Temporal variations in malaria risk in Africa

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Dekan

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"Whoever would study medicine aright must learn of the following subject:

First he must consider the seasons of the year and the differences between them

Secondly he must study the warm and the cold winds, both those which are common to every country and those peculiar to a particular locality…"

Hippocrates 4th – 5th century B.C

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SUMMARY

In sub-Saharan Africa, malaria is a major cause of morbidity and mortality especially among children less than five years of age and pregnant women. Malaria situations are very diverse because of many factors involved in malaria transmission and the great variety of their local combinations. These include climatic, ecologic, social, economic and cultural factors. A number of epidemiological approaches have been used to try and reduce malaria situations to a manageable number of types and classes for efficient planning and targeting of appropriate malaria control strategies. Modelling and mapping of malaria have long been recognized as important means to developing empirical knowledge of this kind. Recently, the availability of new data sets, innovative analytical tools and statistical methods has resulted in the development of more comprehensive malaria maps for east, west and central Africa. However, most risk maps that have been produced so far do not take into account seasonal variation in malaria transmission. Seasonality affects the dynamic relationship between vector mosquito densities, inoculation rate, parasite prevalence and disease outcome. Quantitative description and mapping of malaria seasonality is therefore important for modelling malaria transmission dynamics and for timely spatial targeting of interventions.

This thesis is part of an on going effort within the MARA/ARMA (Mapping Malaria Risk in Africa/Atlas du risqué de la Malaria en Afrique) collaboration towards the development of improved malaria risk maps for Africa. The main objective is the development of an empirical model of malaria seasonality by fitting classical and modern statistical models to clinical and / or entomological indices where available. This work

also intended to identify important determinants of between-year and between-area variation that may be useful for developing climate based seasonal forecasting models for malaria epidemics.

Chapter 1 gives an overview of the transmission and epidemiology of malaria in Africa and set the rational for this work. The initial focus of the analysis was on southern Africa, until recently this was the only region with reasonably comprehensive clinical malaria case data in the continent and therefore offered an ideal starting point. This region has a long history of successful malaria vector control by indoor residual spraying (IRS) with insecticides and this may have an impact on the level of malaria endemicity and consequently what we are modelling. Chapter 2 therefore reviews the historical impact of IRS in southern Africa. Chapters 3 evaluate the impact of the El Nino Southern Oscillation (ENSO) phenomenon on annual malaria incidence in Southern Africa. This is the main driver of inter-annual and seasonal variability in climate in most regions in Africa, and is important because ENSO events alter seasonality in climate in a way that influences malaria seasonality. Chapter 4 uses Zimbabwe to examine the spatio-temporal role of climate on year to year variation of malaria incidence. This country has a heterogeneity of climatic suitability for malaria transmission and reflects varying epidemiological profiles that occur in Southern Africa. Chapter 5 uses Zimbabwe as an example towards the development of an empirical model of malaria seasonality based on clinical malaria case data. Chapter 6 assesses the potential for use of the entomological inoculation rate (EIR) to describe malaria seasonality in Africa. Chapter 7 improves on work done in chapter 6 by modelling and mapping seasonal transmission of malaria

transmission using an approximation based on discrete Fourier transformations which remove noise in the original time series and allows for the description important / main seasonal components in EIR in relation to those of meteorological covariates. The work described in these chapters culminated in five scientific publications and one working paper

Chapter 2 showed that Southern African countries that sustained the application of IRS reduced the level of transmission from hyper- to meso-endemicity and from meso- to hypo-endemicity. This means that in instances where pre-control malariometric indices are not available one can not assume to be modelling baseline endemicity. Preferably, where the data are available the ideal situation will be to develop pre- and post-control models to evaluate changes in the malaria risk pattern over time.

Chapter 3 found that contrary to east Africa where ENSO events and in particular El Nino has been linked to changes in climatic condition and increase in epidemic risk, in Southern Africa, ENSO has the opposite effect during El Nino years, with heightened incidence during La Nina years. However, the impact of ENSO also varies over time within countries, depending on existing malaria control efforts and response capacity. From this analysis it is clear that in order to lay an empirical basis for epidemic forecasting models there is a need for spatial-temporal models that at the same time consider both ENSO driven climate anomalies and non ENSO factors influencing epidemic risk potential.

Chapter 4 confirmed that there is considerable inter-annual variation in the timing and intensity of malaria incidence in Zimbabwe. The modelling approach adjusted for unmeasured space-time varying risk factors and showed that while year to year variation in malaria incidence is driven mainly by climate the resultant spatial risk pattern may to large extent be influenced by other risk factors except during high and low risk years following the occurrence of extremely wet and dry conditions, respectively. It is likely therefore that only years characterized by extreme climatic conditions may be important for delineating areas prone to climate driven epidemics, and for developing climate based seasonal forecasting models for malaria epidemics.

Chapter 5 employed the Bayesian spatial statistical method to quantify the relative amount of transmission in each month. This method smoothed for unobserved or unmeasured residual variation in malaria case rates while adjusting for environmental covariates enabling us to interpret the spatial pattern of malaria in seasonality. This work also demonstrated the feasibility of using Markham's seasonality index (previously used for rainfall) to describe malaria seasonality. In this analysis the index was used to summarize the spatial pattern of the modelled seasonal trend by displaying the concentration of malaria case load during the peak season across, which is important for malaria control.

Chapter 6 adopted Markham's seasonality index to characterize seasonality in EIR in relation to environment covariates. This work successfully identified rainfall seasonality and minimum temperature as predictors of malaria seasonality across a number of sites in

Africa. However, model predictions were poor in areas characterized by two rainfall peaks and irrigation activities. The seasonality concentration index performed better in areas with a unimodal seasonal pattern, and this might have had an adverse effect in the analysis in areas with a bimodal seasonal pattern. This highlighted the need for an improved quantification of malaria seasonality to model the complex and varied seasonal dynamics across the continent.

Chapter 7 used an approximation of the discrete Fourier transform to the model relationship between seasonality in EIR and meteorological covariates. This was used to predict the seasonal average as well as the magnitude and timing of the main seasonal cycles. This allowed for the estimation of the overall degree and timing malaria seasonality and the duration of transmission across sub-Saharan Africa. Model predictions can be used to estimate the average seasonal pattern of malaria transmission across the continent. This analysis presents the first step towards the development of improved models of malaria seasonality, and as more data become available the models can be further refined.

In conclusion the Bayesian analytical framework used in this study enhanced our ability to evaluate the relationship between malaria and climatic / environmental factors, and improved considerably the identification of important associations and covariates. Climatic and associated environmental determinants of seasonal and between year-variation in malaria, including the impact of ENSO identified in this work, provide valuable information for the development of climate based seasonal forecasting models

for malaria. Furthermore, an approximation of the discrete Fourier transformation of the data enabled us for the first time to develop empirical models and maps of the seasonality of transmission of malaria at a continental level. These are positive developments for the malaria modelling, mapping and control community in general.

ZUSAMMENFASSUNG

In Afrika südlich der Sahara ist Malaria eine der Hauptursachen von Morbidität und Mortalität, wovon besonders Kinder unter fünf Jahren und schwangere Frauen betroffen sind. Die Facetten der Malaria sind sehr unterschiedlich da viele Faktoren die Malariatransmission beeinflussen und diese lokal in vielen verschiedenen Kombinationen vorkommen. Zu den Faktoren zählen klimatische, ökologische, soziale, ökonomische und kulturelle Elemente. Mit der Hilfe von verschiedenen epidemiologischen Ansätzen wurde versucht, die unterschiedlichen Bilder der Malaria zu überschaubaren Typen und Kategorien zu reduzieren um eine effiziente Planung und zielgerichtete Kontrollstrategien zu ermöglichen. Computermodelle sowie Kartierungen der Malaria sind seit langem anerkannte, wichtige Mittel zur Entwicklung dieses empirischen Wissens. Seit kurzem ermöglichen die Verfügbarkeit von neuen Datensets sowie neue analytische Hilfsmittel und statistische Methoden die Entwicklung von umfassenderen Malaria Karten für Ost-, West- und Zentralafrika. Allerdings wurde bei den meisten entwickelten Risiko-Karten die saisonale Variation der Malariaübertragung nicht berücksichtigt. Diese Saisonalität beeinflusst die dynamische Beziehung zwischen der Vektor Moskitodichte, der Inokulationsrate, der Prävalenz der Parasiten sowie dem Ausgang der Krankheit. Daher sind die quantitative Beschreibung und die Kartierung der Malaria-Saisonalität wichtig für die Modellierung der Malariatransmission und der Planung von zeitlichen und räumlichen angepassten Interventionen.

