitivity overall and in both seasons.

The risk map for the dry season was characterized by low risk across the entire study area, with pockets of elevated risk scattered along the northern, western and south-eastern peripheries of the study area (Figure 2A). In contrast, the risk map for the rainy season depicted relatively increased risk of finding a positive household (>50%) in the eastern part of the study area along the Mozambique border. There was a gradient east to west with a decline in the predicted risk (Figure 2B).

Importantly, high predicted risk may not imply a high probability of finding a positive household, depending on the precision of the estimate. Examination of the maps of prediction accuracy indicated that the prediction uncertainty was higher in the dry season than in the rainy season (Figure 2C and 2D). For the rainy season, the prediction uncertainty did not exceed 0.1 across most of the study area. However, there were areas with prediction uncertainty in the range of 0.1-0.2 eastwards along the Mozambique border. For the dry season, prediction uncertainty ranged as high as 0.6, with areas scattered along the northern, western and south-eastern peripheries of the study area having the highest uncertainty. Comparing the prediction maps to the corresponding maps of uncertainty for both seasons showed that prediction uncertainty was high at locations where the predictions themselves were high.

Discussion

The application of high-resolution remote sensing data and geostatistics to develop seasonal malaria risk maps at a fine spatial resolution may be crucial to achieving the goal of malaria eradication. This study used active surveillance data collected prospectively over a period covering high (rainy season) and low (dry season) expected transmission rates in a
region of resurgent malaria in eastern Zimbabwe. The study revealed heterogeneity of malaria risk over a small geographic area and identified important environmental determinants of the observed spatial pattern of malaria risk. Using a geostatistical approach, the model predicted household malaria risk and allowed for the estimation of uncertainty in predictions. The resulting maps predicted elevated risk during the rainy season, particularly in low-lying areas bordering with Mozambique. In contrast, the risk of malaria was low across the study area during the dry season with foci of malaria scattered along the northern, western and south-eastern peripheries of the study area. The predicted risk maps provide an empirical basis for identifying priority areas for malaria interventions.

The environmental factors found to be related to malaria are consistent with previous data on the epidemiology of malaria and vector biology in Zimbabwe. Environmental factors previously identified as driving malaria transmission in the country include season, elevation, rainfall, temperature and vapor pressure [1, 15, 16, 25]. The model predicted higher risk of malaria among households sampled in the rainy season, located near the Mozambique border and in sparsely populated areas. Additionally, elevation limited malaria transmission during the rainy season. Previous research in Zimbabwe suggests that malaria transmission does not typically occur at elevations exceeding 1,200 meters [1]. Although the range of elevations for enumerated households was between 607 and 1,514 meters, for sampled households the range was limited to between 674 and 1,234 meters. The limited range of elevation in the sampled households may be a result of logistical challenges reaching areas at higher elevations. Consequently, differences in malaria risk during the dry season related to elevation may have been masked by the under-representation of households at higher elevations.

The study identified proximity to the Mozambique border as an important driver of malaria transmission in this District, even after adjustment for elevation. The border areas
of countries with neighbors with a higher burden of malaria often have higher malaria transmission as a result of cross-border movement. In Mpumalanga Province, South Africa, which borders more southerly provinces of Mozambique (Gaza and Maputo), a map of average malaria incidences showed the greater risk of malaria among individuals living within 5 kilometers of the Mozambican border compared to other inhabitants [26]. A receptive risk map for malaria in Namibia found that the highest receptive risks of malaria transmission were along the borders with Angola and Zambia [27]. In the present study, a gradient of malaria risk was identified during the rainy season: compared to households closer to the border with Mozambique, households further away had a lower risk of malaria. These findings emphasize the need for regional collaborations to control malaria.

The high-resolution risk maps present a new cartographic resource describing important seasonal and spatial heterogeneities in malaria transmission in Zimbabwe. The predicted risk map for the rainy season showed that malaria risk increases from west to east of the study area. In contrast, during the dry season, much of the study area had a low risk but there were foci of malaria transmission scattered across the district. The risk map for the dry season produced a weaker fitting model than for the rainy season, in part, attributable to fewer cases identified during the dry season. In addition, areas predicted to have elevated risk carried higher levels of prediction uncertainty, underscoring the need to acknowledge prediction uncertainties when interpreting malaria risk maps for disease control. Understanding the prediction uncertainty may help in the identification of areas in need of additional sampling to develop a more accurate map of the seasonal and spatial variation of malaria risk.

This study has several important limitations. Firstly, the uneven geographical spread of household data may limit the power to identify spatial heterogeneity particularly in the peripheries of the study area where prediction uncertainty was highest. Spatial
predictions are more precise and accurate in areas that lie closer to sampled households. While there is less confidence about predictions in parts of the study area, the analytical approach quantified the prediction uncertainty. The smoothed maps of prediction uncertainty can be harnessed to prioritize future data collection in parts of the study area exhibiting higher uncertainty. Secondly, the analytical approach included only explanatory variables that were available or could be computed for any geographic location within the study area. Consequently, individual level data and household characteristics available through questionnaires administered during ongoing surveys were not included in the models. It is likely that other factors related to age, socio-economic status, occupation, travel history and use of preventative measures may influence the observed distribution of malaria in Mutasa District.

