Analysis of the Geographical Patterns of Malaria Transmission in KwaZulu-Natal, South Africa using Bayesian Spatio-Temporal Modelling

By

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Abstract

Malaria is one of the most important public health issues that is still affecting millions of people around the world, especially in Africa. Africa accounted for 80% of the 216 million cases worldwide and 91% of deaths. It poses serious economic burdens on communities and countries at large. However, through temporal and spatial mapping of the disease populations at risk can be identified timeously and resources distributed accordingly.

Since malaria is a climatic disease geostatistical approaches can be utilised in modelling its spatial distribution. Bayesian geostatistical methods enable the mathematical descriptions of the environment-disease association. Significant environmental predictors of malaria transmission can be identified which can also allow for the development of a malaria epidemic prediction model. This model can serve as a surveillance system for early detection and containment of the disease. Therefore, it is crucial to understand the complex dynamics of malaria transmission so malaria control programmes can be more effective and efficient in managing this public health issue.

In South Africa, malaria is transmitted in 3 provinces: KwaZulu-Natal, Mpumalanga and Limpopo. Although malaria is highly seasonal in these areas and KwaZulu-Natal has experienced tremendous achievements in decreasing morbidity and mortality due to malaria, it still remains in an unstable condition that needs constant control and surveillance. The aim of this study was to investigate which environmental/climatic variables are drivers of malaria incidence in KwaZulu-Natal and subsequently develop methods to produce risk maps using Bayesian spatio-temporal modelling.

It emerged from the research that the main environmental/climatic drivers of malaria incidence in KwaZulu-Natal were the day temperature of the previous month, altitude and forest land cover type. This was due to the different ways these three factors affect the three-way interaction of the vector, the parasite and the human host. The predicted risk maps showed that incidence rates ranged from 0.2 to 5 per 1000 inhabitants in the study area. This prediction was based on only the climatic factors, however, non-climatic factors also affect malaria transmission through vector control strategies like Indoor Residual Spraying among others.

Declaration

I, Noluthando Ndlovu declare that

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List of Abbreviations

ACT   Artemisinin Combination Therapy

AIC   Akaike Information Criterion

BIC   Bayesian Credible Interval

CAR   Conditional Autoregressive

CDC   Centres for Disease Control

DDT   Dichloro Diphynl Trichloroethane

DOH   Department of Health

ENSO   El Nino Southern Oscillation phenomenon

GIS   Geographic Information System

IRS   Indoor Residual Spraying

ITN   Insecticide-treated Nets

LST   Land Surface Temperature

MCMC   Markov Chain Monte Carlo

MODIS   Moderate Resolution Spectroradiometer

NASA   National Aeronautics and Space Administration

NDVI   Normalized Difference Vegetation Index

SAWS   South African Weather Service

STATTSA   Statistics South Africa

WHO   World Health Organization

Chapter One: Introduction

1.1. Background

Malaria is an ancient disease that has been affecting people since the beginning of recorded time. It poses serious economic, social and health burdens in tropical and subtropical countries where it is predominantly found (Mandal et al., 2011). Malaria still remains a huge public health issue regardless of how many years of research has been conducted on how to combat this disease. The WHO 2012 report showed that malaria is presently endemic to 104 countries worldwide and is transmitted in 99 of them. Seventy-nine of those countries are classified as being in the control phase, 10 are in the pre-elimination phase and another 10 in the elimination phase. Another 5 countries do not have ongoing transmission and are classified as being in the prevention of re-introduction phase (WHO, 2012). Although efforts of combating malaria have yielded dramatic decreases in malaria cases and deaths in most endemic regions, in its 2012 World Malaria Report, the WHO reported devastating statistics that in 2010 655,000 people died from this disease, with 86 percent of the victims being children under 5 years of age. The vast majority of cases (80%) and 91% of the total deaths of the 216 million cases worldwide occurred in Africa (WHO, 2012).

In 2011, an estimated 3.3 billion people were found to be at risk of malaria, although out of all the affected geographical regions, the population in sub-Saharan Africa is at the highest risk of contracting the disease due to a variety of socio-economic factors (WHO, 2012).

The majority of the population in Southern Africa lives in areas that are free of malaria, whilst countries like Mozambique and Zimbabwe are in the control phase and South Africa is in the pre-elimination phase while Namibia, Botswana and Swaziland are in the elimination phase. Malaria is highly seasonal in these parts, usually occurring during the rainy summer months. During the transmission season, parts of the population in these countries are temporarily at high risk (with the exception of Swaziland) (Coleman et al., 2010; Moonasar et al., 2012). In 1957 MacDonald described the malaria epidemic as: "an acute exacerbation of disease out of proportion to the normal to which the community is subject" (MacDonald, 1957). Epidemics are common in zones of unstable malaria (Hay et al., 2001). As a result of the seasonality of malaria in these parts communities do not acquire immunity from the disease (Gerritsen et al., 2008). Thus it remains in an unstable condition that can only be

controlled by providing the necessary control measures to deal with it when transmission levels are elevated (Moonasar et al., 2012).

Malaria is caused by a parasite that is transmitted from one person to another through the bite of the Anopheline mosquito. Humans contract malaria from the bite of the malaria-infected mosquito. When the mosquito bites an infected person, it ingests microscopic malaria parasites found in the person's blood. The malaria parasite must grow in the mosquito for a few or more days before infection can be passed to another person. Therefore, if the mosquito bites another person, the parasites go from the mosquito's mouth into the person's blood. They feed on the blood cells, multiply inside the liver, thereby destroying the red blood cells causing a cut off in blood circulation which could lead to premature death (Abeku, 2006). Symptoms of malaria include fever, shivering, pain in the joints, vomiting, anaemia, hemoglobinuria, retinal damage, and convulsions. The classic symptom of malaria is the cyclical occurrence of coldness followed by rigor then fever and sweating lasting four to six hours. This occurs every two days in plasmodium vivax (*P.vivax*) and plasmodium ovale (*P.ovale*) infections, while every three days for plasmodium malariae (*P.malariae*) (Dongus et al., 2009).

Malaria can be prevented by the use of mosquito coils and repellants, spraying the insides of houses (where most *Anopheles* species feed and rest) with insecticides (indoor residual spraying) and by sleeping under the bednets that have been treated with long-lasting insecticides (Alonso et al., 2011). Mass screening and treatment (MSAT) with effective anti-malarial drugs can also reduce malaria transmission (Griffin et al., 2010).

The biggest challenge that faces any success of all the numerous interventions in trying to control this disease remains the parasites fast adaptation to anti-malarial drugs and insecticides. With no foreseeable vaccine in sight control programs are the way in which communities can fight against the disease, however, action must not slow down as it has been proven that the disease re-emerges if interventions cease or are no longer effective (Mandal et al., 2011).

However, the level of malaria risk and transmission intensity exhibits significant spatial and temporal variability related to variations in climate, altitude, topography, and human settlement pattern (Gosoniu, 2008). The advent of a new generation of Remote Sensing

technologies and the increase in the Geographic Information Systems (GIS) modeling capability have led to developments in modeling the spatial distribution of malaria. This has made it possible to explore and characterize different sets of spatial and temporal disease patterns at a very fine geographic resolution. Spatial and temporal mapping of the malaria disease can help in the detection of populations at risk (Zacarias and Andersson, 2011). Malaria risk maps can guide malaria control at areas of highest need; the distribution of limited resources can assist in the evaluation of the effectiveness of intervention programmes. The maps can also help decision-makers to objectively assign resources to areas where they are most needed (Riedel et al., 2010). GIS-generated maps provide visual information regarding the location of epidemic-prone areas and vulnerable population groups (Thomson and Connor, 2000). Geographic modelling of malaria distribution is central to understanding spatial and/or spatio-temporal patterns. The patterns often reflect a range of human host factors, diversity in vector distribution and human-vector contact (Zacarias and Andersson, 2010).

Bayesian approaches in particular have been adopted by a number of studies modelling the spatial distribution of malaria due to their flexibility and robustness in disease mapping, spatial statistics and decision-making (Zacarias and Andersson, 2010). Bayesian geostatistical analysis has been applied widely in malaria and used also to estimate parasitaemia risk for a number of countries and regions in Africa, including West and central Africa, Somalia, Zambia, Kenya, Angola and Tanzania (Stensgaard et al., 2011). Using statistical modelling mathematical descriptions can be given of the environment-disease relation, can identify significant environmental predictors of malaria transmission and can also provide predictions of malaria risk. The Bayesian approach also has uncertainty assessment capabilities which have increased its usage in disease mapping (Zacarias and Andersson, 2010).

Thomas and Connor (2001) state that early detection, containment of the disease and prevention of malaria epidemics are all constituents of one of the four elements from the global malaria strategy. Therefore, by understanding the complex dynamics of malaria transmission, early warning systems can be developed to ensure that communities at risk are provided with the adequate resources needed to protect themselves against the disease and control programs will thus be more effective and efficient. The Bayesian approach to spatio-

temporal modelling has been identified to be the superior method in analysing malaria transmission and mortality (Thomas and Connor, 2001).

1.2. Justification

From the global point of view, malaria is the most important vector-borne disease (WHO, 2009). The use of remote sensing and GIS in mapping vector-borne diseases such as malaria has been explored in Africa (Thomas and Connor, 2001). Spatial prediction of malaria vector distribution has been undertaken for large areas over the African continent using remotely sensed data to map temperature, moisture and vegetation cover. These coarse spatial resolution data are currently being used in early warning systems for malaria epidemics (Thomson et al. 1999). Remotely sensed coverage can provide information in a more accurate and timely fashion than do alternative methods such as spatial interpolation of e.g. widespread rainfall data (Hay et al. 2001).

Disease mapping is carried out to summarise spatio-temporal variation in risk. This information may be used for simple descriptive purposes, to provide information on the health needs of the population so as to provide context for further studies or to compare the estimated risk map with an exposure map to gain understanding the cause of the disease (Elliot et al., 2000).

This has resulted in a fast growing trend of modelling, such as mathematical and statistical modelling, as a way for prediction of future disease transmission. The type of modelling that can be done can be described in two categories: (1) mathematical and statistical modelling as has been previously mentioned or deterministic models. Deterministic models are based on how certain biological factors are influenced by climatic factors such as temperature and rainfall (Yang et al., 2010). For example, the malaria parasite requires certain temperatures and moisture levels to reproduce and survive.

The mathematical or statistical approach proposed for this study requires the development of a new environmentally driven mathematical dynamic model which takes into account known risk factors quantitatively. By developing such models combined with population, morbidity and mortality data the burden of disease can be estimated and enhance malaria control (Yang et al., 2010). Furthermore, the identification of which key environmental factors that govern malaria transmission can give a deeper understanding of malaria transmission and in future

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provide methods for forecasting future trends. Malaria can be transmitted in a wide range of eco-epidemiological settings because a wide range of vectors are able to transmit the disease. As a result of the range of eco-epidemiological settings, variations in malaria transmission can occur across relatively small areas (Reid et al., 2010), thus trying to map transmission at a community level becomes more significant whereas other studies have focused more at country, provincial or district level. With Bayesian geostatistics in disease mapping both environmental covariates and spatial autocorrelation will be estimated simultaneously and this in the process the model identify by variable selection which environmental covariate is significantly associated with transmission.

Finally, the model developed will allow for routine and repeated spatio-temporal modelling of regions in risk of malaria by altering the environmental inputs of the model to fit the specified area. This will provide accurate and timeous transmission maps for malaria control programs and ultimately ensure resources are being allocated to the areas of greatest need. In regions such as South Africa where malaria transmission is highest depending on seasons and how well control programs are being managed, it will be important to understand exactly which environmental covariate makes a contribution to high transmission and when.

1.3. Aims and Objectives

This research is aimed at using Bayesian spatio-temporal modelling in determining the geographical patterns of malaria transmission in KwaZulu-Natal, South Africa. By mapping the geographical patterns and estimating the disease burden more efficient malaria control programs can be designed, implemented and evaluated.

The objectives of this study are to:

- estimate and map malaria seasonality in KwaZulu-Natal based on environmental and clinical malaria case data

- develop rigorous statistical models for identifying which climatic variables are associated with malaria transmission.

- produce incidence maps based on the climatic variables significantly correlated with malaria transmission

- assess spatio-temporal patterns of malaria transmission in KwaZulu-Natal and produce transmission maps adjusted for seasonality and climate factors

Maps of malaria seasonality will indicate the start and length of transmission season in KwaZulu-Natal which will assist in timing malaria control interventions and in mapping malaria risk. Maps of malaria transmission and its spatio-temporal changes adjusted for seasonality and ecological predictors will help in judging the needs of malaria control programs and act as a baseline for estimating effectiveness of national control programs. Rigorous statistical methods for variable selection will be developed. Models that can explain temporal patterns of mortality and its causes; assess effects of health system changes on mortality and predict mortality in a given site and Bayesian spatio-temporal methods enabling the risk factor analyses and mapping of malaria.

1.4. Structure of the Thesis

Chapter two reviews the relevant literature on how the geographical patterns of malaria transmission can be analysed. Firstly, malaria as a disease will be outlined and its impacts globally and locally. The use of Geographical Information Systems and Remote Sensing in disease mapping will be reviewed and how it can contribute to spatio-temporal modelling. Subsequently, Bayesian approaches will be outlined and reviewed in the geo-statistical framework. Finally, the selected environmental determinants of malaria transmision and control measures will be discussed to show their relevance to the study.

Chapter three describes the background to the study area.

Chapter four provides a detailed description of the materials and methods employed for the study by firstly outlining the data used and the techniques used in data management, model formulation and development.

Chapter five presents and discusses the main findings pertinent to this study. The results of the spatio-temporal modelling are outlined. Malaria incidence maps produced will be presented.

Chapter six will conclude the study. The aim and objectives presented initially are reviewed to establish if they were achieved by this study. A brief overview of the key findings and implications of the study will be provided. Finally, the limitations of this study are evaluated and recommendations for future research in this field are suggested.

Chapter Two: Literature Review

2.1. Introduction

Malaria is a serious public health issue in sub-Saharan African countries. It is estimated that it kills a child every 30 seconds in Africa (Florens et al., 2002). The endemicity of malaria varies substantially in these countries and at times only affecting certain districts or areas predominantly (Da Silva et al., 2004), leaving the population with little or no acquired immunity (Mabaso and Ndlovu, 2012). In South Africa, three provinces are affected by malaria: KwaZulu-Natal, Limpopo and Mpumalanga with malaria affecting mostly the Northern areas that are closer to the Mozambican, Swaziland and Zimbabwean borders. Although it has been noted that malaria cases have been decreasing in South Africa since the year 2000 as a result of malaria control programs, an estimated 10% of the population still live in malaria-endemic areas and are at risk of contracting the disease (Moonasar et al., 2012).

Epidemics such as malaria pose huge economic losses at country, community and household level (Mabaso and Ndlovu, 2012) and depress economic growth. Malaria also retards social development through effects such as reduced working hours due to sickness or attending to the sick, income spent on financing health care, which in turn leads to impacts at national level because of massive health care budgets, reduced productivity of the work force and so on. Malaria is also estimated to have cost endemic countries in Africa 3% of their economic growth every year (Craig, 2009). Malaria has furthermore been recognized as a disease of poverty by institutions such as the World Health Organization (WHO) and UNICEF as it is concentrated in the world's poorest countries: 90% of malaria deaths have occurred in sub-Saharan Africa (Worrall et al., 2005). Coleman et al. (2010) suggest that many of the factors affecting malaria incidence are directly or indirectly linked to the socio-economic status of a household (Coleman et al., 2010). The discovery of an interactive effect between HIV infection and malaria morbidity exacerbates the potential for devastating health consequences in populations with large numbers of individuals who are co-infected. In resource-poor countries in Africa, malaria prevention and treatment consume large proportions of health budgets, and since it poses a threat to indigenous populations as well as visitors, it acts as a deterrent to tourism and foreign investment in these countries (Kleindschmidt, 2001). The local variation in factors such as altitude, climate, house construction, distance from vector

breeding sites, use of personal protection measures and household crowding index lead to malaria incidence to vary at very small adjoining geographical areas (Coleman et al., 2010).

Consequently, in these countries it is crucial that resources are allocated effectively and efficiently. In addition, the potential value of predicting malaria outbreaks and epidemics has been recognised, thus malaria early warning systems can be put in place so protection measures are distributed timeously (Coleman et al., 2008). The variations in climatic conditions and malaria incidence have an impact on the effectiveness of interventions. Malaria endemicity is also not homogenous at country level, so complementary local systems are required to allow redistribution of local resources to areas experiencing outbreaks. If all these mechanisms are adequately understood, health officials will be in a better position to respond with preventative measures (Mabaso et al., 2006).

The extensive application of Geographical Information Systems (GIS) and spatial statistical methods in mapping and modelling the distribution of vector borne diseases like malaria has led to a number of risk maps being produced at country and regional level (Bhunia et al., 2012). By analysing geo-referenced malaria case data against environmental data using a systematic and repeatable staged process of variable selection we can determine which factors contribute to transmission and mortality in different geographical settings (Craig et al., 2007).

2.2. Malaria Transmission

It is imperative to understand the stages of the life cycle of the parasite that are relevant in the study of transmission of the disease before we discuss the factors that determine the spatial and temporal distribution of malaria.

Several insects are known to be vectors of human diseases but mosquitoes were the first insects to be associated with the transmission of a disease. Our understanding of the malaria parasites began with the discovery of the parasites in the blood of malaria patients by Alphonse Laveran. William MacCallum discovered the sexual stages in the blood of birds infected with a related haemotozoan, *Haemoproteus columbae* (Cox, 2010). In 1878, Manson, a British doctor practising in China showed that mosquitoes transmitted human *filariae* (Chernin, 1983). Later on, in 1897, Ronald Ross discovered *oocysts* on the gut wall

of a mosquito that fed on a malaria patient (Hagan and Chauhan, 1997). A year later, Italian zoologist G.B. Grassi and his colleagues were the first to describe the complete cycles of the human malaria parasites, and indicated that the species of genus *Anopheles* was responsible for malaria transmission (Esposito and Habluetzel, 1997; Cox, 2010). There are hundreds of species of the *Anopheles* genus but only 40 transmit malaria (Morrow, 2007). Parasites are transmitted from person to person by the female mosquitoes of the genus *Anopheles* (Bray and Garnham, 1982; Florens et al., 2002; Eckhoff, 2011).

Different species of the parasite occur in different regions (Gemperli, 2003). Of the five species of the protozoan parasites of the genus *Plasmodium* that cause malaria in humans, *P.falciparum* is the most widely distributed and Pathogenic in Africa. The other four (*P.malariae P.vivax, P.knowlesi and P.ovale*) have limited distribution in Africa and are generally less life-threatening (Abeku, 2006). *P.vivax* is less dangerous but more widespread (WHO, 2012).

2.2.1. The Life-Cycle of the Malaria Parasite

The human malaria parasite has a complex life-cycle that requires both a human host and an insect host (Eckhoff, 2011). The humans and other vertebrates act as the intermediate host for the parasite, and sexual reproduction takes places in the mosquito (Matteelli and Castelli, 1997). The life cycle of *P.falciparum* can be divided into three stages: exo-erythrocytic cycle (A in Figure 2.1), erythrocytic cycle (B in Figure 2.1) and the sporogonic cycle (C in Figure 2.1). The sporogonic cycle takes place within the mosquito vector and it is affected by environmental factors. This is an important stage of the life-cycle as it determines the probability of transmission (Abeku, 2006).
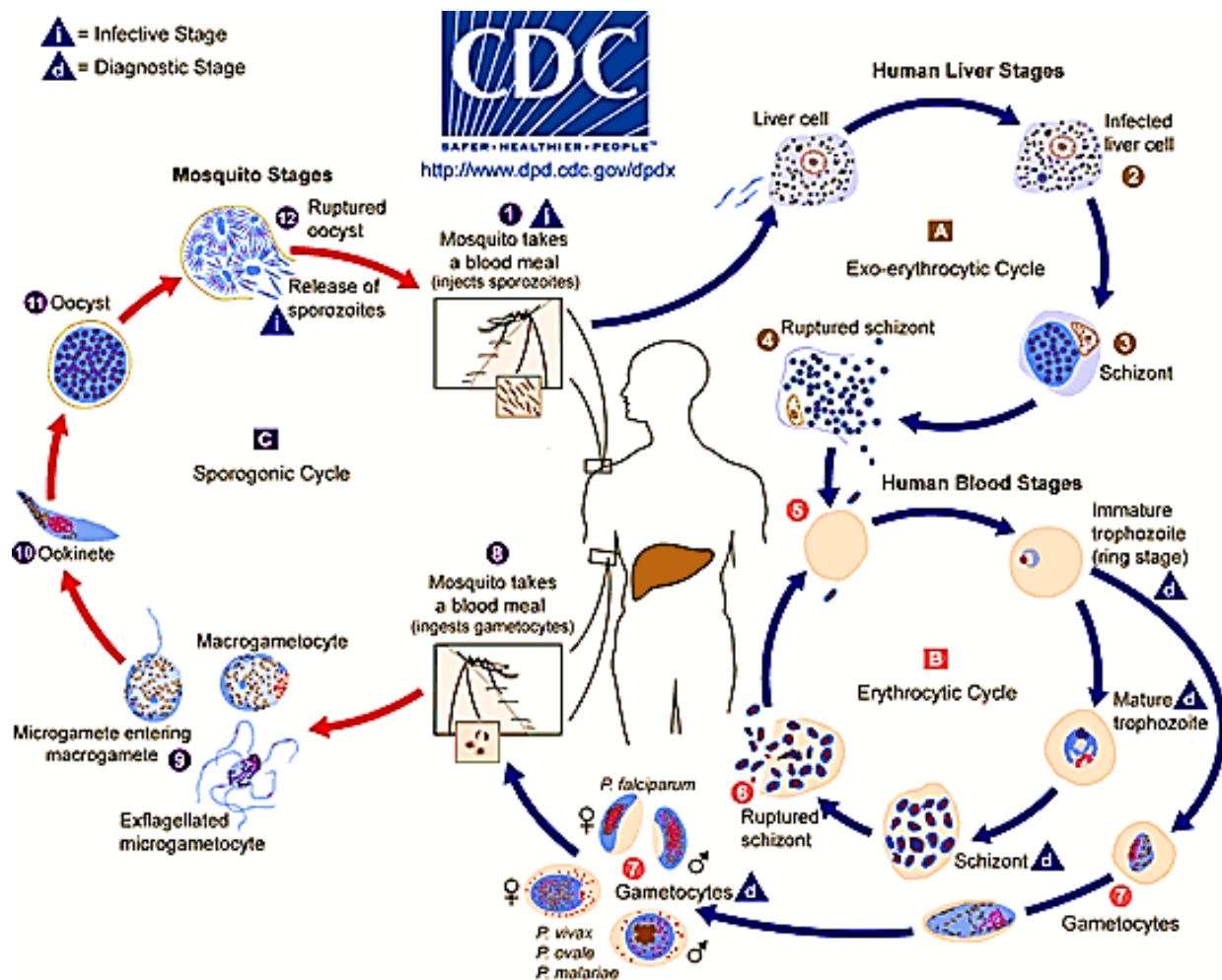
Figure 2.1 The life-cycle of the malaria parasite in the human host (Source: Centers for Disease Control)

The life cycle of the parasite begins with the inoculation of the parasite into the human body by the female *Anopheles* mosquito (Eckhoff, 2011). The sporozoites reach the liver and invade each liver cell within 30 minutes. The trophozoites then start their intracellular asexual division within the liver and after completion of this phase; thousands of erythrocytic merozoites are released from each liver cell. The time taken for the completion of the tissue is variable, depending on the infecting species (5-6 days for *P. falciparum*). The merozoites invade the red blood cell (RBC), and develop through the stages of rings, trophozoites, early- and mature shizonts; each mature schizont consists of thousands of erythocytic merozoites (Florens et al., 2002). These merozoites are released by lysis of the RBC and immediately invade uninfected red cells. This whole cycle of invasion – multiplication – release – invasion takes about 48 hours in *P. falciparum* infections (Fujioka and Aikawa, 2002). This repeating cycle depletes the body of oxygen and causes fever, triggering the onset of disease symptoms (Gosoniu, 2008). The contents of the infected cell that are released with the lysis of the RBC

stimulate the Tumor Necrosis Factor and other cytokins, which results in the characteristic clinical manifestations of the disease. A small proportion of the merozoites undergo transformation into gametocytes (Florens et al., 2002). Mature gametocytes appear in the peripheral blood after a period of 8-11 days of the primary attack in *P. falciparum*, they rise in number until three weeks and decline thereafter, but circulate for several weeks (Cuesters and Smith, 2009). When a female mosquito bites an infected human the gametocytes are ingested. The gametocytes undergo sexual reproduction in the mosquito's stomach forming a zygote then the zygote multiples to form sporozoites which in turn make their way into the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle (Gosoniu, 2008).

