# THE SPATIO-TEMPORAL IMPACT OF CLIMATE CHANGE ON MALARIA TRANSMISSION, CONTROL AND ELIMINATION IN SOUTHERN AFRICA: THE CASE OF ZAMBIA


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**This dissertation is submitted for the degree of Doctor of Philosophy**

**July 2020**

# Dedication

To my lovely wife, Kangachepe Nsewa Lubinda, and our two beloved kids Esnart Thabo and Thebuho Jailos, both of whom were born during my studies.

# DECLARATION

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration except where specifically indicated in the text. It has not been previously submitted, in part or whole, to any university institution for any degree, diploma, or other qualification.

In accordance with the Doctoral College guidelines, this thesis does not exceed 100,000 words, and it contains less than 150 figures.

Signed: _____

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# ABSTRACT

At present malaria causes over 400,000 deaths per annum and an excess of 200 million cases worldwide, with most cases occurring in African countries. In Zambia, as in many other endemic countries, some regions have high malaria prevalence that is highly influenced by climatic and environmental factors. This influence can potentially interfere with intervention program effectiveness and alter distribution and incidence patterns, resulting in poorer health outcomes and higher incidence rates in some countries with associated additional financial costs estimated to be up to US$2.4 billion yearly by 2030.

This study aimed to investigate the spatial and temporal impacts of climate change on malaria transmission, control and elimination efforts in Zambia from 2000-2016. The study modelled Zambian malaria incidence data against a range of socio-environmental datasets, to investigate near-term climatic change and evaluate impacts on control interventions. The results highlighted the importance of understanding evident within-country differences in malaria spatial patterns and how this information can be better used to improve and target implementation of expensive control programmes where they are most needed.

It was established that climate change negatively impacts malaria control efforts, and if ignored, has the potential to suppress ongoing malaria elimination efforts significantly. The results indicate that near-term climate change is likely to increase malaria incidence, particularly in areas where malaria incidence trends have been either increasing or decreasing. While malaria incidence rates are highest in young children age <5 and have been decreasing in the last 10 years, significant increases in malaria were identified in those aged 5 years and older. These could have serious future economic and social impacts. The study also showed seasonally sensitive diurnal temperature range (DTR), often neglected in climate change research, as a significant environmental variable affecting malaria incidences, with a strong seasonal influence. In addition to a general north-south pattern of spatial variation in incidence rates, some high incidence hotspots for malaria were identified, particularly along border areas with neighbouring high endemic countries. The results suggest the urgent need to forge bilateral cross-border malaria initiatives in the fight against malaria with neighbouring high endemic countries. A key recommendation from the thesis is for an adaptive-scaling approach to the implementation of both malaria monitoring and intervention programmes for control and elimination strategies.

# ACKNOWLEDGEMENTS

My greatest thanks to my supervisors, *Prof. Adrian Moore, Dr Yaxin Bi,* and *Dr Sally Cook,* for their guidance, and thoughtful insights throughout my studies. A big thank you to *Dr Hamainza Busiku,* my local advisor for the help and guidance through the data requesting process and for the invaluable conversations and audience, he gave me when I needed them most. Many thanks to *Prof. Ubydul Haque* for tirelessly providing valuable comments, subject guidance and encouragement at every stage of the journey.

Thank you to all-weather friends - Fyatilani Chirwa and Ennie Chipabika for their help and efforts in chasing up documentation to ensure that the study received the approval from Zambian authorities. I also thank my parents and siblings (Solo, Zachs, Febby, Alex, Moze, Alex, Laz, and Aggie) for continually encouraging and supporting me throughout my studies.

A big thanks to Dr Gary Napier of the University of Glasgow for the help with his R code, helping me adapt it to my needs. Many thanks to David Rogers for coming to my aid whenever I faced technical challenges.

A massive thanks to Japhet Matoba and Mukuma Lubinda for the help rendered, and the resourcefulness. Thank you to friends Dr Alison Cartwright and Dr Ben Strachan for their help in proofreading my work and the insights in formatting and style. Thanks to Dr Gabriel Gaffney, Temilola Olanrewaju, and Andrew Rice being the last standing *G077* crew of my time, and all other well-wishers including Oluwashina Akinsanmi, Peruth Nakriyowa, and Robert Runya for cheering me on.

Most of all, thankful to Jehovah God, for the *excellent health that no money can buy, through good times, tough times, & COVID-19 times, his word is always true.*

*"[1]He that dwelleth in the secret place of the most High shall abide under the shadow of the Almighty. [2]I will say of the Lord; He is my refuge and my fortress: my God; in him will I trust." Psalm 91*

Lastly, the list would not be complete without appreciating my local church, RCCG – KGG congregation for welcoming me into the family of believers, and their homes, for their prayers and encouragement throughout my studies.

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# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ACT | Artemisinin-based combination therapy |
| AIDS | Acquired Immuno-Deficiency Syndrome |
| AL | Artemether-lumefantrine |
| ANC | Antenatal care |
| BYM | Besag York & Mollié model |
| CAR | Conditional Autoregressive |
| CDC | Centers for Disease Control and Prevention |
| CHAZ | Churches Health Association of Zambia |
| CHW | Community health worker |
| CQ | Chloroquine |
| CSO | Central Statistical Office |
| DDT | Dichloro-diphenyl-trichloroethane |
| DHA-PQ | Dihydroartemisinin-piperaquine |
| DHIS2 | District Health Information System 2 |
| DHO | District Health Office |
| DHS | Demographic and Health Survey |
| DIC | Deviance Information Criterion |
| DRC | The Democratic Republic of the Congo |
| DTR | Diurnal Temperature Range |
| E8 | Southern Africa Malaria Elimination Eight Initiative |
| EIR | Entomological Inoculation Rate |
| EPI | Expanded Program on Immunisations |
| ESRI | Environmental Systems Research Institute |
| GIS | Geographic Information System |
| GLMM | Generalised Linear Mixed Models |
| Global Fund | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| GMEP | Global Malaria Eradication Program |
| GMRF | Gaussian Markov random field |
| GRZ | Government of the Republic of Zambia |
| GTS | Global Technical Strategy |
| HC | Health Posts |
| HF | Health Facility |

| | |
|---|---|
| HFCA | Health facility catchment area |
| HIV | Human Immunodeficiency Virus |
| HMIS | Health management information system |
| iCCM | Integrated community case management |
| INLA | Integrated Laplace Approximation |
| IPCC | Intergovernmental Panel on Climate Change |
| IPTi | Intermittent Preventive Treatment for infants |
| IPTp | Intermittent preventive treatment for pregnant women |
| IRS | Indoor Residual Spraying |
| ITN | Insecticide-Treated Net |
| LGM | Latent Gaussian models |
| M&E | Monitoring and evaluation |
| MCMC | Markov Chain Monte Carlo |
| MDA | Mass drug administration |
| MeSH | Medical Subject Headings |
| MIP | Malaria in pregnancy |
| MIS | Malaria indicator survey |
| MoH | Ministry of Health |
| NDVI | Normalised Difference Vegetation Index |
| NGO | Non-governmental organisation |
| NMCC | National Malaria Control Centre |
| NMEC | National Malaria Elimination Centre |
| NMEP | National Malaria Elimination Program |
| NMESP | National Malaria Elimination Strategic Plan |
| NMSE | Normalised Mean Squared Error |
| NMSP | National Malaria Strategic Plan |
| OLS | Ordinary Least Squares |
| OOB | Out-Of-Bag |
| OP | Organophosphate |
| OPD | Outpatient department |
| ≥5s | People aged five years and older |
| PCR | Polymerase chain reaction |
| PMI | President's Malaria Initiative |
| PML | Pseudo-Marginal Likelihood |
| RBM | Roll Back Malaria |

| | |
|---|---|
| RDT | Rapid diagnostic test |
| RHCs | Rural Health Centre |
| RW2 | Random Walk of order 2 |
| SBCC | Social Behavior Change Communication |
| SIR | Standardised Incidence Ratios |
| SMC | Seasonal Malaria Chemoprevention |
| SMR | Standardised Mortality Ratios |
| SP | Sulfadoxine-Pyrimethamine |
| TB | Tuberculosis |
| TPR | Test Positivity Rate |
| UHC | Urban Helth Clinic |
| <5s | Under-fives |
| Under-fives | Children aged under five years old |
| UNICEF | United Nations Children's Fund |
| USAID | United States Agency for International Development |
| WAIC | Watanabe Akaike Information Criterion |
| WHO | World Health Organization |
| WMR | World Malaria Report |

# CHAPTER ONE

## GENERAL INTRODUCTION

This chapter presents a brief background of the study. It outlines the key concepts, the aim, specific objectives, and the structure of this thesis.

# 1.1 Introduction

This chapter is a brief introduction to the overall study and thesis. It highlights the contextual nuances of the study's subject, malaria, and introduces broader key themes that would aid a general understanding of subsequent chapters. It also sets the ecological and epidemiological scenes and their complexity in the understanding of malaria transmission dynamics. The chapter shows how environmental variables vis-à-vis climate generally provide the ecological conditions necessary for sustained malaria transmission. The chapter also briefly discusses malaria prevention, management, and other contemporary themes that contribute to and define the current state of malaria disease in affected countries.

# 1.2 Malaria Epidemiology

### 1.2.1 Global to local malaria

At least 3.4 billion of the world's population are at risk to malaria infections (Jackson, Johansen, Furlong, Colson, & Sellers, 2010; World Health Organization, 2019c). Malaria is a parasitic disease transmitted by *Plasmodium* (*P.*) species, and spread from one person to another by female Anopheles mosquitoes. There are five human malaria parasites; namely, *P. vivax, P. ovale, and P. malariae, P. knowlesi, and P. falciparum* (Stramer & Dodd, 2018; Wanger et al., 2017). *P. falciparum* accounts for the highest mortality and morbidity worldwide followed by *P. vivax and P. knowlesi*. Figure 1.1 shows the general global distribution of malaria species and associated numbers of infections in 2015.

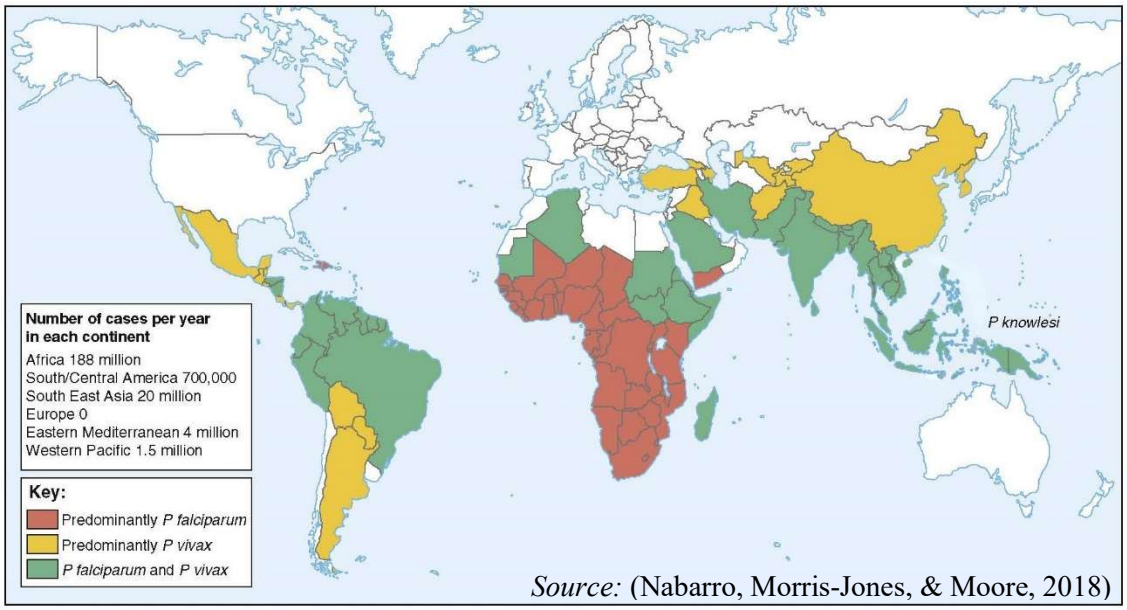


Figure 1.1: The distribution of primary malaria species

Generally, *P. falciparum* is the dominant species in Africa. Based on 2017 malaria estimates, *P. falciparum* comprised 99.7% of all infections in Africa, 62.8% of those from South-East Asia, 69% from the Mediterranean, and 71.9% from the Western Pacific (World Health Organization, 2019c). In contrast, *P. vivax* is dominant only in the Americas, accounting for about 75% of the total malaria infections there (World Health Organization, 2018e, 2019c).

Despite being preventable and curable, malaria still inflicts huge annual death tolls among those exposed to the infection (Shretta et al., 2017). Children aged below five years old, pregnant women, mobile populations, as well as HIV/AIDS patients, are the most vulnerable groups to malaria (Wilson, 2017). For example, in 2018 alone, children under 5 years old comprised 67% of the total malaria deaths worldwide (World Health Organization, 2019c).

In the last century, the overall geography of global malaria endemicity has declined by half (Hay, Guerra, Tatem, Noor, & Snow, 2004). In the last fifty years alone, the number of endemic malaria countries declined from 106 to 86. The global annual malaria incidence and mortality rates dropped by 36% and 60%, respectively (Feachem et al., 2019). This is partly as a result of improvements in economic development (Gething et al., 2010), extensive implementation of malaria interventions such as insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS), the availability of early and rapid malaria diagnosis, and enhanced access to effective treatment using Artemisinin-

based combination therapies (ACTs) (Kleinschmidt et al., 2009; Okumu & Moore, 2011; West et al., 2014).

Despite this progress, changes in global population characteristics have seen an increase of over 3 billion people currently residing in places with considerable malaria risk (Hay et al., 2004). For instance, rapid population growth has driven the increase in the population living in malaria-endemic areas of Africa. Today, over half of the population on continental African still live in areas with a substantial intensity of malaria (Noor et al., 2014).

Challenges, such as mosquito resistance to common insecticides, particularly pyrethroids and the threats from parasite resistance to ACTs, have stalled progress in various parts of the world. Co-infections with other infectious diseases like HIV and Tuberculosis (TB) increase the risk of parasites and clinical episodes of malaria in adults, and pregnant women infected with HIV have higher malaria frequency and parasite density than those uninfected (Wilson, 2017). Similarly, infants born to malaria-HIV co-infected women have a risk three to eight times higher of postnatal mortality than infants born to mothers with only one of the two infections. Pregnant women, particularly first pregnancies, also have increased susceptibility to malaria infections and subsequent severity of the disease (Lufele et al., 2017).

### 1.2.2 Malaria disease progression

A clinically simplified view of malaria disease progress sequence from the point of a plasmodium-infected bite is as follows (World Health Organization, 2014b):

$$\boldsymbol{Infection \rightarrow asymptomatic\ parasitaemia \rightarrow uncomplicated\ illness \rightarrow severe\ malaria \rightarrow death}$$

The geographical intensity of malaria transmission is the determinant of the distribution pattern of clinical disease.

In areas of periodic or highly seasonal malaria endemicity, often in various parts of the world outside the African continent, malaria transmission intensity has strong seasonal and annual cycles over relatively fine spatial scales. The limited transmission hinders the acquisition of broader population immunity and creates a highly homogeneous geographical risk across all ages. In the event of a delay or lack of treatment, everyone has a high probability that the disease will grow into severe malaria and possibly death.

The presence of some level of immunity against malaria offers protection from malaria severity, while people with no or partial-immunity (naïve individuals) are among the most vulnerable groups. Other highly susceptible groups to severe malaria include non-immune travellers who visit malaria-endemic areas (Franco-Paredes & Santos-Preciado, 2006; Jacquerioz & Croft, 2009; Schlagenhauf & Petersen, 2008).

While partial-immunity to clinical disease is often acquired from repeated infections or in early childhood, it results in low-risk malaria in later ages. In stable transmission environments, clinical malaria is restricted to younger children before they acquire immunity. During this time, children have a high risk of developing substantial malaria parasite densities, which foster the disease to progress towards severe malaria and possibly rapid death.

Older children and adults with partial immunity, on the other hand, rarely suffer severe clinical malaria in such endemic areas. However, they might still have low blood parasite densities, without exhibiting symptoms, but they are still capable of infecting mosquitoes. These are also called asymptomatic and are a challenging group to capture through the self-reporting passive surveillance health system because they do not seek care.

Asymptomatic malaria is most common in areas of sub-Saharan Africa (Snow & Omumbo., 2006). Where people have been exposed to infrequent infections since childhood, or when transmission levels are really low, the protection from acquired immunity changes. This is because immunity wanes when people become less exposed either by way of moving out of endemic areas for prolonged periods or due to the decline of malaria in their area.

Malaria epidemics are common in such areas or areas with unstable malaria transmission whenever the entomological inoculation rate (EIR) or biting rate increases due to sudden increases in vector mosquito density or survival. These often exhibit extremely high incidence coupled with severe malaria across all age groups. For example, a recent (2019) outbreak in Burundi, a place with unstable malaria transmission, 7.2 million incidences were recorded and over 2700 mortalities in the space of 10 months (World Health Organization, 2019b).

The drivers of the malaria outbreaks in Burundi include climate change, the permanent presence of mosquito breeding sites, the expansion of rice cultivation, the change in vector behaviour, the low coverage of preventive interventions, and other vulnerability

factors within the population (Checchi et al., 2006; World Health Organization, 2019b). Past malaria epidemic outbreaks occurred in 2017 when all districts in Burundi were affected and resulted in 6.2 million cases and 2700 deaths, and many others have been documented since 1999 (Checchi et al., 2006; Guthmann et al., 2007; Legros & Dantoine, 2001). Similar outbreaks include those around the East African Highlands (Hammerich, Campbell, & Chandramohan, 2002; Lindsay & Martens, 1998; World Health Organization & UNICEF, 2003).

### 1.2.3 Regional Malaria Disease Burden

In 2018, about 405 000 malaria deaths were recorded globally, down from an estimated 416 000 and nearly 500 000 deaths in 2017 and 2010, respectively (World Health Organization, 2019c). There were about 228 million infections of malaria in 2018 alone, a slight decline from the previous year's 231 million and a change from the two preceding years that saw global malaria increases. Africa consistently carries an excessively high proportion of both malaria cases and deaths which often account for at least 90% of global totals (World Health Organization, 2013, 2014a, 2015d, 2016b, 2017b, 2018f, 2019c).

While most of the malaria burden is in sub-Saharan Africa, other WHO regions such as the Mediterranean, South-East Asia, Western Pacific and the Americas, are equally at risk (World Health Organization, 2019c). The distribution of malaria, however, exhibits strong regional patterns. The 2019 world malaria report documented that the top 11 countries which contributed 85% of the global malaria burden, and top six that contributed more than 50% are all in sub-Saharan Africa (World Health Organization, 2019c).

## 1.3 Climate change and Health

### 1.3.1 Climate Change and Human disease

Weather, climate, environmental factors and health are all intertwined in a complex web that continues to show intuitive effects on humanity (Hajat, Vardoulakis, Heaviside, & Eggen, 2014). A range of observable threats to humanity and its survival are imminent due to these climate change and environmental factors. Extreme weather such as floods, aridity, cold or heatwaves in places where they are not usually expected has a direct effect on humans including that experienced indirectly through unprecedented variations in

disease patterns due to changing ecology and biotic systems. They also include those of a human/socioeconomic nature due to loss of cultivation and habitats, leading to strife and subsequent mass migrations (McMichael & Lindgren, 2011; Nabi & Qader, 2009; Smith et al., 2014; Watts et al., 2015). In Africa, it is projected that temperature increases across the continent may expand diseases and their range and increase mortality in addition to other indirect effects such as shortages of water and threatened food security (Costello et al., 2009).

In 2009, climate change was considered to be a substantial global health threat in this century (Costello et al., 2009). Today, the significance of climate change globally threatens to outweigh the gains in human social and economic development, including global health (Watts et al., 2015). While the poorest countries and regions are generally the most susceptible, the unpleasant effects of a changing climate affect the entire global community in various ways, leaving no region untouched (Semenza et al., 2008; Watts et al., 2015).

Long-term changes in temperature alter the nature of the risk from several diseases such as malaria and other heat-related illnesses. Many more diseases influenced by temperature and precipitation patterns include yellow fever, cholera, dengue virus, zika, chikungunya, West Nile virus, TB, malaria, elephantiasis, and meningitis in Africa. These diseases present well documented negative economic and developmental costs of climate on the population and countries involved (Gallup & Sachs, 2001; Stern, 2007).

Climate equally influences the prevalence of many respiratory diseases, like asthma and allergies (Ariano, Canonica, & Passalacqua, 2010; Bell & Greenberg, 2018; Shea, Truckner, Weber, & Peden, 2008). There is also evidence that concentrating resources on resolving threats from climate change and health is valuable to economies and is often more profitable than mitigating the consequences (Stern, 2007). At the community level, reductions in vector-borne diseases foster better productivity and development, which could lead to reductions in household poverty (World Health Organization, 2019a).

Other indirect health-related effects of climate include the transmission of zoonotic diseases, HIV/AIDS, Cancer, Mental Health, Heat Stress, stress-related disorders and respiratory illness (Portier et al., 2017).

Although the body of literature generally discussing the effects of climate change on health, and other infectious diseases like Arbo-viruses, has increased (Paavola, 2017;

Salas & Jha, 2019; Watts et al., 2016), malaria remains among the leading cause of morbidity and mortality among diseases, especially in the global south (Challe et al., 2018; Guinovart, Navia, Tanner, & Alonso, 2006).

### 1.3.2 The link between malaria transmission and climate change

Malaria is one of the diseases whose inherent relationship with climate continues to prompt health, ecological and environmental practitioners to explore the complex climatological, epidemiological, and environmental intricacies that as a consequence result in poor human health outcomes (Sadoine, Smargiassi, Ridde, Tusting, & Zinszer, 2018).

Although the link between malaria outbreaks and climate is sometimes contested, most studies (Alonso, Bouma, & Pascual, 2011; Mabaso & Ndlovu, 2012; Midekisa, Beyene, Mihretie, Bayabil, & Wimberly, 2015; Wandiga et al., 2010) show that malaria endemicity in much of Africa is climate-driven. A number have also shown that changes in climate variables that affect malaria may trigger a transmission upsurge, particularly along the peripheries of stable zones, such as elevation areas (highlands) (Tonnang, Kangalawe, & Yanda, 2010).

Global models often predict increased malaria risk in parts of Africa especially in the highlands (Bouma, Baeza, terVeen, & Pascual, 2011; Chaves & Koenraadt, 2010; Jury & Kanemba, 2007), and declines in the northern Sahel (Caminade et al., 2011). Although still contested, it is argued that the new areas and populations of projected regional malaria spread would be greater than those where the disease would no longer exist. This is predominantly due to the lack of or partial immunity of the people in these new areas, which threatens severe adverse effects. The threat applies across all ages, according to the evidence in the Highlands of East Africa (Bouma et al., 2011; Lindsay & Martens, 1998). When considering cases globally/within East Africa projected epidemics have particularly been observed in Ethiopia, Uganda, Kenya, Sudan, Tanzania, Rwanda, and Burundi (Checchi et al., 2006; Hammerich et al., 2002; Legros & Dantoine, 2001; Negash et al., 2005; World Health Organization & UNICEF, 2003).

While the survival of the vector mosquito depends on the environmental conditions around it, transmission intensity is influenced by several other aspects associated with the pathogen, the mosquito, the people as hosts, and ecology (World Health Organization, 2019a). The mosquito vector (Anopheles) lays its eggs in aquatic habitats, where they

hatch into larvae, and soon emerge as full-fledged mosquitoes (Moller-Jacobs, Murdock, & Thomas, 2014). Female mosquitoes search for blood meals for their eggs to develop. Various Anopheline species prefer different aquatic habitats, mostly ranging from shallow freshwater collections (often rain-fed especially in the tropics) to broader/deeper or even slow-moving water, often in open lakes, rivers and swamps (Ohm et al., 2018; Ondiba, Oyieke, Athinya, Nyamongo, & Estambale, 2019).

Environmental factors such as heat, moisture, precipitation, and land use/landcover, influence the transmission of malaria by stimulating the availability and distribution of mosquitoes. For example, climate conditions affect the range, survival and reproduction of mosquitoes and pathogen's incubation periods responsible for malaria (Nabi & Qader, 2009; Semenza et al., 2008; Wu, Lu, Zhou, Chen, & Xu, 2016). The rising temperature in highland areas due to global warming is also predicted to increase the elevation of malaria patterns exposing these highly populated areas to high risk, especially in Africa and Latin American countries (Ermert, Fink, Morse, & Paeth, 2012; Siraj et al., 2014).

Such ecological conditions could stifle or exacerbate malaria transmission. Conducive ecological conditions such as optimal temperature, high relative humidity, and availability of aquatic habitats increase mosquito survival (Ohm et al., 2018; Ondiba et al., 2019). Due to substantial seasonal variation in weather, malaria transmission patterns mostly follow seasonality, with the highest transmission and epidemics occurring during periods of rainfall. The intensity, however, varies from place to place.

To introduce and sustain malaria transmission, a vector mosquito species should have several characteristics, including:

- The threshold of abundance – the occurrence or abundance of vector mosquitoes are associated with the ecological environment. There needs to be high enough numbers of mosquitoes to ensure a high probability man-vector contact.
- Length of survival – the vector mosquitoes need to live long enough to have at least two blood meals (first to pick up the infection and then for transmitting it to another person).
- Vectorial capacity – the mosquito should carry enough malaria infection parasites to ensure this can be transmitted to the next host.
- Availability of humans - A competent vector and a suitable climate for parasite infectivity in mosquitoes are not enough to trigger a malaria outbreak. The

mosquito needs sufficient access to people. Poor housing, especially in rural Africa, is linked to high exposure to mosquito vectors.

Hence, the transmission is higher in areas where the vector lives longer and/or has a preference to feed on humans rather than on animals. This is cited as the key reason why Africa accounts for the highest proportion of malaria cases globally (World Health Organization, 2019a).

### 1.3.3 The African Mosquito and malaria

*Anopheles gambiae* is the highly efficient African malaria vector, which is also highly anthropophagic (human biting), and classified as indoor-biting and resting, but also portrays outdoor resting tendencies. Blood feeding is either indoor or outdoor, on condition of the mosquito species. In contrast, *An. arabiensis* generally exhibits outdoor biting, resting, with occasional indoor biting, and resting. These tendencies depend on alternative host availability. Aspects of the environment, climate, and vector control interventions, can affect mosquito behavioural to factors such as biting or resting. Table 1.1 shows a summary of Africa's vector mosquitoes, driving the majority of transmission.

Table 1.1: Malaria Vector Mosquitoes in Africa

| | | | Biting behaviour | | | Resting behaviour | |
|---|---|---|---|---|---|---|---|
| **Ecological zone** | **Vector species** | **Aquatic habitats** | **Anthropophily / Zoophily** | **Exophagy / Endophagy** | **Peak biting time(s)** | **Exophily / Endophily** | **Remarks** |
| Forest, savannah, Sahel, (wetter, more humid) | An. gambiae s.s. | Shallow, open, sunlit pools: borrow pits, drains, brick pits, car tracks, ruts, hoofprints around ponds, wells. Also pools of receding rivers, backwater, rainwater filling in natural depressions, etc. | Predominantly anthropophilic | Predominantly indoors | mid-night to dawn | Indoors and outdoors | High diversity, incipient speciation |
| savannah, Sahel (drier) | An. arabiensis | Small, temporary, sunlit, clear, and shallow freshwater pools. Can include slow-flowing, partially shaded streams and a variety of large and small natural and man-made habitats and rice fields | More zoophilic than An. gambiae s.s. | More exophagic than An. gambiae s.s. | Early evening and early morning | Predominantly outdoors | Very variable behaviours |
| All zones, except sub desert and coastal areas | An. funestus s.s. | Permanent, clear, fresh waters, slightly shaded, with floating or erect vegetation, and containing little organic matter or mineral salts: swamps, edges of lakes and ponds, pools in a stream and river banks, rice fields (esp. Madagascar and Mali) | Highly anthropophilic | Indoors | Mid-night to dawn, but generally later than An. gambiae s.s. | Predominantly indoors | Belongs to Funestus Subgroup |

*Source: WHO 2018*

## 1.4 Malaria interventions

Malaria is preventable and curable using available effective interventions. Several key malaria interventions are recommended and generally available in malaria-endemic countries.

i. Insecticide Treated Nets (ITNs)/Long-lasting insecticidal nets (LLINs): LLINs has been key to in the prevention or reduction of malaria burden in recent decades. Nets are the most widely implemented intervention especially by populations highly exposed to malaria
ii. Indoor residual spray (IRS): Most malaria vectors exhibit indoor resting behaviour after a successful bite of the host. IRS is the spray coating of internal house walls or any other surfaces using insecticides. These could kill any mosquito that rests on or is exposed to the coated surface. This intervention prevents the transmission of potential infection to another person.
iii. Intermittent Preventive Treatment in Infants (IPTi-SP): This is when a full course of antimalarial medication is given to infants, whether they were infected or not with malaria. Treatment is given to help reduce malaria or anaemia in their initial twelve months.
iv. Intermittent Preventive Treatment in Pregnant Women (IPTp): IPTp is a full dose of an antimalarial drug administered to women who are pregnant. Pregnant women receive this regardless of whether they are infected or not with malaria. The objective is to minimise all maternally related episodes of malaria infections or deaths.
v. Seasonal Malaria Chemoprevention (SMC): This is when intermittent courses of malaria drugs are administered to children especially, in areas with strong seasonal transmission during a malaria season. This provides up to 75% efficacy against mild or severe malaria in children under five years old.
vi. Mass drug administration (MDA): MDA is when there is an area-wide (defined geographical area) administration of antimalarial treatment to all members of a defined population at approximately the same time.

The current crop of effective malaria interventions generally interrupts the transmission cycle either at the vector (i & ii) or the parasite (iii - vi) levels. The two vector inventions

(IRS and ITNs/LLINs) are the most universally applied, and widely accepted methods for malaria prevention. From 2000 to 2015, infections from *P. falciparum* in endemic Africa declined by 50%, while clinical disease fell by 40% (Bhatt et al., 2015). During the same period, over 600 million (68%) cases were averted in Africa alone, due to the high usage of ITNs, while an estimated 13% were achieved through IRS usage, especially in areas with high coverage (World Health Organization, 2019a).

Human population densities may influence the selection of appropriate vector control interventions. For example, stable malaria transmission results from highly and continuously exposed populations with an elevated frequency of malarial parasite inoculation (World Health Organization, 2017a, 2019a).

In order to achieve and sustain high coverage of interventions for populations at risk, a high standard of implementation is essential. Universal coverage of people at risk using cost-effective interventions against the vector provides the most efficient and prompt chance for the reduction of malaria and is generally recommended. Targeted interventions, however, remain key due to inadequate funds, especially in low resource settings.

## 1.5 Climate and Malaria Transmission in sub-Saharan Africa

As Africa already bears 90% of the world's malaria burden (deaths and cases) (World Health Organization, 2015d, 2016a), the lack of mitigation, adaptation or preparedness for climate change may result in further increased malaria burden (World Health Organization, 2015b). For example, countries with a high risk that also suffered increasing malaria incidence between 2010 and 2016 include Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, South Sudan, Tanzania, Uganda, and Zambia (World Health Organization, 2017b), are all located in Africa.

The people residing in Africa are at higher risk from climatic influences because they are highly exposed, but with low adaptive capacity. For this reason, the current study was undertaken in Zambia with a key objective of contributing not only to the local knowledge on the specific effects of climate change but with relevance to the whole African Continent.

In 2015, the adoption of the Global Technical Strategy (GTS) for malaria, by the World Health Assembly stimulated activities towards the goal to eliminate malaria in $\geq 10$ countries by the year 2020. Since 2016, 21 malaria-endemic countries have now been

identified as having a higher probability of eliminating malaria by 2020. These countries are symbolic of a concerted ambition to reduce indigenous malaria cases to zero by the end of 2020, and are collectively termed the "E-2020 malaria initiative".

History shows that many European countries are malaria-free today. They benefited from the first global malaria eradication campaign of 1955 (Bruce-Chwatt & De Zulueta, 1980). Dichlorodiphenyltrichloroethane (DDT) was the mainstay of the malaria-control efforts, whose focus was to eliminate Anopheles mosquito vectors (Hast, Searle, Chaponda, Lupiya, Lubinda, Sikalima, et al., 2019). The Global Malaria Eradication Program (GMEP) goal was to apply IRS using DDT on suitable house wall surfaces to decrease the longevity of mosquitoes (Hamoudi & Sachs, 1999; Packard, 1998).

Sustaining transmission depends on the abundance of vectors, vector propensity in biting humans, the ratio of infectious bites, the vector longevity (life span), and the reproduction time in the vector. Among these, the key is the longevity of the mosquito vector. The logic behind IRS is that because the pathogen requires a number of days to mature inside the mosquito, during this period, the infected mosquito searches for a host to feed-on is the optimal time to spray. Hence, spraying would shorten the survival of adult female anopheles, should they become exposed to a sprayed surface.

The GMEP was carried out across Europe, Asia, and in parts of Latin America with great success, however, Africa was not formally included in this program (Griffin et al., 2010). During this period, from 1955 to 1969, the anopheles vector was eliminated, and soon after, malaria elimination was achieved in Europe (Hamoudi & Sachs, 1999). However, in many continental tropical countries, especially in Latin America and most Asian counties, the situation remained unchanged as control efforts suffered from a rise in insecticide-resistant anopheles. Meanwhile, in Africa, despite malaria being by far one of the most significant health problems very little if anything was done by way of intervention measures between 1970 and the late 1990s (Moss, Shah, & Morrow, 2016).

From 1970 and up until the launch of the Roll Back Malaria (RBM) initiatives in 1998 (Nájera, González-Silva, & Alonso, 2011; Rabinovich et al., 2017), no real priority or focus was given to the global fight against malaria including Africa. RBM's goal was to halve malaria by the year 2010. By 2007, a renewed global call for the malaria eradication agenda (malERA) mainly to reduce the effects of malaria was launched (Nájera et al., 2011). This would be achieved through combinations of ITNs, early diagnosis and treatment with ACT or by IPTp and IPTi.

While the logistics and health infrastructure needed for therapy are still inadequate in many places, and the need to meet funding requirements remains a challenge, past lessons learnt, improvements in capacity and increased experience has helped some countries make good progress (Moss et al., 2016).

Today, the challenge of malaria in sub-Saharan Africa, the place where control of malaria had either not been attempted or accomplished before is even higher. Many Sub-Saharan countries are experiencing increases in malaria burden (Assele, Ndoh, Nkoghe, & Fandeur, 2015; Nkumama, O'Meara, & Osier, 2017; World Health Organization, 2018e, 2019c). Recent outbreaks of malaria in some countries and sporadic resurgences in others highlight the continual threat of malaria resurgence or re-establishment. Even after elimination, several factors may contribute to epidemics or resurgence of malaria in previous eliminated areas.

Nonetheless, thanks to the GMEP many endemic countries are determined to not only bring malaria under control but also to eliminate the disease. With the advancement in current intervention tools and ongoing epidemiological studies of malaria now possible at temporal and spatial scales, there is hope again as these tools allow people to gain a more sophisticated understanding of the malaria parasite, the mosquito, the human, and the environment.

## 1.6 Rationale and Study Justification

Many climate models of the global scenario show contradicting results from place to place (Rogers & Randolph, 2000). It is evident that the effects of climate change are not evenly spread across countries, showing different impacts from geographic, economic and social mediating factors (World Health Organization, 2015a). For malaria, the complexity is amplified by the reciprocation between two or more species of a host and a pathogen or quite often vectors and hosts. These make the collective impact of climate on disease outcomes subtle (Lafferty, 2009) and often challenging to measure.

Conventionally, scientific studies have often focussed on long-term changes in climate. Their models concentrate on prospective analogues of climatic changes through predictions of how these changes could affect people via variations in weather patterns and extreme events (IPCC Working Group II, 2001).

Furthermore, climate change effects on malaria outcomes depend on population density, spatial scale, temporal scale, and current interventions, improved health infrastructure, all

of which can affect the ability to detect specific climate change impacts. Hence, the relationship between climate and malaria remains a complex one because impacts may often be location-specific. In fact, it is more often considered important from a grassroots operational perspective to understand and detect fine-scale impacts rather than global-scale changes (Altizer, Ostfeld, Johnson, Kutz, & Harvell, 2013).

The global (World Health Organization, 2015b, 2016b), regional (Elimination8 Secretariat, 2017), and national (Presidential Malaria Initiative, 2016) malaria programme agendas have in the last decade been realigned towards elimination and eventual eradication, against the predictions of the possible future increases of malaria due to climate change. The explicit and persisting climate change and the observed effects of short-term weather variability on the vector mosquito survival (longevity) and its reproduction provide an opportunity to examine the outcomes of this relationship and include other non-environmental based variables.

The 'one size fits all' approach to attempt to model or forecast malaria is unlikely to be successful. Similarly, the precise forecasting of the future of malaria is at a global scale which is based on projections where the inputs are from a few locations only or a limited number of parameters (Nabi & Qader, 2009). This often does not capture the intricate socio-economic, cultural and demographic heterogeneities often exhibited by small area geographical scales, particularly at sub-national, sub-regional or sub-district levels.

Therefore, more research in local settings is needed to understand the location-specific effects of climate change and other factors on malaria, alongside other parameters, as well as providing local results to inform global models.

Climate change-induced health risks cause varying levels of stress and tend to pose more challenges for some local communities than others. In a heterogeneous state of community capacity to handle risk, it does not mean that two communities exposed to similar hazards will react in the same manner. Capacity often depends on the unpredictable interaction between several community-level socioeconomic and cultural, co-exposure conditions and processes that influence the ability of communities, or regions to respond (Bell & Greenberg, 2018; L. Comfort et al., 1999; Leichenko & O'brien, 2002).

Africa faces the largest environmental health burden and has the most vulnerable populations to climate change but the least coping capacity, and potentially the most inadequate resilience to recovery (Bell & Greenberg, 2018; Bohle, Downing, & Watts,

1994). Defining predicted impacts of climate change reveals probable susceptibility to the ecological, socio-cultural, or epidemiological vulnerability of the population. There is a need, therefore for comprehensive, context-specific, global maps of climate change and outcomes (Wu et al., 2016), but these must be built from fine-scale models.

The drawbacks of current top-down approaches to modelling climate change impacts are their failure or inability to account for the differences vulnerabilities suffered by people in such environments. This could be through resistance or by mitigation when the event happens (Jones, Boer, Magezi, & Mearns, 2005; Stonich, 2000). Top-down approaches provide, at best, only a generalised context of potential prospects of regional and local climate conditions. At the same time, subsequent improvements in this type of modelling will bring more uncertainties as a result of increased volumes of data and the complexity of processes being modelled (Pielke Sr, 2013; Pielke Sr & Wilby, 2012; Trenberth, 2010).

## 1.7 Malaria transmission in Zambia

### 1.7.1 Past progress in the fight against malaria

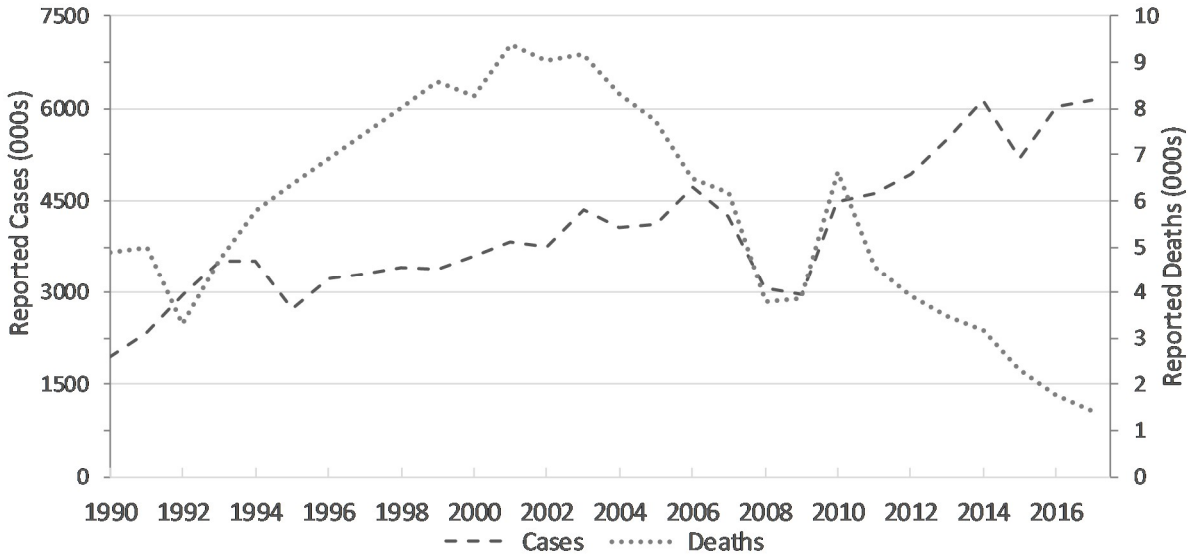


Figure 1.2: Malaria in Zambia from 1990- 2017 (*source: WHO 2008, 2010; PMI 2018, 2019)*

Zambia has, since the early 2000s been motivated to be a frontline country in the fight against malaria (Chizema-Kawesha et al., 2010). Figure 1.2 shows that malaria cases and deaths were increasing before the early 2000s and declined until 2008. Since 2008, deaths continued declining while cases started increasing again. The parasite prevalence survey of 2006 was pivotal in influencing the renewal of the malaria control programme (World

Health Organization, 2008). The majority (98%) of malaria cases in the country are from *P. falciparum* (Sitali et al., 2019).

Over the period from the late 1990s to 2017, Zambia consistently implemented malaria interventions and made great strides in reducing malaria mortality and incidence (Chizema-Kawesha et al., 2010; Loewenberg, 2018). Between 2000 and 2006 and before scale-up of control efforts, Zambia saw a 33% decrease in malaria infections and a 24% decrease in deaths among children <5 years old. In 2008, it also saw a 61% decrease in in-patient cases and 66% decrease in deaths compared to the baseline period (2001-2002) (Barnes, Chanda, & Ab Barnabas, 2009). Severe anaemia in children under-5 years old declined by at least 50% from 14% in 2006 to 7% in 2012, and 6.4% in 2015 (Presidential Malaria Initiative, 2019). Malaria prevalence confirmed by microscopy reported a further decline of 7%, from 22% to 15% between 2006 and 2012. However, the period from 2012 to 2015 saw an increase from 15% to 19%.

This overall progress is often attributed to Zambia's consistency in fighting malaria with the benefits of the intervention scale-up being realised in subsequent years, as indicated both through the surveillance and survey data (Presidential Malaria Initiative, 2019; World Health Organization, 2008). For example, between 2000 and 2006, Zambia was one of only six countries that had distributed sufficient mosquito nets, i.e. ITNs, including LLINs (58%), covering over 50% of people at risk of malaria. Zambia first completed a nationwide distribution of LLINs between 2006 and 2007, and it was one of only two countries that had completed nationwide targeting of all households (World Health Organization, 2008). High ITN ownership and usage across all provinces were also reported between 2006 (World Health Organization, 2008) and 2018 (Presidential Malaria Initiative, 2019), increasing from only 26% in 2000 (Baume & Marin, 2008), 50% in 2006 (Baume & Marin, 2008; World Health Organization, 2008) to 77% in 2015 (Masaninga et al., 2018).

Zambia was also among the first of two African countries to start ACT distribution in 2004 (Barnes et al., 2009), and one of the few where at least 50% of all children with fever were treated with antimalarial drugs (World Health Organization, 2008). During the same period, Zambia was also the earliest adopter of the nationwide use of Artemether/lumefantrine (AL), moving away from high Chloroquine treatment failure in 2002 (Chizema-Kawesha et al., 2009; Sipilanyambe et al., 2008). Furthermore, Zambia was among the few countries where intermittent preventive treatment using sulfadoxine-pyrimethamine among pregnant women was substantially high (61%), against a mean

usage of 18% across the top 16 countries on the continent (World Health Organization, 2008).

Although IRS is not the primary malaria preventive strategy, the (re-)introduction or subsequent expansion of IRS by coverage of at least 90%, between 2000 and 2010 had incremental benefits (Masaninga et al., 2013). Access to treatment may have varied within the country, especially between rural and urban areas. For example, higher proportions of children receive antimalarial treatment in urban than rural areas (World Health Organization, 2008), and IRS was mostly applied in urban areas (Masaninga et al., 2013).

### 1.7.2 The persistent challenge of malaria

In spite of all these efforts, malaria in Zambia is still a significant public health problem (Lowa, Sitali, Siame, & Musonda, 2018). In 2006, for instance, Zambia was still among the top 20 countries known to have contributed about 90% malaria cases as well as deaths in the WHO Africa region. This list included five other neighbouring countries (Malawi, Angola, Mozambique, Tanzania, and DRC) (World Health Organization, 2008). As of 2019, although Zambia has progressed considerably, three of its immediate neighbours, Angola, Mozambique and DRC remain in the top six of countries with the highest malaria globally (World Health Organization, 2019c). Given that mosquitoes do not recognise political borders, having neighbouring countries with high malaria rates is a potential issue for Zambia and something that is examined explicitly in chapter 6.

It has been argued that some of the observed progress achieved in Africa in the last two decades was not entirely due to interventions alone (Meyrowitsch et al., 2011), given that malaria cases and deaths reported worldwide, even in countries outside Africa fell by 50% over the period 1997–2006 (World Health Organization, 2008). The argument suggests that other factors not related to interventions such as urbanisation, changes in land use and agricultural practices, as well as economic development, may have impacted mosquito vectors and resulted in the reduction of malaria infections cases (Meyrowitsch et al., 2011).

Caution should be exercised when interpreting national-level figures as they are not characteristic of overall trends within Zambia, be it the provincial level, district level or sub-district level (Presidential Malaria Initiative, 2019). For example, the report cites how between 2012 and 2015, malaria cases had the most significant relative declines of up to 12% in observed parasite prevalence in Eastern and Southern Provinces. In contrast, malaria increases were recorded between 2012 and 2015 in 7 provinces (Central,

Copperbelt, Lusaka, Muchinga, Northern, North-Western, and Western), whereas one, Luapula Province, persisted without change.

In 2017, the Zambian government launched the National Malaria Elimination Strategic Plan (National Malaria Elimination Centre, 2017; Presidential Malaria Initiative, 2018). The plan is a revision to the 2015 strategic plan, guiding the long-term vision to create a malaria-free Zambia, with the year 2021 as the initial timeline (National Malaria Control Programme, 2015; National Malaria Elimination Centre, 2017; Presidential Malaria Initiative, 2019). The plan would be implemented through quality-assured and equitable access to cost-effective interventions for preventing or controlling malaria. The plan involves a dual approach to target different transmission strata based on their classification. Districts with <50 cases per 1000 population would receive essential intervention on surveillance and elimination while districts having >50 cases per 1000 population efforts would concentrate on reducing the malaria burden and strengthening the health system. The former group comprise the malaria elimination zones, while the latter constitute the malaria control zones.

Nonetheless, the diverse socio-economic and epidemiological landscapes of Zambia create complex challenges for malaria control efforts increasing the risk of creating large areas of both high and low transmission potential across the country. The differences in malaria risk are determined by several key drivers such as the urban-rural divide (with a higher risk in rural areas); socio-economic circumstances (greater risk in generally poorer localities); and the physical environment (high-risk humid river basins compared to low risk drier plateaux).

Since 2014, there has been increasing interest in obtaining finer granularity (below Provincial level) in the reporting and mapping of malaria incidence information to help identify and target the higher malaria burden experienced in many rural districts. In Zambia, this is particularly important in several provinces including the northern parts of Central and Western Provinces, the districts in the rural areas of the Copperbelt, as well as in the lowlands found in Eastern Province.

Until now, very few nationwide studies have been conducted at district or sub-district (health facility) levels. Countrywide analyses at the health facility level are very scarce and generally limited in scope to the simple point-based mapping of annual rates. Therefore, it was a primary objective of this thesis to focus on district and sub-district

(health facility) level analyses of rates, risk and trends (See chapters 3, 4 and 6) to help address the information and knowledge deficit.

This level of detailed analysis has been made possible by improvements in the recording and accuracy of morbidity and mortality data since 2000 (discussed in detail in chapter 2). Improvements have been made in reporting of malariometric measurements such as parasite prevalence by smear microscopy, in outpatient and in-patient malaria cases, RDT positivity rates and malaria parasite prevalence in the under-fives. Therefore, the study pursued a comparative impact assessment of climate change on age-related malaria vis-à-vis malaria interventions (*see Chapter 5*).

### 1.7.3 Malaria and climate studies in Zambia

Very few previous studies focused on the relationship between climate variables and malaria in Zambia. A Medical Subject Headings (MeSH) search using a range of key terms in PubMed returned only four relevant studies, each of which was conducted at different spatial scales, using different data sources and with varying geographical extent. These studies are, however, not directly comparable to the present study due to differences in the quality of data used, the spatial scales of analyses, and the levels of malaria transmission in their study areas.

The first study by Nygren et al. (2014) collected weekly malaria data from 2011 to 2013 and used the normalised difference vegetation index (NDVI), night surface temperature, rainfall and night dew point to model health facility level malaria transmission within Southern province. Their results showed a significant association with environmental variables (dew point, temperature, and NDVI) across the low, moderate, and high transmission zones (Nygren et al., 2014). These variables were also significant both in malaria peak and off-seasons and were the best predictors of malaria in the low transmission season using autoregressive integrated moving average (ARIMAX) models. Nonetheless, this study was spatially concentrated in the Southern province only, where transmission is generally lower compared to the rest of country, and may have been affected by the short temporal scale covering only one season and is therefore not seasonally robust.

A second district-wide study was conducted in Nchelenge district (in Luapula province) using household-level cross-sectional surveys conducted every two months between 2012 and 2015 (Pinchoff et al., 2015, 2016). The study used rainfall, temperature, and relative humidity obtained from a single micro-weather station to establish study area seasonality.

The study modelled elevation, seasonality, NDVI and degree of the slope as the key environmental variables. Using multivariate models, environmental factors were significantly associated with the proportion of RDT positive individuals at the household level. In particular, seasonality and distance to streams were strongly associated with higher malaria in both high and low malaria transmission seasons (Pinchoff et al., 2015). This study showed that, despite the rainy season showing higher malaria risk, the dry season still exhibited relatively high risk suggesting that other factors were important. This was especially the case with the high network of streams that showed a 12% rise in risk for every 250 meters distance closer to river segments of the first order or category 1 sized stream which often have a peri-annual flow.

The third study focused on household-level malaria data from four malaria indicator surveys (MIS) conducted between 2006 and 2012. The study evaluated malaria control intervention scale-up coverage of ITNs and IRS on parasite prevalence in children under five years old against climate variables (cumulated rainfall, humidity, temperature suitability, and enhanced vegetation index) that were collated at the provincial level (Bennett et al., 2016). The study used Bayesian geostatistical models of malaria prevalence to establish the association between malaria, intervention variables (IRS and ITN coverage) and climate variables. While the study showed that a combination of factors, both climate-related and those associated with a reduction in intervention coverage contributed to the observed malaria reduction and resurgence (Bennett et al., 2016). Temperature and rainfall both influenced the potential for increased transmission intensity as determined by intra-annual climatic variability. The study partly inspired the inclusion of the age-specific comparative study of malaria and interventions presented in Chapter 5.

Finally, the most recent example is a study by Shimaponda-Mataa et al. (2017), which used geoadditive and semiparametric models focusing on the influence of climatic factors (rainfall, minimum temperature, and maximum temperature) between 2009 and 2012. This is the smallest scale among the studies whose analysis of malaria was carried out at the province level, particularly in Lusaka, Western, Luapula and North-western provinces. The study reported a strong positive association between malaria incidence and environmental variables, particularly precipitation and minimum temperature (Shimaponda-Mataa, Tembo-Mwase, Gebreslasie, Achia, & Mukaratirwa, 2017). The small spatial scale of the study, however, would limit its usability at policy levels and

conceals essential subnational variations that coincide with the general implementation of interventions in Zambia.

Thus, while these studies help describe the dynamics of malaria transmission at various subnational scales of analysis in Zambia, they are generally not comparable due to differences in the data sources, methods, scales and variables used. From this brief discussion of relevant studies in Zambia, it is clear that there is a lack of countrywide district-level analysis of climatic variables. Such studies would help to capture a more holistic view of prevailing subnational variations in malaria incidence, intervention distribution, and the significance of climatic variables as potential predictors of transmission during Zambia's fight against malaria between 2000 and 2016.

Based on the literature search, it was clear that there has been no nationwide sub-provincial level long time series study exploring the association between climate change and malaria transmission in Zambia. This observation provided the motivation and incentive to include climate change as a primary focus of this thesis. This study explores the spatial and temporal interplays between climate change, the environment, and malaria transmission at district and sub-district levels from 2000 to 2016. It examines the implications of near-term climate change on the current national malaria control and elimination programs in the country.

This study endeavours to identify, measure, analyse and hopefully better understand the fine-scale dynamics of country-wide climate change effects on malaria within Zambia. It is hoped that the outcomes from the study provides relevant information that is helpful to strategic policy makers and intervention program officers as they strive to eradicate malaria from the country.

## 1.8 Aim

The aim of this thesis is to investigate the spatio-temporal impacts of near-term climate change and other environmental factors on the transmission, control and potential elimination of malaria in Zambia. Four specific objectives were formulated to achieve this aim (See also Figure 1.3).

i. Determine the spatio-temporal patterns of malaria incidence and mortality rates, risk and trends in Zambia from 2000 to 2016
ii. Investigate the spatio-temporal impacts of near-term climate change on the rates, and trends between 2000 and 2016

iii. Investigate climate change and the dynamics of age and malaria incidence and malaria control interventions between 2000 and 2016

iv. Model Health Facility level malaria and evaluate its potential for in-country and inter-country malaria control and elimination efforts

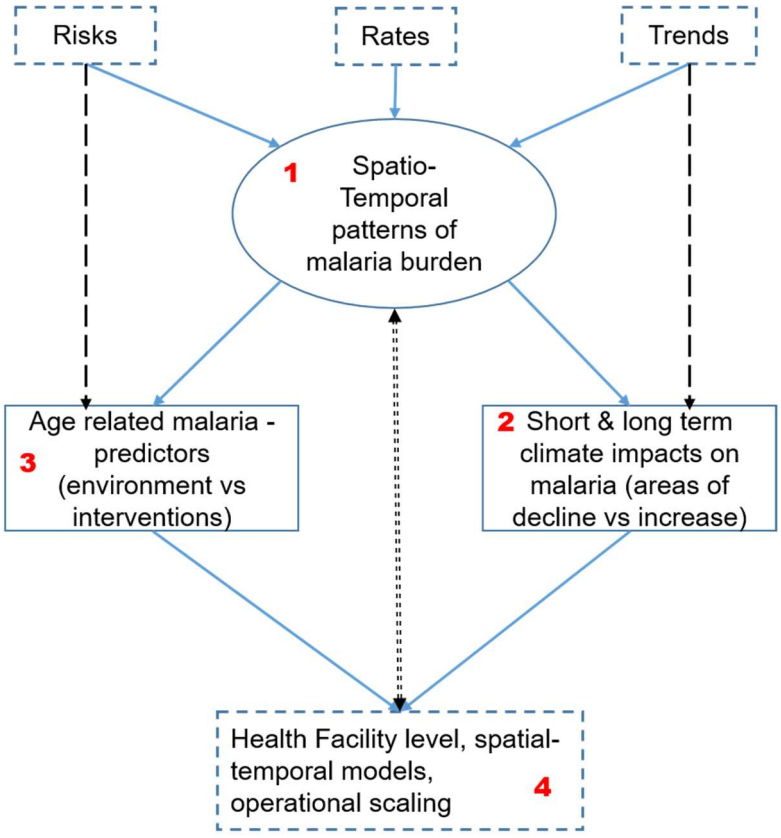


Figure 1.3: Summary of the scope of work covered this study

## 1.9 Thesis outline and overview of Chapters

This thesis follows an academic paper (manuscript) format, with each of the four results chapters being presented as stand-alone contributions that are based on papers that have been either submitted or to be submitted to peer-reviewed academic journals. Each paper is presented as a separate chapter in the most updated form before the final manuscript submission. As such, each has its introduction, methods, results, discussion, and conclusions sections with independent reference lists depending on the targeted journal format requirement.

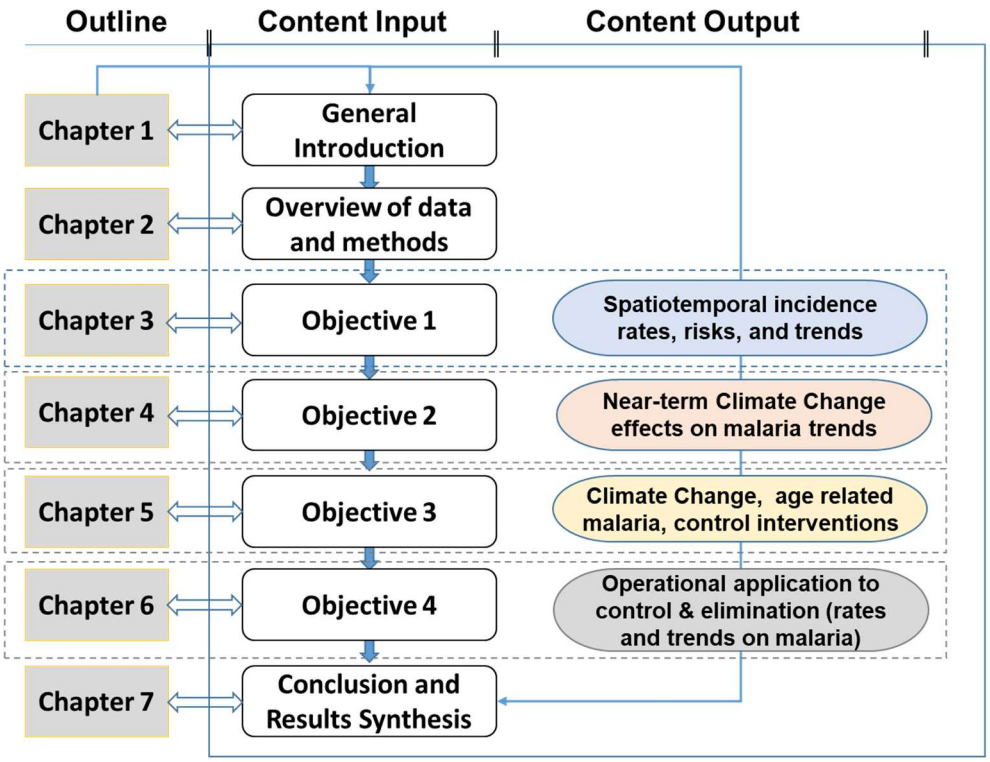


Figure 1.4: Graphical representation of the Thesis study outline

**Chapter 1:** This current chapter gives a general overview of the study background aim and presents the aim, specific objectives, and the thesis structure.

**Chapter 2: Overview of data sources, pre-processing, and data quality**

This chapter provides background information on Zambia and focusses on describing the data and statistical modelling techniques used in the study. It also briefly discusses some of the limitations of the available datasets and what preliminary adjustments were applied before the modelling and analyses in subsequent chapters.

**Chapter 3: The spatiotemporal modelling of malaria incidence patterns (rates, risks, and trends)**

This chapter is an independent chapter based on the first paper. It characterises the base spatio-temporal distribution of malaria incidence and mortality in Zambia at the District scale level. It proposes a novel alternative method for identifying and quantifying malaria burden to help facilitate better targeting of strategies and intervention programs in high and low burden settings.

**Chapter 4: The impact of near-term climate change on malaria trends**

This chapter presents the results from a district-level analysis of near-term climate impacts on malaria. It provides an in-depth comparison of these impacts in contrasting

areas of increasing and decreasing trends over a 16 year period. The chapter considers the diurnal temperature range (DTR) as an alternative measure to the more widely used mean temperature variable. It investigates how intervention programmes are being impacted by seasonally sensitive near-term climate change.

**Chapter 5: The effects of climate change on age-related malaria and control interventions**

This chapter considers the use of both parametric and non-parametric statistics to model the effects of climatic and socio-demographic variables on age-specific malaria prevalence vis-à-vis control interventions. Particular attention is given to people aged ≥5 years and those in rural areas.

**Chapter 6: Health Facility Spatio-temporal modelling of malaria incidence and risk in Zambia, 2009-2015**

This chapter focusses on a health facility level analysis of over 32 million reported malaria cases from 1743 health facilities in Zambia between 2009 and 2015 using Bayesian trend and spatio-temporal Integrated Laplace Approximation (INLA) models. A comparison is made between the Health Facility and district level malaria trends as part of an evaluation of the potential for adaptive scaling approach as an effective and resource-efficient means of developing and implementing intervention strategies.

**Chapter 7: Conclusions and Future Work**

This chapter considers how the aim and objectives of the study have been achieved and provide a synthesis of the overall study findings, the main conclusions and recommendations for further follow-on research.