Heterogeneity in the spatial distribution of malaria in this small geographic area will help understanding of the local malaria epidemiology. More importantly, the study identified areas of high risk where additional control efforts should be conducted as a strategic priority to reduce malaria transmission. The models and maps were aimed at local policy and decision making and these results will help in the development of long-term and sustainable strategies for malaria control in Mutasa District, Zimbabwe.
References


### Table 5: Characteristics of 398 sampled households by RDT status in Mutasa District, October 2012 – April 2015

<table>
<thead>
<tr>
<th>Variable</th>
<th>All sampled household n=398</th>
<th>RDT positive households n=66</th>
<th>RDT negative households n=332</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation (m)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.004</td>
</tr>
<tr>
<td>Distance to first order streams (m)</td>
<td>787 (758, 822)</td>
<td>774 (747,802)</td>
<td>790 (760, 827)</td>
<td></td>
</tr>
<tr>
<td>Distance to second order streams (m)</td>
<td>611 (378, 782)</td>
<td>614 (340,791)</td>
<td>609 (380, 777)</td>
<td>0.8</td>
</tr>
<tr>
<td>Distance to third order streams (m)</td>
<td>1,281 (974, 1,556)</td>
<td>1,411 (1,031, 1,700)</td>
<td>1,265 (970, 1,513)</td>
<td>0.03</td>
</tr>
<tr>
<td>Distance to forth order streams (m)</td>
<td>1,709 (627, 2,255)</td>
<td>1,625 (626, 2,111)</td>
<td>1,731 (640, 2,269)</td>
<td>0.6</td>
</tr>
<tr>
<td>Distance to nearest health facility (m)</td>
<td>1,640 (580, 3,926)</td>
<td>1,886 (905, 3,931)</td>
<td>1,613 (570.7, 3,838)</td>
<td>0.3</td>
</tr>
<tr>
<td>Distance to main road (m)</td>
<td>1,573 (761, 3,098)</td>
<td>1,922 (916, 4,151)</td>
<td>1,499 (753.4, 2,850)</td>
<td>0.03</td>
</tr>
<tr>
<td>Distance to Mozambique border (m)</td>
<td>5,907 (4,523, 8,789)</td>
<td>4,796 (2,859, 6,955)</td>
<td>6,516 (4,695, 8,940)</td>
<td>0.001</td>
</tr>
<tr>
<td>NDVI</td>
<td>0.2 (0.2, 0.3)</td>
<td>0.2 (0.2, 0.3)</td>
<td>0.2 (0.2, 0.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Slope of landscape (degree)</td>
<td>4.3 (2.6, 7.1)</td>
<td>4.2 (2.7, 6.2)</td>
<td>4.3 (2.6, 7.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Number of houses within 250m circular buffer</td>
<td>17 (9, 40)</td>
<td>11 (8, 25)</td>
<td>18 (9, 42)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NDVI=Normalized Difference Vegetation Index, RDT=rapid diagnostic test, IQR=interquartile range
Table 6: Univariate and multivariable logistic regression models of environmental factors associated with household RDT status in Mutasa District, October 2012 - April 2015

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Models</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Rainy Season</td>
<td>2.47</td>
<td>1.41, 4.48</td>
</tr>
<tr>
<td>Distance to Mozambique border (per km)</td>
<td>0.84</td>
<td>0.76, 0.93</td>
</tr>
<tr>
<td>Elevation (per 10 m)</td>
<td>0.96</td>
<td>0.91, 0.99</td>
</tr>
<tr>
<td>Distance to second order stream (per km)</td>
<td>1.95</td>
<td>1.16, 3.31</td>
</tr>
<tr>
<td>Number of structures within 250 meters</td>
<td>0.74</td>
<td>0.51, 1.02</td>
</tr>
<tr>
<td>Interaction: Elevation (per 10 m) and rainy season</td>
<td>0.87</td>
<td>0.80, 0.94</td>
</tr>
</tbody>
</table>

OR = Odds ratio, CI = confidence interval
Figure 6: Map of Mutasa District, Zimbabwe, indicating positive and negative households
Figure 7: Categorical maps of predicted household malaria risk and uncertainty by season for Mutasa District, October 2012 – April 2015

A: Predicted household malaria risk during the dry season
B: Predicted household malaria risk during the rainy season
C: Prediction uncertainty during the dry season
D: Prediction uncertainty during the rainy season
CHAPTER 5:
INITIAL EVIDENCE OF A REDUCTION IN MALARIA INCIDENCE FOLLOWING INDOOR RESIDUAL SPRAYING WITH ACTELLIC 300 CS IN A SETTING WITH PYRETHROID RESISTANCE: MUTASA DISTRICT, ZIMBABWE

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Abstract

Background: In Zimbabwe, more than half of malaria cases are concentrated in Manicaland Province, where seasonal malaria epidemics occur despite intensified control strategies. Recently (2013-2014), pyrethroid and carbamate resistance was detected in the major malaria vector in Eastern Zimbabwe, *Anopheles funestus*. In response, a single round of indoor residual spraying using pirimiphos-methyl (an organophosphate) was implemented in four high burden districts of Manicaland Province from November 1-December 19 2014. The objective of this study was to evaluate the effect of this programmatic switch on malaria morbidity reported from health facilities in Mutasa District, one of the worst affected districts in Manicaland Province.

Methods: Number of weekly malaria cases for each health facility 24 months prior to 6 months after the 2014 spraying round were obtained from passive case surveillance. Environmental variables were extracted from remote sensing data sources and linked to health facility. Negative binomial regression was used to model the weekly number of malaria cases, adjusted for seasonality and environmental confounders.

Results: From December 2012 to May 2015, 125,442 malaria cases were reported from 42 health facilities in Mutasa District. Based on a higher burden of malaria, 20 out of 31 municipal wards were sprayed in the district. Coverage of the population was 92.1%. During the 6 months after the 2014 spraying round, a period where transmission would have otherwise peaked, in health facilities in sprayed wards, the incidence malaria was 43% lower than the preceding 24 months. In contrast, there was no significant change in malaria incidence in health facilities in unsprayed wards during the same period.

Conclusion: This study demonstrated that pirimiphos-methyl is a promising insecticide for the control of the *An.funestus* population in Eastern Zimbabwe that is resistant to pyrethroids and carbamates.
Introduction

Malaria is a public health problem in Zimbabwe, which lies in the southern fringe of malaria transmission in sub-Saharan Africa [1]. Approximately half of the population of 12.9 million is at risk of malaria infection [2, 3]. During 2013, 377,872 cases and 351 deaths were attributed to malaria in the country, with the greatest burden of malaria among children under five years, pregnant women and people living with HIV/AIDS [3–5]. *Plasmodium falciparum* accounts for 98% of all reported malaria cases and *Anopheles gambiae* is the major malaria vector in most of the country. In Zimbabwe, the epidemiological pattern of malaria transmission varies spatially and temporally, and is largely driven by elevation and rainfall patterns [5, 6]. The rainy season spans November to April, while peak malaria transmission usually occurs between February and May as a result of the preceding rains.