2.3. The Malaria Parasite in the Vector

Anophelines are found worldwide, except in Antarctica, but the transmission of malaria occurs predominantly in tropical and subtropical regions (CDC, 2009). Among these, the *Anopheles gambiae* complex and *Anopheles funestus* are the primary vectors in Africa. *Anopheles gambiae sensu stricto* and *Anopheles arabiensis* are the most widely distributed species of the *Anopheles gambiae* complex in sub-Saharan Africa (Walker, 2008; Pock Tsy et al., 2003).

Although these siblings are morphologically distinguishable, they exhibit different behavioural attributes. *Anopheles gambiae sensu stricto* is predominant in humid areas, prefers feeding on humans (anthropophilic) and rest mainly indoors (endophilic) (Walker, 2008). *Anopheles arabiensis* on the other hand is more tolerant in the drier savannah regions; it feeds on animals (zoophilic) and rests outdoors. Both species breed in temporary habitats such as pools, puddles and rice fields. *Anopheles funestus* prefers permanent water bodies with vegetation such as swamps and marshes, feeds both indoors and outdoors, mainly on humans and rests indoors (Levine et al., 2004). Identification of the distribution of particular species is important since malaria vector control measures may have to take into account the behavioural difference between species to be effective (Walker, 2008). For example, indoor biting and indoor resting habits make mosquitoes more susceptible to control by residual insecticide on interior walls of houses, and to other insecticide treated materials such as bednets (Kleinschmidt, 2001; Levin et al., 2004; Mabaso, 2007).

After the blood meal, the malaria parasite enters the mosquito and the gametocytes continue their development (Sporogony). Uninfected *Anopheles* mosquitoes become infected if they feed on a person with mature gametocytes in their peripheral blood (Kleinschmidt, 2001). The male and female gametes fuse and form into a zygote. These transforms into an ookinete which penetrates the gut wall and becomes an oocyst. The oocyst divides asexually into numerous sporozoites which reach the salivary gland of the mosquito, where they can be transmitted when the mosquito next takes a blood meal. The sporogony in the mosquito takes about 10-20 days dependent on air temperature and thereafter the mosquito remains infective for 1-2 months, if it survives. There is no sporogony at temperatures below 15° C (Florens et al., 2002; Morrow, 2007). The incubation period of the parasite in the vector takes 13 days to complete at 24° C for *P.falciparum*. The vector will only become infective if it survives this *sporogonic* cycle (Kleinschmidt, 2001).

Only the female mosquito takes a blood meal (male Anopheles feed on nectar) which is necessary for the development of eggs. Two to three days after the blood meal, which is taken during the night or at dawn, the female anopheline lays around one hundred eggs. During her life of several weeks, she can therefore produce more than 1000 eggs (CDC, 2009). The eggs are always laid on the water surface, with preference for swamps or shallow water. They may also breed in water containers or tree holes. The oval eggs are one millimetre long and require about two weeks to develop into adult mosquitoes. They fly only short distances of a few kilometers. Their preferred location is close to human houses (Gemperli, 2003).

2.3.1. Vector Ecology

Anopheline mosquitoes are generally small, about 8mm long with dark-spotted or dappled wings. Their posture when resting or feeding is distinctive- head down, body at an angle and hind legs raised (Figure 2.2). This is in contrast with the horizontal position maintained by most other mosquito species (DOH, 2008; CDC, 2009).
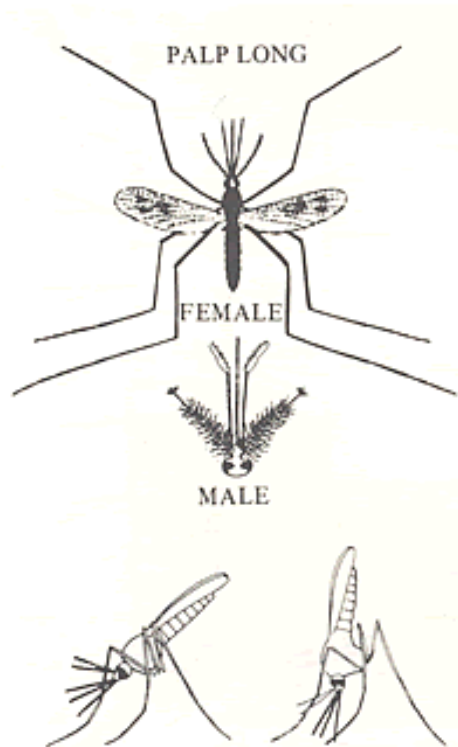
Figure 2.2: Anopheles adults showing typical resting position (SOURCE: Centers for Disease Control)

The short fly range and the preferred locations for hosting and breeding are responsible for large local differences in the geographical distribution of the anopheline. The adults are carried by wind but few are found further than 1-2 km from their larval site. They fly more quietly and bite more subtly than other mosquitoes. They generally prefer clean water for the development of their larval stages in contrast to the dirty water found in drains, and rubbish preferred by the *Culicine* family (DOH, 2008). Adults may also rest inside motor vehicles, aircraft and trains, and can be transported considerable distances. In this way infected mosquitoes have been responsible for local transmission of malaria infections in non-malaria areas, particularly near airports and major truck stopovers. *Anopheles* prefer to feed near ground level and feed selectively on the lower leg rather than the arms or upper body, thus it is especially important that insect repellent is applied to the lower leg and foot when in a sitting or standing position (Walker, 2008; CDC, 2009).

The effect the environment has on the malaria vector is further determined by rainfall and temperature which affect mosquito survival and the duration of the parasite life cycle in the vector (Takken and Lindsay, 2003).The vectorial capacity of *Anopheles funestus* can often exceed that of *Anopheles gambiae* in some localities (Minakawa et al., 2001). *Anopheles*

funestus breeds in permanent or semi-permanent swamps or in pools along streams and river systems, and *Anopheles gambiae* complex prefer temporary aquatic habitats (Lyons et al., 2013). Consequently, *Anopheles funestus* are less dependent on rains and become abundant during the dry seasons when *Anopheles gambiae* are low. Thus, *Anopheles funestus* is often considered a vector species that bridges malaria transmission during the dry season (Mabaso et al., 2007).

2.4. Determinants of Malaria Transmission

Malaria transmission is affected by different factors such as environmental conditions (Musa et al., 2012), the socio-economic status of the individual (Coleman et al., 2009), population movement and urbanization (Tatem et al., 2013), restricted access to health services, poor quality of health services (Snow et al., 2003) or water management methods (e.g. irrigation, dam constructions that increase the mosquitoes population near human habitats (Matthys et al., 2006). Several authors such as Montosi et al. (2012), Lyons et al. (2013) and Tanser et al. (2003) among others have identified climate to be the main driver of malaria transmission and climate variability influencing the level of transmission intensity. Malaria is affected by climate variability at both seasonal and inter-annual scales (Montosi et al., 2012).

According to Gemperli (2003), the main effect the environment has on the malaria vector is the influence factors such as temperature and rainfall have on the mosquito's survival and the duration of the parasites life cycle in the vector. Malaria transmission will thus depend on whether the mosquito vector and parasite had the ability to coexist long enough for transmission to occur (Gemperli, 2003).

2.4.1. Temperature

Temperature can affect malaria transmission in several ways (Abeku, 2006) as it can manipulate the distribution of malaria transmission through its effect on sporogonic duration and mosquito survival (Musa et al., 2012). When temperatures increase up to approximately 30° C the sporogonic period or the *Plasmodium* parasite within the vector will be shortened (Abeku, 2006). However, temperatures above 30° C result in a high turnover of vector populations which will impact the survival of the vector negatively as there will be a production of weak individuals and high mortality (Musa et al., 2012). The increased temperature can in contrast also accelerate the development period of the aquatic stages of the

vector from 20 to 7 days resulting in transmission rates being higher as the parasite will most likely reach an infective stage before the vector dies (Abeku, 2006). When the temperature is as low as 16° C the parasites will cease to grow and thus be unable to complete their cycle and further spread the disease (Snow et al., 1999; Musa et al., 2012). The vectorial capacity of the *Anopheles* is also modified by temperature. Temperature ranges between 22° C and 30° C are optimal as they lengthen the life-span of the mosquitoes and increase the frequency of blood meals taken by the female, as well as an increased frequency of host-vector contact. The female can then have a blood meal once every 48 hours (Snow et al., 1999; Gemperli, 2003; Montosi et al., 2012). Thermal induced death occurs between 40 ° C and 42 ° C depending on the mosquito species (Musa et al., 2012). When temperatures reach a minimum, African vector populations can be obliterated. As a consequence of all the temperature requirements, malaria transmission becomes less frequent at high altitudes. For example, there are no *Anopheles* species near the equator above 2500 meters altitude and above 1500 meters altitude in other regions (Gemperli, 2003).

2.4.2. Rainfall and Humidity

Musa et al. (2012) states that although rainfall does not affect the parasite directly it does play a critical role for malaria transmission by providing a medium for aquatic mosquito stages. Abeku (2006) agrees with this by stating that heavy rain or floods can also cause an outbreak of malaria, especially in areas in the vicinity of large rivers. Rainfall also increases relative humidity which is important for the survival and behaviour of all anopheline mosquitoes. Thus rainfall and humidity impact on the living conditions of the *Anopheles* to a great extent by providing breeding sites for mosquitoes to lay their eggs, increasing the vector population. Mosquitoes are usually found in areas with annual average rainfall between 1100 mm and 7400 mm (Snow et al., 1999; Gosoniu, 2008; Musa et al., 2012). Temporary breeding pools that get created by increasing rainfall provide ideal conditions for vector breeding. Conversely, excessive rainfall can be negative for the transmission cycle as it can flush out the mosquito larvae and destroy breeding places by changing the breeding pools into streams. An exceptional drought can also just turn the streams into pools which would be favourable for the breeding sites again and at times such opportunistic mosquito breeding sites have preceded epidemics (Gemperli, 2003).

The interaction between rainfall, runoff, evaporation and temperature controls the ambient air humidity which in turn affects the survival and behaviour of Anopheles mosquitoes

(Gemperli, 2003). Rainfall and humidity effects are inherently linked as they both have a significant effect on the longevity of adult vectors (Abeku, 2006). When the average monthly relative humidity is less than 60% the lifespan of the mosquito is shortened enough to make it unsuitable for it to transmit malaria (Musa et al., 2012). Higher values lengthen the lifespan of the mosquito and enable it to infect more people. The vegetation index has been shown to be a successful indicator as a proxy for rainfall and humidity (Gemperli, 2003).

Hay et al. (2001) demonstrated that it takes three months before malaria incidence reaches a peak following a significant rainfall when they conducted a study in north-western Kenya. However, it has been noted that the relationship between rainfall and malaria has been confounded by population movements, environmental changes and also changes in malaria control measures (Abeku, 2006).

2.4.3. Vegetation

The remotely sensed normalized difference vegetation index (NDVI) is the most widely used index for vegetation coverage. It has been found to have broad applications as it fluctuates along with other meteorological and environmental variables which determine biomass and photosynthesis reflecting the distribution of plants and trees. NDVI can facilitate the identification of high risk zones for various vector-borne diseases such as malaria (Bhunia et al., 2012).

Gosoniu (2008) discussed how vegetation type and the amount of green vegetation are important factors in determining mosquito abundance, as they provide feeding provisions and protection from climatic conditions. The author further states that this can affect the presence or absence of the human hosts and the therefore the availability of blood meals (Gosoniu, 2008). Although vegetation density generally has a favourable impact on malaria transmission, Kleindschmidt (2001) argues that forest vegetation may inhibit *An. gambiae* because of a lack of sunlight.

Montosi et al (2012) also recently considered the role, in addition to the other determinants, that soil water can contribute in driving malaria incidence. They hypothesized that hydro-climatic variability should be an important factor in controlling the availability of mosquito breeding habitats; thereby governing mosquito growth rates (Montosi et al., 2012).

2.4.4. El Niño Southern Oscillation

The term El Niño (or "Christ Child" in Spanish) apparently originated in the 19th century as a name fishermen gave to an anomalously warm current that appears off the Peruvian coast around Christmas (Katz, 2002). In the 1960s a link was made between the atmospheric Southern Oscillation and the oceanic El Niño and is now referred to as the El Niño Southern Oscillation (Moonasar et al., 2012). The ENSO phenomenon can be described as the cyclic warming and cooling of the equatorial Pacific Ocean coupled with changes of the atmospheric pressure across the Pacific. Although at first it was thought to be a local phenomenon, it has been recognised to be the most important climatic cycle contributing to worldwide inter-annual variability in climate and the likelihood of climatic anomalies. The two extremes of ENSO are El Niño (a warm event) and La Niña (a cold event) which create rainfall and temperature fluctuations. Their impact varies across the world and can result in droughts in some areas and flooding in others (Kovats, 2000; Katz, 2002).

According to the Climate Prediction Center (CPC) and Kovats (2000) during a strong El Niño ocean temperatures can average 2 ° C to 3.5 ° C above normal between the date line and the west coast of South America. These areas of exceptionally warm waters coincide with regions of above-average tropical rainfall. The El Niño and La Niña episodes typically last approximately 9 to 12 months. They often form during June to August, reach peak strength during December to April, and then decay during May to July of the following year. However, some episodes have been known to last two years and even as long as three to four years. While their periodicity is quite irregular, El Niño and La Niña occur every 3 to 5 years on average (CPC, 2012).

The fluctuations in ocean temperatures during El Niño and La Niña are accompanied by even larger-scale fluctuations in air pressure known as the Southern Oscillation. The negative phase of the Southern Oscillation occurs during El Niño episodes, and refers to the situation when abnormally high pressure covers Indonesia and the western tropical Pacific and abnormally low air pressure covers the eastern tropical Pacific with the opposite mechanism occurring for La Niña episodes (Jones et al., 2007; CPC, 2012; Delgado-Petrocelli, 2012).

A number of studies investigating climatic parameters that affect malaria incidence have found a correlation between the ENSO phenomenon and malaria incidence. There is strong

evidence to suggest that ENSO is associated with heightened risk of malaria in regions of the world where climate is linked to the ENSO cycle and disease control is limited (Kovats, 2000; Abeku, 2006). Bouma and van der Kaay (1996) demonstrated that epidemics were more prevalent in a year with a wet monsoon following a dry Nino year during the period 1868-1943 in Sri Lanka. The same correlation was found by Bouma et al. (1997) in Columbia where malaria cases increased by 17% during an El Niño year and 35% in post El Niño years (Kovats, 2000; Abeku, 2006). Based on the relationships established in that study it was proposed that this El Niño-malaria relationship can be used to predict high- and low-risk years for malaria in Columbia. Bouma and Dye (1997) also presented findings that in Venezuela malaria mortality and morbidity increased by more than 36% between 1975 and 1995 post-El Niño years. In 1997 an El Niño caused abnormally high rainfall that resulted in a severe epidemic (Abeku, 2006). Heavy El Niño rains were also associated with the 1998 malaria epidemic in Tanzania (Jones et al. 2007). Abeku (2006) reported that rainfall during and following El Niño was found to much higher than normal in Kenya in 1997. A positive correlation was established between the increased rainfall and vector density one month later leading to conclusions that heavier than normal rainfall associated with El Niño may have initiated epidemics (Abeku, 2006).

Delgado-Petrocelli (2012) found that during El Niño there was a shortening of the life cycles of the two vectors and a corresponding extension during La Niña which could result in fewer cases of malaria and dengue fever in the latter. Kiang et al. (2006) concur that malaria is correlated with the rainy season and thus the ENSO events may either increase or decrease malaria transmission. In parts of Southern Africa, a strong El Niño event is typically followed by drought and a La Niña proceeded by flooding. Rainfall patterns change due to ENSO events which can affect mosquito breeding sites and thus can subsequently affect variation in malaria transmission. However, ENSO appears to have the opposite effect in Southern Africa during El Niño conditions with La Niña in fact coinciding with heightened incidence (Mabaso et al., 2007). Mabaso (2007) also noted that while South Africa and Swaziland may have demonstrated the strongest associations of epidemics with ENSO, other oceanic systems such as the Quasi-Biennial and Quasi-Periodic Oscillations in the Indian Ocean, which have a moderating effect on the impact of ENSO, could distort the exact effects.

El Niño is a fairly complex climatic phenomenon, and since it is not the same as an extreme weather event it is difficult to attribute any single epidemic to it. No two events are alike,

with each event being different in magnitude and in duration (Kovats, 2000). The difficulty with the indices used to quantify the strength of the ENSO events is that they are not always the same; therefore you cannot have standard thresholds for all regions. What could appear to be a weak event could have devastating impacts and vice versa.

2.4.5. Anthropogenic Factors

Land use changes can alter the physical and chemical characteristics of mosquito breeding habitats as they can influence climatic conditions like temperature or evapotranspiration which are determinants of the abundance and longevity of mosquitoes (Abeku, 2006; Gosoniu, 2008). Development activities can also affect malaria transmission as they could result in ecological changes that could be favourable to malaria transmission. Deforestation is a product of development that mosquitoes are very sensitive to as the changes in environmental conditions like humidity and temperature that occur affect species distribution, density and survival. These changes will consequently influence the incidence and prevalence of malaria (Rubio-Palis et al., 2013).

Conversely, Tatem et al. (2013) argue that urbanization has reduced malaria transmission significantly. Urbanization involves the physical landscape modification and transformation of environments as a result of a demand for resources. Generally urbanization results in significant socio-economic changes which will improve health, wealth and housing. These factors in turn cause significant parasitological, entomological and behavioural effects that result in reduced malaria transmission within the urban core and surrounding peri-urban areas (Matthys et al., 2006; Tatem et al., 2013).

Urban agriculture, which is common across Africa, has also been linked to malaria transmission. Some crop systems create ideal mosquito breeding sites and thus promote malaria transmission. Matthys et al. (2006) observed that *Anopheles* larval habitats increased in rice paddies and agricultural trenches in the Ivory Coast. Lindblade et al. (2000) suggested that the cultivation of natural swamps increase malaria transmission after conducting a study in the Ugandan highlands. Another study conducted by Minakawa (1999, 2001) in the Kakamega forest located at an altitude between 1500 – 1700 meters in Kenya, reported that the survival of *Anopheles gambiae* larvae was drastically reduced in forest habitats compared to habitats exposed to direct sunlight suggesting deforestation facilitates malaria transmission in the highlands (Omukunda et al., 2012).

2.5. Malaria Immunity, Morbidity, Mortality and Endemicity

Malaria is the most important parasitic and vector-borne disease with an estimated 3.3 billion people living in areas that have some risk of malaria transmission and about 1.2 billion people (one-fifth of the world's population) living in areas with a high risk of transmission (more than one reported case per 1,000 inhabitants per year) (Alonso et al., 2011).

Globally, there are about 300 million clinical episodes of malaria and between 1 to 3 million deaths per year (Coleman et al., 2008). Approximately 80% of cases and 90% of deaths are estimated to have occurred in the African region, with children under five years of age and pregnant women being the most severely affected (Abeku et al., 2003; Gemperli et al., 2004; Worrall et al., 2005). Pregnancy compromises a woman's immune system making her more vulnerable to malaria as it suppresses her immunity (Worrall et al., 2005). High parasitemia is observed during the first pregnancy and declines with subsequent pregnancies. When a mother is infected with malaria there is a higher chance of a termination of pregnancy, stillbirth and a reduction of the chances of survival of a new-born (Gemperli, 2003). Infants are, however, protected due to maternal anti-bodies in the first 3 – 6 months of life. After that, they are vulnerable to clinical malaria episodes until they have developed their own immunity. Depending on the intensity of exposure to the parasite, children can develop relative tolerance to malaria infections in their first few years of life (Kleindschmidt, 2001).

2.5.1. Classification of Malaria Endemicity

Malaria was endemic in most countries around the world until the mid-19th century. In the Northern hemisphere it was distributed as far as the Arctic Circle, with an estimated 90% of the world's population living in malarious areas. The few countries that did not have malaria included the Pacific Islands. By the second half of the 19th century, large parts of northern and central Europe and North America were free of malaria as a result of changes in agricultural land practices and an improvement of the housing structures. By the late 19th century, after the discovery of the malaria parasite in 1880 and its mode of transmission in 1897, most of the northern countries in Western Europe had virtually eliminated malaria before World War II (Mendis et al., 2009).

The four levels of endemicity, in increasing order of transmission intensity are as follows: hypoendemic, mesoendemic, hyperendemic and holoendemic malaria, respectively (Abeku, 2006).

- In hypoendemic areas there is very little malaria transmission. The parasite and spleen rates typically do not exceed 10% in children aged 2-9 years (Icchpujani and Batia, 2002; Morrow 2007). As result of the low risk in infection, most of the populations in these areas lack effective immunity against the disease (Carmago et al., 1996).

- Mesoendemic areas have moderate transmission. The parasite and spleen rates range between 11% and 50% in children aged 2-9 years (Icchpujani and Batia, 2002; Morrow, 2007).

- Areas that have intense seasonal transmission but that is not sufficient enough for a very high proportion of the population to develop protective immunity are called hyperendemic areas (Morrow, 2007; Mathew, 2008). The spleen and parasite rates are between 51% and 75% in children aged 2-9 years. The adult spleen rates are usually high (>25%) (Icchpujani and Batia, 2002; Morrow, 2007).

- Holendemic areas have perennial, intense transmission resulting in a considerable degree of immunity outside of early childhood (Mathew, 2008). Spleen rates are over 75% in children 2-9 years but low in adults. Parasite rates are over 75% among infants 0-11 months (Icchpujani and Batia, 2002; Morrow, 2007).

High endemicity levels characterize stable malaria (Mathew, 2008). Epidemics are unlikely to occur in these areas and any fluctuations in incidence, besides normal seasonal changes, are not likely to be pronounced (Abeku, 2006). In areas with stable malaria, adults usually show a high level of immunity to malaria, and therefore, only the children are often at risk of severe disease and death due to malaria. The effects of changes in weather conditions such as rainfall or temperature have little or no bearing on transmission (Àguas et al., 2008).

Areas with unstable malaria, conversely, have low to moderate transmission. Any fluctuations in incidence are highly likely to be noticeable. If there are any slight changes in transmission, major epidemics can ensue (Abeku, 2006). The disease affects the whole population, regardless of age, due to the low levels of immunity as a result of fluctuations in transmission or low intensity of transmission (Mathew, 2008).