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# CHAPTER TWO

## Methods Overview

This chapter introduces the methods applied in the study. More detailed descriptions of specific methods applied in each chapter are covered in the respective chapters (3, 4, 5, and 6) as they were written in the manuscript formats for publication. The chapter first provides a brief context of the study area and how the health system is organised in Zambia. It then highlights the types and sources of data that were available to the study, with particular attention given to the spatial and temporal resolution of the data. The chapter also covers the pre-processing methods applied to the data before the full analyses were conducted. It concludes with a brief discussion of the ethical considerations and approval for the data access.

## 2.1 Introduction

Chapter 2 introduces the study's geographical context and how this plays into the choices of studies presented in subsequent chapters. It sets up the metrics used in the current study to map and visualise malaria transmission dynamics, burden, and climate change. The primary variables used in this study include (i) Malaria (incidence and mortality); (ii) Temperature indices (minimum, mean, maximum, and diurnal range); (iii) Vegetation index (normalised difference vegetation index - NDVI); (iv) Precipitation (minimum, mean, and maximum); (v) Elevation; (vi) socio-demographic (population density); and (vii) interventions such as indoor residual spray, and Insecticide-treated nets/Long-lasting insecticide-treated nets (IRS and ITNs/LLINs). Among the key climatic variables considered in this study, diurnal temperature range (DTR) has very rarely been used, while mean variables (temperature) has often been the most considered. We, however, use DTR to show novel effects not captured by any of the other temperature variables (*see Chapter 4 for details)*.

## 2.2 Study Area

This study was conducted in Zambia, a landlocked country in Southern-Central Africa, bordering eight other countries, including Angola, Botswana, Democratic Republic of Congo (DRC), Malawi, Mozambique, Namibia, Tanzania, and Zimbabwe (Figure 1.2). Zambia has an approximate land mass of 752,000 sq. Km, with a population of circa 17 million people.

Zambia being landlocked shares national borders with some countries with very poor malaria epidemiologic status. This geographical juxtaposition has tended to complicate Zambia's approach to epidemiological issues, which are often are intertwined and influenced by the economic status and interdependence with its neighbours. This means that countries like Zambia cannot successfully control or eliminate malaria without engaging in cross-border malaria initiatives. Zambia is currently threatened by the potential effects of cross-border malaria from DRC in the north, Angola in the north-west, Mozambique and Malawi in the south-east and Tanzania in the East. Similarly, it poses threats to two of the well-established malaria elimination frontline countries of Botswana and Namibia in the south. It is for this reason that a key area of interest in this study is the role of cross-border malaria transmission dynamics (*see Chapter 6*).

### 2.2.1 Zambia's Climate

Zambia experiences a tropical or sub-tropical climate that is dependent on elevation. It experiences a hot and humid rainy season between November and April. The dry season extends from May until November. The beginning of the dry season is signified by a period of cold weather, usually between the month of May and August. It gets increasingly hotter between September and November. During this time, the temperatures are extremely high, but with little humidity. May to August represents the coolest period, characterised by cold nights, particularly in the south, where temperatures can often reach 0 °C. Dry months extend from June to August. During this time, it basically never rains in most areas, and October usually is the hottest month of the year (Gannon et al., 2014).

Rains start around mid-to-late November. The season extends until late April (the rainy season). Humidity is relatively higher during the rainy season and occurs predominantly in the form of torrential downpours or thunderstorms; hence, floods are quite regular. Although the rain distribution pattern across Zambia is homogeneous from November and March, the quantity fluctuates substantially. There is significant variability across the country with a substantial gradient between the north and the south in terms of quantity of rainfall, start and end dates (Hachigonta, Reason, & Tadross, 2008).

The weather is heavily influenced by shifts in the inter-tropical convergence zone (ITCZ) (meeting belt of the subtropical high-pressure belts of the northern and southern hemispheres) (Hachigonta & Reason, 2006). The northern region of the country, namely, the Copperbelt, the Northern, and the North-Western provinces represent the wettest areas. Here, annual rainfall exceeds 1000 mm or up to 1400 mm in places (Brigadier, Barbara, & Bathsheba, 2015; Gannon et al., 2014). The most arid areas are in the south-west, including the southern part of Western and Southern provinces, and the River Zambezi divides Zambia, Namibia and Zimbabwe. Here, rainfall is around 600 mm or less per year.

Zambia's temperatures vary according to altitude and latitude. On the plateau, in the central and southern part of the country, the night temperature between May and August drops so low, to become cold. The altitude in most of the plateaux ranges between around 900 to 1,500 m. However, some places slope down to about 500 m along the southern Zambezi River (and in Lake Kariba), and in the east along the Luangwa River. In contrast, altitudes in the northern plateau region can be around 1,800 m (near Mbala), reaching 2,200 m in the northeast, near the border with Malawi.

Winters are milder, particularly nights, along the lowlands in the north located < 1000 m, and on the shores of Lake Kariba in the south. Meanwhile, the far north experiences consistently high temperatures even in winter, because it is only 8 degrees south of the Equator. Here, with about 1200 mm of annual rainfall, the downpours are between December and March and are prolonged for the rest of Zambia. In most years, typically > 100 mm falls from April to November, while it seldom rains between the month of May and October.

### 2.2.2 The administrative structure of Zambia

Zambia is currently administratively divided into 10 provinces (previously 9), and over 103 districts (previously 72). The creation of additional districts and province was done after the 2010 census and has been ongoing since then with some created or realigned as recent as 2018. The Zambian Ministry of Health is responsible for the provision of health functions such as service delivery, coordination, management, and policy. Various coordination structures exist through the national, provincial, district and community levels. The district coordinates the overall health service delivery at both districts as well as all lower-community levels (Presidential Malaria Initiative, 2019).

The government runs public health facilities that provide the majority of healthcare and comprise the basic healthcare set of high-impact interventions. Health services offered are either at no cost or based on cost-sharing. The cost may depend on the location of the facility or level of the health facility (Hjortsberg & Mwikisa, 2002). In all rural districts, these services are provided absolutely free.

### 2.2.3 The structure of Zambia's health system

Zambia has a free universal public health care system, similar in form to the NHS in the UK that is available to all citizens of the country. Healthcare is offered at various levels of health facilities such as community, health posts, health centres, and at hospitals of levels 1, 2, 3, and central hospitals across the country (Zambian Ministry of Health, 2013). All health posts (HPs), health centres (HCs), or level 1 hospitals operate within the confines of the district, while levels 2 and 3 hospitals, with a referral or specialised function, are at the provincial level and central level respectively (Presidential Malaria Initiative, 2019; Zambian Ministry of Health, 2013).

Level one hospitals (District Hospitals), operate within the district level. They are the third primary level of health care after referral hospitals. District Hospitals generally serve populations from 80,000 to 200,000. They provide such services as medical, surgical,

obstetric or complex diagnostic services. They also offer full clinical functions which support HC referrals.

Second level hospitals (Provincial or General), operate at the province level. They should provide for catchment areas with more than 200,000 but less than 800,000 people. They generally offer services similar to those of 3rd level but are less specialised. They also often act as referrals for level one hospitals, including training (Zambian Ministry of Health, 2013).

Level three hospitals (Specialist) are the highest referral facilities in the country. These cater for populations >800 000. They are subspecialised in internal medicine, training and research. They receive nearly all complex diseases that cannot be handled at 2nd level hospitals.

Below the hospital, there 3 kinds of health facilities available, urban health centres or clinics (UHC), Rural Health Centre (RHCs), and Health Posts (HP). The former caters for catchment populations of between 30,000 and 50,000, while the latter caters for about 10000 people. The lowest level for health care is provided at the health post level. They provide care to communities that are distant from health centres. Their catchment populations are about 3,500 in rural areas and between 1,000 to 7,000 in urban areas. For sparsely populated areas, they are often located within a 5 km radius. They offer essential health services such as first aid but rarely have higher level curative functions (Zambian Ministry of Health, 2013).

A nation-wide enumeration conducted in 2012 found 1956 health facilities. However, more facilities were constructed since then, with about 650 newly constructed HPs and 2nd and 3rd level hospitals. Some 2nd level hospitals have also been upgraded to 3rd level (Presidential Malaria Initiative, 2019). In 2010, it was estimated that about 99% of urban households live within the 5 km radius of a health facility, compared to half for those in rural areas.

The National Malaria Elimination Center (NMEC), based in the country capital Lusaka, provides mostly technical but not operational assistance at these levels. NMEC, (formerly National Malaria Control Centre- NMCC) is one of Ministry of Health's operational policy arms, tasked to lead the implementation of malaria efforts in Zambia. They provide technical leadership and coordination in line with the National Malaria Elimination Strategic Plan. NMEC collaborates with various partners, such as financial donors, local and international NGOs, and academic institutions. They ensure that all malaria research

is coordinated to avoid duplication of efforts, but also encourages partners to contribute to the broader national malaria agenda partly.

The NMEC is the custodian of malaria data. Malaria is reported via the health management information system (HMIS) from paper to district health information system 2 (DHIS2). The health data is collected from public facilities, mission health facilities and some private health facilities, reported monthly. Data originates from the health facilities through to the district and subsequently to the provincial level. These records are then transmitted to the HMIS, which sits within the Ministry of Health. The NMEC has access to these data through the HMIS. It maintains a web-based version of the data management system through the DHIS2.

### 2.2.4 A brief overview of Health financing in Zambia

Zambia has undergone several health care user fee changes since its independence in 1964. During the first 27 years (1964 – 1991) after Zambia's independence, health care services were provided free of charge. However, in the wake of the structural adjustment programme (SAP) implemented after the change of government in 1991, health care user fees were introduced in all public facilities (Lépine, Lagarde, & Le Nestour, 2018; Masiye, Chitah, Chanda, & Simeo, 2008). These were intended to remove public subsidies and government involvement in the provision of most social services such and promote community-driven participation, empowerment, responsibility and accountability in the health care planning and provision. With the withdrawal of government subsidies, user fees could also help generate supplementary income to enhance quality improvement of services. These fees consisted of each district determining a flat consultation fee to cover consultation and drugs, based on the population's ability to pay (Carasso, Lagarde, Cheelo, Chansa, & Palmer, 2012).

As of 2006, the monetary range of this fee was typically described as very low for primary health care (McPake, Brikci, Cometto, Schmidt, & Araujo, 2011) being between US$ 0.14 and US$ 0.27 or 5% - 10%, comparable to one day's average GDP per capita at the time. However, not all individuals could be charged these fees as patients aged <5 and >65 years old, pregnant women, indigents and those with a predefined illness such as HIV/AIDS and TB were exempt. Generally, children and the elderly were the most commonly exempted, comprising 66% and 7% respectively of all exemptions in 1998 (Lépine et al., 2018).

In January 2006, Zambia changed the health care policy vis-à-vis the removal of all health user fees from all rural districts which comprise 75% of the total districts (n = 72) in the country (Lépine et al., 2018; Masiye et al., 2008). This policy change was partly meant to enhance universal access to health for all (Carrasso et al., 2010). It was argued that user fees were hindering equitable access to health care and led to a rise in poverty levels (Masiye, Seshamani, Cheelo, Mphuka, & Odegaard, 2006). The policy change was implemented in all publicly funded facilities, including both government-run and mission facilities. Nonetheless, these facilities were still allowed to charge all patients coming from outside the catchment area and foreigners.

By 2007, the remaining 18 districts had user fees removed from all health facilities located in peri-urban areas where they were still enforced. Finally, in January of 2012, this policy for free health care was extended to the rest of the areas meaning health care was free for all citizens of the country. Since 2018, Zambia has been considering introducing another change towards an insurance-based health care system, but this had not been introduced at the time of writing this thesis. Several studies have shown that abolishing fees does not necessarily guarantee the beneficial effects initially intended. This is because such benefits may be heavily dependent on other contributing factors such as the levels of demand for healthcare services and the levels of success in the implementation process of the policy (Gilson & McIntyre, 2005; Meessen et al., 2011).

#### 2.2.4.1 Perceived effects of health-seeking and access due to change of user fee policy

Although this is a highly debated issue in the literature, few studies from sub-Saharan Africa have suggested any increases in health care service utilisation are due to the subsequent removal health care fees (Hatt, Makinen, Madhavan, & Conlon, 2013; Lagarde & Palmer, 2008). These studies are, however, critiqued for their lack of methodological robustness in identifying the underlying causal impacts due to the policy (Lépine et al., 2018). Other evidence from more rigorous studies investigating the potential effects of free primary or curative care found no associated increase in the use of health care services in Mexico and India, except in Ghana where 3.7% increase of utilisation of service was reported (King et al., 2009; Mohanan et al., 2014; Powell-Jackson, Hanson, Whitty, & Ansah, 2012, 2014).

In Zambia, just like elsewhere, it was expected that individual income enables people to use public health care services and that a change in the cost of care-seeking options could change health-seeking behaviour. Contradictory results from 4 studies have been reported

based on whether income affected the use of health care services in Zambia (Chama-Chiliba & Koch, 2016; Lagarde, Barroy, & Palmer, 2012; Lépine et al., 2018; Masiye, Chitah, & McIntyre, 2010). More recent studies have shown that the removal of patient user fees from Zambia's health care in 2006 did not significantly alter the likelihood of primary care health-seeking behaviour in the population (Chama-Chiliba & Koch, 2016; Chitalu & Steven, 2017; Lépine et al., 2018). While two studies reported a substantial increase in outpatient visits from routine data (Lagarde et al., 2012; Masiye et al., 2010), the two studies could not explain the cause for their observation (Lépine et al., 2018). Besides, extending the period of the baseline of the assessment to the period between 1998 and 2006 shows that there was already was an increasing trend in health care utilisation as shown by Lépine et al., (2018)

In fact, besides the observed methodological challenges associated with the two studies, it has been argued that part of the observed increase may have been from richer patients previously seeking care in the private sector. In addition, as the demand for primary health care is price inelastic (Lépine et al., 2018), it is possible the demand was primarily driven by other factors, such as indirect financial costs, instead of a low fee. Furthermore, information from the Living Conditions Monitoring Survey of 1998 indicates that indirect access to care may well be important. For example, due to economic development, the public health system in Zambia still experienced an increase in patients seeking care from 36% in 1998 to 57% in 2004, of which 90% of these sought care from a government and mission run facilities. Only 6% went to private health care providers. This report is corroborated by later studies which show that although fees were removed nationally, over 10% of patients from rural areas still reported huge health costs often due to transport which comprised over 70% of total costs incurred (Kaonga, Banda, & Masiye, 2019; Masiye & Kaonga, 2016).

Thus, although the general potential effects of removing these health care charges from Zambia's health system have often been connected with a potential rise in health care utilisation, results from several studies have been mixed and do not fully support this assertion. Nonetheless, it was acknowledged that this change led to a virtual monetary transfer of about US$1.1 for the 50% most impoverished population per health visit (Lépine et al., 2018). Bennet et al. (2014) who looked at malaria data suggest that there was some evidence of an increase in all-cause OPD over the period 2011-2013 but could not ascertain whether this increase caused a rise in the total malaria OPD, or may be a result of increases in the total malaria OPD. This is because large proportions of all

outpatient attendance were due to malaria. From their comparison, the authors concluded that increases in non-malaria OPD were slight (Bennett et al., 2014).

The abolition of fees would have been expected to increase health care utilisation if the fees created a significant financial barrier to accessing health care. However, Zambia's situation suggests this was not the case, as other factors like physical distance from the health facilities or perceived inadequate benefits of health care are suggested as the key drivers behind low utilisation and thus support the conclusions that removing financial barriers may still not have yielded significant impacts. This can also be further supported by a follow-up study from 2014, which found that 30% and 45% of patients in rural and urban health centres respectively, still incurred health care costs and that public sector primary healthcare access was highly reliant on individual socioeconomic status, disease type and the district of residence (Masiye & Kaonga, 2016). It is, therefore, challenging to accurately quantify the actual effects of financial healthcare accessibility changes during the period of this study, and particularly on reported malaria cases.

### 2.2.5 The evolution of Zambia's HMIS system over the study period

Since 2000, Zambia's collection of health-related indicators, including malaria data, has been through the Health Management Information Systems (HMIS). In this system, the collection of malaria data from health facilities was paper-based, collected quarterly from 2000 to 2008. Each facility would record aggregated health information and transmit it to the district as part of its monthly reporting. The district office would prepare these and send on to the provincial health office, before finally being reported to the Ministry of Health under which the national malaria control centre (NMCC) falls. With the growing need to improve timeliness for disease monitoring purposes, the frequency of data collection was increased to monthly from 2009.

Further need for improvements to provide a better quality of data essential for the malaria programme prompted the move to implement the District Health Information System 2 (DHIS2) in 2013 (Chisha et al., 2015). DHIS2 is a web-based aggregate reporting system for the various health administration levels (national, provincial, and district). This system helped accelerate data reporting and access to various stakeholders and for prompt policymaking.

The DHIS2 has since 2014 enhanced data quality, optimised the data workflow, thereby increasing the timeliness, and subsequent access to information. The implementation of DHIS2 encouraged the direct reporting of health facilities using mobile phones, making

weekly reporting and monitoring of malaria cases possible. Currently, Zambia has actively rolled out weekly malaria reporting in several districts, especially in urban areas of Lusaka, Southern, and Western provinces since 2011 (MACEPA, 2011). DHIS2 is also used by the National Malaria Elimination Programme (NMEP) for receiving data from facilities and community levels especially those in low malaria settings as part of the overall national goal to pursue malaria elimination in such places.

2.2.6 Changes to Zambia's network and expansion of health facilities from 2000 onward

During the period of this study from 2000 - 2016, the number of health facilities in Zambia increased from 1285 in 2000, 1400 in 2006, 1883 in 2010, about 1900 in 2015, and 2500 in 2016. The increase was made up from a combination of government, mission (faith-based), and private providers (CSO, 2012; Ferrinho, Siziya, Goma, & Dussault, 2011; Hoppenbrouwer & Kanyengo, 2007; Zambian Ministry of Health, 2013). During the period between 2000 and 2000 and 2015, Zambia's population increased by 56.5%, while the total number of health facilities increased only by 47% in the same period. It was, however, very challenging to source a consistent and accurate total number of facilities by district or to document changes in the geographic accessibility to healthcare over the study period other than noting the approximated increases between 2000 and 2016. Based on a comparison between population growth and the increase in health facilities, it seems evident that and acceptable to suggest that the construction of new health facilities was population growth driven.

This study could not source evidence accurately estimate how much the change in geographical access to health facilities has made on health-seeking behaviours by district or province and can only assume they were equally distributed across the country. It can also be further argued that the population growth ratio was consistent with the provision of health care facilities per person and would not have significantly changed the availability of health facilities per head of population. For example, the health facility ratio per 10 000 population was 1.3 in 2000, 1.19 in 2006, 1.44 in 2010, 1.23 in 2015, and 1.57 in 2016. Hence, if health facility availability was the key determinant, then rates of malaria would have stayed the same unless other factors were at play. These factors could include – climate change favouring malaria infections, the geographical variance of sub-district malaria intervention distribution, or associate differences in the cultural attitudes towards utilisation of malaria interventions, all of which would affect the effectiveness of interventions against malaria.

Figure 2.1 shows the general location of Zambia within Africa and its administrative sub-divisions at provincial and district levels.

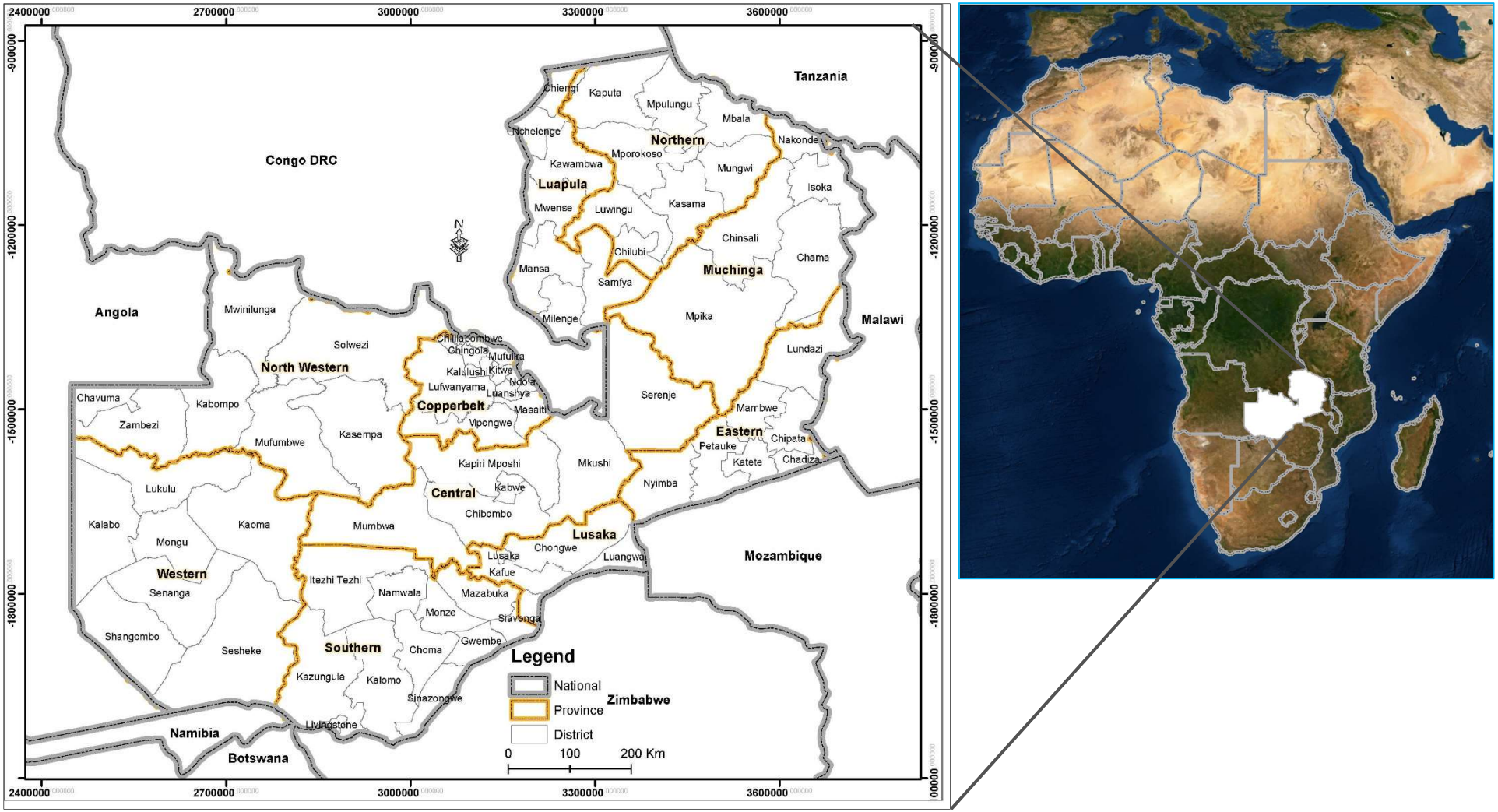


Figure 2.1 The Location of Zambia in Sub-Saharan Africa

## 2.3 Types of data and their sources

The overall study used a variety of ecological/environmental data, malaria epidemiological data, data on malaria interventions as well as socio-demographic information at different scale levels and time periods.

### 2.3.1 Malaria Epidemiological data

Access to data on malaria epidemiology was obtained through the Zambian Ministry of Health (MoH) via the National Malaria Elimination Centre's (NMEC) health management information system (HMIS). The HMIS contains data from the year 2000. Disease information is obtained from records collected by districts that have been aggregated from health facilities records and are more or less complete since 2000 (World Health Organization, 2008).

Between 2000 and 2007, a malaria case was defined as a "*fever with parasites*" which generally includes all those that would need treatment using antimalarial drugs. Malaria mortality refers to the direct consequences of malaria infection, which primarily include the death from a progression of mild or severe disease to death (Greenwood et al., 1987; Mudenda et al., 2011). From a clinical perspective, a simplified sequence from the point of a plasmodium-infected bite is as follows (World Health Organization, 2014):

$$\boldsymbol{Infection \rightarrow asymptomatic\ parasitaemia \rightarrow uncomplicated\ illness \rightarrow severe\ malaria \rightarrow death}$$

This is what is generally being measured by the health system and is one of the key indicators of malaria burden in a country. However, this measure is very often regarded as an underestimation of total malaria burden (Greenwood et al., 1987; Mudenda et al., 2011; Snow et al., 1992) because the true burden depends on several other factors such as transmission intensity, age, acquisition of immunity, parity, co-morbidities, and health system factors such as access and quality of health care. Verbal Autopsy remains the primary diagnostic method of confirmation. However, it has poor specificity for malaria because malaria can simultaneously be both a contributory and an underlying cause of death. Confirmatory accuracy, therefore, still depends on many other factors within and outside the health care system. (Reyburn et al., 2004; Taylor et al., 2004) (Lynch, Korenromp, & Eisele, 2012; Mudenda et al., 2011; White, Dondorp, Faiz, Mishra, & Hien, 2012).

### 2.3.2 Measuring the malaria burden using clinical incidence rate

Various malaria metrics exist. Some are directly collected using the parasite measurements, vector mosquito measures, or clinical disease measurements. The most commonly collected and utilised measuring clinical malaria is the incidence rate (Snow, Guerra, Noor, Myint, & Hay, 2005). Incidence of clinical malaria is the rate of new cases occurring per 1000 population. This is often measured directly, from passive case detection (i.e. routinely collected health facility infections) or active case detection (proactive measure such as cohort surveys) of disease burden. It can also be measured indirectly via spatial estimates or through malaria mortality data (Tusting, Bousema, Smith, & Drakeley, 2014).

While each metric has value, the usefulness of a measure of ongoing or transmission variation depends on metric precision. Factors that affect the accuracy or precision of most metrics of malaria include issues of general bias and seasonal variations (Tusting et al., 2014). This has significant consequences for current malaria surveillance as well as the appraisal of malaria control and intervention programmes. Measuring change in transmission requires two factors, a baseline which can be problematic against contextual seasonality, and trending, which can complicate the attribution of effects.

The precision of malaria estimates requires consistency in diagnostics. Another factor may include the presence of considerable disparities in health-seeking behaviour, especially for estimations entirely dependent on passive case detection. Incidence varies relatively as a result of the acquired immunity of some individuals or due to other diseases (Ghani et al., 2009). This creates asymptomatics, a proportion which differs according to endemicity or equally varies due to household genetic influences, which may affect the advancement of the disease to develop symptoms or even severe malaria (Mackinnon, Mwangi, Snow, Marsh, & Williams, 2005). Clinical malaria, as measured by incidence rate, however, is still the gold standard used in clinical trials, particularly those for control interventions. This is despite their imperfect accuracy for various transmission settings as assessment tools for variation in transmission (Tusting et al., 2014).

The advantages of routinely collected data are their immediate sensitivity to changes in incidence and the accessible day-by-day collection of malaria data by control programmes. This makes it easy to integrate with other data types to help with program evaluation and improvement. Nonetheless, the consistency depends on factors such as coverage and the quality of a surveillance system (The malERA Consultative Group on Health Systems, 2011). When estimations are done via passive detection of cases, the cost

tends to be lower than estimations from active case detection, which is why data from passive case detection is more readily available.

For this reason, the approach to use trend measures (and optionally risk) as an additional parameter was proposed. This approach utilised various model outputs in combination, and the full description is explicitly described in Chapter 3 and partly in Chapter 6.

Since 2001, all patients seeking care due to fever within the public sector could receive a malaria diagnostic test free of charge (Hjortsberg & Mwikisa, 2002). Between 2000 and 2008, the main malaria test available in most health facilities was a microscopy examination of a blood slide. However, the WHO reported that children from most of sub-Saharan Africa aged below five years received treatment for all fever cases without parasite confirmation (World Health Organization, 2008). Thus, due to the shortage of medical personnel and the high volume of suspected malaria cases in most public facilities, diagnosis by clinical symptoms alone remained a large part of the malaria diagnosis process.

Figure 2.2 shows both the malaria data captured by the HMIS (inside the dotted line) alongside the non-treatment-seeking and asymptomatic malaria cases which together comprise the total and true malaria burden in Zambia. The HMIS collects outpatient department (OPD), and inpatient cases of malaria data in the form of clinical cases, confirmed infections, and deaths disaggregated into children under five years and those five years and older.

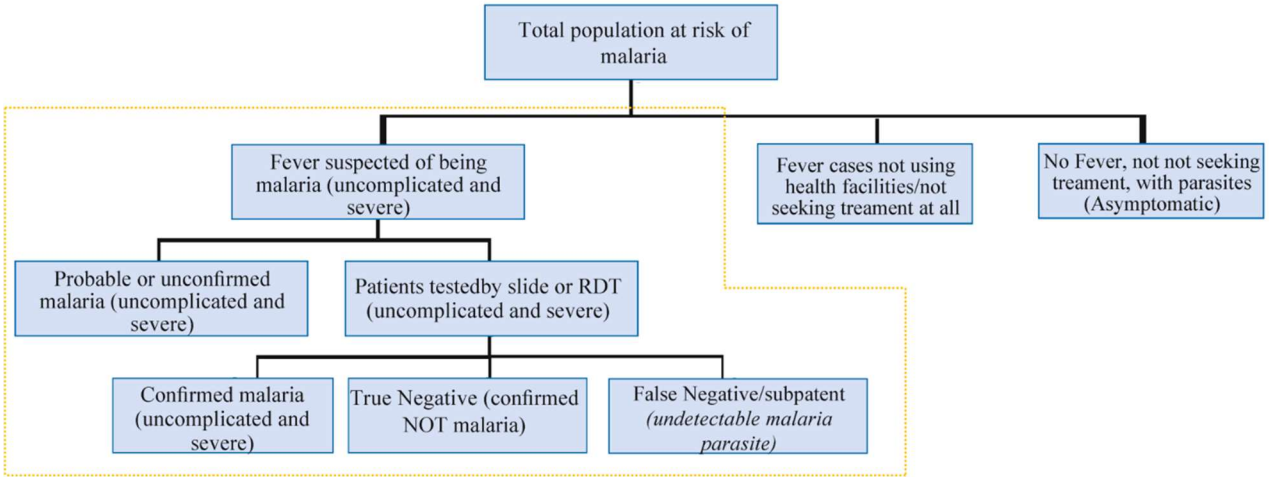


Figure 2.2: Summary of total malaria burden (with malaria cases data captured through the HMIS inside the dotted line

Globally, routine malaria surveillance records remain the most abundant source of information on malaria control progression in endemic countries (Endriyas et al., 2019; Ohiri et al., 2016). However, as already demonstrated (e.g. Figure 2.2), most of this data suffers from a variety of quality and completeness issues (Ashton et al., 2017). Consequently, using this data comes with inherent issues around potential bias through underreporting (due to record incompleteness) or over-reporting (due to the addition of unconfirmed malaria cases often treated without a confirmatory test). Although the routine collection of records has improved in terms of data quality in recent years, these data may still need to accommodate for treatment-seeking and sub-clinical malaria to reflect a more accurate picture of the overall malaria epidemiology (Ashton et al., 2017; World Health Organization, 2008). Nevertheless, most malaria control programs still use the raw un-adjusted (reported) malaria datasets for their everyday decision-making.

The WHO's methods of working routinely collected data including adjusting reported malaria cases for reporting completeness, care-seeking rates, and parasite positivity rates (the probability that patients were had the parasite), and is represented by the equation:

(2.1)

$$= \frac{Cases_{public\ confirmed} + Cases_{public\ presumed}\ X\ Test\ Positivity\ Rate_{public}}{Reporting\ completeness}(1 + treatment\ seeking\ rate)$$

In this study, these adjustments were applied to the raw data along with other additional data quality checks and adjustments. Data standardisation, multiple imputations for missingness, and treatment-seeking were utilised to adjust the data for inherent quality issues as much as possible. These were performed depending on the spatial resolution of the data, availability of information on the basic adjustment terms, and the type of models or analysis being undertaken (see chapter 4, 5 and 6 methods).

Malaria data between the year 2000 and 2008 was only available with a quarterly temporal resolution with the district being the smallest level of spatial disaggregation. The data between 2009 and 2016 was available at relatively higher spatial (health facility level) and temporal (monthly) resolutions. Malaria data is routinely reported in two broad age categories, namely, children (<5 years) and all others (≥5 years). This crude form of age reporting is consistent with the national and global malaria priorities adopted decades earlier due to the high susceptibility risk, vulnerability, and severity of exposure to malaria infection among young children. In the last two decades it was a priority to track progress in under-five malaria mortality and incidence which defined the subsequent focus on the under-fives in all Malaria Indicator Surveys (MIS), Demographic Health

Surveys (DHS), and global malaria reports (Murray et al., 2012; World Health Organization, 2008).

The data for malaria obtained for this study consists of reports of the numbers of outpatients and inpatients (suspected) treated based on their clinical symptoms, and (confirmed) of laboratory tests carried out using rapid diagnostic tests (RDT), and slide positivity. This study used about 79 million malaria case and over 100,000 malaria death records.

### 2.3.3 Socio-demographic and interventions data

Demographics data such as the national, provincial and district level populations in Zambia were compiled and estimated from publicly available and published national census reports for the years 2000 and 2010 (Central Statistical Office, 2000, 2012). Additional post census population estimates were accessed via the Central Statistics Office (CSO) official annual district projections (Central Statistical Office, 2013). Health facility-level population counts, however, were either derived from a combination of health facility headcount population estimates and CSO official estimates generated by district offices.

These baseline population estimates were used to calculate the malaria incidence and mortality rates at various scale levels as well as being used to generate population densities and malaria intervention coverage rates.

Information on all interventions implemented in the study areas was requested from the MoH and provided together with malaria data. In this study, two main interventions were used, as described in Chapter One. ITNs/LLINs and IRS (Masaninga et al., 2013), were the two primary malaria interventions implemented during the study period. Information about ITNs is collated from various ITN distribution systems such as antenatal clinics (ANCs), expanded paediatric Expanded Program on Immunizations (EPI) clinics, and through regular mass campaign distribution channels (Presidential Malaria Initiative, 2018, 2019). This information was only available at the district level and a yearly temporal resolution. Environmental datasets

This study utilised many environmental data types drawn from various sources. Table 2.1 summarised of all the environmental datasets accessed and used in the overall study. Specific details about each can be found in methods sections of subsequent chapters. Precipitation, temperature, vegetation index, land cover-land use, humidity, and elevation are the primary environmental datasets used.

Table 2.1: Summary of Ecological Datasets and their Sources

| Variable name | Data Source | Launch | Spatial resolution | Temporal Resolution | Data Format |
|---|---|---|---|---|---|
| Temperature | NCEP Climate Forecast System Reanalysis (CFSR) | 1981 | 20km | Daily | CDAS |
| Relative Humidity | Copernicus/ECMWF | 1979 | 10km | 3 Hourly | GRIB |
| Precipitation | Climate Hazards Group archive | 1981 | 5km | Daily | netCDF4 |
| Vegetation Index | Copernicus Global Land Service (CGLS) | 1998 | 1km | 10 Days | netCDF4 |
| Landuse / Landcover | Copernicus Global Land Service (CGLS) | 1979 | 1km | Annual | GeoTIFF, netCDF4 |
| Temperature | Copernicus/ECMWF | 1979 | 10km | Daily | netCDF4 |
| Elevation | Shuttle Radar Topography Mission (SRTM) | 2000 | 30m | - | GeoTIFF |

The selection of the data sources was based on satisfying the spatial and temporal data requirements, as well as being suitable for the various analytical and statistical techniques used in the study. Most of this was secondary data, pre-processed by the source. Environmental/ecological variables data were extracted using the R program's Raster package (Hijmans, 2019). The method directly applied remote sensing/modelling using data analytics techniques to analyse the data. It also indirectly extracted and aggregated them according to area units of non-spatial structures such as health facility, district, or province-level to conform to other data variables from different sources.

## 2.4 Modelling methods applied

Two major small area statistical approaches were applied via Bayesian spatio-temporal conditional autoregressive (CAR) models, and Integrated Nested Laplace Approximates (INLA) (Rue, Martino, & Chopin, 2009).

### 2.4.1 Using Integrated Nested Laplace Approximation

The approach was developed for its computational efficiency as a substitute to Markov Chain Monte Carlo (MCMC) methods. The approach is often used for fitting Latent Gaussian models (LGM), which have been very popular in epidemiological studies (Blangiardo, Cameletti, Baio, & Rue, 2013).

In contrast with MCMC models, which use simulation methods and are often computationally expensive, INLA utilises approximation methods from a Bayesian framework for model fitting. Hence, in the class of LGMs, INLA can fit models quicker than MCMC-based methods. This model includes both spatially structured as well as unstructured components, a global linear trend, which represents a temporal effect; and a

specific time and space interaction trend (Blangiardo et al., 2013). In the implementation, it accounts for the spatio-temporal correlation implicit in the model *(specific model details are explained in Chapter 6).*

### 2.4.2 Bayesian Hierarchical models

The study also utilised the specialised Gaussian Markov random field (GMRF) of conditional autoregressive (CAR) structure. These spatiotemporal models represent the neighbourhood of the districts through an adjacency matrix that detects whether areas are spatially contiguous to produce a binary value interpreted as spatial closeness for polygons that share boundaries. The models incorporate spatio-temporal autocorrelation in the response variable through latent random effects, using CAR-type prior distributions and spatio-temporal extensions. The Deviance Information Criterion (DIC), Watanabe Akaike Information Criterion (WAIC) along with its associated log pseudo-marginal likelihood (PML) were utilised to initially select the best conditional autoregressive models to use given the available data (Lee, Rushworth, & Napier, 2018; Spiegelhalter, Best, Carlin, & Van Der Linde, 2002; Watanabe, 2013) *(see Chapters 3, and Chapter 4 for details).*

The study also used a variety of supporting models, mainly implemented as mixed-effects models. These models were selected due to their flexibility and capability to capture spatial correlation and potential temporal changes within the random effects surface (Lawson & Lee, 2017; Lee, Mukhopadhyay, Rushworth, & Sahu, 2016). They also generally reduced the effects of collinearity of well-known spatially smooth environmental-based covariates involved in malaria transmission.

### 2.4.3 The new approach of malaria stratification using incidence rate, risk and trend

The rationale partly follows the need to have more robust measures of malaria burden to aid accurate stratification. It also builds on various past stratifications of malaria risk zones in Zambia. Before 2015, for example, Zambia's malaria was epidemiologically categorised into three transmission zones: low (parasite prevalence <1%); low stable (≤ 10%); and high (>20%) (Chanda, Kamuliwo, et al., 2013; Masaninga et al., 2013; National Malaria Control Center (NMCC), 2011). Low, stable and high transmission zones extended around south-eastern, north-western/south-central, and northern and eastern Zambia, respectively (Kamuliwo et al., 2013). Since 2017, malaria stratification is based on two strata <50 cases and ≥50 cases per 1000 population (National Malaria Elimination Programme, 2017) based on incidence rate alone. The study also provides an

alternative nationwide risk map, based on malaria incidence rates, risk, and trends at with district-level spatial resolution (discussed in Chapter 3), as well as a health facility level malaria risk map based on malaria trends (discussed in Chapter 6).

The modelling techniques mentioned earlier were used to propose a novel methodological approach for stratifying high and low burden areas. While incidence rate remains the most utilised, against its weaknesses as a malaria metric (as discussed earlier), the proposed approach allows a malaria program to adopt or adapt the approach and easily apply it in their routine stratification of malaria. The method enables malaria programs in countries like Zambia to precisely apply a twofold approach of targeting high-burden areas with intensive control measures while pursuing malaria elimination efforts in all other areas (*see Chapter 3, and Chapter 6*).

## 2.5 Study Ethics and relevant Permission

We obtained study authorisation from the National Health Research Authority, and Reviewed by and approved by the Ulster University review board (Ref: 17/0049) and the Zambian ERES Converge IRB (Ref: 2017-Sept-011). Hence, the data is considered a property of the Republic of Zambia, and can be freely requested through the MoH, but cannot be shared without prior approval of the ministry.

## 2.6 Chapter Summary

This chapter introduced the core data and main analytical techniques with much fuller and more specific details being provided within each of the four results chapters and their associated supplementary appendices.

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# CHAPTER THREE

## Modelling of Malaria Risk, Rates, and Trends: A Spatiotemporal approach for identifying and targeting sub-national Areas of High and Low Burden

This chapter is based on a manuscript submitted for second-round review in *PlosComputational Biology Journal.* This paper relates to objective number *one* of the thesis.

# Abstract

While mortality from malaria continues to decline globally, incidence rates in many countries are rising. Within countries, spatial and temporal patterns of malaria vary across communities due to many different physical and social environmental factors. To identify those areas that are most suitable for malaria elimination or targeted control interventions, Bayesian models were implemented to estimate the spatiotemporal variation of malaria risk, rates, and trends and determine the areas of high or low malaria burden compared to their geographical neighbours.

The study presents a methodology using Bayesian hierarchical models with a Markov Chain Monte Carlo (MCMC) based inference to fit a generalised linear mixed model with a conditional autoregressive structure. This study modelled clusters of similar spatiotemporal trends in malaria risk, using trend functions with constrained shapes and visualised high and low burden districts using a multi-criteria index derived by combining spatiotemporal risk, rates and trend of districts in Zambia.

The results indicate that over 3 million people in Zambia live in high-burden districts with either high mortality burden or high incidence burden coupled with an increasing trend over 16 years (2000 to 2015) for all age, under-five and over-five cohorts. Approximately 1.6 million people live in high-incidence burden areas alone. Using the proposed method, the study developed a platform that can enable malaria programs in countries like Zambia to target those high-burden areas with intensive control measures while at the same time pursue malaria elimination efforts in all other areas.

This method enhances conventional approaches and measures to identify those districts, which not only had higher rates but also increasing trends and risk can be used. This study provides a method, and a means that can help policy makers evaluate intervention impact over time and adopt appropriate geographically targeted strategies that address the issues of both high-burden areas, through intensive control approaches, and low-burden areas, via specific elimination programs.



**Keywords:** Malaria elimination; stratification; Control; spatiotemporal modelling; High-burden high-impact; targeted interventions

## 3.1 Introduction

Malaria transmission trends and risk of infection are usually heterogeneous in time and space. The ability to detect common spatial and temporal variations of malaria burden in sub-national settings is of great interest and a considerable challenge to malariologists and public health experts in endemic countries.

The global decline of malaria incidence rates has stalled, or the rate of reduction slowed in some countries, particularly sub-Saharan Africa (World Health Organization, 2018f). The 2017 and 2018 World Malaria Reports highlight this stagnation (Alonso & Noor, 2017; World Health Organization, 2017b, 2018f) and have led to the World Health Organisation's (WHO) launch of a new country-focused approach known as "*high-burden to high-impact"* malaria response. They also call for the development of novel methods to address the problem (Ghebreyesus & Admasu, 2018; World Health Organization & RBM, 2018).

Despite the continued fight against high malaria endemicity for the last half-century, Zambia is among those sub-Saharan countries affected by the reported stagnation in malaria progress (Kamuliwo et al., 2013; National Malaria Elimination Programme, 2017). With a massive scale-up in interventions (Chizema-Kawesha et al., 2010; Kamuliwo et al., 2013; Masaninga et al., 2013; National Malaria Control Programme, 2012) in the last decade, Zambia achieved considerable progress, resulting in a move from control targets to elimination aspirations (A. Comfort et al., 2017). Zambia embraced the currently renewed global interest for malaria elimination, and strategically positioned itself within a regional and global malaria eradication context.

However, Zambia's geographical location complicates its malaria control status vis-à-vis its elimination aims. For example, Zambia's northern and south-eastern neighbours (Angola, Congo DR, Tanzania, Malawi, and Mozambique) are often among the WHO's list of *highest-burden countries* (World Health Organization, 2017b, 2018f). In contrast, some of its southern neighbours are regional frontline target countries in the E-2020 malaria elimination programme (E8 Secretariate, 2018). Similarly, this northern vs southern epidemiological contrast is manifest sub-nationally as; generally, Zambia's northern regions have high malaria infections while the southern regions experience the opposite (President's Malaria Initiative (PMI), 2017; Zambia National Malaria Elimination Centre, 2017).

Uncertainty in progress both regionally (E8 Secretariate, 2018) and nationally (Loewenberg, 2018) has not prevented Zambia from moving forward with its aim to eliminate malaria.

In the past, countries generally embarked on countrywide elimination efforts or intensifying control in low-burden or high burden areas, respectively. Traditionally delineating these areas was logically based on incidence alone. As elimination and control are becoming a focal problem of subnational importance, malaria programs have to deal with the challenge of accurately delineating areas to pursue elimination in and those in which to intensify control strategies, in addition to the challenge posed by border areas.

In order to ascertain the robustness of methods used for selecting these areas of a high or low burden to inform optimal control or elimination strategies and as a measure of progress towards country elimination targets, scholars have started thinking of better or more robust alternatives. Kitojo et al. recently compared multiple data sources such as the use of malaria tests from antenatal care against population-wide prevalence surveys in children under five years of age to examine them as a measure for malaria trends and progress towards Tanzania's elimination at subnational levels (Kitojo et al., 2019).

Routlege et al. (2019) used malaria individual-level cases for geostatistical estimates of spatio-temporal transmission to estimate the timeline to elimination or any imminent risk of resurgence in China (Routledge et al., 2019), and Amratia et al. (2019) used a combination of serology data, case tracing, and case reports in Haiti (Amratia et al., 2019) to comprehensively capture the transmission landscape. These studies are part of a subsequent search for more robust methods for country-specific transmission classification approaches to help inform the recently coined concept "*high-burden, high impact*" approach to tackling malaria. This approach encourages a much more targeted in-country implementation of malaria interventions according to the available resources and evidence.

These studies cite the inadequacy of incidence or prevalence as a single metric, and their methods provide alternatives for multi-metric approaches using multiple data sources besides routine data. Despite their contribution towards a similar objective, the studies reviewed earlier have inspired Zambia's case but did not methodically inform the approaches used in the current study due to the substantial country-specific differences in the types of malaria data available, and the reliability of alternative data sources. As most endemic countries like Zambia have sufficient routinely collected data and very limited

population-based survey alternatives, there were no options for triangulating multiple data sources. Nonetheless, it does still allow for alternative multi-metric approaches using a single data source by combining three different methods of classification to understand better and guide the overall classification used to measure the progress towards malaria control and elimination goals.

This is because, while malaria incidence or prevalence rate is a good indicator of how many people need treatment, it certainly only offers a snapshot of infections at a given time point, while missing other important underlying factors such as asymptomatic malaria, and case seeking difference. Travel and human movement remain key to malaria elimination, especially in low transmission settings, and local reductions in prevalence are unlikely to persist if surrounding areas maintain much higher prevalence. Hence, targeting interventions towards outliers with unusually high levels of malaria burden surrounded by low transmission areas after accounting for spatial trends are likely to be more sustainable in the long term.

While the logic of targeting high burden areas using incidence alone is adept, deep-rooted in decades of its use, remains justifiable, and is well supported, the challenge comes with how low-incidence areas with increasing malaria may still be ignored if the basis remains incidence alone. Ignoring such areas with low but increasing malaria incidence (as a low priority with business as usual) compounds the problem soon after because of these areas of initially low incidence progress to moderate or even high incidence status. Considering the trend, however, reflects not only the stability in spatial patterns but also temporal patterns and gives equal weighting even where elimination efforts may be ongoing or planned.

In Zambia's approach, elimination is targeted explicitly in subnational areas where the disease exhibits a low incidence. At the same time, control measures are maintained and implemented in the rest of the country (Zambia National Malaria Elimination Centre, 2017). With insufficient levels of funding for malaria control, the *"High burden to high impact"* approach could help reinvigorate the fight against malaria (World Health Organization & RBM, 2018) through the more focused and strategic use of evidence-based decision making that can deploy the most effective malaria control tools in areas where they can have maximum impact. The approach presented in this paper supports the identification and targeting of high-burden areas. It facilitates the optimisation and prioritisation of locally owned country-led health strategies and priorities to achieve their impact maximisation. The study adds to the literature advocating that although disease

incidence is primarily the basis for decisions on disease control or elimination choice areas, intervention deployment, and decision making on this basis alone may be inadequate, but can be optimised without incurring any additional data collection cost.

The study also highlights the ability of the method in defining and measuring high or low burden areas in line with the *high-burden high-impact* strategy in order to optimise the delivery of control interventions and tools (World Health Organization & RBM, 2018). The logic to target hotspots and high burden areas is a well-received concept among malaria control programs. Identifying the precise quantity and location of highest-burden areas would help programs focus their limited resources by targeting such areas for further investigations, treatment, prevention efforts, and any media campaigns. For example, cost-prohibitive strategies such as mass drug administration (MDA) become feasible for every individual in a small-targeted community hotspot but not feasible for population-wide application. For instance, Zambia has mostly used targeted IRS to enhance and supplement universal ITN coverage (Kamuliwo et al., 2013); hence such accurate classification is essential in order to ensure the correct application of interventions to true areas of need. Targeting intervention efforts to those places with the highest disease burden relative to surrounding areas is essential because most malaria hot spots are in themselves risks and a source of malaria infections for surrounding areas. Targeting these would help generate a ripple effect that can significantly reduce transmission rates and risk across the recipient areas.

This study investigated the spatiotemporal malaria risk, rate, and trends of all 72 districts in Zambia between 2000 and 2015 using the following process: i) estimate the relative risk and rates of malaria for each district for all ages, under-fives and the five years and older, ii) model overall spatial clustering and any related temporal trends and iii) apply a rigorous, but reasonably straightforward, matrix to identify and visualise high burden malaria districts to help inform and support national control and elimination targets. This approach supports and addresses the call for the targeted control or elimination of malaria based on delineated sub-national zones defined by high-burden clusters of risk, rate, and trend.

## 3.2 Methodology

| **Nomenclature for equations used.** | | | |
|---|---|---|---|
| $\phi$ | Random effects | $\mathbf{D} = d_{tj}$ | Temporal neighbourhood matrix |
| $\rho s, \rho \mathcal{T}$ | Dependence parameters | $\mathcal{T}^2 \boldsymbol{Q}(\boldsymbol{W}, \rho s)^{-1}$ | Variance |

| | | | |
|---|---|---|---|
| $\mathcal{T}_t^2$ | Temporary-varying variance parameter | $\rho\mathcal{T}$ | Temporal autoregressive parameter |
| $\delta$ | Overall temporal trend | $f_s(t\|\gamma_s)$ | Spatial trend |
| $\boldsymbol{W}$ | Adjacency matrix | $k$ | Spatial unit |
| $\omega_{kj}$ | Spatial closeness of areal units | $\omega_\kappa$ | Binary indicator where $\omega_{ks} = 1$ |
| $\psi$ | Latent component | $\boldsymbol{\lambda}$ | Region-wide probability |
| t | Timepoint | $\boldsymbol{\alpha}$ | Priori distribution |

### 3.2.1 Study area

Zambia is a landlocked country in South Central Africa, neighbouring eight other malaria-endemic countries (Central Statistical Office, 2013; Kamuliwo et al., 2013), three of which, represent the frontline region-specific Elimination8 [E8] and E-2020 malaria elimination countries (Elimination8 Secretariat, 2017). Zambia's geographic location creates a heterogeneous and complex malaria transmission landscape that is suitable for tailored micro-geographic intervention approaches.

### 3.2.2 Spatial, population, and malaria data

District populations in the period from 2000 to 2015 were estimated using intercensal and postcensal exponential population growth model information from the Central Statistics Office (CSO) reports from 2000 and 2010 (Central Statistical Office, 2012). Post census population estimates and age groups of under-five and over-five-year-olds were obtained from the 2013 CSO report (Central Statistical Office, 2013). The derived estimates formed the basis for calculations of malariometric indices such as mortality and morbidity rates by age groups. The study obtained malaria epidemiological data through the Ministry of Health (MoH). Clinical and microscopy-confirmed malaria deaths and cases disaggregated by age groups were reported quarterly before 2008. With the countrywide introduction of rapid diagnostic tests (RDTs) between 2008 and 2011 (Chanda, Kamuliwo, et al., 2013; Chizema-Kawesha et al., 2010; National Malaria Control Programme, 2012; Steketee et al., 2008; World Health Organization, 2011; Yukich et al., 2012), clinical and confirmed cases were reported separately and monthly (Mukonka et al., 2015). In order to retain the usability of the full dataset from 2000 to 2015, the study analysed data annually. It maintained the 72 original districts and used a combination of both confirmed cases and unconfirmed malaria cases. Malaria standardised incidence ratios (SIR) per 1000, and standardised mortality ratios (SMR) per 10,000 people were computed using a simple formula: SIR = (Observed Cases/Expected Cases) & SMR = (Observed deaths/Expected deaths).

The data's completeness reporting during the period of study was not available at district or health facility level. Hence, a national average extracted from WHO's world malaria reports (WMR) were generally high with a median = 87%, mode = 87%, mean = 88.3%, and SD =2.97%. Information on the missingness of data was only available at the district level. Thus, although missingness was dealt with at the district level, it is highly likely that any variations at the facility level will not be detected. However, missingness at district level stood at 3.4% in deaths among those aged 5 years and over, 2.7% in under 5 deaths, and only 0.1% among reported morbidity.

Random Forest was utilised to impute the 5% of missing values in the data. From missing values among malaria deaths alone, the normalised mean squared error (NMSE) often used to represent error derived from imputing missing values was 0.22 (20%), while it was 0.072 (7%) for missing case values and 0.094 (9%) overall for the whole dataset.

We, however, did not adjust them for confirmation rates by use of Test Positivity Rate (TPR) because TPR was neither available nor collected between 2000 and 2008. In most instances, information on testing is not available at facility or district levels after 2009 and 2015 [1].

### 3.2.3 Spatio-temporal modelling

Conditional Autoregressive (CAR) prior method was implemented. The CAR method incorporates spatiotemporal generalised linear mixed models for unique areas with inference in a Bayesian environment using Markov Chain Monte Carlo (MCMC) simulations (Bennett, 2012; Hamra, MacLehose, & Richardson, 2013; Mabaso, Vounatsou, Midzi, Da Silva, & Smith, 2006; Reid, Haque, Roy, Islam, & Clements, 2012). The model choice is based on its robustness and capability to estimate the effects of risk factors on response variables such as incidence and mortality (Lee et al., 2018).

The study used the models for identifying clusters of neighbouring districts (Charras-Garrido, Abrial, Goër, Dachian, & Peyrard, 2012) that display a repeated high risk (Napier, Lee, Robertson, & Lawson, 2018) of malaria compared with other adjacent areas. These models account for spatiotemporal variations within the same environment, mainly when using the CARBayesST R package (Lee et al., 2018; R Core Team, 2013). Malaria data counts are observed within districts with an assumption that the data has an independent distribution using a Poisson model. The model hierarchy defined and specified within its prior distributions would accommodate for any spatial correlations within the data *(See Appendix A).*

The two main models performed in this study included generalised linear mixed models of various forms. The first generates spatiotemporal patterns in the mean response with a general temporal effect but separate independent spatial effects for each year (Napier, Lee, Robertson, Lawson, & Pollock, 2016). This model is defined by Equation (1):

$$\psi = \phi_{kt} + \delta_t,$$

where

$$\phi_{kt}|\phi_{-kt}, \mathbf{W} \sim N\left(\frac{\rho s, \sum_{j=1}^{K} \omega_{kj}\phi_{jt}}{\rho \sum_{j=1}^{K} \omega_{kj} + 1 - \rho}, \frac{\mathcal{T}_t^2}{\rho \sum_{j=1}^{K} \omega_{kj} + 1 - \rho s}\right),$$

$$\delta_t|\boldsymbol{\delta}_{-t}, \mathbf{D} \sim N\left(\frac{\rho\tau, \sum_{j=1}^{N} d_{tj}\,\delta_j}{\rho\tau \sum_{j=1}^{N} d_{tj} + 1 - \rho\tau}, \frac{\mathcal{T}_t^2}{\rho\tau \sum_{j=1}^{N} d_{tj} + 1 - \rho\tau}\right), \quad [1]$$

$$\mathcal{T}_1^2, \ldots, \mathcal{T}_N^2, \mathcal{T}_T^2, \sim \text{Inverse} - \text{Gamma}(a, b),$$

$$\rho s, \rho\mathcal{T} \sim \text{Uniform}(0,1).$$

The study implemented this model to show the common overall spatial effects for all periods, a common temporal trend, and independent space-time interactions.

The second model is used for districts based on their temporal trends in the risk of malaria infection or death, with trend functions optimised by fixed parametric forms or constrained shapes (Napier et al., 2018). The model's effects were utilised to follow a multivariate autoregressive process with order 1, using the Equation [2]:

$$\psi = \phi_{kt} + \sum_{s=1}^{S} \omega_{\kappa s}\, f_s(t|\gamma_s),$$

$$\phi_k|\phi_{-k} \sim N\left(\frac{\rho \sum_{j=1}^{K} \omega_{kj}\phi_j}{\rho \sum_{j=1}^{K} \omega_{kj} + 1 - \rho}, \frac{\mathcal{T}^2}{\rho \sum_{j=1}^{K} \omega_{kj} + 1 - \rho}\right), \quad [2]$$

$$\mathcal{T}^2 \sim \text{Inverse} - \text{Gamma}(a, b),$$

$$\rho s, \rho\mathcal{T} \sim \text{Uniform}(0,1).$$

$$\omega k = (\omega k1, \ldots, \omega kS) \sim \text{Multinomial}(1; \boldsymbol{\lambda}),$$

$$\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_S) \sim \text{Dirichlet}\big(\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_S)\big),$$

Where $\phi_{-k} = (\phi 1, \ldots, \phi k-1, \phi k+1, \ldots, \phi K)$.

The model was implemented with 4 MCMC chains, 20000 samples obtained by generating 220 000 samples, and removed the first 20 000 as burn-in. Thinning was applied to the remaining 200 000 by 10 to reduce the autocorrelation. The outputs from

this model include a spatial visualisation (map) with credible intervals, a trend classification probability, a slope of trend change and summaries of the trend outcomes and parameters. However, although the study used all these for the interpretation of results, none of them is discussed in the text except the trend visualisation.

Finally, the study classified and visualised districts as high-burden or low-burden based on a matrix score using the combined values of relative RIsk, RAtes, and risk Trend (RIRAT) implemented in ArcGIS 10.5 (Figures 3.6 & 3.7) *(See also Appendix A-methods).*

## 3.3 Results

### 3.3.1 The spatiotemporal trend of malaria mortality and incidence rates from 2000 to 2015

Preliminary analysis of results show temporal progress in the reduction of malaria mortality; however, the trend of malaria incidence remains high. Figure 3.1a shows a significant decline of about 80% in overall malaria mortality from over 11 500 deaths in 2000 down to near 2300 in 2015. Mortality rates among under-five children showed the most significant decline from 28 down to only 3.3 per 10 000 population at a 95% confidence interval, representing a circa 90% decline. Mortality among the over five population also declined from about 5.9 to 0.58 per 10 000 population.

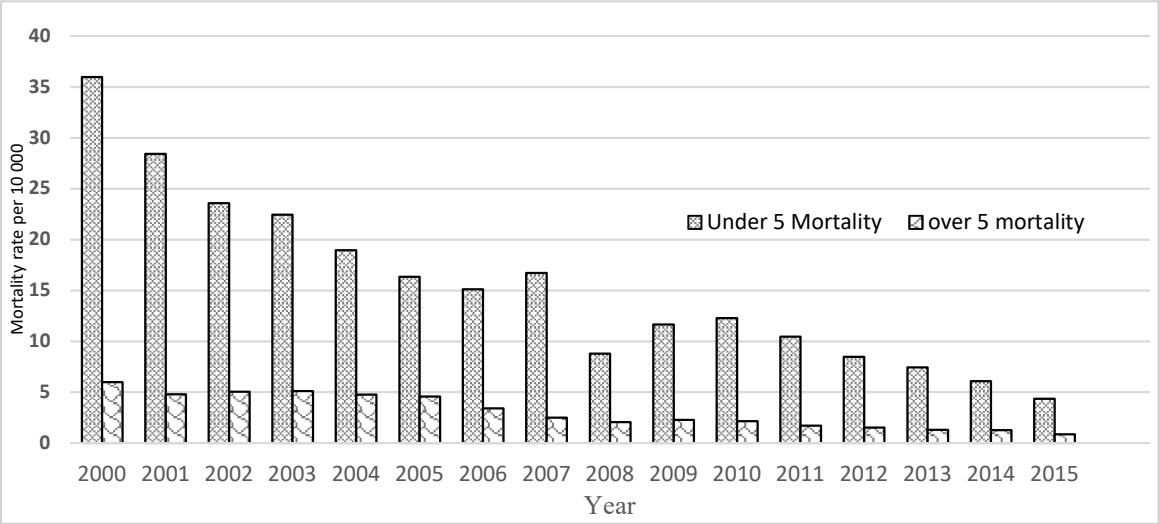



Figure 3.1a: Comparative temporal trend in malaria mortality among under 5 and over 5 populations

Figure 3.1b shows a significant reduction in incidence rates among under-five children from 1457 to 680 (95% CI) per 1000 population with an average reduction of 44 cases annually. Meanwhile, there was a 14% increase in malaria incidence among the five years and older, from 224 to 255 per 1000 population, but this was not statistically significant at 95% CI.