Diese Doktorarbeit ist Teil einer laufenden Bestrebung innerhalb der MARA/ARMA (Mapping Malaria Risk in Africa/Atlas du risqué de la Malaria en Afrique) Kollaboration

für die Entwicklung von verbesserten Malaria-Risikokarten für Afrika. Das Hauptziel ist die Entwicklung eines impirischen Modells der Malaria Saisonalität durch die Anpassung von klassischen und modernen statistischen Modellen an klinische und/oder entomologischen Indices. Des Weiteren beabsichtigte diese Arbeit die Identifizierung von wichtigen Determinanten der „zwischen-jährlichen“ und örtlichen Variationen, welche nützlich sein könnten für die Entwicklung von klimatisch basierten, saisonal vorhersagenden Modellen von Malaria-Epidemien.

Im Kapitel 1 wird ein Überblick über die Übertragung und Epidemiologie der Malaria in Afrika gegeben und die Notwendigkeit dieser Arbeit begründet.
Zu Beginn lag der Fokus der Analysen in Südafrika, da dies bis kürzlich die einzige Region innerhalb des Kontinentes war, welche über ausreichend umfangreiche klinische Daten von Malariafällen besass, und sich daher als idealer Startpunkt auswies. Südafrika besitzt eine lange Geschichte der Malaria-Kontrolle durch das Besprühen von Wänden innerhalb von Häusern mit Insektizid („Indoor Residual Spraying“ (IRS)). Dies könnte einen Einfluss auf den Level der Malaria-Endemizität haben und folglich auch auf unser Model. Daher wird im Kapitel 2 der historische Einfluss von IRS in Südafrika beschrieben. Das dritte Kapitel evaluiert den Einfluss des „El Niño und die Southern Oscillation“ (ENSO) Phänomen auf die jährliche Malaria-Inzidenz im südlichen Afrika. In den meisten Gebieten von Afrika ist das ENSO Phänomen die Hauptkraft der zwischenjährlichen und der saisonalen Variabilität des Klimas und ist wichtig, weil es die die Klima-Saisonalität so modifiziert, dass die Malaria-Saisonalität ebenfalls beeinflusst

wird. Kapitel 4 untersucht durch das Beispiel von Zimbabwe die räumlich-zeitliche Rolle des Klimas auf die Jahr-zu-Jahr Variation der Malaria-Inzidenz.
In Zimbabwe herrscht eine Heterogenität von Klimas, bei welchen die Malaria-Übertragung möglich ist und welche die unterschiedlichen epidemiologischen Profile, welche im südlichen Afrika vorkommen, widerspiegeln. In Kapitel 5 wird durch das Beispiel von Zimbabwe die Entwicklung eines impirischen Modells der Malaria Saisonalität auf der Basis von Daten von klinischen Malariafällen aufgezeigt. Kapitel 6 untersucht das Potential der entomologischen Inokulationsrate (EIR), die Malaria-Saisonalität in Afrika zu beschreiben. Kapitel 7 geht einen Schritt weiter als Kapitel 6 in dem für das Computer-Modell und die Kartierung der saisonalen Malaria-Übertragung eine Approximation angewendet wurde, welche auf einer diskreten Fourier Transformation beruht. Diese entfernt Störungen in der ursprünglichen Zeitreihe und erlaubt die Beschreibung der wichtigsten saisonalen Komponenten der EIR in Beziehung zu den meteorologischen Kovariaten. Aus der vorgängig beschriebenen Arbeit resultierten fünf bereits publizierte wissenschaftlichen Artikel sowie ein Manuskript, welches noch in Bearbeitung ist.

In Kapitel 2 wurde gezeigt, dass in Ländern des südlichen Afrikas durch die kontinuierliche IRS-Applikation die Transmission von Hyper – zu Meso und von Meso- zu Hypoendemizität gesenkt wurde. Dies bedeutet, dass ohne malariaometrische Indices für die Zeit vor einer Malariakontrolle nicht davon ausgegangen werden kann, dass man das Modell einer ursprünglichen Endemizität erstellen kann. Wo die Daten erhältlich

sind, sollte daher für die Evaluation der Änderungen des Malariarisikos über die Zeit Idealerweise sowohl ein Prä – als auch eine Postmodell entwickelt werden.

In Kapitel 3 wird gezeigt, dass im Gegensatz zu Ostafrika, wo ENSO Ereignisse und im speziellen das El Nino Phänomen mit der Änderung von klimatischen Konditionen und eines erhöhten Malaria-Risikos in Einklang gebracht werden, im südlichen Afrika ENSO Ereignisse während El Nino Jahren den Gegenteiligen Effekt bewirken. Erhöhte Inzidenzen treten im südlichen Afrika währen den La Nina Jahren auf. Allerdings variiert der Einfluss von ENSO ebenfalls über die Zeit in den verschiedenen Ländern, je nach existierenden Malaria-Kontrollprogrammen und Reaktionskapazitäten. In Anbetracht dessen ist klar, dass es für die Entwicklung einer empirischen Basis eines Modells, welche Epidemien voraussagenden sollte, ein räumlich-zeitliches Modell nötig ist, welches gleichzeitig ENSO abhängige klimatische Anomalien sowie Faktoren, welche nicht von ENSO verursacht sind und das Epidemie-Risiko beeinflussen, integriert.

In Kapitel 4 wird bestätigt, dass in Zimbabwe eine beträchtliche zwischen-jährliche Variation sowohl im zeitlichen Auftreten als auch in der Inzidenz der Malaria vorkommt. Das Modell, welches ungemessene räumlich-zeitliche Risikofaktoren einbezog und berichtigte, zeigte, dass während die Jahr-zu-Jahr Variation der Malaria Inzidenz hauptsächlich durch das Klima verursacht wird, das resultierende örtliche Malaria Risiko beträchtlich durch andere Faktoren beeinflusst werden kann. Die Ausnahmen bilden Jahre mit sehr hohem oder sehr niedrigem Risiko nach extrem nassen, respektive extrem trockenen Zuständen. Es ist daher gut möglich, dass nur Jahre, welche durch extreme

klimatische Verhältnisse gekennzeichnet sind, für die Beschreibung von Epidemie-gefährdeten Gebieten sowie für die Entwicklung von klimatisch basierten, saisonalen Malaria-Epidemien vorhersagenden Modellen wichtig sind.

In Kapitel 5 wurden mit Hilfe der „Bayesianischen Methode die relativen Häufigkeiten der monatlichen Übertragungen quantifiziert. Diese Methode verminderte nicht detektierte oder nicht gemessene Restvariationen der Malariafalldaten während es umweltbedingte Kovariaten korrigierte. Dies ermöglichte die Interpretation der örtlichen Muster der Malariasaisonalität. Zusätzlich konnte diese Arbeit zeigen, dass der „Markham's Saisonalitätsindex" (welcher früher für Regenfalldaten benutzt wurde), auch für die Beschreibung der Malaria Saisonalität geeignet ist. Für diese Analyse wurde mit Hilfe des Indexes das örtliche Muster des berechneten saisonalen Trends zusammengefasst, indem die, für die Malariakontrolle wichtige, Dichte der Malariafälle während der Hauptsaison aufgezeigt wurde.

In Kapitel 6 wurde mittels des „Markham's Saisonalitätsindex" die EIR in Bezug auf umweltbedingte Kovariaten charakterisiert. Dabei konnte in mehreren Regionen Afrikas die Niederschlagsjahreszeitlichkeit sowie die Minimums-Temperatur erfolgreich als Prädikatoren der Malaria-Saisonalität identifiziert werden. Allerdings waren die Voraussagungen des Models in Gebieten mit zwei Regenfall-Höchstwerten und Bewässerungsaktivitäten ungenügend. Es zeigte sich, dass der Index für Regionen mit einem unimodalen saisonalen Muster besser geeignet war, was eine Beeinträchtigung der Analysen von Regionen mit einem bimodalen saisonalen Muster bedeuten könnte. Dies

unterlegt den Bedarf einer verbesserten Quantifikation der Malaria-Saisonalität um die komplizierten und mannigfaltigen saisonalen Dynamiken zu simulieren.