However, in reality, there are several situations where conditions do not necessarily fit into these broad classes of transmission. For example, in some areas of unstable malaria, transmission is highly seasonal but intensive. Meaning, there is usually a predictive pattern each year associated with occasionally explosive epidemics. Some areas are characterized with highly seasonal but very little or no transmission for several years. Areas with intense seasonal transmission can also be affected by true epidemics followed by successive abnormally dry periods (Abeku, 2006).

According to Snow et al. (2005) malaria has been geographically restricted; however, it remains entrenched in the poor areas of the world where climates are favourable for transmission. Within countries, parasite prevalence rates in children are the highest among the poorer populations living in rural areas (WHO, 2012). Infant mortality is high in endemic regions (Gemperli, 2003). Although malaria is endemic in three provinces in South Africa, almost all South Africans (including residents of seasonal malaria transmission areas) are non-immune and are consequently at increased risk for developing severe malaria (Moonasar et al., 2011).

The incubation period (the time between the inoculation of the parasite and the first medical symptoms) for *P. falciparum* malaria is approximately 8 – 15 days (Gemperli, 2003). The mild clinical symptoms of *P. falciparum* infection often present as a fever and a variety of other associated symptoms such as headaches, body pains, rigors, diarrhoea, coughing and myalgia (Snow et al., 1999; Moonasar et al., 2011). Diagnosis is made by detection of the parasite with a microscopic examination of a blood smear, or with the use of rapid malaria antigen test (Moonasar et al., 2011). However, in endemic countries infected individuals such as older children and adults are often asymptomatic, or only exhibit mild, non-threatening clinical symptoms (Kleindschmidt, 2001; Snow et al., 2003). The most severe form of malaria morbidity is cerebral malaria, which is defined in clinical terms as the presence of coma due to malaria, and it is accompanied by obstruction of capillaries in the central nervous system (Snow et al., 1999). The major complications of malaria include: hypoglycaemia, renal failure, severe anaemia, acute respiratory distress syndrome (ARDS) and metabolic acidosis (Moonasar et al., 2011). Severe anaemia is a life-threatening condition in young children and often warrants a blood transfusion in a hospital setting (Snow et al., 2003; Moonasar et al., 2011).

Acquired immunity is developed after repeated infections. Residents of tropical countries typically develop immunity where high levels of malaria transmission are present the whole year. However, this developed immunity can be lost if the individual leaves the endemic area for a long period of time and may be at risk of malaria if they are exposed again (Kleindschmidt, 2001).

However, malaria is an entirely preventable and treatable disease, provided that recommended interventions are properly implemented (Florens et al., 2002; Griffith et al., 2007). These include (i) vector control through the use of insecticide-treated nets (ITNs), indoor residual spraying (IRS) and, in some specific settings, larval control (Geissbuhler et al., 2009); (ii) chemotherapy for the most vulnerable populations, particularly pregnant women and children; (iii) confirmation of malaria diagnosis through microscopy or rapid diagnostic tests (RDTs) for every suspected case, and (iv) timely treatment with appropriate anti-malarial medicines (according to the parasite species and documented drug resistance) (Griffith et al., 2007; WHO, 2011; Davis et al., 2013).

2.6. Malaria Control Interventions

Several African countries have reported a decrease in malaria due to increased access to effective anti-malarial drugs and major upgrades and improvements of vector control measures (Protopopoff et al., 2013). Vector control currently remains the most effective tool to prevent and control malaria transmission. Control measures are targeted at each stage of the malaria transmission cycle: the mosquito vector, the parasite and the human host (Gosoniu, 2008). They work by reducing human-vector contact and the reduction of the lifespan of the adult female *Anopheles* mosquitoes so that they do not survive long enough to transmit the parasite (Mabaso et al., 2004). Delves et al. (2013) also discuss the potential significant effects of interventions that prevent parasite transmission from human host to vector. The primary vector control measures that have benefited large parts of southern Africa are Indoor Residual Spraying (IRS) and Long-Lasting Insecticide-Treated Nets (Alonso et al., 2011) which are both recommended by WHO (Mabaso et al., 2004).

The WHO recommended particular focus on early diagnosis and prompt treatment as well as fast detection and containing of epidemics. However, neither disease risks, nor people, nor health systems are evenly distributed thus efforts need to target affected populations and high

risk areas first. As malaria control is a dynamic process that depends on the local epidemiological context and resources available the timing of interventions needs to coincide with high risk periods that are appropriate for those particular transmission settings to achieve maximum and equitable benefits (Gosoniu, 2008; Craig, 2009).

2.6.1. Vector Control

Chemical insecticides have been used for over 60 years to control malaria against *Anopheles* mosquitoes. In the beginning, pyrethrum that was extracted from flowers was sprayed in houses as a short-term knock down insecticide (Hargreaves et al., 2000). In southern Africa, the first experimental adult mosquito control with pyrethrum was carried out in 1931 in KwaZulu-Natal, which led the way for worldwide use of residual insecticides against adult mosquitoes (Mabaso et al, 2004). However, after World War II the more residual organochlorides (e.g. DDT) were seen to be more effective (Hargreaves et al., 2000). The effectiveness of DDT against indoor resting mosquitoes led to the adoption of the Global Eradication Programme of Malaria in 1955 (co-ordinated and supported by the WHO). In the first 10 years of implementation, the results were spectacular, with malaria being eradicated in countries like the United States (Mabaso et al., 2004). IRS involves the application of insecticides on the walls and ceiling of a residential structure in areas affected by malaria in order to kill and repel the adult vector of mosquitoes that choose to rest on these surfaces. This implies that IRS is most effective against mosquito species that are resting indoors (Pluess et al., 2010; Hlongwana et al., 2013).

2.6.1.1. Insecticide-treated Bednets

The WHO recommends the use of four groups of insecticides: organochlorides, pyrethroids, organophosphates and carbamates for IRS (Hlongwana et al., 2013). Although historically organochlorines were the insecticide of choice for use in IRS, the majority of African countries now use pyrethroid insecticides for IRS (Fossog Tene et al., 2013). As suggested by Hill et al. (2006), Miller et al. (2007) and Shah et al. (2011), in an area of high malaria transmission intensity, the use of insecticide treated nets (ITNs) has been recognized as an effective means of malaria vector control for reducing mortality and severe morbidity in young children and pregnant mothers. Bednets were re-introduced in the latter part of the 1980s. They were used as a protection of the user(s) against the bites of malaria infectious mosquitoes, and thus reduce the transmission risk. Untreated bednets, however, did not provide adequate protection, presumably because the mosquitoes were able to bite the

occupants through the netting, or the nets would eventually get torn as a result of excessive use, giving the mosquitos' easy access to the blood host (Takken, 2002). By treating the bednets with a deposit of a quick-acting insecticide of low human toxicity between a sleeper and host-seeking mosquitoes, a chemical barrier is created to the often incomplete physical barrier provided by the net. Essentially, ITNs can be considered as mosquito traps to bait mosquitoes by the odour of the sleeper (Curtis et al., 2003). For ITNs to be effective, however, there needs to be active involvement from community members to ensure that the nets are being used, even during seasons when their use is uncomfortably hot and when there may not be enough irritation from nuisance insects to use them as there may still be enough vectors to make them dangerous (Curtis and Mnzava, 2000).

2.6.1.2. Indoor Residual Spraying

In areas of low transmission intensities, particularly in Southern Africa, house spraying with residual insecticide (IRS) like pyrethroids and DDT has been widely used as an effective vector control methods. IRS has also helped to eliminate malaria from great parts of Asia, Europe, Russia and Latin America between the 1940s and 1960s (Mabaso et al., 2004; Pluess et al., 2010; Kigozi et al., 2012).

In South Africa, malarial epidemics used to extend as far as southwards down the east coast as Port St Johns (Eastern Cape) and as far inland as Pretoria in the northern part of the country (Mabaso et al., 2004). DDT was used in South Africa from 1946 but its use as a larvacide was discontinued in the early 1960s as a result of mounting pressure from environmentalists on the increasing scientific evidence of its adverse environmental effects. By 1996 DDT was completely phased out for malaria control and was replaced by Deltamethrin, a synthetic pyrethroid that was considered to be environmentally friendly and cost effective (Mabaso et al., 2004; Gericke et al., 2002; Maharaj et al, 2005). However, by the year 2000 parasite resistance to anti-malarial drugs, especially chloroquine, became evident after the highest number of cases (61 934) since the epidemics of the 1930s was recorded (Maharaj et al., 2005; N'Guessan et al., 2007; Bateman, 2008). According to the National Department of Health (DOH) (2007) other contributing factors were that the country had also experienced unusually heavy rains following several years of drought (which would have increased the number of breeding sites for mosquito vectors). As well as the large number of economic migrants from Mozambique and Zimbabwe, who could have potentially been carrying malaria parasites, which resulted in the large number of imported cases and

unexplained local upsurges and lacking of finding index cases during sporadic outbreaks (DOH, 2007).

DDT was then reintroduced in March 2000 but only in traditional structures (mud, wood or reed). The western-type structures (cement-plastered and painted) were continued to be sprayed with pyrethroids. By March 2002, all structure types were sprayed with DDT and pyrethroid spraying was completely eliminated (Maharaj et al., 2005). Currently, IRS is the primary vector control measure in South Africa, with almost 100 % protection (WHO, 2012).

Spraying needs to be carried out between once and three times per year; the timing is dependent on the insecticide and the seasonality of transmission in a given setting (Pluess et al., 2010). Malaria transmission has since been eliminated in most of the country, but it still continues to plague the populations living in the north-eastern border regions adjacent to Mozambique and Swaziland (Maharaj et al., 2012). This was attributed to the introduction of artemisinin-based combination therapy (ACT) in February 2001 that occurred to address the resistance of *Plasmodium falciparum* to monotherapies (Davies et al., (2013). Maharaj et al. (2005) argues that other factors such as the introduction of an effective drug, cross-border control and low rainfall could have attributed to the decrease in malaria cases. For IRS to be effective, however, community members need to make sure that they do not refuse spray teams to apply the insecticide on their homes. Another thing that hinders the effectiveness of IRS is that in some countries, people have a tendency to re-plaster mud walls as soon as they have been sprayed, thus covering up the insecticide deposit (Curtis and Mnzava, 2000).

N'Guessan et al. (2007) also notes that the two approaches to malaria prevention (ITNs and IRS) are not mutually exclusive, and in malaria-endemic areas where ITN coverage is still limited, the feasibility of introducing IRS to reduce transmission would be ideal.

2.6.2. Insecticide Resistance

Currently, the main threat to effective malaria control is the selection of insecticide resistance measures (Asidi et al., 2012). Resistance is expressed as reduced excito-repellency and mortality of mosquitoes that are exposed to insecticide-treated materials (Takken, 2002). Several authors such as Protopopoff et al. (2013) and Hlongwana et al. (2013) have reported increasing resistance to pyrethroid insecticides in some African countries such as Tanzania and South Africa. Resistance against pyrethroids has also been recorded in Asia and South

America (Takken, 2002). WHO (2012) has also expressed concerns that resistance is now becoming widespread. The main factor thought to be driving resistance is the heavy reliance on a single class of insecticides (Moszynski, 2012). Edi et al. (2012) agree that to keep vector resistance from undermining control programs, insecticide-resistance management strategies must reduce the current overreliance on pyrethroids.

Pyrethroid resistance in insects is complex and presents at different levels as pyrethroids can have three different effects- repellency, mortality and exiting behaviour. Resistance mechanisms can develop against each of these (Takken, 2002) or on multiple insecticide-resistance mechanisms (Edi et al., 2012). The increase of drug resistant malaria parasites has been implicated in the spread of malaria to new areas and the re-emergence of malaria in areas where the disease was thought to be eradicated (Chanda et al., 2011). Insecticide-resistant mosquitoes were one of the main obstacles that prevented the success of the Global Malaria Eradication plans in the middle of the last century. There are great concerns that currently nothing has changed as pyrethroid resistance was the cause of a malaria epidemic in KwaZulu-Natal in the year 2000 (Hargreaves et al., 2000; Hlongwana et al., 2013) and recently, in Mexico, pyrethroid resistant *Anopheles* went from effectively zero to 20 % after only three years of using IRS (Read et al., 2009). Read et al. (2009) suggested the use of "evolution-proof" insecticides. These insecticides would have properties that retard and even entirely prevent the spread of resistance which could subsequently provide sustainable control (Read et al., 2009).

Case management has relied largely on anti-malarial drugs. The main antimalarials in use are chloroquine and sulfadoxine-pyrimethamine (SP), which are inexpensive and widely available (White, 2004). According to White (2004) resistance has emerged to all classes of anti-malarial drugs, with the exception of artemisinins. He states that if artemisinins are also lost to resistance, we may be faced with untreated malaria. *Plasmodium falciparum* is now highly resistant to chloroquine in most malaria-infected areas. Resistance to SP is also widespread and has developed more rapidly (White, 2004).

2.6.3. Elimination

According to WHO (2012), malaria elimination is defined as the reduction to zero of incidence of infection caused by human malaria parasites in a defined geographical zone as a

result of deliberate efforts. Continued measures are required to prevent the re-establishment of transmission (WHO, 2012).

Kelly et al. (2011) states that out of the 99 countries with endemic malaria 32 are now committed to some kind of elimination strategy. However, a major obstacle to the upgrade of services in malaria-endemic countries is weak health information systems and surveillance needed to monitor the progress of effective public health responses and/or programme adjustments (Kelly et al., 2011). Maharaj et al. (2012) agree that malaria elimination in South Africa is possible given that certain criteria are met like the continued support of existing malaria programmes, cross border malaria control initiatives, as well as operational research on vector distribution and insecticide resistance. They also believe that surveillance systems need to be refined in order for information to be routinely collected (Maharaj et al., 2012).

Given the effectiveness of antimalarial tools and interventions, it would be feasible to effectively control malaria in all parts of the world. Malaria could also be entirely eliminated from countries and regions where the transmission intensity is low to moderate and where health systems are strong (Mendis et al., 2009). Similar to Maharaj et al. (2012), Mendis et al. (2009) believe that elimination can be achieved with the re-orientation of control activities, moving away from a population-based coverage of interventions, to one that is based on a programme of effective surveillance and response.

In South Africa in particular, malaria is transmitted along the northern and eastern borders, so there has been collaboration on malaria control with neighbouring countries. In the past decade two initiatives were established to deal with cross border malaria transmission, namely, the Trans-Limpopo Malaria Initiative (TLMI) and the Lubombo Spatial Development Initiative (LSDI). The TLMI was established to reduce transmission between south Zimbabwe and the Limpopo Province. The LSDI is a joint programme between the governments of Swaziland, Mozambique and South Africa. The rational for the establishment of the LSDI was that since the Lubombo area consists of poor communities that are affected by malaria, eradicating malaria in this region would subsequently increase tourism and thus aid in economic development in these areas (Moonasar et al., 2012).

Current efforts explicitly acknowledge that for malaria to be eliminated, efforts need to be sustained in the long-term and should incorporate multiple activities, interventions,

approaches, organizations and disciplines. Seven distinct themes that have been recognised in securing malaria elimination include: (1) drugs and vaccines, (2) modelling, (3) vector control, (4) monitoring and surveillance systems, and (5) integration strategies (Hall and Fauci, 2009). According to Slutsker and Kachur (2013) the current challenge is to know where people are being infected and adapt the tools that programmes are currently running. Although malaria is being eliminated in many areas, it still remains a resilient and dangerous enemy. Some countries that previously had uniformly high levels of malaria transmission now have a varied malaria landscape: low transmission in some areas and malaria "hotspots" in others. Therefore, once it is known where people are being affected with malaria, approaches can be tailored to match the need (Slutsker and Kachur, 2013).

2.7. Spatial Epidemiology

Spatial epidemiology is concerned with the describing and understanding of geographic variation in disease with respect to environmental, genetic, demographic, behavioural and infectious risk factors (Elliott and Wartenberg, 2004). Disease mapping is conducted to understand spatial and spatio-temporal variation in risk. This information can be used for basic descriptive purposes, to provide information concerning the health needs of a population or, to compare estimated risk or exposure so as to obtain ideas as to disease aetiology (Elliott et al., 2000). Geographical correlation can be investigated to establish whether geographical variations in exposure to environmental variables like temperature and water have any relation to the health outcomes of individuals as measured on a geographical scale (Elliott et al., 2000).

Spatial epidemiology began in 1855 with the seminal work of John Snow on the transmission of cholera. Snow mapped cases of cholera together with the location of water sources in London where he showed that contaminated water was the major cause of the disease. In the 19th and 20th centuries spatial analysis was mostly employed by plotting the observed disease cases or rates (Frerichs, 2001). Nowadays, computer based cartographic methods, modern statistical methods and satellite derived data allow an integration to address both tasks and even go further by providing predictions at new locations (Gemperli, 2003).

2.7.1. GIS and Remote Sensing

GIS has emerged as the core of spatial technology in spatial epidemiology studies. It is being used in various applications such as locating the study population by geocoding addresses (geo-referencing), using proximity analysis to contaminant source to establish a proxy for exposure, as well as integrating environmental monitoring data into the analysis of the health outcomes (Nuckols et al., 2004). Essentially, a GIS is a powerful, computerized database management system that allows for the capture, storage, retrieval, analysis and display of data within a geographic context (Figure 2.3) (Vine et al., 1997). All methods of collecting information about the earth without actually being in contact with it are forms of Remote Sensing (RS). Remotely sensed data can be acquired via satellites, aerial photography and radars. Basically, remote sensing is the collection and analysis of radiant energy coming from different sources for the purpose of extracting useful information like the presence and distribution of patterns and objects (Nuckols et al., 2004).
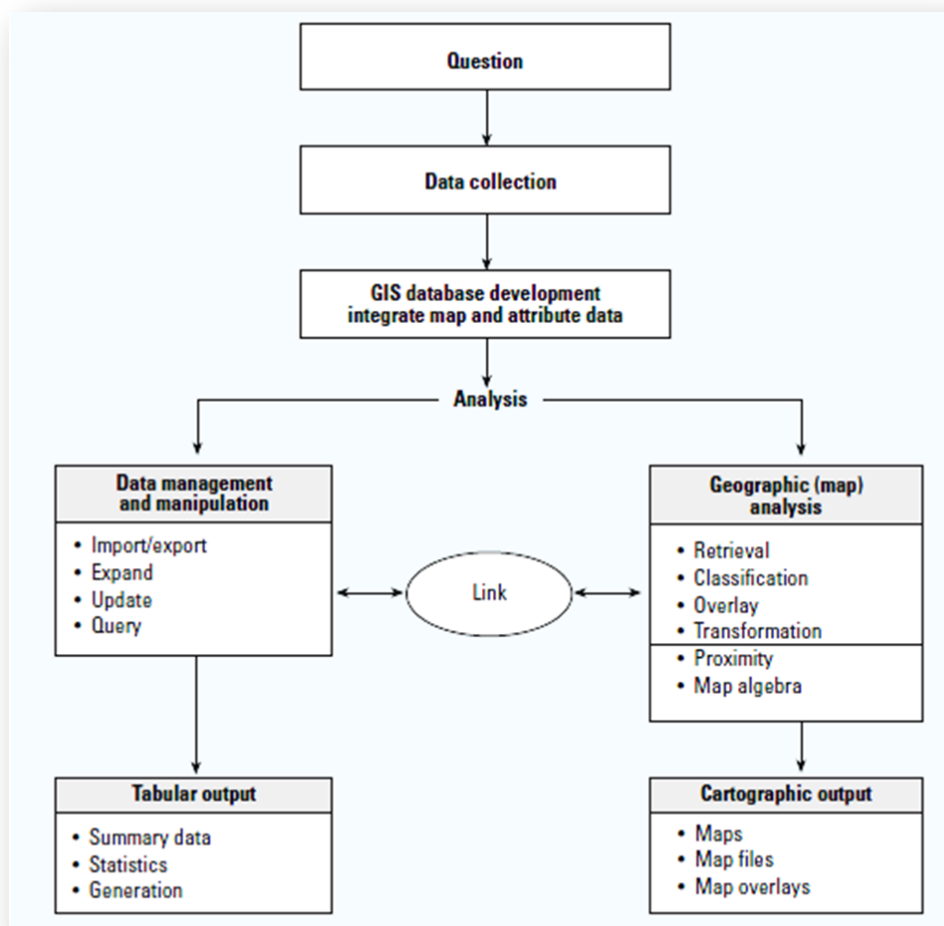
Figure 2.3: Functionality of a GIS (SOURCE: Nuckols et al., 2004)

The key strength, however, of Geographic Information Systems is their interdisciplinary approach to the solution of problems. They go beyond conventional methods of discovering and visualizing new patterns and relationships that would have otherwise remained invisible. They achieve this by classifying data coming from different sources into layers, and then link these layers by spatially matching them (Figure 2.3). These layers can then be queried and analysed to produce new information theories (Boulos et al., 2001). In order for survey data to be used in GIS, it must be geo-located or geo-referenced. This is often accomplished by using the Global Positioning System (GPS). The GPS is a system of 24 satellites that allows the co-ordinates of any point on or near the earth's surface to be measured with high precision ((Boulos et al., 2001; Saxena et al., 2009). Further research is also often needed to investigate the relationship between satellite-derived proxies on environmental conditions and ground climate data (Gosoniu, 2008). Combined with data from surveillance activities, GIS and GPS tools are ideal for generating base maps, mapping breeding habitats and analysis of high disease prevalence (Saxena et al., 2009; Reid et al., 2012).

Since the 1990s RS and GIS have provided useful tools for mapping malariological indicators in Africa. Craig et al. (1999) produced a climatic suitability map of malaria transmission in sub-Saharan Africa and Snow et al. (1999) estimated the number of people at risk of malaria worldwide, by continent. In addition some authors have integrated RS and GIS to produce maps of malaria vector distribution and maps of vector breeding sites. The relationships between the disease prevalence and vector distribution could never have been so completely studied without this technology (Saxena et al., 2009).

Malaria mapping is based on estimating the relation between malaria transmission and environmental or climatic factors as the biological parameters are directly influenced by meteorological variables, therefore this relation can be used to predict malaria transmission at locations where information is not available (Thomson et al., 1997). GIS and remote sensing data from earth-observing satellites can facilitate this kind of epidemiological research by improving aptitudes for spatially-explicit risk profiling and early warning systems (Yang et al., 2010).

2.7.2. Spatial Statistical Methods

Since the pioneering work by Ross, in 1910 and MacDonald in 1957, significant progress has been made in understanding malaria through the development of deterministic and

mathematical models and their statistical inference with incidence (Eckhoff, 2011; Montosi et al., 2012). Deterministic models are usually called biology-driven models which typically rely on biological data and meteorological variables collected by ground-based or satellite-driven observations. Mathematical and statistical models on the other hand require the development of new, weather dependent mathematical dynamic models, which take into account the known risk factors quantitatively (Yang et al., 2010). In recent years, biology-driven and statistical models have been developed to improve our understanding of the likely impact of climate on malaria transmission. Craig et al. (1999), for example, developed a fuzzy-logic, climate based distribution model. Giardina et al. (2011) developed a Bayesian geostatistical model to estimate the burden of malaria in Senegal. Gemperli et al. (2004) constructed a Bayesian hierarchical geostatistical logistic model to investigate the spatial patterns of infant mortality in Mali. Abellana et al. (2008) also used the same methods to study the seasonal effect on the spatial distribution of the incidence of malaria in children under 10 years of age living in Mozambique.

2.7.2.1. Spatio-temporal Modelling

Even though the global distribution of malaria is affected by human anti-malarial interventions, the control of malaria also needs to take into account temporal and geographical patterns (Craig, 2009).