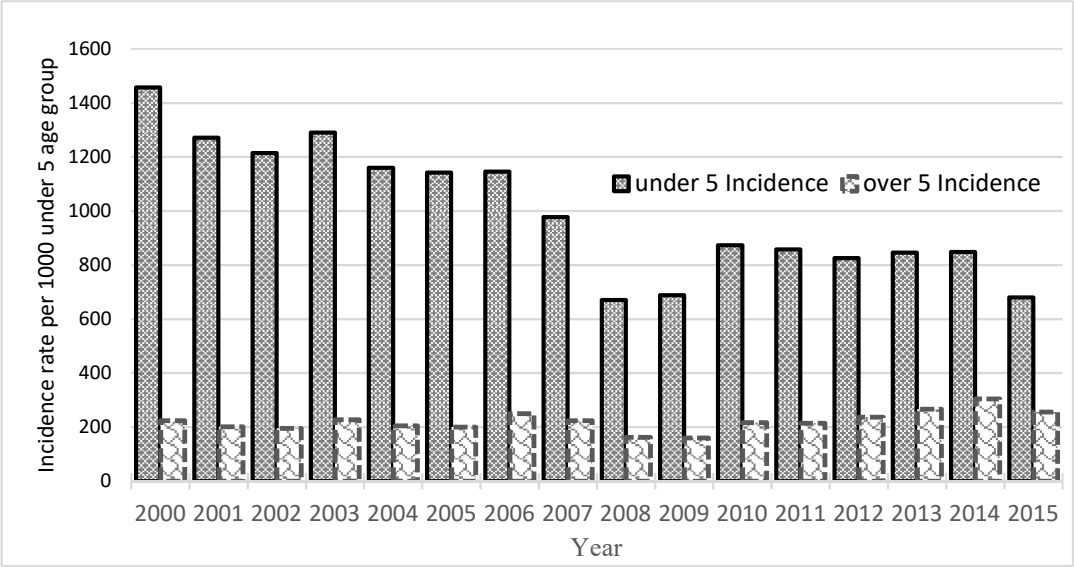



Figure 3.1b: Comparative temporal trend in malaria incidence among under 5 and over 5 populations

Figure 3.2 shows the spatiotemporal trends of malaria mortality (3.2a, 3.2b) and incidence (3.2c, 3.2d) for all ages. Figures 2b and 2d show temporal trends highlighted by the posterior national median (red) and 95% credible intervals (black) for (i) country-wide mean mortality rates and (ii) the level of spatial standard deviation in mortality and incidence trends. The blue dots are mortality and incidence rates for each district by year. The figures confirm that mortality has declined steadily over the study period with a significant decrease in spatial variance across the 72 districts resulting in a homogenously low risk across the whole country by 2015. In contrast, incidence rates have been unstable with a noticeable increase since 2008, along with an increase in spatial variance across the 72 districts.

Figure 3.2: Box plots vs spatial-temporal trends and deviations of transmission

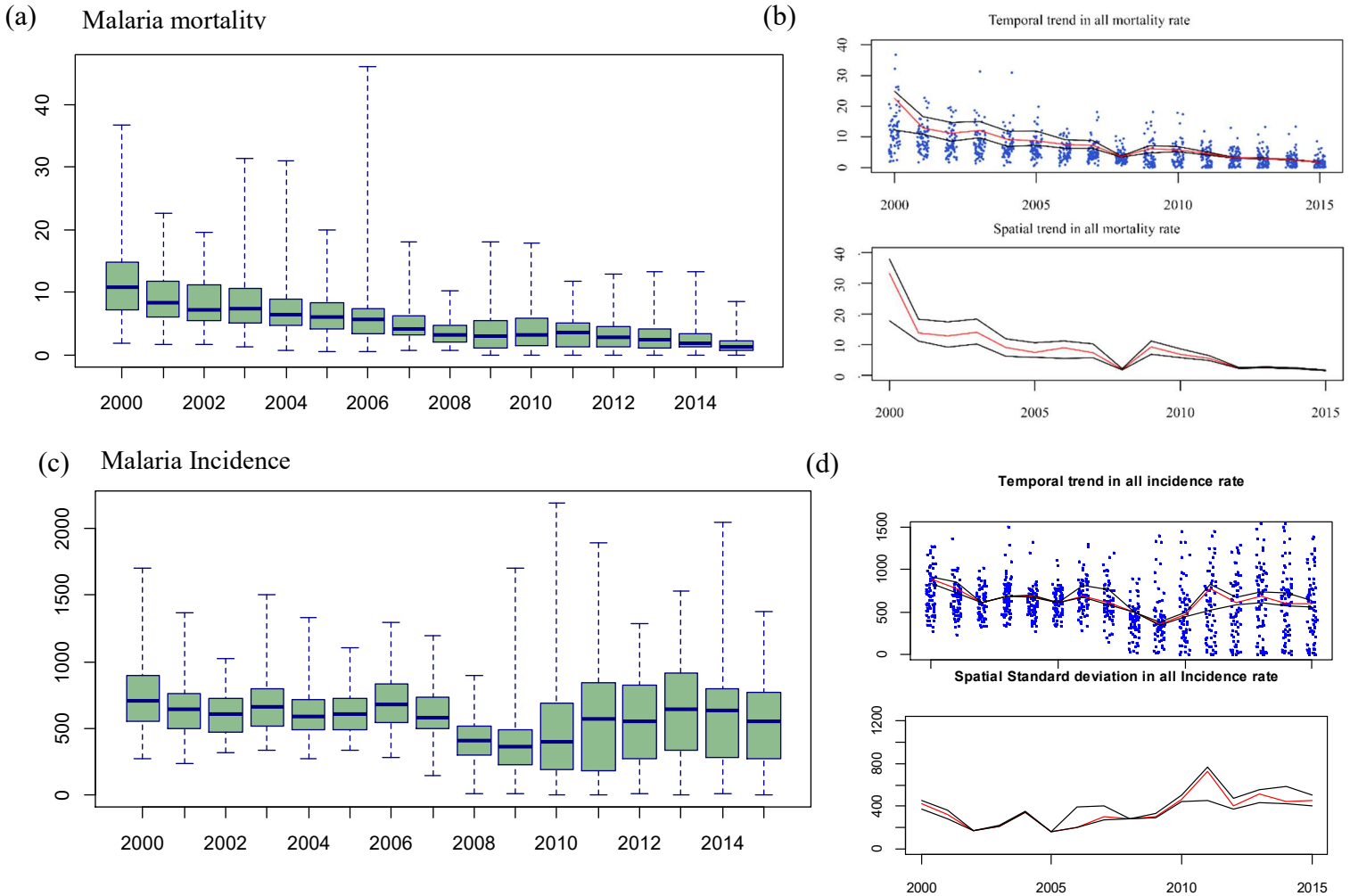



Fig. 3.2a. Box plots showing temporal trends of all age malaria mortality and incidence (2b) from 2000-2015. Mortality decline comes with spatial homogeneity (2c), while the increase in incidence (2d) grew increasingly unstable and spatial transmission

Although the introduction of RDTs around 2008/9 may have affected the observed malaria trends, the results presented here still conform to those obtained from Zambia's malaria indicator surveys (MIS) from 2006, 2008, 2010, 2012, and 2015, which indicated a decline in malaria between 2006 and 2008, but a speedy rise from 2008 to 2015. This confirms the inherent consistency in the trend captured in the routinely collected data as well. This is further validated by the improving quality of HMIS data observed from the declining portion of unconfirmed malaria reported in the HMIS from 55% in 2011 to only 20% in 2015 (*see Appendix A, and Figure S3.3*).

However, these observed spatial variances may be a result of factors such as staggered interventions especially IRS, which is not applied consistently in specific districts but rather targeted to supplement LLINs in very high transmission areas. This means that chances were high to have areas sprayed in one year and not another depending on the preceding year's transmission levels. RDT stock-outs (Chanda, Kamuliwo, et al., 2013; Leung, Chen, Yadav, & Gallien, 2016; Presidential Malaria Initiative, 2019; USAID | Deliver Project, 2016; Vledder, Friedman, Sjöblom, Brown, & Yadav, 2019; World Bank, 2010; Yadav, 2010; Zambia Ministry of Health Logistics Pilot Program Steering Committee, 2011) (recorded at ≈ 20% in 2015) or any differences in the adoption of RDT usage by clinicians could also cause such spatial variations. Further observation made was that the decline of 2008 predates RDTs by 2 years and comes on the backdrop of removal of health facility user fees that instead should have increased the cases captured and foster a rise rather than a decline.

Nonetheless, it would be fair to assume that RDT adoption or stock could be an issue due to commodity distribution inefficiencies following this RDT implementation, especially for districts further away from the initial national/central hub. Hence, massive stock-outs, especially in further off rural districts were common before the optimisation of the supply chain (Vledder et al., 2019). These flaws in the medical supply chain management of commodities and equipment have been acknowledged in many other studies and reports (Chanda, Kamuliwo, et al., 2013; Leung et al., 2016; Presidential Malaria Initiative, 2019; USAID | Deliver Project, 2016; World Bank, 2010; Yadav, 2010). Nevertheless, the study acknowledges that although these persistent stock-outs have significantly reduced, they may still have random effects across the period mixed in with spatially observable differences.

The spatial patterns for both mortality and incidence rates can be seen in Figures 3.3a and 3b.

### 3.3.2 Spatial patterns of malaria risk from 2000 to 2015

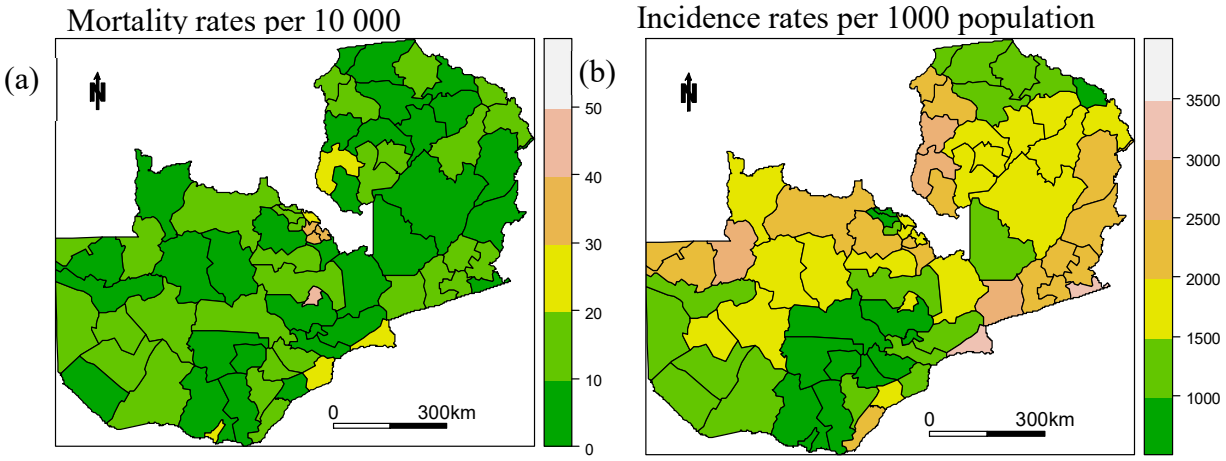



Figure 3.3: Spatial patterns of malaria mortality and incidence rates, 2000 to 2015

Figure 3.4 shows the district level relative standardised mortality risk (SMR) and standardised incidence risk (SIR) for all age, under 5 and over 5 categories. The interpretation of the risk scores is that an SMR/SIR of 1.5 corresponds to a 50% higher risk compared with the countrywide average. In comparison, an SMR/SIR of 0.9 denotes a 10% lower risk. Based on the calculated SMR, few districts indicate a higher risk of mortality among under-five populations. Notably, some districts in the Eastern and Northern provinces have more than a 250% higher risk of malaria mortality for the under-five age group above the national average. Generally, the Eastern province had the highest risk across the country. The figures also support the temporal trends observed earlier in that the under-fives have a higher risk compared to the over-five age-group. The risk of infections also shows the similar but less extreme variance in spatial patterns with concentrations of low-risk areas in the south and parts of the central and northern provinces.

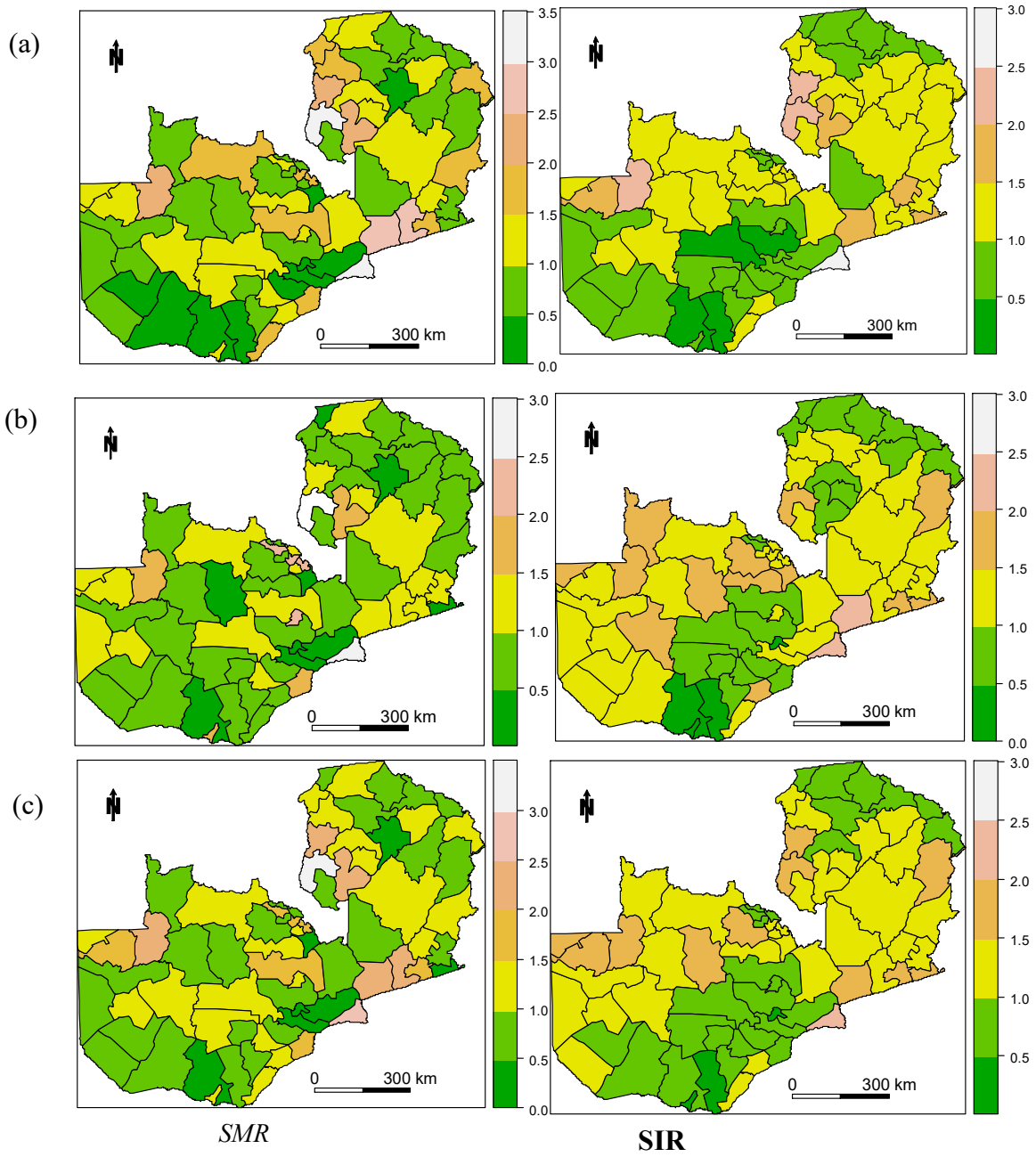



Figure 3.4: Relative risk of mortality (SMR) and incidence (SIR) among under-five, five and over (& both ages), 2000-2015

*(a) = Under-fives, (b) = five and over, (c) = both ages combined*

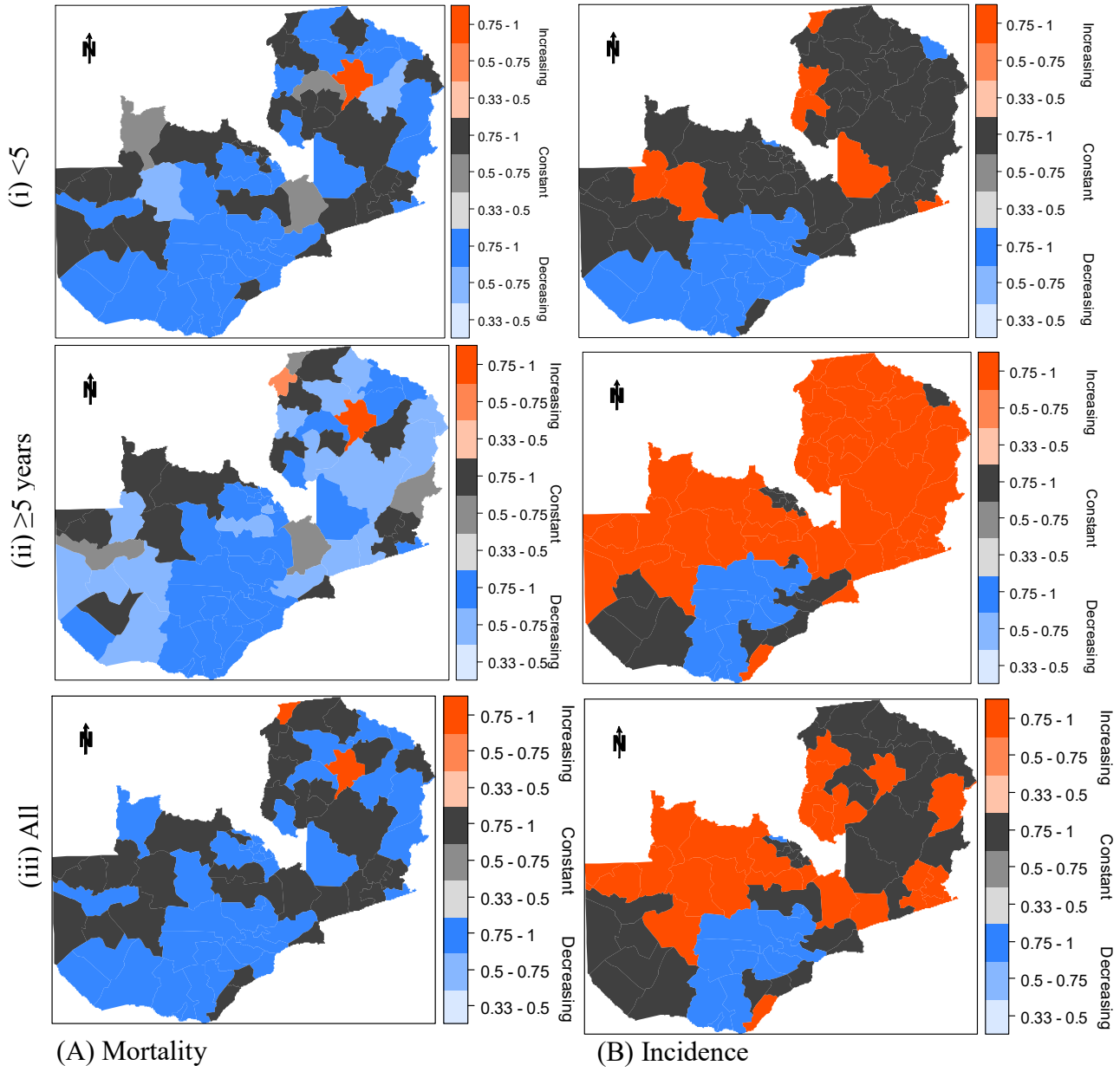
### 3.3.3 Spatial Clustering of areas exhibiting similar malaria trends

Figure 3.5 shows the distribution of district clusters exhibiting similar temporal malaria risk trends. Districts were categorised as having either an increasing trend (red), a constant/no change trend (black) or a decreasing trend (blue) with the darker/deeper the shading, the higher the posterior probability for that trend and vice versa. There was very

little to no posterior uncertainty in the under-five mortality and incidence risk classifications assigned to each of the three trends *(increasing, constant/no-change,* and *decreasing*). In contrast, minimal uncertainties (*probability = 0.5 - 0.75*) are visualised in the *increasing* over-five mortality clusters and *no-change* in all-age clusters.

With regard to mortality trends, in those districts with either a constant or decreasing trend, the pattern of change in trend over time has levelled-off and currently remains

Figure 3.5: Temporal trend of malaria under-five children and over five age group mortality and incidence trends, 2000-2015




The *red* trend shows *increasing,* the b*lue* trend shows *declining,* and the *black* trend shows *constant/no change.* Classifications are based on the maximum a posteriori probabilities: the *darker/deeper* the shading, the higher the posterior probability for that trend and vice versa.

steady. However, in those districts where the mortality trend has been increasing (i.e. 7% of districts for under-fives and 32% districts for over fives) the pattern of increase during the 16 year study period has been rising. This would indicate that there is a worsening situation in malaria mortality in those areas, creating a real potential to negatively influence national mortality figures if this situation continues *(See Appendix A- Figure 3.S1).*

Progress in reducing under-five mortality over the 16-year study period is consistent and evident across risk, rates, and trends while incidence across the three age categories is less consistent and more varied. Only 3% (2) of districts showed an increasing trend in under-five mortality while 71% and 26% experienced a decreasing trend or no-change, respectively (Table 3.1). For incidence risk in the under-fives, however, there was an increase in 10% of districts (mainly around the northern half and easternmost border region,), a decrease in 20% of districts around southernmost areas. In comparison, 45% remain unchanged (clustered mainly around the middle half of the country). The mortality trend among those aged five years and older is more varied (Table 3.1) with 3%, 69%, & 28% of districts either increasing, decreasing or no-change, respectively with a model classification certainty of 75-100% (Figure 3.5a [ii]).

A large cluster of districts in the southern region has a decreasing trend relative to the rest of the country (Figure 3.5b (i-iii).

Table 3.1: Summary description of malaria mortality and incidence trends in <5 years old children, ≥5 years age group, and all age combined

| | Mortality | | | Incidence | | |
|---|---|---|---|---|---|---|
| **Age group** | **Districts** | **%** | **Trend** | **Districts** | **%** | **Trend** |
| under 5 | 19 | 26.4% | No change | 45 | 62.5% | No change |
| | 51 | 70.8% | Decrease | 20 | 27.8% | Decrease |
| | 2 | 2.8% | Increase | 7 | 9.7% | Increase |
| over 5 | 20 | 27.8% | No change | 17 | 23.6% | No change |
| | 50 | 69.4% | Decrease | 10 | 13.9% | Decrease |
| | 2 | 2.8% | Increase | 45 | 62.5% | Increase |
| overall | 31 | 43.1% | No change | 34 | 47.2% | No change |
| | 39 | 54.2.8% | Decrease | 13 | 18.1% | Decrease |
| | 2 | 2.8% | Increase | 25 | 34.7% | Increase |

**NB** *% represents the proportion of the 72 districts assigned to each trend, i.e. Decrease, Increase, or No-change.*

The trend for over-five incidence in Table 3.1 shows that over half of all districts (62%) are increasing, while only 14% are decreasing and 24% exhibit no-change (all results are statistically significant at a 95% credible interval).

### 3.3.4 A classification matrix for determining overall malaria burden

While rate and risk trend clusters show a clear picture of overall district-level classification, i.e. decline, no-change or increase (Figure 3.4 and Table 3.1), reviewing these trends separately may conceal or mask the overall underlying picture which in turn might undermine the actual implications of these trends for malaria control. For instance, a district with high risk, high rate, and showing no-change in trend could be more

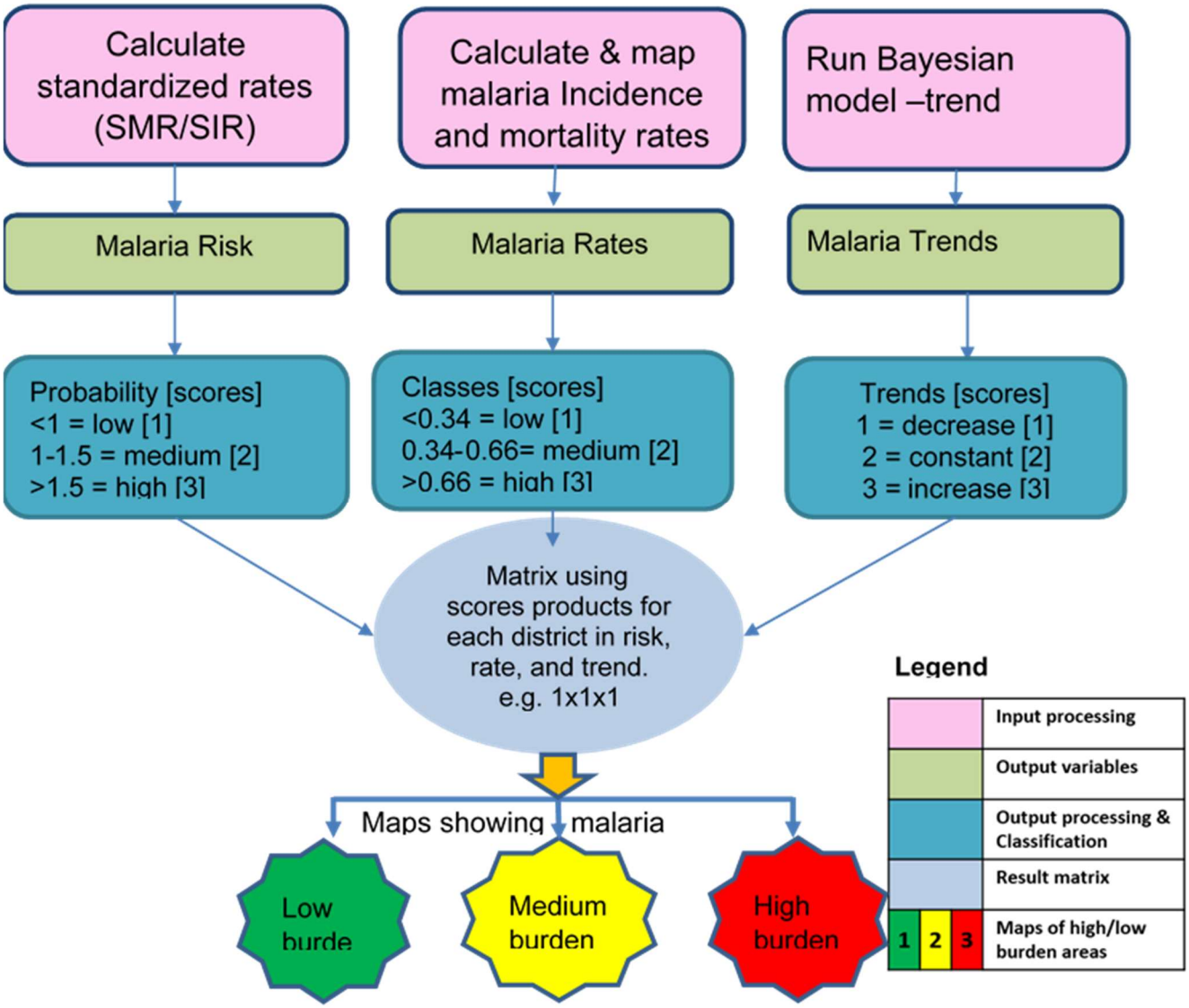



Figure 3.6: Data preparation and processing to determine areas of highest/lowest burden

*Stages of data analysis from initial, intermediate, to final outputs. The classes relate to 1, 2, 3 scores with 1= low, 2 = medium and 3 = high applied to risk, rates, and trends.*

alarming compared to a district that has low risk, low rate and no change or an increasing trend. Therefore, the study created a matrix (RIRAT) of the combined indices for malaria risk, rates, and trends to accurately classify high-burden and low-burden districts (Figure 3.6) (*See Appendix A -methods for matrix detail*).

Figure 3.7 shows comparative district level maps for mortality and incidence burden for the two age categories on the spectrum of *low (green), medium (yellow),* and *high (red)* -burden (*See Appendix- Table 3.S1 for details*). Figures 7a and 7c show the districts in 2015 (mostly in Eastern and Luapula provinces) with the highest under 5 mortality-burden (8 districts) or highest incidence-burden (8 districts) representing an estimated half a million children in that age cohort. Twelve unique districts were classified with either high-mortality or high-incidence burden while four had both. For the five years and older, 15 districts were identified as high-incidence burden areas representing approximately 2 million people in that age group. Only two districts had both high-mortality and high incidence burden representing about a quarter-million vulnerable

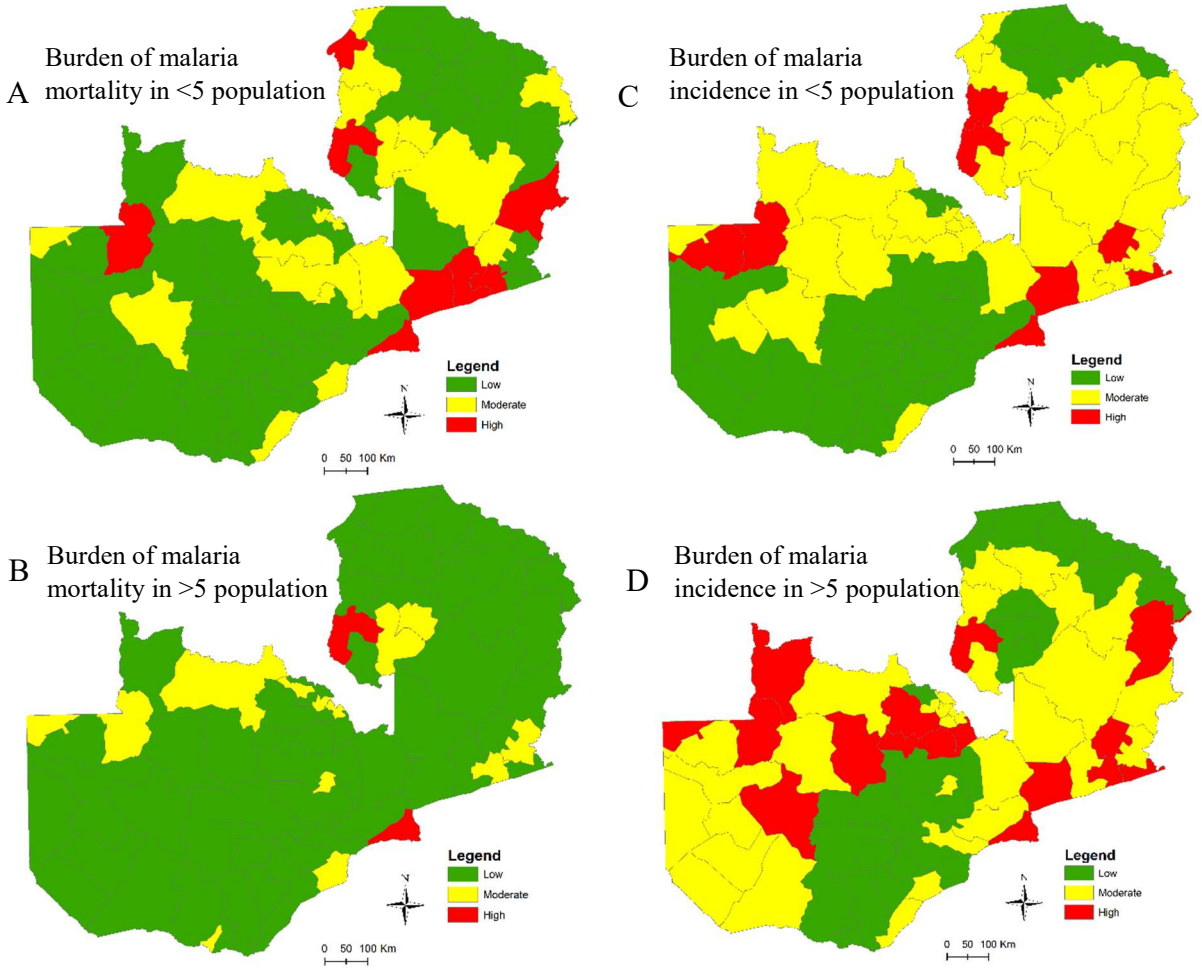



Figure 3.7: High/low burden malaria mortality (3.7a & 3.7b) and incidence (3.7c & 3.7d) districts using matrix scores of risk, rate, and trends

people, while an additional 1.5 million people aged over five lived in the 13 districts with a high-incidence burden only.

Derived from matrix score, more than 3 million people live in districts with generally high incidence risk, high incidence rates and an increasing trend. This population is exposed to at least twice the risk of malaria compared to other areas in the country.

To assess the method further, differences among incidence classification of those aged ≥5 years were observed through a comparison of the derived results using raw rates alone against the method. There was a considerable difference in the proportion of districts classified as high or low burden compared to those identified by the method. For example, only 55% of districts identified as high incidence using raw rates alone were also deemed high-burden using the overall weighted combined method. Similarly, 45% of those districts identified as high in the raw rates dropped into the moderate burden category, and 30% of districts identified as low ended up as moderate-burden districts. The differences observed here highlight the limitations of using raw incidence rates as a basis for identifying and targeting intervention strategies at the subnational level.

## 3.4 Discussion

These findings have important implications for malaria policy in Zambia, and the various intervention approaches used within the country. As shown, in both age groups, it is clear that there has been remarkable progress in mortality reduction but less so in incidence reduction. Both the under-five and the over five age groups experienced a similar rate of reduction in mortality (85% and 90% respectively). However, the under-fives continue to experience approximately five times the incidence rates and at least 2.5 times the mortality burden compared to those aged five years and older.

Without overemphasising the observed declining malaria mortality, the overall results would indicate that more can still be done to further reduce the under-five mortality burden by targeting the highest-burden areas. The benefit of the high precision district-level analysis presented in this study provides an opportunity to move away from the *one-size-fits-all* approach, and optimise resource deployment in a more focused, efficient and geographically targeted manner. The findings also demonstrate how a small number of high burden areas can skew the national averages and overshadow the actual progress achieved so far in the country as a whole. This study has provided a means of determining

districts with high malaria burden where, if prioritised, targeted malaria control efforts could help maximise impact *(Appendix A -Figure 3.S2).*

With proposed sub-national elimination approaches soon to be implemented in Zambia, the method, based on an analysis of 16 years of data has identified those areas that are most suitable for malaria elimination *(Appendix A - Figure 3.S2).* The method can be applied to help other countries identify high-burden areas and achieve maximum impact through the appropriate use of tools and interventions efficiently and effectively. This is important when considering the use of expensive interventions such as indoor residual spraying, which requires rounds of minimum spray coverage thresholds of up to 85% (Pinder et al., 2015).

An additional point of particular interest in Zambia is that most high-burden areas comprise districts along the national borders with Angola, Democratic Republic of Congo, Malawi, Tanzania, and Mozambique. All these countries are unequivocal, high-burden malaria-endemic countries that have often been ranked among the top ten high-burden countries in the world. This observation highlights the significance of the need for countries to engage in bilateral and collaborative regional malaria initiatives for successful control along borders. While Zambia is part of the Elimination8 countries cross-border malaria collaborations, this only applies in southern bordering countries. No such formal undertakings are present with Zambia's northern bordering countries (Elimination8 Secretariat, 2017).

The patterns and trends presented here reflect Zambia's geographic location and adjacency with contrasting high-burden and low-burden neighbouring countries and highlight the potential influence and impact of cross-border malaria risk in border districts (Chihanga et al., 2016; Simon et al., 2013). This method, if carefully applied, could additionally benefit other low resource countries and encourage broader regional collaborations, particularly for targeted cross-border initiatives.

This study has presented an empirical but rigorous approach for the identification of high-burden/low-burden malaria incidence and mortality in affected countries. In the case of Zambia, it would be proposed that a review of the current under-five malaria intervention strategies be done, especially for high-mortality burden districts so that any potential problems or issues can be identified and addressed. It would also be recommended that

more focus is given on ongoing operational research to assess the progress and identify specific challenges at the community level (Haque et al., 2010).

While this study focused more on the identification of high burden malaria control areas than those most suitable for elimination, the approach still provides sufficient evidence and information that can accurately inform both control and elimination approaches. The approach provides the information base needed to facilitate further research into the specific factors that might explain within-country differences between regions and age cohorts, including the value and impact of intervention programmes over time. For example, Figure 3.8 shows the relationship between mortality and incidence trends with significant malaria policy changes and guidelines on interventions and diagnostics in Zambia between 2000 and 2015.

Of interest is the post-2008 trend of increasing incidence rates despite the various intervention strategies. The spatio-temporal modelling and the identification of those specific areas where incidence burden and risk is highest provide essential information to support future geographically targeted initiatives. Such initiatives could replace expensive country-wide programmes, thus facilitating more efficient and effective use of scarce resources.

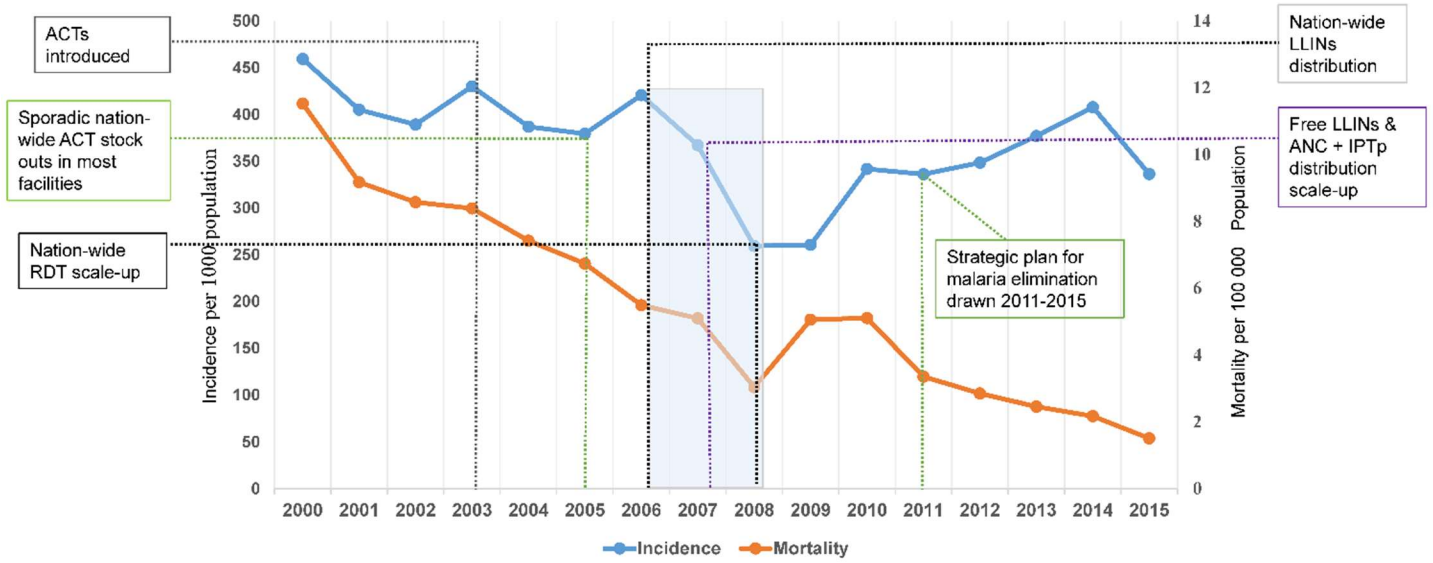
It is recognised that some of the changes in malaria policy, diagnostics, definition, and collection methods during the 16 years may have introduced potential biases in this study. The incorporation of malaria cases by clinical symptoms added some level of non-malarial fever burden, and which could lead to an over-estimation, especially between 2000 and 2008. This bias, however, would be declining in the post-2008 period *(see Appendix A)*.

It is also worth noting that the long period of analysis on which this study is based saw several health care data system changes which may contribute to some of the observed trends in the results. For example, it is realistic to expect a widening financial and geographic access to healthcare as a result of an increased number of available health facilities, and /or removal of patient user fees could increase the clinical incidence of malaria over time. Nonetheless, evidence from literature did not fully support this assertion as studies generally report contradictory result on the effects of financial changes (*See Section 2.2.4 and 2.2.4.1 for details)*. Furthermore, greater use of RDTs might reduce the clinical incidence of malaria and may, to a greater extent, counteract

this. Furthermore, there is evidence of improvements in record-keeping and data completeness. For example, the move from HMIS to DHIS2 in 2014 might have reduced misreporting, and improved feedback to health facilities and thereby reduce variations in the clinical incidence data set over time.

Such barriers to incorporating these relevant covariates reflecting changes in the healthcare data system over time, in addition to the lack of consistent data on the number of facilities per district through the whole study period make it extremely challenging to ascertain and quantify the extent to which the analysis here could have been affected. Nonetheless, the results obtained from this study are still valuable, as they are in line with the current, generally accepted and well-known limitations of the types of data used by the malaria programme. Besides, similar trends showing increasing malaria in most parts of the country have been reported from malaria indicator surveys conducted between 2006 and 2012 (Bennett et al., 2016). These partly confirm that, despite the given limitations of HMIS data, it still captures the true malaria dynamics with adequate accuracy compared to survey data. This may be due to the often high reported average health-seeking behaviour across the country, as shown in many past World Malaria Reports (WMR) (World Health Organization, 2011, 2015e, 2018e).

Figure 3.8: Incidence and mortality trend against major policy changes




Significant malaria policy changes and guidelines, interventions and diagnostics in Zambia 2000- 2015. Note that this study did not include any changes that were progressive, e.g. IRS. Major policy changes undertaken in Zambia, 2000–2015 (Source of data: Steketee *et al*. 2008, Chanda *et al.*, 2013, Redditt *et al.* 2012, Kamuliwo *et al. 2015*)

- ✓ 2003: Chloroquine (CQ) replaced by artemisinin-lumefantrine (Coartem®) as first-line malaria treatment and new diagnosis and treatment guidelines for malaria to reflect drug policy change launched;
- ✓ 2006: Use of Insecticide Treated Nets (ITNs) adopted;
- ✓ 2006-8: Training of additional microscopists, scale-up of RDTs distribution; free distribution of insecticide-treated bed-nets (ITNs) through antenatal care (ANC) and intermittent preventive treatment (IPT) using sulfadoxine-pyrimethamine (SP);
- ✓ 2011: Consideration for future elimination begins with the alignment of NMCP strategic plan 2011-2015 with the national vision *"a malaria-free Zambia by 2030"*]

For example, the observed changes in prevalence rates over time may in some parts have been influenced by changes in diagnostic tools or methods used in case reporting rather than representing real changes in malaria incidence. This could be more relevant in rural health facility settings (Mukonka et al., 2015) where limited availability of trained human resources still exist. It also noted that this study gives a long-term time-series of mean trends, risks and rates up to 2015, and therefore presents conclusions accurate to this period of study. Usage for present decision-making would have to be based on an analysis of more recent and relatively short time datasets of 3 to 5 years.

In this study, other potential limitations that could have influenced some of the observed results may include: i) the potential presence of unquantifiable effects due to the lack of reliable subnational treatment-seeking rates capable of indicating existing subnational variations if present, ii) uncaptured subclinical malaria which is long known to have a severe impact on transmission, especially in the older age groups due to partial immunity; and iii) the unknown effects of any differences on how quickly RDT use was adopted across the country. These if present may affect the conclusions of what the actual malaria burden in the population is (*see Appendix A for details on asymptomatic malaria*).

Having said that, the increasing availability (reduced lag) and improvement (inaccuracy) of health management information system (HMIS) data presented here provide a much greater opportunity for such data to be used with more confidence in the future. This is particularly true given the more expensive alternatives such as surveys that may not always provide comprehensive longitudinal information and analysis at the times when it is most needed.

## 3.5 Conclusion

The study has presented a method here that augments conventional measures of identifying malaria risk and provides a practical approach for the identification of areas of high and low malaria burden at the sub-national level within countries. By applying a rigorous spatio-temporal approach that uses longitudinal rates, risks and trend clusters, policymakers can determine priority areas to deploy scarce resources for high impact control interventions in high-burden areas and elimination strategies in low burden areas.

This easy to implement and replicable methodology will help those policy makers and malaria control/elimination program staff in malaria-endemic countries who may not be

fully cognisant of or technically skilled in advanced statistical methods. The novelty of the method is not in the statistical algorithms, which are well-established techniques in their own right, but in the approach of combining the typically independent measures of rates, risk, and trend over time and space that better represent malaria prevalence within a country and are easy to replicate and use at an operational and practical planning level.

The application of this approach could be extremely beneficial to countries embarking on their malaria elimination strategies as part of the global malaria eradication agenda. This could be particularly effective through informed sub-national programs at even finer levels of geographic aggregation, such as health facility catchments, which are suitable for targeted control and elimination strategies.

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# CHAPTER FOUR

## Near-Term Climate Change Impacts on Sub-national Malaria Transmission

This chapter is based on a manuscript submitted for the first-round review in *Nature Scientific Reports Journal.* This chapter relates to objective number two.

# Abstract

The role of environmental factors, and climate change in particular, on global malaria, have been highlighted by recent World Health Organisation (WHO) reports, but little is known about short-term effects at sub-national levels. Bayesian spatio-temporal modelling was implemented to examine district-level malaria trends in Zambia from 2000 to 2016 and negative binomial mixed regression models to investigate the relationship of near-term environmental change with malaria incidence. It included the diurnal temperature range (DTR) as an alternative environmental measure to the more standard and widely used mean temperature. The results show that intra-regional near-term variations in the environmental variables are significantly associated with malaria incidence. The analysis indicates that DTR, as a consequence of increasing minimum and decreasing maximum temperatures, is a key influential factor in malaria incidence rates, even in those areas where there is a general declining trend in rates.

Additionally, it is evident that the impact of DTR is seasonally sensitive, with the majority of effects occurring in the first and second quarters of the year. So, for the first time, this study has been able to demonstrate how the substantial investment in intervention programmes are negatively impacted and offset by near-term climate change, most notably since 2010. Based on the findings relating to the importance of seasonality, it is argued that targeted season-specific interventions, such as Seasonal Malaria Chemoprevention (SMC), in those areas with an increasing trend in malaria could be a very efficient, cost-effective means of reducing rates quickly.



**Keywords**: Climate Change, Trends, Increasing malaria, Diurnal Temperature Range

## 4.1 Introduction

An estimated 3.4 billion people in 92 countries are at risk of malaria infection (World Health Organization, 2018b). Malaria eradication is possible within a generation, although achieving this goal requires improvements and continuous progress in socio-economic and environmental trends (World Health Organization, 2018b). At the same time, there needs to be improved coverage of current malaria intervention activities. The World Health Organisation (WHO) indicates that climate change could cause approximately a quarter million additional deaths per year between 2030 and 2050, from malnutrition, malaria, diarrhoea and heat stress (World Health Organization, 2018a). It has been noted that the impacts of climate change on malaria transmission are already being felt in most regions. However, some places continue to make good progress against malaria over the last decade (World Health Organization, 2018f).

The African continent continues to carry the highest burden of malaria in the world while recording the lowest mean relative humidity and precipitation compared to Australia, Asia, Europe, North America, and South America (Climate.copernicus.eu, 2019). Such variations persist across various climate variables (e.g. temperature) and spatial scales down to the smallest level where the changes have a direct effect on individual wellbeing and survival. The general association of variable malaria incidence with a range of climate measures has been evident at various geographical scales from the global to the very small area level within countries (Aal & Elshayeb, 2012; Abeku et al., 2004; Caminade et al., 2014; Ferrao, Niquisse, Mendes, & Painho, 2018; Gething et al., 2010; Hurtado, Calzada, Rigg, Castillo, & Chaves, 2018; Imai et al., 2016; Moukam Kakmeni et al., 2018; Parham & Michael, 2010; Semakula et al., 2017; Tompkins & Thomson, 2018; Zhai et al., 2018).

Zambia, for example, has experienced considerable progress in reducing malaria mortality in the last two decades (Chizema-Kawesha et al., 2010; World Health Organization, 2008). This progress came as a result of progressively better case management, prompt diagnostics (e.g. using rapid diagnostic tests (RDTs)) (Mukonka et al., 2015) and a large scale-up of malaria interventions through vector control measures such as insecticide-treated nets (ITNs) and indoor residual spraying (IRS) (Chanda et al., 2011; Chizema-Kawesha et al., 2010; Kamuliwo et al., 2013). Many districts within the country have transitioned from having a ubiquitously high malaria mortality burden to having only a few deaths annually (Shimaponda-Mataa et al., 2017). Previously, high rates were mainly attributed to delays in seeking treatment, self-medication, and low

immunity, especially in children aged under five years old (Presidential Malaria Initiative, 2019).

Between 2000 and 2016, Zambia's within-country malaria incidence rates generally declined in most areas before increasing again post 2008. This trend has occurred despite improvements in the quality and availability of RDTs since 2009, and the uniform distribution of interventions applied as a national strategy over the intervening period. Consequently, while Zambia experiences a moderate-to-high and spatially heterogeneous malaria transmission pattern countrywide (Pinchoff et al., 2015), the question remains as to why the burden of malaria has not decreased in all areas despite the application of various control measures (Nkumama et al., 2017).

Climate change, among other factors, has been cited as a potential cause for the persisting malaria incidence and the notable increases in some areas (Bennett et al., 2016; Shimaponda-Mataa et al., 2017) as the condition is particularly sensitive to changes in temperature and rainfall. The distribution of mosquito vectors depends on a range of factors such as the biology of the mosquito species, the local ecology, and the effectiveness of vector control programmes (Benelli, Jeffries, & Walker, 2016; Carpenter, Pearson, Mitchell, & Oaks Jr, 1991).

Climatic factors are also strongly associated with mosquito reproduction habits, whereby extreme conditions can restrict their longevity resulting in potential changes in vector density and infections. Recognising this connection, studies of the impact of purportedly anthropogenic induced climate change on malaria have increased in recent years (Arab, Jackson, & Kongoli, 2014; Bennett et al., 2016; Caminade et al., 2014; P. Martens et al., 1999; W. . Martens, Niessen, Rotmans, Jetten, & McMichael, 1995; W. J. . Martens, Jetten, & Focks, 1997; Ukawuba et al., 2017; Van Lieshout, Kovats, Livermore, & Martens, 2004).

In order to understand the role of short term changing environmental conditions (i.e. climate change) in explaining different malaria trends at the sub-national district level in Zambia, this study investigated the potential role of climate variables in transmission dynamics over seventeen years (2000-2016). All districts that showed a declining trend in malaria incidence were selected and compared with those that had an increasing trend with respect to the temporal trends in quarterly temperature (maximum, minimum, and diurnal ranges), precipitation, the normalised difference vegetation index (NDVI) and elevation.

## 4.2 Methods

### 4.2.1 Study Area - Demographics and information on malaria

Zambia is a Southern African country of 752,000 km$^2$, with a population of c. 17 million people and has a tropical climate (Central Statistical Office, 2013). This study acquired estimated district level populations from intercensal and postcensal exponential population growth models based on the Central Statistics Office (CSO) reports from 2000 and 2010. Routinely collected malaria epidemiological data were obtained from Zambia's Ministry of Health (MoH) through the National Malaria Elimination Centre (NMEC). Since 2009, all confirmed malaria incidence data were derived from a laboratory diagnostic test or a rapid diagnostic test (RDT) result, while the presence of malaria symptoms, including a fever but with no confirmed diagnostic testing, was defined as unconfirmed (or clinical) malaria. The data were adjusted for reporting completeness, missingness, treatment-seeking, and outliers at the district level.

### 4.2.2 Climate and ecological data

Environmental variables were obtained from satellite-based imagery datasets. Daily precipitation data were extracted from the Climate Hazards Group archive with a spatial resolution of 5 x 5 km (Funk et al., 2015); daily temperature data were sourced from NCEP Climate Forecast System Reanalysis (CFSR) at the 20 x 20 km level (Saha et al., 2012). Normalised Difference Vegetation Index (NDVI) was obtained from Copernicus Global Land Service (CGLS) at the 1x1 km and 10-day spatio-temporal resolutions (Smets, Jacobs, Swinnen, Toté, & Wolfs, 2018; Smets et al., 2013). All the environmental variables were extracted by district using the R Program raster package (Hijmans, 2019).

The study extracted aggregated quarterly mean, minimum and maximum seasonal rainfall (mm) averages as well as mean (Tmean), maximum (Tmax), and minimum (Tmin) values of temperature ($^{\circ}$C) for the period from January 2000 to December 2016 for all 72 districts. The choice of the two primary climate variables (temperature and rainfall) was based on current evidence from the literature confirming an existing relationship between malaria, temperature and rainfall (Abiodun, Maharaj, Witbooi, & Okosun, 2016; Blanford et al., 2013; Colón-González, Tompkins, Biondi, Bizimana, & Namanya, 2016; Krefis et al., 2011; Mohammadkhani, Khanjani, Bakhtiari, & Sheikhzadeh, 2016; Nkumama et al., 2017; Odongo-Aginya, Ssegwanyi, Kategere, & Vuzi, 2005; Okuneye & Gumel, 2017; Suk, 2016). Seasonality was matched with yearly quarters calculated as January-March

(Quarter 1), April - June (Quarter 2), July - September (Quarter 3), and October - December (Quarter 4). Most published studies show a 1-3 months lag in incidence reporting (Aal & Elshayeb, 2012; Darkoh, Larbi, & Lawer, 2017; A. H. . Kilian, Langi, Talisuna, & Kabagambe, 1999; Phung, Talukder, Rutherford, & Chu, 2016; Wu et al., 2016), which fitted with the quarterly definition. Computations of mean seasonal (quarterly) trend detection and change-point analysis for Tmax, Tmin, Tmean, mean rainfall, and maximum rainfall variables, were applied to detect any trending of climate change points in the data. Diurnal temperature range (DTR) was computed and extracted from the daily Tmin and Tmax variables for the duration of the study.

Other groups such as the Malaria Atlas Project utilised mosquito larval conditions based on their capability of affecting adult mosquitoes' life-history traits and in the long run influencing malaria transmission (Lyimo, Takken, & Koella, 1992; Moller-Jacobs et al., 2014; Okech, Gouagna, Yan, Githure, & Beier, 2007). It is not surprising that most available studies, including the Malaria Atlas Project, measured periods of successive days within the temperature range suitable for Anopheles larval development. However, this study used DTR whose relationship with adult mosquito survival, and vectorial capacity is directly associated with common control interventions such as treated bednets, IRS, repellents and screening, all of which are used to control and primarily target the adult stage. The rationale for the choice of DTR as an environmental variable in this study was because it captures the period within which the temperature range is suitable for adult mosquito biting, and thereby directly translating these effects into potential transmission cases and capture the clinical onset of malaria case symptoms with at least seven days of lag from the time of the infectious bite.

This choice corroborates with more recent evidence from Murdock et al. (2016), who show the effects of increasing DTR leading to an overall decrease in mosquito vectorial capacity and an increase in mosquito mortality. Current model results from directly supporting this and show that DTR is also a better predictor of clinical malaria infections. In *An. Gambae* for example, the increase in DTR by 3 °C from temperatures ≥27 °C significantly reduced the vectorial capacity to levels that potentially halve transmission. DTR significantly affects adult mosquito longevity when it is at its widest range. It can increase the mosquito’s transmission potential through the daily rate of inoculations, and subsequently, determine the probability of future infective bites from a currently infected case.

DTR has demonstrated its direct biological plausibility effects on clinical incidence through directly affecting mosquito survival, and by influencing biting activity (Murdock, Sternberg, & Thomas, 2016). As shown by Murdock et al., (2016), this directly translates into the potential for DTR to increase or decrease malaria infections driven by adult mosquito activity.

### 4.2.3 Data analysis and overall models used

The study implemented mixed models using binomial regression analysis to establish the independent effects of environmental conditions on the malaria incidence trends exhibited by each district. It also tested for any apparent effects in the variation of vector interventions to control for differences in malaria vector interventions deployed in these areas.

An analysis of Zambia's malaria trends between 2000 and 2016 was run, first by classifying the district spatio-temporal trends into declining, increasing, or constant (Napier et al., 2018). A Bayesian hierarchical mixture model was implemented with an inference through Metropolis-coupled Markov chain Monte Carlo ((MC)$^3$) model. The inference was based on a sample size of 200,000 iterations, $M$ = 4 parallel chains, a thinning of the degree of 10, and a burn-in of 20,000. The study used Gelman's trace plots and visual diagnostics to determine the convergence of the models (Gelman, Carlin, Stern, & Rubin, 2004; Hamra et al., 2013).

The general model structure and formulae of the temporal model are given by equation (1):

$Y_{kt} \sim p(y_{kt}|\mu_{kt})$, where $K = 1, \dots, K, t = 1, \dots, N,$

$$g(\mu_{kt}) = O_{kt} + \boldsymbol{X}^T{}_{kt}\boldsymbol{\beta} + \phi \sum_{s=1}^{s} \omega_{ks} f_s(t|\boldsymbol{\gamma_s}) \qquad (1)$$

Where malaria trends $f_s(t|\gamma S)$ estimated in the study were represented by (a) Constant trend - $\beta_1$; (b) Linear increasing trend - $\beta_1 + \gamma_1 t$, with $\gamma_1 > 0$; and (c) Linear decreasing trend - $\beta_1 + \gamma_2 t$, with $\gamma_2 < 0$. The trends classification is summarised according to the following:

a. Constant: $f(t) = 0$.
b. Linear: $f(t|\gamma) = \gamma t$, which can be constrained as increasing via the prior specification by $\gamma \sim N(0, 1000)\mathbb{I}[\gamma > 0]$ or decreasing via $\gamma \sim N(0, 1000)\mathbb{I}[\gamma < 0]$, whereby $\mathbb{I}[.]$ is an indicator function.

A more detailed description of this model is given elsewhere (Lee et al., 2018; Napier et al., 2018).

The model outputs were used to map the malaria trends of the 72 districts over 17 years of the study period, from which the areas that exhibited an increasing trend or declining trend in malaria incidence risk among both under 5 children and those 5 years and older were selected. Regression against environmental and intervention variables known to have a biologically plausible effect that either stifles or exacerbates malaria transmission were implemented. These included climate variables such as temperature, rainfall, normalised difference vegetation index (NDVI), all known to affect mosquito vectors, and malaria indoor residual spraying (IRS) and insecticide-treated nets (ITN), known interventions as vector prevention or management mechanisms.

The preliminary analysis explored the regression suitability of fixed and random effects models for the variables. The tests used are presented in *Appendix B - Table 3.S2*. The diagnostic plots obtained from both linear models informed decisions made from the pre-analysis comparisons and mixed models diagnostics using plots from generalised linear and logistic regression models (*Appendix B - Figure 4.S1*). To detect trends in climatic variables, the study utilised several climate-sensitive tests such as linear regression, and other parametric and non-parametric statistics as applied in other studies (Jaiswal, Lohani, & Tiwari, 2015; Wijngaard, Klein Tank, & Können, 2003). It detected distribution trends at 95% significance by the Mann-Kendall test, Multivariate (multisite) Mann-Kendall test, Pettit's test, and Seasonal slope estimator. The Cox-Stuart Trend Test and the Buishand's Range Tests helped in change point detection and homogeneity testing in climatic variables.

The spatiotemporal mixed model allowed for spatio-temporal autocorrelation via random effects, which capture autocorrelation remnants in the malaria data after the impact of the known covariates have been accounted for. It also tested for the presence of spatial autocorrelation in the data by computing the residuals from a simple over-dispersed Poisson log-linear model that incorporated the covariate effects.