In Kapitel 7 wurde durch eine Annäherung der diskreten Fourier Transformation die Beziehung der Saisonalität der EIR und den umweltbedingte Kovariaten simuliert. Damit wurden der jährliche Durchschnitt sowie die Grössenordnung und Zeitintervalle der relevanten saisonalen Zyklen berechnet. Dies ermöglichte die Schätzung des Ausmasses und des Timings der Saisonalität sowie der Dauer der Transmission in ganz Afrika südlich der Sahara. Vorhersagen der Computer-Modelle ermöglichen es, die durchschnittlichen saisonalen Muster der Malariaübertragung über den ganzen Kontinent zu schätzen. Diese Analysen sind der erste Schritt in der Entwicklung eines verbesserten Models der Malaria-Saisonalität und umso mehr Daten erhältlich werden, desto besser ist es möglich das Model zu verfeinern.

Dank der Bayesianischer Methode waren wir besser in der Lage, die Beziehung zwischen Malaria und klimatischen/umweltbedingten Faktoren zu evaluieren. Zusätzlich konnten wir die Identifikation von wichtigen Assoziierungen und Kovariaten massiv verbessern. Klimatische und umweltbedingte Faktoren, einschliesslich des ENSO, welche für die saisonalen und zwischen-jährlichen Variationen der Malaria verantwortlich sind, geben wertvolle Informationen für die Entwicklung von klimatisch basierten Modellen für die Vorhersage der saisonalen Malaria. Des Weiteren konnte zum ersten Mal ein empirisches Modell sowie Karten der Saisonalität der Malaria-Transmission auf der kontinental Ebene entwickelt werden, in dem die Daten mit Hilfe der „diskreten Fourier

Transformation“ angenähert wurden. Dies sind positive Entwicklungen sowohl für die Simulationen, Kartierungen als auch für die Malariakontrolle im Allgemeinen

ABBREVIATIONS

AIC	Akaike information criterion
AR (1)	First order autoregressive process
AVHRR	Advanced very high resolution radiometer
BHC	Benzene hexachloride
CAR	Conditional autoregressive process
CAR (1)	First order conditional autoregressive process
CAR (γ)	Gamma conditional autoregressive process
CRU	Climate research unit
DDT	Dichloro diphynyl trichloroethane
DALYs	Disability-adjusted life years
DIC	Deviance information criterion
EIR	Entomological inoculation rate
ELISA	Enzyme-linked immunosorbent assay
ENSO	El Nino southern oscillation phenomenon
GLMM	Generalized linear mixed models
IRS	Indoor residual spraying
ITNs	Insecticide treated nets
IPTi	Intermittent preventive treatment in infants
MARA	Mapping Malaria Risk in Africa
MCMC	Markov Chain Monte Carlo simulation
MEWS	Malaria early warning systems
NDVI	Normalized difference vegetation Index

NMCP	National Malaria Control Programme
NVDCP	National Vector-Borne Disease Control Programme
NOAA	National Oceanic and Atmospheric Administration
RS	Remote sensing
RBM	Roll Back Malaria
SAMC	WHO Southern African Malaria Control
SST	Sea surface temperature
SOI	Southern oscillation index
WHO	World Health Organization

TABLES

FIGURES

Chapter 1: Transmission and epidemiology of malaria in Africa

Background

Malaria remains one of the most devastating vector-borne parasitic diseases despite more than a century of efforts to eradicate and control it. The disease is a major growing threat to the public health and economic development of countries in the tropical and subtropical regions of the world, particularly in sub-Saharan Africa (Najera 1989; Carter and Mendis 2002). Recently renewed interest in malaria control and prevention has prompted demands for novel approaches and more effective implementation of proven strategies (Sachs 2002). Given the variable nature of the disease, its vectors and the vulnerability of particular human populations, all effective methods of attack against malaria should be employed according to epidemiological conditions of the area concerned (Bruce-Chwatt 1980; Molineaux 1988). These include a complex interplay between environmental, social, cultural and economic factors which operate at different spatial and temporal levels. Careful study and evaluation of the role of these factors is essential to the understanding of malaria epidemiology and for prioritizing interventions.

Modelling and mapping of malaria has long been recognized as an essential tool for epidemiologists more especially as a way for reducing uncertainties in decision making for malaria control managers by disentangling and simplifying the complex dynamics of malaria transmission (Mckenzie 2000).

Transmission biology of malaria

Human malaria is a mosquito-borne infectious disease caused by a protozoan blood parasite of the genus *Plasmodium* and transmitted by infected female mosquitoes of the genus *Anopheles*. Among the four species of *Plasmodium* infecting humans (*P. falciparum, P. vivax, P. malariae, and P. ovale*) the most common species in sub-Saharan Africa is *P. falciparum*, which causes the most severe and life threatening form of the disease (Gillies and De Meillon 1968; Gills 1993). Its main symptom is fever. Out of about sixty anopheline mosquitoes able to transmit malaria to humans the primary vector species include *Anopheles funestus* of the *A. funestus* group as well as *A. arabiensis* and *A. gambiae sensu stricto* both members of the *A. gambiae* complex (Coluzzi 1984; Coetzee e*t al*. 2000). These are the most efficient vectors of the malaria parasite incriminated in transmitting the most severe and deadly form of malaria in Africa. Although there are different species of malaria parasite, the basic life cycle of each follows the same pathway.

Life cycle in the human host

The parasite is transmitted to humans by sporozoites (infective stages) in the saliva during blood meal. The female mosquitoes need blood meals to produce their eggs. Soon after entering the human host, the sporozoites invade hepatocytes (the liver cells) initiating the liver stage, where they multiply by schizogony (asexual reproduction). In the case of *P. vivax* and *P. ovale* some sporozoites may differentiate into hypnozoites, responsible for late relapse of the infection (Molineaux 1988; Oaks 1991; Gilles 1993).

Growth and division in the liver takes between 6-15 days depending on the *Plasmodium* species, thousands of merozoites (blood infecting stages of the parasite) are formed. These are released into the bloodstream where they invade erythrocytes (the red blood cells) initiating the blood stage. In the red blood cells each merozoite matures and divides by schizogony into daughter merozoites, which rapture the blood cells and invade more red blood cells. The rupturing of red blood cells is associated with the onset of clinical presentation of malaria, the periodic fevers (Molineaux 1988; Oaks 1991; Gilles 1993). After invading red blood cells, some merozoites develop into male and female gametocytes (sexual forms), which are ingested by a mosquito during blood meal, initiating sporogony.

Life cycle in the vector

Inside the mosquito gametocytes transform into micro- and macro-gamates (male and female gametes respectively), which fuse to form a zygote (sexual reproduction). The zygote matures to form the ookinete that become attached to the midgut wall and develops into the oocyst. The oocyst divides by sporogony, giving rise to thousands of sporozoite-stage parasites that rapture the oocyst and migrate to the salivary glands. The cycle begins again with the injection of sporozoites by a female *Anopheles* mosquito to another human host during blood meal (Molineaux 1988; Oaks 1991; Gilles 1993). Consequently, the geographic distribution of the parasite follows that of its carrier, and the presence of the human host along with suitable climatic / environmental conditions determine the extent of malaria transmission and distribution.

Malaria transmission determinants

The transmission of malaria is complex, involving life cycles in both the human host and anopheline vectors as explained above and depends on the interaction of ecological and biological factors of both the human and vector populations. Malaria vectors vary considerably in their ability to transmit malaria. The feeding habits and prevailing climatic / environmental conditions affect their vectorial capacity (new infections produced by the vector per case per day) which determines how malaria is transmitted and expressed in individuals and populations (Gillies and De Mellion 1968; Hunt *et al.* 1998). For example, within members of the *Anopheles gambiae* species complex, *A. gambiae s.s.* feed on humans (anthropophilic) both indoors (endophagic) and outdoors (exophagic) and rests mainly indoors (endophilic). *An. arabiensis* is more likely to feed on animals (zoophilic) and rest outdoors (exophilic). On the other hand *Anopheles funestus* is highly anthropophilic and both endophilic and exophagic.