In epidemiological studies, the reported cases of a disease are often expressed as daily, weekly or monthly counts (Hay and Pettit, 2001). Apart from the causal links, the relationships that exist between the host and the vector and the parasite illustrate the temporal element of malaria transmission (Mboera et al., 2010). The human life cycle is a matter of years, the mosquito life cycle a matter of days and weeks, while the interaction between the humans and mosquitoes waxes and wanes over weeks and months. The parasites life cycle plays out in the human in days, and days to weeks in the mosquito, while the interaction with the human host develops over months and years (Bray and Garnham, 1982).

Spatial and temporal variation in transmission intensity is particularly important in low transmission areas where few infected mosquitoes are caught and focal "hotspots" of malaria transmission may exist (Oesterholt et al., 2006). A host of issues, however, make characterizing the natural phenomena underlying the spatial and temporal patterns in malaria risk difficult. The differences between malaria vectors mean that particular events, such as

the rainy season, can lead to an increase in vector capacity for most vectors but an initial decrease for others. When variability is due to ecological drivers, further complications can occur due to host immunity, which could be a possible explanation for intra-annual and inter-annual variation (Reid et al., 2012).

2.7.2.2. Spatial Dependency

A particular issue when analysing spatial data is that geographical data are correlated in space. When data are in close geographical proximity, the risk estimates will tend to be positively correlated as the areas share a number of similar characteristics, including both social and physical environment (Elliot and Wakefield, 2000). That is to say, responses that are geographically close are assumed to be similar (Wakefield et al., 2000). In the case of malaria, spatial correlation exists in both small and large scales, reflecting the transmission of malaria infection by the mosquitoes which fly over short distances and effects environmental factors which determine mosquito survival over large areas (Gemperli, 2003). Vector borne diseases in tropical countries are often not rare and the spatial correlation is often much stronger due to links with the climatic and environmental variables (Kleinschmidt, 2001). According to Elliot and Wakefield (2000) and Kleinschmidt et al. (2000), an analysis which does not take such dependencies into account may give false precision and potentially create bias in the estimates of effect.

Many statistical methods assume independence of observations (Sainani, 2010). When using this method to analyse spatially correlated data, the standard error of the covariate parameters are underestimated and the statistical significance is overestimated (Ver Hoef et al., 2001; Gemperli, 2003; Gosoniu, 2008; Sainani, 2010).

There are three kinds of spatial data: point level (geostatistical), areal (lattice) and point patterns (Vine et al., 1997). Spatial statistical methods incorporate spatial correlation according to the way geographical proximity is defined (Gemperli et al., 2003). Proximity further depends on the geographical information, which can be available at areal level or at point-location level (Vine at al., 1997). Areal unit data are aggregated over contiguous units (countries, districts, census zones) which partition the whole study area. Proximity in space is defined by their neighbouring structure. Point-referenced or geostatistical data are collected at fixed locations (households and villages) over a continuous study area. Proximity in geostatistical data is determined by the distance between sample locations (Diggle, 2000;

Gemperli, 2003). Questions of interest that arise concerning this kind of data are whether events are appearing sporadically or are they clustered and which risk factors are associated with such clusters (Diggle, 2000; Elliott and Wartenberg, 2004).

Exploratory tools (variogram for geostatistical data, Moran's I and Geary's C for areal data and clustering statistics for point pattern data) describe the geostatistical pattern of the areal data and are available in most statistical packages (Cressie, 2000; Wakefield et al., 2000; Abellana et al., 2008). However, these statistics are unable to filter the noise present in the data due to variable sample size between locations and produce smooth maps highlighting disease patterns (Wakefield et al., 2000).

2.7.2.3. Spatial Prediction

Spatial and spatio-temporal distributions of both physical and socio-economic phenomena can be estimated by functions depending on location in a multi-dimensional space. Most interpolation and prediction methods were developed to predict values of spatial phenomena in unsampled locations (Mitas and Mitasova, 1999). Spatial interpolation can be conducted on the basis of many different assumptions and by many different methods. The simplest- and perhaps the most often used- is to assume that the unobserved value at any unsampled area is best described by that of the nearest observed values, or the average of the surrounding areas (Briggs, 2000).

In geostatistics, spatial prediction is referred to as Kriging. Matheron (1963) coined this term in honour of the South African mining engineer D.G Krige. Prediction by kriging is based on the assumption that covariance between points is entirely a function of distance between them as modelled by means of the variogram. Another assumption is that the underlying mean of the quantity that is being predicted is constant (the assumption of stationarity) (Kleinschmidt et al., 2000). Bayesian kriging allows estimation of the prediction error, a feature which is not possible in kriging estimators (Diggle et al., 1998). Geostatistical methods have occasionally been applied to disease mapping. Diggle et al. (2002) used Bayesian kriging for mapping malaria prevalence. They applied MCMC to map malaria in the Gambia (Diggle et al., 2002).

Chapter Three: Study Area

3.1. Location of Study Area

The study area is located on the south east of South Africa (30°34´35´´ S, 30°34´35´´ E) and has a long shoreline along the Indian Ocean. The KwaZulu-Natal province borders three other provinces domestically (Mpumalanga, Free State and the Eastern Cape) and the countries of Mozambique, Lesotho and Swaziland (Figure 3.1). The districts outlined in red in Figure 3.1 were the ones selected for this study.
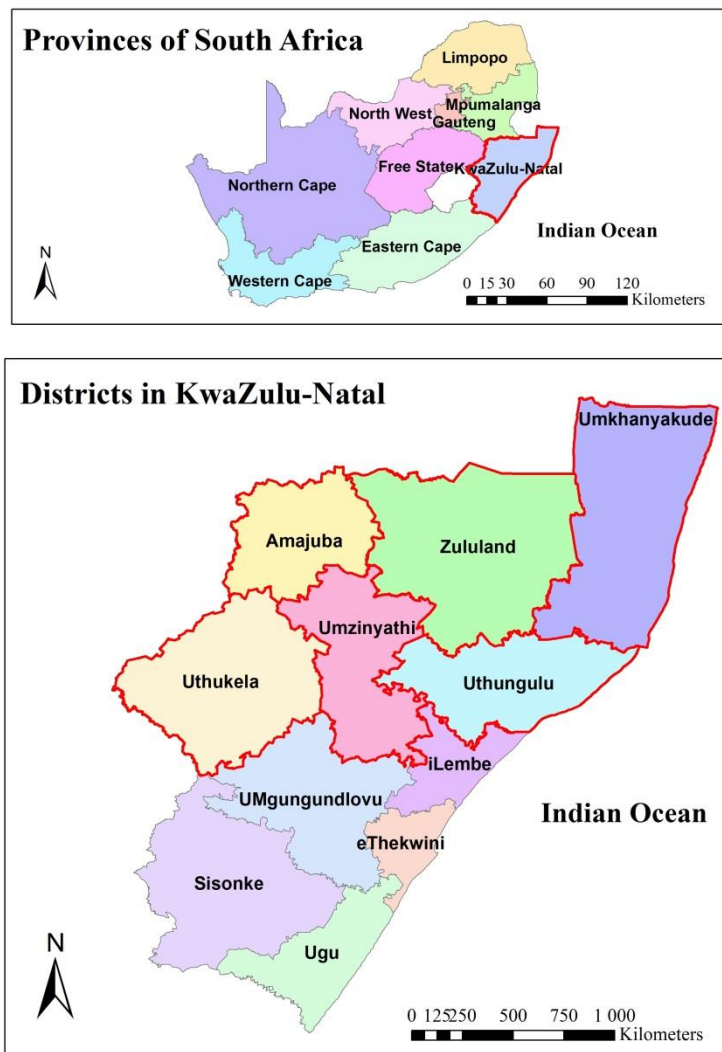
Figure 3.1 Map showing study area

Occasionally limited focal transmission may occur in the North West and Northern Cape Provinces along the Molopo and Orange Rivers as these water bodies provide favourable

breeding sites for survival of vectors such as Anopheline mosquitoes. The altitude varies between 3444 meters at the Drakensberg and 0 meters at the sea (Figure 3.2).
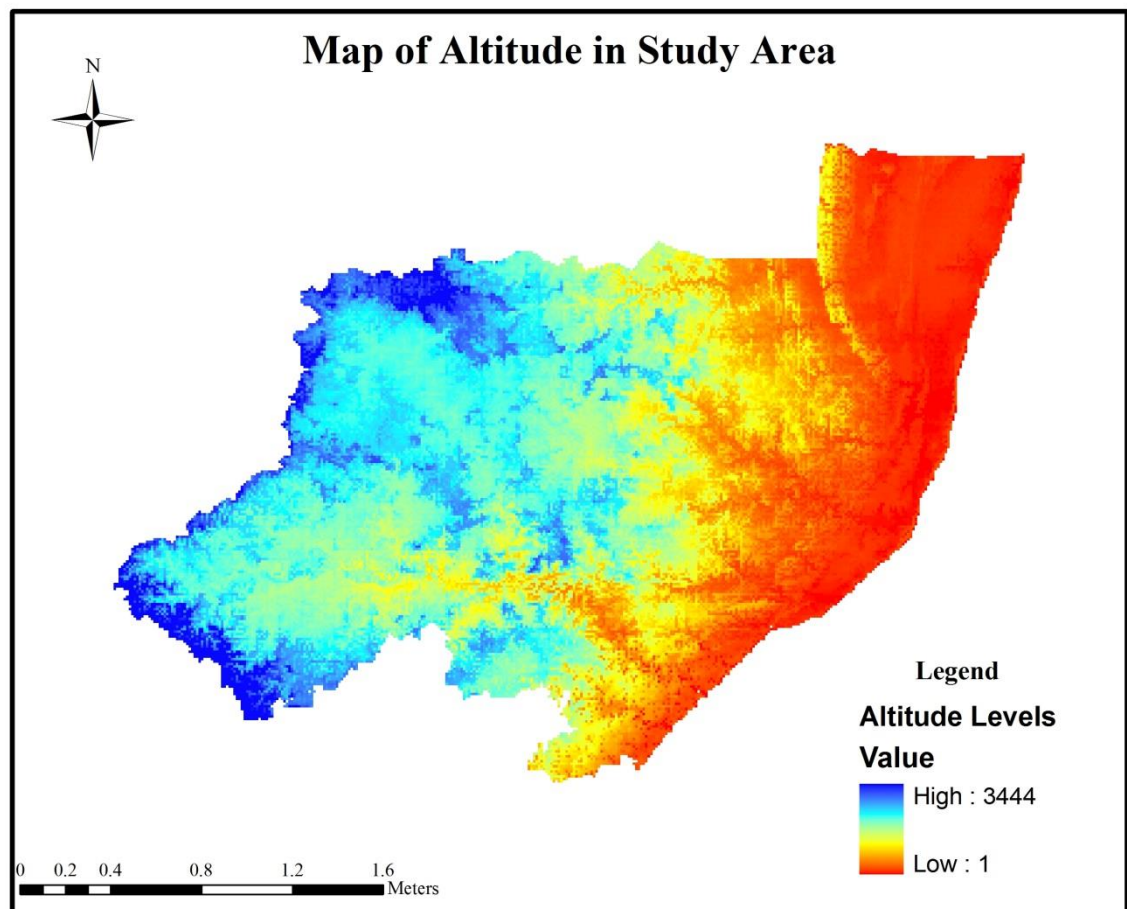
Figure 3.2: Map Showing Range of Altitude in Study Area (Source of data: MODIS, 2012)

3.2. Demographics

The population was estimated to be 10,819,130 in 2011 spread along eleven districts, one of which is a metropolitan district (eThekwini), which makes it the second most populous province in South Africa. With an average density of 110 people per km^2 and occupying a total area of 94 361 km^2 KwaZulu-Natal is a densely populated province. In terms of habitat 54% of the population live in rural areas (STATSSA, 2011).

3.3. Vegetation

KwaZulu-Natal's vegetation (Figure 3.3) varies from tropical and subtropical types at the coast, through rolling grasslands and Tundra types in the Drakensberg. Bushveld is found in the low-lying hot and dry areas of Northern KwaZulu-Natal and in most of the river systems in the Midlands mistbelt, highland sourveld, mountains of the Drakensberg and in the high rainfall areas of the coastal belt, different forms of forest are found (Figure 2). Tall grassland is also characteristic in the northern plains of the province, while the grassland is typically short in the cold highland areas (Camp, 1999).
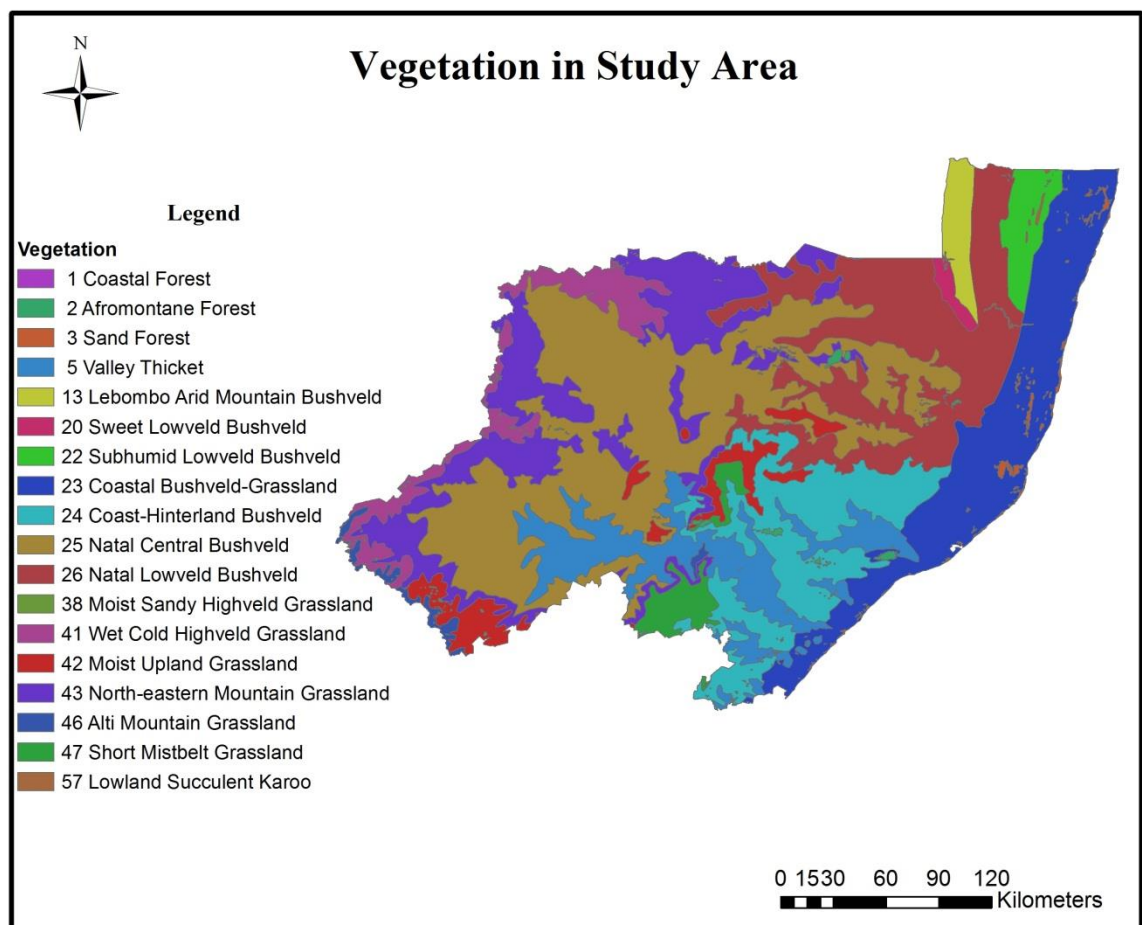

Figure 3.3: Map showing vegetation types in study area (Low and Rebelo, 1996)

3.4. Topography

The province is divided into three different geographic areas: a lowland region, a central region and the two mountainous areas. The lowland region along the Indian Ocean is extremely narrow in the South, widening in the northern part of the province. The central

region is the Natal Midlands which is an undulating plateau rising toward the west. The two mountainous regions are the Drakensberg Mountains in the west and the Lebombo mountains in the north. The Tugela River flows west to east across the centre of the province and is the region's largest river (Camp, 1999).

3.5. Climate

KwaZulu-Natal has a varied climate due to the complex and diverse topography. The range of the topography levels goes from sea level to over 3000 meters, which results in a considerable range in temperature. The coast is subtropical with the inland regions becoming progressively colder. The mean annual rainfall exceeds 900 millimeters over most of the province with hot and humid summers (October-April) and mild winters (May to September). In South Africa the malarious provinces have rainfall measures between 500 millimeters and 2000 millimeters annually (SAWS, 2010).

Along the coastal areas the summer temperatures vary from 24° C to 32° C with winter temperatures averaging 20° C. The Midlands generally has a mild climate with relatively high summer rainfall and dry winters. The high elevation of the Drakensberg that peaks over 3000 meters means that the temperatures are more moderate all year round than the coastal areas. During the rainy summer season daily thunderstorms are likely and continuous rain for up to a week is not uncommon but this can be balanced out by long sunny stretches. Snow on the higher peaks is also not unusual during the summer months and there can also be heavy winter snow with temperatures plummeting below 0° C at night (SAWS, 2010).

3.6. Malaria Cases

The Department of Health has in the past expressed the difficulties in quantifying the burden of malaria as the disease may be asymptomatic amongst migrant workers, reports being often inadequate and incomplete and in addition some patients (especially economic migrants from neighbouring countries) may give incorrect personal details. In addition, these migrants might not report to the formal health systems due to fear of being deported making the malaria estimates imprecise (DOH, 2008).

The malaria case data are reported to the Epidemiology and Surveillance Directorate through two parallel systems, surveillance data from the three malaria high risk provinces viz. Mpumalanga, KwaZulu-Natal and Limpopo are sent quarterly to the Directorate. Data from

the other six provinces that have a relatively low to no risk malaria are received though the passive notification system (DOH, 2008).
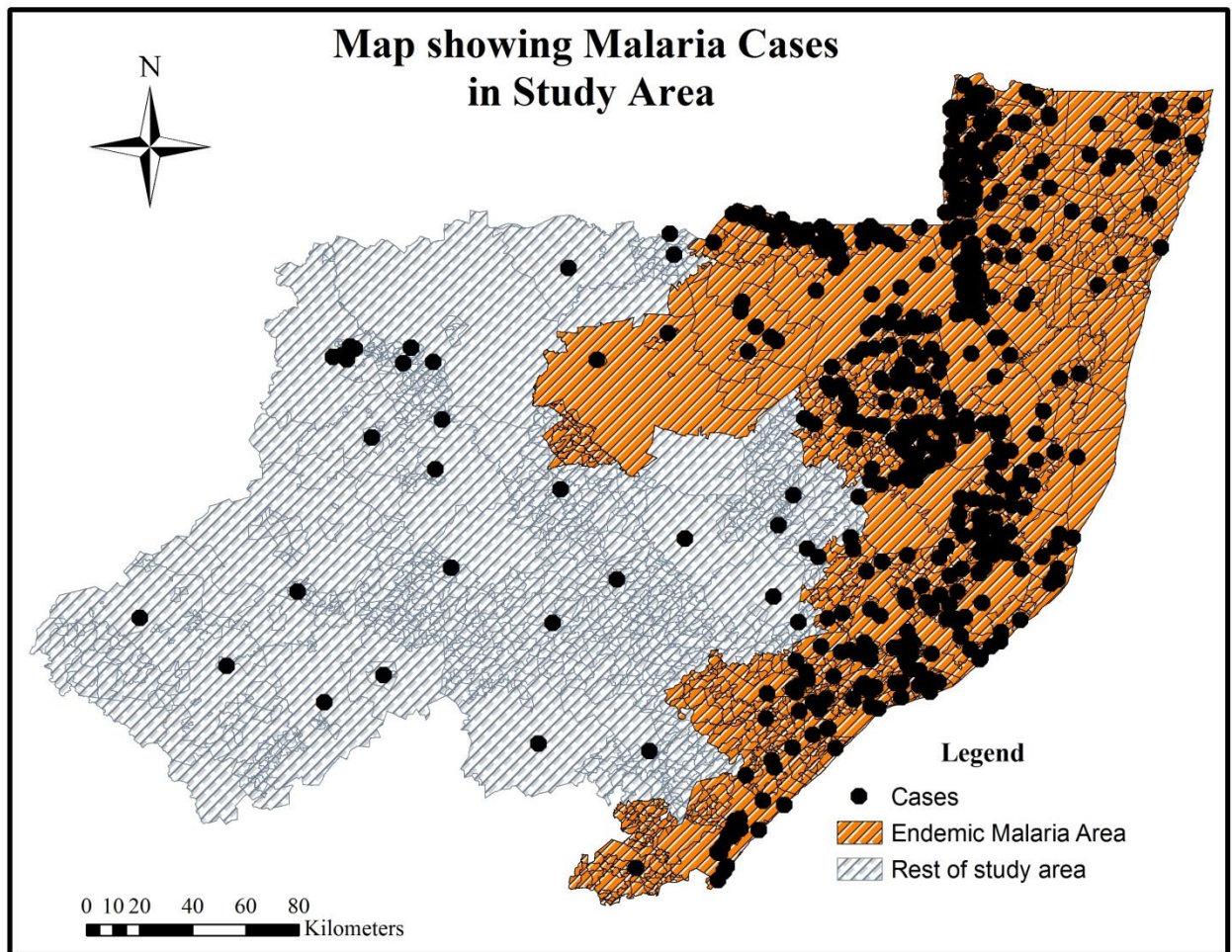
Figure 3.4: Map showing location of malaria cases in study area (Data Source: Medical Research Council, 2012)

Figure 3.4 illustrates the passive malaria cases reported in the study area. This data was collected by the South African Medical Research Council from January 1998 to July 2011 but for the purposes of this study only the cases from the year 2000 to July 2011 were used as that is the period the environmental/climatic data is used. Each point on the map relates to all the residential areas where there were observed cases. In Figure 3.4 the endemic malaria area is shown separately from the rest of the study area. It is evident on the map that most of the cases were observed in the endemic malaria area.

3.7. Socio-economic Factors

For many years the socio-economic status of a community has been used as an indicator to characterize malaria treatment behaviours and the community's adherence to malaria control programs. Factors such as distance to health centres and education levels of the household heads can influence malaria treatment seeking behaviours and in the understanding and selection of malaria intervention for the household (Lowassa, 2012).

Malaria contributes approximately 40% of all outpatient visits in rural areas, with children under five and pregnant women contributing the highest proportions (DOH, 2010). According to the census conducted in 2011 in South Africa, almost 26% of persons aged between 5 and 24 years of age are not attending any educational institution in KwaZulu-Natal. The 2011 census also revealed that of the persons aged 20 years and older, only 30.8% of them had matriculated from high school in KwaZulu-Natal (STATSSA, 2011). The Census conducted in 2011 in South Africa concluded that 47.6% of the population in KwaZulu-Natal was unemployed. In addition, 28.4 % of the population still reside in informal dwellings and 22.1% still have no access to electricity (STATSSA, 2011). Malaria has been associated with poverty at the macroeconomic level according to Coleman et al. (2010) stating that in areas of hyperendemic malaria in Sub-Saharan Africa, risk has been associated with personal protection measures alongside with the location of the housing, as well as the structure of the home. In a study they conducted in South Africa, they found that people living in traditional mud-wall houses had increased risk of malaria than those who lived in Western-styled brick-wall dwellings. These traditional types of houses also provide conditions that are favourable for mosquito and human contact as there are many potential access points for mosquitoes in mud walls, which would consequently increase the risk of malaria infection (Coleman et al., 2010).

Chapter Four: Material and Methods

4.1. Introduction

The aim of the study is to analyse the geographical patterns of malaria incidence in KwaZulu-Natal, South Africa. A correlation has been found to exist between environmental covariates and malaria transmission therefore in this study a number of environmental factors were required to assess the relationship between the environmental covariates and malaria transmission. This chapter will outline which data was used for the study, as well the methods that were used in order to achieve the aim of the study. This will include a detailed section on data description and finally the model formulation and analysis.