Malaria control in Zimbabwe relies on case management, insecticide-treated nets (ITNs) and indoor residual spraying (IRS), which have successfully interrupted malaria transmission. Nationally, the number of malaria cases has been declining [3, 7]. However, the success of the program has been challenged by malaria resurgence particularly in Manicaland Province, which continues to experience more than the expected number of malaria cases. In 2013, Manicaland Province accounted for 51% and 35% of all the country’s malaria morbidity and mortality burden, respectively, despite encompassing less than 14% of the national population [2, 3]. One of the reasons for the resurgence was the development of pyrethroid resistance by *An.funestus*, the malaria vector in the area [8, 9].

Recent (2013-14) insecticide resistance monitoring using standard World Health Organization (WHO) testing methods showed that *An.funestus* was highly resistant to pyrethroids and carbamates. However, the vector susceptibility tests conducted with organochlorines (DDT and dieldrin) and organophosphates (malathion, fenitrothion and pirimiphos-methyl) all showed 100% mortality after 24 hours [10]. These results indicated
that vector control tools dependent on pyrethroids are unlikely to effectively kill the primary malaria vector in Mutasa District. Insecticide resistance has serious implications for malaria control, especially because pyrethroids are the main insecticides used by the Zimbabwe National Malaria Control Program (NMCP) until recently.

In response to insecticide resistance, the President’s Malaria Initiative (PMI) through the United States Agency for International Development (USAID) and in collaboration with the Ministry of Health and Child Care (MOHCC) switched insecticide class from pyrethroids used in 2013 to an organophosphate-based insecticide in four high transmission districts in Manicaland Province (Chimanimani, Mutasa, Mutare and Nyanga) during the 2014 IRS campaign. The goal of this study was to evaluate the population-level impact of the switching to organophosphates on malaria morbidity in Mutasa, one of the four targeted districts. The underlying study hypothesis is that IRS using an organophosphate-based insecticide would result in lower malaria case incidence at health facilities in sprayed areas during the subsequent high transmission season (December 2014 - May 2015). Results of this evaluation will support the optimization of vector control efforts in Mutasa District, and guide the selection of insecticides for future IRS operations in the country.

Methods

Study area

Mutasa District, situated in the north-eastern border of Zimbabwe and Mozambique, covers an area of 622 km² and stretches from 18.20° to 18.58°S latitude and from 32.71° to 33.06° E longitude. Elevation rises from 600 meters in the valleys to 2,500 meters in the mountains. The district had an estimated 169,756 residents representing 42,479 households at the time of the 2012 census [2]. The district is irrigated by two major rivers,
the Honde and the Pungwe; and the major economic activity is agriculture. The average daily temperature is 21.5°C. November is the hottest month with an average daily temperature of 24.5°C and July is the coolest month with an average daily temperature of 16.3°C. Malaria transmission in the study area is characterized as seasonal and unstable with major outbreaks during the rainy season. In 2014, Mutasa District received 2,352 millimeters of rainfall between November and April and 96 millimeters during the dry season as measured at the Southern Africa ICEMR station in Hauna, the main town in the lower valley. The population covered by pyrethroid-based IRS in Mutasa District was 88% in 2012 and 91% in 2013. ITNs were not distributed in 2012, distributed to the general population in 2013 and limited to boarding schools in 2014.

*Indoor residual spraying with pirimiphos methyl*

An organophosphate, pirimiphos methyl (Acetellic 300 CS, Syngenta, Sweden) was selected for the 2014 spraying round in Mutasa District. Trained and experienced spray operators conducted the IRS operations between November 1, 2014 and December 19, 2014. From among the district’s 31 municipal wards, 20 malaria-prone wards were selected; these included 43,103 structures and covered a population of 87,275. According to PMI, coverage of the population found was 92.1%, while coverage based on structures found by spray operators was 87.3% [11].

*Malaria case data*

In Mutasa District, the MOHCC’s well-established health management information system (HMIS) routinely collects weekly malaria-related data at the health-facility level. Indicators collected include the number of positive rapid diagnostic tests (RDT), patients clinically diagnosed with malaria, and malaria deaths, all stratified by age (< 5 years and ≥ 5
years). This passive surveillance system has previously been used to monitor secular trends in malaria morbidity and assess the impact of malaria interventions [12]. The system is operational at 43 health facilities offering malaria diagnosis and treatment; two-thirds of these facilities are government funded. Geographic coordinates of the health facilities and the size of catchment area population for each health facility were acquired through the district health team or field visits. Catchment area population size was adjusted for population growth by assuming linear growth during monthly intervals, summing up to an annual population growth of 4% (as projected by the 2012 census) [2].

The primary dependent variable was the weekly number of malaria cases confirmed by RDT at each health facility. Data prior to the completion of the 2014 spray round included 105 weeks (2012 week 50 – 2014 week 50) and data following the completion of the 2014 spraying round included 24 weeks (2014 week 51 – 2015 week 22). Weekly confirmed malaria case counts at each health facility were standardized as rates per 1,000 population using estimates of the population in each health facility catchment area.

**Primary exposure variables**

To assess whether or not weekly malaria incidence decreased following the IRS round and whether this decrease exceeded that which might be expected on the basis of trends prior to the 2014 spraying round, spray status (sprayed versus unsprayed), period (pre vs. post-IRS) and a spray-status- by-period interaction were entered as independent variables. The binary variable indicating the period before and after the completion of the 2014 spraying round was created to allow the estimation of the difference in malaria morbidity between the pre- and post-intervention periods in health facilities located in unsprayed wards. The spray status modeled the difference between health facilities in sprayed and unsprayed wards prior to the 2014 spraying round. The spray-status-by-
period interaction assessed whether there was significant heterogeneity in the IRS effect between health facilities located in wards that were sprayed versus unsprayed.