The capacity of the mosquito to transmit malaria is based on several key parameters of the vector population (Coluzzi 1984). These include the density of vectors in relation to humans, number of blood meals taken per vector per day, daily survival of the vector, and parasite incubation period in the vector. The transmission of malaria requires that environmental conditions are suitable for both the mosquito and the parasite (Molineaux 1988; Oaks 1991; Gilles 1993). The vectorial capacity of *A. funestus* can often exceed that of *A. gambiae* in some localities (Gillies and De Meillon 1968; Fontenille *et al.* 1984; Fontenille *et al.* 1997). *A. funestus* breeds in permanent or semi-permanent swamps or in pools along streams and river systems, and *A. gambiae* complex prefer temporary

aquatic habitats. Consequently, *A. funestus* are less dependent on rains and become abundant during the dry seasons when *A. gambiae* densities are low. Thus, *A. funestus* is often considered a vector species that bridges malaria transmission during the dry season (Gillies and De Meillon 1968; Cohuet *et al*. 2004).

Only anophelines surviving longer than the sporogonic cycle (extrinsic phase of parasite development in the mosquito) can transmit malaria. The female mosquitoes need blood meals to produce their eggs. For transmission to occur there must be sufficient time for them to take a blood meal, for the parasite to develop, and for the mosquito to take another blood meal and thus transmit the parasite to a second host. Factors that affect the lifespan of the female anopheline, and consequently the completion of the sporogonic cycle include ambient temperature, relative humidity and rainfall. The time required for the complete maturation of the parasite in mosquito also varies according to the *Plasmodium* species (Molineaux 1988; Oaks 1991; Gilles 1993).

Generally, sporogony cease at temperatures below 16 ^{o}C and above 40 ^{o}C, and at 20-30 ^{o}C the parasite develops optimally in the vector. Higher temperatures shorten parasite development and increase the number of times blood meals are taken as well as breeding activity of *Anopheles* mosquitoes. High relative humidity (greater than 60%) prolongs the life of the vector and transmission is extended under such conditions (Molineaux 1988; Oaks 1991; Gilles 1993). The effect of rainfall is more complex. In addition to increasing the extent of vector breeding sites, rainfall modifies temperature and relative humidity, two important conditions for malaria transmission. Without sufficient rainfall mosquitoes

are unable to survive and as a result parasites cannot infect humans. However, too much rainfall, or rainfall accompanied by storm can flush away breeding larvae. Not only the amount or intensity of rainfall, but also the months of the year or intervals at which it occur (i.e. seasonality) affect vector activity, transmission and disease risk.

Malaria epidemiology

Malaria Risk

Human malaria risk worldwide is estimated to be 350 to 650 million clinical cases each year (WHO 2005; Snow 2005), with about 90% of these occurring in Africa, south of the Sahara, mostly in young children, as well as in a significant number of pregnant women. Other high-risk groups include non-immune travelers, refugees, displaced persons and laborers entering endemic areas (WHO 2000a). Malaria related aneamia, hypoglaceamia, respiratory distress and low birth weights are included when defining the burden of malaria. Other nonspecific symptoms include chills, discomfort, fatigue, headache, muscle pain, cough and organ failure. The World Bank ranks malaria as the leading cause of lost disability-adjusted life years (DALYs) in Africa with an estimated 35 million of future life-years lost from disability and premature death (World Bank 1993).

It is estimated that malaria kills between 1.5 and 2.7 million people world wide each year, about 1 million deaths occur in children under 5 years of age, especially in sub-Saharan Africa (WHO 2000a). Childhood malaria deaths, resulting mainly from severe anaemia, hyoglycaemia, cerebral malaria and metabolic acidosis presenting as respiratory distress

(Marsh *et al*. 1995; Murphy and Breman 2001), constitute nearly 25% of child mortality in Africa (WHO 2000a).

The morbidity and mortality associated with malaria have a crippling effect on social and economic development of most countries in Africa. It incapacitate the labour force, lowers educational achievements, discourage tourism and business investment. Recent estimates suggested that the economic losses due to malaria in Africa are actually about US$12 billion per year and the needs for malaria control have been estimated to US$3 billion (WHO 2000b). The economic burden of ill health on individual households can also be substantial and in some cases catastrophic, especially for poor households. An African family may spend up to 25% of their income on malaria prevention and control (Breman *et al*. 2004).

Malaria control efforts

Efforts to reduce the burden of malaria are as old as human societies. However, over a century into the history of scientific malaria control, too little has changed particularly in Africa where malaria causes untold suffering and impedes social and economic development (Najera 1989, Carter and Mendis 2002). The malaria eradication campaign between the 1950's and 1960's was the first globally coordinated attempt to bring malaria under control. The focus was indoor residual spraying (IRS) with persistent insecticides (mainly DDT) against house dwelling adult female mosquitoes supplemented in some instances by case treatment campaigns. Dramatic reduction in malaria was achieved in many parts of the world. However, the goal of eradication proved elusive in most

endemic countries in the tropics and in particular sub-Saharan Africa (Kouznetsov 1977; Bruce-Chwatt 1984).

Since the end of the eradication campaign in 1969 failure to interrupt transmission in much of Africa led many to discount the value of vector control particularly IRS. As a result since the 1970's international interest in malaria and funding for malaria research and control declined in most countries in the continent. In 1987 a Malaria Control Strategy for Africa was initiated in response to the increasing burden of malaria in the continent and the concern of national authorities. Difficulties in implementation and continued concerns of African countries led to the adoption of the Global Malaria Control Strategy in 1992 which focused on case management through early detection and prompt treatment (WHO 1993a and 1993b).

This was followed by a formulation of a new movement in 1998 aimed at developing global and local partnership to halve the burden of malaria by 2010 through Roll Back Malaria (RBM). The RBM strategy recommends four evidence-based approaches towards malaria control. These include prompt treatment with effective drugs; selective and sustainable prevention relying on vector control (mainly through insecticide treated materials); intermittent preventive treatment in pregnant woman and infants; emergency and epidemic preparedness and response (WHO 1998). Recently, new global initiatives for malaria control in Africa include improving health conditions of the poor through the United Nations Millennium Development Goals, research development funded by the

Bill and Melinda Gates Foundation and scaling up of disease control through the Global Fund (Shiffman 2006).

However, as was in the past contemporary control strategies face a variety of challenges. In Africa the rapid spread of drug resistance first to chloroquine and very recently to sulfadoxine-pyremethamine has greatly increased the cost and difficulty of case management. Drug treatment strategies are also compromised by inadequate health care infrastructure and poor distribution of drugs. Furthermore, poorly constructed dwellings, non compliance of affected communities, vector behaviour (such as feeding outdoors) and development of insecticide resistant vector populations combined with the complex dynamics of malaria transmission pose a serious threat to the effectiveness of vector control strategies (Hamoudi and Sachs 1999). This is compounded by the varying intensity and spatial-temporal dynamic of malaria transmission. Overcoming these challenges relies on advancing our understanding of malaria epidemiology which requires investigation of the underlying dynamics of malaria risk (Snow *et al*. 2005).

Description of malaria risk

The description of malaria risk depends on a great number of factors from a diverse set of domains. These factors can be roughly classified into those that influence transmission intensity (extrinsic factors such as climate), i.e. the potential for the transmission of the malaria parasite as discussed in the preceding sections, and those that influence disease risk (intrinsic factors such as host immunity), i.e. the potential morbidity and mortality in

the human population as a consequence of transmission (Molineaux 1988; de Vries 2001).

Basically, the level of malaria transmission relates to the pattern, spectrum and magnitude of disease outcome. Hence the intensity of transmission provides a useful indication of the likely age-structured risk of severe clinical disease in a given population (Snow and Marsh 2002). In Africa, the enormous heterogeneity in the parasite species and strain, rates of infection, human host genetic make up and level acquired immunity creates a variety of possible outcomes with respect to disease outcome. Individuals show a wide range of responses on contact with the malaria parasite and not everyone infected with malaria becomes ill or dies (Snow and Marsh 1998; Gupta *et al*. 1999).

The main source of heterogeneity is the acquisition of some protective immunity against the disease, which is closely associated with age and depends on the degree of exposure to the malaria parasite. An area with malaria cases mainly in young children has very high transmission intensity under such conditions severe cases occur in infants while older children and adults suffer less severe disease indicating high degree of acquired immunity. The distribution of such immunity only reduces the incidence of clinical malaria attacks without preventing infection (Snow *at al*. 1998b; Gupta *et al*. 1999). On the other hand if cases occur equally across the ages, all age groups are susceptible to severe malaria and this indicates a lack of acquired immunity, and low transmission intensity (Mills 1984; Oaks *et al*. 1991; Gilles 1993).