4.2. Data Description and Acquisition

4.2.1. Malaria Data

For spatial analysis to be feasible health event data must be spatially located. The clinical cases of malaria were obtained from the malaria information system of the KwaZulu-Natal province. This system has been developed by the South African Medical Research Council (MRC), a national research organisation in South Africa, using Microsoft Access for data entry and validation. Malaria is a notifiable disease in South Africa. The case reporting system aims to capture all cases that have been confirmed parasitologically through both active and passive surveillance. Active surveillance is achieved through screening measures where teams would go into a community with known risk of malaria, or in areas where there was suspicion of parasite carriers. Blood smears would then be taken of all the community members with particular emphasis on those presenting with a fever or who had previously had a fever, those who had travelled to a malaria risk area and possible migrants from malaria endemic areas. After the introduction of RDT's in 1998, the need for active surveillance decreased as all suspected malaria patients could now get a blood test at a primary health care facility. Only the cases that tested positive through either RDT or microscopy were notified and entered into the system.

In the course of the passive surveillance process, patients visit health facilities, and after they are parasitologically diagnosed with malaria, the health worker notifies the case on the prescribed notification form and reports on the travel history of the patient. The health

facilities are visited twice a week in the malaria areas during high transmission periods to ensure that all notifications are collected and the availability of drugs is monitored.

Clinical case data was collected for the period of 1998 to June 2011 for cases that have been reported in health facilities. In South Africa, a suspected malaria infection is confirmed or excluded with a blood test diagnosed using microscopy and/or RDTs. Only the passive, spatially referenced, local cases were considered for this study thus locations that were not geo-referenced in the database were eliminated from the study. Only the locations that fell into the selected districts (Umkhanyakude, Uthukela, Amajuba, Umzinyathi, Zululand and Uthungulu) were selected for analysis as these are the more malaria prone areas. The reason for this was that the malarial area in KwaZulu-Natal is in the northern areas close to the Mozambican and Swaziland borders and any cases found in the rest of the provinces are generally treated as imported cases from people who had travelled to malarious areas of the province. The clinical case data included information on the individual such as sex, age, the year of diagnosis, type of mosquito species that infected them and their residential name and health facility name where they were screened as well as the co-ordinates of the residential name. Cases or locations were also eliminated from the study if they had missing values for any of the climatic/environmental variables analysed in the study.

4.2.2. Population Data

The calculation of area-specific disease risk requires an accurate estimate of the population at risk. The estimated population for each district was obtained from the national statistics department, Statistics South Africa (STATSSA) and the AfriPop website http://www.afripop.org/ for population at sub-place level. The AfriPop project provides large area spatial demographic datasets that are per grid square estimates of numbers of people. AfriPop utilises satellite imagery for mapping settlements- specifically 30 meter resolution Landsat Enhanced Thematic Mapper (Edi et al., 2012) satellite imagery. The population data is available at a spatial resolution of approximately 100 meters (Figure 4.1) and was extracted for each individual place in the study area. For full details on the AfriPop project see Tatem et al. (2004, 2007) and Linard et al. (2010).
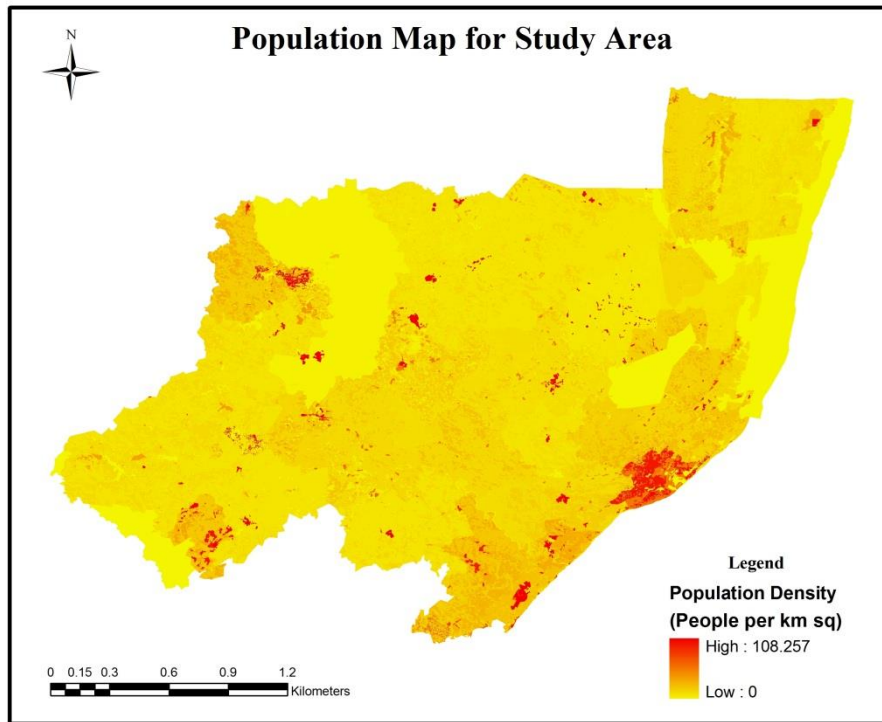
Figure 4.1: Population Map for the Study Area for 2010 (SOURCE: AfriPop, 2010)

The AfriPop population data was available for the year 2010 and the census data from STATSSA was available for the years 2001 and 2011. There was also a community survey performed in South Africa in 2007 by STATSSA. For the non-censual years population estimates were obtained by applying the annual population growth rate for each district obtained from STATTSA (2012). The population was extracted at each observed case location from the Afripop dataset and the population for each year was estimated by applying the annual growth rate to the Afripop dataset.

4.2.3. Environmental Variables

Environmental data was obtained from Moderate Resolution Imaging Spectroradiometer (MODIS). MODIS has a spatial resolution varying between 250 meters and 1 kilometer. Estimates of environmental and climatic factors like temperature, vegetation or land coverage can be obtained from the MODIS satellite. The available periods can be daily, 8-days, and 16- days, monthly and/or yearly depending on the factor. The following meteorological data was obtained from the NASA's EOSDIS Reverb Tool website

(http://reverb.echo.nasa.gov/reverb/):

4.2.3.1. Temperature

The MODIS global land surface temperature and emissivity product was used for temperature. It is comprised of daytime and night-time land surface temperatures (LST). The data has been collected from March 5 2000 until July 2011 with a spatial resolution of 1 kilometer. The data is composed of the daily 1 kilometer clear sky LSTs averaged over an 8 day period. LST data were used as proxies of day (maximum) and night (minimum) temperature.

4.2.3.2. NDVI

The MODIS NDVI data are provided every 16 days at 1 kilometer spatial resolution. The data are provided from February 24, 2000 to July 2011. The MODIS NDVI product is computed from atmospherically corrected bi-directional surface reflectance's that have been masked for water, clouds, heavy aerosols, and cloud shadows. The NDVI was considered as proxy for vegetation and moisture.

4.2.3.3. Land Cover Type

The MODIS Land Cover Type product provides data characterizing five global land cover classification systems. It has an annual temporal resolution with a 500 metre spatial resolution. Since it is only available from the year 2001 until 2009 at the time it was downloaded, for the purposes of the study the same values of the year 2001 were used for the year 2000 and also the same values were used from the year 2009 were used for the year 2010 and 2011 since it is a fair assumption that land cover types would not have changed drastically for that time period.

This product includes a set of five layers in which land cover is mapped using different classification systems including the International Geosphere-Biosphere Programme classification, a 14-class system developed at the University of Maryland.

The classes were then further grouped into a land cover classification scheme and differentiated according to the occurrence of the *Anopheles* mosquito (Lindblade et al., 1999) and human activity (Table 4.1).

Table 4.1: Land Cover Classification Scheme

Main Class	Sub-Class
1. **Dry Non-Forest Vegetation**	Bush-/Shrubland Grassland/Savanna
2. **Forest**	Forest/Woodland
3. **Wet Non-Forest Vegetation**	Wetland Large-scale Agriculture
4. **Non-Vegetation**	Bare Soil/Rock Building/Settlement/Infrastructure Roads/Tracks
5. **Water**	Standing open water Flowing open water

4.2.3.4. Altitude

The Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) was used to determine the altitude in the study area. The ASTER GDEM covers land surfaces between 83°N and 83°S and is comprised of 22,702 tiles. The ASTER GDEM is distributed as a Geographic Tagged Image File Format (GeoTIFF) files with geographic coordinates (latitude, longitude). This was obtained from the USGS website www.usgs.gov .

4.2.3.5. Rainfall

The rainfall data was downloaded from the Africa Data Dissemination Service (ADDS) website http://earlywarning.usgs.gov/fews/africa/index.php that is implemented by NOAA's Climate Prediction Center. The data are provided as decadal (10-day) Rainfall Estimates at an 8 kilometer spatial resolution. The daily data are in geographic coordinates using the Albers Equal Area conical projection (Clarke 1866 spheroid). The daily totals are summed to produce the decadal totals and the decadal totals are then projected to the coordinate system.

4.2.3.6. Water Bodies

The data for the water bodies was obtained from the Environmental Science Research Institute (ESRI) website www.arcgis.com . Two datasets were provided separately and used

in conjunction: the world linear water dataset and the world water bodies' dataset. The World Linear Water dataset provides a base map layer for rivers and streams of the world, whilst the World Water Bodies dataset represents the open water rivers, lakes, seas, and oceans of the world. The water bodies' data was used a proxy for the distance to water bodies. The shortest Euclidean distance between the centroid of each pixel and the closest water body was calculated in ArcGIS version 9.3 (ESRI; Redlands, CA, USA).

4.3. Pre-processing

The satellite imagery data was linked to the malaria case data so as to extract data in only the 141 unique locations in the study area. To be able to process the data and extract the values at the desired locations with ArcGIS or any other program the files have to first be converted into geo-referenced tiff picture files. To achieve this, the MODIS Reprojection Tool offered under http://lpdaac.usgs.gov/landdaac/tools/modis/index.asp was used for this task. A MS-DOS batch file was created to convert the files automatically instead of individually converting each file as there were many files to process.

Values were extracted using ArcGIS 9.3 (ESRI; Redlands, CA, USA) from the geo-referenced tiff files at each of the 141 observed unique locations using the WGS 1984 projection. This was done for each of the environmental covariates: LST, NDVI, land cover type, altitude, and rainfall. The distance to water bodies from each observed location was also calculated in ArcGIS 9.3 (ESRI; Redlands, CA, USA). Since this study was conducted over a long time period and there were many files to process and extract values from, the command line window in ArcMap was used to create batch files to run the processing automatically for the extraction of values.

4.3. Data Management

All data management was efficiently conducted using a data analysis and statistical software called Stata MP Version 10.1 (Stata Corporation, College Station, TX, USA) which is a full featured programming language for Windows, Mac, UNIX and Linux.

4.3.1. Conversion of Database Files

Before the files produced in ArcGIS could be used in Stata they had to be converted first into ASCII files that Stata could read. The .dbf files from ArcGIS containing all the information

regarding what value was extracted at each observed location were converted into .csv files using Microsoft Visual FoxPro version 9.0 (Microsoft Corporation, Albuquerque, NM, USA). Batch files were created to automatically convert the files in FoxPro as there were too many to manually convert. For other covariates that did not have many files needed for conversion, like land cover for example, Stat/Transfer version 7 (Circle Systems, Seattle, WM, USA) was used to convert the ArcGIS .dbf files into .dta Stata files.

4.3.2. Data Management

The first step was to clean the malaria cases data of any inconsistencies like missing values or incorrect spelling of names until a final set of cases was obtained that would be the working data. Although the malaria case data dated back to 1998, as a result of that MODIS satellite imagery for the environmental covariates was generally only available from February 2000; and some at an even later time than that, only the cases dating from May 2000 until July 2011 were included in the analysis.

The following step was to link the environmental variables to the cases. The remote sensing proxies are averaged over different time periods (lag time) prior to the disease and are lined to the corresponding incidence data of that period. The following periods were considered (i) current month (aligned with the case); (ii) previous month; and (iii) two months before the case.

The linking was performed for all the individual covariates and then a final master file including all the covariates and cases together was created. This was the master file that would be used in the analysis.

4.4. Statistical Analysis

4.4.1. Exploratory Analysis

The incidence data were modelled via a Negative Binomial regression. Exploratory analysis was conducted in Stata 10.1 (Stata Corp., College Station, TX, USA) to assess the relationship between the monthly malaria transmission and the monthly values of each climatic variable. For categorical variables like land cover, new categories were created.

4.4.2. Bayesian Geostastical Methods

Bayesian methods have been applied extensively in recent years for modelling both areal unit data and geostatistical data because they allow flexible modelling and inference and provide computational advantages via the implementation of Markov chain Monte Carlo (MCMC) methods (Wakefield et al., 2000). The realization that Markov chains could be used in a wide variety of simulations came on to mainstream statistics with Gelfand and Smith (1990). The rapid emergence of BUGS (Bayesian inference Using Gibbs Sampling) software provided another compelling argument to use MCMC algorithms at large (Lunn et al., 2009; Robert and Casella, 2011). MCMC simulation can be implemented in the WinBUGS statistical software which includes specific functions to fit conditional and joint models (Wakefield et al., 2000). WinBUGS/OpenBUGS is the current, windows-based, version of the BUGS software. The conceptual design of the software is based on constructing an internal representation of the probability model that is analogous to the way in which it may be visualized as a graphical model. Each quantity in the model is represented by a node and nodes are connected by lines or arrows to show direct dependence in graphical modelling. To clarify the qualitative nature of the model, details of the distributional assumptions and deterministic relationships are "hidden" (Lunn et al., 2000).

If we have data *y* and unknown parameters *θ*, the Bayesian approach would be to treat all unknown quantities as random variables and assign a *prior* probability distribution to each. To obtain a full probability model for all observable and unobservable quantities, a joint probability distribution (i.e. likelihood) can be specified. In order to make inferences about *θ* we use Bayes' theorem to construct the *posterior* distribution, i.e. the joint distribution of all model parameters conditional on the observed data:

$$p(\theta \mid y) \propto p(y \mid \theta)p(\theta),$$

Where, throughout, (p.|.) and p (.) denote conditional and marginal probability distributions respectively. Thus, the posterior is proportional to the likelihood *p(y | θ)* multiplied by the prior *p (θ)* (Lunn et al., 2000).

With regards to areal data, simultaneously autoregressive (SAR) models, conditional autoregressive (CAR) models and modifications have been suggested as prior specifications in the Bayesian approach . The autoregressive model of order one is one of the most commonly used in time series models (Hay and Pettitt, 2001). In geographical mapping of diseases and mortality rates specification in the Bayesian models are employed assuming

Poisson count data (Diggle et al., 2000). Kleinschmidt et al. (2001) have implemented CAR models for mapping incidence rates data. Gelfand and Vounatsou (2003) extended CAR model for mutinomial response data with application to geographical mapping of allele and haplotype frequencies.

4.4.3. Bayesian Distributed Lag Model

A Bayesian distributed lag model was used to identify the lag time which gives the best fit. A distributed lag model is a regression model that includes lagged exposure variables, or distributed lags as covariates. Its distributed lag function describes the relationship between the lag and the coefficient of the lagged exposure variable. The distributed lag model assesses how a covariate at time t, say X_t, causes an influence on the mean value of the response variable Y_t. This method is a necessity when the dependent variable reacts to changes in one or more of the explanatory variables only after a lapse of time. This delayed reaction suggests the inclusion of lagged explanatory variables (distributing the effect of the explanatory variable over several periods) into the specification of the model. It is typically assumed that the coefficients of lagged variables are not all independent but functionally related (Ravines et al. 2006; Welty et al., 2008). The specification of a model is complete after specifying a prior distribution of all parameters of interest when using the Bayesian approach. Following Bayes' theorem, the posterior distribution is proportional to the product of the prior by the likelihood (Ravines et al. 2006; Welty et al., 2008).

4.4.2.1. Model Formulation

The following equation was used to model the incidence data:

$$N_{it} \sim NB\ (\mu_{it}, r)$$

$\log(\mu_{it}) = \log(P_{it}) + trend + seasonality + EO + spatial + temporal$

Where N_{it} : observed number of malaria cases at sub-place i and month t;

     μ_{it} : expected average number of cases

     P_{it} : population count

     r : dispersion parameter

(Trend) $f_T(t)$: A function of time, i.e. $f_T(t) = \beta * t$

(Seasonality) $f_S(t)$: $f_S(t) = \alpha_1 * \cos(2\pi t / T) + \alpha_2 * \sin(2\pi t / T), t = 1\ldots 12$

EO   : $\beta_1 * X_{1it} + \beta_2 + X_{2it} \ldots + \beta_k * X_{kit}$

(Spatial) $\phi = (\phi_1, \phi_2 ... \phi_L)^T$: ϕ arises from a spatial Gaussian process

$\phi \sim N(0, \Sigma)$, $\Sigma_{ij} = \sigma^2_\phi \ exp \ (-\rho d_{ij})$: d_{ij} is the Euclidean distance between places *i* and *j*

(Temporal) $e = (e_1, e_2, ... e_T)^T$: *e* arises from an autoregressive process

$$e_t \sim N(\gamma e_{t-1}, \sigma^2_e)$$

N_{it} arises from a Negative Binomial distribution. The relation between μ_{it} and the vector of *k* associated predictors $X_i = (X_{i1}, X_{i2}, .., X_{ik})^T$ observed at location s_i is modelled via the equation $log(\mu_{it}) = log \ (N_i) + X_{it}^T \ \beta + w_i + e_t$, *where* X_{it} where $\beta = (\beta_1, \beta_2, ..., \beta_k)^T$ is the regression co-efficient vector, and ω_{it} and ϕ_{it} are location-dependent random effects (Giardina et al., 2012; Karagiannis- Voules et al., 2013). Bayesian inferences consider model parameters to be random (Link and Barker, 2010). Therefore, for regression coefficients we often assume that:

$$\beta_k \sim N(0, \sigma^2_k), \sigma^2_k \text{ is large (i.e. 1000)}$$

In order to introduce spatial dependence, the random effects $\phi = (\phi_1, \phi_2, ..., \phi_n)^T$ must be assumed to be distributed according to the Multivariate Normal (MVN) distribution with a mean of 0 and covariance matrix Σ. Therein each element σ_{ij} is defined by an exponential parametric function of the distance d_{ij} between locations s_i and s_j, i.e. $\Sigma = \sigma^2_\phi \ exp \ (-\rho d_{ij})$ (Giardina et al., 2012; Karagiannis- Voules et al., 2013). The spatial variation is represented by the parameter σ^2_ϕ and the parameter controlling the rate of decay with increasing distance is ρ. Spatial correlation is introduced in parameters $\varphi_1, \varphi_2 ... \varphi_L$ seen as samples from a continuous spatial process:

$$\phi \sim MVN(0, \Sigma) = \frac{|\Sigma|^{-\frac{1}{2}}}{(2\pi)^{\frac{1}{2}}} exp(\frac{-1}{2} \phi^T \Sigma^{-1} \phi)$$

Σ is the spatial covariance matrix. Non-informative priors were assigned for the parameters, while multinomial priors were assigned for the covariates (Dellaportas et al., 2002; Ntzoufras, 2002; Link and Barker, 2010).

4.4.2.2. Implementation in BUGS

MCMC methods, like Gibbs Sampling, have been used extensively in Bayesian inference. The software BUGS (Bayesian Analysis using Gibbs Sampling) is a well-known tool for conducting this task. This package was developed by David Spiegelhalter and colleagues at

the MRC Biostatistics Unit in the United Kingdom and is available freely from http://www.openbugs.info/w/ .

This model was implemented in OpenBUGS Version 3.2.1. 120 000 iterations of the MCMC were run with a burn-in phase of 5 000 iterations. Spatial random effects were used to take into account the spatial correlation present in the data at sub-place/community level. Temporal random effects were used at monthly intervals to account for temporal correlation. Spatial correlation was incorporated by assuming an autoregressive process in the random effects. The total number of covariates was 20 and the best set of covariates was indicated by the model with the highest posterior probability (Mabaso et al., 2006; Giardina et al., 2012; Karagiannis- Voules et al., 2013).

There are two ways of modelling seasonality, one way is to create indicator variables and the other is by using harmonic terms. Both of these were used for this study. The models were fitted using the MCMC technique which is the most commonly used computational method for fitting Bayesian models (Link and Barker, 2010).

Prior distributions were assigned to the parameters so as to complete model specification. For the variance an inverse-gamma prior was assumed and a gamma distribution for the spatial decay parameter ρ. Non-informative Gaussian distributions with a mean of zero and a variance of 100 were assigned for the priors of the regression coefficients. The covariates were standardized in order to avoid the effect of scale and reduce the computational time for the MCMC (Dellaportas et al., 2002; Link and Barker, 2010; Giardina et al., 2012). The related BUGS code can be found in the Appendix A.

4.4.2.3. Prediction

A grid of 1 km^2 resolution covering the study area was created using ArcGIS 9.3 (ESRI; Redlands, CA, USA) resulting in approximately 75 000 pixels. Predictions were based on a geostatistical model using the posterior samples of the environmental variables that were selected by the spatio-temporal model to be significant contributors to malaria transmission in the area. The malaria incidence at each pixel level was estimated using R version 3.0.1 (R Development Core Team 2008; available at http://www.r-project.org/) (Giardina et al., 2012). Details on the related R-code are provided in Appendix B.

Chapter Five: Results and Discussion

5.1. Introduction

This chapter presents the results and a detailed discussion of the aim and objectives of this study. A descriptive analyse of the data is presented followed by the results of the spatio-temporal modelling of the incidence data. Subsequently, the results of the prediction are presented in the form of risk maps and they are discussed.

5.2. Descriptive Analysis

Table 5.1 shows the descriptive statistics of the data from the population, land cover type, rain levels, NDVI, day and night temperatures (LST), altitude and distance to water bodies for the duration of the study (May 2000- July 2011).