**Potential confounding variables**

To account for seasonal variations in malaria cases, indicator variables of the calendar month in which the case was reported were introduced to the model. Additionally, to account for year-to-year variation of malaria cases, indicator variables representing the years 2012, 2013 and 2014 were entered into the model (2015 was the reference).

Several environmental variables that affect the survival and reproduction of the malaria vector and the development, survival, and reproduction rates of the *Plasmodium* within *Anopheles* were included as potential explanatory variables. Elevation, rainfall estimate (RFE), day and night land surface temperature (LST) and Normalized Difference Vegetation Index (NDVI) were extracted from remote sensing sources for each health facility. Elevation data was estimated at 90 meter resolution from the Shuttle Radar Topography Mission (SRTM) digital elevation model. Decadal (10 day) RFE data were downloaded via the Africa Data Dissemination Service (ADDS). RFE is an estimation of rainfall from the Meteosat 7 satellite that has been calibrated against ground-based rain gauge data. Day and night LST and NDVI were obtained from Moderate Resolution Imaging Spectroradiometer (MODIS) sensor aboard the NASA satellites Aqua and Terra. Daily day and night LST data, expressed as °C were extracted from MOD11A products with 0.25 km by 0.25 km spatial resolution. LST is a proxy for the prevailing temperature of the air. Sixteen day composite NDVI was extracted from MOD13Q1 products with 1 km by 1 km spatial resolution. NDVI correlates well with the amount of vegetation and typically ranges from -1 to 1. Values close to 1 indicate very dense vegetation, while values zero and below represent water or impervious land forms.
The time unit of analysis in this study was the week. Parasitological data were collected on a weekly basis, while environmental data obtained from remote sensing were obtained at different temporal resolutions. Consequently, all time-varying environmental data were rectified into weekly values by taking averages of daily values and disaggregating decadal values. Due to cloud cover and satellite malfunctions, day and night LST were missing for 0.36% and 0.33% of daily values, respectively. Missing values were imputed by assuming a linear trend for non-missing data. In other words, the difference between two succeeding data points was assumed to be equally distributed among the times with no observed value in between. To account for possible elapsing (lag) time in the effect of time-varying environmental variables on the outcome (weekly number of malaria cases confirmed by RDT), lags up to 3 months were incorporated. Three months was chosen as the maximum biologically plausible lag between malaria incidence and environmental variables.

Statistical analysis

Descriptive statistics were used to examine the characteristics of the sample prior and following the 2014 spraying. Rather than conduct facility-level analyses for each of the health facilities, this study conducted a negative binomial panel data model at the district-level in which the dependent variable was the number of malaria cases by health facility and week. The number of weekly malaria cases confirmed by RDT for a health facility was modeled by using a negative binomial regression model for all health facilities with catchment area population size as the regression offset to model the rate of RDT positivity. Poisson regression models for the RDT confirmed cases were consistently over-dispersed (greater variation in the data than the Poisson model can accommodate) throughout the analysis and hence replaced with negative binomial regression, which allows for a scaling
factor on the model variance to account for over-dispersion. Further, regression inference was based on a generalized estimating equations (GEE) approach to account for the within health facility repeated measures correlation [13].

With the aforementioned negative binomial GEE regression approach in place, variables with a \( p \)-value <0.05 in the univariate regression models were considered as potential candidates for the multivariable selection process. A manual stepwise backwards elimination approach was used to select environmental variables and their associated lags. Selection of the model with the best fit, the best working correlation structure in GEE and optimal lag sizes for time-varying environmental factors were determined by comparing quasi-likelihood under the independence model criterion (QIC) values of different models. The QIC is a modification of the Akaike Information Criterion (AIC); similar to the AIC, a model that minimizes the QIC is considered the best fit [14]. Results were expressed in terms of incidence risk ratios with 95% confidence intervals, describing the expected change in the incidence rate of malaria when the exposure variable is positive or increasing. A \( p \)-value <0.05 was considered statistically significant. The root mean square error (RMSE) standardized by catchment area population was used to evaluate the agreement between observed and predicted malaria cases for the entire district. The RMSE per 1,000 catchment area population was also calculated by health facility to determine differences in predictions by health facility.

To assess the impact of the 2014 spraying round over time on model predictions, sensitivity analyses were conducted varying the cutoff point dividing the time from the week IRS began to the week IRS was completed. The optimal breakpoint was considered the point (week) where the QIC was smallest. Environmental data was linked to the health facility reports mapped in ArcGIS 10.2 (Redlands, California); all statistical analyses were carried out in STATA 11.2 (College Station, Texas).
Ethical considerations

The Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health, the Biomedical Research and Training Institute and the Medical Research Council of Zimbabwe approved this research. The analysis was based on malaria reports collected routinely by the NMCP in Zimbabwe. Reports are aggregated and thus do not include individual patient identifiers. Additionally, it was not necessary or possible to obtain individual consent, as this was a retrospective analysis of existing data collected by the NMCP.

Results

After excluding one health facility that started reporting data only in April 2013, the analytical sample comprised 42 health facilities that had complete data on the weekly number of malaria cases from December 2012 to May 2015. During the 129-week study period, 125,442 malaria cases were reported; of which 23,392 (18.6%) were among children below the age of five years. The total number of weekly cases of malaria during the study period ranged from 81 in 2013 week 33 to 3,752 in 2014 week 12. The average number of malaria cases per facility per week was 23 with a variance of 3210, clearly indicating over-dispersion.

Several significant associations were found between malaria incidence and environmental variables in both the univariate and multivariate negative binomial regression model (Table 2). After adjustment, an increase of 10 millimeters in RFE resulted in a 2% increase in malaria incidence 6 weeks later (IRR 1.02, 95% CI 1.01 – 1.03), while each 1°C increase in night LST at a 10 week lag resulted in a 2% increase in malaria incidence (IRR 1.02, 95% CI 1.01 – 1.04). Malaria incidence decreased with increasing
elevation; every 100-meter increase in elevation was associated with a 20% reduction in malaria (IRR 0.80, 95% CI 0.73 – 0.88). Malaria incidence reduced 19% with every 1,000 meter increase in distance from a second order stream (Table 2).