The maintenance of acquired immunity requires exposure to repeated infections, and the temporal pattern of exposure plays an essential role in the impact of infection in the exposed individual. This is reflected in the climate driven seasonal fluctuation of the intensity of transmission and resultant malaria cases which can be very different from one year to the next (Gilles 1993). Age and season therefore reflect the different states of dynamic equilibrium between malaria transmission, parasite load and immune defenses (Paul *et al*. 2004). This makes modelling of malaria transmission and disease risk a great challenge and forms the rationale for mathematical and statistical approaches to describe the dynamics of malaria risk (McKenzie 2000).

Modelling malaria risk

Mathematical models offer important insight into the process underlying dynamics of malaria transmission and have been successfully used to compose effective interventions (Mackenzie 2000). In 1910 Ross used the first simple mathematical model to show that it is sufficient for the elimination of malaria to bring the mosquito population below a certain threshold (Ross 1911). In the 1950's MacDonald extended Ross's basic model to show that it is far more effective to use insecticides on adult mosquitoes than their larvae (Macdonald 1957). Since then mathematical models have continued to contribute to the theoretical basis of malaria control.

To date most mathematical models are either directly related to the Ross-MacDonald models or borrow from their concept, which includes factors that directly influence malaria such as mosquito density and survival, biting frequencies and parasite

development rate (Dietz 1988; Mckenzie 2000). However, until recently only few models have been statistically calibrated (i.e. formally fitted to data) because of a lack of extensive longitudinal data and adequate statistical techniques. In addition, simulation results from those models were not presented with confidence intervals allowing for assessment of their reliability (Cancre *et al.* 1999). Most recently, an innovative mathematical modelling platform has been constructed to simulate the potential impact of interventions on malaria epidemiology (Smith *et al*. 2006). This employs a stochastic modelling framework to predict the relationships between different components which include transmission parameters, intervention scenarios and their cost effectiveness. However, these kinds of models are less suitable to determine the most effective moment and geographical position for control methods to be applied.

New statistical approaches that take into account time and point reference, including model inference about model parameter values, calculation of confidence intervals for model predictions, model checking and hypothesis testing are now available. These operate within the framework of Generalised Linear Mixed Models (GLMM) (Littel *et al*. 1996) and Bayesian spatial models using Markov Chain Monte Carlo simulation (MCMC) (Wakefield *et al*. 2000). All these methods have already started contributing in helping to identify the best choices of outcomes and parameters for improving the mapping of malaria risk in Africa.

Mapping malaria risk

Risk maps by definition are outcomes of models of disease transmission based on spatial and temporal data. These models incorporate, to varying degrees, epidemiological, entomological, climate and environmental information (Kitron 2000). Describing spatial and temporal variation in transmission and disease risk is fundamental to epidemiological understanding and control of malaria. Decades of experience confirm that successful malaria control depended on accurate identification and geographical reconnaissance of high-risk areas in order to target control measures (Wijeyaratne 1999; Carter *et al*. 2000).

However, in the past, global, continental and regional maps of malaria risk were largely based on expert opinion, limited data, as well as crude geographical and climate iso-lines with no clear and reproducible numerical definition (Craig *et al.* 1999). In recent years the availability of new data sources such as remote sensing (RS), and mapping tools such as computerized geographic information systems (GIS) for quantitative analysis of spatial data provided unprecedented amount of information and increased capability to describe, predict and communicate risk and the outcome of interventions (Hay *et al.* 2000; Kitron 2000; Thomson and Connor 2000; Bergquist 2001). These developments lead to the formation of a GIS based continent wide initiative, the Mapping Malaria Risk in Africa / Atlas du Risque de la Malaria en Afrique (MARA/ARMA) collaboration with the aim of producing an atlas of malaria risk for rational and targeted control across the continent (Snow, Mash and Le Sueur 1996a; Le Sueur *et al*. 1997).

The MARA/ARMA project defined the theoretical distribution and duration of malaria transmission across the whole of Africa based on biological constraints of climate on parasite and vector development (MARA/ARMA 1998; Craig *et al.* 1999). Furthermore, the malaria distribution model was used to estimate the number of people at risk at a continental level (Snow *et al.* 1999). Several malaria risk maps have also been produced using malaria data collected as part of the MARA/ARMA collaboration. These maps have been developed using parasite prevalence data at a country and regional level in Kenya and West Africa, respectively, with new methods developed each time, discriminant analysis (Snow *et al.* 1998); kriging techniques including generalized linear mixed models (GLMM) (Kleinschmidt *et al.* 2000; Kleinschmidt *et al.* 2001a); Bayesian spatial models employing Markov Chain Monte Carlo (MCMC) inference (Gemperli 2003). In southern Africa, the first spatial and temporal analysis of malaria risk was carried out in a small area in KwaZulu-Natal, South Africa using clinical incidence rates rather than parasite rates as in the above-mentioned studies by applying conditional autoregressive models fitted using MCMC (Kleinschmidt *et al*. 2001a & 2001b).

Recently, a transmission model based approach has been used for mapping malaria risk in Mali, West and Central Africa (Gemperli *et al*. 2006a; Gemperli *et al*. 2006a). This approach requires an input of malaria seasonality to underlie the maps. Seasonality in malaria transmission is an important but neglected consideration in malaria mapping, most malariometric indices used are either collected during the rainy or dry season, and this introduces bias in the maps if not accounted for (Gemperli 2003). Besides,

seasonality in climate affects the dynamic relationship between vector mosquito inoculation rate, parasite prevalence and disease outcome.

In the Mali analysis Gemperli *et al*. (2006a) assumed a constant transmission season for each location across the country. In the subsequent analysis of the West and Central African data Gemperli *et al*. (2006b) attempted to overcome this problem by using a modified version of the Tanser *et al*. (2003) climate suitability model of malaria seasonality which estimates duration and timing of season at each location by classifying months as suitable or not suitable for transmission. However, it would be preferable to use a seasonality model that predicts quantitative variation in intensity of transmission between months, rather than simply classifying them dichotomously. An improved map of the seasonal risk pattern is also important for timely spatial targeting of malaria control efforts.

Rationale for the study

In most parts of sub-Saharan Africa malaria transmission is highly seasonal with considerable interannual variability and propensity for epidemics in some parts. This is to a large extent driven by climate and associated environmental determinants. However, although the basic relatioship between transmision, climate and environment is well known (Molineaux 1988; Thomson *et al*. 1997; Craig *et al*. 1999), variability as a result of their complex interaction in both space and time pose a serious challenge for the description of malaria risk and disease control. Particularly because effective implementation of control measures requires that risk areas and risk periods be identified.

Study aim

The main aim is to develop an empirical model of malaria seasonality and to identify potential climatic and environmental predictors of seasonal and inter-annual variation using time series of parasite positive clinical cases and entomological inoculate rates (EIR) where available for modelling malaria transmission dynamics and for timely spatial targeting of interventions.

Specific objectives

1. Review the historical impact indoor residual spraying (IRS) with insecticide on the malaria situations in southern Africa.
2. Evaluate the effect of the El Nino Southern Oscillation (ENSO) as measured by the Southern Oscillation Index (SOI) on annual malaria incidence in Southern Africa.
3. Examine the spatio-temporal role of the effect of climate in inter-annual variation of malaria incidence in Zimbabwe.
4. Use Zimbabwe as an example towards the development of an empirical seasonality model based on clinical malaria data.
5. Assess the potential use of entomological inoculation rate (EIR) and a seasonality concentration index for describing malaria seasonality in Africa.
6. Develop an empirical model and map of the seasonality of malaria transmission for sub-Saharan Africa based on the seasonality in EIR and meteorological covariates.