## 4.3 Results

### 4.3.1 Malaria Incidence trends from 2000-2016

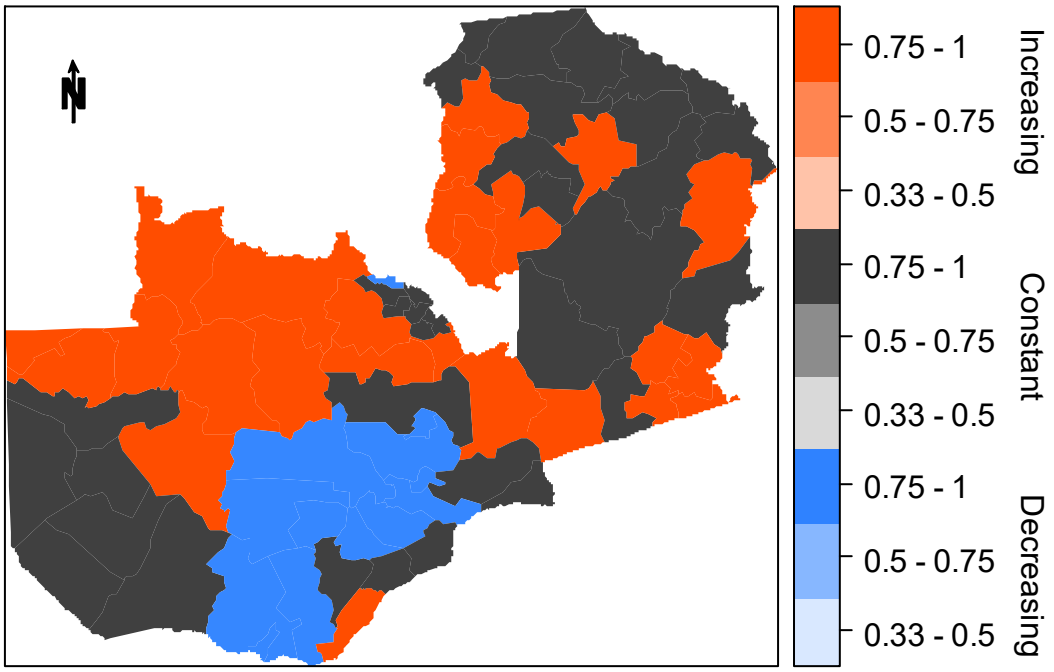



Figure 4.1: Malaria trends in Zambia districts between 2000 and 2016

Figure 4.1 shows the posterior probabilities of disease trends assigned to each district, categorised as either having an increasing trend, a constant trend or a decreasing trend. The classification is based on the maximum posterior probabilities to capture uncertainty — the darker/deeper the shading, the higher the posterior probability for that trend and vice versa. There was very little posterior uncertainty in the trend classifications for all districts. Of Zambia's 72 districts, 25 (35%) were identified with increasing malaria, while 13 (18%) were classified with declining malaria and 34 (47%) had neither declining nor increasing malaria (i.e. a generally mixed non-significant trend for the two population age categories). There is a very distinctive spatial pattern of district clustering with areas of declining malaria mostly being located in the southern part of the country

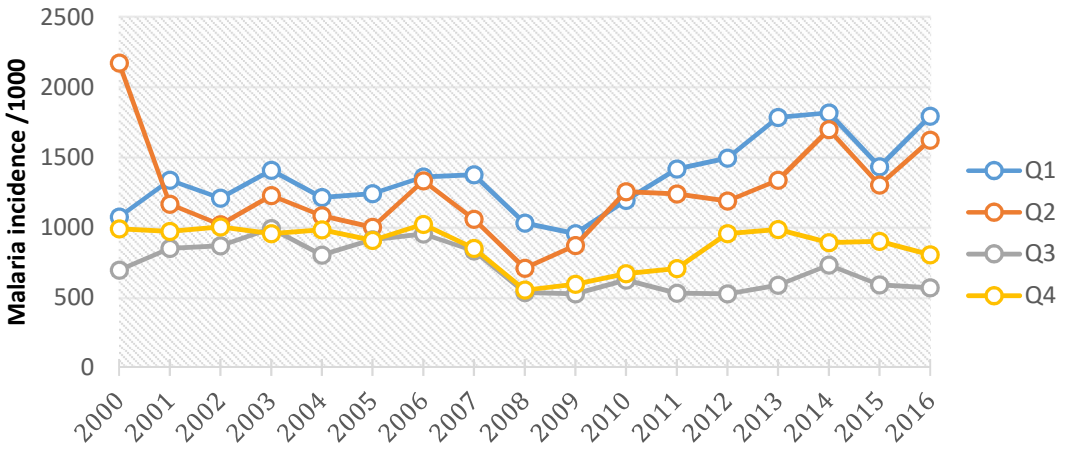



Figure 4.2: Mean Seasonal/Quarterly malaria transmission 2000-2016

During the study period, there is a uniform seasonal malaria trend between 2000 and 2008 (Figure 4.2). After 2008, the first and second quarters (Q1 and Q2) exhibit a general increase in the mean incidence per 1000 population, Q3 remains relatively constant (pre and post-2008) while Q4 maintains the new lower level attained by 2008. The figure shows that most of the observed increases in seasonal malaria during the study period were due to changes in Q1 and Q2, representing the months from January to June. However, this trend is not consistent across all 72 districts *(see Appendix B figures)*.

4.3.2 Short-term climate variable trends in areas classified with declining or increasing malaria

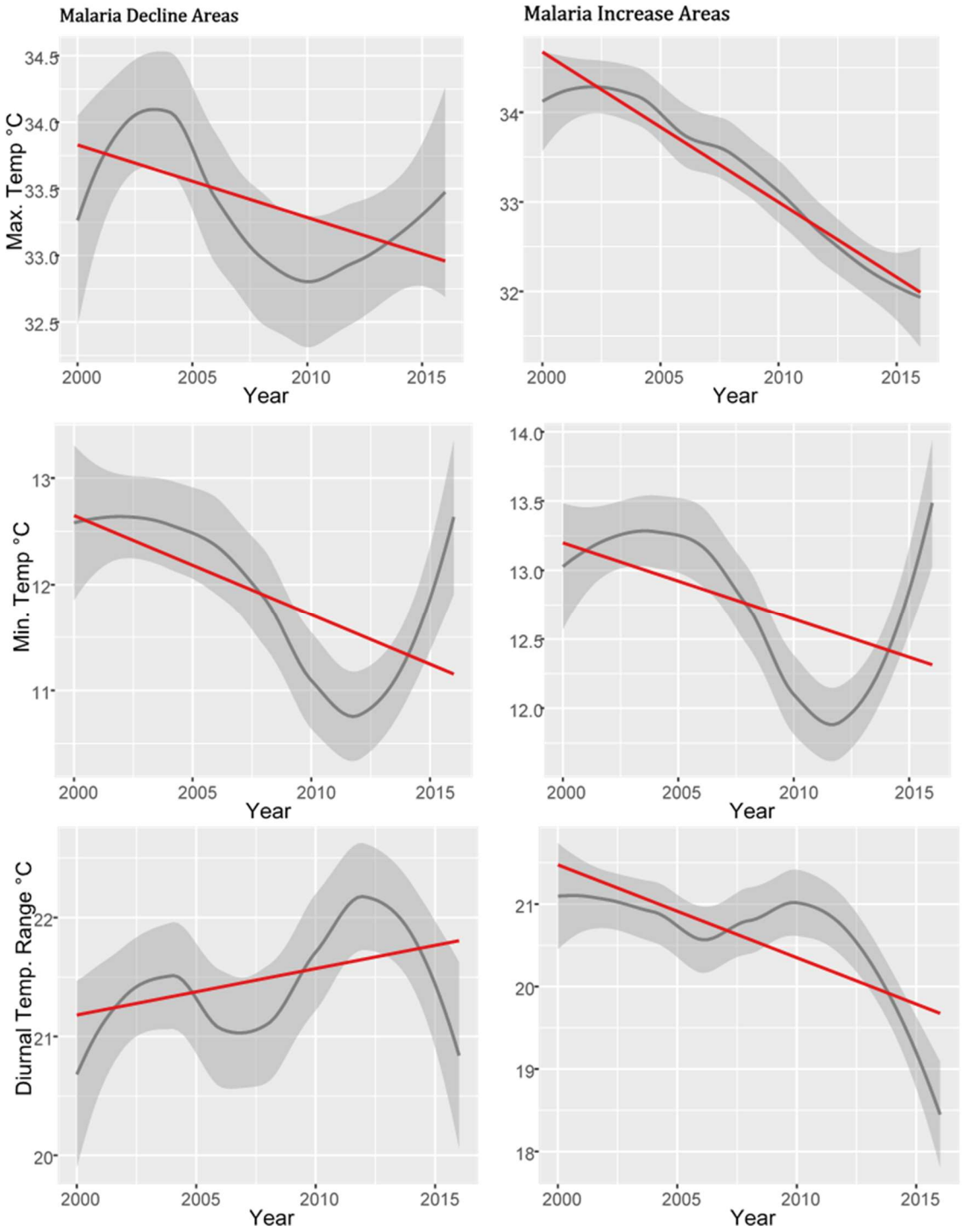



Figure 4.3: Temporal trends of Temperature variables in 72 districts

*Shaded areas show the inter-quartile range of the measured data, while the red line is the regression line.*

The results in Figure 4.3 show that the temporal trend for temperature was generally declining in areas with declining malaria. There was a very small but significant decline in Tmax with slope = -0.05, $R^2$ = 0.005 (95%, p = 0.03) and equally small but significant increase in Tmin with slope = 0.09, $R^2$ = 0.02 (95%, p = 0.001). This supports the observed non-significant increase (slope = 0.04, $R^2$ =0.002, p = 0.12) in the diurnal range

and indicates that temperature has been reasonably stable in areas of declining malaria. The DTR also has a strong negative relationship with malaria.

The temperatures in areas with increasing malaria trends also declined. However, there were much greater significant declines in both Tmax and Tmin (slopes = -0.14, and -0.07; $R^2$ = 0.04 and 0.01, $p < 0.05$), respectively. There was also a significant difference in the two slopes as the Tmax had a slope twice as that of Tmin (slope, $p = 0.004$), and validating the observed significant decline in DTR (95% CI) during the study period.

Table 4.1: Regression model of environment and malaria

| Variable | Estimate | Std. Error | Pr(>\|z\|) |
|---|---|---|---|
| Areas with Declining Malaria (AIC = 34647) | | | |
| DTR | -0.19859 | 0.07828 | 0.0112 * |
| Tmin | 0.16239 | 0.07131 | 0.0228 * |
| Tmax | -0.22441 | 0.08876 | 0.0115 * |
| Elevation | -0.06927 | 0.09595 | 0.4704 |
| NDVI | 0.08429 | 0.07011 | 0.2293 |
| Mean Rain | -0.01751 | 0.05218 | 0.7372 |
| Max Rain | -0.06918 | 0.04707 | 0.1417 |
| | | | |
| Areas with Increasing Malaria (AIC = 17842) | | | |
| DTR | -0.08990 | 0.01617 | 2.71e-08 *** |
| Tmin | 0.028166 | 0.013510 | 0.0371 * |
| Tmax | -0.122918 | 0.016230 | 3.64e-14 *** |
| Elevation | -0.04081 | 0.05617 | 0.4675 |
| NDVI | -0.04081 | 0.01687 | < 2e-16 *** |
| Mean Rain | -0.04382 | 0.01702 | 0.0100 * |
| Max Rain | -0.00831 | 0.01209 | 0.4919 |
| **Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1** | | | |

Table 4.1 and *Appendix B - Figures 4.S1*, - Figure 4.S3 show details of the regression model results of environmental variables against malaria incidence. In areas of declining malaria, only Tmax and DTR had significant negative correlations while Tmin had a positive effect. NDVI, Elevation, and rainfall (min and max) were not significant (see Figure 4.S1 and 4.S2). For those areas with an increasing malaria trend, mean rainfall and temperature (Tmin, Tmax, & DTR) showed significant effects. In contrast, maximum rainfall and elevation had no significant relationship with malaria (*Appendix B -Figures 4.S1 and 4.S3*). Overall, the results demonstrate a much stronger correlation of environmental variables with malaria in areas of declining malaria.

Further analysis to examine the more recent trend from 2010 to 2016 revealed an overall decline of DTR across the whole country (Figure 4.S4). This is validated by specific trend-based results, which show that districts with increasing malaria had increases in Tmin (slope = 0.19, $R^2$ = 0.02), but a continued decline of Tmax (slope = -0.22, $R^2$ = 0.01). Both trends (statistically significant- 95%), further denote a continuous decline in DTR with higher regression coefficients during the post-2010 period. In comparison, areas with declining malaria experienced a significant ($p<0.05$) increasing trend in Tmin (slope = 0.22, $R^2$ = 0.02) but a non-significant ($p>0.05$) increasing trend in Tmax (slope = -0.08, $R^2$ = 0.001). There was no significant difference in the slopes of Tmin and Tmax and the trend for DTR, which, although declining, was not statistically significant.

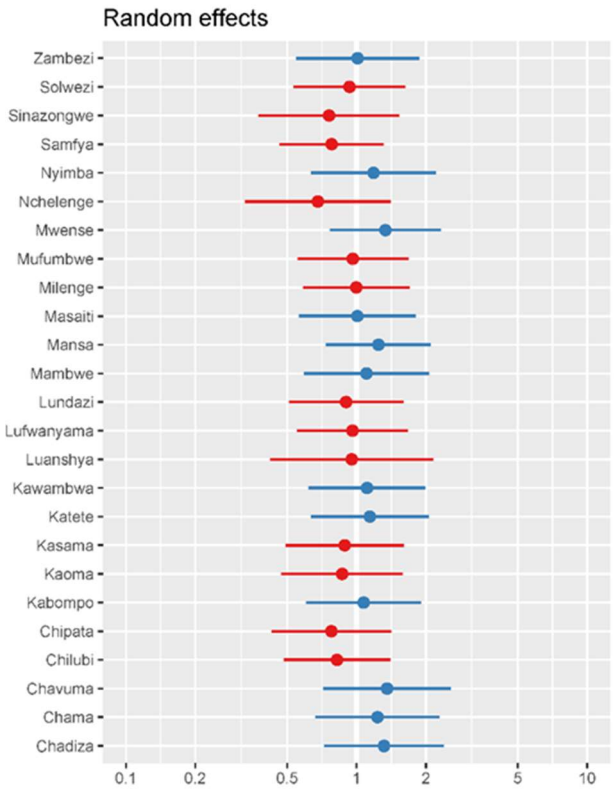



*Figure 4.5: Areas of increasing malaria*

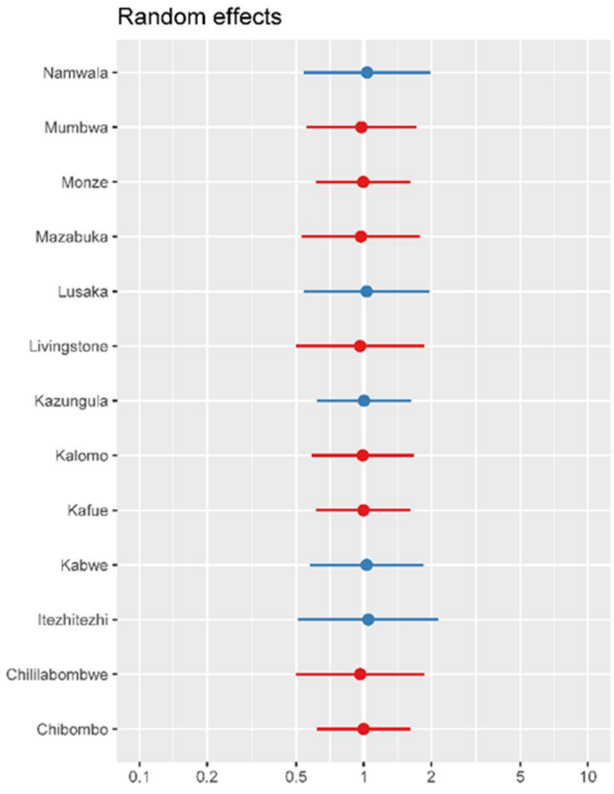



*Figure 4.4: Areas of declining malaria*

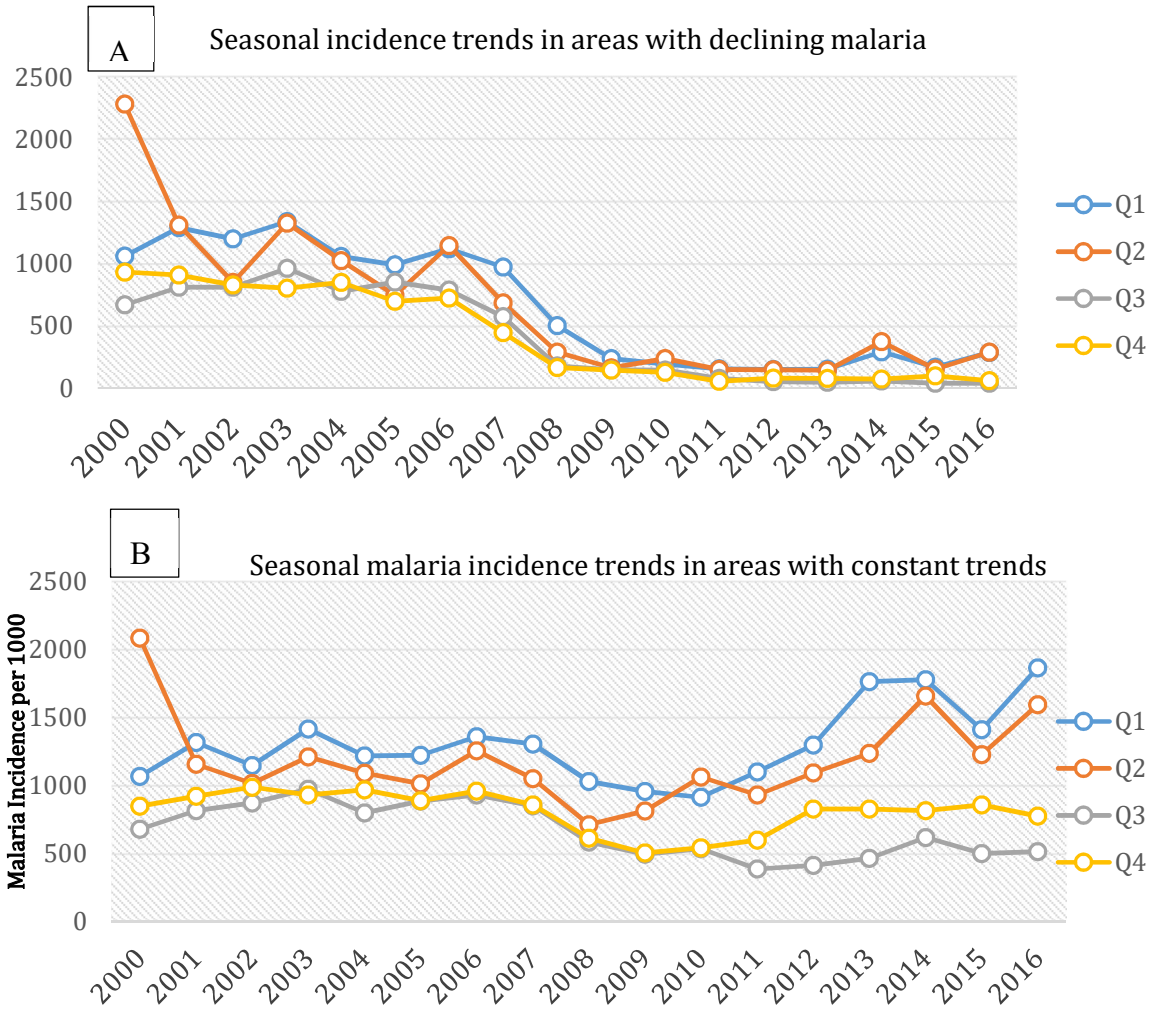
*Red respresent districts with average SDs below the Mean while Blue repsents the opposite*

*Appendix B - Figures 4.S5a and 4.S5b* show that the standard deviations of random effects relative to the model outcomes between districts with increasing malaria and those with declining malaria are very different. Declining areas tend to have a more uniformly low standard deviation about the intercept (*Appendix B - Figure 4.S5a*), with random effects quantiles ranging between -0.05 and 0.05 (*See Appendix B-Figure 4.S6*). In contrast, the large variations existing among districts with increasing malaria, indicate that there may be different probabilities of success depending on the

interaction in response to model variables with wider random effect quantiles at least seven times higher (range between -0.37 -0.37) than those of districts with declining malaria) *(see Appendix B - Figure 4.S5b and Figure 4.S7).*

4.3.3 Seasonality Trends

Further analysis of seasonal malaria between areas with differing trends (increasing, decreasing or constant) indicated a direct relationship with variances in the seasonal DTR. For example, there was no spatial or temporal seasonal difference in areas with declining malaria, with all seasons experiencing similar declining trends (95%) across the study period. The same was true for seasonal DTR, which exhibited a non-significant declining trend in Q1 and Q2, but significant increasing trends in Q3 and Q4 (Figure 4.4a and 4.5a).



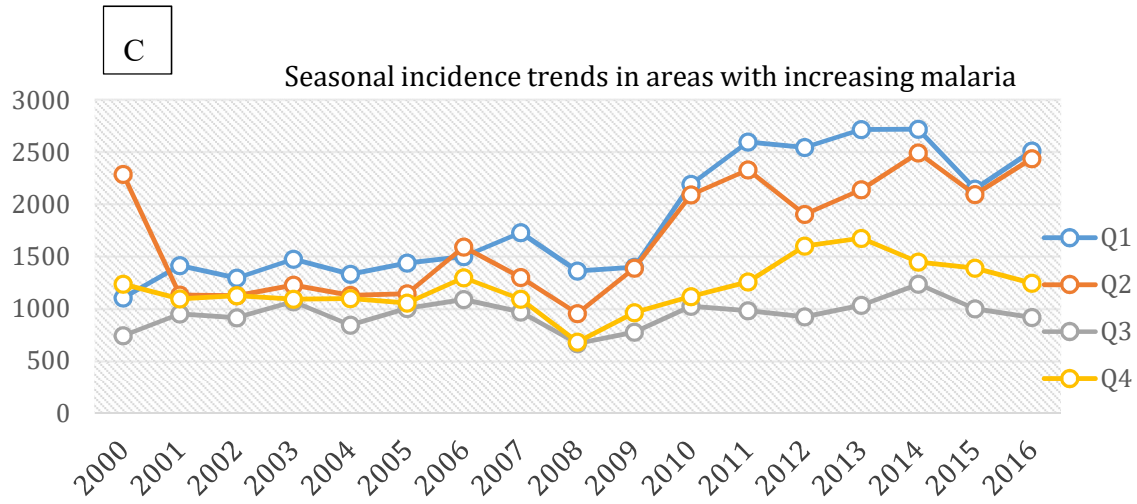



Figure 4.6: Seasonality of malaria in areas of decline, increase, or constant trends

In contrast, areas with increasing malaria had distinguishable significant increases ($p<0.05$) in Q1 and Q2, which become more acute after 2008 (Fig 4.4c). A possible argument that the observed differences might be an artefact of changes in reporting is questionable, as it would be expected that improved reporting should have resulted in increased trends across all the annual seasons and all districts. Figure 4.4c, for instance, shows a clear split in trends between the first half of the year and the second half with a significant increase ($p<0.05$) in the first two quarters. The opposite was true for DTR (Figure 4.5c) which had significant declines ($p<0.05$) in Q1 & Q2, but a declining trend in Q3 and Q4 which was not statistically significant *(see Appendix B - Table 4.S1 for full details*). Figures 4.4b and 4.5b characterise the trends presented above and falling mostly within non-significant trends in either malaria or temperature variables and are not discussed here.

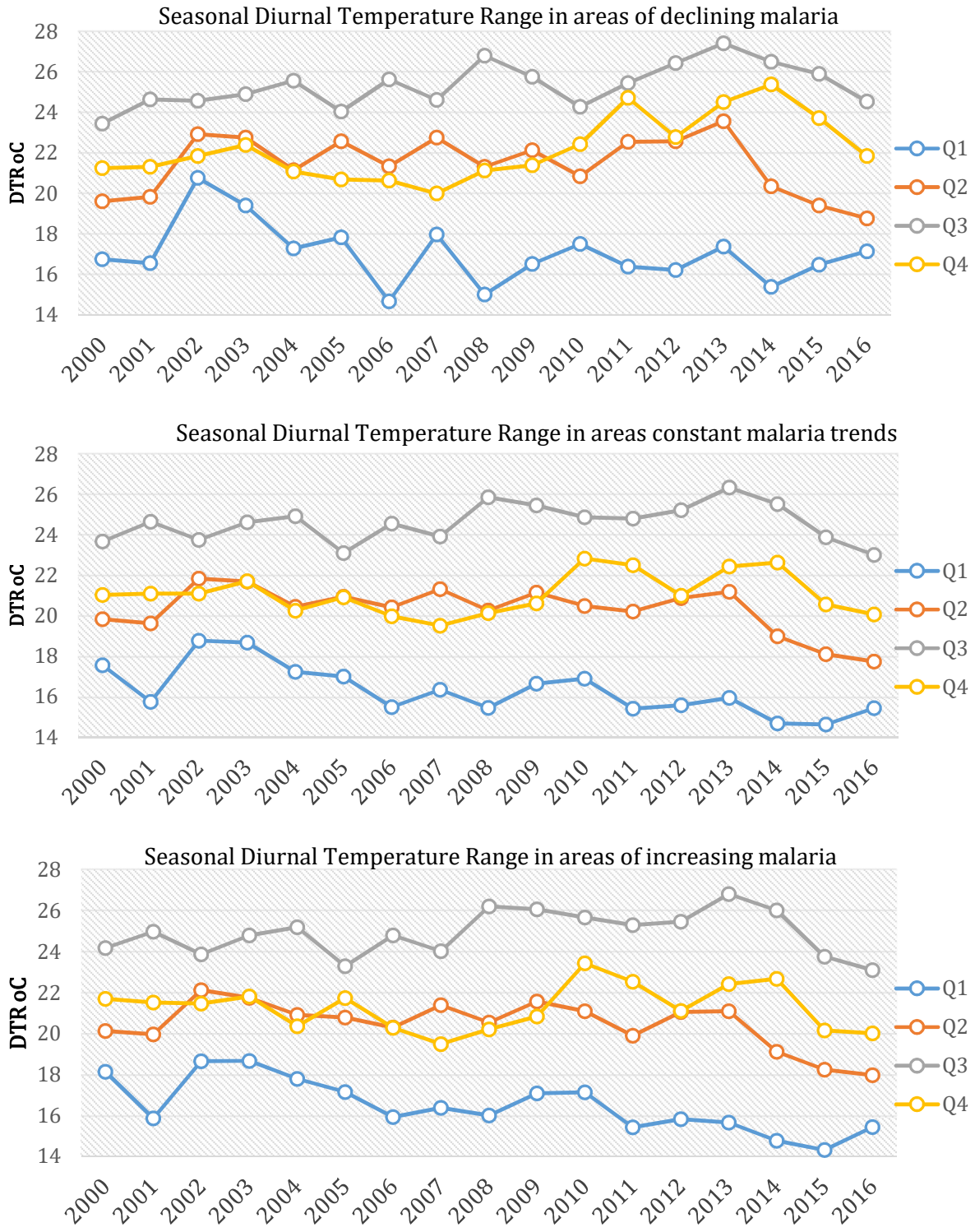



Figure 4.7: Seasonality of DTR in areas of decline, increase, or constant trends

4.3.4 Trends in malaria vector interventions

This study investigated the role of malaria interventions, particularly mosquito nets (ITNs/LLINs) and indoor residual spraying (IRS) (*Appendix B - Figure 4.S8*).


Figure 4.8: Malaria interventions implemented in areas of malaria decline vs increase

The results indicate that there was no significant difference in intervention distribution and coverage reported between the two areas (slope = 0.26, p>0.05). The regression statistics also indicate that the slopes of LLIN coverage are not significantly different (95%) from zero, nor are the intercepts of the two trend areas. IRS, however, showed that there was a significant difference in the amount of spraying between the two areas. In the regression analysis between malaria and intervention variables (LLINs and IRS) (*see Appendix B - Figure 4.S1*), it was observed found that LLINs and IRS showed negative effects in areas of declining malaria. However, IRS was not statistically significant, while neither showed any significant effects in areas with increasing malaria.

## 4.4 Discussion

The results presented above confirm that there are prevailing spatio-temporal differences in malaria progress within Zambia over the period 2000 to 2016. The analyses show that while some areas exhibit continuous declines, others have experienced increasing trends, and some had no discernible change. These differences

occur despite the reported uniformity in the deployment of interventions across the country.

Findings obtained from this study suggest changes in the seasonality of malaria incidence in districts where malaria is increasing (especially in Q1 and Q2) and support the case for more targeted interventions, such as seasonal malaria chemoprevention (SMC) in those areas (Bousema et al., 2013, 2016; Carter, Mendis, & Roberts, 2000; Walker, Griffin, Ferguson, & Ghani, 2016). Such micro spatio-temporal targeting has the potential to be a more cost-effective means of reducing infections in those areas of highest risk to levels where they could become areas for potential elimination, as experienced in other countries (Kitojo et al., 2019) where SMCs have been successfully introduced.

The results here demonstrate that there are significant near term spatio-temporal variations in environmental variables at the intra-regional district level in Zambia and that they are associated with similar variances in malaria incidence.

While the frequency of extreme weather events is typically used to measure climate change effects (i.e. extreme temperatures in minimums, maximums and range), the observed general temperature dynamics during the period of the analysis may imply that in some cases a narrowing of the temperature range could support more favourable all-year-round malaria transmission conditions compared to wider-ranges that may provide temporary transmission cut-offs (via extreme highs and lows). This could explain why malaria is consistently high in areas with a narrowing diurnal range, as shown in the study, where the narrowing is a consequence of near-term trends away from high and low-temperature extremes.

The study has shown here that the change in malaria prevalence rates corresponds with significant increases in minimum temperature and declines in maximum temperature. This confirms the significance of the relationship between temperature and malaria, whereby a rise in minimum temperature causes a subsequent rise in malaria, as does a decline in maximum temperature. Most studies tend to use the mean value of environmental variables to look for such effects. However, the study here showed that using mean values alone may not detect the more subtle trends, like a narrowing of the diurnal temperature range, that produce more favourable

transmission conditions and associated increases in malaria infection rates (Braganza, Karoly, & Arblaster, 2004; Roget & Khan, 2018).

The observed increase in malaria incidence when the temperature in the malaria transmission suitability range narrows is consistent with theories which state that infectious rates are lower in periods of extraordinarily high or lower temperatures. This observation is corroborated by the argument that even minimal changes in temperature trends significantly increase parasite transmission because organisms can amplify such small variances (Chaves & Koendraat, 2010).

The use of DTR provides the potential for a single reliable measure that can be used to understand better the dynamics of the transmission range of malaria in spatio-temporal studies at the sub-regional level within all countries at risk of malaria infection.

The results also support the contention (Murdock et al., 2016) that An. *gambiae* mosquitoes (which are one of Zambia's primary vectors) can experience substantial reduction effects in their vectorial capacity by over 80% with increasing optimum temperatures. Similarly, a decrease around the optimum temperature could increase transmission potential by over 600%. In contrast, increases in diurnal temperature range alone can reduce vectorial capacity by half, with range increases of around 9 °C or higher exacerbating the adverse effects on daily mosquito survival (Murdock et al., 2016; Paaijmans et al., 2010).

It has been argued, quite correctly, that in order to impact improvements made in reducing malaria prevalence within countries, the potential negative effects of climate change would have to exceed the combined beneficial effects of economic development and increasing malaria control efforts (Gething et al., 2010). It is proposed here that, based on the evidence since 2000, the true potential and positive effects of economic development and/or interventions in some parts of Zambia are being impacted and offset by the negative effects of near-term climatic change at the sub-regional district level.

Such a phenomenon has been observed elsewhere where, for example, the application of intervention programmes has been consistent throughout the year while malaria outbreaks tend to be seasonally high (Kiszewski & Teklehaimanot, 2004). It may well be that while the observed temporal trends in temperature variance coincide with a

significant up-scaling in national intervention programmes, the observed variations in vector response to these interventions and malaria infections (via insecticide-associated selection) may be primarily controlled by local vector compositions (Lobo et al., 2015).

Differing levels of urbanisation and rurality within and between districts may be another potential factor that influences IRS effectiveness, as urban districts have a higher probability of receiving IRS than their rural counterparts. This may be due to factors such as population density, ease of access and better-targeted structure surface suitability for spraying (World Health Organization, 2015c), which potentially create a systematic bias favouring urban areas. Nevertheless, IRS remains a supplementary intervention strategy to LLINs. Where effective, it should reduce the annual seasonal peaks of malaria transmission equally, which is persistent in contrast to the observed seasonal increases found here. Similar results showing persisting malaria burden despite a scale-up of control interventions have been reported elsewhere (Mukonka et al., 2014).

Therefore, while economic development and/or urbanisation may well be important in the fight against malaria in Africa, the results here indicate that the level of positive influence such factors may have could well be negatively impacted and offset by seasonally variable near-term (and by inference long-term) climate change at sub-national spatial scales. It is acknowledged that environmental conditions alone cannot sustainably control or eliminate malaria in the tropics, as their effects do not act in isolation.

Nonetheless, the study has shown that changes in near-term small-scale environmental factors play a significant role in the complex matrix of factors that influence malaria rates. As such, these need to be incorporated as part of ongoing monitoring and analyses of rates and in elimination planning at the sub-national level. The relationship between intervention programmes and near-term environmental change may well be the difference between a successful malaria reduction/elimination program and persistent malaria transmission. Thus, if care is not taken, and climate change continues to drive these increases, there is a genuine danger that malaria in those areas of current decline might well start to increase again, thereby reducing the current malaria control and elimination agenda into a second failed global malaria program.

It is imperative to acknowledge that the impacts of short-term climate change on malaria are at hand and undeniable. Planning for adaptation, mitigation, and continuous monitoring is essential if minimisation of the imminent effects, especially at the micro-scale community level has to be achieved. SMCs may provide an opportunity to target those areas with high seasonality impacts, especially in under 5 children. Consequently, it is essential that environmental change monitoring is considered along with monitoring of interventions and prevalence rates so that appropriate preventive mechanisms to counteract transmission, such as SMC, can be introduced. The study findings highlight how essential the discussion about climate change and malaria still is today and demonstrates the seriousness of the potential consequences if it is ignored.

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# CHAPTER FIVE

## Climate change and the dynamics of age-related malaria incidence in Southern Africa: A focus on Zambia

This chapter is based on a manuscript submitted for the first-round review in the Journal *Environmental Research.* This chapter relates to objective number *three*

# Abstract

In the last decade, many malaria-endemic countries, like Zambia, have achieved significant reductions in malaria incidence among children <5 years old but face ongoing challenges in achieving similar progress against malaria in older age groups. In parts of Zambia, changing climatic and environmental factors are among those suspected factors behind high malaria prevalence. Changes and variations in these factors potentially interfere with intervention program effectiveness and alter the distribution and incidence patterns of malaria differentially between young children and the rest of the population.

The study used parametric and non-parametric statistics to model the effects of climatic and socio-demographic variables on age-specific malaria prevalence vis-à-vis control interventions. Linear regressions, mixed models, and Mann-Kendall tests were implemented to explore trends, changes in trends, and regress malaria against environmental and intervention variables.

This study shows that while climate change affects the whole population, its impacts are felt most by people aged ≥5 years. Climate variables influenced malaria substantially more than mosquito nets and indoor residual spraying interventions. It establishes that climate change is negatively impacting malaria control efforts by exacerbating the transmission conditions via more conducive temperature and rainfall environments, which in turn are exacerbated by cultural and socioeconomic exposure mechanisms. It is argued that an intensified communications and education intervention strategy for behavioural change targeted explicitly at ≥5 aged population where incidence rates are increasing, is urgently required and call for further malaria stratification among the ≥5 age groups in the routine collection, analysis and reporting of malaria mortality and incidence data.



**Keywords**: Climate change, malaria interventions, age, Bayesian Models

## 5.1 Introduction

Like many other southern African countries, Zambia has made considerable progress in malaria mortality reduction in the last decade, achieving declines of up to 70% between 2010 and 2015 (Elimination8 Secretariat, 2019). However, in both mortality and incidence, this trend is not consistent across age groups (typically reported as <5s or ≥5). Trends in official published prevalence rates show that there were subnational declines in most administrative districts (N=72) during the period 2000-2008 before experiencing a sustained increase between 2010 and 2017 (of 43%) in both age categories (Kamuliwo et al., 2013; World Health Organization, 2018f). While over the whole of the study period (2000-2016), incidence rates in <5 children showed a 53% decline and those aged ≥5 had a 13% increase in malaria. Little has been done to consider age group targeted malaria intervention responses, especially among ≥5s and most published studies and available data continues to be analysed for the <5 and ≥5 age group categories.

Among suggested reasons for increasing malaria prevalence in several areas is mosquito resistance to dichloro diphenyl trichloroethane (DDT) used in indoor residual spraying (IRS); chemical pyrethroids in long-lasting insecticide nets (LLIN) (Chanda et al., 2011; Loewenberg, 2018; Manyando, 2016); population movement (K.M. Searle et al., 2017), and environmental factors driven by climate change (Bennett et al., 2016; Manyando, 2016).

Trends in temperature and rainfall, especially in regions of extreme climate diversity (Yue & Hashino, 2003), are often studied to detect significant spatiotemporal change (Adarsh & Reddy, 2015; Bisanzio et al., 2018; Drápela & Drápelová, 2011; Freeman & Bradley, 1996; Jaiswal et al., 2015; Jhajharia et al., 2013). However, few studies have examined comparative differences in how climate-induced ecological changes affect various population age groups vis-à-vis malaria communities. This is becoming ever more important given the recent trends in increasing rates for the ≥5 population. While the primary focus of intervention programmes has been the highest risk <5 cohort, there remains a danger that, if left unattended, rates in the ≥5s could continue to rise resulting in considerable health and socio-economic burdens on communities. The economic consequences alone could be substantial, particularly if increases occur disproportionately in younger, economically active populations.

Studies have shown that the rates in some areas are being driven by the five to fifteen (Hast, Searle, Chaponda, Lupiya, Lubinda, Kobayashi, et al., 2019; Kapesa et al., 2018;

Teh, Sumbele, Meduke, Ojong, & Kimbi, 2018) and fifteen to twenty-five-year old cohorts (Bouyou-Akotet et al., 2014; Griffin, Ferguson, & Ghani, 2014; Nkumama et al., 2017; Pinchoff et al., 2016; Wotodjo et al., 2018) which supports concerns about the future long term economic impacts on communities through related impacts on economic productivity and capacity. However, with data generally being collected and reported in only two age categories it remains challenging to determine whether the reported increases in the ≥5 category rates are being driven by differentially higher rates in the five to fifteen category, the over forty fives or some other cohort in between.

It is predicted that in the near future, malaria will become an adult disease shifting from children to those older (Bouyou-Akotet et al., 2009; Brasseur et al., 2011; Brooker et al., 2017; Carneiro et al., 2010; Ceesay et al., 2008; Mawili-Mboumba et al., 2013). Possible reasons in support of this contention include successfully targeted intervention programmes at the very young along with various social, cultural, and economic behavioural factors, which increase exposure and reduce the uptake and effectiveness of interventions in the older age groups. Such factors may include; how communities socialise, the time they go to bed, how late they stay before entering their homes, how early they wake, their daily economic activities and their attitudes toward interventions and health-seeking. To date, little is understood and investigated on the potential impact of the changing climate or environmental variables on differential age-related malaria incidence rates.

The study used malaria prevalence data to explore the extent of influence that environmental variables have had on the observed increase in the prevalence of malaria because of climate change. This study follows on from work by Bennett et al. (2016) on the relative effect of climate variability study on malaria prevalence in 0-59-month-old children over four survey periods using sampled malaria survey data.

The study investigated age-specific trends in malaria incidence in Zambia in relation to intervention programmes and climatic/environmental variables. Both <5s and ≥5 age-groups were investigated for i) the role of malaria control measures on the observed increase or decline of age-related malaria prevalence without the impact of climate change; ii) the role of climate change in the observed increase or decrease in malaria prevalence without control measures; and iii) the role of climate change in the observed increase or decrease in malaria prevalence after adjusting for control measures.

## 5.2 Methods

### 5.2.1 Study Area

Zambia is a country in south-central Africa, with a typically tropical climate and approximately 18 million people living in an area of 752,000 sq. Km (Central Statistical Office, 2013). The population is comprised of c. 20% of children <5 and 80% aged ≥5 years old. Based on a pre-analysis of rainfall and temperature variables, the study classified seasonality to coincide with annual calendar quarters and to align with conventional transmission time lags. It then investigated "seasonality" based on mean seasonal shifts of up to one-month lag mainly via the seasonal onset of rains based on a recent study (Makondo & Thomas, 2020).

Seasonality was synchronised according to annual quarters from January-March (Quarter One), April - June (Quarter Two), July - September (Quarter Three), and October - December (Quarter Four). The data is within the typical one to three months lag applied by many studies between the variables and incidence reporting (Aal & Elshayeb, 2012; Darkoh et al., 2017; A. H. . Kilian et al., 1999; Phung et al., 2016; Wu et al., 2016), suitable for the quarterly definition.

Data was adjusted for the varying quality using reporting completeness, health-seeking, and missingness. The study used Random Forest for multiple imputations to estimate the values of the 5% missingness in the data. Equation one summarises the final adapted calculation of estimated malaria cases (WHO Malaria Policy Advisory Committee, 2018):

$$= \frac{Cases_{presumed} + Cases_{confirmed}}{Reporting\ completeness}(1 + treatment\ seeking\ rate) \quad (1)$$

Computations of seasonal (quarterly) average trends detection and change-point analysis were applied for maximum, minimum and mean temperatures (Tmax, Tmin, Tmean respectively), diurnal temperature range (DTR), mean rainfall, and maximum rainfall variables, to identify the presence of trends or significant climate change points in the data. Population data were obtained from national census reports and population estimates (Central Statistical Office, 2013). Data on malaria and interventions were obtained from the National Malaria Elimination Centre, via the Ministry of Health (Chizema-Kawesha et al., 2010; Yukich et al., 2012). *(See Appendix C file for the full discretion of data and their sources).*

5.2.2 Modelling and statistics

To ensure model suitability and adequately detect patterns between malaria and environmental variables, the study explored the data using simple regression, mixed methods, Ordinary Least Squares regression models (OLS), and the Bayesian Conditional Autoregressive (CAR) prior method. CAR models implemented spatiotemporal Generalised Linear Mixed Models (GLMM) for unique areas (Bennett, 2012; Mabaso et al., 2006; Reid et al., 2012) with inference in a Bayesian environment using Markov Chain Monte Carlo (MCMC) simulations.

Poisson data likelihood was implemented with an autoregressive hierarchy structure specified within its prior distribution to handle any spatial autocorrelation in the data using the CARBayesST R package (Lee et al., 2018). The study then modelled the GLMM using spatiotemporal autocorrelation, via random effect structures from a conditional autoregressive prior distribution (Lee et al., 2018). This model was used to estimate the evolution of the spatial response surface of malaria from 2000 to 2016 *(see Appendix C for further details of the model)*.

The model specification is given by Equation 2:

$$\begin{aligned} \psi &= \phi_{kt,} \\ \phi_t|\phi_{t-1} &\sim N(\rho T\phi_{t-1,}\, \mathcal{T}^2\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1}) \quad t = 2,\ldots,N, \\ \phi_1 &\sim \mathrm{N}(\mathbf{0},\mathcal{T}^2\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1}) \\ \mathcal{T}^2 &\sim \text{Inverse} - \text{Gamma}(a,b), \\ \rho s,\rho\mathcal{T} &\sim \text{Uniform}(0,1). \end{aligned} \qquad (2)$$

| **Nomenclature for equations used** | | | |
|---|---|---|---|
| $\phi$ | Random effects | $\mathcal{T}^2\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1}$ | Variance |
| $\rho s,\rho\mathcal{T}$ | Dependence parameters | $\rho\mathcal{T}$ | Temporal autoregressive parameter |
| $\mathcal{T}_t^2$ | Temporary-varying variance parameter | $\boldsymbol{\alpha}$ | Priori distribution |
| $\boldsymbol{W}$ | Adjacency matrix | t | Timepoint |
| $\psi$ | Latent component | | |

This study also compared these results with those from the generalized linear mixed models (GLMM) with a negative binomial (Brooks et al., 2017; Nakagawa, Johnson, & Schielzeth, 2017) to check for the robustness of the results as the malaria count dataset *Y(t)* and *X(t)* were collected at discrete times $t\in\{1,\ldots,n\}$ by

$$Y(t)=\mu+X(t)+\varepsilon(t) \qquad (3)$$

where μ is the mean value parameter, *X(t)* represents a stationary AR(1) process, with covariance $cov(X(s),X(t))=\sigma 2exp(-\theta|t-s|)cov(X(s),X(t))=\sigma 2exp(-\theta|t-s|)$. The *ε(t)* is the measurement error term, with independently identically distribute (iid) as the normal, i.e. $N(0,\sigma_0^2)$.

The choice on the final models was based on their suitability following Zuur et al.'s protocol (Zuur, Ieno, & Elphick, 2010) and partly using the *DHARMa R package* (Hartig, 2019) *(see Appendix C Table 5.S2 and Figure 5.S1)*. Computation of the seasonal (quarterly) mean trend and applied change point analysis for all temperature and rainfall variables were applied as the premise for determination of trend, change point, and subsequent impact.

Cooks distance and residual diagnostic plots from linear models and other tests were applied to determine which models were suitable for the dataset (Figure 5.S1). Finally, the study also implemented spatiotemporal mixed models, which accounted for spatiotemporal autocorrelation via random effects.

## 5.3 Results

### 5.3.1 Malaria spatial and temporal distribution and trends

The analyses of current malaria trends since 2000 show an increasing overall trend in incidence among those aged ≥5 and a generally declining trend in <5s (Figure 5.1). The trend for the <5s (Figure 5.1(c)) has relatively and consistently been declining (except for 2008 and 2009), while the average rising trend for the ≥5s (Figure 5.1(d)) exhibits a very noticeable increase since 2008.

Figure 5.1: Mean malaria temporal trends

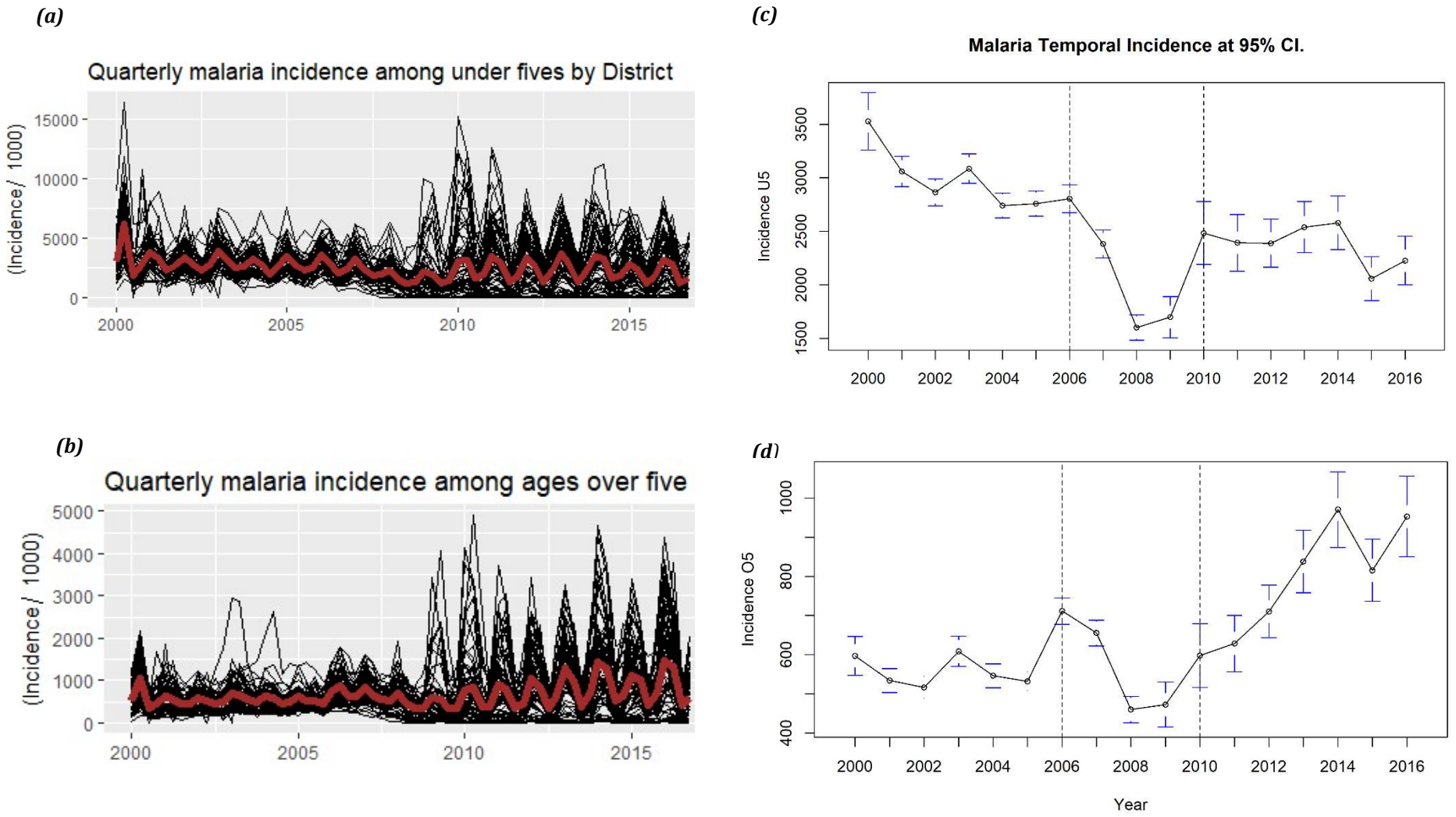



Figure 5.1(a) & 1(b) show individual district incidence temporal trends while (c) and (d) show the mean temporal trend of incidence in Zambia from 2000 to 2016 among under 5 and over 5 years age groups.

Figures 5.1(a) and 5.1(b) indicate that these incidence rates are not consistent across all districts and Figure 5.2(a-d) show that the trends are not consistent geographically across the country either. *Appendix C Figure 5.S2* also shows that the proportion of malaria cases in <5s reduced from about 60% in 2000 down to ≈35% while that of the ≥5s increased from ≈40% to 65%.

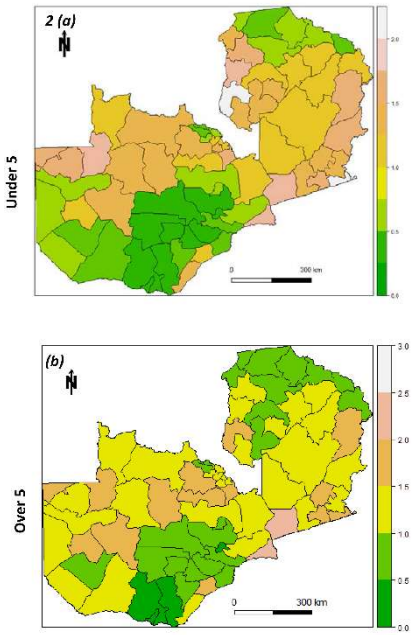



Figure 5.2: Mean malaria incidence risk surface, and individual district trends

Figure 5.2 and Figure 5.*2 (a) & (b)* shows the mean malaria incidence risk in maps among <5 and ≥5s. Individual district Temporal distribution of malaria incidence among <5 children had fewer districts with increasing malaria incidence rate among Zambia's 72 districts from 2000 to 2016 than among people aged ≥5 years.

The study then fitted generalised linear mixed models of Negative Binomial (NB) (2) using quadratic increases in variance with the mean (Brooks et al., 2017; Hardin, Hardin, Hilbe, & Hilbe, 2007). With district as the fixed effects parameter, the results accounted for dependence through random or fixed effect interaction parameters.

Table 5.1: Correlation coefficients and significance testing using negative binomial regression

| Variable | Incidence in under 5s | Incidence in over 5s | Incidence in all ages |
|---|---|---|---|
| LLIN | -0.08 (-0.1 , -0.06)*** | 0.03 (0.01 , 0.06)** | -0.02 (-0.04 , 0)* |
| IRS | -0.08 (-0.11 , -0.05)*** | -0.01 (-0.03 , 0.02) | -0.04 (-0.07 , -0.02)** |
| Minimum Temperature | 0.09 (0.06, 0.12)*** | 0.08 (0.05 , 0.11)*** | 0.08 (0.05 , 0.11)*** |
| Maximum Temperature | -0.11 (-0.15 , -0.07)*** | -0.25 (-0.29 , -0.21)*** | -0.17 (-0.21 , -0.14)*** |
| DTR | -0.12 (-0.16 , -0.08)*** | -0.19 (-0.23 , -0.16)*** | -0.15 (-0.15 , -0.19*** |
| Population Density | -0.25 (-0.38 , -0.12)*** | -0.35 (-0.43 , -0.26)*** | -0.32 (-0.43 , -0.22)*** |
| Elevation | -0.08 (-0.22 , 0.05) | -0.1 (-0.23 , 0.04) | -0.1 (-0.23 , 0.03) |
| NDVI | 0.2 (0.17 , 0.24)*** | 0.16 (0.13 , 0.2)*** | 0.19 (0.16 , 0.23)*** |
| Mean Rainfall (mm) | -0.04 (-0.07 , -0.01)* | -0.09 (-0.12 , -0.06)*** | -0.07 (-0.1 , -0.04)*** |
| Maximum Rainfall (mm | -0.01 (-0.04 , 0.01) | 0.03 (0.01 , 0.06)** | 0.01 (-0.01 , 0.03) |
| Latitude | 0.03 (-0.04 , 0.09) | 0.01 (-0.05 , 0.08) | 0.03 (-0.03 , 0.09) |
| Longitude | 0.01 (-0.03 , 0.06) | -0.03 (-0.08 , 0.01) | -0.01 (-0.06 , 0.03) |

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 5.1 summarises the results from the NB GLMM and the autoregressive (AR) GLMM models. The results show that the interventions (LLIN and IRS) have a more substantial effect on incidence for the <5 than the ≥5s. LLINs had a weak negative correlation (95%: -0·08 – -0.05) among the <5s but a weakly positive correlation (95%: 0·01-0·06) in the older age group.

IRS had a similar effect in the <5s, while the association was not significant in the older age group. Population density had the highest significant correlation coefficients across both age groups (-0.25 in <5s and -0.35 in ≥5s). In contrast, elevation, district latitude, and longitude (of population-weighted centroids – *see Appendix C-[methods and Figure 5.S4]*) all had weak non-significant correlation coefficients. NDVI generally showed a strong significant positive correlation across both age groups (*see* Figure 5.3 & *Figure 5.S5* for detailed summaries of regression slopes).

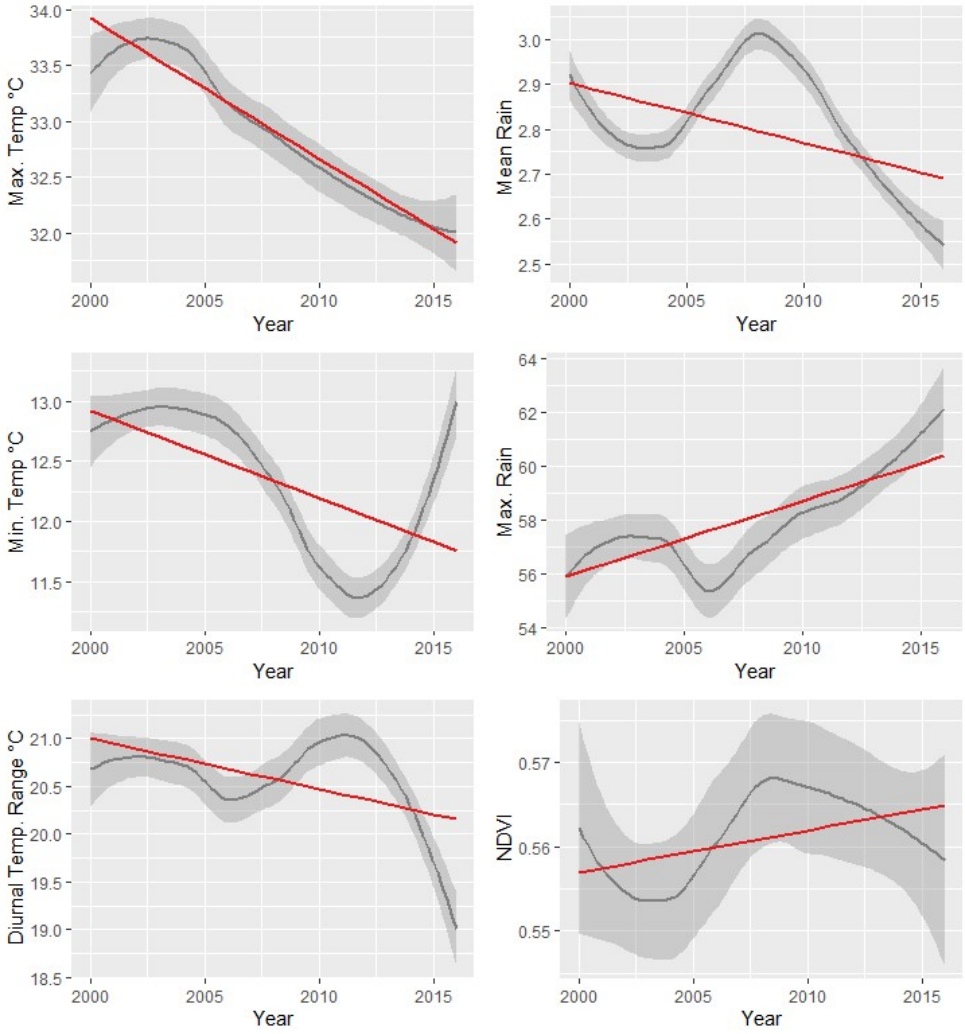
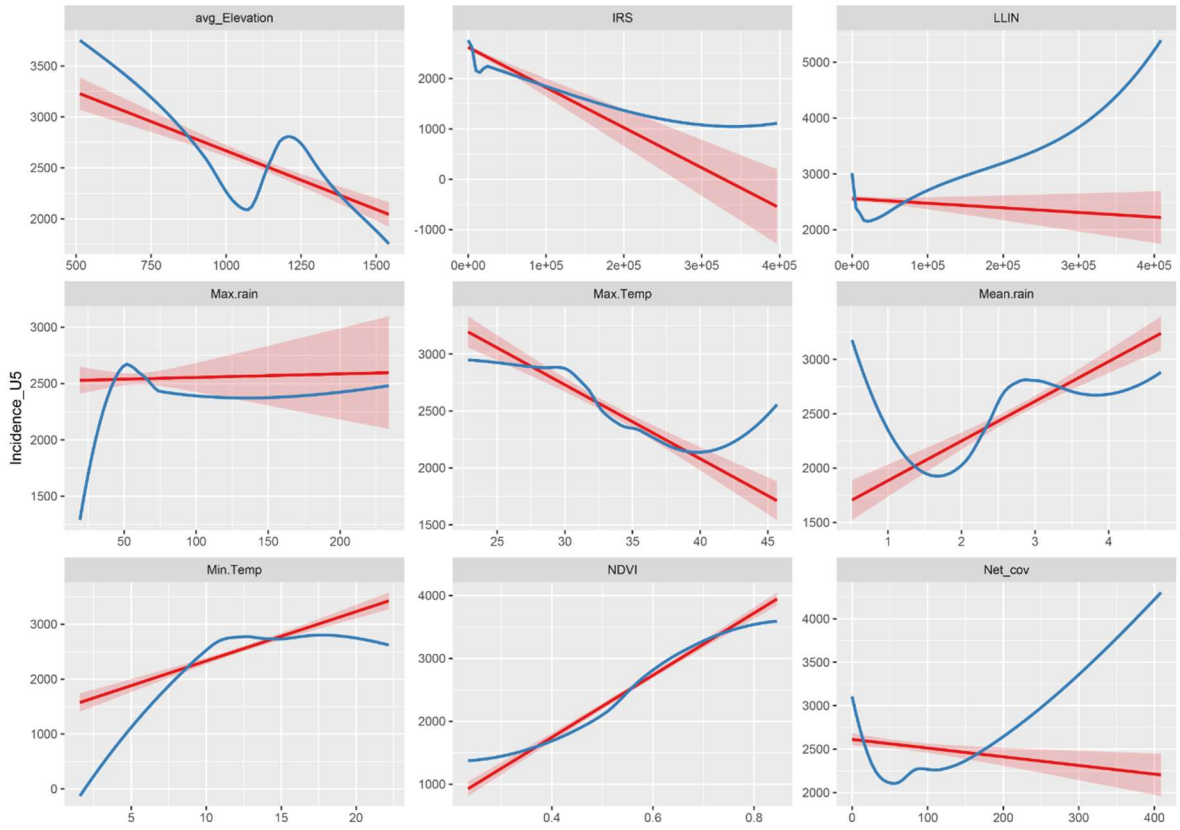



Figure 5.3: Summaries of overall temporal trends of environmental variables from 2000 – 2016 using LOWESS model

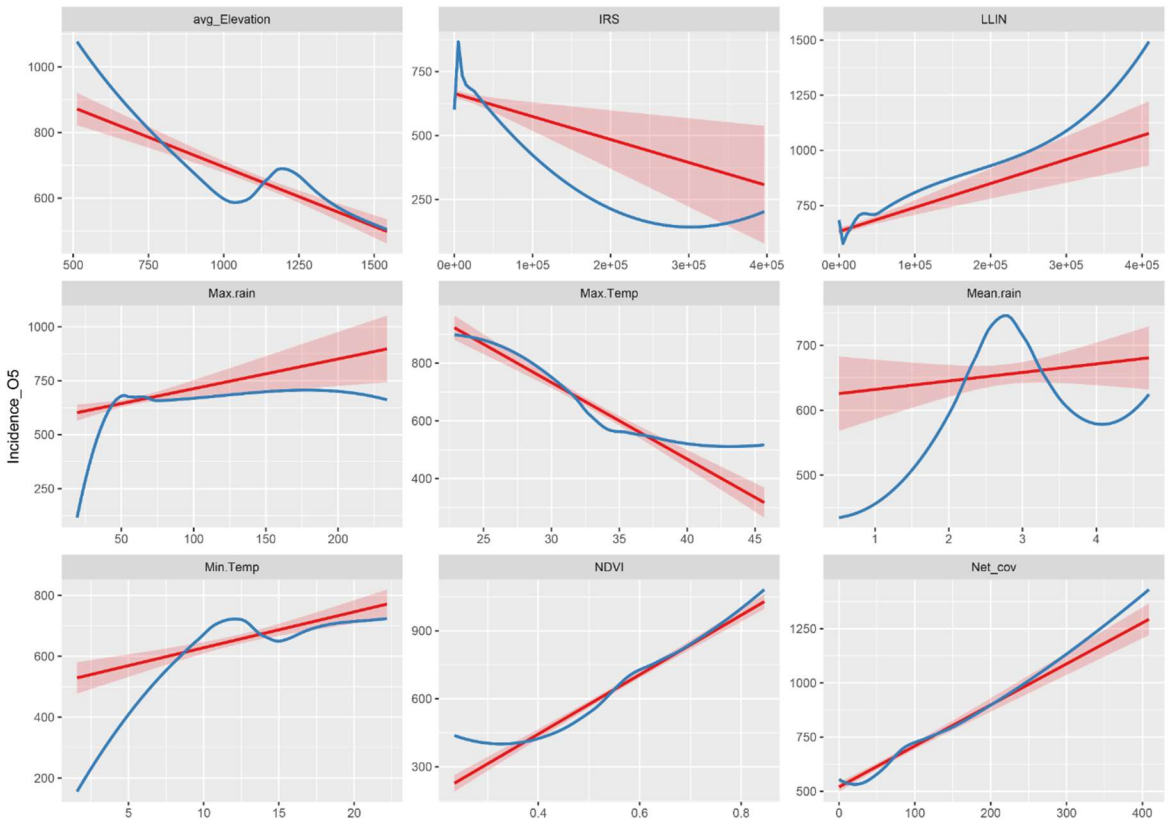
Having excluded mean temperature due to multicollinearity, only minimum and maximum temperature or DTR in the models were used. The maximum temperature showed a significant negative correlation (95%: -0·21 – -0·14) to malaria prevalence across both age categories, whereas minimum temperature had a significant positive (95%: 0·05 – 0·11) correlation. Similarly, DTR had even more definite significant negative (95%: -0·19 – -0·11) coefficients in all ages (95%: -0·12 and -0·19 among <5s and ≥5s respectively).