Adjusting for annual and seasonal trends, environmental variables and clustering at health facilities, there were no significant differences in malaria incidence between health facilities in sprayed wards compared to unsprayed wards prior to the intervention (IRR 0.79, 95% CI 0.43 – 1.43). In sprayed wards, there was a 43% decline in predicted malaria cases after the 2014 IRS campaign compared to before (IRR 0.57, 95% CI 0.43 – 0.74). In contrast, there was no observed change in predicted malaria incidence after the 2014 IRS campaign compared to before in health facilities located in unsprayed wards (IRR 1.21, 95% CI 0.96 – 1.56) (Table 2).

The observed weekly cases for the study area agreed closely with the predicted counts throughout the study period (Figure 2). For the 129-week period of interest, the final model predicted 134,995 cases across all 42 health facilities, whereas, 125,442 cases were reported (Table 3). However, there was some variability by health facility in how closely the predicted and observed total number of cases matched. The observed number of malaria cases was higher than expected given the surrounding environmental conditions and seasonal variations at Old Mutare, Sheba, and Hauna Clinic. The model also over-predicted the number of malaria cases given the surrounding environmental conditions and seasonal variations in some health facilities, including Zongoro, Chisuko and Dreaanane health facilities. The RMSE per 1,000 catchment areas population was poor for Sagambe, St Peter’s, and Chisuko health facilities and good for Dreaanane, Mutasa and Samanga health facilities (Table 3).

The model with first order autoregressive (AR1) correlation was found to fit the data reasonably well compared to other choices of a working correlation matrix. The fit of
the final model was assessed using the QIC and RMSE. The addition of environmental variables to the model improved the model fit and predictions, as the QIC was lower for the final model than the null model (QIC for the null 17,867 versus QIC for the full model 4,158). The sensitivity of the findings to different cut-offs for the binary variable indicating time prior versus post the 2014 IRS campaign, found minimal differences on the estimates, suggesting the results are robust to the cut-off used.

Discussion

In order to reduce vector population and interrupt disease transmission, IRS with appropriate insecticides is essential. Due to local vector resistance, the Zimbabwe NMCP with support from PMI began a large-scale IRS campaign with organophosphates in four high transmission districts in Manicaland province – Chimanimani, Mutare, Mutasa and Nyanga. Using health facility surveillance data, the present study reports on the impact of switching from pyrethroids to OP on malaria morbidity in one of the four high transmission districts selected. In the subsequent high transmission season following the switch from pyrethroids to organophosphates, there was evidence of a 43% decline in malaria incidence reported by health facilities from wards treated with organophosphates, after accounting for possible confounding by environmental variables. Previous research shows that switching to organophosphates effectively reduced biting rates and vector densities in areas with pyrethroid resistant strains in Ghana, Benin and Tanzania [15–18]. Although previous research focused on using entomological data to show the reduction in the vector population following application of Actellic, organophosphates, this study adds to the literature by showing an interruption in malaria transmission using health facility surveillance data.
In the present study, there were variations in rainfall and temperature over the study period, and these changes were associated with changes in malaria incidence. The study results also indicated malaria transmission in Mutasa District was driven by rainfall, proximity to second order streams, elevation and temperature. These results concur with previous research, which found that elevation [5], temperature, and rainfall [6, 19] are positively associated with malaria incidence. After adjustment for climatic variables and seasonality, malaria incidence rates decreased following the 2014 IRS campaign, supporting the plausible conclusion that switching to organophosphates in this setting contributed to the observed public health benefits. No major political, socio-economic or health-care changes with the potential to reduce malaria morbidity by almost half occurred in Mutasa District during the study period.

Typically, data from health facilities only includes data on the number of suspected cases. The HMIS in Zimbabwe is more sophisticated in that it allows reports of confirmed malaria cases. In calculating incidence rates, the denominator used was the catchment area population size. The reliability of this value has been questioned as this assumes that people will visit the closest health facility in their catchment area. The main results did not change after including an offset for catchment area population size. This indicates that the reported catchment area population size may be a reliable estimate. The study also underscores the utility of HMIS data in the evaluation of population level interventions. The HMIS has the advantage of providing quality data quickly and easily, with minimal additional investment. Additionally, HMIS reflects the burden of disease on the health system. Results from this study further suggest that passive surveillance data from the HMIS in Zimbabwe was sufficiently sensitive to detect IRS related reduction in malaria morbidity among residents of Mutasa District.
There are several important limitations of this study that should be highlighted. Causal inferences between spraying and improvements in malaria incidence should be made with caution as spraying was not implemented as an intervention in a randomized control trial. However, data from 14 health facilities located in unsprayed wards were included in the analysis to serve as a comparison and help understand possible changes in malaria morbidity unassociated with the 2014 IRS campaign. Although the univariate model indicated that health facilities in unsprayed wards carried a lower burden of malaria, the multivariable model showed no significant differences between health facilities in sprayed and unsprayed wards prior to the IRS pilot, suggesting that climatic variables included in the model adequately adjusted for differences. However, it should be noted that although the study adjusted for environmental factors, it did not account for other factors like population movement, changes in treatment seeking behaviors, or changes in the coverage of ITNs during the study period. The model developed in this analysis assumed that these factors remained constant over the study period. This seems reasonable given that the rural population of Mutasa District is relatively stable, with access to health facilities providing malaria diagnosis and treatment. Additionally, although the number of suspected malaria cases was not explicitly modeled, a descriptive analysis does not indicate changes in diagnostic practice over the study period (data not shown). The HMIS in Zimbabwe has been in place for decades and has previously been used to evaluate the impact of changes in malaria morbidity[12], construct empirical seasonality maps [19] and describe the spatial and temporal distribution of malaria [20, 21].