Table 5.1: Descriptive Statistics

	Mean	Standard Deviation	Minimum	Maximum
Population	3081	8940	21	84149
Land Cover	2.35641	0.7011067	1	4
Rain (mm)	21.71368	19.82373	0	140
NDVI	0.6056713	0.127185	0.19775	0.90455
LST Day (° C)	26.78731	4.26693	18.2	41.28667
LST Night (° C)	16.83997	3.376079	7.64	29.19
Altitude (m)	219.1538	2.189699	7	1349
Distance to water bodies (m)	5534.33	4536.44	45.32	22615.37

Figure 5.1 illustrates the number of malaria cases per year from May 2000 to July 2011. During this period a total of 5,549 (mean 462; 95 % CI 3895 – 7203) confirmed malaria cases were notified in the study area. The number of cases per year ranged from 3193 in 2000 to 32 in 2011. You can clearly see a steady decline in the number of cases from the high number in 2000, when there was a malaria epidemic in South Africa following the change of insecticide used for indoor residual spraying from DDT to pyrethroids, to the numbers remaining

consistently low by the end of study period of July 2011. The average number of cases was

highest between January and April and the lowest average number of cases was in December.
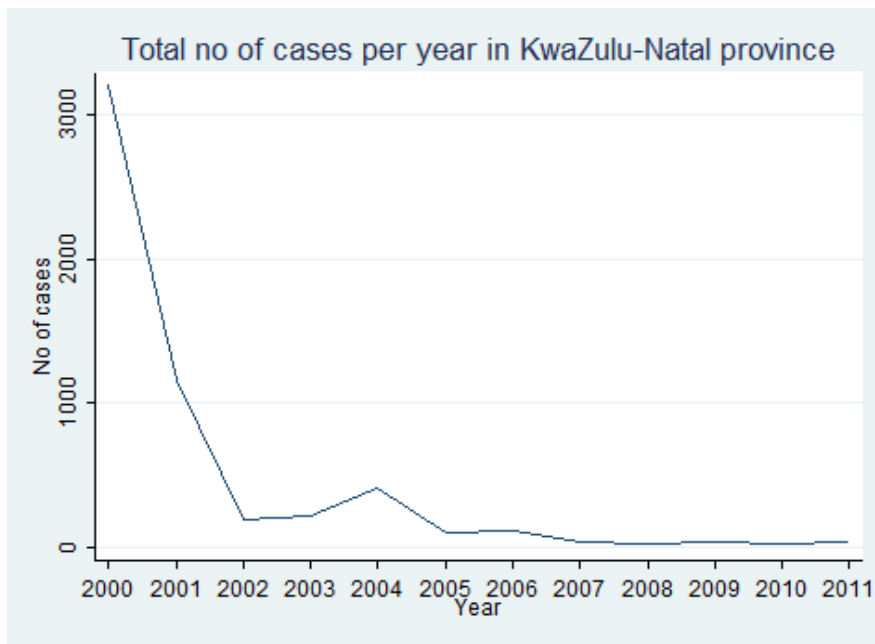
Figure 5.1: The total number of cases per year in the KwaZulu-Natal province
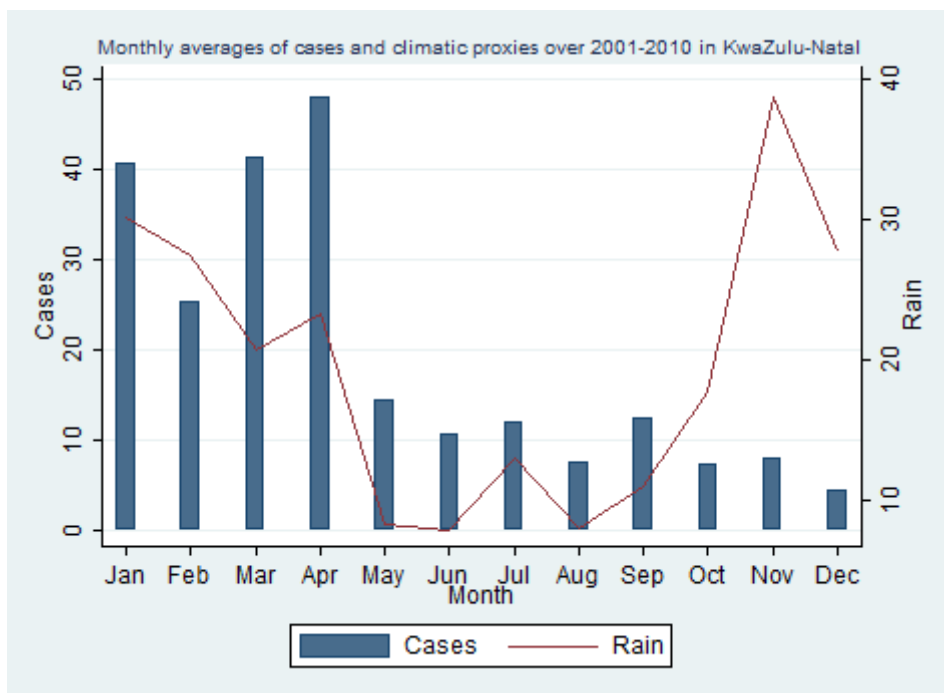
Figure 5.2: Monthly averages of cases and rainfall over 2001-2010 in KwaZulu-Natal

In Figure 5.2 the monthly average number of cases is illustrated with the monthly rainfall

values from January 2001 to June 2010 (the years 2000 and 2011 were excluded as some

months were missing). The rainfall values ranged from an average of 8mm in June to 39mm in November. Rainfall is lowest during the winter months and highest during the hot summer months.
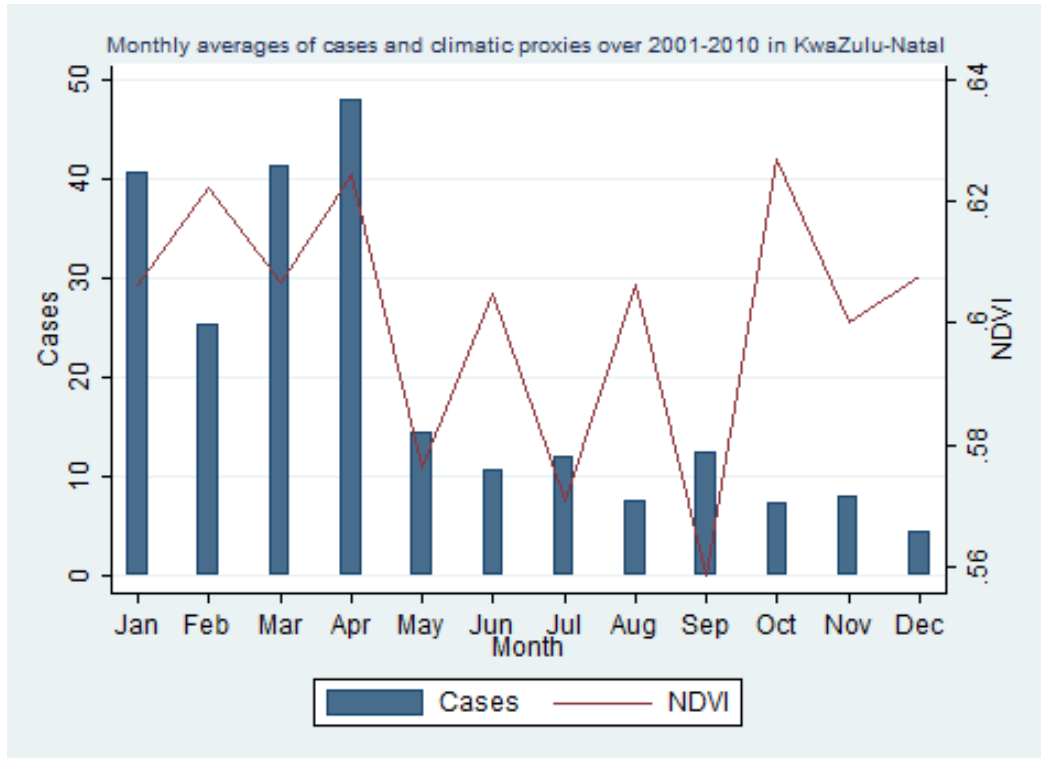
Figure 5.3: Monthly averages of cases and NDVI over 2001-2010 in KwaZulu-Natal

The monthly average values of NDVI are illustrated in Figure 5.3 where it can be seen that they are decreasing from values of 0.56 between May and September and increasing again to 0.62 from October. Since NDVI is used to monitor and measure plant growth and vegetation cover the highest NDVI values are consistent with the Summer/Spring season in South Africa when the amount of green vegetation is at its peak until April. The highest numbers of cases seem to be coinciding with the highest values of NDVI between January and April. The NDVI and rainfall values follow a similar pattern.
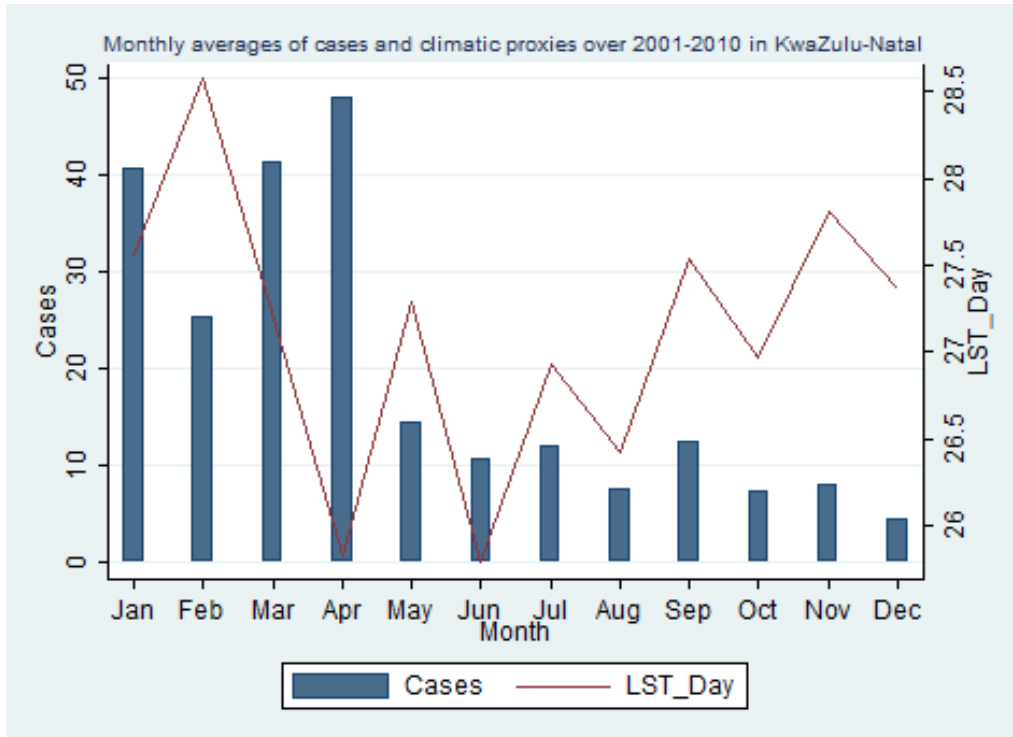
Figure 5.4: Monthly average cases and day temperature over 2001-2010 in KwaZulu-Natal
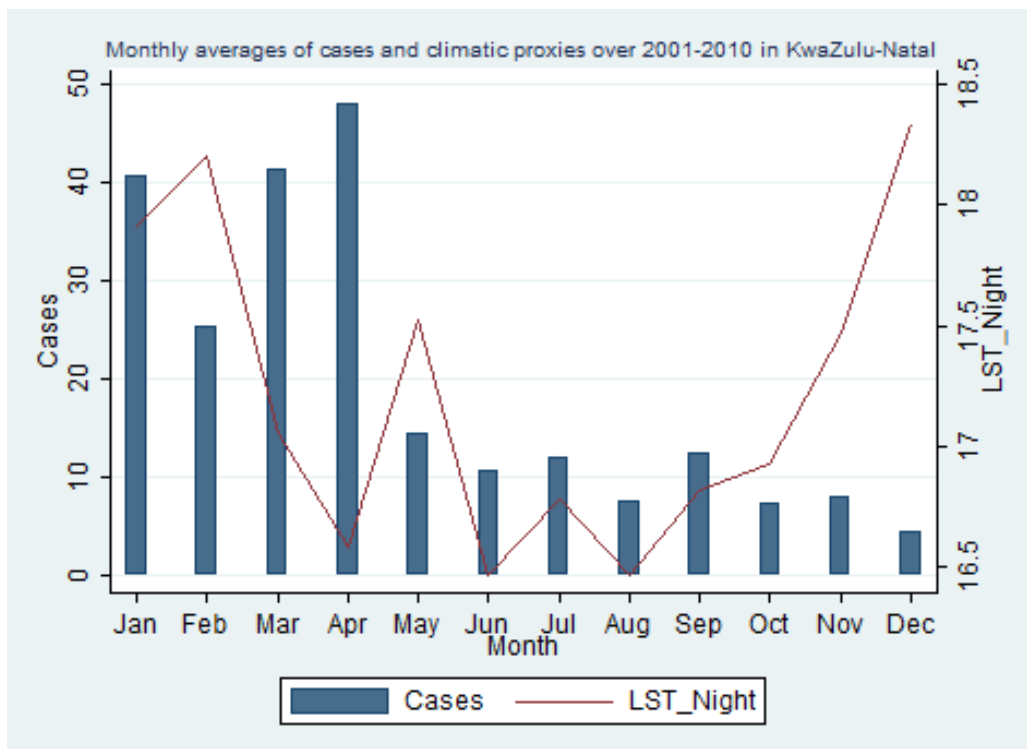
Figure 5.5: Monthly averages of cases and night temperature over 2001-2010 in KwaZulu-Natal

The range of day temperature values is demonstrated in Figure 5.4 where the average day temperature per month ranges from its lowest at 26 ° C in July to almost 29 ° C in February. In Figure 5.5 the night temperature range of values is shown and it fluctuates between a low of 16 ° C in September to almost 18 ° C from November to April.

Although the malaria cases were prevalent throughout each year, transmission was distinctly seasonal increasing between September and April and decreasing from May to August. Distinct peaks are also apparent from January to April each year.

5.3. Exploratory Analysis

The results of the preliminary exploratory analysis conducted in Stata 10.1 (Stata Corp., College Station, TX, USA) are presented in Table 5.2. This was done to assess the bivariate association between explanatory variables and incidence. If a variable was found to be not significant, it would not have been used in the subsequent analysis.

Table 5.2: Results of Negative Binomial Bivariate Analysis

Parameter	IR	IRlow	IRhigh	LRtest	AIC
Rain_0	0.996	0.988	1.003	71.274	4572.447
Rain_lag1	1	0.993	1.007	69.787	4573.933
Rain_lag2	1.004	0.998	1.009	71.591	4572.129
NDVI_0	2.021	0.856	4.77	72.33	4571.39
NDVI_lag1	1.13	0.468	2.727	69.861	4573.859
NDVI_lag2	0.5	0.204	1.222	72.137	4571.583
LST Day_0	1.055	1.025	1.086	83.374	4560.347
LST Day_lag1	1.078	1.05	1.107	100.842	4542.878
LST Day_lag2	1.054	1.027	1.083	85.125	4558.596
LST Night_0	0.995	0.96	1.03	70.295	4557.696
LST Night_lag1	1.036	1.004	1.068	74.926	4550.264
LST Night_lag2	0.99	0.959	1.023	69.896	4569.771
Land use	0.723	0.609	0.858	83.385	4560.335
Altitude	0.998	0.998	0.999	97.916	4545.804
Distance to water bodies	0.925	0.90	0.95	73.693	4525.674

Lag 1 is one month before the case and Lag 2 is 2 months before the case; IR: Incidence Rate; LR: Likelihood Ratio*;* AIC: Akaike Information Criterion

The non-spatial model (Table 5.2) identified land use type and altitude as the main determinants that increased malaria incidence in KwaZulu-Natal.

5.4. Distributed Lag Model

The estimated values of the parameters of β_i are presented in Table 5.3. In Table 5.3 the only significant environmental/climatic variables are altitude, forest land cover type and the day temperature of the previous month, which all have negative means. Moreover, they all have a negative 95% Bayesian credible interval (BCI), which means that they all have a negative effect on malaria incidence.

Table 5.3: Posterior Estimates of the Coefficients in the Distributed Lags Model

Parameter	Mean	Std. Dev.	Median	95% BCI Interval
Constant	-6.912	0.6907	-7.048	[-7.914, -4.948]
Sine	0.2279	0.1237	0.2287	[-0.01643, 0.4716]
Cosine	-0.04982	0.1306	-0.0536	[-0.2971, 0.2155]
Altitude	-0.2414	0.1165	-0.244	[-0.4629, -0.002645]
Distance to Water bodies	0.08673	0.1069	0.0866	[-0.1229, 0.2979]
Land use:				
Dry non-forest vegetation	-	-	-	-
Forest	-0.4034	0.1893	-0.4034	[-0.7731, -0.03214]
Wet non-forest vegetation	-0.1734	0.1942	-0.1739	[-0.5537, 0.205]
Non-vegetation	1.193	0.898	1.197	[-0.5734, 2.924]
Rain_0	0.02742	0.05324	0.02789	[-0.07658, 0.1329]
Rain_lag1	-0.02816	0.05295	-0.02824	[-0.1318, 0.07464]
Rain_lag2	0.02013	0.05344	0.02007	[-0.084, 0.1257]
NDVI_0	0.05537	0.07417	0.05548	[-0.08875, 0.2035]
NDVI_lag1	-0.1638	0.08723	-0.1621	[-0.3391, 0.002887]
NDVI_lag2	-0.04854	0.07994	-0.04845	[-0.2052, 0.1097]
LST Day_0	-0.04411	0.09519	-0.04596	[-0.2265, 0.1463]
LST Day_lag1	-0.3168	0.1084	-0.3177	[-0.5291, -0.1032]
LST Day_lag2	0.1348	0.09209	0.1327	[-0.04061, 0.3175]
LST Night_0	0.08287	0.06919	0.08223	[-0.05378, 0.2178]
LST Night_lag1	0.08486	0.07127	0.08425	[-0.05514, 0.2259]
LST Night_lag2	0.01967	0.06503	0.01935	[-0.1081, 0.1474]

Both the bivariate and multivariate models selected altitude and land use type as being the most significant variables, however, the bivariate model did not select temperature as being one of the main determinants of malaria transmission in KwaZulu-Natal. The multivariate model was able to distinguish precisely which land use type was contributing the most to transmission in the study area.

5.4.1. Altitude

Altitude influences the distribution and transmission of malaria indirectly through its effect on temperature and in the study area malaria incidence followed the pattern of altitude: the incidence rate decreasing with increasing altitude. As altitude increases, temperature decreases so the high altitude areas are colder and the low altitude areas are much warmer. The primary effect of increasing altitude is a reduction in vector abundance (Drakeley et al., 2005). Kulkarni et al. (2006) stated that vector densities declined rapidly with increasing altitude in Tanzania as well as a 50% decrease in the annual human biting rate for every 86-meter rise in altitude.

According to the WHO (2012) the major eco-epidemiological stratum of malaria in Ethiopia is classified according to the altitude. The malaria free highland areas have altitudes above 2500 meters, whereas the areas that are affected by frequent epidemics being the highland fringe areas with altitude levels between 1500- 2500 meters and the lowland areas below 1500 meters characterized with a seasonal pattern of transmission (WHO, 2012).

The diverse and complex topography of KwaZulu-Natal results in the considerable range in temperature as well, with the coastal areas being subtropical and the inland climate becoming progressively colder as you move inland. The elevation map (Figure 3.2) in Chapter 3 clearly illustrates how the altitude increases as you move from the coastal areas to the more inland areas. The Drakensberg mountains on the western side of the province have a moderate temperature all year round that is typically cold as they peak over 3000 meters. There have even been incidents of snow falling during the summer months. The warmer temperatures are experienced on the coast along the Indian Ocean.

5.4.2. Temperature

Transmission intensity changes with climate, in particular temperature, since it affects the development of the vector and of the parasite within the vector. The day temperature of the previous month also had a negative effect on incidence and a possible explanation for this was that at higher temperatures the mosquito's development is interrupted. Temperature affects the life cycle of the malaria parasite and the time required for the parasite to complete its development in the gut of the mosquito is about 10 days but it can be shorter or longer dependent on the temperature. Between 21° C to 27° C the time needed for development decreases to less than 10 days. However below 18° C, the life cycle of *P. falciparum* is

limited. Therefore, if the day temperatures of the previous month were not conducive for the development of the vector or for transmission to occur, the incidence rates of the following month would subsequently decrease.

Another possible explanation is that mosquito activity is generally higher at night where minimum temperatures prevail. During the day mosquitoes hide themselves in houses or vegetation. Also, when the night temperature is high in the summer months, people are less likely to protect themselves against being bitten and thus give mosquitoes an opportune moment to strike. The range of night temperatures in this study area range from 8° C to 30° C and the optimum temperature for the parasite to complete its development in 27° C which means they can operate indoors at night when they prefer and not necessarily transmit malaria during the day.

5.4.3. Land Cover

Forest land cover type had a negative effect on incidence according to the prediction model in KwaZulu-Natal. This is consistent with that mosquitoes generally prefer habitats that are exposed to direct sunlight as Minakawa (1999, 2000) found in Kenya, where the survival of *Anopheles gambiae* larvae was drastically reduced in forest habitats. This is also evident in other studies (Munga 2006, 2009 and Stefani et al. 2013) that have suggested that deforestation is associated with an increase in malaria risk. Krefis et al. (2011) also found that an increase of 10% in forested areas was associated with a 47% decrease of malaria incidence in Ghana. Adult vector abundance is positively associated with the availability of aquatic habitats that provide conditions that are ideal for the deposition of eggs. Areas with the highest malaria risk are typically found within just a few hundred meters of such larval habitats (Krefis et al., 2011).

Land use changes such deforestation are able to modify the temperature and relative humidity patterns in the area. Afrane et al. (2006) conducted a study in western Kenya to assess the possible effect of deforestation on the microclimate. They found that deforestation increased the mean and maximum temperatures in the area and that mosquitoes in deforested areas laid more eggs and thus had better fecundity (the number of offspring a female mosquito can produce) than mosquitoes in forested areas. Generally, deforestation substantially facilitated malaria transmission due to an increase in vectorial capacity (Afrane et al., 2006).

Munga et al. (2007) investigated the effect land cover types have on mosquito productivity by creating semi-natural larval habitats within three land cover types (natural swamp, forest and farmland) and infesting them with *Anopheles gambiae* larvae. The pupation rate in forest and swamp habitats was significantly lower than in farmland habitats. Larval survivorship is affected by land cover changes as result of its influence on water temperature and nutrients in the aquatic habitats (Munga et al., 2007).

5.5. Model-based Prediction Map

The model-based prediction maps were produced for the year 2010 as this was the most recent full year for which there were malaria case data available. The predicted malaria incidence rates ranged from 0.2 to 5 cases per 1000 inhabitants (Figures 5.6- 5.11). The district with the highest predicted risk of malaria is the Umkhanyakude district, specifically the Umhlabuyalingana, Jozini and The Big 5 False Bay municipalities in north-eastern KwaZulu-Natal. The malaria risk maps (Figures 5.6- 5.11) showed the incidence rates to be highest from January to April and lower during the June to August months.

What was unique about these prediction risk maps is that they were produced at the sub-place level at a 1 kilometer resolution. Incidence maps have previously been produced mainly at the district level or municipal level. Malaria transmission is a very dynamic process that can affect close neighbouring communities differently as a result of slight changes in either climate and environmental factors or maybe socio-economic status. It is thus important for surveillance to occur at the community level to avoid a blanket approach of one-strategy-fits-all to the communities when their incidence levels are not necessarily the same.

5.5.1. The Impact of Climatic Factors

All the factors included in the prediction model were environmental/climatic and influence malaria transmission in diverse ways: either by affecting the host, the parasite or the vector. If incidence rates are high, exclusively as a result of weather, theoretically, this can occur for several reasons. A greater starting population can occur if there were unexpectedly warm and moist conditions. Those conditions would allow for the survival of mosquitos and breeding that would not typically occur. A greater number of breeding pools would also be made available if there was a lot of rain. Generally, if there are ideal climatic conditions for mosquitos to breed and survive and feed there will be a larger parasite and vector population.

The longer the favourable season persists, the greater the number of people that are infected at the beginning of the transmission season. The more weather conditions change to create favourable conditions, the more vector populations will grow and transmission increase at faster rates.

However, in KwaZulu-Natal, it has been shown that the impact of climatic factors can be diminished with the application of residual insecticides. Although the areas that are most prone to malaria are providing favourable climatic conditions for malaria transmission to occur, the continued use of IRS, among other control initiatives, is proving to be decreasing the number of cases drastically. Essentially, the predicted risk maps illustrate incidence rates that would prevail in KwaZulu-Natal in 2010 if malaria control strategies or socio-economic status were not taken into account. Accurate information is crucial in understanding the distribution of malaria for planning tools and evaluating malaria control. By producing prediction maps it is also possible to understand distribution patterns and transmission intensity in places which it has not been measured.