Chapter 2: Historical review of malaria control in southern African with emphasis on the use of indoor residual house spraying

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Abstract

Indoor residual house spraying (IRS) mainly with dichlorodiphenyltrichloroethane (DDT) was the principal method by which malaria was eradicated or greatly reduced in many countries in the world between the 1940s and 1960s. In sub-Saharan Africa early malaria eradication pilot projects also showed that malaria is highly responsive to vector control by IRS but transmission could not be interrupted in the endemic tropical and lowland areas. As a result indoor residual spraying was not taken to scale in most endemic areas of the continent with the exception of southern Africa and some island countries such as Reunion, Mayotte, Zanzibar, Cape Verde and Sao Tome. In southern Africa large-scale malaria control operations based on indoor residual house spraying with DDT and benzene hexachloride (BHC) were initiated in a number of countries to varying degrees. The objective of this review was to investigate the malaria situation before and after the introduction of indoor residual insecticide spraying in Swaziland, Botswana, Namibia, South Africa, Zimbabwe and Mozambique using historical malaria data. We show that immediately after the inception of indoor residual house spraying with insecticides, dramatic reductions in malaria and its vectors were recorded. Countries that developed national malaria control programmes during this phase and had built up human and organizational resources, made significant advances towards malaria control. Malaria was reduced from hyper- to meso-endemicity and from meso- to hypo-endemicity and in certain instances to complete eradication. Data are presented on the effectiveness of indoor residual house spraying as a malaria control tool in six southern African countries. Recent trends in and challenges to malaria control in the region are also discussed.

Introduction

Control of malaria represents one of the world's greatest public health challenges, especially in sub-Saharan Africa where most of the disease occurs nowadays. In the past decades, efforts to control malaria have been met with mixed success. Since the discovery of the connection between *Anopheles* vectors and malaria transmission in 1897, vector control strategies have been the most widely used malaria control measures. Before World War II vector control measures included environmental sanitation through drainage and landfills to eliminate larval mosquito habitat; biological control through the use of larvivorous fish in ponds; larviciding with oil and Paris green. All these methods were proven to be effective, especially in Europe, but malaria continued to be a problem on a global scale (Najera 2000).

The availability of dichlorodiphenyltrichloroethane (DDT) and other insecticides in the 1940s marked a new era for malaria control in the world. The effectiveness of DDT against indoor resting mosquitoes led to the adoption of the Global Eradication Programme of Malaria in 1955, coordinated and supported by the World Health Organization (WHO). For the first 10 years (1957-1966) the results were spectacular; malaria was completely eradicated in the United States as well as in the former Soviet Union and European countries. Disease incidence was also significantly reduced in many countries in the tropical region of South-East Asia, India and South America. However, gains made in some of the countries particularly in the tropical regions could not be sustained and there were reverses due to financial, administrative or operational problems, resistance or behaviour of vectors, or to the inadequate development of basic

health services (Najera 2001). The time-limited eradication policy was eventually abandoned in 1969 and replaced by a long-term Global Malaria Control Strategy in 1992.

In Africa, south of the Sahara, several malaria eradication pilot projects were initiated between the 1940s and the 1960s in countries such as Liberia, Cameroon, Nigeria, Senegal, Burkina Faso, Benin, Togo, Rwanda, Burundi, Uganda, Tanzania and Kenya. The intention was to assist governments to improve techniques to the point where transmission was interrupted and eradication could be undertaken. These pilot projects demonstrated that malaria was highly responsive to control by IRS with insecticides (mainly DDT). Significant reductions in anopheline vectors and malaria were recorded but transmission could not be interrupted (Kouznetsov 1977; Payne *et al*. 1976; Bradley 1991; Najera 2001). Subsequently, international interest in malaria and funding for malaria research and control declined in most countries on the continent. As a result residual spraying was not taken to scale in large parts of sub-Saharan Africa with the exception of southern Africa and islands such as the Reunion, Mayotte, Zanzibar, Cape Verde and Sao Tome.

In southern Africa the first experimental adult mosquito control with pyrethrum was carried out in 1931 in KwaZulu-Natal, South Africa, and this led the way for the worldwide use of residual insecticides against adult mosquitoes (de Meillon 1936). By the 1940s, large-scale malaria control operations based on house spraying with DDT and BHC (benzene hexachloride) were successfully initiated in South Africa, Zimbabwe and Swaziland. The danger of unexpected epidemics was minimized; morbidity and mortality

were drastically reduced, and in certain areas such as southern KwaZulu-Natal the disease was eradicated (Kouznestov 1977).

Today malaria is a resurging global phenomenon, with explosive epidemics, altered geographical distribution and resurgence in areas where it had been brought to low levels (Roberts *et al*. 2000). It is clearly important therefore to look at the history of malaria and its control in regions where significant and sustained strides were made towards control, particularly in Africa. In this paper, we examine the historical impact of vector control on the malaria situation in southern Africa, and how the control programmes evolved in the region with an emphasis on the use of IRS, which has been and continues to be the backbone of malaria control in the region.

Selected countries and data collection

This review focuses on six southern African countries for which historical malaria data and related information could be accessed, i.e. South Africa, Swaziland, Botswana, Namibia, Zimbabwe and Mozambique. The intensity of malaria transmission in the region varies considerably and includes malaria-free areas as well as unstable and stable transmission areas. Among the selected countries malaria is predominantly stable in Mozambique, which as a result has the greatest burden of the disease. In the other five countries, malaria is predominantly unstable. These areas are often prone to epidemics which can result in high levels of morbidity and mortality if not prevented or contained. IRS is the main vector control strategy in these countries, and over 13 million people are currently protected by IRS in the region (SAMC 2000).

Malaria data and related information used were collected as part of the MARA/ARMA project (Mapping Malaria Risk in Africa / Atlas du Risque de la Malaria en Afrique) through literature searches and country visits (MARA/ARMA 1998). Data sources included national malaria control programmes, national archives and libraries, as well as academic institutions in the region.

In South Africa, publications by Sharp *et al*. (1988), le Sueur (1993), Sharp and le Sueur (1996) document the history of malaria control from the early 1930s to the mid 1990s. A number of unpublished documents and reports were also sourced from Dr. Frank Hansford of the former National Institute of Tropical Diseases in Tzaneen, South Africa.

In Swaziland, early malaria control efforts (1947-1957) are well documented in published and unpublished papers by the chief medical officer Dr. O. Mastbaum. Consistent records of malaria data are also available from annual reports produced by the Ministry of Health since 1947 as well from various WHO reports.

In Botswana, the Ministry of Health and Central Statistics compiled the only available consistent malaria information since 1980. Prior to this, only scanty information dating back to the 1930s and early 1950s could be sourced from national archives, as well as from two WHO reports produced in 1962 and 1974 (WHO 1962; Chayabejara *et al*. 1975).

In Namibia, past malaria data and related information were available from a 1950 publication by Dr B. de Meillon (de Meillon 1951). A series of malaria data dating from the 1960s until the early 1990s were sourced from the National Institute of Tropical Diseases in Tzaneen as well as from numerous WHO reports before and after 1990. However, since the early 1990s the National Vector-borne Disease Control Programme (NVDCP) within the Ministry of Health has been responsible for malaria and related information.

In Zimbabwe, Alves and Blair (1953, 1955), Harwin (1969, 1979), Taylor and Matambu (1986) give a historical account of malaria control efforts in that country from the mid-1940s to the mid-1980s. Some information is also contained in a number of unpublished reports from the Blair Research Institute in Harare, Zimbabwe.

The 20-year history of malaria control experience (1946-1956 and 1960-1969) in southern Mozambique is documented in a number of unpublished reports (Soero 1956; Ferreira 1958; Schwalbach & de la Maza 1985). Recent information on malaria control in Mozambique was sourced from Barreto (1996) and Sharp *et al*. (2001).

Malaria situation before control with IRS

Prior to the introduction of IRS, malaria was hyper-endemic with intense seasonal transmission in endemic areas of most countries in the region. Pre-control spleen and parasite rates from random surveys carried out in selected areas in South Africa (Wilson

and Garnham 1950); Swaziland; Botswana (Mastaum 1944); Namibia (de Meillon 1951); (Mastbaum 1957b); Zimbabwe (Alves and Blair 1953) and southern Mozambique (Martins 1941) were highest in young children and there was a decline in infection with increasing age indicative of a fairly stable transmission (Table 2.1.). The geographical distribution of malaria was also more extensive, and most countries experienced severe epidemics.

In South Africa, malaria epidemics used to extend as far southwards down the east coast as Port St. Johns (Eastern Cape) and as far inland as Pretoria in the northern part of the country (le Sueur *et al*. 1993). In Swaziland, the highest infections were found in the lowveld (150-500 meters) and relatively low infections were found in the middleveld (500-1000 meters) while malaria was absent from the highveld zone (1000-4000 meters) (Figure 2.1.).