Despite these potential limitations, health surveillance systems provide a feasible and efficient means of collecting longitudinal data on measures of malaria morbidity. The pronounced decline in malaria morbidity observed is evidence supporting the benefit of switching to an insecticide class with a different mode of action in response to pyrethroid
resistance. Although the IRS strategy implemented by ZNMCP and PMI was successful, continued entomological monitoring will be necessary. Additionally, with emerging resistance to multiple insecticides, this approach may not be sustainable over time. There is need for the development of novel strategies to manage insecticide resistance.
References


15. PMI|Africa IRS (AIRS) Project Indoor Residual Spraying (IRS 2) Task Order Dour: Ghana End of Spray Report.


Tables and Figures

Table 1: Sample characteristics in sprayed and unsprayed wards, pre and post IRS intervention in Mutasa District, Zimbabwe

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Sprayed wards</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number of reporting health facilities</td>
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<td>28</td>
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<tr>
<td>Catchment area population</td>
<td>117,504</td>
<td>117,504</td>
<td>117,504</td>
<td>117,504</td>
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<tr>
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<td>&lt;5 years</td>
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<td>5 + years</td>
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<td>14</td>
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<td>Catchment area population</td>
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<td>55,659</td>
<td>55,659</td>
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<td>Catchment area population</td>
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<td>173,163</td>
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<td>Total number of malaria cases reported</td>
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<td>5 + years</td>
<td>39,597</td>
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Table 2: Univariate and multivariate incidence rate ratios from negative binomial regression*

<table>
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<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>p</th>
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<td>Adjusted IRR</td>
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* Adjusted for season (month and year indicators) and health facility, with an offset of log of population size and an autoregressive correlations structure specified.
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Figure 1: Geographic Distribution of Health Facilities in Mutasa District, Zimbabwe
Figure 2: Observed and predicted weekly malaria counts in Mutasa District, 2012-2015
CHAPTER 6: CONCLUSION

Author:
Mufaro Kanyangarara¹

Affiliation:
¹ Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Discussion of Main Findings

The findings of this dissertation contribute to the understanding of the epidemiology of malaria in Mutasa District, Zimbabwe and the implications for malaria control by shedding light on person, place and time. Presented below is a brief summary of the main findings for each of the research chapters.

A multilevel analysis of malaria risk factors using data from household surveys in Mutasa District was presented in Chapter 3. In total, 1,161 individuals nested within 398 households were included in the study. Being sampled during the rainy season, living in a sparsely populated area, living in a house that had recently been sprayed and living close to the Mozambique border were associated with increased odds of having an RDT positive result. Being 25 years or older and sleeping under a bed net was associated with a lower odds of having an RDT positive result. Malaria clustering was evident as 50 households tested positive for malaria and 16 of those contained more than one malaria-infected household member. The findings provide useful clues that elucidate the risk factors for malaria that can be used to direct public health strategies.

Chapter 4 presented an application of high-resolution remote sensing data and geostatistics to identify important environmental determinants of the observed spatial pattern of malaria risk and provide a visual description of the spatial pattern of household malaria risk by season. The prediction model predicted higher risk of malaria among households sampled in the rainy season, located near the Mozambique border and in sparsely populated areas. Additionally, elevation limited malaria transmission during the rainy season. The resulting maps showed elevated risk during the rainy season particularly in low-lying areas bordering Mozambique. In contrast, the risk of malaria was low across the study area during the dry season with foci of malaria scattered along the northern, western and southeastern peripheries of the study area.
Finally, the recent detection of pyrethroid resistance prompted a switch to an organophosphate based insecticide in the 2014 spraying round, and Chapter 5 presents an evaluation of impact of this programmatic switch on malaria incidence using health facility based surveillance data. Using a pre/post quasi-experimental design carried out using 105 weeks pre-intervention and 24 weeks post intervention data, the study showed a large reduction in malaria incidence in sprayed areas indicating that the organophosphate had a substantial epidemiological effect. The findings provide evidence to guide the selection of optimal insecticide formulations, timing of subsequent spraying and the generation of data for cost-effectiveness analyses.

In considering the findings of all the research chapters, several overlapping themes emerge that represent the picture of malaria epidemiology in Mutasa District. Firstly, rainfall, elevation and temperature are precipitating factors for malaria transmission in Mutasa District, which corroborates with previous research done in Zimbabwe and other parts of Southern Africa [1–3]. After adjusting for seasonality, the multilevel model (Chapter 3), the spatial prediction model (Chapter 4) and the impact evaluation (Chapter 5) all indicate the positive effect of rainfall on the transmission of malaria. The lead-time between rainfall and malaria incidence was 6 weeks. Night temperature with a lead-time of 10 weeks was positively associated with malaria incidence in the study area. In addition to rainfall and temperature, elevation plays a significant role in malaria transmission. The multilevel model (Chapter 3) suggested, though not with statistical significance, that malaria risk decreased with elevation, with a lower risk among individuals living above 850 meters compared to individuals living below 800 meters. The spatial prediction model (Chapter 4) showed that for every 100-meter increase in elevation, there was an 11% decrease in the odds of a household having at least one case of malaria. The resulting risk map for the rainy season showed that as elevation increased moving from east to west, there was an east to
west decrease observed in household malaria risk. A rise in elevation is expected to
decrease transmission and prevalence of malaria by limiting temperature and thus
shortening the incubation period of the parasite in mosquitoes. Areas along the eastern
border with Mozambique have elevations below 500 meters, while areas along the higher
elevation western boundary rise to above 2,000 meters.

The high risk of malaria along the Mozambique-Zimbabwe border cannot only be
considered an effect of altitude. Not only does the presence of lower-lying areas closer to
the border provide a conducive environment for malaria transmission, but proximity to
Mozambique, a highly malaria endemic area with poor public health infrastructure, and
frequent human population movement also contribute to the heavy transmission of malaria
in this border district. Mutasa District has 43 health facilities offering malaria diagnosis and
treatment free of charge. On the other hand, just across the border in Mozambique, such
services are not present at this time. Some malaria cases observed in Mutasa District are
imported and this may explain the significantly higher than expected cases of malaria
reported at St Peters, Sagambe and Chisuko, which typically see an influx of imported
malaria cases. As it is challenging to monitor frequent movement of the local people, little is
known about human movement patterns in Mutasa District. Nonetheless, a higher incidence
of malaria was observed near the border, which implies a need to consider the role of
population movement on malaria epidemiology as it may be undermining the success of
malaria control in Zimbabwe.