Figure 5.4: Regression slopes of the relationship between malaria, environmental and interventions by age. *The Red line is a regression line, and the red shading represent P.values, while the Blue line is the mean distribution of data.*

**(a)**




**(b)**



Finally, mean rainfall was negatively correlated (95%: -0·1 - -0·04) to malaria prevalence across both age categories while maximum rainfall was positively correlated, but was only significant (95%: 0·01 – 0·06) in the older age group (see Table 5.1 and Figure 5.4(a) & 4(b)).

### 5.3.2 Impact of Climate, and importance of Interventions on current malaria distribution

Although, only mean rainfall showed a significant (95%) declining trend, temperature trends show declines in maximum (adjusted $R^2 = 0{\cdot}025$) and minimum temperature ($R^2 = 0{\cdot}011$). The observed trend changes in malaria along with those of temperature coincide with a switch and scale-up in nation-wide intervention programmes between 2008 and 2010, making it difficult to evaluate the specific effects of either environmental changes or interventions on changing rates in malaria.

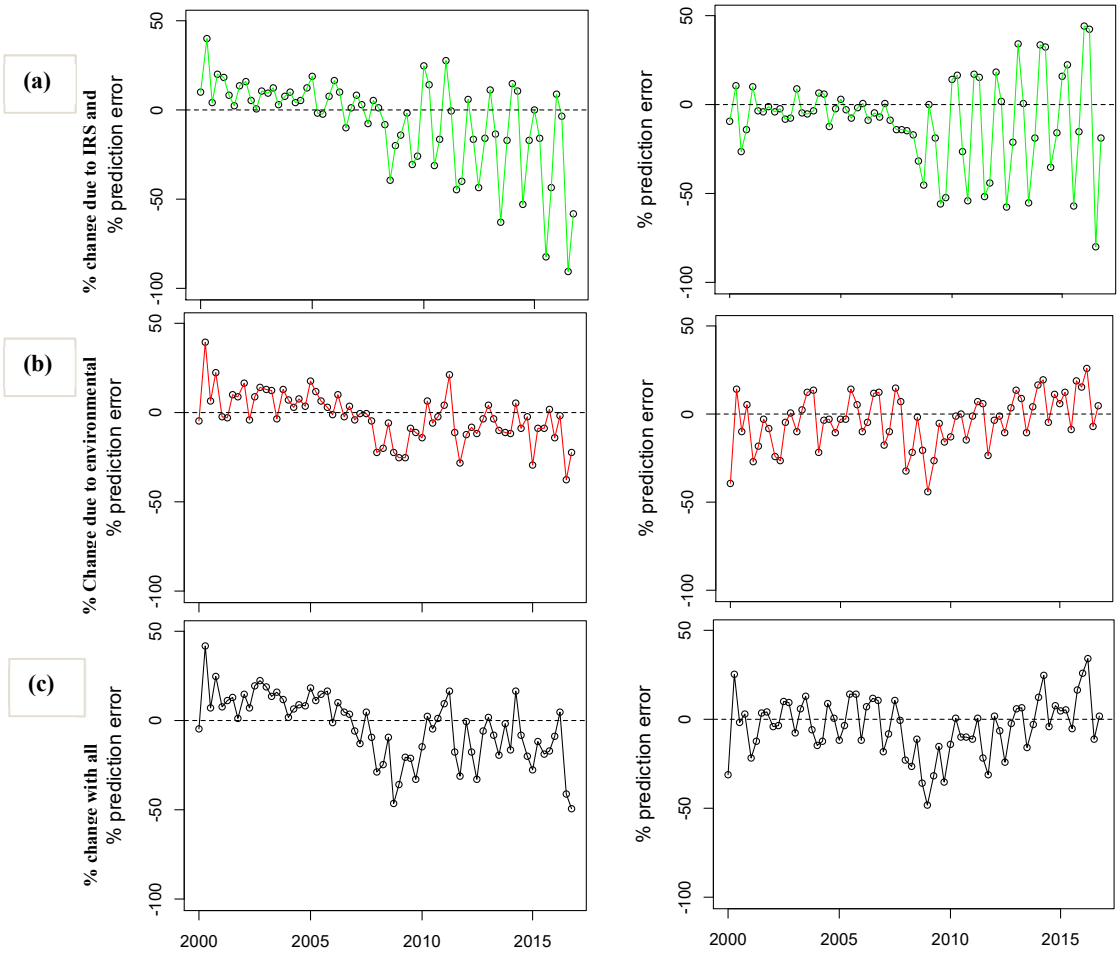



Figure 5.5: Percentage model prediction error by scenario

In order to address this problem, further modelling and visualisation of the effects of isolated climatic variables on malaria transmission were done by fitting Bayesian models to compare predicted versus actual incidence rates while controlling for interventions and vice versa.

For both age-groups, the results show that environmental variables had a better model prediction accuracy (Figure 5.5(*a-f*) and Figure 5.S3) and were better predictors exhibiting a more substantial influence on malaria transmission. The study also reports that environmental variables had better prediction accuracy in the ≥5 age group than in <5s, while models from interventions made better predictions in the <5 malaria rates (Figure 5.S5 *(a-f)* and Figure 5.*S3*).

Although this effect was subtle between the period 2000 and 2006, from 2008 onwards, however, environmental variables are highly influential, with consistent prediction accuracy compared to interventions for the same period. The years 2007 and 2014 were characterised by a significant scale-up in nets (Figure 5.S7 using a 30% attrition rate (A. Kilian et al., 2011; Pulkki-Brännström, Wolff, Brännström, & Skordis-Worrall, 2012; Tan et al., 2016)) and may be associated with a significant decline in <5 malaria prevalence in successive years.

In summary, modelling of predicted malaria cases using environmental variables and holding LLIN & IRS constant showed a much higher positive impact than when the environment is held constant. However, as indicated earlier, environmental effects on post-2006 intervention predictions have lower variance and mostly high off-season prevalence and low peak-season prevalence (Figure 5.S6).

Predicted values from all variables combined were similar to observed malaria while predicted values using only environmental variables were more accurate than those modelled from interventions alone. Environmental variables had more influence on prevalence than interventions, and their respective models also had relatively lower prediction accuracy and better comparative model performance using Deviance information criterion (DIC), Watanabe-Akaike information criteria (WAIC) and the loglikelihood (Figure 5.S3). While the temporal trends of temperature were not statistically significant in themselves, they did suggest that changes in intra-periodic variability of temperature range might well be an essential factor.

## 5.4 Discussion

The results presented in Figures 5.1, 5.2 and 5.S3, despite discordances in trends between mortality and incidence, form the backdrop for Zambia's current malaria policy agenda. However, the policy does not include any age-specific guidelines, apart from the World Health Organisation recommendations for LLINs and intermittent preventive therapy for infants (IPTi) and pregnancy (IPTp), coupled with effective treatment of malaria infections following prompt diagnosis (World Health Organization, 2018c).

The corresponding reported change in overall prevalence rates with a significant rise in minimum temperature post-2010, and an observed decline in maximum temperature, confirm the significance of the relationship between temperature and malaria. It was found that an increase in minimum temperature causes a subsequent rise in malaria, as does a decline in maximum temperature. This validates the observed trends in malaria; especially post 2010, where significant environmental changes tend to favour a more suitable transmission range (Figures 5.3, 5.4a, & 5.4b). The increasing minimum temperatures towards less extreme lows are favourable for higher malaria transmission, as is a narrowing DTR. These reported changes are further supported by the decline in the DTR in many districts and increasing malaria prevalence trends in both age-groups, similar to those found elsewhere (Bennett et al., 2016).

DTR had a stronger independent association with the ≥5s age group (-0·19) than the <5s (-0·12), both being statistically significant (95%). The decline in maximum temperature and the corresponding increase in minimum temperature result in the observed decline in the DTR. The result is a move towards longer malaria transmission seasons and shorter malaria off-peak seasons. It may also result in an all-year-round transmission cycle in some areas. The observations here support the conclusion that ≥5s have a stronger significant association of increasing malaria incidence and risk with DTR and a higher environmental risk exposure than children <5 years old. The findings support the call for further malaria stratification among the ≥5 age groups as shown in other study findings of malaria mortality (Dondorp et al., 2008) and incidence (Gerardin, Ouédraogo, McCarthy, Eckhoff, & Wenger, 2015; Griffin et al., 2014).

Taking age into perspective might imply that few people among the ≥5s are actively using the LLINs. It was also clearly shown that IRS was more effective than LLINs among the ≥5s. Factors affecting this may include higher adult exposure to vector mosquitoes especially during extended working hours (i.e. economic influences), and spending evening times (peak biting hours) outdoors (i.e. social factors) compared to younger children. High LLIN misuse predominantly by fishing communities (Baume, Reithinger, & Woldehanna, 2009; Brieger, 2017; Eisele, Thwing, & Keating, 2011; Minakawa, Dida, Sonye, Futami, & Kaneko, 2008), high resistance of mosquitoes to pyrethroids (Chanda et al., 2011; Loewenberg, 2018; Manyando, 2016), low exposure to IRS due to targeted coverage and low LLIN usage thresholds despite high ownership (Brieger, 2017) especially among poor households have all been reported to undermine the expected protective effects of LLINs. Such information, where available, and in association with appropriate monitoring of environmental factors, may further help to understand the source of limited intervention effectiveness in different parts of the country.

The decrease in the <5 prevalence rates may be an indication that more comprehensive and effective implementation of interventions is needed in this target population. The converse might also in part explain the malaria increase among ≥5s, whereby culturally at the household-level, priority and effort is given to the implementation of intervention measures among the <5s and pregnant mothers relative to the ≥5s. Hence, an observed delay in disease onset from initially protected <5s leads to more disease episodes happening later in older ages when culturally and practically they become a lower priority. Such challenges undermine the expected positive effects of interventions from materialising in the older age group. Consequently, an intensified communications and education intervention strategy for behaviour change that targets a more active and aggressive uptake of interventions among the ≥5s is urgently required.

As malaria transmission intensity and prevalence are still at least five times higher in the <5s than the ≥5s, careful consideration must be taken to monitor the transmission dynamics among the ≥5s, taking account of region-specific socio-economic and cultural nuances. If left unchecked, the rate of transmission increase observed during the study period could soon outweigh that of the <5s. Should this happen, it would

have significant direct economic and social impacts on local communities, where the economically productive population would directly carry the burden.

Other studies reported small-scale movement patterns during peak biting hours, frequently among <18-year-olds (Hast, Searle, Chaponda, Lupiya, Lubinda, Kobayashi, et al., 2019), and higher RDT positivity odds (8·8) among 5-17-year-olds (Hast, Chaponda, Muleba, Kabuya, Lupiya, Kobayashi, et al., 2019; Pinchoff et al., 2016), as inferred effects of delayed malaria onset. It can be concluded that the ≥5s are often highly exposed to environmental risk through everyday activities to and from high-risk environments. This is especially true for those engaged in fishing, farming or the school age-group who spend most of the time in risky areas outdoors (Hast, Searle, Chaponda, Lupiya, Lubinda, Kobayashi, et al., 2019; Pinchoff et al., 2016) and are less likely to sleep under bed nets that are prioritised for children <5 years old.

These results strongly suggest the need for more granulated disaggregation of age groups in the routine collection, analysis and reporting of malaria data. The introduction of data reporting protocols in 5-17 and ≥18-year-olds would capture the 40% school-going population, and the more economically active population, respectively. School-based interventions show great potential in the reduction of anaemia, and the risk of *Plasmodium* infections, and as such are a potentially cheaper alternatives for addressing the high malaria burden among schoolchildren (Ayi et al., 2010; Clarke et al., 2017; Maccario et al., 2017; Staedke et al., 2018).

The study has shown that climate change has, to a considerable extent, offset the impact and the expected effectiveness of interventions. This trend is likely to continue with the consequence of increasing the minimum scale and cost of interventions needed to achieve an adequate observable reduction in malaria incidence rates. Climate variables, particularly temperature, are becoming increasingly more suitable for malaria transmission in many areas, and can broadly explain the observed high and increasing malaria transmission rates in parts of Zambia.

While the analyses show that intervention measures like IRS and LLINs have not fully offset negative environmental influences, it is noted that, if adequately applied, they still offer considerable potential for optimisation of their impact where resistance is contained (Chanda, Chanda, et al., 2013), and high ITN use is encouraged. Thus, climate change has a significant effect on malaria prevalence, and the older population

age groups are more affected because intervention measures are better implemented and applied amongst the <5 age group.

This study has, among other limitations, the nature of the data used to measure the intervention effect. Although such data is often widely used for similar purposes, it introduces errors outside of the researcher's control. District use of the availability or distribution of bednets as a measure for implementation has associated errors, for example, even using the rate of two people per net may not fully capture or accurately measure the effective use of these interventions. This is because though often used as a proxy for bednet coverage, successful distribution or implementation of bednet interventions does not always translate into true usage patterns within each district. The inability to measure within district supply patterns and the lack of verified/confirmed bednet use (other than as reported) may have subtle underlying influences in the capturing of the true effects from interventions among the populations within districts and subsequently on the associations with environmental variables on malaria incidence found in this study.

Nonetheless, this study has captured the fundamental and underlying transmission dynamics between the two age groups and explained malaria prevalence in Zambia's decade of success in reducing mortality. This information can help intervention program strategies to focus on and take advantage of periods of less suitable temperatures and rains by driving malaria rates down to unrecoverable levels using such tools as mass drug administrations.

## 5.5 Conclusion

The study established that although <5 children remain at a higher risk of malaria, those aged ≥5 years have a consistently increasing risk, more so than previously thought and which, if ignored, could soon be a significant problem for Zambia and other similar southern African countries. The results corroborate those of earlier studies on the <5s (Bennett et al., 2016) but highlight that people aged ≥5 years are being affected by climate change-driven transmission. The findings also augment the information and evidence base that could help to understand better the drivers behind the current spatial and temporal trends in malaria prevalence in Zambia.

It is evident that even short-term environmental change plays a crucial role in high malaria transmission and must be considered when planning and implementing intervention programmes, especially for elimination purposes in low transmission contexts. The study has shown that the influence of climate change on malaria at the sub-national level is real and must be an essential part of appropriate preparedness and remedial action against the disease in tandem with direct remedial environmental interventions. Finally, it should be noted that although climate change constitutes only some of the numerous influencing factors, it should not be treated as the sole or primary factor in malaria transmission (Chaves & Koenraadt, 2010; Molyneux, 2014). Similarly, uncertainty regarding the magnitude of climatic impacts on malaria should not be a reason for neglect either!

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# CHAPTER SIX

## Health Facility Spatio-temporal modelling of malaria incidence and risk in Zambia, 2009-2015

This chapter is based on a manuscript to be submitted for consideration *Nature Communications Journal.* This chapter relates to objectives number four

# Abstract

The considerable spatial and temporal variability inherent in malaria transmission within countries means that targeted implementation of malaria elimination interventions at subnational levels is a practical necessity. Identifying the spatio-temporal rates, risks and trends at different administrative geographies within malaria-endemic countries is crucial for the development and introduction of cost-effective, subnational elimination and control intervention strategies.

To date, there have been very few fine-scale nationwide studies of malaria at the base operational health facility level. The study used Bayesian trend and spatio-temporal Integrated Laplace Approximation (INLA) models to analyse over 32 million reported malaria cases from 1743 health facilities in Zambia between 2009 and 2015. The results show that there was an overall increasing average trend in national malaria incidence over the period. There was a clear north to south continuum of spatial transitioning from areas of increasing malaria to areas of decreasing malaria. Over 47% of health facilities (incorporating 4.8 million people) have an increasing trend of malaria, while 26% (incorporating 5.1 million people) have a decreasing trend (95% credible interval).

Optimised hotspot detection methods identified significant high-risk hotspots (95% CI) along the borders with the Democratic Republic of Congo and Mozambique prompting a recommendation for countries like Zambia to instigate urgent, bilateral cross-border malaria initiatives with neighbouring high endemic countries. A comparison of health facility and higher-level district trends identified significant sub-district level variations in trends. It supports the recommendation for an adaptive scaling approach in the implementation of both malaria monitoring and interventions for control and elimination strategies.



**Keywords**: Malaria elimination, Control, Health facility, Stratification, Hotspot

## 6.1 Introduction

Malaria remains one of the leading causes of death in children and pregnant women in sub-Saharan Africa (World Health Organization, 2019c). With global progress in reducing incidence rates now levelling off, malaria is generally on the rise, especially in some high-burden African countries. The current pressures of funding demand that available, often limited resources, be more effectively directed at targeting those areas and populations where the most significant impact can be achieved (Espié et al., 2015; Korenromp et al., 2016; Winskill, Walker, Cibulskis, & Ghani, 2019).

With considerable spatial and temporal variability generally inherent in malaria transmission within endemic countries (Bousema et al., 2012; Ihantamalala et al., 2018), targeted implementation of interventions is a practical necessity (Winskill et al., 2019). It also highlights the importance of pursuing strategies that are suitable for malaria elimination in both low-moderate and high transmission settings. The process of choosing the most appropriate strategy comes with many challenging and complex issues and decisions such as *timing* (when to embark on malaria elimination); *strategy* or *tools* (which malaria interventions to implement); *stratification* (where to apply them); and *application* or *implementation thresholds* (what intensities to use for each).

This is especially true for those countries approaching the pre-elimination and elimination stages in their fight against malaria. Targeted interventions, particularly in elimination settings, aim to interrupt local transmission as it becomes increasingly concentrated in small areas that are often very hard and costly to reach (Shretta et al., 2017). Understanding the fine-scale spatio-temporal dynamics of prevailing malaria epidemiology is imperative to facilitate and successfully target those remaining residual reservoirs and infection hotspots (Bousema et al., 2012, 2013).

Zambia is one of those countries concurrently pursuing intensified control strategies as well as pre-elimination and elimination strategies at the district level. This approach has been gaining momentum since 2007 (Nájera et al., 2011; Rabinovich et al., 2017) following the recommendation to use a malaria continuum measure rather than specifically targeted milestones to monitor progress (Rabinovich et al., 2017). In this context, pursuing malaria control or elimination at subnational scales was designed to aid strategic targeting and the delivery of suitable malaria intervention strategies and resources for different transmission intensities. In the all-important elimination phases, this would mean identifying and targeting the hardest to reach hotspots of malaria.

This paper investigated the spatially structured temporal trends that characterise fine-scale malaria burden in Zambia as a means of providing the relevant operational-level evidence base required by decision-makers, public health officers, policy practitioners and disease surveillance experts. The overall aim is to generate the information needed to help countries attain better cost-effectiveness, foster improved policy integration and sustain the levels of progress already achieved in their fight against malaria. For example, the findings will help improve the geo-spatial stratification of risk in small areas for better targeting and improved efficiency in the allocation of health service resources and malaria intervention planning.

## 6.2 Methodology

### 6.2.1 Health Facility data

Monthly reported malaria case data for 2531 health facilities was obtained from the Zambian District Health Information System (DHIS2)/ Health Management Information System (HMIS) for the years 2009-2016. Of the total, 398 (15.7%) of health facilities reported zero malaria cases for the period and were excluded. Another 214 (8.4%) facilities were excluded because they only had data for a single year (2016) meaning they were either newly constructed facilities and/or not fully operational during the whole of the study period.

A further 76 facilities, randomly spread across the country, were excluded from the analysis because they had no recorded baseline population information to use as a denominator in calculating incidence rates and standardised risk ratios. The reported malaria case data for these health facilities accounted for 0.8% of all recorded cases over the study period. After separating 100 hospitals from the dataset, the remaining 1743 facilities comprised the complete dataset analysed (Figure 6.1) (*and see Appendix D*). The final working dataset includes 1743 monthly health facility reports, comprising at least 146, 000 observations, and capturing over 32 million cases over seven years (2009 - 2015).

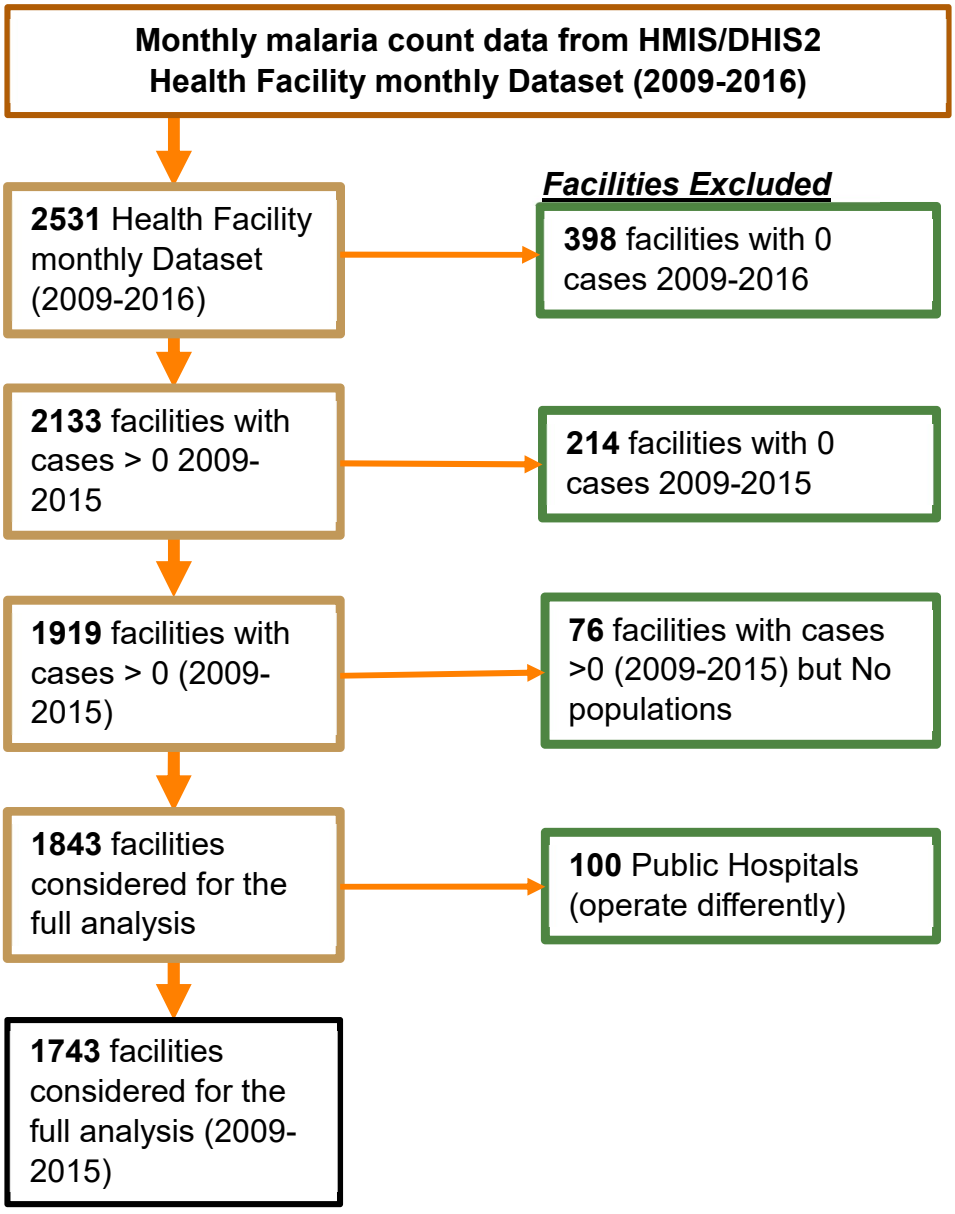


Figure 6.1: Summary Schema of final facility-level analysis

### 6.2.2 Spatiotemporal models and hotspot analysis

The study implemented a Bayesian trend model, and a spatio-temporal Integrated Laplace Approximation (INLA) model to analyse spatio-temporal trends over the seven-year study period. INLA is a deterministic approach of algorithms by Rue *et al.* (2009), designed for inference in a Bayesian environment, centred on integrated nested Laplace approximations. It is considered a flexible subclass of structured additive regression models, intended for latent Gaussian models (Bakka et al., 2018). INLA benefits from the speed of its computation, thereby allowing for Bayesian inference separate from the complex Markov Chain Monte Carlo (MCMC) algorithms.

The study used the Integrated Laplace Approximation (R-INLA) package approximation strategy (Rue et al., 2009), as implemented in the R program (R Core Team, 2013). And given the extensive number of observations in the dataset (over 145 000), the *simplified Laplace approximation,* because it is relatively less computationally intensive than the full Laplace and generally compensates for a slight loss in accuracy (Rue et al., 2009). The study also leveraged computation power from the shiny *SSTCDapp* (Chang, Cheng, Allaire, Xie, & McPherson, 2017) to be able to run several comparative model fitting performance tests, so that it could determine and select the model with the best fit, using comparisons of deviance information criterion (DIC).

This study applied spatio-temporal models with prior distribution for the spatial random effect with a reparameterised modification (BYM2) (Riebler, Sørbye, Simpson, & Rue, 2016) of the Besag, York, and Mollié model (BYM) (Besag, York, & Mollié, 1991). The BYM2 model contains both an Intrinsic Conditional Auto-Regressive (ICAR) component and an ordinary random-effects component for spatial auto-correlation and non-spatial heterogeneity (Morris et al., 2019). The model allows all parameters to have clear reading and a straightforward selection of hyperpriors (Morris et al., 2019). The models were implemented with a random walk of order 2 (RW2) prior distribution for the random temporal effect and an unstructured temporal random effect. A space-time interaction of type (ii) random effect term was further added to account for both spatial and temporal autocorrelation.

The study computed a spatial neighbourhood matrix from an ESRI shapefile (ESRI, 1998) within which two health facilities were considered neighbours if they shared a common border. It then fitted health facility catchment areas made from Voronoi polygons to generate a unique geographic catchment area with an associated year ID for the temporal variable with RW2. This assumes that variables take periodic random steps away from previous values, using independently and identically distributed (iid) size steps. Finally, a Bayesian temporal model to detect specific malaria trends over the study period was implemented. ESRI's ArcGIS 10.6 was also utilised for the optimised hotspot analysis *(see Appendix D [methods]).*

## 6.3 Results

### 6.3.1 Spatio-temporal patterns of health facility level malaria rates and risk

There was an overall increase in the national average trend in malaria incidence at the health facility level between 2009 and 2014 with one slight yearly decrease in 2015

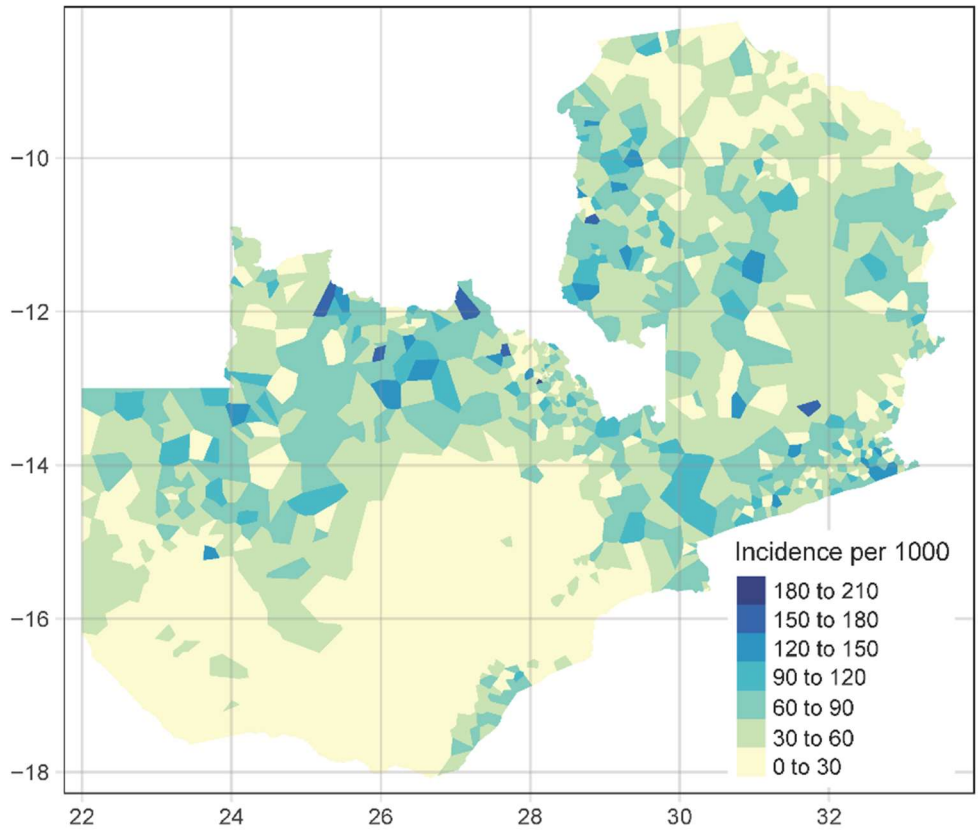


Figure 6.2: Mean crude malaria incidence rates 2009- 2015 (*Appendix D - Figure 6.S1)*.

Figure 6.2 shows the pattern of the mean geographical distribution of malaria incidence from 2009 – 2015 at the health facility level. Generally, the pattern mimics that of malaria risk presented in Figure 6.3, where large areas of low malaria incidence are observed in the southern parts of the country with progressively increasing incidence rates as one moves northwards.

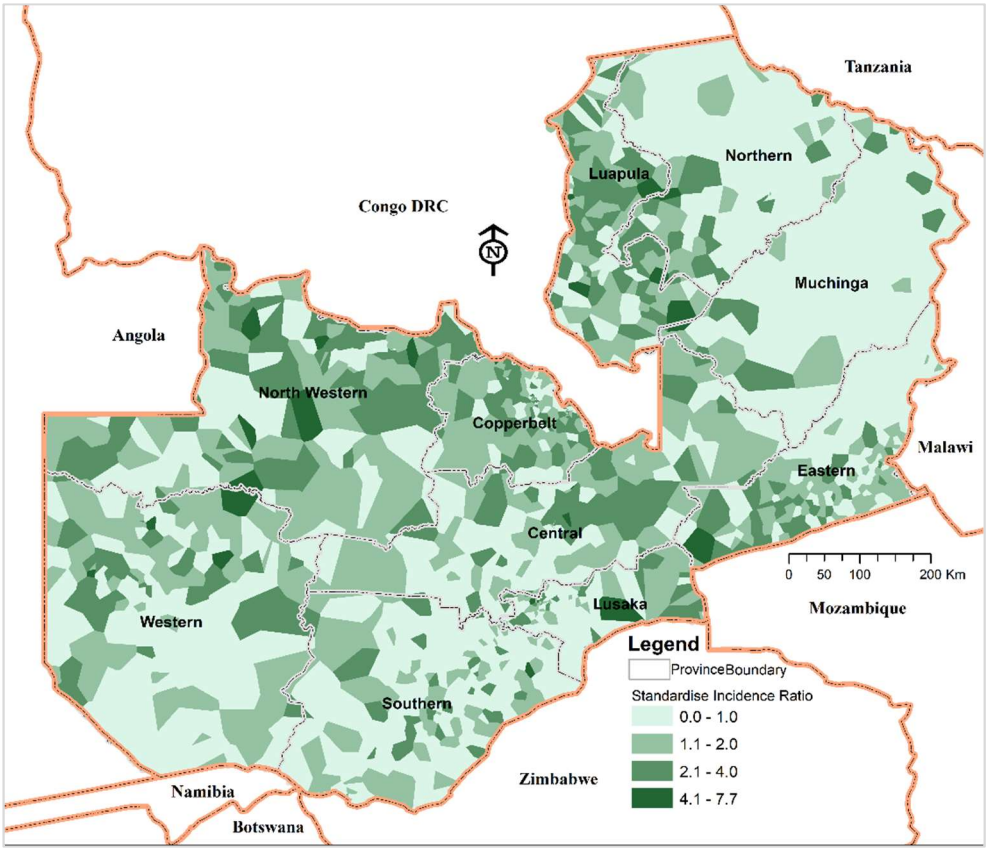


Figure 6.3: Standardised malaria incidence ratio (Risk)

High malaria risk is observed in the north-west parts of Zambia, mostly around the Luapula province, with the high-risk pattern extending almost continuously in a south-easterly direction towards the Mozambique border. This high-risk area generally follows the national boundary with the Democratic Republic of Congo (DRC), covering the three North-Western provinces of Luapula, Central and Copperbelt. Other noticeable high-risk health facilities are found further towards the south-east of Zambia along the Mozambique border.

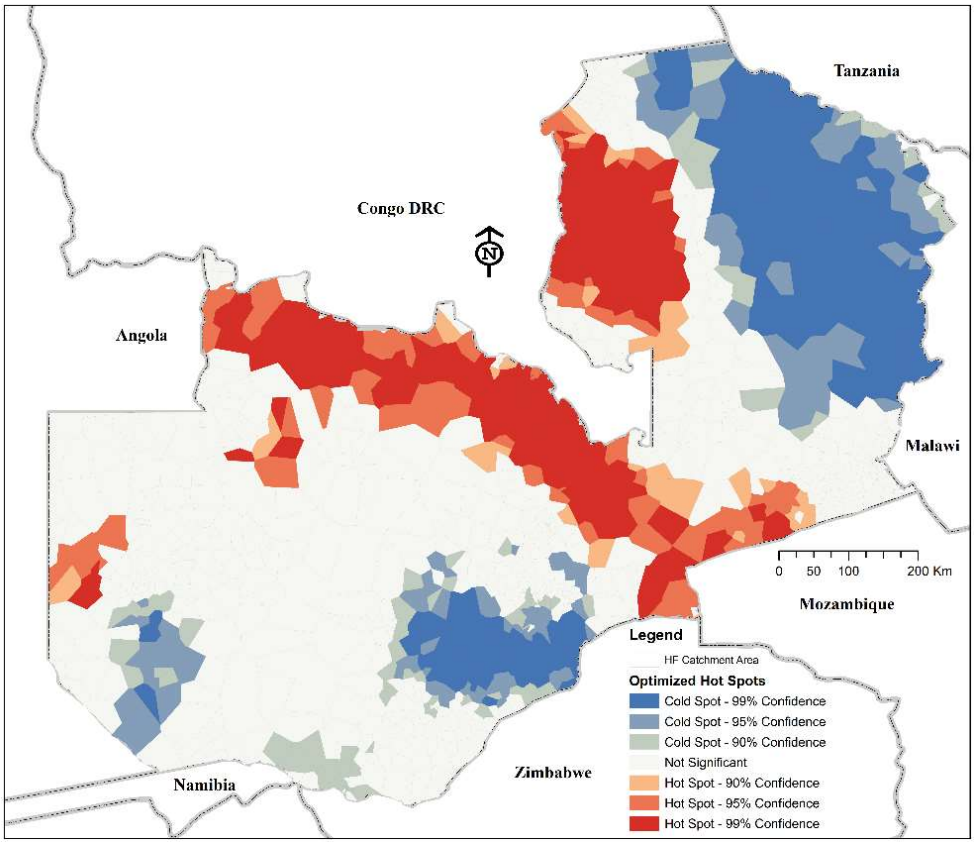


Figure 6.4: Significant malaria risk hot spots and cold spots

Using optimised hotspot detection methods, implemented in ArcGIS 10.6, it was observed that four statistically significant malaria high-risk hotspot regions comprising 578 (33%) health facilities and four low-risk cold spot regions comprising 484 (27%) health facilities (Figure 6.4. The two most significant hot spots areas follow Zambia–DRC and Zambia-Mozambique borders while the distinct low-risk cold spots are in the north-east and south-east of the country. Within both the hot and cold spot clusters, minimal variability was detected through outlier detection tests *(see Appendix D Figure 6.S2).*

The modelling of trends indicates that there is a strong spatial context to the stratification of areas from increasing to decreasing trends and vice versa (Figure 6.5). Generally, the southern parts of Zambia have a declining trend. These areas are adjacent to other parts of south-western Zambia with a mix of no significant trend (no change), partly declining, or increasing trends. In northern Zambia, many areas with no significant trend change in malaria tend to be continuous with areas of increasing trends. At the same time, there are very few areas with declining trends in this region.

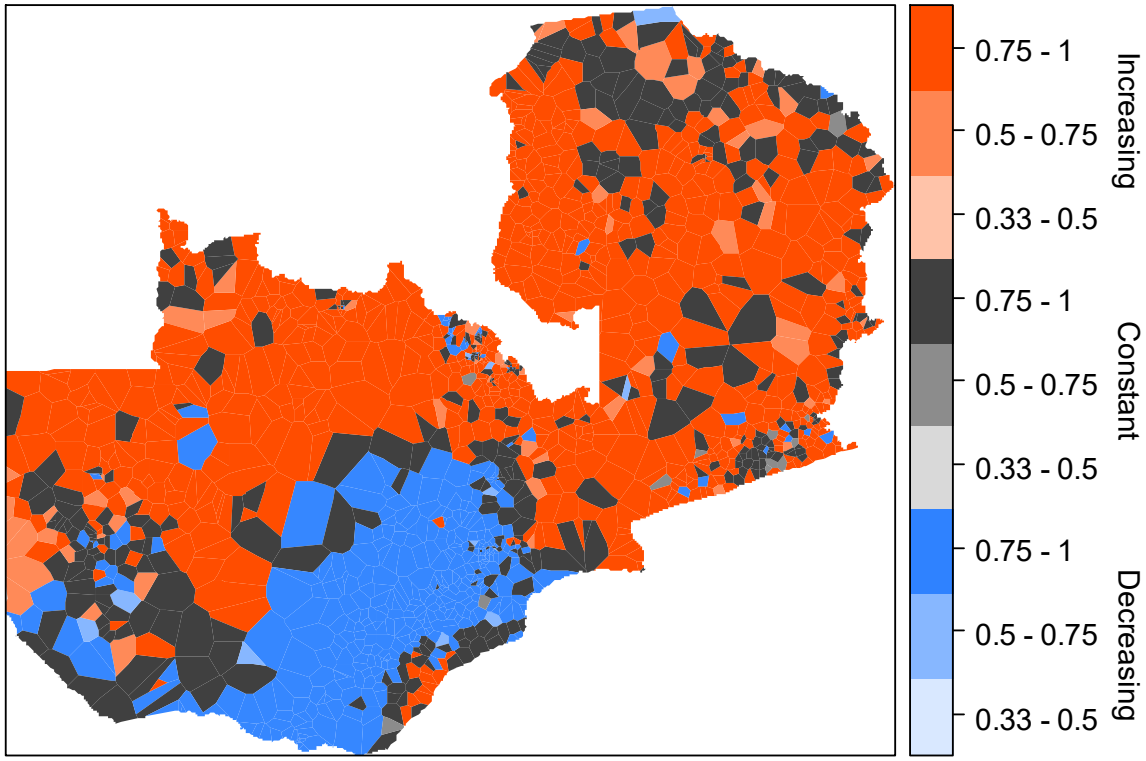


Figure 6.5: Health-facility-level malaria trends between 2009 and 2015

Detailed results from the model indicate that 27% of health facilities (469, incorporating 5.1 million people) had a significant average (linear) declining trend, 26% (448 incorporating 3.1 million people) had no significant trend change and 47% (826 incorporating 4.8 million people) had a significant average (linear) increasing trend (*see Appendix D - Table 6.S1 for significance levels*). Health Facilities with a decreasing trend were more likely to be located in urban areas (including the national capital, Lusaka) with much larger catchment populations compared to those with increasing trends which tended to be more rural with smaller populations (hence the differences in health facility percentages and population numbers).

The results from the R-INLA model using posterior means of incidence rates and posterior exceedance probabilities (greater than a threshold of 50 cases per 1000 population) show the spatial, temporal, and spatio-temporal patterns in the data. The value of 50 cases per 1000 population was used as it is the current threshold set by the Zambian national malaria elimination program whereby areas with a value below 50 are considered for malaria elimination interventions or, if above, for more intensified control interventions.

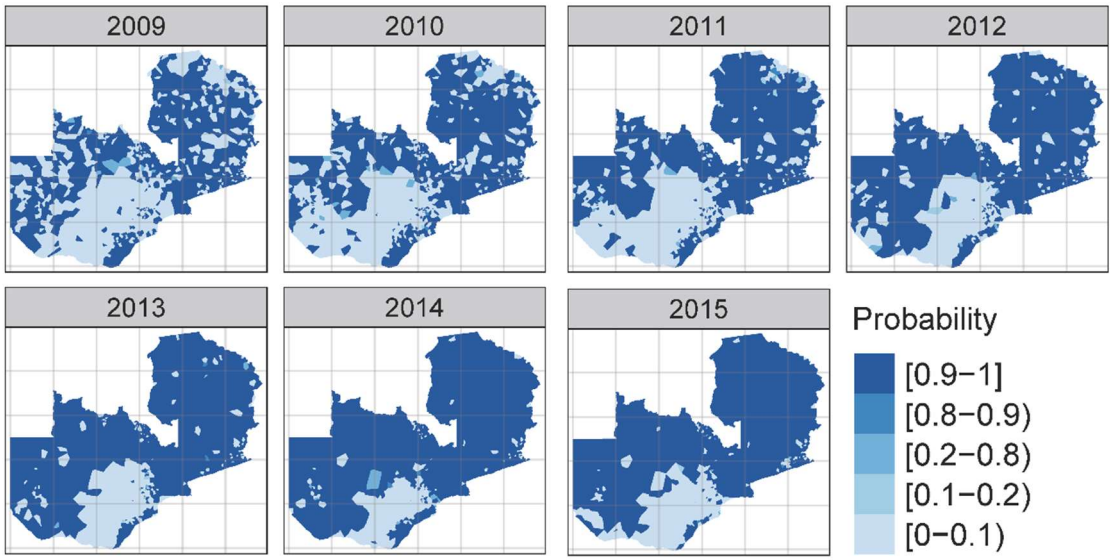


Figure 6.7: Posterior exceedance probabilities of threshold 50

The posterior exceedance probabilities are the likelihood that areas have a higher incidence than expected and, as seen in Figure 6.6, the higher than expected incidence rates occur predominantly in the northern regions, similar to the pattern of mean incidence rates presented in Figure 6.2. Of note, however, is the very distinct and continuous annual increase in the number of health facilities reporting higher than expected rates over the seven-year period with an equally distinct north-south spatial drift. All the results were statistically significant at 95% credible intervals.

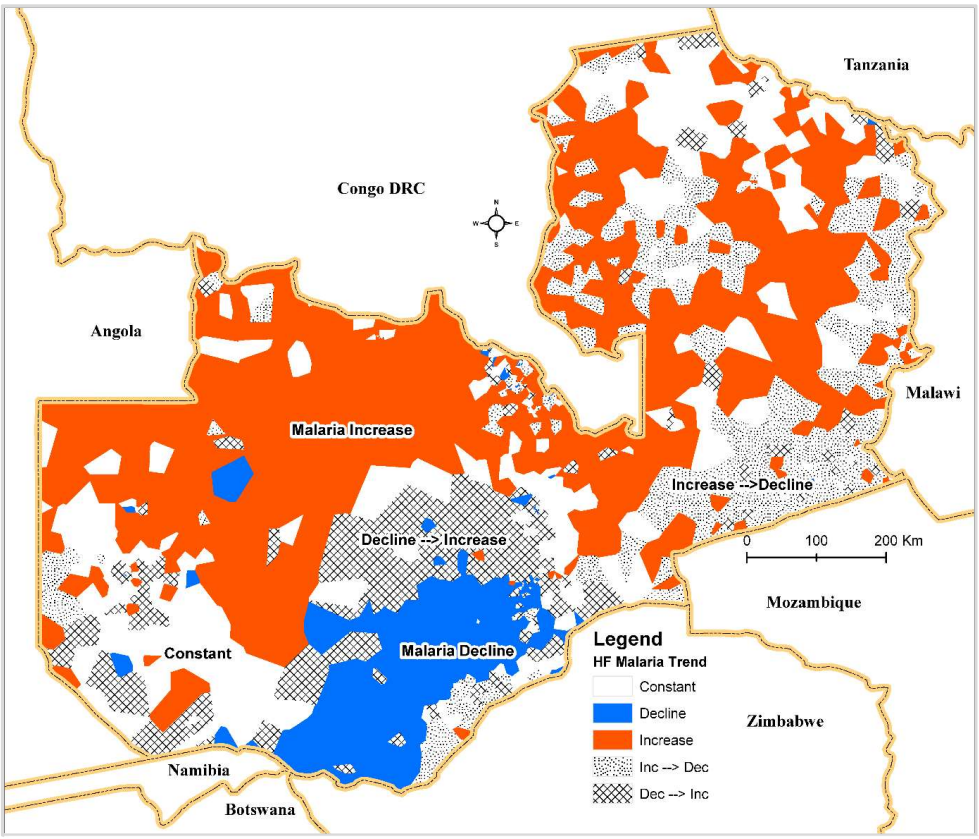


Figure 6.6: HF Malaria Incidence Trends between 2009 and 2015, 95% Credible Interval

The study further modelled and mapped (Figure 6.7) the seven-year trends using the year 2011as the baseline change point and applying a more detailed five class stratification *of continuous yearly Increase, continuous yearly Decrease, remained Constant, changed from an Increase to a Decrease, and moved from a Decrease to an Increase*.

The continuous yearly increasing trend category accounted for the highest proportion of health facilities (31%), followed by areas with a change from an increase to a decrease (19%). Those areas with a decreasing or constant trend each accounting for 18% of Health Facilities, while the proportion of areas moving from a decrease to an increase accounted for 12%. There was a clear continuum of spatial transitioning of regions from areas of declining malaria to areas of increasing malaria, for instance, in the southern province, where the concentration of areas with declining malaria (*blue*) is virtually encircled by areas whose trend was moving from declining to increasing (*hatched*). In Eastern Province and along the North-West border of the country, there is a distinct geographical clustering of areas transitioning from increasing trends to declining trends (*dots*) that are adjacent to substantial areas with increasing trends.

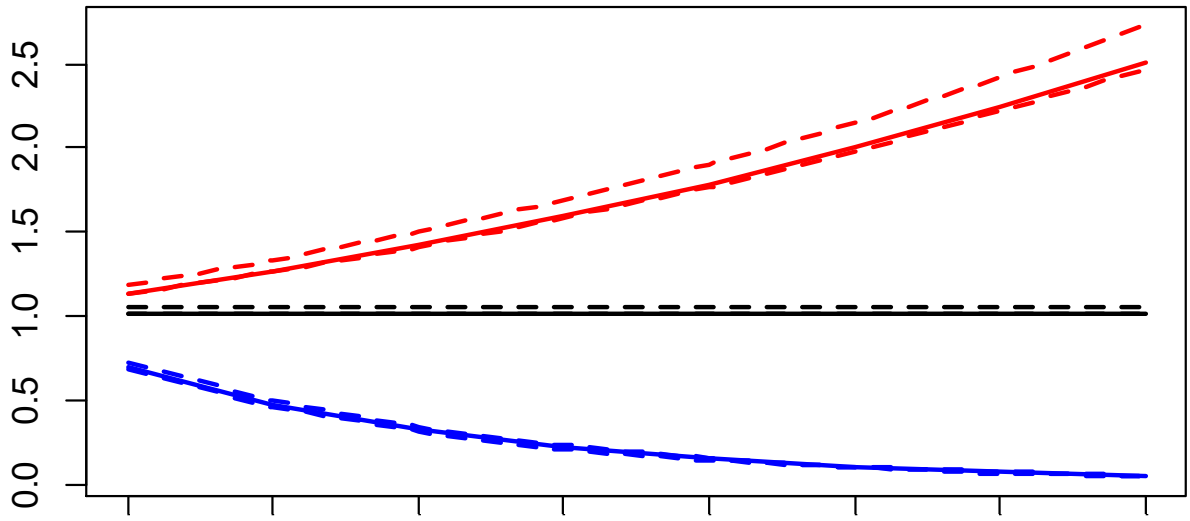


Figure 6.8: Overall rate of trend change

The rate of change between those health facilities that experience a declining trend and those with an increasing trend indicates that health facilities with increasing malaria have a much sharper rate of change (Figure 6.8).

**Comparison of Health Facility and District level trends**

The study compared the Health Facility level (Figure 6.5) results with those from the administrative district level *(Appendix D - Figure 6.S3)* to examine the influence of spatial

scale on malaria trends, and investigate the potential and relative value of each as an optimal operational scale level for malaria control and elimination efforts.

Table 6.1: Trend variation between District and HF level trend models

| Facility Trend | District Trend | # of facilities | % | Change |
|---|---|---|---|---|
| **Decline** | **Increase** | 10 | 0.6% | **1.4%** |
| **Increase** | **Decline** | 14 | 0.8% | |
| **Increase** | **Increase** | 524 | 30.1% | |
| **No change** | **No change** | 276 | 15.8% | **67.5%** |
| **Decline** | **Decline** | 377 | 21.6% | |
| **Decline** | **No change** | 58 | 3.3% | |
| **No change** | **Decline** | 82 | 4.7% | **31.1%** |
| **Increase** | **No change** | 272 | 15.6% | |
| **No change** | **Increase** | 130 | 7.5% | |

There was little cross-trend variation in malaria risk between the district and health facility-level. Table 6.1 shows that at least 67% of health facilities exhibited the same trend as that observed in the district in which it was located. Just over 15% of Health Facilities had an increasing trend where the associated district had no change. In comparison, only 1.4% (24/1743) of facilities had a trend difference from a decline to an increase or vice versa. There was a statistically significant ($p<0.001$) positive correlation (Kendall Tau_b = 0.66) between District-level trends and Health facility trends.

Using Zambia's 2015 district-level population estimates (Central Statistical Office, 2013), the proportion of the total population living in areas with different average trends showed that 37% (5.76 million) of people live in districts with declining malaria, 34% (5.2 million) live in districts with no trend change, and 29% (4.5 million) live in districts that had an increasing malaria trend.

At the Heath Facility level, where the recorded total population was 13.73 million compared to the district level total of 15.46 million, similar proportions of populations living in areas with a declining trend, 37% (5.1 million) were observed. There were differences in proportions of populations in facilities with no change and those that had an increasing trend with 28% (3.8 million) and 35% (4.8 million) respectively. The total

recorded health facility-level population was 10% lower than the estimated district level total.

## 6.4 Discussion

The countrywide micro-scale analysis of malaria at the Health Facility level shows that between 2009 and 2015 there has been a relative increase in Zambia's malaria incidence that is mostly being driven by a north-south transmission pattern very closely associated with proximity to the borders of neighbouring countries with high malaria rates.

The incidence and risk patterns show a strong cross border influence with the DRC and Mozambique, both of which have consistently presented with the second and fourth highest malaria incidence rates in the world (World Health Organization, 2013, 2014a, 2015f, 2016c, 2017b, 2018e) during 2011-2019. Similarly, the recent WHO world malaria report 2019 indicates that four of Zambia's adjoining neighbours together accounted for over 24% of global malaria mortality (DRC 11%, Tanzania 5%, Angola 4%, and Mozambique, 4%) (World Health Organization, 2019c).

These observations demonstrate how important it is for countries to actively pursue collaborative cross-border malaria initiatives with neighbouring high endemic countries. For Zambia, this will become even more essential as the country progresses its relatively short-term plans to eliminate malaria. While Zambia already has strong cross-border collaborations along its southern borders, funded through regional initiatives of the Elimination8 (Lover et al., 2017; The Global Fund, 2018), evidence of such bilateral initiatives with the DRC or Mozambique are as yet to be seen.

Despite cross-border meetings held in 2011, proper functioning or bilateral operational initiatives, are now long overdue if Zambia is to make significant headway with its control efforts in these border regions. As the E8 states, "a country will never achieve and sustain malaria elimination as long as transmission continues in neighbouring countries" (Elimination8 Secretariat, 2018). The fact remains that mosquitoes and malaria do not respect political boundaries, and consequently, eliminating malaria cannot be achieved and sustained by independent within-country initiatives alone.

The spatiotemporal analysis suggests there are geographically large and relatively stable hot and cold spot distributions of incidence rates across the country. In comparison with higher-level District trends, nearly 70% of all Health Facilities presented with the same trend pattern as the districts they were situated in which would initially tend to suggest

that pursuing intensive malaria control or elimination efforts at the sub-district (i.e. Health Facility) level may not yield additional benefits vis-à-vis the additional increase in logistical and operational costs.

On the other hand, the analysis of health facility level trends (Figure 6.7) revealed some very interesting patterns that are extremely relevant for the monitoring and planning of intervention strategies going forward. Firstly, the observed trends in the eastern region show a very distinct geographical clustering of areas that are transitioning from having increasing rates to decreasing rates. These areas tend to be contiguous with other areas that are continually increasing, and they are predominantly along the eastern border region of the country. This is significant as this region has received intensive intervention activity from the government as part of a deliberate, targeted intervention strategy since 2013. The results provide evidence that the strategy and programme are delivering tangible successful outcomes even in a relatively short period and in those areas where it is needed most.

Secondly, the patterns found in the southern part of the country showed that there is a significant cluster of areas with relatively low incidence rates that are transitioning in the opposite direction from a decreasing to an increasing trend. Similar to the eastern region, these areas are contiguous with areas that have a continuous declining rate. The results show that there is a substantial reduction in the number of areas where malaria is declining suggesting a deterioration in the general malaria situation that is not evident at the higher district level but is very obvious at the health facility level.

The implications of this are that some areas of decline, as measured at the sub-district level, may be changing but are not receiving adequate attention or appropriate levels of interventions and consequently are starting to regress and lose the gains made over the previous two decades. The findings also lead to the conclusion that in the southern region, a sub-district health facility level intervention strategy is urgently required to stop the changing trend from decreasing to increasing rates.

It was also found that 15% of all health facilities have an average increasing rate but are located in districts where the malaria trend has been constant over the last seven years. While those health facilities are not geographically clustered in any particular region of the country, they do show that sub-district targeting of resources, even in districts where malaria is generally constant could be beneficial.

Limitations in this study include those relating to the population denominators used to convert the counts of malaria into incidence rates. This is despite the fact that the populations used for calculating malaria incidence rates at health facility-level are official estimates from district census figures. These counts have accuracy issues that are driven by the data sources from which they were obtained. Hence, the clinical incidences values derived in the analysis may not fully reflect the actual incidences obtainable if such population denominators were truly accurate and highly reliable. It is, therefore, possible that some of the observed facility-level variations in clinical incidence may be explained by the use of inaccurate population denominators, thus causing under or overestimations. Nonetheless, the population denominators used in this study still represent the best available official dataset, used by the Ministry of Health.

Nonetheless, this study has shown that malaria trends vary depending on the scale level at which they are being measured and that adopting a single scale level approach (e.g. administrative districts in Zambia) for the monitoring and implementation of intervention strategies may not be as effective or efficient as a dual or multi-scale level approach (e.g. district and health facility level). The study would suggest that in general, higher district-level strategies may well be appropriate for those areas where incidence rates are high, and trends are increasing but that health facility level strategies may be more efficient and effective in areas with low rates and stable or decreasing trends.

The work of Bousema et al. supports the contention that areas with widespread malaria transition would benefit from high-level untargeted community-wide approaches (Bousema et al., 2013, 2016). Their findings and recommendations further support the proposal for an adaptive multi-scale approach to intervention planning. They showed that micro-scale targeting of interventions below the Health Facility level would not be most effective at the hotspot or 'nucleated' household level where spillover benefits into the surrounding local community are limited. This approach, however, would be suitable at the sub-health facility level in areas where rates are low, and trends are rising.

Those Health Facility areas where rates may be significantly different and higher than the average trend of their district could be the ones most suitable for targeted micro-scale hotspot interventions and strategies such as focal Mass Drug Administrations, or test and treat/step D community strategies (Kelly M. Searle et al., 2016).

## 6.5 Conclusion

It is strongly recommended that countries re-assess and carefully reconsider their malaria programmes and strategies (including monitoring) to accommodate for the dynamics of malaria incidence rates and trends at different operational scale levels. The nationwide analysis of health facility level trends in Zambia has identified that there are significant sub-district level variations in malaria trends that are positive in some regions in the east and negative in the south. The results demonstrate the value of establishing national-level monitoring and reporting of malaria incidence and trends contemporaneously at both the district and health facility levels.

The study has shown how such an approach can help governments identify those areas where the planning and operationalisation of intervention strategies are appropriate at the district level and where a sub-district approach is more appropriate. This has significant implications for resource efficiencies and savings through adaptive scaling and targeting of interventions where they are most needed. This means, not only targeting those areas with the highest rates and increasing trends but also including those areas where substantial gains have already been made, rates are low, but they are now in a negative transition phase and at risk.

Maintaining recent gains against malaria should be equally as important in countries like Zambia, where the aim is to extend the regions currently designated for malaria elimination. The study also highlights the importance of border effects on rates, trends and observed malaria burden (Pringle et al., 2019) in countries like Zambia. For endemic countries pursuing malaria elimination with neighbours that have a poorer epidemiological status, the study stressed the urgency for such countries to form meaningful bilateral cross-border malaria initiatives. In the case of Zambia, the DRC, Angola, and Mozambique are the immediate priorities.

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# CHAPTER SEVEN

## Overall Summary, Discussion, Conclusions and Recommendations

The agenda pursued by endemic malaria countries to move from high malaria burden to low malaria burden or from malaria control to malaria elimination is not straightforward. Many aspects of the fight against malaria are both complex and interlinked, and approaches need to be systematic and holistic. In this study, the aim was to investigate climate change and the past and present spatio-temporal dynamics on the malaria burden. This was investigated in relation to factors that could potentially stifle success (e.g. ecological and demographic) as well as those that could potentially help nations succeed (e.g. interventions) as they embark on programmes to achieve a malaria-free Southern Africa, as an extension of the E8 malaria elimination efforts.

## 7.1 The bigger picture perspective

Overall, this study aimed to investigate the spatial and temporal impacts of climate change on malaria transmission, control and elimination efforts in Zambia. In order to achieve this, several objectives were defined and subsequently formulated as stand-alone but related results chapters in the thesis. The first stage explored the past and current spatial and temporal epidemiology of malaria in Zambia by analysing 16 years of quarterly sub-national malaria incidence and mortality data using a novel approach of creating a composite measure of malaria burden incorporating: risk, rates and trends at the sub-national district level.

The results highlighted the need and importance of understanding observable spatial heterogeneities of malaria, despite the introduction of a uniform and generally universal policy of implementing malaria interventions within the country. The findings strongly emphasise the importance and value of applying robust mapping and spatial analytical techniques in providing valuable information that can support a more efficient, practical, and effective implementation of expensive intervention programmes. The results also identified some significant differences between the under 5 and over 5 age categories, and in particular, the somewhat counterintuitive trend of increasing malaria in the over fives where one might have expected to see gains in malaria immunity.

The findings from this first stage of analysis guided and formed the focus for the second and third stages. The second stage was an examination of the potential role that near-term climate change might play in explaining the observed differences in malaria trends at the district level. The findings clearly showed that near-term climate change, marked by a strong seasonal pattern, had impacted areas with either increasing or decreasing malaria incidence trends. The study also highlighted the importance of diurnal temperature range as the most significant environmental variable, something previous studies had neglected to examine or identify.