In Botswana, very little information is available on the malaria situation prior to the implementation of IRS. However, in 1939 a travelling dispensary noted the disease as occurring all year round in the riverine communities, indicating fairly stable transmission in these areas, while in villages away from such areas it was distinctly seasonal with fewer cases seen during winter months. The spleen rate varied from 40% to 84% in different villages (Medical Officer 1939).

In Namibia, the only information available on the malaria situation before the beginning of the IRS operation in the mid 1960s is from studies by de Meillon (1951) and

Schoemann (1951). These surveys showed that malaria was highest in the north eastern part of the country decreasing towards the west, varying from meso- to hypo-endemic in the central districts, and fading to an epidemic-prone situation in the southern part of the country.

In Zimbabwe, a more stable transmission was found to occur in low lying areas and frequent epidemics occurred at higher altitude (Taylor & Matambu 1986). In southern Mozambique, the Maputo region experienced stable seasonal transmission (Soero 1956; Ferreira 1958; Schwalbach & de la Maza 1985).

Malaria vectors of the *A. gambiae* complex and *A. funestus* were also widespread and found in high densities indoors throughout the malarious areas in South Africa (Swellengrebel & de Meillon 1931), Swaziland (Mastbaum 1957b), Botswana (Mastbaum 1944), Namibia (de Meillon 1951), Zimbabwe (Alves & Blair 1955) and Mozambique (Soeiro 1956).

Table 2.1. Pre-control spleen and parasite rates from random surveys carried out in selected areas in Swaziland (Mastbaum 1957b); Botswana (Mastaum 1944); Namibia (de Meillon 1951); South Africa (Wilson and Garnham 1950); Zimbabwe (Alves and Blair 1953) and southern Mozambique from (Martins 1941).

SOUTH AFRICA (1932)								
Age groups	**Transvaal and Northern KwaZulu-Natal Transmission season**							
(Years)	Spleen (%)							Parasite (%)
0-1	63							60
2-5	92							91
6-10	87							76
11-15	74							64
16-25	52							51
>25	46							34
SWAZILAND (1945-1948)								
	Lowveld Area (150-500 meters)				**Middleveld Area (500-1000 meters)**			
	Transmission season		Non transmission season		Transmission season		Non transmission season	
	Spleen (%)	Parasite (%)	Spleen (%)	Parasite (%)	Spleen (%)	Parasite (%)	Spleen (%)	Parasite (%)
< 1	17	38	11	13	5	14	1	2
1-5	64	76	47	51	23	31	9	15
6-10	68	78	61	56	23	32	16	20
11-15	49	55	42	37	24	43	13	13
16-20	30	49	26	23	20	37	6	11
>20	29	44	19	15	18	36	6	8
BOTSWANA (1944)								
	Ngamiland South Non transmission season				**Chobe Non transmission season**			
	Spleen (%)			Parasite (%)	Spleen (%)			Parasite (%)
0-5	43			33	86			73
6-14	42			18.3	44			55
>14	25			8.3	11			11
NAMIBIA (1950)								
	Kavango Transmission season				**Ovambo Transmission season**			
	Spleen (%)			Parasite (%)	Spleen (%)			Parasite (%)
0-1	48			74	30			19
2-5	79			90	34			58
6-10	52			75	36			63
11-20	30			65	26			60
21-30	13			48	9			50
>30	10			25	7			33
ZIMABWE (1948)								
	Bushu Reserve Transmission season							
								Parasite %
1-3								72
	SOUTHERN MOZAMBIQUE (1937-1938)							
	Maputo region							
	Spleen (%)							Parasite (%)
< 1	56							80
1-5	69							92
5-10	53							83
10-15	38							72

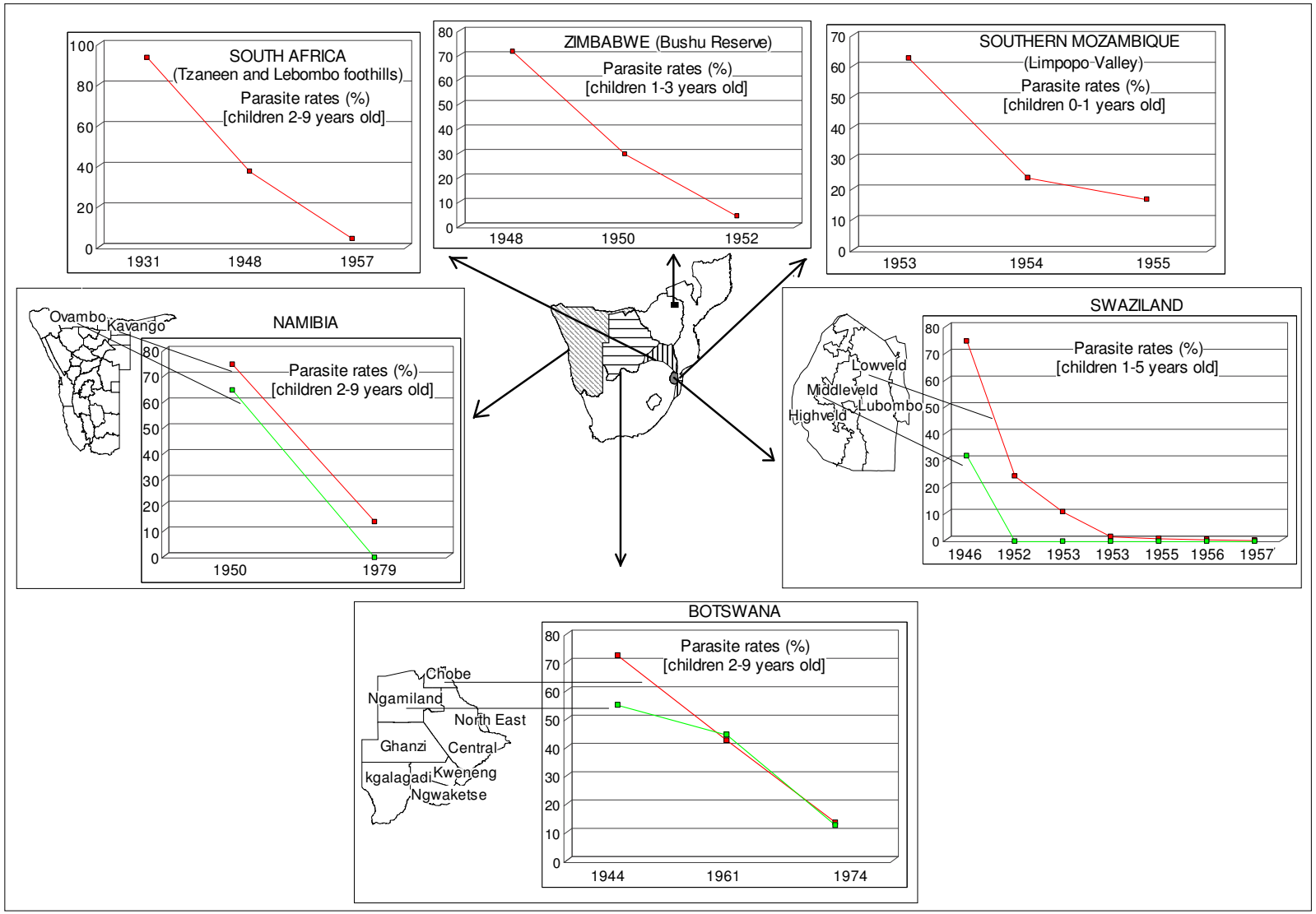

Figure 2.1. Parasite rates before and after the inception of malaria control by IRS (arrows show the start of IRS) in Swaziland, Botswana, Namibia, South Africa, Zimbabwe and southern Mozambique (for references on country data see main text).

Implementation of IRS programmes

Table 2.2. summarizes the start of IRS programmes in the region and changes in residual insecticides applied over time. The first trial testing of the residual application of pyrethrum was undertaken. In 1946, DDT replaced pyrethrum as the insecticide of choice (Sharp *et al*. 1988; le Sueur *et al*. 1993). In 1956, malaria became a notifiable disease, total coverage of all malarious areas was achieved for the first time in 1958, and by 1970 South Africa had a well-structured malaria control programme (Sharp & le Sueur 1996). In 1996, the pyrethroid deltamethrin was introduced for IRS in line with international trends to replace DDT. Subsequently, *A. funestus,* which had disappeared since the 1950s re-emerged in 2000 and was shown to be pyrethroid-resistant (Hargreaves *et al*. 2000). As a result, national policy reverted back to the use of DDT, and surveillance has since indicated that *A. funestus* has again disappeared (Ministry of Health 2003).