Another emerging key theme was the protective effects of ITNs and IRS. A
significant protective effect of use of ITNs on individual malaria risk was detected in the
multilevel modeling in Chapter 3, adding to existing evidence on the importance of ITNs for
malaria control. Despite high levels of pyrethroid resistance of local populations of An.
funestus, ITNs still provided good protection. Two commonly used RBM indicators of ITN
ownership and use are: the proportion of households possessing mosquito net(s) and the proportion of children less than 5 years of age who slept under a net the preceding night. Reported bed net ownership was high but usage was moderate (81.7% and 52.1% respectively). In this population, approximately 42.7% of individuals in the study did not have access or use an ITN, increasing their risk of malaria by around 85%. There was also seasonality in ITN use, with more use in the rainy season than in the dry season. This suggests the need for the distribution of free ITNs to the entire population and research into the effectiveness of ITN distribution strategies in order to achieve universal coverage.

In the multilevel model (Chapter 3), recent IRS was associated with increased infection with malaria parasites. While this finding is out of line with the literature, these results most likely derive from high pyrethroid resistance as well as targeted application of IRS to high burden households. The findings from the evaluation (Chapter 5) support that IRS with organophosphates was associated with fewer cases of malaria reported from health facilities located in sprayed wards.

**Limitations**

Limitations worth noting can be thought of in the context of threats to internal and external validity. Internal validity can be defined as the “soundness of study design, conduct and analysis in answering the question that it posed for the study participants”, while external validity can be defined as the “degree to which the results of the study may apply, be relevant, or be generalized to populations or groups that did not participate in the study” [4]. Confounding can present a threat to internal validity. In all three analyses, attempts were made to adjust for potential confounding to increase internal validity. The multilevel framework used in Chapter 3, allows for the simultaneous addition of individual and household level factors. Furthermore, the quasi-experimental design used in Chapter 5
mitigated many known biases of evaluations using health facility based data, by controlling for important confounding factors and using RDT confirmed malaria cases as the outcome. Prior analyses of similar data evaluating the impact of malaria control interventions have failed to control for environmental variables [5] and many have been based on reports of suspected malaria cases.

Despite efforts to control for confounding, it is possible that some important factors influencing malaria transmission were not addressed in the analyses. For the multilevel model (Chapter 3), even after adjustment, the final model explained only 69% of the between household variance in individual malaria risk, suggesting there was some residual confounding. For the IRS evaluation (Chapter 5), changes in testing procedures, coverage of ITNs, and other contextual factors may have influenced malaria incidence; adjustment for these variables was not possible due to a lack of data.

Several exposure variables such as bed net ownership and usage and recent indoor residual spraying were self-reported and are subject to recall limitations and social desirability bias, and may compromise the validity of responses. For bed net ownership, interviewers confirming the physical presence and number of bed nets owned mitigated this bias. Sensitivity and specificity issues regarding the use of RDTs for the diagnosis of malaria need to be acknowledged. A disadvantage of using RDTs to detect parasitemia is the low sensitivity when parasite densities circulating in the bloodstream are low. As a result, individuals negative for malaria by RDT may still be infectious to mosquitoes. Conversely, there is a potential for false positives in individuals recently but not currently infected.

The biological validity of the analyses conducted in Chapter 3 and 4 depends upon the assumption that individuals were infected by malaria parasites within their own homes. The analysis in Chapter 5 assumes that the environment surrounding health facilities is a good proxy for the environmental surrounding most households in that catchment area. It is
possible infection occurred while individuals were farming or while traveling to areas with higher malaria endemicity. In such cases, the associations demonstrated here between malaria and the environment surrounding households may be artificial. Both these possibilities are likely as some of the observed malaria cases may have been contracted while farming or during recent travel. In the case of the evaluation in Chapter 5, it is possible some individuals do not frequent the health facility in their catchment area.

External validity within the Mutasa District setting can also be affected by ways in which participants were selected in the different studies, and whether they are representative of the total population. For the first two studies, the sampling was not random and sampling of grids was done to ensure logistical feasibility to reach areas. Households within grid cells however were randomly selected. Additionally, data for the first two studies included individuals and households that were part of cross-sectional surveys conducted only once, and longitudinal households. Using repeated visits from the longitudinal cohort may alter the natural history of malaria transmission and as such, the analysis was restricted to the single visit conducted at cross-sectional households and the initial visit to longitudinal households. For the IRS evaluation, data from all but one health facility in Mutasa district were used. Assessing the burden of malaria from those who sought treatment at these health facilities might not be representative of those who sought treatment elsewhere. However, given Mutasa District is rural and health facilities are fairly accessible, it is likely that the majority of the population sought medical care one of the health facilities when malaria symptoms developed and are thus representative of the majority of malaria cases occurring in the community. While lessons learned from Mutasa District can be applicable to other settings in SSA, the uniqueness of should be considered prior to generalization of findings to other settings.
Recommendations for Future Research

Several possible directions for future research emerge from the knowledge gained in this dissertation. It is important to incorporate entomological data as the spatial heterogeneities of household malaria risk may be related to the spatial temporal distribution of vector mosquitoes. The multilevel model could incorporate data on vector density or proximity to vector breeding sites. Potentially this might allow further explanation of the between household variance. Addition of such information to the spatial risk modeling might lead to better prediction models and narrower uncertainty ranges. The spatial heterogeneity of the observed malaria incidence may also be due to the spatial and temporal distributions of habitats of vector mosquitoes that differ according to the conditions of the local environment. In addition to evaluating the impact of vector control on the burden of malaria at health facilities, incorporating entomological monitoring will allow the accurate assessment of short-term impact on the vector population.