The third stage investigated the role of malaria interventions and changing climatic and ecological predictors on age-related (<5 years and ≥5 years old) malaria transmission dynamics. The analyses found that climate variables had a more substantial influence on malaria than interventions and that the relationship was stronger in the ≥5 than in the <5s while the effect of interventions was stronger in the <5s. It was established that climate change negatively impacts malaria control through more conducive temperature and

rainfall environments that are compounded by cultural and socioeconomic exposure mechanisms.

The final stage of analysis drew on the findings from the three earlier stages. It focused on applying the composite malaria burden measure introduced in stage one to examine fine-scale health facility level spatio-temporal patterns and trends. Optimised hotspot detection methods identified significant high-risk hotspots particularly along border areas with neighbouring high endemic countries drawing attention to the criticality of bilateral cross-border malaria initiatives in the fight against malaria. A comparison of health facility level results with those at district-level revealed important spatial scale differences highlighting the potential benefits that could be realised from a flexible adaptive-scaling approach to the implementation of both malaria monitoring and intervention programmes for control and elimination strategies.

The following sections discuss the key findings of each of the original objectives in more detail before some concluding remarks and recommendations from the thesis.

## 7.2 Objective 1: Determine the spatio-temporal patterns of malaria incidence and mortality rates, risk and trends in Zambia from 2000 to 2015

Chapter Three presented a malaria situation analysis to characterise the subnational spatio-temporal patterns of malaria between 2000 and 2015 in Zambia from which there were four key outcomes. The study introduced a new method for sub-national stratification of malaria using three core input metrics - rates, risk, and trends. Targeted interventions, particularly in elimination settings, aim to interrupt local transmission, especially where it becomes increasingly clustered. Zambia's approach to simultaneously pursue sub-national malaria elimination in areas with low malaria incidence while intensifying control strategies in areas with higher malaria suggested the need for robust stratification approaches (Presidential Malaria Initiative, 2019).

The present study established a more robust alternative stratification method that is responsive and sensitive to needs in both malaria control as well as elimination needs. It used a flexibly weighted or unweighted classification of malaria burden through a composite method that accounted for the trend, the risk, and incidence rates for implementation of strategic and targeted interventions.

Area-based malaria stratification using incidence rates alone captures the current state of malaria in snapshots of time. It does not, however, provide the information required to adequately plan for near future intervention strategies without accounting for trends in a broader classification strategy. The inability to detect and monitor trend changes, especially in areas undergoing malaria elimination efforts, has the real potential to threaten past gains and undo many years of time and investment on intervention programmes.

Many countrywide programs in southern Africa continue to use incidence rates as the primary source of information to pursue strategies for the control or elimination of malaria. Having easy access to essential evidence from trends could help inform better decision making on the need for alternative strategies in both high and low burden contexts. For example, not being able to detect and address an increasing trend in malaria incidence rates in an area with low burden could have significant implications later if that trend persists and results in increasing burden.

Neglecting increasing trends in low burden elimination areas, while focusing attention and resources in the high burden control areas could well lead to a situation of shifting gains and losses whereby achievements in control areas are offset by the loss of hard-earned gains in low burden elimination areas. It is therefore critically important in a national context that governments and policy makers have the ability to consider both rates and trends right across the malaria epidemiological spectrum when planning control and elimination strategies.

The model developed here incorporates trends as a key element in defining malaria risk and addresses many of the current limitations identified above. It also highlights the importance of trends in defining malaria burden. For example, malaria burden trends are significant, especially if, as this study has shown, the dynamics of malaria transmission indicate an increasing trend in older children/young adults that affects economic productivity. Measures that take account of trends, such as the one developed here, can provide valuable additional complementary information to standard measures like disability-adjusted life years (DALYs) for monitoring and planning purposes.

Other important outcomes from the study results in Chapter three included the establishment that while malaria was linearly declining or constant in a majority of districts, it was increasing in others. The method demonstrated that 35% of districts in Zambia, containing over 3 million people, with high mortality or incidence burden had

experienced an increasing trend over the period from 2000 to 2015 despite the generally universal and uniform distribution of malaria interventions across the country.

The results also showed that these trends were not uniform across those aged <5 and ≥5-year-olds. Often, the <5 age group exhibited a significant decrease in malaria incidence while the ≥5s showed an increase. This implies that malaria is gradually shifting to becoming an older/adult disease with potentially severe negative economic consequences for already economically disadvantaged developing countries. This is a counterintuitive finding which defies the usual narrative that malaria exposed populations over the age of five years would have been exposed enough to the disease enabling them to develop partial-immunity (Chiyaka, Garira, & Dube, 2007; Doolan, Dobaño, & Baird, 2009), and prompts the need to investigate further (World Health Organisation, 2014).

These significant findings provided the foundation and basis for further study (in chapters 4, 5 and 6) to investigate what potential external factors, particularly ecological and environmental, could help explain these differences and what implications they might have for strategic intervention planning.

With the current challenges faced in the quest to increase domestic and international funding, efficient prioritisation and subsequent use of currently available limited resources should be optimised. The value of the spatio-temporal statistical techniques here is that they provide triangulated and adaptable metrics to aid geographically targeted intervention, prevention and control strategies based on these methods and findings.

## 7.3 Objective 2: Investigate the spatio-temporal impacts of near-term climate change on the rates, risk and trends between 2000 and 2016

Chapter Four, drawing on the key findings from Chapter three highlighting the variable trends and risk of malaria burden between districts, was primarily focussed on the potential impacts that short or near-term climate change may have had on these trends. The rationale for focusing specifically on climate was that the programmes for malaria interventions, such as LLNS and IRS, had in theory been applied uniformly nationwide and as such the expectation would have been that malaria rates and trends would have declined reasonably equally across the country. So, the hypothesis was that some other key influential factor was contributing to the observed variances.

Also, while the effects of longer-term global climate change on health have been comprehensively modelled and reported, little is known about the possible ongoing effects of short-term climate change at sub-national levels. Consequently, in this section Bayesian spatio-temporal modelling was used to examine district-level malaria trends in Zambia from 2000 to 2016 and negative binomial mixed regression models applied to investigate the relationship of near-term environmental change with malaria incidence.

The results showed that intra-regional near-term variations in the environmental variables are significantly associated with malaria incidence and that Diurnal Temperature Range (DTR), as a consequence of increasing minimum and decreasing maximum temperatures, is a key influential factor in malaria incidence rates, even in those areas where there is a general declining trend in rates.

The study also found that the impact of DTR is seasonally sensitive, with the majority of impact occurring in the first and second quarters of the year. This study has demonstrated how substantial investments in intervention programmes are negatively impacted and offset by near-term climate change, most notably since 2010. It is subsequently argued that targeted season-specific interventions, such as Seasonal Malaria Chemoprevention (SMC), in those areas with an increasing trend in malaria could be a very efficient, cost-effective means of reducing rates quickly.

These findings are significant in that they have provided clear evidence that short term climate change can influence malaria transmission rates at sub-national scales and, if not monitored and taken into consideration by strategists and planners, has the potential to undermine expensive investment in implementing broad nationwide intervention strategies. It highlights a possible lack of recognition, or at worst, neglect of the important role that environmental factors and near-term climate change must play in effective frontline operational planning against malaria.

The findings prompted the recommendation for targeted intervention programmes based on key environmental factors. For example, study results strongly support other studies using mosquito population models (Chaves & Koendraat, 2010; Murdock et al., 2016) that show narrowing DTR has a significant association with mosquito activity and infectivity based laboratory experiments. This, however, creates corroborative implications which in our study translates to the disease triggering an increased risk of malaria in the first and second quarters of the year. This increasing seasonal risk could be mitigated by the use of geographically targeted seasonal malaria chemoprophylaxis

(SMC). The recommendation is that targeted SMC particularly for four months from January to April in districts with increasing malaria, could effectively reduce the overall malaria burden (Diawara et al., 2017; WHO, 2013).

## 7.4 Objective 3: Investigate climate change and the dynamics of age and malaria incidence and malaria control interventions between 2000 and 2016.

This chapter focussed specifically on age-related malaria dynamics, looking in particular at any differences between the under-five age group and the rest of the population. It was not possible to break down the over 5 category into more meaningful subgroups as this was the way the data had been recorded, reported and provided by the NMEC. Of particular interest was the potential influence of environmental and climate change factors on incidence rates as well as the influence of interventions. The specific interest with interventions was because many intervention programmes, whilst administered uniformly in the population, tend to be targeted and more actively applied in the very young. This is very much in line with government and global policies and priorities.

The chapter revealed how climate variables influence malaria incidence substantially more than intervention programmes (mosquito nets and indoor residual spraying) with the impacts being more profoundly felt in the ≥ 5 age category, and more noticeable in rural areas. Interestingly, and as initially suspected and hypothesised, it was found that interventions have a more significant impact on the <5s.

The results also show that while the overall malaria incidence trend for the < 5's is decreasing, it is actually increasing in the over ≥5's. Just as important, it was established that climate change negatively impacts malaria control efforts by exacerbating the transmission conditions via more conducive temperature and rainfall environments, which in turn are exacerbated by cultural and socioeconomic exposure mechanisms.

A direct consequence of this is that the anticipated returns from substantial financial and resource investment in national intervention programmes in Zambia, and quite possibly in other similar endemic countries as well, are not being realised, due to near-term climatic influences. The investment in malaria interventions globally was US$4.3 Billion in 2016 and estimated at around US$119.5 Million in Zambia for the same year, (Haakenstad et al., 2019; Patouillard, Griffin, Bhatt, Ghani, & Cibulskis, 2017).

It is neither reasonable nor practical to expect that resources should, could or would be diverted from interventions to climate change activities. However, strategists and planners must recognise the effects and impacts that climate change can make and use the available evidence, as shown in this thesis, to pro-actively modify and target approaches and resources at those areas where the most considerable benefits can be realised. Failure to do so will result, if it has not already, in the introduction of operational complications and disappointing outcomes for within-country malaria strategic planning and resource management.

Most previous studies on the impact of climate change on malaria either focused on children only (Bennett et al., 2016; McCord, Conley, & Sachs, 2017; Shah et al., 2019), or all ages (M'Bra et al., 2018; Midekisa, Beyene, Mihretie, Bayabil, & Wimberly, 2015; Ukawuba et al., 2017) or did not highlight the importance of age in the relative impacts of climate and interventions (Sadoine et al., 2018). The role of age is often downplayed, even though malaria is becoming an older age disease (Nkumama et al., 2017). This study has shown that while malaria interventions remain effective in young children and tend to somewhat moderate the effects of ecological predictors, the situation is very different for those aged five years and over.

The findings strongly suggest that an intensified communications and education intervention strategy for behavioural change targeted explicitly at ≥5 aged population is urgently required and could bring significant improvements in incidence rates. Similar evidence from other studies shows that 5-18 year olds may be responsible for the observed high transmission rates in the ≥5s (Hast, Searle, Chaponda, Lupiya, Lubinda, Kobayashi, et al., 2019; Pinchoff et al., 2016) which supports the contention and recommendation here that school-based intervention programs would be the most appropriate measures to capture the most affected age group (Swana et al., 2018).

These findings also support the call for further malaria stratification among the ≥5 age groups in the routine collection, analysis and reporting of malaria mortality and incidence data. Better age stratification would help further identify and understand which specific age groups are responsible for the observed rise in incidence rates. These effects have potentially significant social and economic consequences (e.g. DALYs) where the economically productive population would directly carry the burden with knock-on effects on the already vulnerable economically dependent young and old populations.

## 7.5 Objective 4: Model Health Facility level malaria and evaluate its potential for in-country and inter-country malaria control and elimination efforts

This chapter focused on a sub-district (health facility –level) spatiotemporal analysis of malaria trends and incidence patterns over a seven-year study period (2009-2015).

It was initially intended to replicate and include the analyses from chapter four and investigate the potential influences of climate variables and climate change at the health facility level. After some preliminary analyses using generalised additive models (GAM) and mixed models, it was decided that this was not feasible. There were two main reasons. The first was that the raw data supplied at Health Facility level pre 2009 was not reliable or comprehensive enough to facilitate the calculation of detailed, robust incidence rates with sufficient confidence. As such, the study period was reduced to only seven years of duration, restricting the potential to capture near-term climate change. Secondly, some preliminary results demonstrated that there was a lack of variance in the climate variables data (e.g. temperature, humidity, and rainfall) between health facilities within districts thus limiting the potential to identify environmentally driven patterns and trends.

Future research, however, could explore the health facility level effects of climate variables across the entire country. Such a study could use fine-scale prediction surfaces of malaria suitability against actual malaria incidence from health facilities. It could also help re-calibrate the national-level ecological suitability or risk at a very fine-scale. Such fine-scale mapping would be useful for micro-scale larviciding or larval habitat identification studies, especially hotspot mosquito vector breeding sites.

Given those limitations, the health facility level analysis focussed on spatio-temporal trends using the composite malaria burden method developed in chapter 3. Several interesting findings were made. Firstly, it was shown that the average trend in national malaria incidence was increasing over the period and that there was a clear north to south continuum of spatial transitioning from areas of increasing malaria to areas of decreasing malaria. Nearly 4.8 million people reside in health facility catchment areas with an increasing trend of malaria, while 26% (incorporating 5.1 million people) have a decreasing trend (95% credible interval). In a comparison of trends at the district level, it was found that almost exactly one-third of Health Facilities have a trend different to that

of their parent district and over two-thirds of those (20% of all health facilities) have a worse tendency.

The results also show that using regional district level incidence alone to stratify malaria control or elimination may miss some vital clues that can only be observed if trends are considered alongside rates. For example, it was shown that the recent and ongoing pre-elimination efforts being implemented in Zambia's Eastern province might be causing a decline in malaria incidences. At the same time, some areas in the southern region, with generally low malaria incidence and earmarked for elimination have started experiencing malaria increase. This has potential implications for creating zero gains as progress made in one area gets offset by losses incurred elsewhere.

The results show that there is considerable variance in malaria trends and risk between the district and health facility levels and that the majority of within-district variance occurs in districts that have low incidence rates and either a constant or declining trend. These findings are important as they suggest that in some areas where malaria is considered to be less of a risk and possibly be designated for elimination, based on the district level data, may well have underlying negative trends indicating malaria may be on the increase again. Figure 7.1 shows the trends from a random set of health facilities relative to the 50 cases per 1000 threshold that currently determines whether an area is marked for either malaria control or malaria elimination interventions.

These findings suggested that an adaptive scaling approach may be beneficial in the implementation of both malaria monitoring and interventions for control and elimination strategies. For example, it may still be appropriate to have district-level strategies in areas where malaria is high, and trends are increasing. At the same time, a health facility level strategy might be more effective in those districts with low rates and constant or declining trends but with considerable differences among their health facilities. It has only been through a nationwide spatio-temporal analysis at two scale levels, using the novel composite malaria risk model, which provides the detailed evidence not only to identify the differences but also the means through which new strategies can be developed, implemented and monitored.

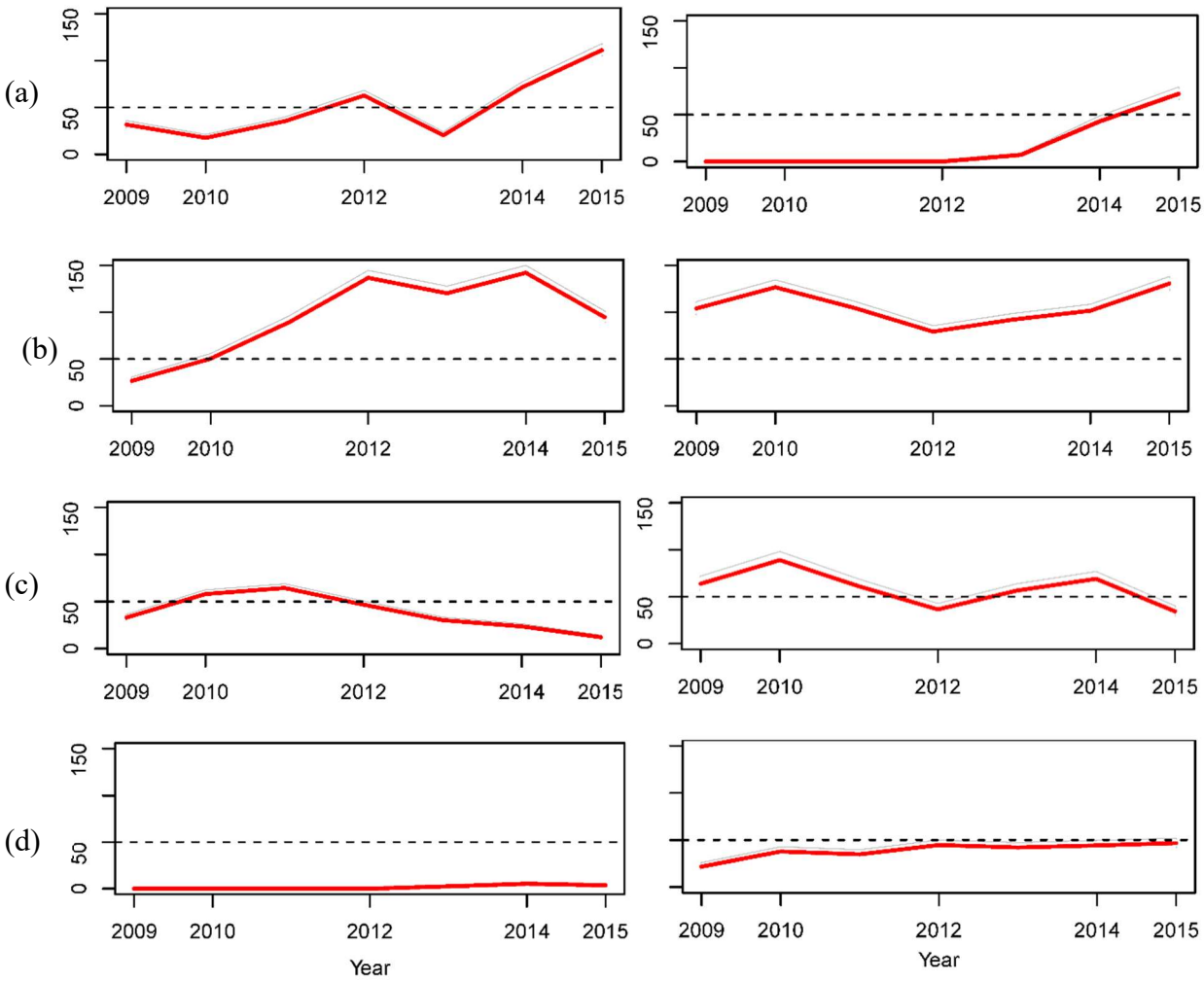


Figure 7.1: Health Facility malaria spatio-temporal trends of incidence using 50 cases/1000 probability exceedance threshold

*Low – High: Elimination to control (b) High - Control (c) Constant: Elimination or control (d) Low: Elimination*

The second key result presented in chapter 6 indicated substantial cross-border influences on patterns of malaria transmission, primarily along the DRC, Mozambique, and parts of the Angolan borders. A stretch of nearly 2000 km of shared border with DRC and parts of the Angolan borders exhibited generally higher risk and incidence rates compared to the rest of the country. A similar pattern is observed in an area of about 560 km along the Zambia -Mozambique border. In addition to the figures presented in Chapter 6, Figure 7.2 shows that a high malaria incidence and an increasing health facility level malaria trend extends at least 100 km inland from these borders. The results from Chapter 6 also suggest that the observed cross-border patterns of high malaria are expanding outwards from the immediate border areas and may soon threaten the regions of malaria elimination where malaria has consistently been generally declining.

Without the benefit of further in-depth studies, it is challenging for this study to determine the relative roles of ecological factors (mosquitoes) or human factors (infected humans)

in creating the very distinct observed border patterns. In reality, it is most likely a complex combination of both.

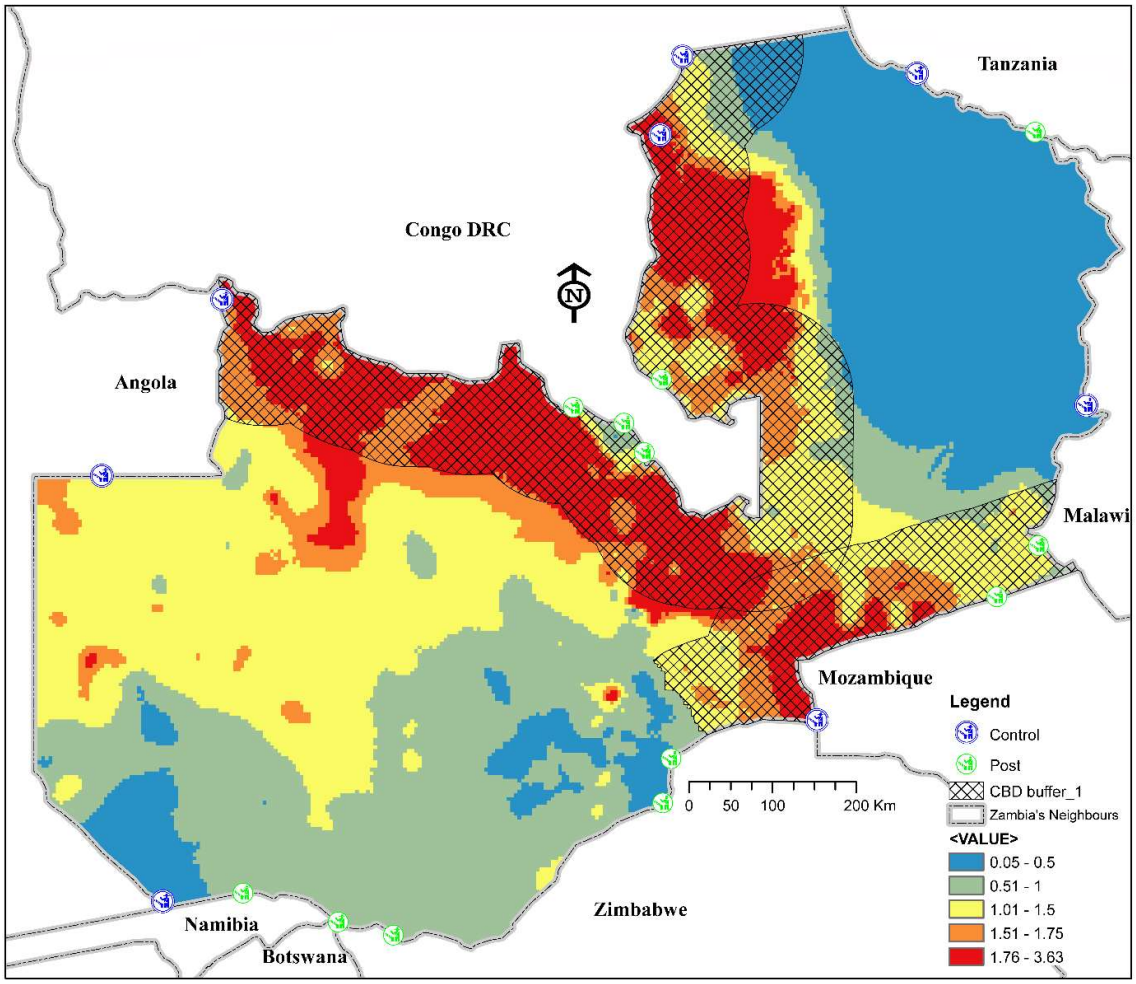


Figure 7.2: Smoothed cross-border malaria risk between Zambia, DRC, Angola, and Mozambique

For example, a recent study conducted in a border town on the DRC and Zambia border, in Northern Zambia's Nchelenge district, showed a lack of genetic diversity in malaria parasites across the border, which suggested this region as being a contiguous transmission zone and that transmission is primarily ecologically driven (Pringle et al., 2019). Alternatively, some border posts in Zambia's Eastern province exhibit a potential influence from human movement across the border where substantial socio-economic activities, such as micro-scale trading and entrepreneurship, are driving high population cross-border movement (Al Zahrani et al., 2018). Cross-border malaria could equally occur in these areas because of limited or no access to interventions for preventing, diagnosing and treatment of malaria (Wangdi, Gatton, Kelly, & Clements, 2015; World Health Organization, 2018d) due to remoteness, socioeconomic and/or political complicating factors that are common along many border areas.

Where human movement is the primary issue, setting up dedicated health posts at the border points could help with mitigation, such as those implemented successfully in the southern border regions via cross-national agreements (Elimination8 Secretariat, 2018). These findings prompted a very strong recommendation for Zambia to urgently establish bilateral or multilateral malaria control agreements with neighbouring high endemic countries.

The land-locked geographical location of Zambia makes it impossible for the country to eliminate malaria anytime soon, without successfully engaging all its neighbours. While the country enjoys southern-based cross-border malaria initiatives through the E8, the imminent threat of cross-border malaria is not in the south but the northern border regions. High endemic neighbouring countries, especially the DRC, Angola, and Mozambique, pose severe threats to Zambia's success in controlling malaria in the northern regions, especially along the DRC border.

## 7.6 Challenges and limitations of the study

It is worth noting that there were several data and related methodological challenges that posed some limitations in this study. First, the health facility level catchment areas are not part of the regular census or officially recognised population count administrative units for data collection. Hence, there is an inherent lack of accurate denominator service populations of health facilities. While some health facilities may have very accurate but limited records from their catchment headcounts, these counts are not deemed official. They cannot be used for analysis for decision making. The most common population denominator is from estimates taken from census district-level population. These population estimates are available and more readily acceptable as official though they have shown some serious accuracy problems in some instances (Walter, 2018).

Furthermore, it remains challenging to accurately ascertain the real population attending specific health facilities, as the geographic distance is not always the reason for the choice of a health facility. Often, other factors such as proximity to the road, quality of services, functional level of service delivery, and physical barriers like rivers and hills (in rural areas), and or any service charges (in urban areas) play a critical role in the choice of health facility, thereby affecting the potential numbers of people attending given health facilities. Thus, some of the observed differences within the district level analysis in this study may well be influenced by unreliable population denominator estimates. Thus, although the study in *Chapter 6* used a combination of sources such as population

headcounts and official census estimations, the primary source was from census estimates, and therefore requires a cautious interpretation of the differences observed in comparison with district-level models.

It must also be highlighted that differentiating disease trends due to climate change was partly challenging because it happens alongside other health care system changes. For example, the period of analysis 2000-2016 saw several potential health care data system changes including the change of malaria diagnostics from microscopy/clinical based between 2000 up to about 2008/9 to more ubiquitously available RDTs since then. Secondly, the changing number of health facilities driven by population increase or health capacity to provide health services as close to the people as possible may well have affected health-seeking behaviours, with a potential to increase the proportion of people attending health facilities due to increased proximity. Such effects, although subtle, may have had some underlying influences on the conclusions and trends found in this study.

Finally, as indicated earlier, it is challenging to discuss the findings on the effectiveness of interventions with certainty as the only information available on 'intervention use' was the annual number of distributed malaria interventions (e.g. bednets) within a district. This is essential information, but it says little about the actual intervention uptake within the district population, especially that of LLINs. It has been documented that some people, especially in rural areas may have access to a bednet but are unlikely to use it (e.g. keeping it for later usage or actively using it for purposes other than intended for malaria prevention). Besides, the records of the annual distribution of bednets don't show the appropriate distribution of bednets within district populations nor the within-district geographical distribution pattern which, if coupled with potentially long delays before reaching some communities, may affect the actual initialisation of effects from the interventions.

It is therefore encouraged that the work presented here and its conclusions should be interpreted and understood alongside specific limitations associated with it as discussed earlier.

## 7.7 Conclusions and recommendations

Overall, the research presented in this thesis found a strong association between near-term climate changes and age-stratified malaria incidence, risk and trends. A common thread throughout has been the use of spatio-temporal modelling techniques to analyse

hitherto unknown geographical malaria trends and associated causal factors in Zambia over a 16 year period since 2000. Adopting this specific approach has enabled the identification of patterns and trends that are implicit in the data, but to date, had never been analysed in this way. The techniques underpinned the development of the risk burden classification method introduced in chapter 3 and used in chapters 4, 5 and 6 (Figure 7.3).

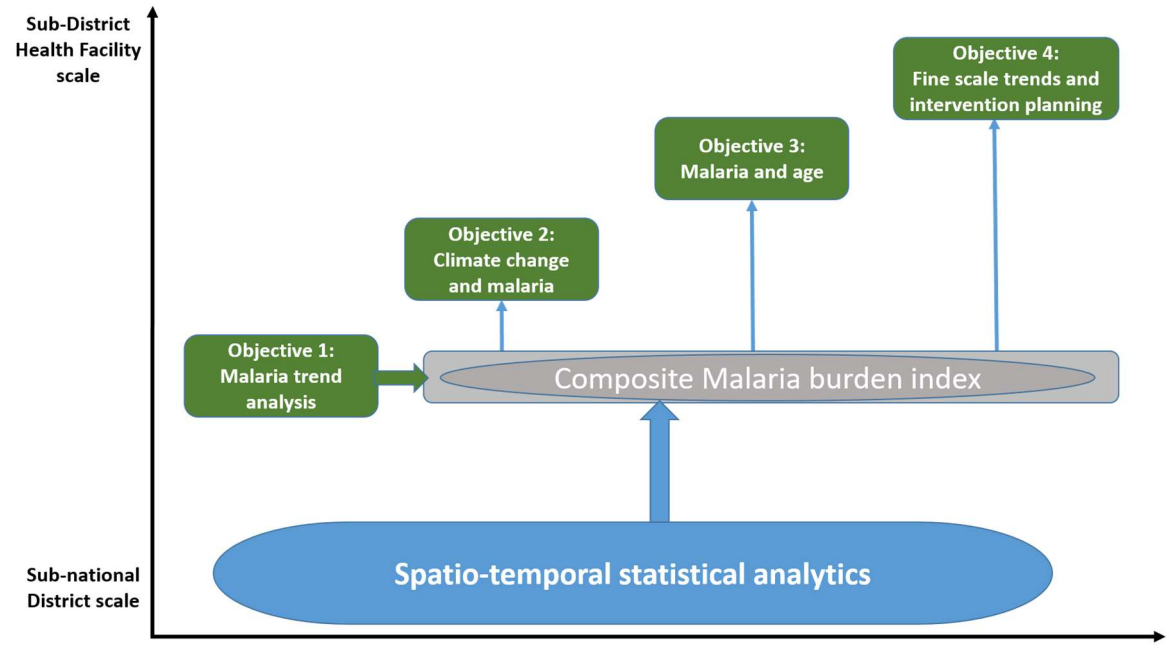


Figure 7.3 Schema of the use of spatio-temporal analytical techniques in the thesis

Along with other cluster analysis techniques, the spatio-temporal methods facilitated the identification of key hot spot areas that would require attention and, where appropriate, specific targeted intervention programmes that could result in significant benefits in terms of reducing malaria and helping Zambia move more quickly towards eradication. Four specific examples are most noteworthy. Firstly, the initial trend analysis in Chapter 3 highlighted many areas where the actual rates of malaria are low but have an underlying increasing trend which, if not addressed, risk losing hard-won gains and a return to high incidence.

Secondly, the analysis in chapter 4 was able to show that intra-regional near-term variations in climate variables significantly influence malaria incidence to the extent that it may well be offsetting any benefits accrued from expensive intervention programmes. This is something that strategic malaria planners may not be aware of and need to know.

Thirdly, the sub-district Health facility-level analysis highlighted significant within-district variances in trends which prompted a recommendation for an adaptive scaling approach to intervention planning, especially in areas where the district rates are low, and trends are stable or declining. Fourthly, the detailed information presented on the significant influence of border effects on incidence highlighted the urgent need for specific cross border initiatives with neighbouring high-endemic countries such as the Democratic Republic of Congo.

While spatio-temporal techniques and algorithms are complex and require specialised skilled analysts, the actual outputs produced, such as those produced in the new three-class burden risk method in Chapter 3, are easy to interpret and understand and can be widely disseminated and used for malaria planning from top national-level strategies to district level health care management.

These four examples highlight the value that has been gained by applying spatio-temporal techniques in analysing malaria data and constitute the main findings and contributions of this thesis. The techniques, like the data, as highlighted in each of the four results chapters, are not perfect and cannot answer all questions. However, this thesis has demonstrated its potential for further research in Zambia and other malaria-endemic countries.

The true value of this work is that it has a tangible real-world applied relevance and the potential to make a positive difference in addressing this disease. As such, it is appropriate and fitting that the thesis concludes with a shortlist of key recommendations, some specific to Zambia and some for all malaria-endemic countries, that have been derived from the research:

## 7.8 Recommendations

Several recommendations already discussed in parts of this Thesis include the following:

i. The strong seasonal increases in seasonal malaria during the study period in districts with increasing malaria suggest the need to test/pilot Seasonal Malaria Chemoprevention.
ii. Zambia's central government should actively pursue bilateral or regional cross-border initiatives with the DRC as well as other bordering countries.
iii. Further research should be undertaken to characterise Zambia's northerly cross-border malaria problems to distinguish, for example, whether this may be due to

the movement of infected people crossing borders, or from malaria transmission, or both.

iv. Introduce an adaptive scaling approach in the monitoring, reporting and operationalisation of malaria interventions in order to benefit from sub-national high-burden, high-impact strategies.

v. Introduce better disaggregation of age in malaria data and reporting, e.g. with a category between 5 and 17 years old to monitor and address an ageing trend in malaria incidence

vi. Pilot targeted interventions or behavioural change campaigns for school-going age groups.

vii. Maintain and improve quality monitoring of the data received through the health management information system (HMIS) to allow for better, more sophisticated use of the data (e.g. spatio-temporal analysis).

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# Appendices

# APPENDIX A: APPENDICES FOR CHAPTER THREE

8.1.1.1 Supplementary methods for Chapter 3

Section 1: Describing and explaining the Health Management Information System (HMIS) dataset used

Section 2: Structure of the Bayesian Hierarchical models used

Section 3: Generating malaria risk and rates

Section 4: Working the Matrix Details

Section 5: The definition of terms used in the paper

8.1.1.2 Section 1: Describing and explaining the HMIS dataset used

Zambia has had a rich and unique HMIS data source since the beginning of the last decade. Disease information from records collected via districts, aggregated from health facilities records, have been more or less complete since 2000 (World Health Organization, 2008). During this period, a malaria case was defined as a "fever with parasites" which generally defines all those cases that would need treatment using antimalarial drugs. The data consists of reports of the numbers of outpatients and inpatients treated based on either their clinical symptoms (suspected cases), or by laboratory tests carried out using RDTs, and slide positivity (confirmed cases).

8.1.1.2.1 *Malaria case and mortality definitions*

Malaria mortality refers to the direct consequences of malaria infection, which primarily includes the death from a progression of mild and severe disease to death (Greenwood et al., 1987; Mudenda et al., 2011). From a clinical view, a simplified sequence from the point of a plasmodium-infected bite is as follows (World Health Organization, 2014b):

$$\boldsymbol{Infection \rightarrow asymptomatic\ parasitaemia \rightarrow uncomplicated\ illness \rightarrow severe\ malaria \rightarrow death}$$

This is what is generally measured by the health system, but is often hugely underestimated (Greenwood et al., 1987; Mudenda et al., 2011; Snow et al., 1992) as the true burden depends on several other factors such as transmission intensity, age, acquisition of immunity, parity, co-morbidities, and health system factors such as access and quality of health care. Hence, while Verbal Autopsy remains the primary diagnostic method of confirmation, it has a specificity that is poor for malaria because malaria can simultaneously be both a contributory and an underlying cause of death, and confirmatory accuracy still depends on many other factors within (Reyburn et al., 2004; Taylor et al.,

2004) and outside (Lynch, Korenromp, & Eisele, 2012; Mudenda et al., 2011; White, Dondorp, Faiz, Mishra, & Hien, 2012) the (quality) health care system.

The use of only two age groups in this study is for two reasons. Firstly, the data was mostly available in three age categories from: <1, 1-4, ≥5. The study grouped the first two categories into 0-4 years to be consistent with the national and global malaria priorities and reporting. Secondly, due to the high susceptibility risk, vulnerability, and severity of exposure to malaria infection or disease among under-five children, it has been a priority in the last decade to track progress in under 5 children mortality and incidence. This priority has since defined the international focus on under-fives reporting in all Malaria Indicator Surveys (MIS), Demographic Health Surveys (DHS), and World Malaria Reports (WMR) (Murray et al., 2012; World Health Organization, 2008).

From 2001, all patients in Zambia who seek care in the public sector due to fever could receive a malaria diagnostic test free of charge, as per health policy guidelines. A microscopy blood slide was the main malaria test available in most health facilities between 2000 and 2008. However, as per WHO guidelines, children from most of sub-Saharan Africa aged below five years received treatment for all fever cases without parasite confirmation (World Health Organization, 2008). Thus, due to the shortage of medical personnel and the high volume of suspected malaria cases in most public facilities, diagnosis by clinical symptoms remained a substantial part of the malaria diagnosis process.

Routine surveillance records were and remain the most abundant source of information on the effects of malaria control in endemic countries worldwide. The records of malaria cases and deaths as submitted to national programs and the WHO vary in quality and most are lacking in their completeness. Hence, using the data as received is always deemed to have some bias, and underreporting issues (due to record incompleteness) or over-reporting due to the combined presumed malaria cases treated without undertaking confirmatory testing. Although routinely collected records have significantly improved in their data quality in recent years, these data still need to be adjusted to reflect a more accurate picture of the malaria epidemiology (Ashton et al., 2017; World Health Organization, 2008).

In order to achieve a more accurate picture of malaria cases or deaths, adjustments should be made on the reported total national cases. The WHO's methods of working routinely collected data include adjusting reported malaria cases for reporting completeness, care-

seeking rates, and parasite positivity rates (in the likelihood that cases were parasite-positive). Historically, while this was the most accurate and objective method, it was applied only in a few African countries that had enough quality in their data (World Health Organization, 2008) making direct comparisons difficult.

In the dataset, however, not all three-adjustment parameters were available for the dataset between 2000 and 2008. The study obtained annual mean national reporting completeness from the WHO's World Malaria Reports of 2008 and 2016 (World Health Organization, 2008, 2016b); extracted and estimated the mean health-seeking rates from three Demographic Health Surveys (DHSs) of 2001-2, 2007, and 2013-14 (Central Statistical Office (CSO), Ministry of Health (MOH) & University of Zambia, 2009; Central Statistical Office (CSO) [Zambia], Ministry of Health (MOH) [Zambia], 2014; Central Statistical Office [Zambia], Central Board of Health [Zambia], 2002) (see subsection on *Treatment seeking studies in Zambia)*.

Data on the slide or malaria-test positivity rates were not available, and all malaria records were reported as a figure comprising presumed and confirmed cases and as such cannot be disaggregated. This was the type of reporting from the year 2000 until 2008 after which the nation-wide scale-up of RDTs became the primary diagnostic test. Therefore, although the study did not incorporate test positivity and cannot confirm the exact number of expected health facility reports that contributed towards the records received, this study did use the reporting completeness to make adjustments.

Consequently, it is possible that treatment-seeking rates may vary at the health facility level, but due to the lack of such fine-scale data, it could not be quantifiable and accounted for in the models. This is partly reflected in how adjusting for treatment-seeking rates was mostly mirrored in temporal trends but not in spatial patterns. This has been addressed in the main text.

Nevertheless, it can be noted that, while these adjustments may be essential to show a more accurate picture of malaria infections in the country, and could affect the observed temporal trends, they will not affect any underlying spatial patterns that would otherwise be observed using raw reported malaria data. Furthermore, it can also be suggested that adjusted rates are only useful when comparing with other countries; otherwise, they are of limited everyday local use by policy makers because all decisions are based on actual records of reported malaria cases or deaths. Hence, adjusted figures often pose a challenge for reasonable comparisons. In comparison, while the results from adjusted studies may

reflect a more accurate general picture, they may not present a similar picture observed on the ground by the malaria programs. This is especially true when applied to subnational level analyses without evidence from specific similar scaled subnational studies.

As the data was available only at the district level, the study first examined individual district counts, before testing for the presence of outliers or the presence of spurious values using Cooks distance test. Two-outliers were found and corrected for, using the district averages from the mean value before and after the outlier. Then, the study examined the dispersion from the median using simple outlier statistics such as the absolute deviation from the median using DHARMa's R package - nonparametric dispersion test via standard deviation of residuals fitted vs simulated data.

Before re-analysing the data, adjusted were made using the equation:

$$= \frac{Cases_{presumed} + Cases_{confirmed}}{Reporting\ completeness}(1 + treatment\ seeking\ rate) \quad [1]$$

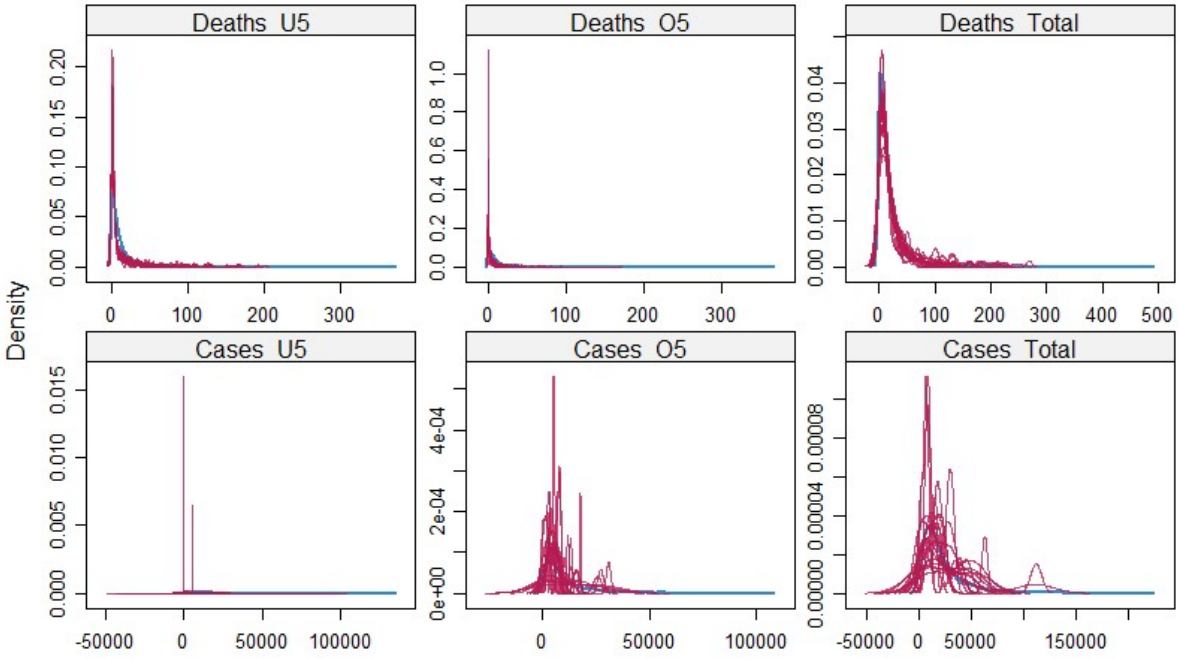
8.1.1.2.2 *Data Missingness*

Margin plots were utilised, missing data patterns and density plots to test for data missingness patterns in the data. There were 3.4%, 2.7%, 1.4% missing for under-five deaths, over five deaths, and across both age groups respectively. Only 0.1% of missing values were in malaria case reports making up 5% of the combined total for missing data in the whole dataset.

The study used multiple imputations to create several complete versions of the dataset by replacing missing values with plausible data values (Stef Van Buuren, 2018). Before settling on a final imputation method, multiple methods were tested for efficiency and error of the imputation algorithms such as Multivariate Imputation by Chained Equations implemented in MICE R package (S van Buuren & Groothuis-Oudshoorn, 2010), the bootstrapping and predictive mean matching (PPM) from Hmisc R package (Harrell Jr & Harrell Jr, 2019), and the MissForest R package (Stekhoven & Bühlmann, 2011) which is random forest-based. In each case, the results were pooled into a single point estimate with an associated standard error (Rubin's rules"). Random Forest method was finally chosen. This method is trained on the observed values from a matrix to estimate the missing values and impute the 5% of missing values in the data. This method yields an out-of-bag (OOB) imputation error estimate removing the need to test for or conduct elaborate cross-validation from the missing values among malaria deaths alone. The

normalised mean squared errors (NMSE) of imputed missing values were 0.22 (22%), and 0.072 (7.2%) for missing case values and 0.094 (9.4%) for the whole dataset. The Figure 3.S4 below shows the density plots show the level of accuracy in missing values of mortality (4.9%) and incidence (0.1%) of imputations.

Figure 3.S4: density plots of imputations




8.1.1.2.3 *Treatment seeking studies in Zambia*

While treatment-seeking behaviour plays a role in how much of malaria/non-malaria fevers are captured at health facilities, available studies (conducted between 2007 and 2017) have shown a geographical bias with up to 80% of studies being undertaken wholly or partly in only one of Zambia's ten Provinces, Southern Province. These studies are geographically biased and therefore not generalisable beyond their respective study areas or sub-regions. For instance, a recent study by Edward et al. (Edward et al., 2018) conducted between 2013-2014 and 2016-2017 on care-seeking practices following the behaviour change intervention in Zambia indicated about 72.3% (N = 173) and 81.8% (N = 209) of the respective intervention and comparison cohort populations sought care. These results were, however, pooled (despite having been across four districts), and reported only as control and intervention districts, making them non-inferable elsewhere.

Other studies also conducted in southern province mostly captured high health-seeking behaviour among community-based malaria management and non-severe pneumonia in children. Over 80% (N range =174 - 362) of the cases were treated at health centres, and

through CHWs (Hamooya, Chongwe, Dambe, & Halwiindi, 2016; Seidenberg et al., 2012; Yeboah-Antwi et al., 2010) whether intervention or at control arms.

In peri-urban settings, a case study of Lusaka showed about 56% (106/189) of caregivers sought care from health professionals (Sasaki et al., 2010). However, it is worth noting that all these studies targeted health-seeking among young children with the help of their caretakers. Information on the utilisation of health services due to fever-related illnesses by people aged 5 years and over remains scanty. It is mostly extrapolated from these studies to all age groups with the assumption of homogeneity across all ages. Given this assumption and as traditionally applied by the WHO, treatment-seeking information was extracted from DHS reports and used those as explained above in earlier sections.

8.1.1.2.4 *Underestimations due to unknown subclinical malaria*

Asymptomatic individuals constitute a significant malaria reservoir of infections leading to sustained transmissions. Many studies show that subclinical or asymptomatic malaria increases as the proportion of malaria cases among febrile illness declines, and transmission continues among people with higher subclinical infections (Björkman, 2018; Harris et al., 2010; Mangeni et al., 2016; Okell et al., 2012). Subclinical is higher in low transmission areas than in high transmission areas (Mangeni et al., 2016; Okell et al., 2012).

The study did not have information on the rates of subclinical malaria, which translates in an absolute systematic underestimation of malaria. The study approach can inform focused investigations of low-transmission settings as part of active case detection to test defined populations without prior screening for symptoms and identify or treat asymptomatic infections. The presence of unaccounted for and uncaptured asymptomatic malaria cases, as shown above, may contribute to underestimations of the actual malaria burden identified in this study.

8.1.1.3 Section 2: Structure of the Bayesian Hierarchical models used

The study area has 72 districts denoted by $k = 1, \ldots, K,$ non-overlapping districts are denoted by $S = \{S_1, \ldots, S_K\}$. The available data aggregated at quarterly time periods are subscripted with $t = 1, \ldots, N$. Thus, the data are available for $K$ rows (Districts) and $N$ columns (Quarters). Response variables are denoted by $\mathbf{Y} = (Y_1, \ldots, Y_N)$ $K \times N$, where $\mathbf{Y}_t = (Y_{1t}, \ldots, Y_{Kt})$ represents the $K \times 1$ observed vector for $K$ district units at period $t$. The vector of selected offsets are indicated by $\mathrm{O} = (\mathrm{O}_1, \ldots, \mathrm{O}_N)_{K \times N}$, where likewise $\mathrm{O}_t = (\mathrm{O}_{1t}, \ldots, \mathrm{O}_{Kt})$ denotes $K \times 1$ column vector of offsets for the period $t$. A vector of known

covariates is denoted through, $\mathbf{x}_{kt} = (x_{kt1}, \ldots, x_{ktp})$ for district *k and* period *t*. The model takes the following structure:

$$Y_{kt}|\mu_{kt} \sim f(y_{kt} \mid \mu_{kt}, v^2) \text{ where } k = 1, \ldots, K, \; t = 1, \ldots, N,$$
$$g(\mu_{kt}) = x^T_{kt}\beta + O_{kt} + \psi_{kt}, \qquad [2]$$
$$\beta \sim N(\mu_\beta, \sum_\beta)$$

The specific model used implements an exact Poisson specification:

$$Y_{kt} \sim \text{Poisson}\,(\mu_{kt}) \text{ and } \ln(\mu_{kt}) = x^T_{kt}\beta + O_{kt} + \psi_{kt}. \qquad [3]$$

8.1.1.3.1 *Model Specification and Structure*

The study used a specialised Gaussian Markov random field (GMRF) of conditional autoregressive (CAR) structure. These spatiotemporal models represent the neighbourhood of the districts through an adjacency matrix W so that $w_{jr}$ expresses whether districts (j, r) are spatially contiguous to produce a binary value interpreted as spatial closeness when ($w_{jr} = 1$), which means that districts share boundaries. In contrast, the opposite is true when ($w_{jr} = 0$) representing the nonexistence of a shared boundary. This study used the CARBayesST R package [2] to fit multiple models using the data likelihood for district j and time point *i* as $Y_{ji} \sim$Poisson ($e_{ji}\theta_{ji}$) and where ($Y_{ji}$, $e_{ji}$) are the observed and expected values respectively.

8.1.1.3.2 *Capturing spatio-temporal random effects*

The model incorporates a spatio-temporal autocorrelation into the response variable **Y** through latent random effects, using CAR-type prior distributions and spatio-temporal extensions. The symmetric nonnegative $K \times K$ neighbourhood controls the spatial relationship through the adjacency matrix **W**= ($w_{kj}$). $W_{kj}$ characterises the closeness between spatial units ($S_k$, $S_j$). The weighted matrix creates higher values for area units with spatial adjacency, but lower or 0 values for areas spatially distant. The matrix **W** creates a binary, ($w_{kj} = 1$ if spatial units ($S_k$, $S_j$) share a common boundary/edge and $w_{kj} = 0$ if not. This binary specification of **W** has to fulfil three conditions, namely; symmetry, non-negativity, and row sum greater than zero. This model treats spatially proximate areal units as spatially autocorrelated while those more distant as conditionally independent.

In order to estimate the evolution of the spatial response surface over time without forcing it to be the same for each time period, the mean response with a single set of spatially and temporally autocorrelated random effects (as seen in Figure 3.2b and 2d) was used. Temporal autocorrelation is in turn induced through mean $\rho T\phi_{t-1}$, while variance

$\boldsymbol{Q}(\boldsymbol{W}, \rho s)^{-1}$) induces the spatial autocorrelation according to the CAR equations used in the models explained earlier. Equation 4 gives the matrix:

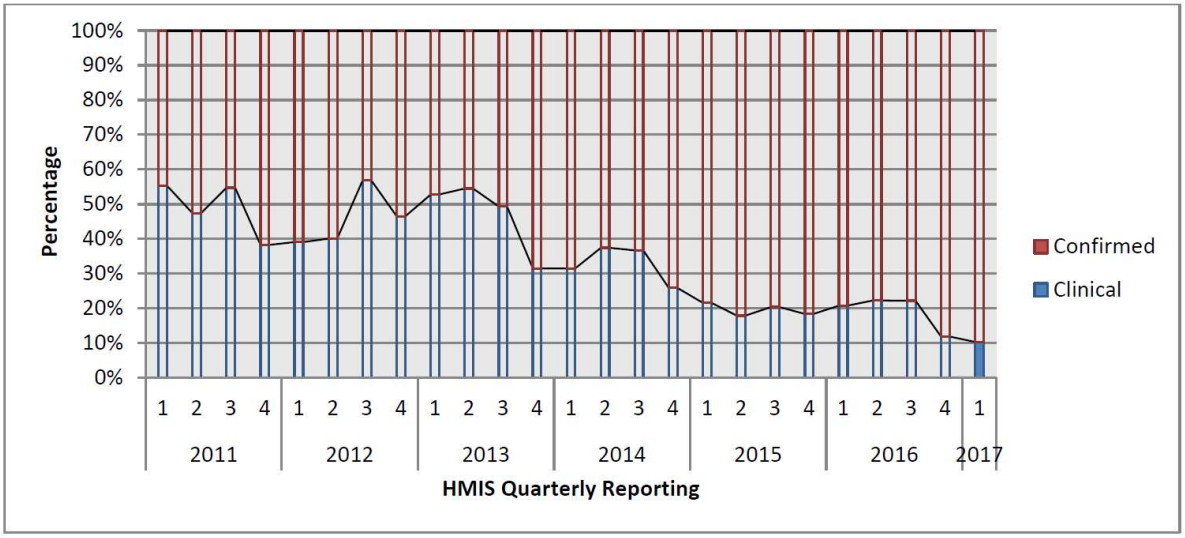
$$(\boldsymbol{W}, \rho s) = \rho s[\text{diag}(\boldsymbol{W}\mathbf{1}) - \boldsymbol{W}] + (\mathbf{1} - \rho s)\mathbf{I} \qquad [4]$$

In equation 5, 1 represents the K × 1 vector of 1's from the binary and the K × K identity matrix is denoted by I. While random effects are zero-mean centred, specific flat priors ($\rho s, \rho \mathcal{T}$) and conjugate priors ($\mathcal{T}^2$) are given and default values (a = 1, b = 0.01) for the latter. The study also tested for the collective temporal autocorrelation across all time points in the data using the Dubin-Watson test. The Cochrane-Orcutt estimation method was implemented to solve the first-order autocorrelation problem. Each of the models implemented deals with autocorrelation in specific terms, but all outputs were also subjected to the two independent autocorrelation tests to confirm the models dealt with it.

The Deviance Information Criterion (DIC) (Spiegelhalter et al., 2002), Watanabe Akaike Information Criterion (WAIC), and its associated log pseudo-marginal likelihood (PML) was applied to initially select the best models to use with the data from among the list of conditional autoregressive models available (Lee et al., 2018). Models with similar structures were prioritised with a final choice made by the DIC and suitability to the objectives of the study.

8.1.1.3.3 *Cluster Trends model*

Figure 3.S5: Diagnostic Confirmation Trend Total Malaria Cases in Zambia, 2011 -2017




*Source: Zambia Malaria Operational Plan 2018*

Figure 3.S5 shows the general reduction in clinical malaria captured in the HMIS. It could be argued that the combination of un-adjusted clinical cases with confirmed malaria cases, and the continuous reduction in clinical malaria (adding about 10% - 50% more cases from 2011 [and more in previous years] due to other malaria-like fevers) should have been captured as a reduction in malaria incidence. However, the study reports an almost counter-intuitive increasing trend with a potential bias for underestimation, which eliminates the probability of these trends being spurious.

With the objective being to show malaria clusters among districts that shared common malaria risk trends, the models used did not include any covariates. This study assessed clustering of malaria risk based on districts shared shape-constrained temporal trends, which allowed the study to test for heterogeneity vs homogeneity in temporal and spatial trends of malaria between two age groups in Zambia over the 16 years' study period.
The model has the capability of identifying clusters of contiguous areal units that exhibit either an elevated or reduced risk of disease compared with neighbouring areas (Anderson, Lee, & Dean, 2014; Charras-Garrido et al., 2012).

In addition to the model structure described above, general model cluster trends are given by:

$$Y_{kt} \sim p(Y_{kt}|\mu_{kt}), \text{where } K = 1, \dots, K, t = 1, \dots, N,$$
$$g(\mu_{kt}) = O_{kt} + X^T{}_{kt}\beta + \phi \sum_{s=1}^{S} \omega_{ks} f_s(t|\gamma) \quad [5]$$

*Figure 3.S1* shows the estimated temporal trends and 95% intervals on the risk scale, namely:

$$\theta_t = \exp\big(\beta_1 + f_s(t|\gamma_s)\big) \quad [6]$$

Equation 7 indicates the constituents of estimates for i) under five ii) over five, and iii) population-wide trend models in Figure 3.S1. Model outputs in Figure 3.S1a (i, ii, iii) show the lines fitting well at the 95% credible interval, with just under half (44%) of the districts (Table 3.1) allocated to a constant trend signifying no change in the risk of under-fives malaria mortality over time. The remainder is shared (29%, 26% - under five and 31%, 23% - over five) between the increasing and decreasing risk trends, respectively. Surprising, the number of no change districts increases to 50% when the two age groups are combined, signifying that not all districts exhibited the same trend between both age

groups as confirmed by the trend maps (Figures 5 A(i), A(ii), B(i) and B(ii)), which exhibit similar levels of spatial variation.

The trend equation formula is:

$$\psi = \phi_{kt} + \sum_{s=1}^{S} \omega_{ks}\ f_s(t|\gamma_s),$$

$$\phi_t|\phi_{t-1} \sim N\left(\frac{\rho \sum_{j=1}^{K} \omega kj\phi}{\rho \sum_{j=1}^{K} \omega kj+1-\rho}\ , \frac{\mathcal{T}^2}{\rho \sum_{j=1}^{K} \omega kj+1-\rho}\right),$$

$$\mathcal{T}^2 \sim \text{Inverse} - \text{Gamma}(a, b),$$

$$\rho s, \rho\mathcal{T} \sim \text{Uniform}(0,1). \qquad [7]$$

$$\omega k = (\omega k1, \ldots, \omega kS) \sim \text{Multinomial}(1; \boldsymbol{\lambda}),$$

$$\boldsymbol{\lambda} = (\lambda_1, \ldots, \lambda_S) \sim \text{Dirichlet}\big(\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_S)\big),$$

where $\phi_{-k} = (\phi_1, \ldots, \phi_k - 1, \phi_k + 1, \ldots, \phi_K)$.

Areas are first clustered according to their temporal trends; then used global probabilities to associate candidate trends in the output and trend interpretation. The model also visualised the classifications assigned to trends using maximum posterior probabilities of certainty thresholds (0.33 – 0.5, 0.5 -0.75, 0.75 - 1). Table 3.S1 shows the trend function interpretation used for the model (Napier et al., 2018).

Table 3.S1 Trends interpretation of results:

| *Trend* | | *Function* | *Identifier* |
|---|---|---|---|
| *(i) Constant* | | $f(t) = 0$ | *Constant* |
| *(ii) Linear* | *Decreasing* | $f(t\|\gamma) = \gamma t$ | *LD* |
| | *Increasing* | $f(t\|\gamma) = \gamma t$ | *LI* |

**Source:** *Napier 2018*

The study also tested monotonic trend alternatives before selecting the one used. The original choice and rationale as the study tested the monotonic alternatives (not included or discussed here) was guided by the understanding that the number of knots controls the wiggliness of the estimated trend (Napier et al., 2018). Ruppert et al. (Ruppert, Wand, & Carroll, 2003) argue that if one is using a linear spline with enough knots, increasing the number of knots has no appreciable effect on a penalised fit, then increasing the degree of the spline is also unlikely to have a noticeable effect. Claeskens et al. (Claeskens, Krivobokova, & Opsomer, 2009) further refined the justification that to prove that a smaller number of knots lead to a smaller averaged mean squared error. Hence, given the small number of time points, Q = 2 was enough, and any more would not have much

effect, although it is believed fewer would lead to larger MSE. However, the final choice of model was not monotonic and therefore did not need knots.

#### 8.1.1.4 Section 3: Generating malaria risk and rates

##### 8.1.1.4.1 *Relative Risk*

An indirect calculation of the Standardised Mortality Ratio (SMR) and Standardised Incidence Ratios (SIR). The SIR/SMR are ratios between observed counts of deaths/incidence in a study population and the expected counts of deaths/incidence, depending on the age-specific rates in a standard population. These ratios are dependent on the demographic size and profile of the study population. High risk is determined when the ratio of observed/expected counts is greater than 1.0 in the study population, while low risk is when the ratio is less than 1.0. In order to make three classes *low, medium,* and *high* that would conform to the model classification for risk trends, the study classified all below 1.0 as low, those between 1.0 – 1.5 as medium (equivalent to 50% increase above national population) and all over 1.5 as *high.*

##### 8.1.1.4.2 *Malaria Rates*

Malaria mortality rates were calculated as death counts per 10,000 population of the specific age group, while incidence rates were calculated per 1,000 population. For comparability between risks and trends, the study scaled all rates to a range of between 0 and 1. It then classified the values into three groupings of 0 - 0.33 = *low*, 0.34 - 0.67 = *medium*, and 0.68 – 1 = *high*.

#### 8.1.1.5 Section 4: Working the composite Matrix for visualising High/Low burden areas

The study created a matrix composed of the district results from the models for trend clusters, rates, and risk. *Incidence and mortality rate**:*** in the output table *(see Table 3.S1)* and as earlier described, it classified mortality and incidence in the range of 1 - 3 where high = 3, medium = 2, and low = 1.