5.5.2. The Impact of Non-climatic Factors

Although climatic/environmental factors are a major limiting attribute in the spatial and temporal distribution of malaria, non-climatic factors can change or outweigh the effect of climate (Craig et al., 2004). It has been suggested that malaria is a disease of poverty that is concentrated in the world's poorest countries (Worrall et al., 2006). The Umkhanyakude district was identified as one of the two most deprived districts in South Africa according to District Health Barometer. The deprivation index is a measure of relative deprivation that takes into account a number of socio-economic factors such as access to piped water and electricity, low education levels and unemployment rates (Day et al., 2012). The Umkhanyakude district is also a very rural district and malaria is generally lower in urban areas than in rural areas. A few reasons for this could be that in rural villages there are plenty of opportunities for vector breeding as there is less space covered by houses compared to urban areas. People living in urban areas may also have better access to health care and malaria prevention strategies than people in rural villages.

South Africa has greatly reduced its malaria burden over the past twelve years, with KwaZulu-Natal having the largest reduction in malaria cases compared to the other two endemic provinces. The general consensus among authors (DOH, 2010; Moonasar et al.,

2012) is that this is mostly attributable to vector control strategies likes IRS where KwaZulu-Natal has attained coverage of greater than 85%. Case management in this province has also been remarkable with approximately 100% diagnosis using RDT, microscopy and treatment of malaria cases. There has also been a strong active case detection program that worked by malaria surveillance agents tracking down each individual malaria case and subsequently surveying neighbouring households for parasites in those areas (Moonasar et al., 2012). The impact of non-climatic factors was most notably evident in the malaria epidemic of the 1999/2000 malaria season following a change of insecticide from DDT to pyrethroids. This action resulted in drug resistance which skyrocketed malaria cases considerably. This proves that vector control is an important mitigating factor of malaria transmission in South Africa.

It is also important to note that malaria in KwaZulu-Natal is primarily a border problem that is attributable to immigrating malaria carriers that cross between the South African and Mozambican borders daily for various reasons. Most of these immigrants are non-symptomatic, they do not go to clinics and thus remain untreated for longer periods of time thereby consequently contributing significantly to local transmission (Sharp and Le Sueur, 1996; Kleinschmidt and Sharp, 2001; Craig et al., 2004). This issue is more evident now in KwaZulu-Natal where malaria programme officials in the Jozini have admitted that they believe that the locals are malaria-free and the cases being reported at this stage are imported cases. Migrants can often bring the parasites back to malaria-free areas and local transmission can be readily established since many of these communities can support vector breeding. This is an issue as in malaria-free areas, the population is generally non-immune.

Another non-climatic factor that cannot be ignored is the HIV/AIDS contribution to the effect it has on the human host to contract malaria. Whitworth et al. (2000) found that adults who were infected with HIV were also at a higher risk of clinical malaria as higher parasite densities were found in the HIV-positive adults. According to the Day et al. (2012) the leading cause of death in the Umkhanyakude district is HIV/AIDS, and there is an increase in the HIV viral load as a result of malaria infection (Craig et al., 2004).

January 2010
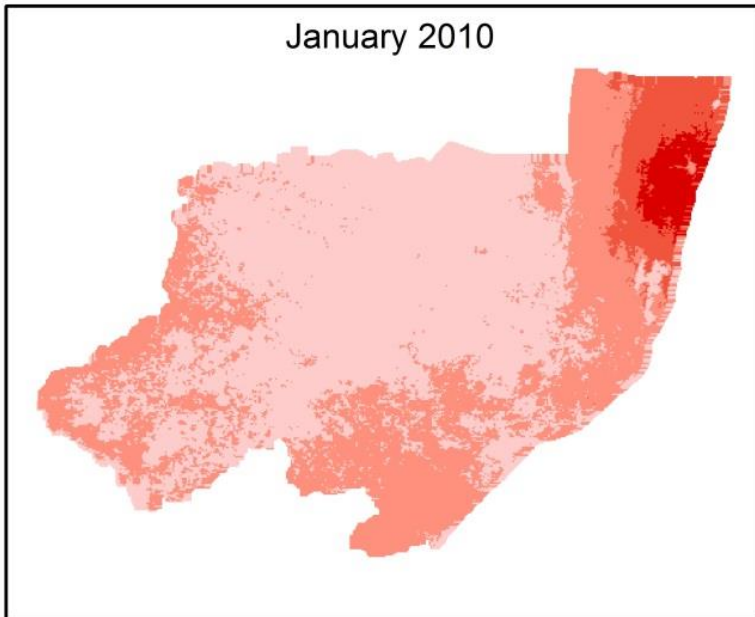
Figure 5.6: Predicted malaria risk maps
01/2010 – 02/2010

Legend

Malaria incidence rates (per 1000 inhabitants)
V3

- 0.2 - 1.0
- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

0 0.15 0.3   0.6   0.9   1.2
Kilometers

N

Spatial Resolution: 1 Kilometer
Datum: WGS 1984

February 2010

March 2010

April 2010

Figure 5.7: Predicted malaria risk maps 03/2010 – 04/2010

Legend

Malaria incidence rates (per 1000 inhabitants)
V3

- 0.2 - 1.0
- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

0   0.15 0.3   0.6   0.9   1.2
Kilometers

N

Spatial Resolution: 1 Kilometer
Datum: WGS 1984

May 2010

June 2010

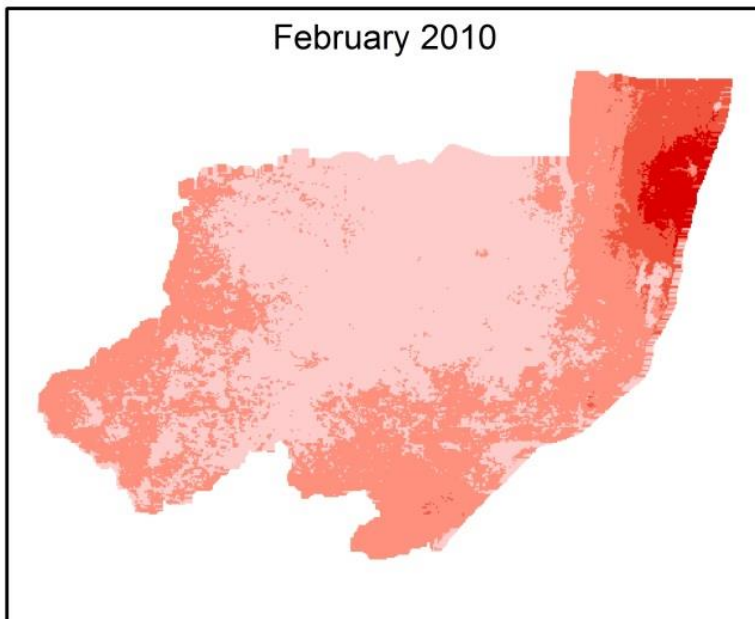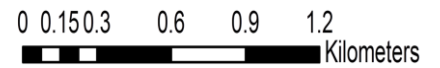**Figure 5.8: Predicted malaria risk maps 05/2010 – 06/2010**

Legend

Malaria incidence rates (per 1000 inhabitants)
V3

- 0.2 - 1.0
- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

0 0.15 0.3   0.6   0.9   1.2
Kilometers

N

Spatial Resolution: 1 Kilometer
Datum: WGS 1984

July 2010

Figure 5.9: Predicted malaria risk maps
07/2010 – 08/2010

Legend

Malaria incidence rates (per 1000 inhabitants)
V3

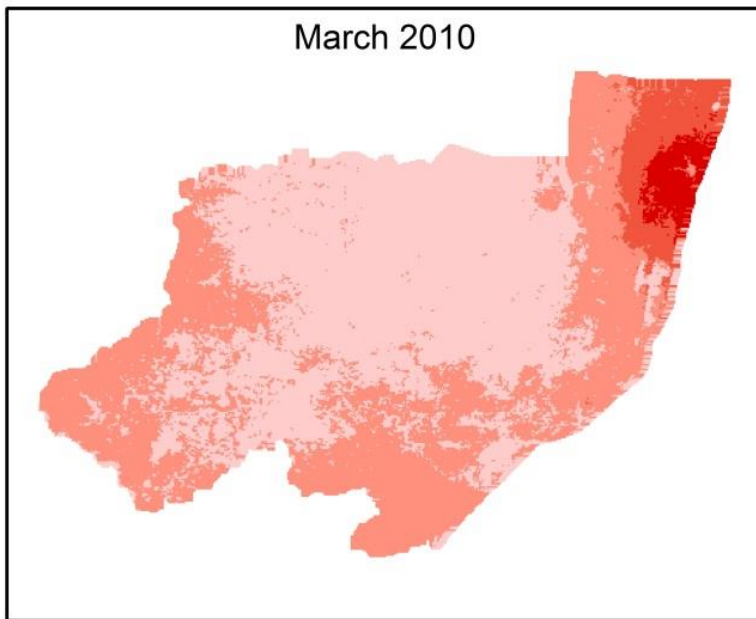- 0.2 - 1.0
- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

| 0 | 0.15 | 0.3 | 0.6 | 0.9 | 1.2 |

Kilometers

N

August 2010

Spatial Resolution: 1 Kilometer
Datum: WGS 1984

September 2010

October 2010
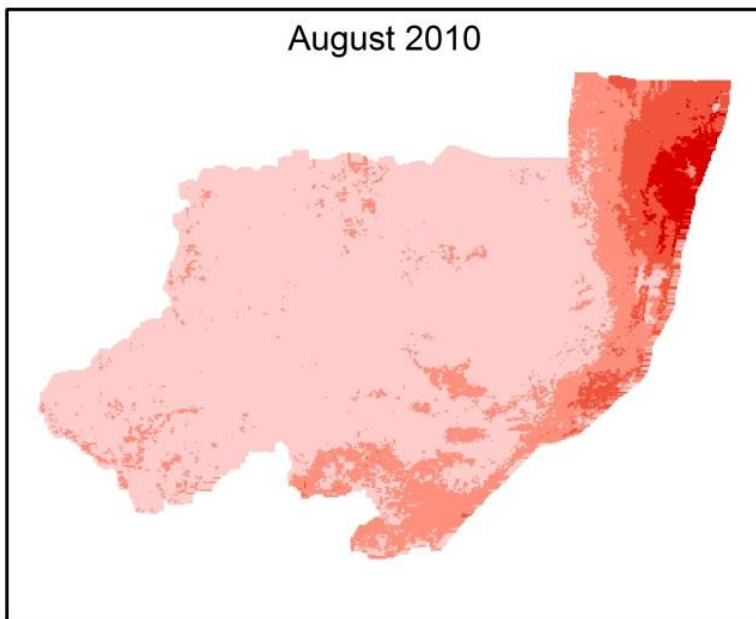
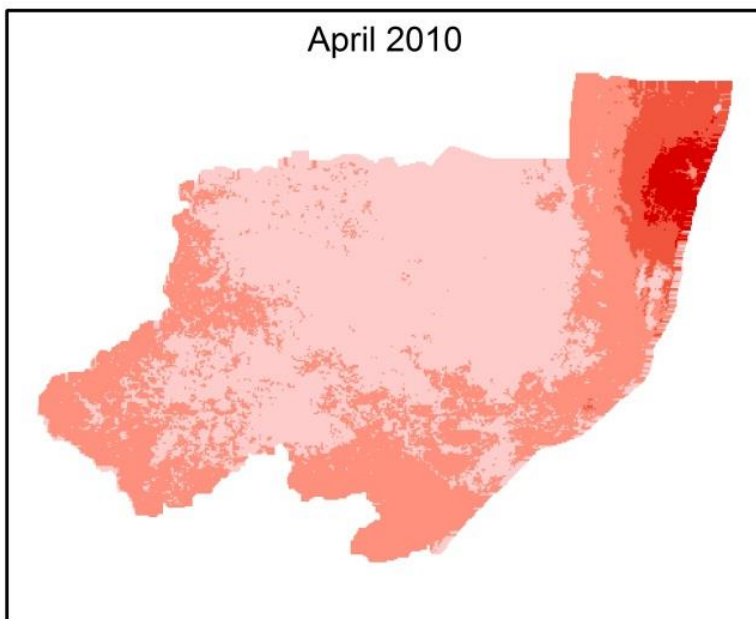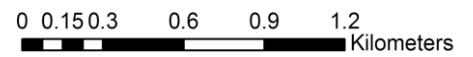**Figure 5.10: Predicted malaria risk maps**
09/2010 – 10/2010

Legend

Malaria incidence rates (per 1000 inhabitants)
V3

- 0.2 - 1.0
- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

0 0.15 0.3   0.6   0.9   1.2
Kilometers

N

Spatial Resolution: 1 Kilometer
Datum: WGS 1984

November 2010
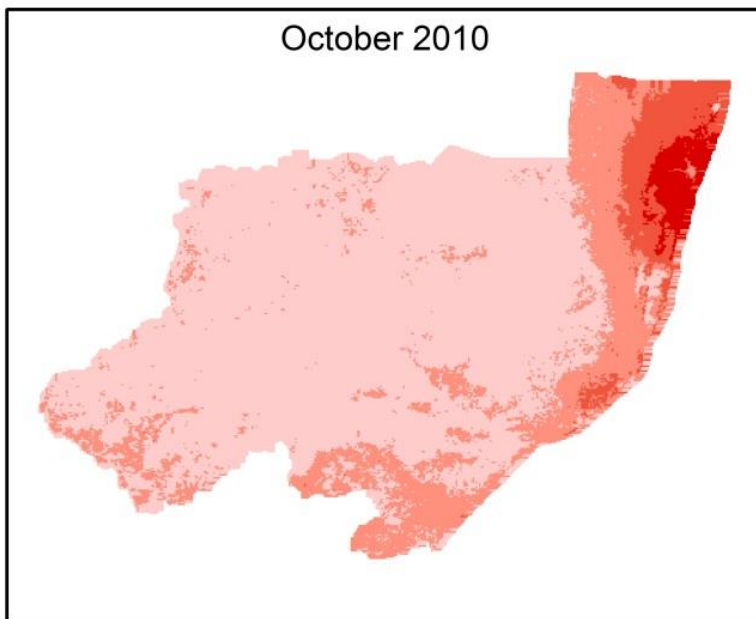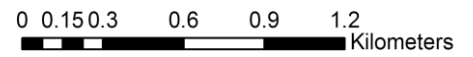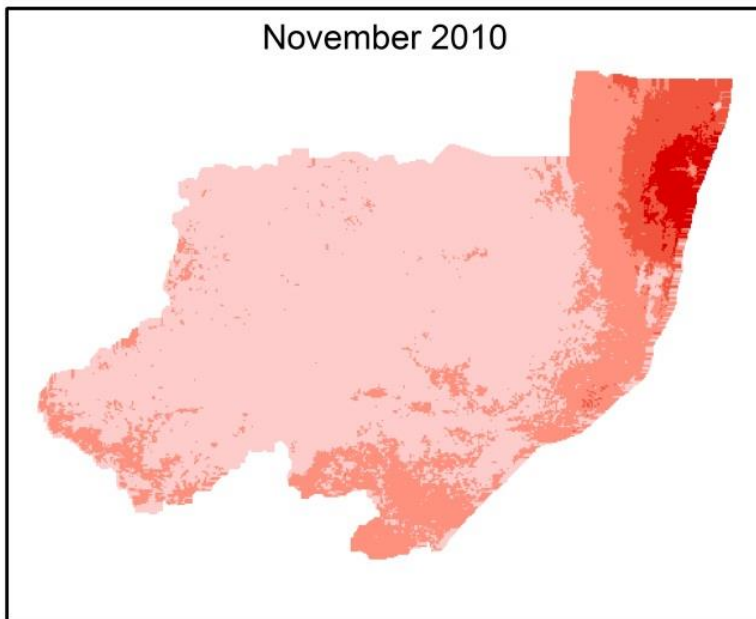
**Figure 5.11: Predicted malaria
risk maps
11/2010 – 12/2010**

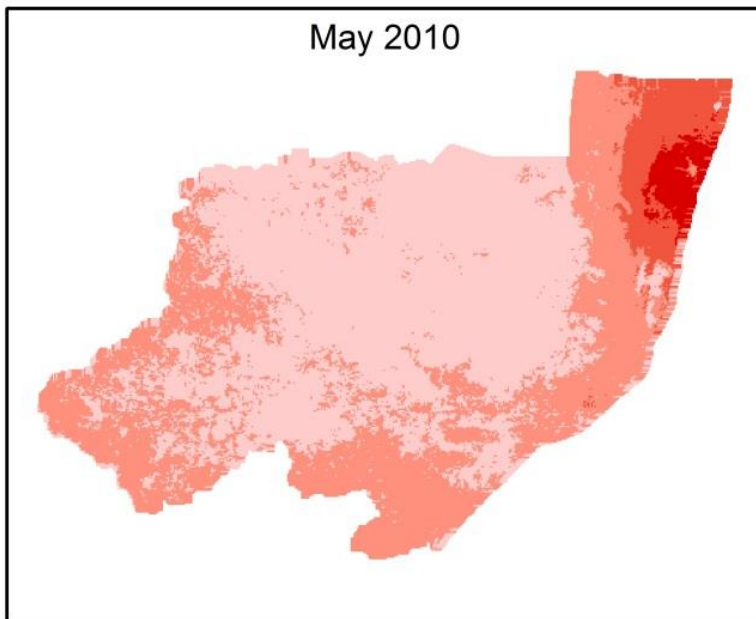**Legend**

**Malaria incidence rates (per 1000 inhabitants)
V3**
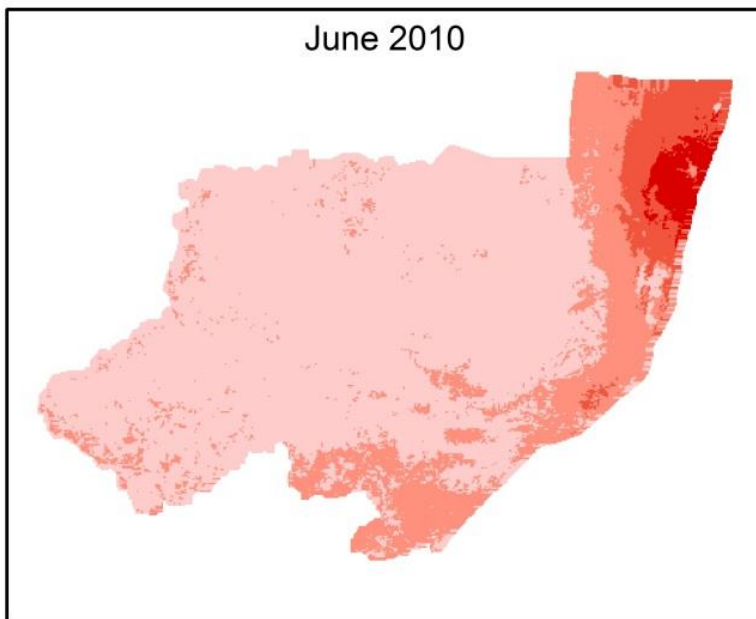
- 0.2 - 1.0
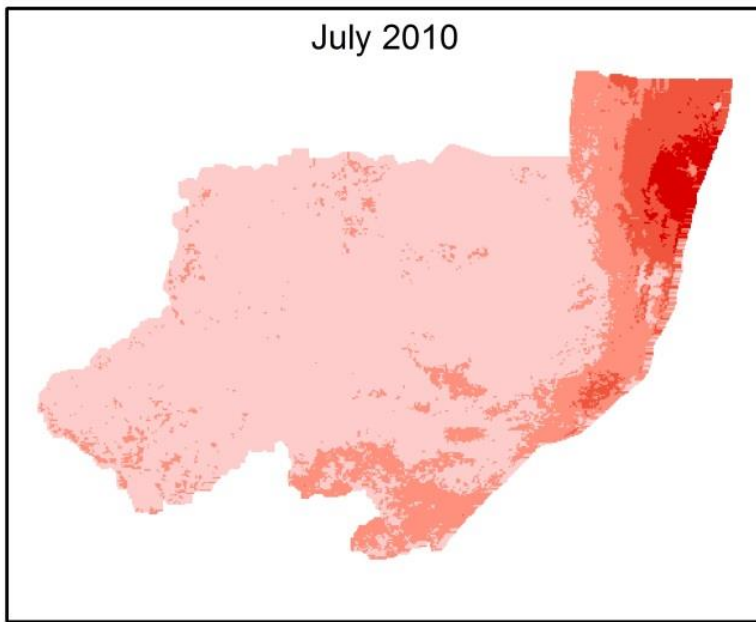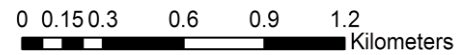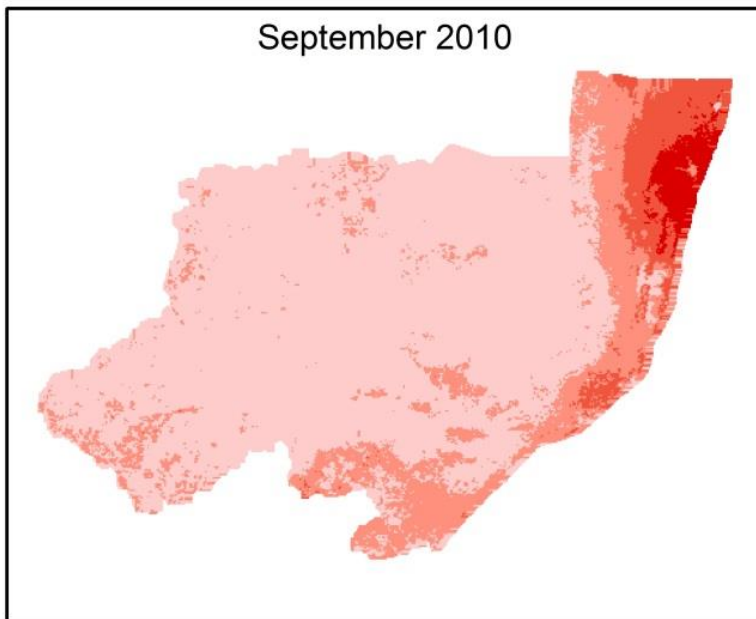- > 1.0 - 2.0
- > 2.0 - 3.0
- > 3.0 - 5.0

Cartographic Information:

0   0.15 0.3   0.6   0.9   1.2
                                          Kilometers

N

December 2010
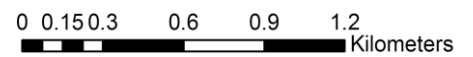
**Spatial Resolution: 1 Kilometer
Datum: WGS 1984**
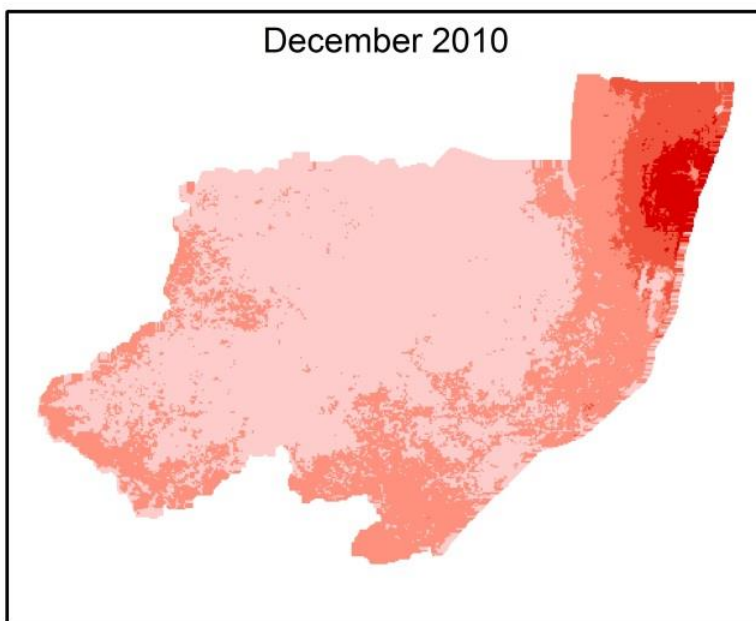
5.6. Accuracy Assessment