Further research is needed to understand ITN ownership and usage, and the barriers related to usage. This information will be helpful in achieving universal coverage as ITN ownership was high, but usage low. Regular assessments of household ITN possession and use as well as malaria knowledge should complement ongoing mass distribution, and findings should be incorporated into program policy. There is need for behavioral change communication approaches that focus on increasing the likelihood that individuals will utilize the nets they already own.

The evaluation presented in Chapter 5 was an assessment of a single spray round based on 105 weeks pre-intervention and 24 weeks post intervention, and can only be regarded as suggestive of an impact. A longer period of time pre-intervention would strengthen the results as the epidemiology of malaria in Mutasa has been changing rapidly.
It would also be worthwhile to consider a longer post-intervention period by considering several spraying rounds to confidently ascertain that the observed trend in malaria incidence was really a result of the IRS intervention. The next spraying round will be carried out in October 2015 and will cover all 7 districts in Manicaland province [6]. Validation of results shown in Chapter 5 could also be done using ongoing household surveys.

The apparent importance of proximity to the Mozambique border in driving malaria transmission raises interesting questions about human population movement. Although the mechanisms at play are not yet clear, this study emphasizes the importance of more research that focuses on understanding aspects of human movement applicable to Mutasa District. One step might be to enhance the HMIS to report number of imported cases and place of origin. This would facilitate understanding the burden of malaria cases that can be attributed to importation. However, it is essential to understand the demographic makeup of the various mobile populations, their actual patterns of mobility and the risk factors associated with that type of movement [7]. New technologies to enhance understanding of spatial and temporal patterns are increasingly becoming available and have successfully been used in the malaria field. These include the use of mobile phone data [8] and the use of GPS data loggers.

**Policy Implications**

The results of this dissertation are only relevant if the information is received by program managers and policy makers; and relevant policies are formulated. The introduction of organophosphates in Manicaland Province illustrates how research results can be implemented into policy. Research indicated *An. funestus* was highly resistant to pyrethroids [9], results were communicated and a review of the insecticide of choice in Manicaland was initiated, which led to the switch from pyrethroids to organophosphates in
the 2014 IRS campaign [10]. Results from this dissertation (Chapter 5) confirm the success of the 2014 IRS campaign. The introduction of a long-lasting formulation of pirimiphos-methyl reduced transmission with direct consequences in lowering the incidence of malaria cases and proved to be a useful approach for the management of pyrethroid resistance. This approach should be considered in other high transmission districts with pyrethroid resistance.

Our results showed that sleeping under an ITN was protective despite high levels of pyrethroid resistance of local populations of *An. funestus*. The protective effect of ITN use demonstrated in this study adds to the vast body of evidence supporting the efficacy and effectiveness of ITNs/LLINs for protection against malaria. Consequently, increasing the coverage and more importantly usage of ITNs has the potential to offer good personal protection. Individuals who slept under a bed net reduced their risk of malaria by around 46%. Based on these findings, ITN use in this area should be increased with the goal of universal coverage.

The high risk of malaria on the Mozambique-Zimbabwe border, brings to the fore the relevance and importance of cross-border initiatives to stakeholders in the region. Results suggest importance of a two-pronged approach that focuses on improving local malaria control while engaging in regional initiatives to ensure cross-border malaria is minimized. Several regional initiatives focused on reducing malaria burden have been formed, but little has been done to mobilize them. One such initiative is Elimination 8, which was launched in 2007 with the goal of regional malaria elimination and is led by the governments of Angola, Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe [11]. In addition, an example of a successful regional initiative that exclusively used IRS is the Lubombo Spatial Development Initiative, which was led by the governments of Mozambique, South Africa and Swaziland. At the time of the study, this
initiative operated in the border regions of these three countries. Following the introduction of IRS in southern Mozambique, there was a significant reduction in \textit{P. falciparum} prevalence, with an overall relative risk of 0.74 for each intervention year. Drastic reductions in reported malaria cases were also observed in South Africa and Swaziland over the same period [12, 13].

Several approaches exist to tackle malaria in border areas, namely: joint collaborations allowing the sharing of data, administration of anti-malaria drugs and protective measures for migrants, surveillance systems at points of entry to facilitate swift treatment and follow-up of individuals infected as well as the use of mobile technology to quantify the volume of cross-border movement as well as likely sources and rates of malaria importation [14].

\textbf{Concluding Remark}

This dissertation contributes towards understanding how malaria risk is distributed in space and time and what factors might explain the observed heterogeneities in Mutasa District. These questions were addressed using a multilevel framework and malaria risk maps built on the theoretical link between environmental factors and malaria transmission. The evaluation of a recent IRS campaign also allowed a discussion of the findings and implications for regaining malaria control in Mutasa District. This research informs national and regional strategies both in the context of the resurgence of malaria and cross-border malaria. Improving malaria control by increasing ITN use and continued use of pirimiphos-methyl make regaining malaria control in Mutasa District a possibility. As the drive to eliminate malaria grows, not only will strengthened country malaria control programs be needed, but also active regional initiatives will be vital.
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Research Assistant, 06/2012 – 03/2014
• Designed and implemented a pregnancy history survey for child mortality and a data completeness assessment in Malawi
• Trained 4 data supervisors and 30 field staff in primary data collection

Harvard University HIV/AIDS Care and Treatment Program, Dar es Salaam, Tanzania
Data Manager/Strategic Information Specialist 07/2009 – 05/2011
• Led a wide range of data management tasks to produce high quality datasets
• Worked with senior data manager to resolve data collection and entry issues
• Provided technical support to clinical staff to develop and implement quality of care indicators
• Participated in the hiring, training and development of data entry team
• Attended and participated in regular partner meetings and workshops

Harvard School of Public Health, Boston, MA
Research Assistant, 05/2008 – 05/2009
• Assessed pediatric growth and neurodevelopment of infants from the Mashi Study in Botswana
• Predicted mortality in children from the Severe Malaria in African Children Network Study using generalized additive models

Teaching Assistant, 09/2007 – 08/2008
• Taught weekly statistical lab to 40 graduate students and graded their assignments and examinations