For *relative risk* (RR), <1 =“*low risk*”, 2 = “*medium risk*” with RR between 1-1.5 (denoting 0.1-50% risk higher risk), while 3 = *“high risk”* with RR more than 50% - 200% higher than the national average. For the *trend classification* by the model, it denotes *decreasing trend = 1*, no-*change* (*constant*) = *2* and *Increasing trend = 3* which inherently meant the equivalents of low, medium and high, respectively. Precisely, a rating scale of high = 3, medium = 2, and low = 1 in all three criteria was chosen.

In the *final mapping* of *high/low* burden areas*,* a similar method was implemented resulting in a logical classification approach recognising a high combined matrix score to

represent an area of *high malaria burden* and consequently an area of high potential impact to effective interventions. The opposite was also true denoting low matrix scores as areas suitable for malaria elimination.

The study then imported this dataset into ArcGIS 10.5, where each combined district score was derived from a product of score across risk, rates, and trend from the matrix. For example, a district with "high RR" (weight 3), "Increasing trend" (weight 3), and a high rate (weight 3) would give a product score of 27 (3 x 3 x 3), while having one of the scores as 2 would make the final score =18 (3 x 2 x 3). It then used manually defined classes to make the class cut-offs, as shown in the matrix *Table 3.S1* to visualise the results. As such, any alternative weighting approach could easily be applied to denote the subjective or objective relative importance of the three components (rates, risk, and trend) for a specific country or region being studied.

Although scores were multiplied across the confusion matrix columns to obtain a total score for each district out of preference for easy mapping of classes, and explored other ways such as addition, averaging, and rescaling to aggregate the matrix scores most logically and understandably. The latter methods did not change the results but made class exclusivity more challenging to achieve, as the range of values was smaller and generated very close scores between categories. Product scores, however, gave the best set of distinctive classes. This study applied the matrix for under-five, over-five age group incidence, and mortality separately to test for age-specific differences.

8.1.1.6 Section 5: The definition of terms used in the paper

WHO: World Health Organization

GTS: Global Technical Strategy

IRS: Indoor Residual Spraying

GIS: Geographic Information System

MIS: Malaria Information System

ACT: Artemisinin-based Combination Therapy

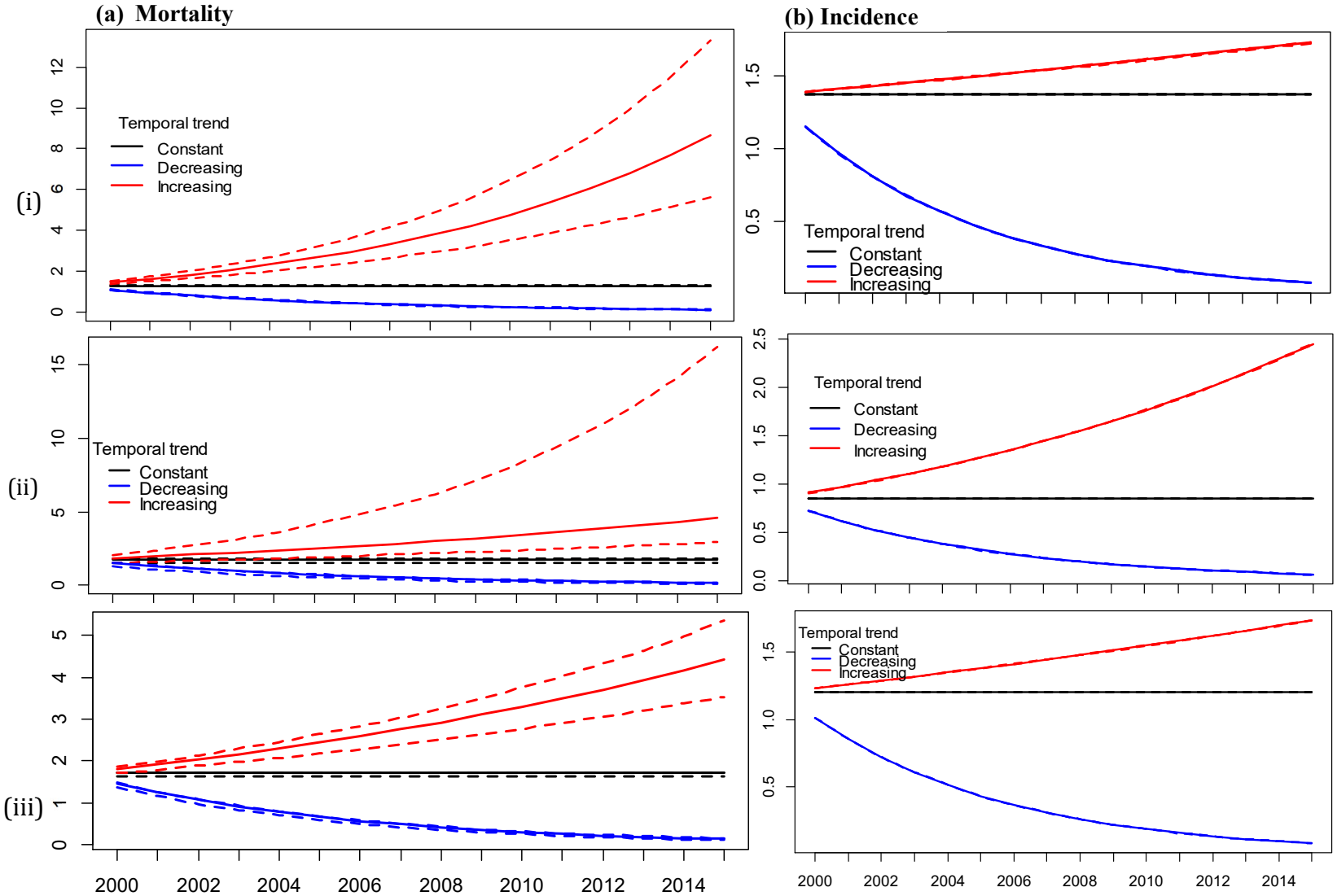
RDT: Rapid Diagnostic Test

E8: Elimination 8 Malaria Initiative

Under-fives: Children aged under five years old

WMR: World Malaria Report

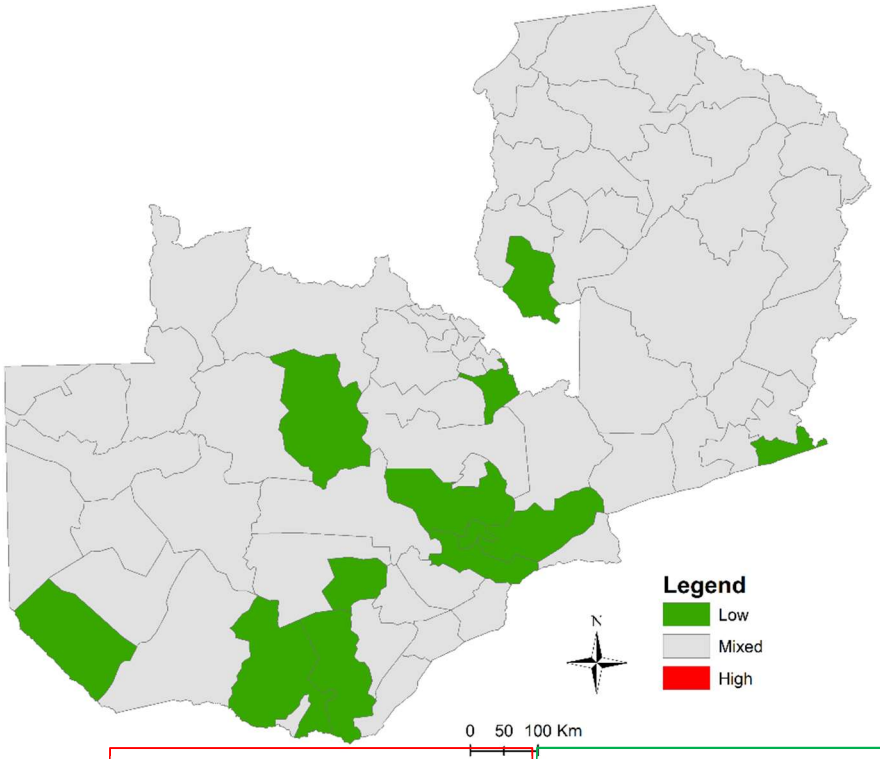
Figure 3.S1: Average temporal trends at 95% credible intervals




*Estimated temporal trends and 95% credible intervals in dotted lines, arranged starting with under-five (i), over-five (ii) and population-wide (iii), for malaria mortality (a), and malaria infections (b),*

Figure 3.S2: Districts with the highest and lowest malaria based on all matrix scores [Trend u5, Risk u5, Rate u5, Trend o5, Risk o5, & Rate o5]

**Malaria mortality**

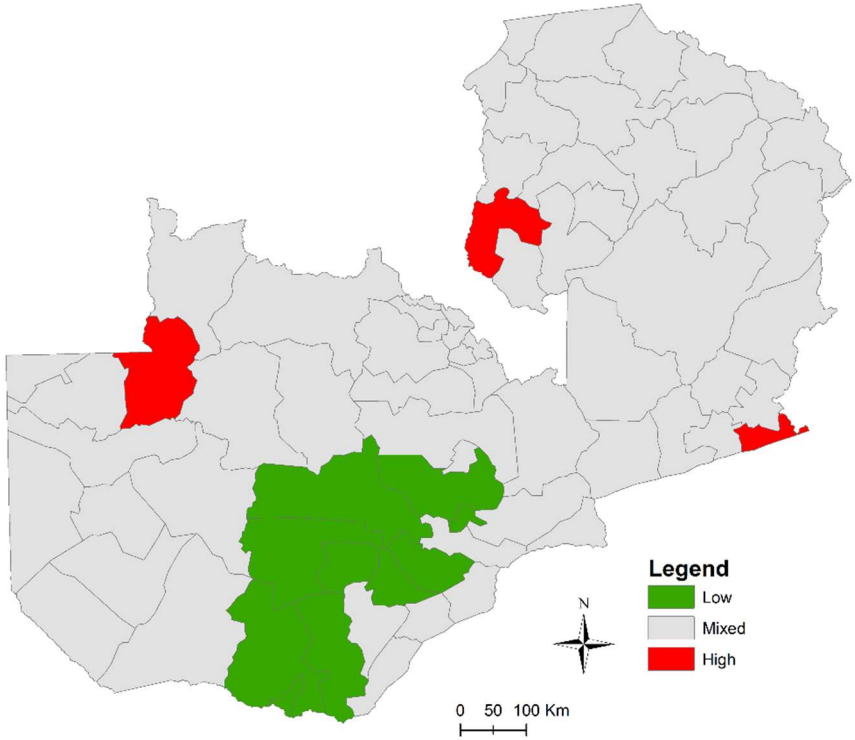



**Red** = High Rate [RI], High Risk [RA] & Increasing Trend [T]

**Green** = Low Rate, Low Risk & Declining Trend

Scores derived using the Mortality Rate, Mortality Risk, and Trend [RIRAT] matrix where the green districts had the lowest scores while the red had the highest scores in the matrix. Here, six variables used in the matrix are <5 Rate, Risk, & Trend, and ≥ 5], Rate, Risk & Trend.

**Malaria Incidence**




**Red** = High Rate [RI], High Risk [RA], & Increasing Trend [T]

**Green** = Low Rate, Low Risk & Declining Trend

Scores derived using the Mortality Rate, Mortality Risk, and Trend [RIRAT] matrix where the green districts had the lowest scores while the red had the highest scores in the matrix. Here, six variables used in the matrix are <5 Rate, Risk, & Trend, and ≥ 5], Rate, Risk & Trend.

Table 3.S2: interpretations of map legend and colours showing arbitrary combinations of scores and their resultant score and colour

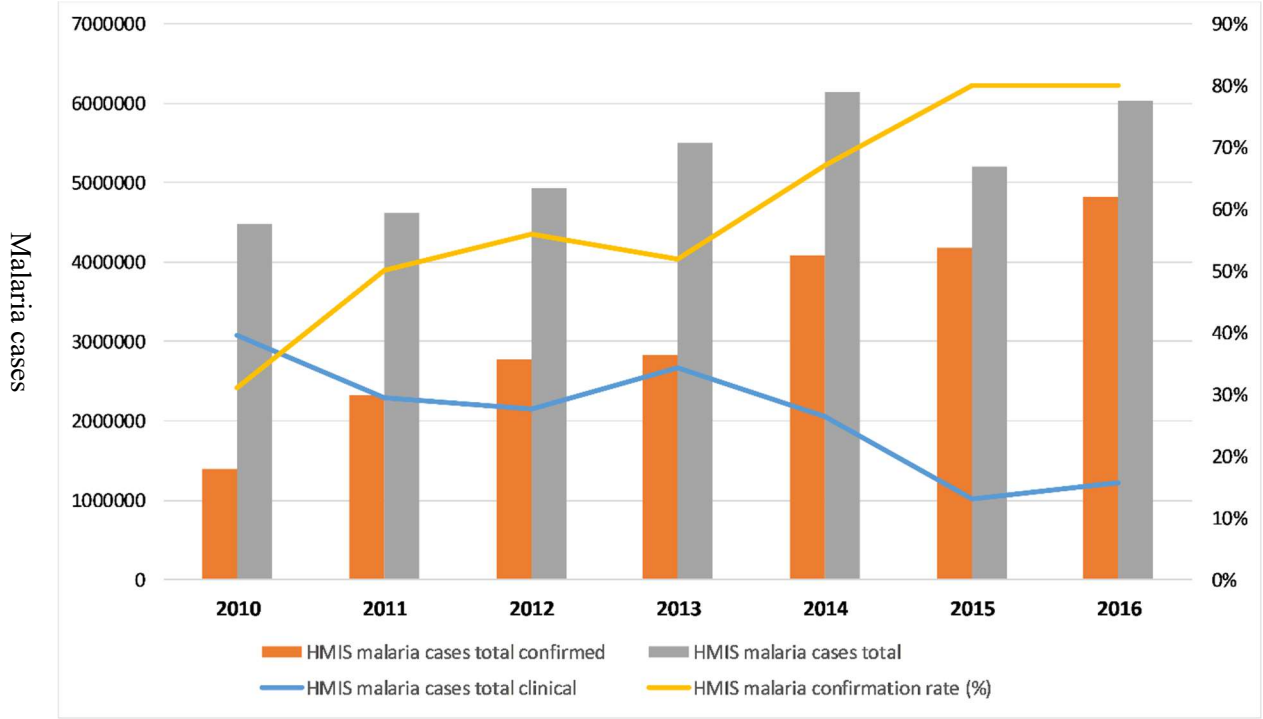
| District | Trend | Risk | Rate | Score | Three Classes | Two Classes |
|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 1 | Low | |
| 2 | 2 | 1 | 1 | 2 | | |
| 3 | 3 | 1 | 1 | 3 | | |
| 4 | 2 | 1 | 2 | 4 | Medium | |
| 5 | 1 | 3 | 2 | 6 | | |
| 6 | 2 | 2 | 2 | 8 | | |
| 7 | 3 | 3 | 1 | 9 | | |
| 8 | 3 | 2 | 2 | 12 | High | |
| 9 | 2 | 3 | 3 | 18 | | |
| 10 | 3 | 3 | 3 | 27 | | |

***District:*** *district code*
***Trend:*** *1=decrease 2=no change 3=increase*
***Risk:*** *1=low 2=medium 3=high*
***Rate:*** *1=low 2=medium 3=high*

***Score:*** *Product of scores expressed by each variable*
***Classes****: The number of map adaptable scaling according to the amount of detail required. i.e. two classes or three class or five classes based on scores*

*Example of map legend colours from variations of matrix scores leading to the high-burden and low-burden maps. Adaptable scaling can be used depending on the amount of detail required.*

Figure 3.S3: HMIS data Quality improvements from 2010-2016



8.1.1.7 REFERENCES

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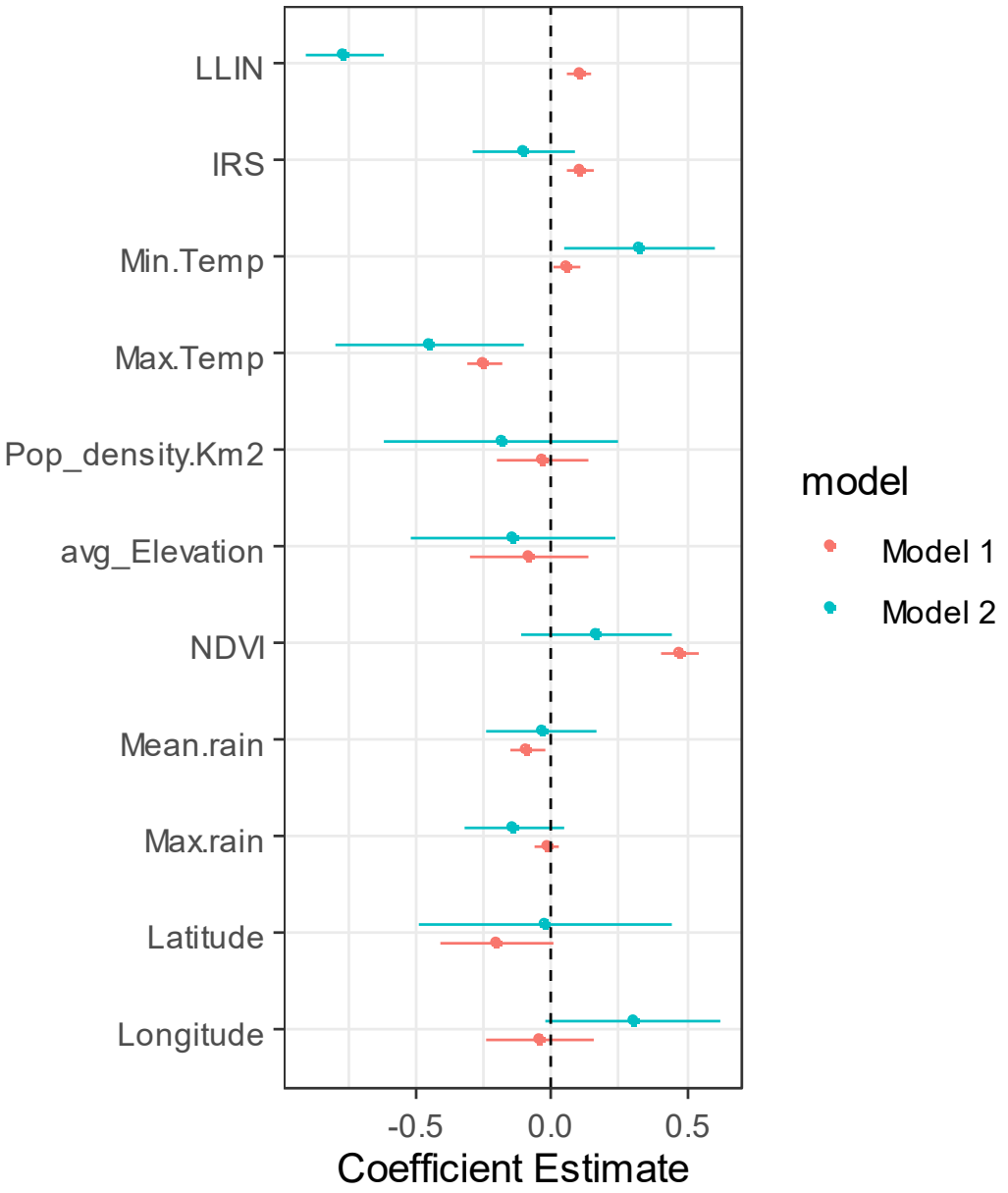
# APPENDIX B: APPENDICES FOR CHAPTER FOUR

## 8.2.1 Supplementary Figures for chapter 4

Figure 4.S1: visualizations of correlation




Model1 = Areas of increasing malaria

Model2 = Areas of declining malaria

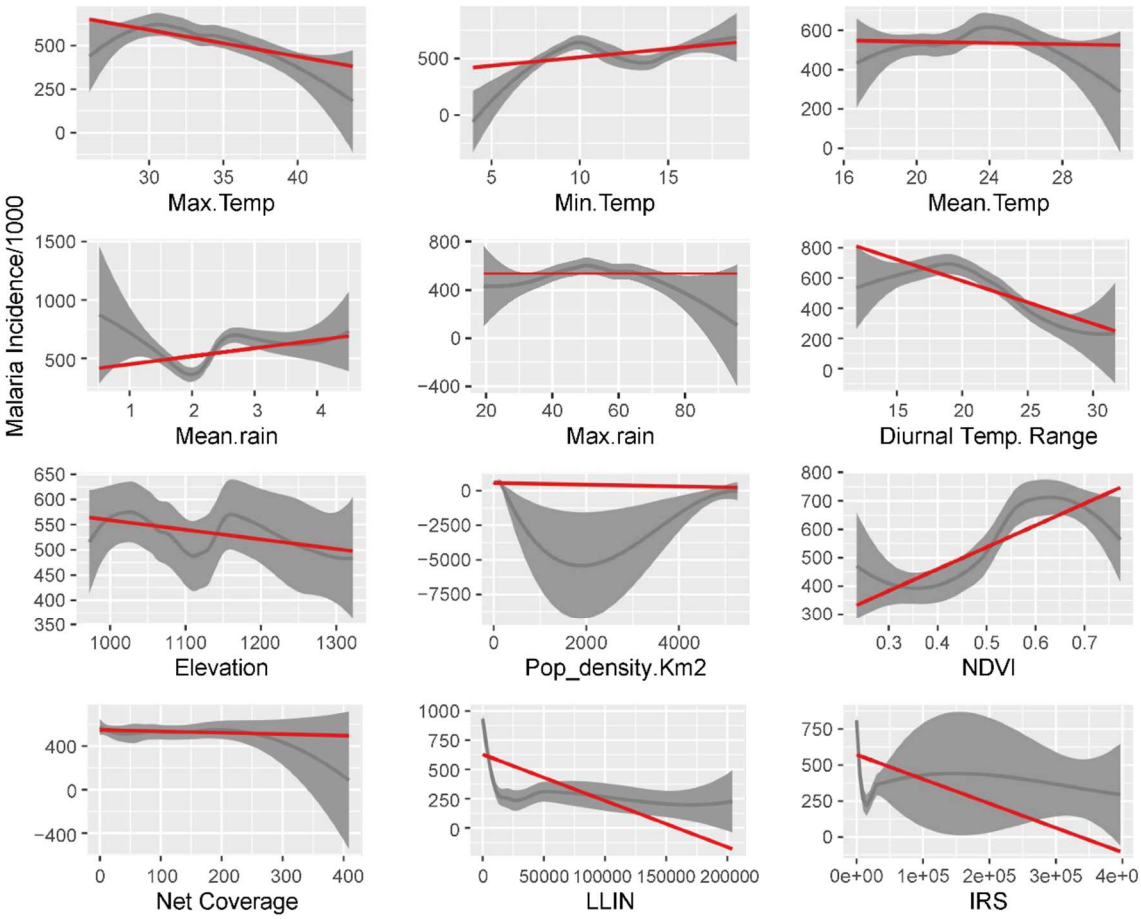



Figure 4.S2: Regression results in areas of declining malaria

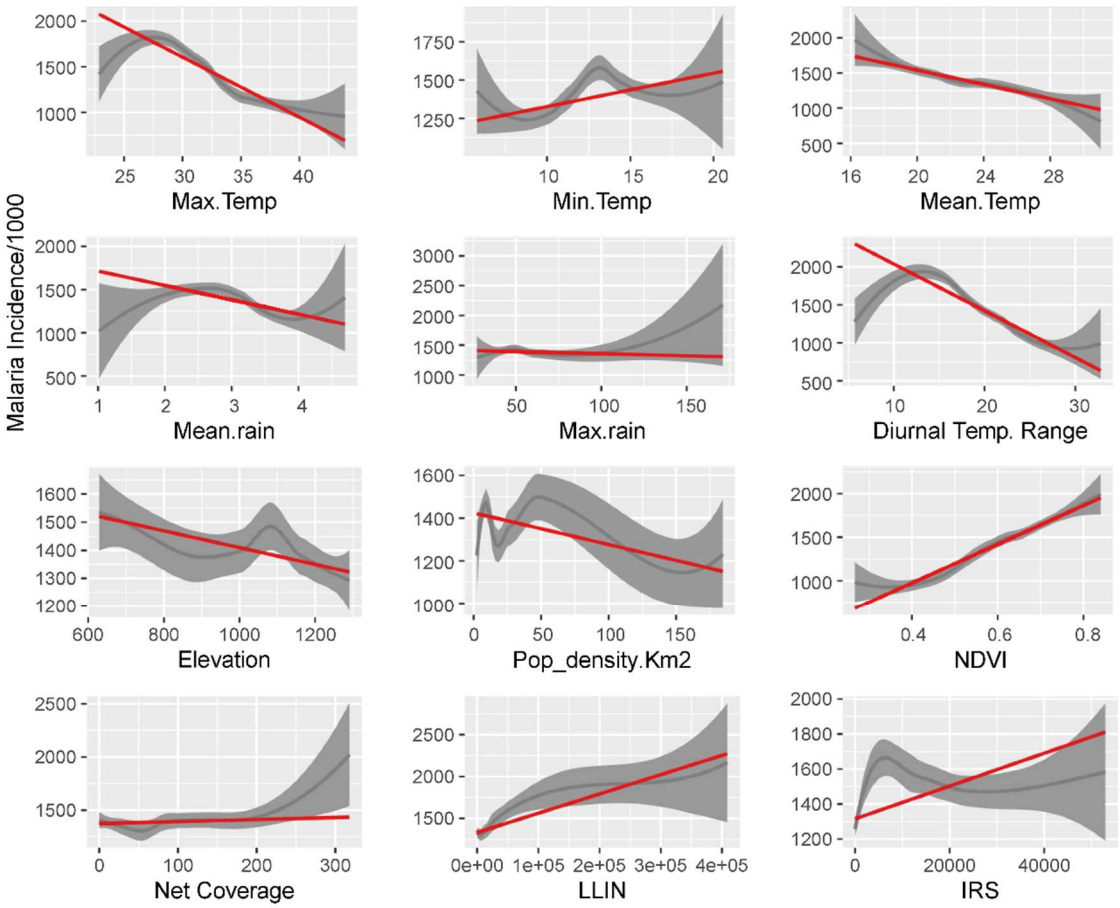



Figure 4.S3: Regression results in areas of increasing malaria

| | Season | Slope | Intercept | $R^2$ | F | P | |
|---|---|---|---|---|---|---|---|
| **Temperature (DTR) – Areas of malaria decline** | Q1 | -0.10892 | 235.7 | 0.13 | 2.33 | 0.15 | |
| | Q2 | -0.04198 | 105.7 | 0.02 | 0.33 | 0.57 | |
| | Q3 | 0.117428 | -210.4 | 0.30 | 6.52 | 0.02 | * |
| | Q4 | 0.1897 | -358.7 | 0.37 | 8.96 | 0.009 | ** |
| **Seasonal malaria trend – Areas of malaria decline** | Q1 | -83.7099 | 168746.7 | 0.79 | 57.97 | 1.58E-06 | **** |
| | Q2 | -99.2363 | 199932.3 | 0.70 | 34.78 | 2.93E-05 | **** |
| | Q3 | -64.8745 | 130681.8 | 0.80 | 58.90 | 1.43E-06 | **** |
| | Q4 | -66.9569 | 134865.9 | 0.86 | 95.30 | 6.85E-08 | **** |
| **Temperature (DTR) – Areas of malaria increase** | Q1 | -0.23652 | 491.3 | 0.67 | 30.63 | 5.72E-05 | **** |
| | Q2 | -0.16497 | 351.5 | 0.43 | 11.23 | 0.004381 | ** |
| | Q3 | -0.00911 | 42.9 | 0.002 | 0.03 | 0.865916 | |
| | Q4 | -0.03933 | 100.1 | 0.035 | 0.54 | 0.475054 | |
| **Seasonal malaria trend – Areas of malaria increase** | Q1 | 99.36241 | -197667 | 0.75 | 43.96 | 8.01E-06 | **** |
| | Q2 | 69.81311 | -138490 | 0.41 | 10.64 | 0.005 | ** |
| | Q3 | 8.418798 | -15953.9 | 0.096 | 1.60 | 0.23 | |
| | Q4 | 22.35414 | -43681.6 | 0.23 | 4.37 | 0.054 | |

Table 4.S1: Summary of DTR seasonality trends vs malaria seasonality

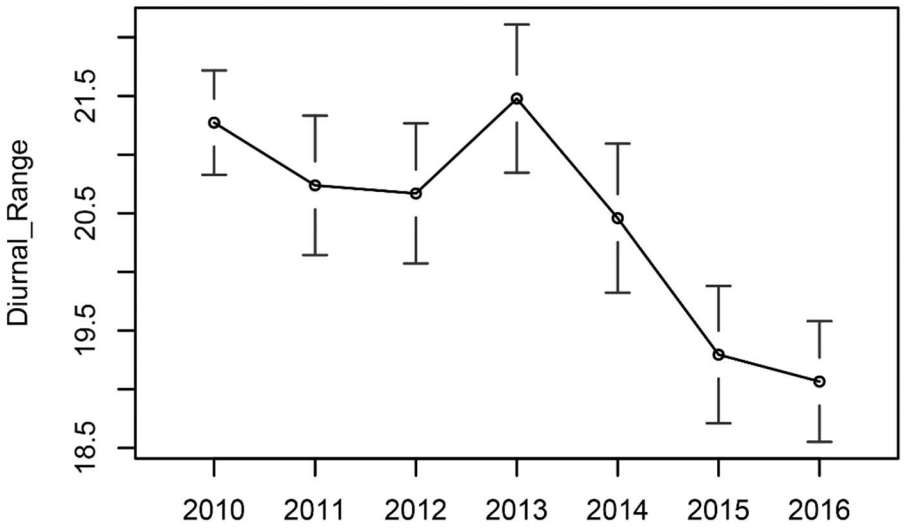



Figure 4.S4: Overall mean DTR trend between 2010-2016

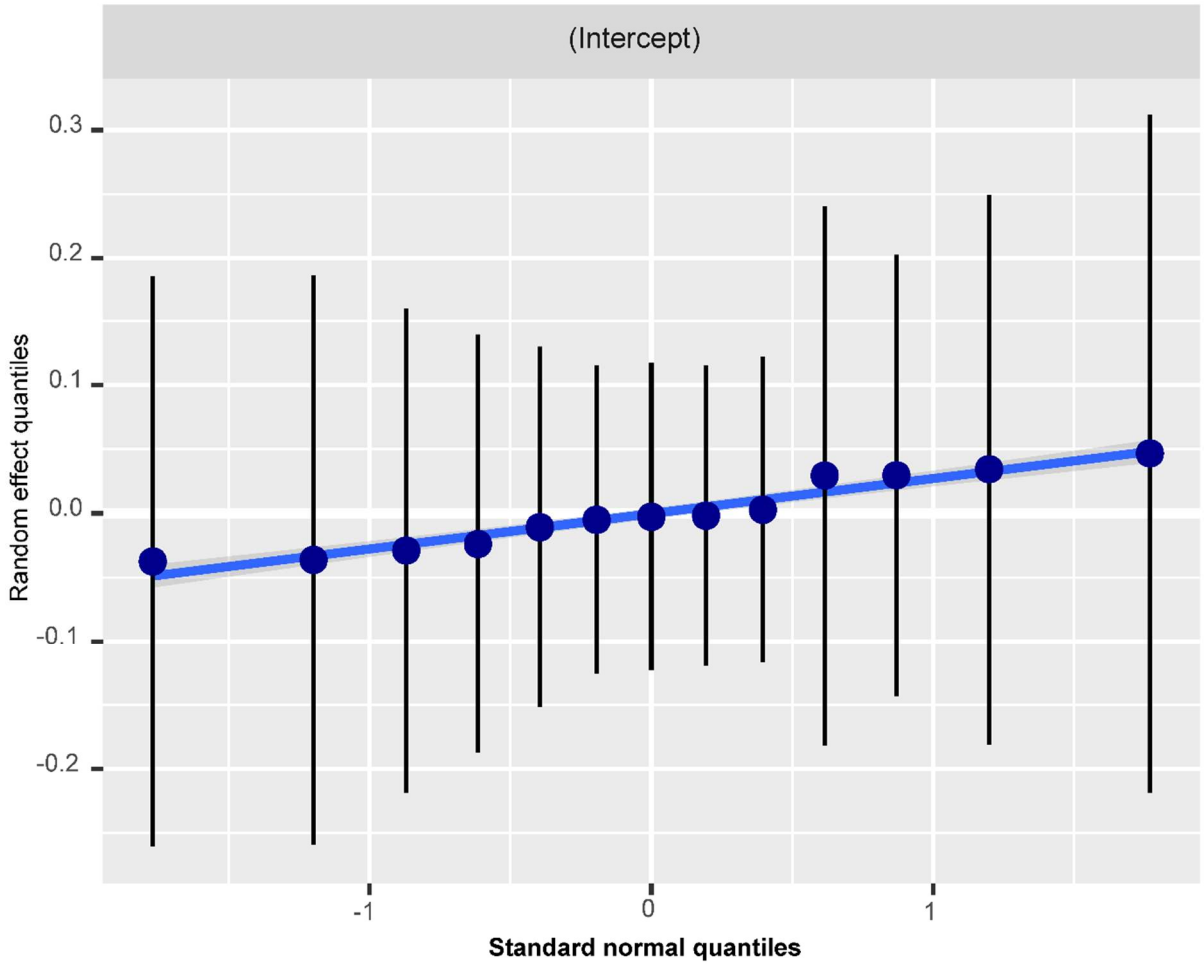



Figure 4.S5: Random effect quantiles in areas of declining malaria

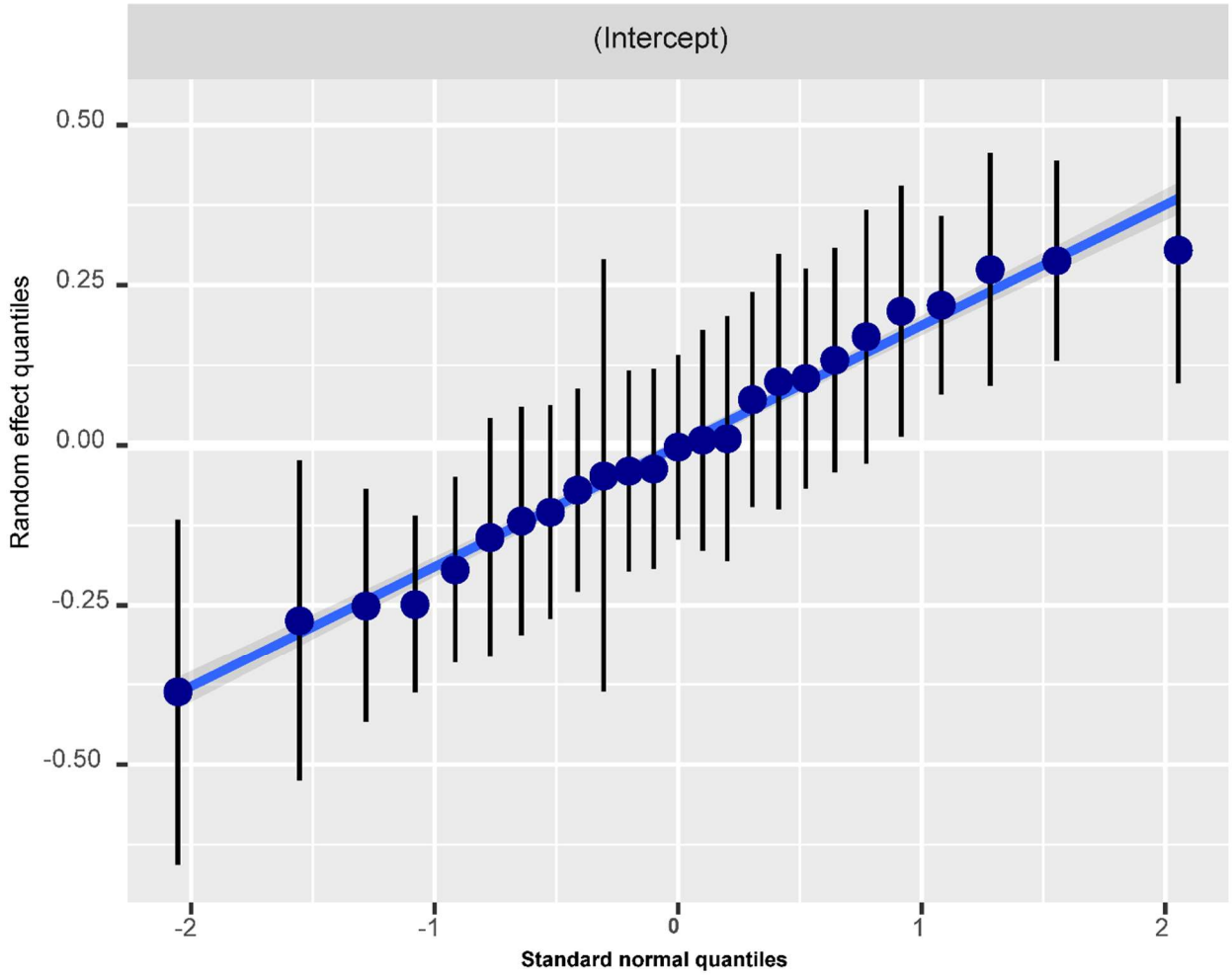



Figure 4.S6: Random effect quantile in areas of increasing malaria

# APPENDIX C: APPENDICES FOR CHAPTER FIVE

## 8.2 Supplementary tables and figures for chapter 5

Table 5.S3: Summary of relevant variables explored in the study.

| Variable | Scale |
|---|---|
| Malaria Incidence data | |
| • *Malaria count data by district (Under 5 & Over 5)* | District level |
| • *District population count data* | District level |
| • *District population density* | District level |
| Environmental variables | |
| • *Maximum Temperature (°C)* | 20km x 20km |
| • *Minimum Temperature (°C)* | 20km x 20km |
| • *Mean Temperature (°C)* | 20km x 20km |
| • *Maximum Rainfall (mm)* | 5km x 5km |
| • *Mean Rainfall (mm)* | 5km x 5km |
| • *Minimum Rainfall (mm)* | 5km x 5km |
| • *Normalized Difference Vegetation Indices (NDVI)* | 1 km x 1 km |
| • *Elevation (m)* | 12.5 m x 12.5m |
| Malaria Intervention Variables | |
| *Long Lasting Insecticide Nets (LLIN)* | District level |
| *Indoor Residual Spraying (IRS)* | District level |

Note: Other additional supporting variables like (date, quarter, or year) were used as covariates while district names and IDs were considered as random

Table 5.S4: Summary of pre-analysis formal goodness-of-fit tests on the simulated residuals in GLMM

| Data structure | Test used | Result with |
|---|---|---|
| 1. **Outliers/Influential observations** | Cook's distance | 149 observations |
| 2. **Multicollinearity** | Variance Inflation Factor (VIF) | Temperature (min, max, mean) |
| 3. **Zero-inflation** | DHARMa (test for zero-inflation) | None |
| 4. **Linear/non-linear structures** | Residual plots from linear models | Inconclusive presence of non-linear |
| 5. **Non-normality** | DHARMa (test for Uniformity) | |
| 6. **Dispersion/ Heteroscedasticity** | DHARMa (test for dispersion) | Strong presence of OD |
| 7. **Temporal Autocorrelation** | Dubin Watson's Test | Strong presence |
| 8. **Spatial Autocorrelation** | Moran's I | Very weak presence |

Note: DHARMa R package was mainly used in testing from GLMM while the rest were mainly done for GLM or LM pre-analyses.

(1). For Uniformity test, results had too many residuals around 0 and 1 which means that too many residuals were at the tails of the distribution than expected from the fitted models.

(2). Cook's distance calculates observations with large values. In the data, 149 observations were deemed influential but these were too many to exclude.

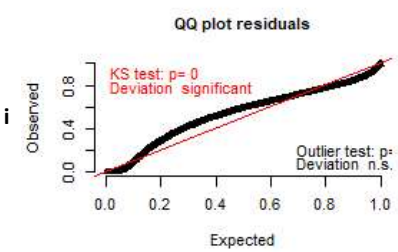
(3). VIF was used to determine collinearity among explanatory variables denoted by very high VIF and correlation coefficients. Temperature variables (min, max, mean) values (≈200 000) and confirmed by high correlations (0.83 and 0.76) as well. The study dropped the mean Temp variable based on biological sense and kept min and max.

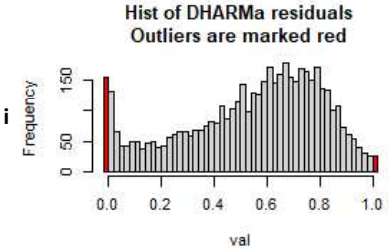
(4). Although it seemed there was a weak presence of overdispersion at first, that disappeared once correction for dispersion was done

(6). Large overdispersion was found in lm, glm, and normal Poisson glmm models, hence the choice for negative binormial

(7). Spatial autocorrelation was not significant while temporal autocorrelation was present and significant.

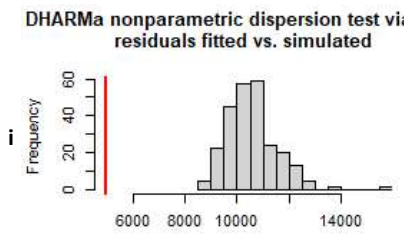
testUniformity(simulationOutput) One-sample Kolmogorov-Smirnov test data: simulationOutput$scaledResiduals D = 0.12669, p-value < 2.2e-16 alternative hypothesis: two-sided

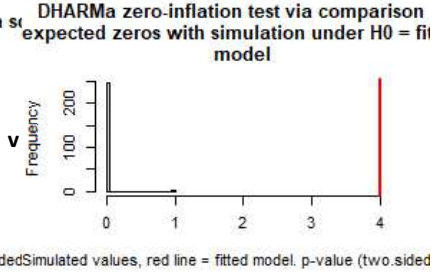



testOutliers(simulationOutput) DHARMa outlier test based on exact binomial test data: simulationOutput outLow = 1.5400e+02, outHigh = 2.7000e+01, nobs = 4.8950e+03, freqH0 = 3.9841e-03, p-value = 0.1234 alternative hypothesis:

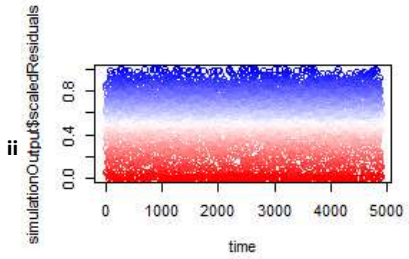
testDispersion(simulationOutput) DHARMa nonparametric dispersion test via sd of residuals fitted vs. simulated data: simulationOutput ratioObsSim = 0.47051, p-value < 2.2e-16 alternative hypothesis: two.sided

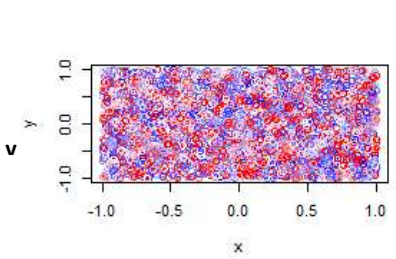



testZeroInflation(simulationOutput) DHARMa zero-inflation test via comparison to expected zeros with simulation under H0 = fitted model data: simulationOutput ratioObsSim = 500, p-value < 2.2e-16 alternative

testTemporalAutocorrelation(simulationOutput) Durbin-Watson test data: simulationOutput$scaledResiduals ~ 1 DW = 2.0259, p-value = 0.3648 alternative hypothesis: true autocorrelation is not 0




testSpatialAutocorrelation(simulationOutput) DHARMa Moran's I test for spatial autocorrelation data: simulationOutput observed = -0.00044970, expected = -0.00020433, sd = 0.00058953, p-value = 0.6773 alternative hypothesis: Spatial autocorrelation

Figure 5.S1: A summary of diagnostic plots used in the data analysis.
The Figure Negative binomial glmmtmb: diagnostic plots showing corrected over dispersion and significant presence of spatial and temporal autocorrelation. These results help to determine and confirm the right model for the data.

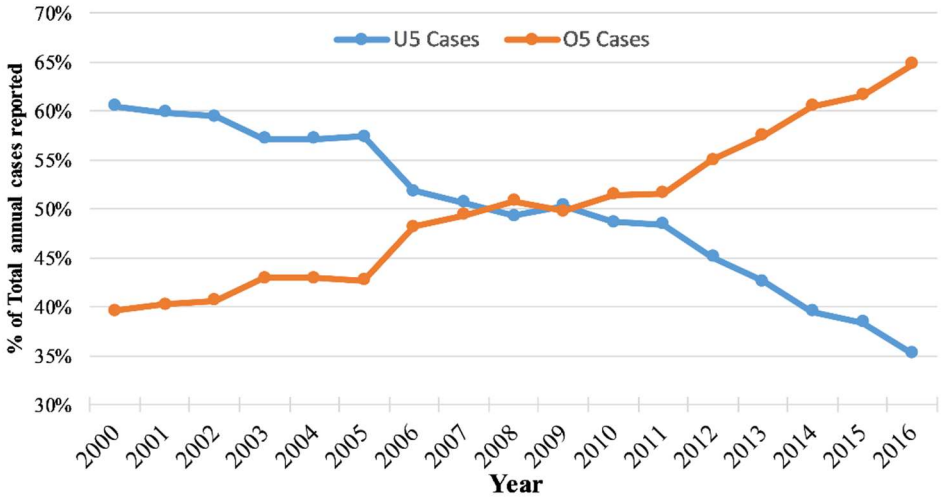



Figure 5.S2 Proportion of cases reported by age-group

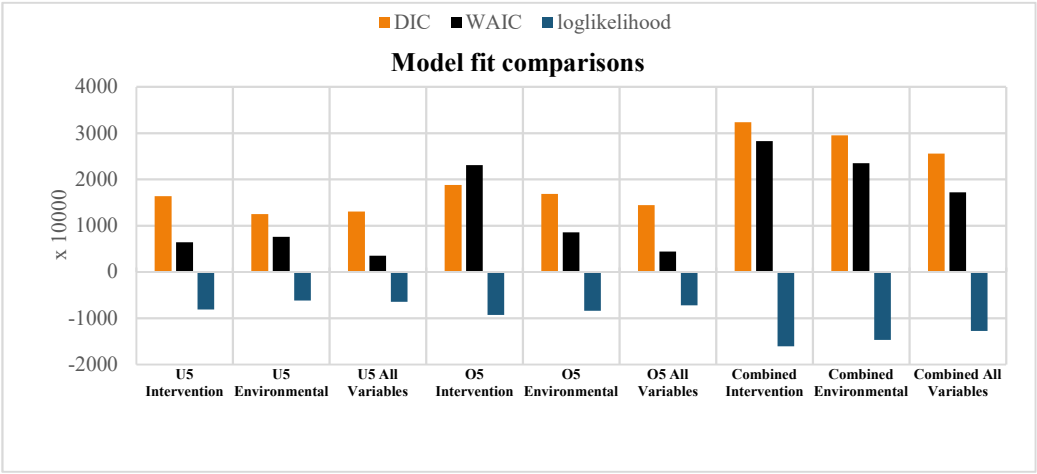



Figure *5.S3:* Model performance comparisons using climate and intervention variables.

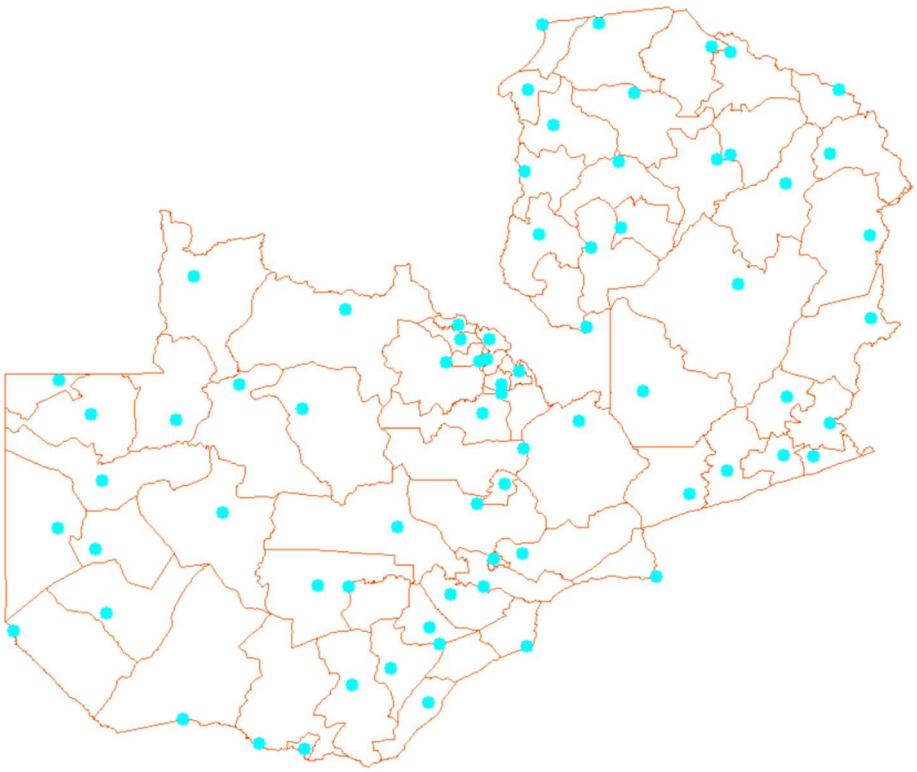
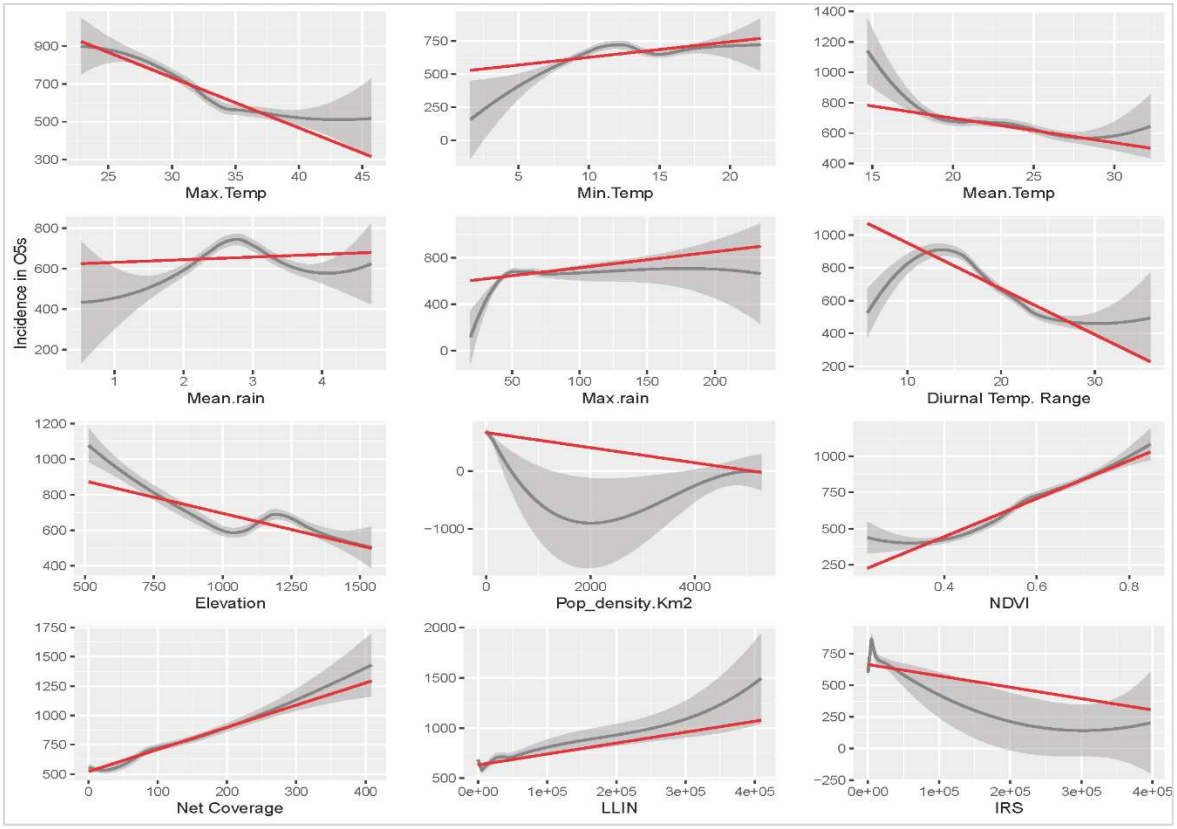
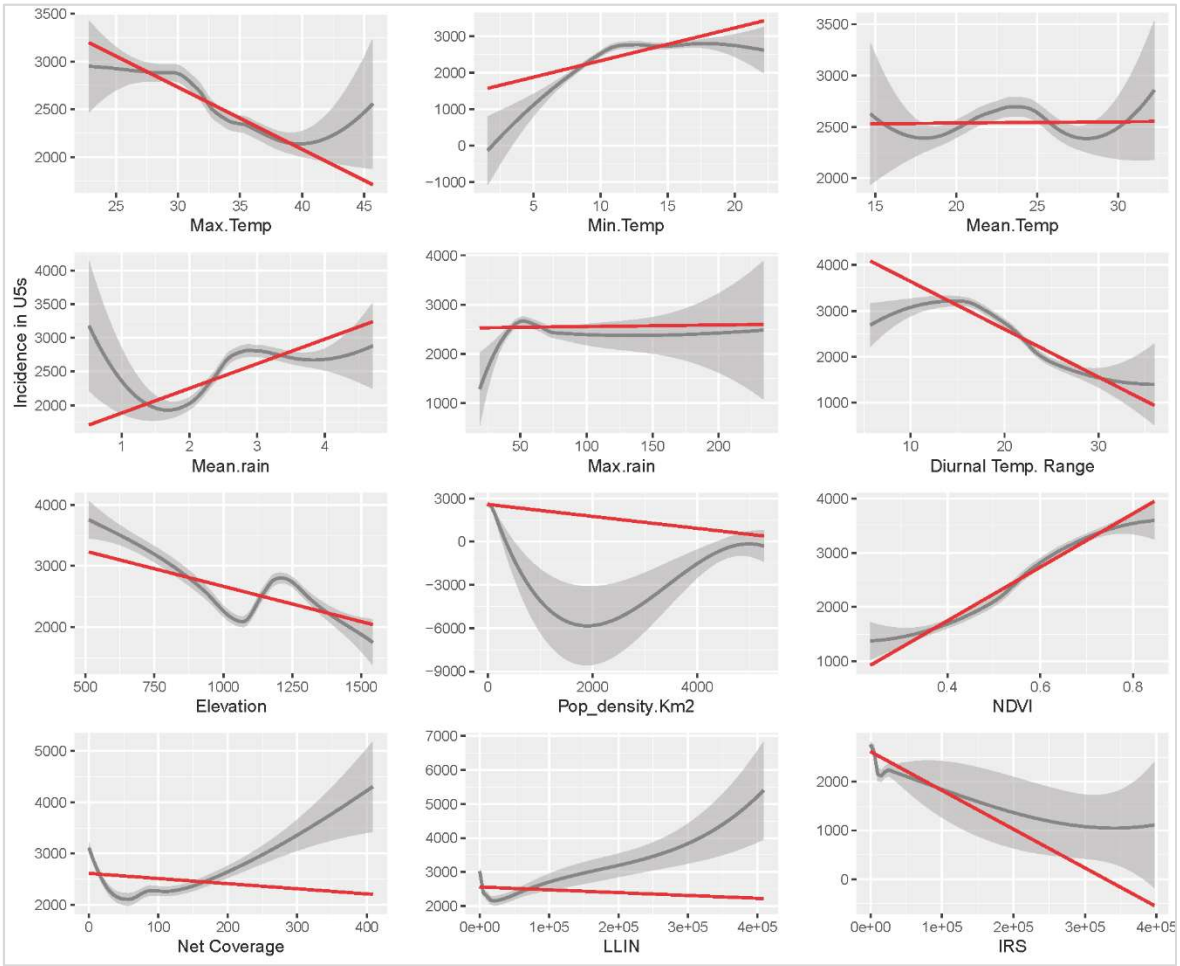


Figure 5.S4: Location of district population weighted centres in Zambia
Population weighted centroids obtained from districts polygons of visually verifiable populated (mostly urban) settlement hubs in Zambia's districts

Fig. S5: Variable observation distribution and regression slopes



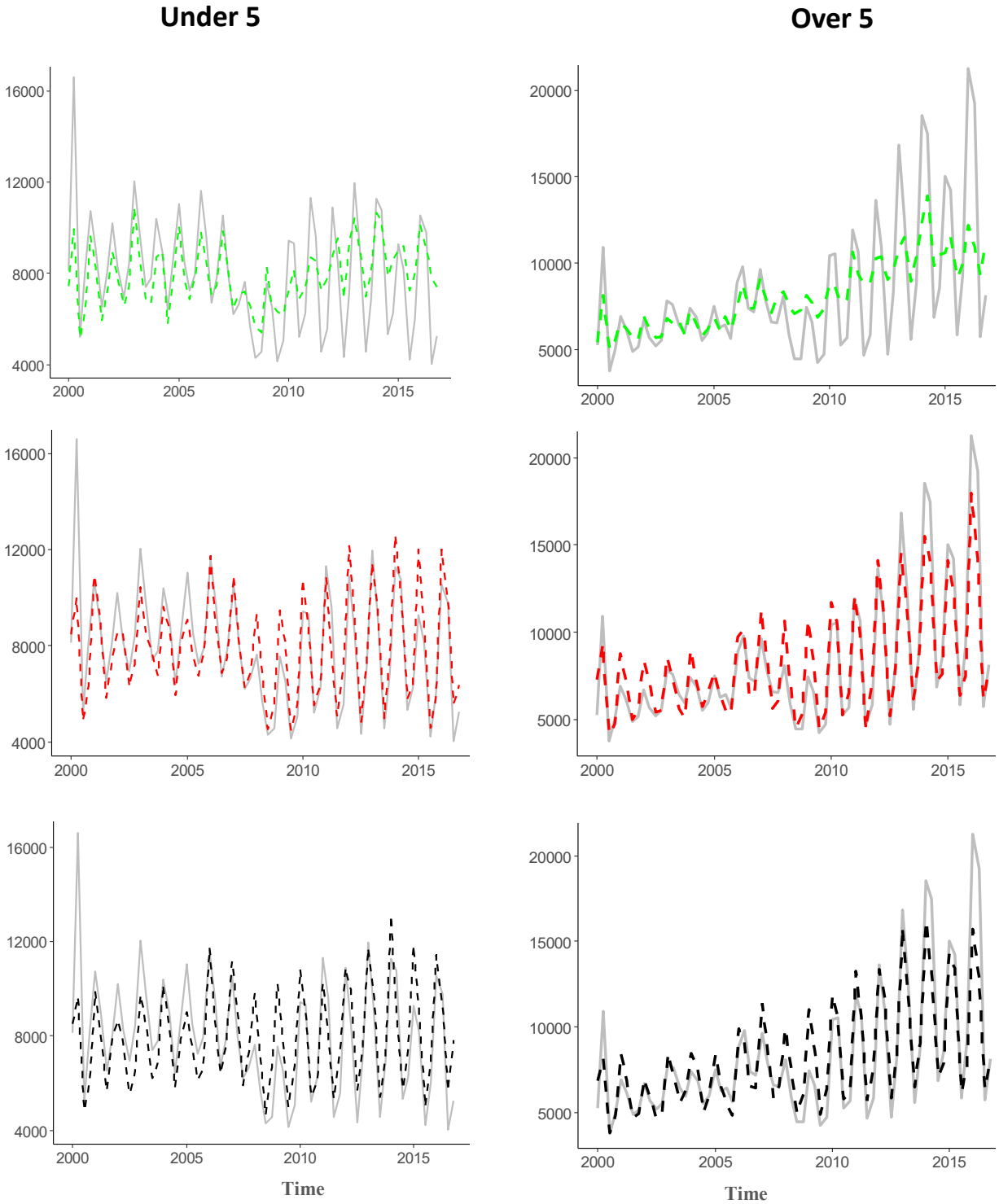



Figure 5.S6: Predicted vs observed malaria case scenarios in under and over five year olds Predicted under five malaria cases using interventions (IRS and LLIN) only vs Climate variables (Tmax, Tmin, Rmax, Rmean, NDVI) only. Green/solid line indicates intervention model while brown/dashed line indicates environmental model.