An accuracy assessment was conducted to assess the accuracy of the observed incidence rates and the predicted incidence rates produced using R. The accuracy assessment was conducted for the four months that coincide with the malaria season in South Africa: March, June, September and December, as a scatterplot as illustrated in Figure 5.12. Bearing in mind that the predicted risk maps were based on only environmental/climatic variables excluding any other interventions like IRS, it is relevant to therefore note that the observed incidence rates would not necessarily be the same as the predicted incidence rates as the cases had dramatically decreased by 2010.
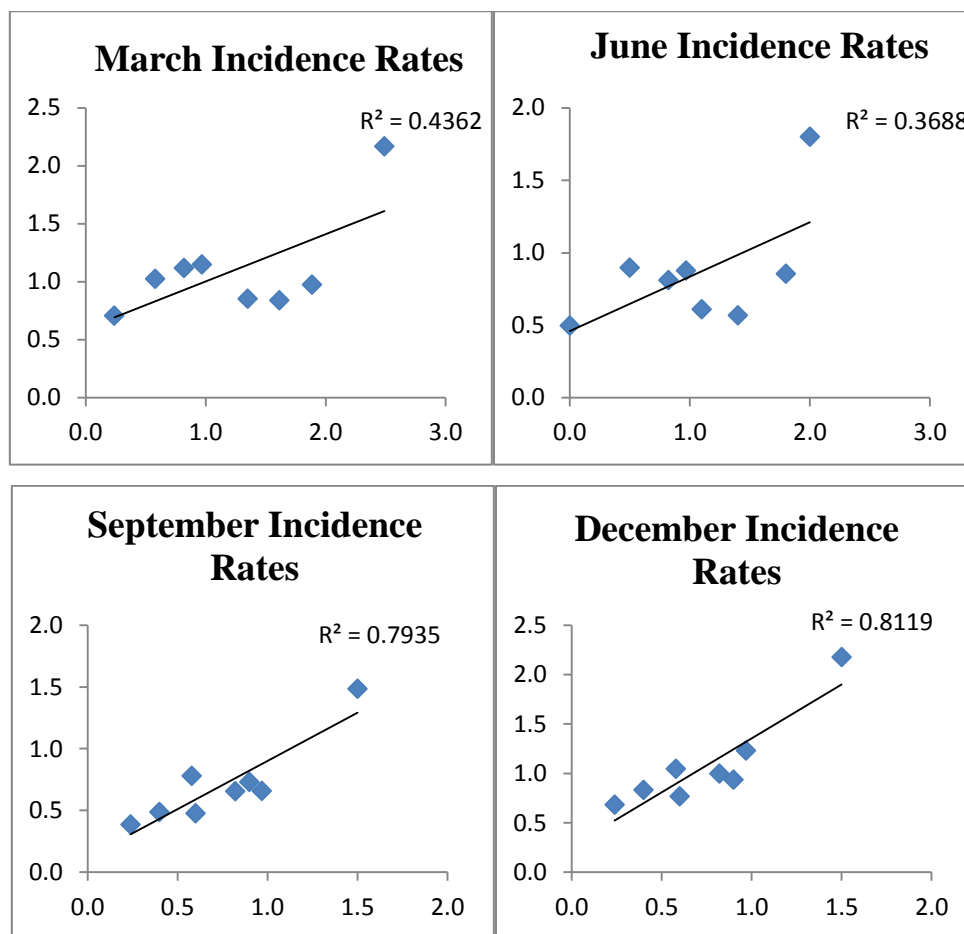
Figure 5.5: Scatterplot showing March and June Incidence Rates

The R-squared value was the lowest for the June Incidence Rates (0.3688) and the highest was for the December Incidence Rates (0.8119) in Figure 5.12. These results illustrate that based on this accuracy assessment of the maps, the most accurate predicted incidence rates, if compared with the observed incidence rates, are for December.

5.7. Conclusion

This chapter outlined the findings of this research and the results conformed to the expectations based on recent literature. It was evident that climate driven models can give malaria control programmes an opportunity to prepare in advance for epidemics as malaria transmission is largely limited by climate. Robust statistical models can be developed to serve as early warning systems provided that good malaria and climatic data are acquired. However, a stronger correlation between malaria variability and climate variability can be established if the affected areas have not been greatly altered by malaria control. Although the research found that some environmental/climatic variables contributed to malaria transmission, the current low number of cases in KwaZulu-Natal suggests that malaria control interventions have also contributed to the pattern of malaria incidence. This underlines the importance of long-term surveillance of climate and coverage and effectiveness of control interventions. The main ideas described in this chapter are explored in Chapter 6 and conclusions drawn from the research.

Chapter Six: Conclusions and Recommendations

6.1. Introduction

This study aimed to analyse the geographical distribution of malaria transmission in KwaZulu-Natal using Bayesian spatio-temporal modelling. To achieve this, the specific objectives were to:

- Estimate and map malaria seasonality in KwaZulu-Natal based on environmental and clinical case data
- Develop rigorous statistical models for identifying which climatic variables are associated with malaria transmission
- Produce incidence maps based on the climatic variables significantly correlated with malaria transmission
- Assess spatio-temporal patterns of malaria transmission in KwaZulu-Natal and produce transmission maps adjusted for seasonality and climate factors.

The key findings are presented and discussed in the previous chapter (chapter five). In this chapter the conclusions and recommendations are drawn with regards to Bayesian spatio-temporal modelling of malaria incidence focusing on primarily the study area in KwaZulu-Natal.

6.2. Summary of Key Findings

There is a dynamic interaction between the disease agent of malaria (*Plasmodium* spp), its mosquito vector (*Anopheles* spp) and the human host. This interaction is affected by a range of genetic, behavioural, climatic and anthropogenic factors. The determinants of malaria transmission vary in time and space and with a different frequency and magnitude.

Spatial epidemiology has paved a way for vector-borne disease mapping and forecasting. The availability of satellite imagery coupled with malaria case data and population data has created an opportunity for robust statistical models to investigate the spatio-temporal trends of malaria incidence. Furthermore, predictive risk modelling is a method that can be incorporated in surveillance systems to monitor the disease and also to allow malaria control programmes to allocate resources adequately to the areas of highest risk.

The distributed lag model revealed that altitude [95% BCI: -0.4629, -0.002645], forest land cover type [95% BCI: -0.7731, -0.03214] and the day temperature of the previous month [95% BCI: -0.5291, -0.1032] were significant indicators of malaria transmission in the study area. They all had a negative effect on incidence levels and the possible explanations of this are all linked to how temperature affects the behaviour and ecology of the vector and parasite and their interaction with the human host. A prediction model produced monthly maps of incidence rates for KwaZulu-Natal for the year 2010. According to the predicted risk maps incidence ranged from 0.2 to 5 per 1000 inhabitants. The predicted risk maps identified the Jozini, Umhlabuyalingana and The Big False Bay as the regions of highest risk. The climate of this region is highly favourable to vector and parasite development which provides ideal breeding for malaria transmission to be high. The effect of non-climatic factors was not included in the modelling, however, it was recognized that the inclusion of these factors could have provided a clearer picture of malaria risk in the study area.

This study successfully illustrated how the Bayesian approach to disease modelling can be used in the development of early warning systems for malaria. More importantly, this kind of information would be valuable to malaria control programmes in their bid to reach zero incidence in South Africa by 2018. Furthermore, these systems would be able to detect which populations are at greatest risk so resources could reach them timeously before the transmission season begins.

6.3. Limitations of this Study

The main limitation of the research was that the modelling did not include data on non-climatic factors, specifically the locations that have been sprayed with insecticides. IRS is a major driving force of malaria incidence in South Africa and including this information in the modelling of malaria transmission would have provided a more accurate geographic distribution of the current incidence rates in KwaZulu-Natal. In addition, running the prediction model in R was extremely time-consuming so access to statistical software like Fortran that are much quicker and computers that have a better capacity to handle computations of large sets of data would have been advantageous. Furthermore, each data source had some weakness, whether it be in terms of availability (accessibility and timeliness), temporal and spatial extent, completeness and accuracy. Lastly, interpolation of the climatic data would have been beneficial as the locations that had missing climatic data

were simply eliminated from the study and further decreasing the sample size of the study area.

6.4. Recommendations for Future Studies

This study has illustrated how Bayesian spatio-temporal modelling can be used to identify the drivers of malaria transmission at the community level using climatic/environmental data. However, the statistical model developed could also incorporate the effects of non-climatic variables to ensure the highest accuracy in predicting malaria incidence. Further studies could thus differentiate between local and imported cases and in the case of KwaZulu-Natal calculate the distance to the border Mozambique as a proxy for the effect of an area being situated in close proximity to another area where control strategies are not as strong. The data of the location of houses that have been sprayed with insecticides should also be obtained as this will be an important parameter to include in the modelling to determine the effectiveness of IRS on malaria transmission. The socio-economic status of the population at risk should also be taken into consideration as factors like dwelling structure, education levels, income levels and access to proper sanitation can affect the ease of transmission as malaria is considered to be concentrated in places of poverty on a global level. KwaZulu-Natal has the highest HIV prevalence in South Africa so the association between HIV can be explored in further studies.

6.5. Conclusion

The predicted malaria risk maps demonstrate how climatic/environmental factors can be utilised in disease forecasting of malaria. The prediction model was able to accurately locate the malaria hotspot in KwaZulu-Natal where incidence rates are highest in the province. It also illustrated the seasonal variation in transmission with the incidence rates being lower during the dry and cold winter months. This information would be crucial to malaria control programmes as they would know exactly where efforts should be targeted and with accurate surveillance epidemics could be prevented in future if the climatic/environmental data is readily available. In addition to monitoring environmental changes, it is important to monitor non-climatic factors in determining malaria transmission, especially in areas such as KwaZulu-Natal where the number of imported cases exceeds and contributes to transmission more than local cases.

The prediction model successfully demonstrated the value of developing robust statistical models that can predict future risk. This will ultimately be instrumental as South Africa moves towards reaching its 2018 goal of reducing malaria incidence to near zero. According to the WHO malaria elimination continuum South Africa is now in the pre-elimination phase category and surveillance systems will be important in ensuring that the current success against malaria is maintained and elevated to having a malaria-free status.

Global climate change is also another important contemporary issue to consider where such climatic/environmental prediction models can be utilised to detect future spatio-temporal patterns of vector borne diseases to prevent epidemics. The Intergovernmental Panel on Climate Change stated that vector-borne diseases have been linked to climate change as warming of the climate is expected to increase latitudinal and altitudinal temperature (IPCC, 2001). The spatial and temporal changes in rainfall, humidity and temperature that are expected to happen as a result of global warming will affect the biology and ecology of vectors differently and will consequently also alter the risk of the disease transmission.

If the risk is identifiable in time, prevention is easier than trying to treat the impacts of the disease. The Bayesian analytical framework used in this research improved the ability to evaluate the relationship between malaria and climatic factors, and improved the identification of significant associations and covariates. The work presented showed the potential and strength of developing statistical models for predicting incidence. The incidence maps produced provide control programmes the geographical position for control efforts to be applied. There is still, nonetheless, opportunity for further refining of models as more relevant data become available.

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APPENDIX

Appendix A: OpenBugs Code

```
model{
for (i in 1:N){
      cases[i] ~ dnegbin(p[i],r)
      p[i] <- r/(r+mu[i])
      log(mu[i]) <- log(population[i])+inprod(b[],X[i,])+e[idtime[i]]+w[idloc[i]]
}

r ~ dgamma(0.01,0.01)

for (i in 1:3){
  b[i]~ dnorm(0.0,0.01)
}

for (i in 1:2){
   b[i+3]~ dnorm(0.0,0.01)
}

for(i in 1:3){
  b[i+5] ~ dnorm(0.0, 0.01)
}

for(j in 1:3)     {
  b[j+8]~dnorm(0,tau.rain)
}

for(j in 1:3)     {
  b[j+11]~dnorm(0,tau.ndvi)
}

for(j in 1:3)     {
  b[j+14]~dnorm(0,tau.tempd)
}

for(j in 1:3)     {
  b[j+17]~dnorm(0,tau.tempn)
}

tau.rain~dgamma(0.1,0.1)
tau.ndvi~dgamma(0.1,0.1)
tau.tempd~dgamma(0.1,0.1)
tau.tempn~dgamma(0.1,0.1)

  # AR(1) prior distribution for temporal random effects:

   e[1] ~ dnorm(0.0, tau2)
```

```
        for (t in 2:T){
                        emean[t-1]<-rho*e[t-1];
                e[t] ~dnorm(emean[t-1], tau.e)
                                        }

  tau2<-(1-pow(rho,2))*tau.e
   rho ~ dunif(0, 1)
   tau.e  ~ dgamma(1,1 )
  sigma.e<- 1/sqrt(tau.e )


#  Gaussian process for spatial random effects:
for (i in 1:Nloc) {
mu1[i]<-0}

w[1:Nloc]~spatial.exp(mu1[], longit[], lattit[], tau.sp, phi, 1)
tau.sp~dgamma(1,1)
sigma<-1/tau.sp
phi~dunif(1.56,3256)
rhoinv<-1/phi
Range<-3/phi

}
```

Appendix B

R Code for Prediction

```
setwd("c:/South_africa/nolu/prediction/Data/")
library(foreign)

# Read data
###################################

N=141    # Number of observed locations
PS=1000  # Posterior sample size

# Read coordinates of observed locations

x=c(-29.54087,-29.51074,-29.44933,-29.44628,-29.37567,-29.33279,-29.15797,-29.10292,-29.02784,-29.02697,
-28.99275,-28.96737,-28.95808,-28.93933,-28.92401,-28.90307,-28.90093,-28.89245,-28.88016,-28.87361,
-28.82550,-28.82481,-28.79698,-28.79663,-28.79337,-28.79124,-28.78454,-28.77710,-28.77546,-28.77231,
-28.76061,-28.75965,-28.75882,-28.75190,-28.73527,-28.71436,-28.71230,-28.69923,-28.69722,-28.66490,
-28.64852,-28.52092,-28.50727,-28.49875,-28.48458,-28.48326,-28.44655,-28.41843,-28.25934,-28.24459,
-28.23047,-28.18550,-28.18312,-28.15810,-28.15073,-28.14547,-28.13451,-28.12000,-28.08950,-28.06690,
-28.05526,-28.03957,-28.00402,-28.00043,-27.99362,-27.99022,-27.97787,-27.97510,-27.97417,-27.96945,
-27.94683,-27.91755,-27.90520,-27.87557,-27.86123,-27.85578,-27.84757,-27.83903,-27.83850,-27.83218,
-27.82453,-27.82195,-27.80815,-27.80681,-27.77334,-27.77215,-27.76997,-27.75905,-27.73680,-27.73318,
```

-27.72940,-27.66914,-27.65093,-27.64900,-27.63118,-27.55490,-27.54962,-27.52960,-27.49479,-27.45173,

-27.45160,-27.45051,-27.43522,-27.42700,-27.42388,-27.41700,-27.40218,-27.39150,-27.37740,-27.37370,

-27.37093,-27.35515,-27.35095,-27.34098,-27.33553,-27.33467,-27.33360,-27.33180,-27.32904,-27.32480,

-27.32463,-27.32460,-27.32367,-27.32307,-27.29366,-27.27500,-27.26683,-27.24450,-27.23290,-27.21332,

-27.20444,-27.15330,-27.14278,-27.09027,-27.06427,-27.06301,-27.05467,-26.98520,-26.97723,-26.94150,

-26.86512)

y=c(31.21190, 31.23137, 31.21837, 31.21041, 31.25617, 31.28516, 31.40205, 30.97906, 31.58276, 31.58765,

 31.37442, 31.48832, 31.75623, 31.53435, 31.57872, 31.47703, 31.72777, 31.47313, 31.48367, 31.70795,

 31.86415, 31.86475, 31.47702, 31.47658, 31.72927, 32.09938, 32.10253, 31.86614, 31.86238, 31.68637,

 31.65590, 31.72902, 32.06894, 31.81000, 31.70941, 32.03669, 32.03677, 32.17240, 31.85472, 31.48457,

 32.05009, 30.86842, 31.99791, 32.09750, 32.24236, 32.36600, 31.96193, 32.18790, 32.12188, 32.03629,

 32.21285, 31.86700, 31.72897, 32.24080, 31.85153, 31.73453, 31.93060, 31.95542, 31.85467, 31.84109,

 31.99360, 30.03623, 31.84516, 32.06055, 32.00170, 32.13080, 30.27503, 31.64230, 31.50468, 32.05475,

 32.00045, 31.78229, 31.99430, 31.59398, 31.62788, 31.82443, 31.91240, 31.86390, 31.76300, 32.15254,

 31.84121, 31.82278, 31.85333, 31.85375, 29.95175, 31.97084, 31.89935, 32.20326, 31.74140, 31.86620,

 29.96352, 31.72120, 31.74438, 31.94400, 32.10698, 32.04560, 32.07873, 31.83150, 32.09711, 31.92263,

 32.03000, 32.57916, 32.05655, 32.09184, 32.21486, 32.07640, 31.56685, 32.06350, 31.19673, 31.99650,

31.40536, 31.75565, 31.78398, 31.99138, 31.70032, 31.51538, 31.46383, 31.57910, 31.40657, 31.89560,

 32.06442, 32.06440, 31.56383, 32.02733, 31.30599, 31.98332, 32.06100, 32.13930, 32.08200, 32.08243,

 32.16770, 32.08522, 31.99052, 32.11882, 32.04317, 32.13672, 32.83050, 32.13297, 32.01212, 32.33588,

 32.26155)

Read predictors at observed locations to obtain the parameters (mean & sd) of standardization

obs.pred=read.dta("../../junk/KwaZulu-Natal_FINAL.dta")

rain_0=obs.pred[,13]
rain_lag1=obs.pred[,14]
rain_lag2=obs.pred[,15]

ndvi_0=obs.pred[,18]
ndvi_lag1=obs.pred[,19]
ndvi_lag2=obs.pred[,20]

lstd_0=obs.pred[,23]
lstd_lag1=obs.pred[,24]
lstd_lag2=obs.pred[,25]

lstn_0=obs.pred[,28]
lstn_lag1=obs.pred[,29]
lstn_lag2=obs.pred[,30]

altitude=obs.pred[,32]
distance=obs.pred[,33]

Read coordinates and predictors at new locations (grid centroids)
Standardise the predictors

```
new=read.dta("stata/pred_feb10.dta")

x_pred=new[,1]
y_pred=new[,2]

const=new[,3]
sine=new[,4]
cosine=new[,5]
pr_altitude=(new[,6]-mean(altitude,na.rm=TRUE))/sd(altitude,na.rm=TRUE)
pr_distance=(new[,7]-mean(distance,na.rm=TRUE))/sd(distance,na.rm=TRUE)
landuse_2=new[,8]
landuse_3=new[,9]
landuse_4=new[,10]

pr_rain_0=(new[,11]-mean(rain_0,na.rm=TRUE))/sd(rain_0,na.rm=TRUE)
pr_rain_lag1=(new[,12]-mean(rain_lag1,na.rm=TRUE))/sd(rain_lag1,na.rm=TRUE)
pr_rain_lag2=(new[,13]-mean(rain_lag2,na.rm=TRUE))/sd(rain_lag2,na.rm=TRUE)

pr_ndvi_0=(new[,14]-mean(ndvi_0,na.rm=TRUE))/sd(ndvi_0,na.rm=TRUE)
pr_ndvi_lag1=(new[,15]-mean(ndvi_lag1,na.rm=TRUE))/sd(ndvi_lag1,na.rm=TRUE)
pr_ndvi_lag2=(new[,16]-mean(ndvi_lag2,na.rm=TRUE))/sd(ndvi_lag2,na.rm=TRUE)

pr_lstd_0=(new[,17]-mean(lstd_0,na.rm=TRUE))/sd(lstd_0,na.rm=TRUE)
pr_lstd_lag1=(new[,18]-mean(lstd_lag1,na.rm=TRUE))/sd(lstd_lag1,na.rm=TRUE)
pr_lstd_lag2=(new[,19]-mean(lstd_lag2,na.rm=TRUE))/sd(lstd_lag2,na.rm=TRUE)

pr_lstn_0=(new[,20]-mean(lstn_0,na.rm=TRUE))/sd(lstn_0,na.rm=TRUE)
pr_lstn_lag1=(new[,21]-mean(lstn_lag1,na.rm=TRUE))/sd(lstn_lag1,na.rm=TRUE)
pr_lstn_lag2=(new[,22]-mean(lstn_lag2,na.rm=TRUE))/sd(lstn_lag2,na.rm=TRUE)

covar_pred=cbind(const, sine, cosine, pr_altitude, pr_distance, landuse_2, landuse_3,
landuse_4, pr_rain_0, pr_rain_lag1, pr_rain_lag2, pr_ndvi_0, pr_ndvi_lag1, pr_ndvi_lag2,
pr_lstd_0, pr_lstd_lag1, pr_lstd_lag2, pr_lstn_0,  pr_lstn_lag1, pr_lstn_lag2)
```

```
#######################################
# Read posterior samples

library(coda)
a=read.coda("../../winbugs/dlag1.txt","../../winbugs/Indexdlag.txt")

ncov=19+1          # no of covariates (betas) + the b1

beta=a[,2:(1+ncov)]
w=a[,(21+135+10+1):(21+135+10+141)]   #spatial random effect
rho=3/a[,1]
sigma=a[,21+135+1+1]

e=a[,(21+1):(21+135)]   #temporal random effect


#specify year and month to predict
pr_month=2
pr_year=2010
idtime=(pr_month+(pr_year-2000)*12)-4


# Calculate distance matrix among observed locations

dist=matrix(NA,N,N)
cov12=matrix(NA,N,1)
for (i in 1:N){
  for (j in 1:N){
    dist[i,j]=sqrt((x[i]-x[j])*(x[i]-x[j])+(y[i]-y[j])*(y[i]-y[j]))
}
}

# Predict at the M locations
```

```r
M=length(x_pred)          # Number of predicted locations
mu.new=matrix(NA,M,PS)


cov=matrix(NA, N, N)


for(k in 1:M){
print(k)
for (i in 1:PS){

  cov=sigma[i]*exp(-rho[i]*dist)          # covariance of random effects among observed
location
   for (j in 1:N){
      dist.new=sqrt((x[j]-x_pred[k])*(x[j]-x_pred[k])+(y[j]-y_pred[k])*(y[j]-y_pred[k]))
      cov12[j,1]=sigma[i]*exp(-rho[i]*dist.new)
  }


  cov.inv=solve(Águas et al.)                          # invert covariance matrix


  mean.w.new=(t(cov12)%*%cov.inv)%*%w[i,]
  var.w.new=sigma[i]-(t(cov12)%*%cov.inv)%*%cov12
  w.new=rnorm(1,mean.w.new,sqrt(var.w.new))


  log.mu.new=covar_pred[k,]%*%beta[i,]+w.new+e[idtime]
  mu.new[k,i]=exp(log.mu.new)


 }
}


# Exporting results to excel for mapping
sd.mu=rep(NA,M)
med.mu=rep(NA,M)
for (i in 1:M){
 med.mu[i]=median(mu.new[i,])
```

```
  sd.mu[i]=sd(mu.new[i,])
}


aa<-cbind(x.pred,y.pred,med.mu,sd.mu)
write.table(aa,"kzn_map.txt",sep=",",row.names=TRUE,col.names=FALSE)
```