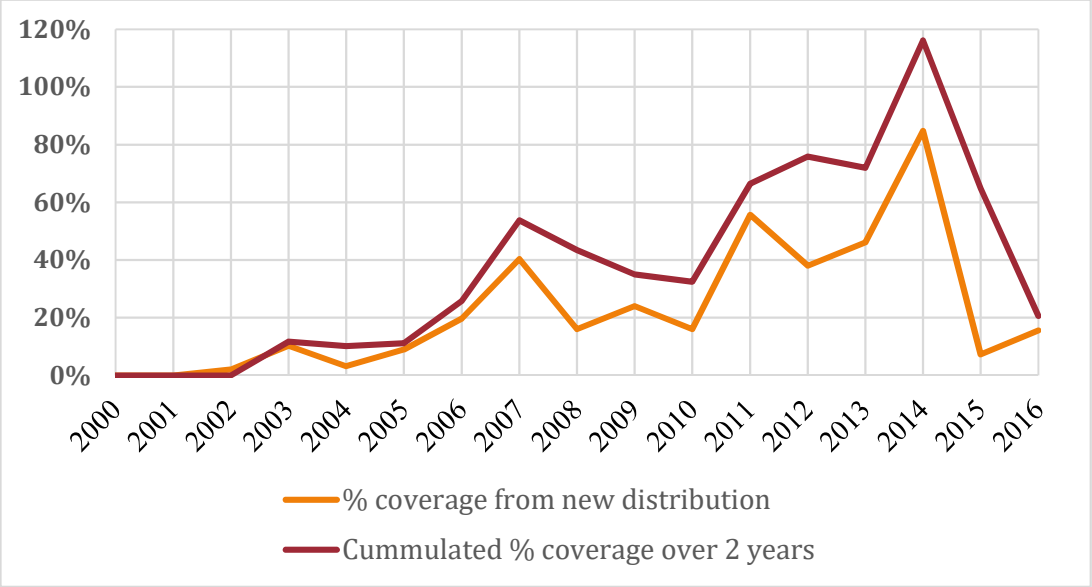



Figure 5.S7: LLIN percentage coverage between the period 2000 and 2016
Bed net coverage with two years accumulated distribution. The Figures are derived using accumulated distribution of LLINs as applied by Tan et. al. (2016) reported 30% attrition rates.

### 8.2.1 Supplementary methods for Chapter Five

#### 8.2.1.1 Demographic, epidemiological and intervention data

Census and post-census populations and age-group (<5 and ≥5 years) estimates were obtained from the central statistics office (CSO) report (Central Statistical Office, 2013) and used to calculate district age-specific malaria morbidity and mortality rates. Routinely collected malaria epidemiological data were obtained from Zambia's Ministry of Health (MoH) through the National Malaria Elimination Centre (NMEC). Malaria data for <5 and ≥5 years were reported collectively as clinical and microscopy or rapid diagnostic test (RDT) confirmed cases up until 2009. Since the countrywide introduction of RDTs (National Malaria Control Programme, 2012; World Health Organization, 2011; Yukich et al., 2012), clinical and confirmed cases have been reported separately (Mukonka et al., 2015).

The study used continuous temporal (quarterly) environmental data, and district level routinely collected malaria data aggregated into a long-term series, disaggregated into <5s and ≥5 year old age-groups, across 17 years from 2000 to 2016. The use of two age groupings of malaria data have for the last decades been endorsed because children <5 years of age were and continue to be the most vulnerable group to malaria, accounting for over 60% of deaths worldwide (Murray et al., 2012; World Health Organization, 2018f, 2019c). The specific focus on young children has also influenced the way malaria data is collected and officially reported. Typically, data is collated, analysed and presented either as <5s or ≥5s.

#### 8.2.1.2 Intervention control data

Vector control data in the form of LLIN and IRS, which have been widely applied in recent years, were obtained from the national malaria elimination programme of Zambia (Chizema-Kawesha et al., 2010; Yukich et al., 2012). An operational coverage rate of two household residents per net was used (Masaninga et al., 2013; World Health Organization, 2008, 2015d). The LLIN records were available from all distribution channels, such as antenatal and <5 clinics, the expanded program on immunisations, and from community-based and nation-wide mass distribution campaigns**.** This study aggregated all data into 72 original districts to facilitate analysis of the full dataset over the whole 16-year study period.

8.2.1.3 Climate and ecological Data

Daily precipitation data (from Climate Hazards Group) with a spatial resolution of 5x5km (Funk et al., 2015); temperature data (from NCEP Climate Forecast System Reanalysis) (Saha et al., 2012) with a 20 x 20 km of spatial resolution; and the 10 daily Normalised Vegetation Index (NDVI) (from Copernicus Global Land Service) with 1x1km spatiotemporal resolutions (Smets et al., 2018, 2013) were collected *(see Table 5.S1).*

The primary climate variable choices (temperature and rainfall) were based on literature evidence of how temperature and rainfall influence both short and long term changes in malaria transmission (Abiodun et al., 2016; Blanford et al., 2013; Colón-González et al., 2016; Krefis et al., 2011; Mohammadkhani et al., 2016; Odongo-Aginya et al., 2005; Okuneye & Gumel, 2017; Suk, 2016). Quarterly mean, maximum and minimum temperatures (Tmean, Tmax, Tmin, DTR) in $^{O}$C, mean rainfall and max rainfall (mm) for the period from January 2000 to December 2016 were extracted using the R Program raster package (Hijmans, 2019) for all 72 districts. Diurnal temperature range (DTR) was computed from daily temperature data.

8.2.1.4 Adjusting reported data for quality

Zambia health information records have more or less been comprehensive for the whole country since 2000 (World Health Organization, 2008), and the quality of data has improved even more since 2010 (Presidential Malaria Initiative, 2018). Nonetheless, the study adjusted the data for varying quality using reporting rates, health-seeking, and data missingness. Reports were aggregated quarterly. In the absence of specific information on district reporting completeness, this was estimated using information from malaria indicator surveys and/or demographic health surveys.

Missing data values were imputed using multiple imputation methods via a trained Random Forest of observed values (missForest R package) (Stekhoven & Bühlmann, 2011), to replace missing values with plausible data values (Stef Van Buuren, 2018). An estimate of 5% missing values was detected in the dataset. Treatment seeking information was extracted from demographic health surveys of 2001-2, 2007, and 2013-14 (Central Statistical Office (CSO), Ministry of Health (MOH) & University of Zambia, 2009; Central Statistical Office (CSO) [Zambia], Ministry of Health (MOH) [Zambia], 2014; Central Statistical Office [Zambia], Central Board of Health [Zambia], 2002), then used to adjust for cases not seeking care or not captured by the HMIS. The final

calculation is summarised in Equation 1 (WHO Malaria Policy Advisory Committee, 2018):

$$= \frac{Cases_{presumed} + Cases_{confirmed}}{Reporting\ completeness}(1 + treatment\ seeking\ rate) \quad (1)$$

The study did not have information on positivity rates; hence, and did not adjust for clinical malaria in the dataset. This means that the conclusions may also capture non-malaria fever, especially between 2000 and 2008, potentially resulting in some malaria over-estimation.

8.2.1.5 Generating Longitude and Latitude representing population centres

Latitude and longitude coordinates were extracted to represent population-weighted centroids, with accuracy being validated in ArcGIS version 10. These locations were used to test for spatial autocorrelation and as spatial variables against malaria (Figure S5).

8.2.1.6 Modelling and Statistics

The dependent variable used in the model is the Poisson data likelihood given that a Poisson family was chosen over "binomial" or "Gaussian" options. This model also suits the need to estimate the evolution of the spatial response surface of malaria over the considered time without coercing it to be the same for each period (Figure 2). This model has the capability of estimating the effect of risk factors such as temperature, rainfall, and NDVI on the response variables of malaria incidence or mortality (Lee, Ferguson, & Mitchell, 2009; Wakefield, 2006).

The model allows for spatio-temporal autocorrelation via random effects, which capture the remaining autocorrelation in the disease data after the effects of the known covariates have been accounted for. Therefore, the study tested for the presence of spatial autocorrelation in the data set by first computing the residuals from a simple over-dispersed Poisson log-linear model that incorporates the covariate effects. These results showed that the assumption of independence is not valid for these data and that spatio-temporal autocorrelation should be allowed for when estimating the covariate effects.

8.2.1.7 Moran's I statistic for under-five malaria mortality

Moran's I permutation test was applied, given the null hypothesis of no spatial autocorrelation and an alternative hypothesis of positive spatial autocorrelation. The Moran's I statistic gave -0·09 (*p.value* = 0·86), indicating the lack of evidence of unexplained negative autocorrelation in the residuals of the <5 age-group malaria

mortality data. We, therefore, fail to reject the null hypothesis that there is no spatial autocorrelation in the values of death among <5 between January and March (first quarter) for this sample. Uncertainty could, therefore, be assumed in this data having spatio-temporal autocorrelation or independence and thence should allow for it during estimations in covariate effects. The results show varying levels of effect on <5 mortality risk by all covariates. However, none of these effects was significant at 95% CI.

8.2.1.8 The capture of spatio-temporal random effects

The model accommodates spatio-temporal autocorrelation into the response variable **Y** through latent random effects, through CAR-type prior distributions and spatio-temporal extensions. The symmetric nonnegative $K \times K$ neighbourhood controls the spatial units through the adjacency matrix **W**= ($w_{kj)}$, where $W_{kj}$ characterises the closeness between a pair of spatial units ($S_k$, $S_j$). The weighted matrix creates higher values for area units with spatial adjacency, but low or 0 values for areas spatially apart.

The matrix **W** creates a binary, ($w_{kj}$ = 1 if spatial units ($S_k$, $S_j$) share a common boundary/edge and $w_{kj}$ = 0 if not. However, this binary specification of **W** has to fulfil three conditions, namely; symmetry, non-negativity, and row sums greater than zero. This model treats spatially proximate areal units as spatially autocorrelated while those spatially apart (not sharing a boundary [$w_{kj}$=0]) as conditionally independent (*see* (Lee et al., 2018) *for more details)*. This model also captures the remaining autocorrelation in the data after accounting for the effects of known covariates. Spatial autocorrelation tests involved computing the residuals from simple over-dispersed Poisson log-linear models first. This model also incorporated covariate effects.

8.2.1.9 Scenario modelling of interventions vs Climate Change

The predicted infection values against observed malaria due to effects from intervention shows that the effect on malaria was not consistent over the study period. The study did not examine model performance on individual districts to highlight which districts had better intervention or climatic models. However, results from the reported effects of diurnal temperature range could be extrapolated through groups of districts with increasing malaria vs those with declining malaria trends.

The conditional multivariate model has a first-order spatially correlated precision matrix. This model was utilised to estimate the evolution of the spatial response surface of malaria from 2000 to 2015. The model specification is given below:



(1)

$$\psi = \phi_{kt,}$$
$$\phi_t|\phi_{t-1} \sim N(\rho T\phi_{t-1,}\mathcal{T}^2\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1}) \qquad t = 2,\ldots,N,$$
$$\phi_1 \sim \mathrm{N}(\mathbf{O},\mathcal{T}^2\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1})$$
$$\mathcal{T}^2 \sim \mathrm{Inverse}-\mathrm{Gamma}(a,b),$$
$$\rho s,\rho\mathcal{T} \sim \mathrm{Uniform}(0,1).$$

The model $\phi_t = (\phi_{1t},\ldots,\phi_{Kt})$ represents a vector of random effects for period *t*, which progresses over time through an autoregressive multivariate process alongside the temporal autoregressive parameter $\rho T$. The temporal autocorrelation, therefore, is induced through the mean $\rho T\phi_{t-1}$, and the spatial autocorrelation by the variance$\boldsymbol{Q}(\boldsymbol{W},\rho s)^{-1}$) respectively. Equation 2 gives the statistical form of this matrix:

$$(\boldsymbol{W},\rho s) = \rho s[\mathrm{diag}(\boldsymbol{W}\mathbf{1}) - \boldsymbol{W}] + (\mathbf{1} - \rho s)\mathbf{I} \qquad (2)$$

In equation Two, 1 represents the K × 1 vector of 1's from the binary and the K × K identity matrix is denoted by I. While random effects are zero-mean centred, specific flat priors (ρs,ρT) and conjugate priors ($\mathcal{T}^2$) are given and default values (a = 1, b = 0·01) for the latter (Lee et al., 2018).

Given that the dataset malaria counts *Y(t)* were collected at discrete times $t\in\{1,\ldots,n\}t\in\{1,\ldots,n\}$ by Equation 3:

$$Y(t)=\mu+X(t)+\varepsilon(t) \qquad (3)$$

Where μ = mean value parameter, *X(t)X(t)* = stationary AR(1) process, with covariance cov$(X(s),X(t))=\sigma 2\exp(-\theta|t-s|)cov(X(s),X(t))=\sigma^2\exp(-\theta|t-s|)$, and $\varepsilon(t)$ is the iid. $N(0,\sigma_0^2)$ measurement error.

Model results were compared using the Watanabe–Akaike information criterion (WAIC) (Watanabe, 2013), the Deviance information criterion (DIC) and the log-likelihood (Gelman, Hwang, & Vehtari, 2014) for evaluating the predictive accuracy of the fitted models. Based on the DIC and log-likelihood, it was observed that the model fitted using climatic/environmental variables alone provided better fit models in both <5 and ≥5 age groups as confirmed by Figure S5 showing higher model prediction error in later years.

Concisely, environmental variables were better predictors of malaria infections than interventions variables. The figures also showed that there was better prediction accuracy of the fitted models in the early years than in the later period, especially in the interventions models. In all three sets of models by age group (<5, ≥5 and all ages),

environmental variables proved to have a more substantial influence. They provided better model fitting estimations, as shown in the *Tables S3 and Figure S5.*

Below are summaries of the results of six models (three for <5 and ≥5 age groups) using interventions variables, climatic variables and all variables combined.

< 5 age group with interventions only

| | Median | 2·5% | 97·5% | n.sample | % accept | n.effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -1·4111 | -1·4116 | -1·4104 | 1e+05 | 45·1 | 224·1 | 14·7 |
| Pop_density | -0·0003 | -0·0003 | -0·0003 | 1e+05 | 45·1 | 2836·1 | -0·2 |
| IRS | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·1 | 0·0 | -Inf |
| LLIN | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·1 | 0·0 | Inf |
| tau2 | 0·3365 | 0·3138 | 0·3614 | 1e+05 | 100·0 | 39503·1 | -20·8 |
| rho.S | 0·1176 | 0·0924 | 0·1454 | 1e+05 | 43·9 | 55120·1 | -4·8 |
| rho.T | 0·3108 | 0·2832 | 0·3381 | 1e+05 | 100·0 | 90238·2 | 10·5 |

< 5 age group with climatic variables only

| | Median | 2·5% | 97·5% | n.sample | % accept | n.effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -1·7652 | -1·7821 | -1·7509 | 1e+05 | 45·2 | 49·7 | -0·7 |
| Elevation | -0·0014 | -0·0014 | -0·0014 | 1e+05 | 45·2 | 40·3 | 15·0 |
| meanrain | 0·4966 | 0·4956 | 0·4978 | 1e+05 | 45·2 | 112·4 | 16·2 |
| maxrain | -0·0009 | -0·0009 | -0·0008 | 1e+05 | 45·2 | 33·7 | -2·2 |
| mintemp | 0·0179 | 0·0177 | 0·0184 | 1e+05 | 45.2 | 39.8 | 18.2 |
| maxtemp | -0.0273 | -0.0276 | -0.0269 | 1e+05 | 45.2 | 40.8 | -6.0 |
| NDVI | 1.9156 | 1.9087 | 1.9237 | 1e+05 | 45.2 | 82.4 | -1.6 |
| tau2 | 0.5020 | 0.4686 | 0.5388 | 1e+05 | 100.0 | 45240.3 | 8.1 |
| rho.S | 0.0738 | 0.0525 | 0.0973 | 1e+05 | 43.8 | 36885.9 | 8·8 |
| rho.T | 0·5449 | 0·5207 | 0·5692 | 1e+05 | 100·0 | 89720·3 | -5·2 |

< 5 age group with all variables combined

| | Median | 2·5% | 97·5% | n.sample | % accept | n.effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -2·2169 | -2·2261 | -2·1995 | 1e+05 | 45·2 | 182·9 | 17·4 |
| Elevation | -0·0007 | -0·0008 | -0·0007 | 1e+05 | 45·2 | 238·0 | 20·6 |
| Pop_density | -0·0001 | -0·0001 | -0·0001 | 1e+05 | 45·2 | 387·3 | -32·7 |
| IRS | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·2 | 0·0 | Inf |
| LLIN | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·2 | 0·0 | Inf |
| meanrain | 0·3383 | 0·3375 | 0·3392 | 1e+05 | 45·2 | 4542·5 | -5·7 |
| maxrain | -0·0015 | -0·0015 | -0·0015 | 1e+05 | 45·2 | 324·7 | -29·0 |
| mintemp | 0·0152 | 0·0150 | 0·0155 | 1e+05 | 45·2 | 251·2 | 67·5 |
| maxtemp | -0·0133 | -0·0138 | -0·0131 | 1e+05 | 45·2 | 112·0 | -28·5 |
| NDVI | 1·7100 | 1·6984 | 1·7156 | 1e+05 | 45·2 | 122·9 | -57·5 |
| tau2 | 0·3690 | 0·3439 | 0·3962 | 1e+05 | 100·0 | 53471·3 | -8·2 |
| rho.S | 0·1036 | 0·0794 | 0·1303 | 1e+05 | 43·8 | 36404·1 | 6·8 |
| rho.T | 0·4184 | 0·3920 | 0·4450 | 1e+05 | 100·0 | 53319·4 | 5·3 |

≥5 age group with interventions only

| | Median | 2·5% | 97·5% | n.sample | % accept | n.effective | Geweke·diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -2·8864 | -2·8871 | -2·8841 | 1e+05 | 45·2 | 24·1 | 3·4 |
| Pop_density | -0·0004 | -0·0004 | -0·0004 | 1e+05 | 45·2 | 102·2 | -8·2 |
| IRS | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·2 | 0·0 | -Inf |
| LLIN | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·2 | 0·0 | -Inf |
| tau2 | 0·3135 | 0·2925 | 0·3365 | 1e+05 | 100·0 | 62793·9 | -4·0 |
| rho.S | 0·1184 | 0·0933 | 0·1462 | 1e+05 | 43·8 | 56038·1 | 2·2 |
| rho.T | 0·3831 | 0·3548 | 0·4098 | 1e+05 | 100·0 | 3347·3 | -4·2 |

≥5 age group with climatic variables only

| | Median | 2·5% | 97·5% | n.sample | % accept | n·effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -4·0102 | -4·0232 | -3·9813 | 1e+05 | 45·2 | 11·7 | 0·9 |
| Elevation | -0·0009 | -0·0009 | -0·0009 | 1e+05 | 45·2 | 13·7 | -3·4 |
| meanrain | 0·1904 | 0·1878 | 0·1921 | 1e+05 | 45·2 | 10·5 | 4·4 |
| maxrain | 0·0063 | 0·0062 | 0·0063 | 1e+05 | 45·2 | 23·4 | 12·2 |
| mintemp | -0·0146 | -0·0152 | -0·0144 | 1e+05 | 45·2 | 23·3 | -21·9 |
| maxtemp | -0·0090 | -0·0095 | -0·0086 | 1e+05 | 45·2 | 21·5 | 4·1 |
| NDVI | 2·8545 | 2·8410 | 2·8677 | 1e+05 | 45·2 | 11·9 | -3·7 |
| tau2 | 0·3970 | 0·3716 | 0·4252 | 1e+05 | 100·0 | 56828·2 | 1·3 |
| rho.S | 0·0356 | 0·0185 | 0·0549 | 1e+05 | 43·8 | 50427·5 | 2·0 |
| rho.T | 0·4627 | 0·4374 | 0·4880 | 1e+05 | 100·0 | 56501·8 | -11·3 |

≥5 age group with all variables combined

| | Median | 2·5% | 97·5% | n.sample | % accept | n.effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | -3·4558 | -3·4645 | -3·4460 | 1e+05 | 45·1 | 1253·9 | 1·3 |
| Elevation | -0·0003 | -0·0003 | -0·0003 | 1e+05 | 45·1 | 719·7 | -39·2 |
| Pop_density | -0·0003 | -0·0003 | -0·0003 | 1e+05 | 45·1 | 4416·8 | 18·9 |
| IRS | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·1 | 0·0 | -Inf |
| LLIN | 0·0000 | 0·0000 | 0·0000 | 1e+05 | 45·1 | 0·0 | Inf |
| meanrain | 0·0729 | 0·0720 | 0·0738 | 1e+05 | 45·1 | 981·5 | -4·4 |
| maxrain | 0·0020 | 0·0020 | 0·0020 | 1e+05 | 45·1 | 164·6 | -27·1 |
| mintemp | 0·0009 | 0·0006 | 0·0011 | 1e+05 | 45·1 | 296·3 | -11·6 |
| maxtemp | -0·0201 | -0·0203 | -0·0199 | 1e+05 | 45·1 | 679·4 | 6·2 |
| NDVI | 2·1567 | 2·1506 | 2·1637 | 1e+05 | 45·1 | 478·5 | 11·6 |
| tau2 | 0·3324 | 0·3108 | 0·3561 | 1e+05 | 100·0 | 58260·2 | -11·9 |
| rho.S | 0·0442 | 0·0262 | 0·0644 | 1e+05 | 43·8 | 54931·1 | 0·6 |
| rho.T | 0·4095 | 0·3833 | 0·4356 | 1e+05 | 100·0 | 83463·1 | 8·2 |

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# APPENDIX D: APPENDICES FOR CHAPTER SIX

## 8.3 Supplementary figures for chapter six

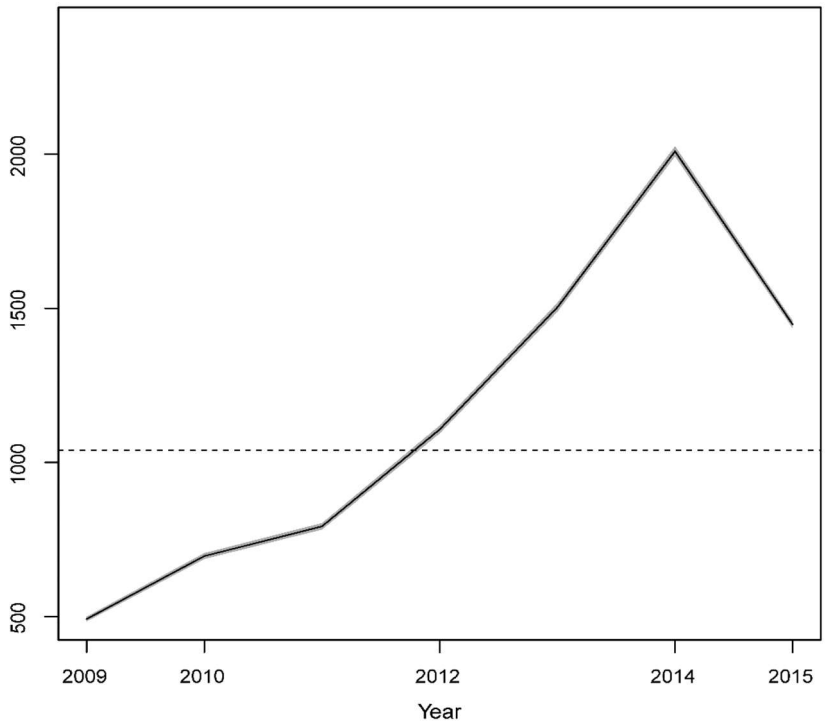


Figure 8.S1: Mean temporal incidence rates

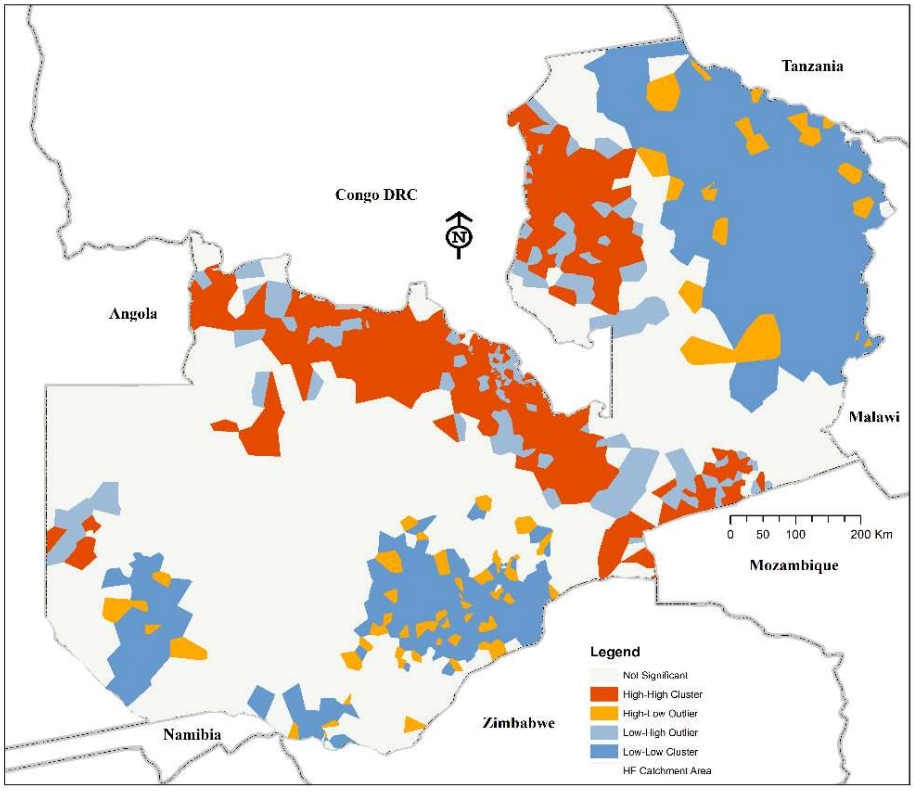


Figure 8.S2: Outliers within both hotspots and cold spot areas

| | Mode | 2.5% | 97.5% | n.sample | %accept | n.effective | Geweke.diag |
|---|---|---|---|---|---|---|---|
| (Intercept) | 0.0104 | 0.0098 | 0.0486 | 10000 | 43.7 | 193.7 | -2.0 |
| gamma.LD | -0.3770 | -0.3870 | -0.3765 | 10000 | 40.5 | 136.3 | 1.7 |
| gamma.LI | 0.1139 | 0.1120 | 0.1194 | 10000 | 41.4 | 3721.9 | -4.7 |
| lambda.Constant | 0.2575 | 0.2359 | 0.3739 | 10000 | 100.0 | 243.8 | -2.3 |
| lambda.LD | 0.2668 | 0.2440 | 0.2876 | 10000 | 100.0 | 2552.4 | 5.3 |
| lambda.LI | 0.4725 | 0.3617 | 0.4956 | 10000 | 100.0 | 288.1 | 2.4 |
| tau2 | 0.2172 | 0.1648 | 0.2583 | 10000 | 100.0 | 434.7 | 4.8 |
| rho | 0.2778 | 0.1759 | 0.3667 | 10000 | 44.0 | 1175.6 | 4.6 |

Table 8.S3: A summary of the estimated trends of malaria

The table also shows estimates within 95% credible intervals of significance. The tau2 and rho are estimators of variance parameters and spatio-temporal dependence or autocorrelation in the model, and all results here are significant statistically significant. The Table trend results are expressed as lambda.LD for [(λ) Linear decline (LD)], lambda.Constant and lambda.LI for [(λ) Linear Increase (LI)], respectively

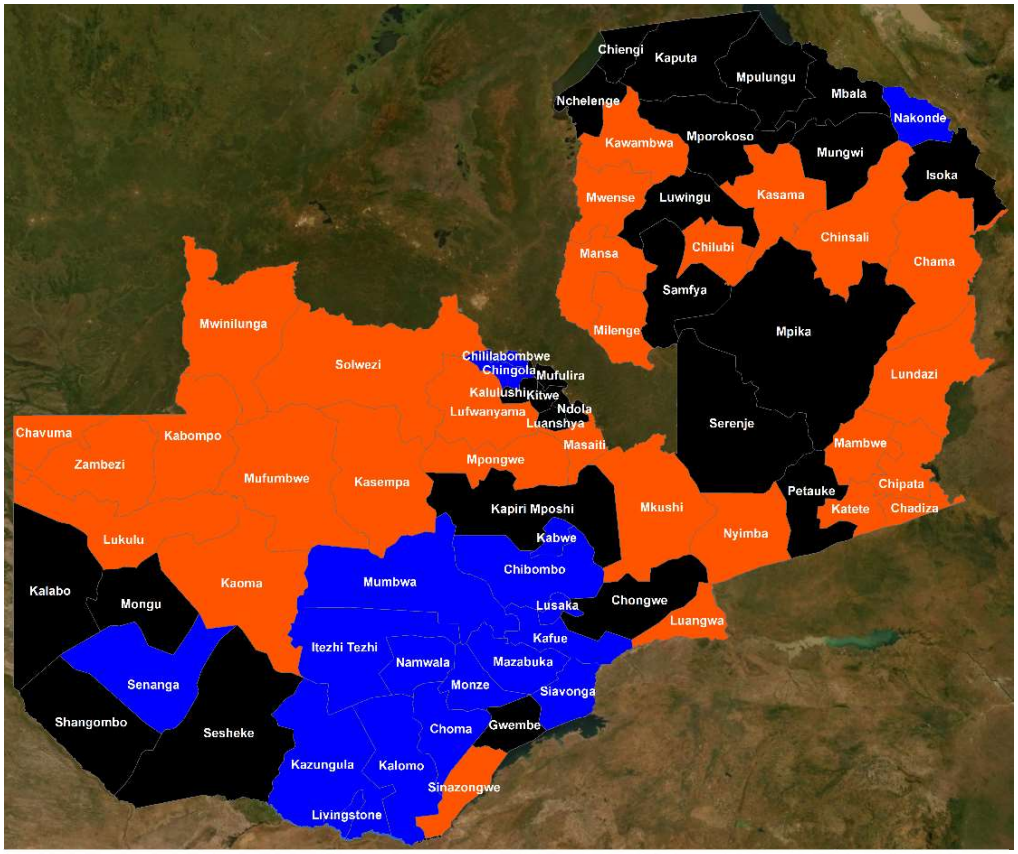


Figure S 8.3: District-level malaria trends between 2000 and 2015

### 8.3.1 Supplementary Methods for Chapter Six

#### 8.3.1.1 Health facility spatio-temporal models

In this study, 76 health facilities from a total of 1819 were excluded due to the lack of population data. Of the Health Facilities excluded eight only had malaria data for 2009-2015, while an additional 10 had data for 2014 and 2015, while the remaining 58 had data for 2015 only. Malaria cases reported at these 76 health facilities accounted for 0.8% of the total reported malaria cases available for analysis between 2009 and 2015.

The data was then divided into two sets, with a separation between 1743 low-level health facilities and 100 higher-level hospitals. The study grouped health posts, health centres, and clinics, together with all private health facilities into the first group for analysis as these are the sites where most of the malaria outpatient department (OPD) screening and treatment happens. The other set was comprised of only public level 3 and referral hospitals where the most severe cases are treated, often as in-patient admissions. This separation helped the study avoid double counts of malaria cases referred to hospitals from lower-level health facilities. All private hospitals were included in the first group because they also provide the services offered by lower-level public health facilities.

#### 8.3.1.2 The implication of the changing number of health facilities

Due to the periodic construction of new health facilities and upgrading some lower facilities to higher-level functions, the number of health facilities with at least one case reported in the HMIS increased by about 600 between 2012 and 2016 (Presidential Malaria Initiative, 2019). While the increase in newly constructed health facilities captured in the reporting system could be misinterpreted as the natural explanation for why there may be increases in recorded malaria cases, in reality, it has little to do with increasing malaria as these new facilities simply enhance access to and improve the quality of health services. This is especially true for urban areas where more people seek health facility services than the initial planned facility capacity or in some rural areas where some villages are far away from the available rural health facilities. Hence, the new health facilities may have affected the specific periodic number of cases usually reported at health facilities around it by sharing both the catchment area, the population, and the disease burden. Consequently, this would not automatically increase malaria cases reported by significant numbers.

Nonetheless, most of these new centres still take a long time to gain the trust of people around them and initially most still opt for the facilities they have experience of even if it is further away (Nguyen et al., 2020). This is often observed in people's frequent preference for hospitals over health facilities even though the health centre nearer to their location is adequately equipped to handle the same disease. While the changing number of health facilities improves the quality of health services offered, it often does not affect the actual long-term district or health facility trend reporting. However, it may temporarily affect a time point-specific record(s) at the surrounding health facilities.

8.3.1.3 Model description of spatiotemporal models using Integrated Nested Laplace Approximations

The study area (Zambia) was divided into Health Facility (HF) catchment areas labelled $i = 1, \dots, n$. $O_i$ denotes the observed number of cases, while the total population at risk of malaria is $N_i$. The number of malaria cases per 1000 population (inhabitants) is then defined as malaria incidence, i.e.

$$Incidence_i = \frac{O_i}{N_i} X\ 1000 \text{ for } i = 1, \dots, n$$

Meanwhile, malaria risk estimation used indirect standardisation of the number of expected cases per HF catchment area $i$ and time $t$. The equation representing this is as follows:

$$e_{it} = \sum_{i=1}^{J} N_{it}\ \frac{O_i}{N_i} \text{ for } i = 1, \dots, n;\ \ t = 1, \dots, T,$$

where $O_i = \sum_{i=1}^{n} \sum_{t=1}^{T}, O_{itj}$ and $N_j = \sum_{i=1}^{n} \sum_{t=1}^{T} N_{itj}$ are the number of cases and population at risk in the group $j$, respectively. The relative incidence rate estimation for each HF catchment area $i$ was modelled by the equation:

$$O_i | r_i \sim Poisson(\mu_i = N_i r_i) \quad \text{for} \quad i = 1, \dots, n,$$

$$\log \mu_i = \log\ \mathrm{N}_i + \log r_{i,}$$

The prior spatial distribution implemented through the BYM2 model to fit the spatio-temporal model, with a random temporal effect $\emptyset = (\ \emptyset_{1,\dots,} \emptyset_T)$ denotes

$$\emptyset \sim N(\ O,\ T_{\emptyset}^{-1} \mathrm{I}_T)$$

where $T_{\emptyset}$ is the precision parameter, $I_T$ is the identity matrix with a dimension $T\ x\ T$, and the model is implemented with a temporal structured random walk of 2nd order (RW2) while assuming the prior distribution to be:

$$\boldsymbol{\gamma} \sim N(\ O_{,}[\ T_{\boldsymbol{\gamma}}\ R_t]\ ^{-})$$

where, $T_{\gamma}$ is the precision parameter, $R_t$ is the structure matrix of RW2 ( $T\ x\ T$), and

$$\boldsymbol{\gamma} \sim N(\ O_{,}[\ T_{\boldsymbol{\delta}}\ R_{\delta}]\ ^{-})$$

where, $T_{\boldsymbol{\delta}}$ is the precision parameter, while $R_{\delta}$ represents the corresponding spatial and temporal structure matrix of $nT$ x $nT$ for the full interaction.

Finally, the model was fitted with an intercept $(\eta^*)$, temporal$(\gamma_t^*)$, spatial $(\xi_i^*)$ and spatio-temporal patterns $(\delta_{it}^*)$ to represent the posterior patterns where:

$$\eta^* = \frac{1}{nT} \sum_{i=1}^{n} \quad \sum_{t=1}^{T} \log r_{it,}$$

$$\gamma_t^* = \frac{1}{n} \sum_{i=1}^{n} \log r_{it} - \eta^*, \qquad \textit{Temporal model}$$

$$\xi_i^* = \frac{1}{T} \sum_{t=1}^{T} \log r_{it} - \eta^*, \qquad \textit{Spatial model}$$

$$\delta_{it}^* = \log r_{it} - \xi_i^* - \gamma_t^* - \ \eta^*. \qquad \textit{Space-time model}$$

The posterior exceedance probability distribution $P(r_{it} > r_0|O)$ , where $r_0$ is the threshold mean rate value for the whole study area $(exp\ (\ \eta))$ is considered when smoothing rates.

To validate these, the decomposition of estimated log risks is equal to the sum of the patterns $\log r_{it} = \eta^* + \xi_i^* + \gamma_t^* + \ \delta_{it}^*$, and is decomposable to the total variability of complete log risks accounting for the sum total of the spatial, temporal, and spatio-temporal variation. These are denoted by:

$$\sum_{i=1}^{n} \quad \sum_{t=1}^{T} (\ \log r_{it} - \ \log r_{it})^2 \ = \frac{1}{n} \ \sum_{i=1}^{n} (\xi_i^*)^2 + \frac{1}{T} \ \sum_{t=1}^{T} (\gamma_t^*)^2 +$$

$$\frac{1}{nT} \sum_{i=1}^{n} \quad \sum_{t=1}^{T} (\delta_{it}^*)^2$$

The BYM2 model implemented here in the analysis has its spatial random effect parameter presented as $\boldsymbol{\xi} = \frac{1}{\sqrt{T_{\xi}}}\ (\ \sqrt{\lambda_{\xi} u_*} + \sqrt{1 - \lambda_{\xi}\, v}\ )$

Here, $u_*$ is the scaled intrinsic Conditional Autoregressive (CAR) model where the generalised variance is equal to 1. At the same time, v is the unstructured random effect.

The expression of a weighted average covariance of matrices to the structured and unstructured spatial components comprises the variance of the overall random effect. A uniform distribution is supplied to the smoothing parameter $\lambda_\xi$ (spatial) as the model was fitted to the BYM2 model for a spatial random effect, and the values $(U, \alpha) = (0.5, 0.5)$ are assigned to the probability $P(\lambda_\xi > U) = \alpha)$ (Adin, Martínez-Beneito, Botella-Rocamora, Goicoa, & Ugarte, 2017).

8.3.1.4 Bayesian Trends Model in Markov Chain Monte Carlo

The study also implemented a Bayesian trends Poisson mixed model in a Markov Chain Monte Carlo (MCMC) environment. The burnin was 10 000; a sample was 110000, and 4 parallel chains, with a thinning of the degree of 10. Gelman's trace plots and visual diagnostics were applied to determine the convergence of the models (Gelman et al., 2004; Hamra et al., 2013). The model structure and equation of the temporal model is denoted by:

$$Y_{kt} \sim p(Y_{kt}|\mu_{kt}), \text{where } K = 1, \dots, K, t = 1, \dots, N,$$

$$g(\mu_{kt}) = O_{kt} + X^T{}_{kt}\beta + \phi \sum_{s=1}^{s} \omega_{ks} f_s(t|\gamma)$$

Where malaria trends $f_s(t|\gamma S)$ estimated in the study were represented by (a) Constant trend - $\beta_1$; (b) Linear increasing trend - $\beta_1 + \gamma_{1t}$, with $\gamma_1 > 0$; and (c) Linear decreasing trend - $\beta_1 + \gamma_{2t}$, with $\gamma_2 < 0$. A more detailed description of this model is given elsewhere in (Lee et al., 2018; Napier et al., 2018).

Finally, Bayesian Empirical Kriging in order to create a smoothed malaria risk surface was also applied using ArcGIS 10.6.

8.3.1.5 Supplementary Results

8.3.1.5.1 *Low Spatial (intra-district) district –level and temporal (annual) trend variation*

Figure 6.S4 shows the mean spatial variation at the Heath facility level, while Figure 6.S3 shows the variation at the district level. When the study considers increasing trend =3, no change = 2, and decreasing trend = 1, it was observed that 18% (13/72) of the districts had at least one health facility catchment with a higher trend in malaria incident rates such as *increase* instead of *no change* or *no change* instead of *decline.* Similarly, 37.5% (27/72)

of the districts had at least one health facility with a malaria incident rate lower than that of the district, such as *decline* instead of *no change* or *no change* instead of *increase.* Only a few districts had a substantial mix of health facility level poll opposite trends to the overall district trend or specific difference between the two absolute trends (decrease as opposed increase, or vice versa) high but the vice versa was slightly higher (See Figure S5). A positive difference of significant trend variation (e.g. 0.71 – 1 [*red*]) means that the trend variation was from a lower trend to a higher one (e.g. *decreasing to no-change or no change to increasing or decreasing to increasing.*), while a negative (*blue*) represent the opposite.

Further confirmation of the similarity between results from district level vs facility-level scales was done across several other tests of association. All of which had similarly high association scores. The range of coefficients of association across several tests was from 0.51 (Cohen's kappa) to 0.86 (Goodman and Kruskal Gamma) (see Table 6.S2 for a summary). The Bartlett test comparing variances, gave an observed $\chi^2$ =1.292, critical value = 3.84, and a computed *p-value* =0.256, showing no significant difference. This further indicated that there is inadequate evidence to suggest that the variances between the two trends were significantly different (see Figure 6.S6).

The mean posterior exceedance probabilities of health facilities in northern areas are higher (Figure 6.S6) than those in the southern region. The same is true with posterior median estimates (Figure 6.S7) which show a similar spatial transitional pattern generally higher in the northern compared to the southern areas. The overall model in INLA, with type II interaction, had a marginal log-Likelihood of -103348.76. The linear predictor and fitted posterior marginal decomposition of the total amount of variability from log rates was 68.05% 3.32%, and 28.63% for Spatial, Temporal, and Space-time, respectively. This model confirms that there is little temporal variance, while the bulk of the variance could be explained by the spatial and the spatio-temporal components. The details of the posterior marginal distributions using precision and variance scales are given in Tables 6.S5 and 6.S6. As discussed in the main paper, the temporal trends presented through posterior median estimates of malaria incidence show a shift southwards, evidently shrinking the areas of generally low malaria (see Figure 6.S8).

Figures 6.S9 shows the Empirical Bayesian smoothed spatial prediction hotspots of malaria incidence risk and the location of border control points and border posts. With the exception of two border posts around eastern Zambia and Mozambique, where

potential cross border malaria risk may be sustained by cross-border human movement, malaria risk between countries can be linked to cross-border environmental conditions. However, further investigation of cross border malaria around Zambia's borders may need to be conducted in order to ascertain and characterise the true malaria dynamics around these areas. Finally, Figure S8 shows the model associated prediction error, generally higher around the central to south where borders are mostly shared with Zimbabwe, and there is a lack of available data. Generally, most areas predicted with significantly low or high malaria risk had low prediction error. Areas showing higher prediction errors might be due to the sparsity of health facilities, which made it harder to predict in these areas.

### 8.3.1.5.2 Figures and Tables only referred in supplementary methods and results

(These partly helped in the overall analysis and interpretation of results)

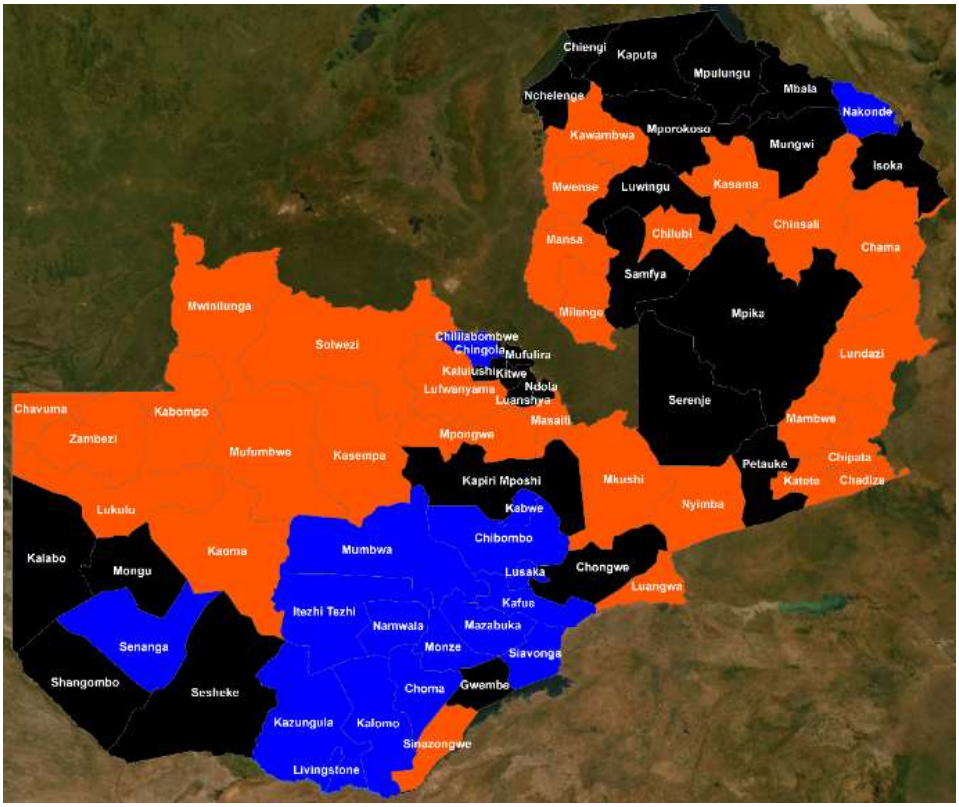


Figure 6.S3: District-level malaria trends

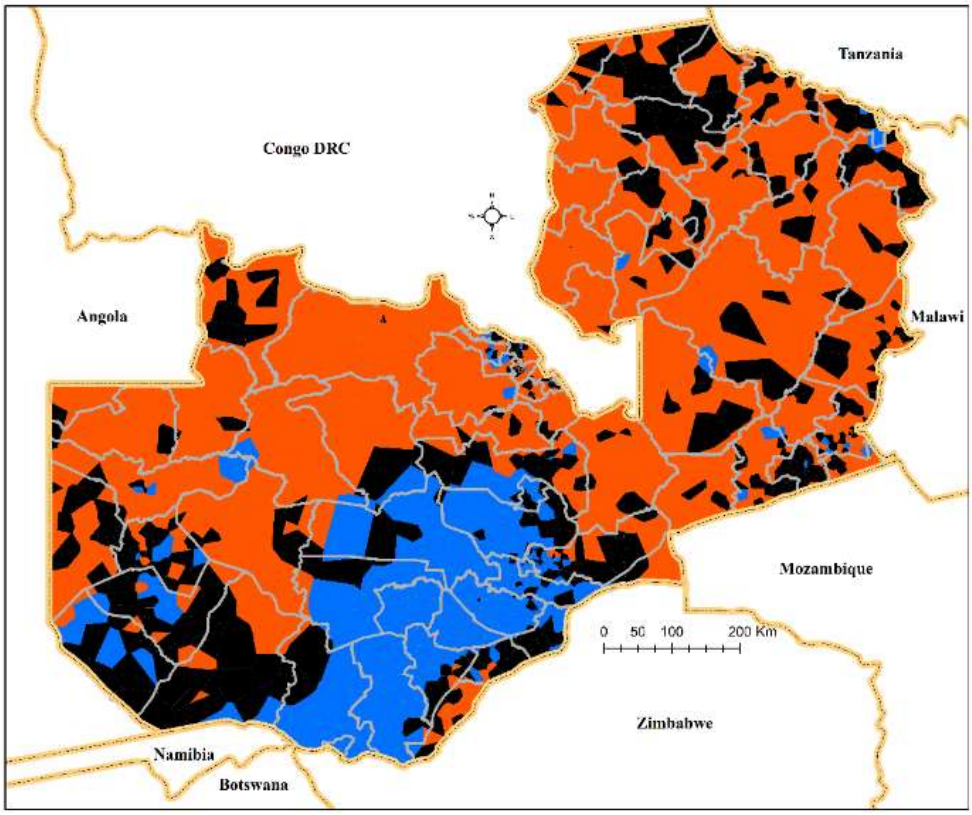


Figure 6.S4: Health Facility malaria trends

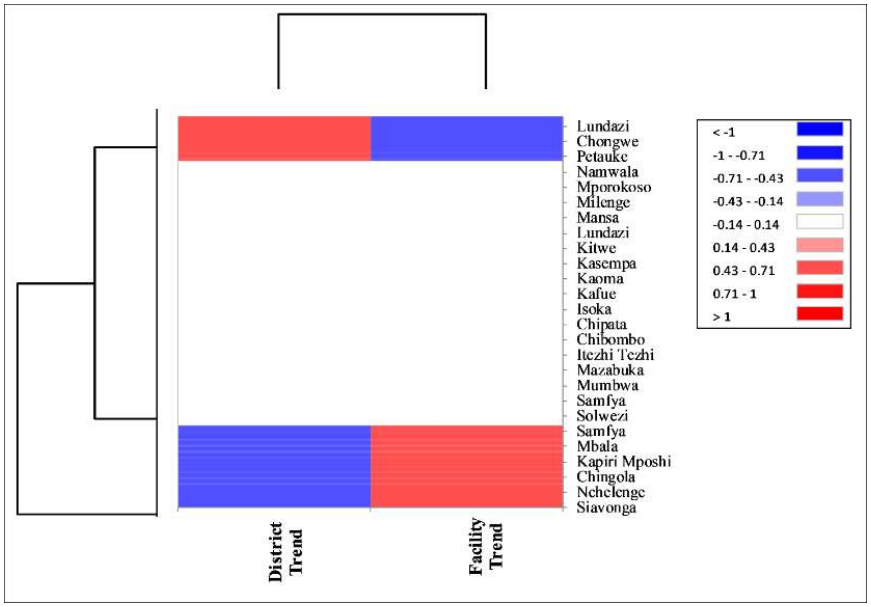


Figure 6.S5: Heat map of trend differences significance between district and HF models

The Fig. shows the districts that had significant differences in trends between district vs health facility level models. It shows which districts what proportion of health facilities with a different trend compared to the trend in the district model; whether decreasing (*blue*) vs increasing (*red*) malaria trend models at HF vs district trends

| Correlation Test | Coefficient | Lower bound 95% | Upper bound 95% | Correlation Test | Coefficient |
|---|---|---|---|---|---|
| Goodman and Kruskal Gamma | 0.859 | 0.835 | 0.883 | Pearson's Phi | 0.830 |
| Kendall's tau | 0.656 | 0.629 | 0.683 | Contingency coefficient | 0.639 |
| Stuart's tau | 0.640 | 0.611 | 0.669 | Cramer's V | 0.587 |
| Somers' D (R/C) | 0.646 | 0.619 | 0.673 | Tschuprow's T | 0.587 |
| Somers' D (C/R) | 0.666 | 0.638 | 0.694 | Cohen's kappa | 0.505 |

Table 6.S2: High correlation between District and Health facility trends

| | mean | sd | 2.5% | 50% | 97.5% |
|---|---|---|---|---|---|
| Intercept | -4.6 | 0.061 | -4.7 | -4.6 | -4.5 |
| Spatial variance component | 3.1 | 0.11 | 2.9 | 3.1 | 3.4 |
| Spatial smoothing parameter | 0.37 | 0.029 | 0.32 | 0.36 | 0.43 |
| Temporal variance component | 0.11 | 0.075 | 0.023 | 0.088 | 0.3 |
| Temporal (non-structured) variance component | 0.21 | 0.089 | 0.0058 | 0.23 | 0.28 |
| Spatio-temporal variance component | 2.1 | 0.021 | 2 | 2.1 | 2.1 |

Table 6.S3: Summary statistics for the variance Scale (mean, standard deviation and quantiles)

| | mean | sd | 2.5% | 50% | 97.5% |
|---|---|---|---|---|---|
| Intercept | -4.6 | 0.061 | -4.7 | -4.6 | -4.5 |
| Spatial precision parameter | 0.32 | 0.011 | 0.3 | 0.32 | 0.34 |
| Spatial smoothing parameter | 0.37 | 0.029 | 0.32 | 0.36 | 0.43 |
| Temporal precision parameter | 14 | 11 | 3.3 | 11 | 44 |
| Temporal (non-structured) precision parameter | 5.4e+02 | 4.3e+03 | 3 | 76 | 3.6e+03 |
| Spatio-temporal precision parameter | 0.48 | 0.005 | 0.47 | 0.48 | 0.49 |

Table 6.S4: Summary statistics for the precision Scale (mean, standard deviation and quantiles)

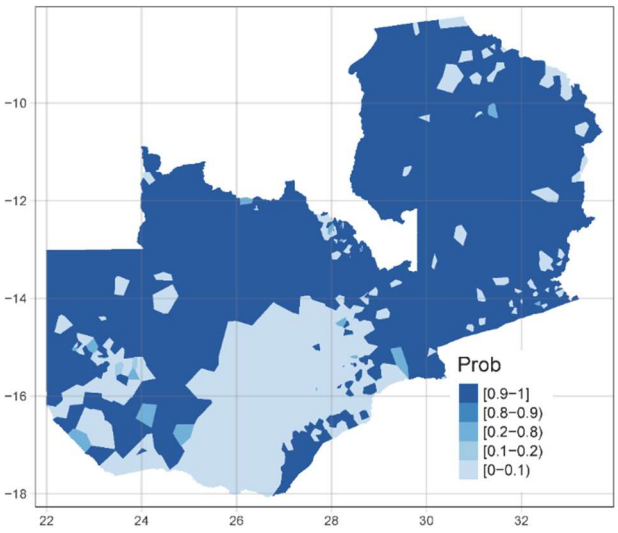


Figure 6.S6: Malaria incidence posterior exceedance probabilities

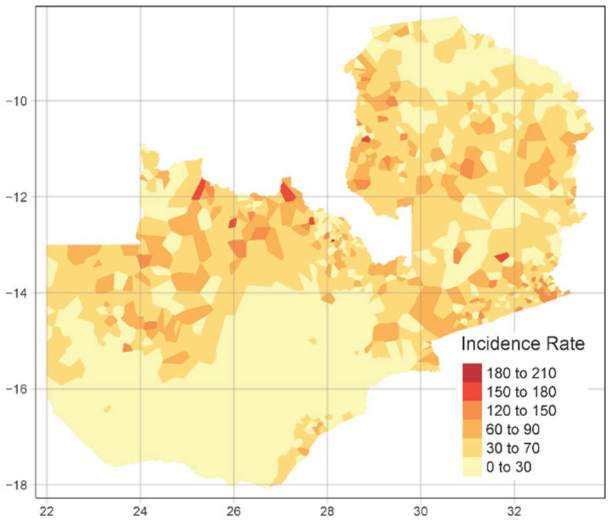


Figure 6.S7: Malaria incidence posterior median estimates/1000

Figure 6.S6 shows a probability scale from 0 – 1, where 0.9 - 1 means is the highest probability of getting malaria and 0-0.1 means low.

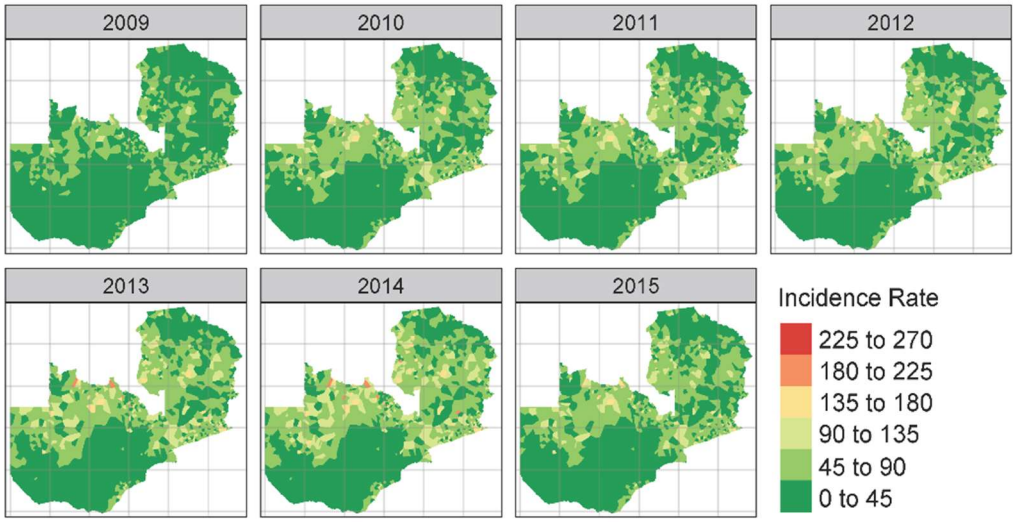


Figure 6.S*8*: Posterior median estimates of malaria incidence per 1000 population

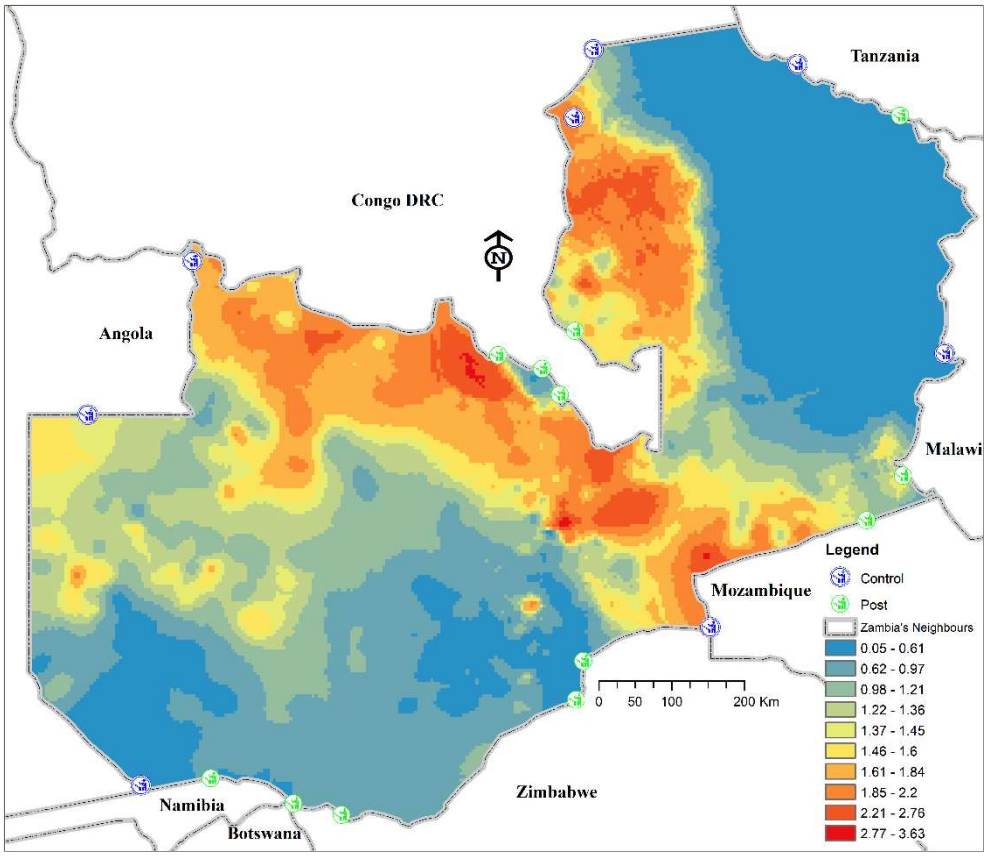


Figure 6.S9: Empirical Bayesian Kriging of malaria risk – Border effect

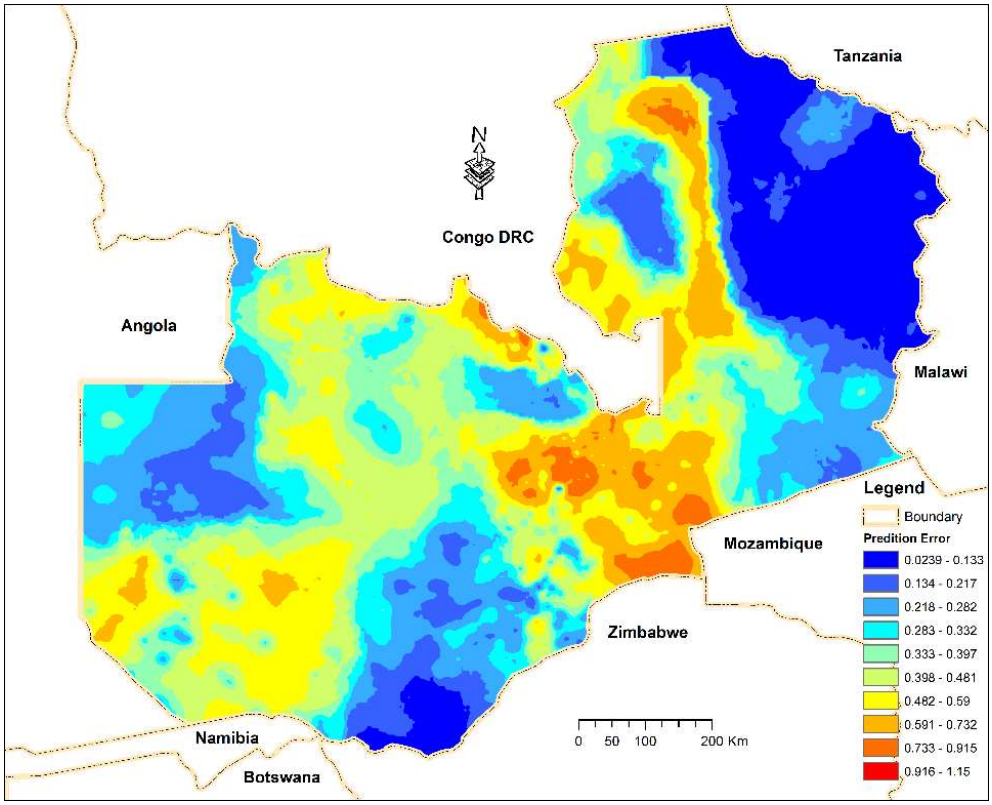


Figure 6.S10: Empirical Bayesian Kriging standard prediction errors

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