In Swaziland, the malaria control programme was launched in 1945. Residual indoor spraying with DDT was initiated on a limited scale in 1947 (Mastbaum 1955). By 1950, coverage of all malarious areas was achieved. During the 1951-1952 transmission season, benzene hexachloride (BHC) was introduced due to a shortage of DDT. From 1955-1956, the efficacy of dieldrin versus BHC was evaluated and no significant difference was found in the vector population density and number of malaria cases in areas sprayed with the two insecticides. However, dieldrin was discontinued due to higher cost (Mastbaum 1956, 1957b). Focal spraying, partly with BHC and partly with DDT, was carried out in the 1960s (Delfini 1969). From the 1980s, spraying of all inhabited structures in malarious areas with DDT and later with synthetic pyrethroids (cyfluthrin) in houses

with painted walls was carried out.

In Botswana, the National Malaria Control Programme was initiated in 1974. However, malaria interventions including spraying of human habitations have been reported as far back as the mid 1940s (Mastbaum 1944). In the 1950s, indoor house-spraying with DDT became the main vector control method (Freedman 1953). DDT remained the insecticide choice until 1971 when Fenitrothion was tried but abandoned again in 1972 because of low efficacy (Chayabejara *et al*. 1975). In 1973, residual spraying with DDT in the malarious districts of Ngamiland, Chobe and Francistown resumed, and in the 1980s a comprehensive vector control programme was organized which lead to improved spraying coverage. In 1998, Botswana stopped the use of DDT and introduced pyrethroids (deltamethrin and lambda-cyhalothrin) as alternative insecticides as a consequence of a lack of availability of good quality DDT (Ministry of Health 1999).

In Namibia, residual spraying with DDT was first carried out in 1965. However, it was only in the 1970s that full coverage of the malarious regions (Ovambo, Kavango and Caprivi) was achieved (Hansford 1990). In 1991, a comprehensive malaria control programme was launched under the auspices of the National Vector-borne Disease Control Programme (NVDCP) within the Ministry of Health and Social Services (MOHSS). To-date residual spraying with DDT is being carried out in traditional housing, with carbamates (bendiocarb) applied only in western-type housing.

Table 2.2. The start of indoor residual spraying (IRS) in countries in the southern African region, the start of malaria control programmes, and changes in residual insecticides applied over time.

Country		Start of IRS and changes of insecticides over-time
South Africa	1931	Pyrethrum [experimental IRS]
	1946	DDT and BHC introduced
	1958	Coverage of all malarious areas achieved
	1960-1996	DDT
	1997-1999	Deltamethrin [policy change]
	2000	DDT [resistance to pyrethroids]
Swaziland	1945	IRS introduced and programme launched
	1947-1950	DDT [coverage of all malarious areas in 1950]
	1951-1960	BHC [shortage of DDT] dieldrin tried but was costly
	1960-1967	BHC and DDT [focal spraying]
	1968-2000	DDT [cyfluthrin in houses with painted walls]
Botswana	1946	IRS introduced [limited scale]
	1950-1971	DDT [improved coverage]
	1972	Fenitrothion tried and abandoned [low efficacy]
	1974	Programme launched
	1973-1997	DDT
	1998-2000	Deltamethrin and lambda-cyhalothrin [policy change]
Namibia	1965	IRS introduced [limited scale]
	1970	Coverage of all malarious areas achieved
	1965-2000	DDT [bendiocarb in western type residential areas]
Zimbabwe	1945	IRS introduced [pilot projects]
	1949	Programme launched
	1957-1962	DDT and BHC
	1972-1973	BHC [equally effective as DDT but cheaper]
	1974-1987	DDT [resistance to BHC]
	1988-2000	Deltamethrin and lambda-cyhalothrin [policy change]
Southern Mozambique	1946	IRS introduced [selected southern areas]
	1946-1956	DDT and BHC [coverage of all targeted areas in 1950]
	1960-1969	DDT [only in Maputo region]
	1993	Deltamethrin and lambda-cyhalothrin [major towns]
	2000	Bendiocarb [selected southern areas]

For references on country data see main text.

In Zimbabwe, indoor house spraying pilot projects with DDT began as far back as 1945. A large scale house spraying programme was initiated in 1949 (Alves & Blair 1953, 1955). Spraying operations were later extended to other parts of the country as part of a "barrier" spraying programme to prevent epidemics and to limit the spread to malaria-free areas. These operations continued until the late 1970s and after 1980 the malaria control programme was reviewed with the aim of reducing morbidity and mortality rather than only preventing epidemics (Taylor & Matambu 1986). In 1988, DDT was replaced by deltamethrin and lambda-cyhalothrin due to the international lobby against persistent organic pollutants (Freeman 1995).

In Mozambique, residual house spraying with DDT and BHC was first introduced in 1946 in the southern part of the country in the semi-urban area of Maputo city and in the rural area of the Limpopo Valley (Soeiro 1956; Ferreira 1958). Between 1960-1969, residual spraying with DDT was carried out in southern Mozambique (Maputo region) as part of the malaria eradication experiment (Schwalbach & de la Maza 1985). The escalation of civil war in the late 1970s led to a complete breakdown of malaria control measures. Following the cessation of hostilities in the 1990s, IRS mostly with lambdacyhalothrin and partly with deltamethrin was re-introduced but only in suburban areas in the majority of provincial capitals (Barreto 1996). In 2000, IRS with carbamates (bendiocarb) was re-introduced in the rural parts of Maputo province as part of the Lubombo Spatial Development Initiative (LSDI), a trilateral agreement between Mozambique, Swaziland, and South Africa aimed at protecting communities against

malaria in the Lubombo region in order to create a suitable environment for economic development and promotion of eco-tourism (Sharp et al. 2001).

Impact of indoor residual spraying (IRS)

The introduction of indoor residual insecticide spraying had a huge impact on the malaria situation in the region, particularly immediately after its implementation (Figure 2.1.). Generally, in most of the countries under review other control measures such as attempts at drug prophylaxis, environmental sanitation and larviciding were tried prior to IRS, but with limited success.

In South Africa, a dramatic reduction in number of malaria cases was observed after the first indoor spraying with pyrethrum in 1932 in the KwaZulu-Natal province (le Sueur *et al*. 1993). Malaria cases for the month of April (peak month) dropped from about 1400 in 1931 to about 1000 in 1932 and to below 100 in 1934. Dramatic declines in hospital admissions due to malaria were also reported in the malarious areas of the former Transvaal province of South Africa, from 1177 cases during the 1945/46 transmission season to 601 in 1946/47 coinciding with the availability of DDT in 1946, and falling to 454 in 1948 and to a low of 61 cases in 1951. Parasite rates in children 2-5 years old in the Tzaneen and Lubombo foothills were reduced from 94% recorded in 1931 (Swellengrebel & de Meillon 1931) to 38% in 1948 (Ministry of Health 1949) and to 4,9% between 1956 and 1957 (Brink 1958).

In Swaziland, considerable gains were made shortly after the implementation of residual spraying with total parasite rates in children 1-5 years being reduced from 75% in 1946 to 24% (n=409) in 1952, 11% in 1953, 1.7% (n=1639) in 1954, 1,1% (n=438) in 1955, 0,7% (n=2248) in 1956 and 0.4% in 1957 (Mastbaum 1954, 1955, 1957a,b; Ministry of Health unpublished data). A similar reduction had already been achieved in the middleveld areas over the past three seasons.

In Botswana, initial IRS with DDT in the mid-1940s and the intensified residual spraying campaign in the 1950s are evidenced by the low parasite rates recorded by WHO in 1960 and 1979 in previously hyper-endemic districts. In the Chobe district parasite rates in 2-9 year olds were further reduced from 43% (n=575) in 1961-62 to 14% (n=222) in 1973-1974 and in Ngamiland from 45% (n=944) to 13% (n=564), respectively (WHO 1962; Chayabejara *et al.* 1975).

In Namibia, after the first residual spraying with DDT in 1965, average parasite rates in 2-9 year-olds in the malarious regions of Kavango and Ovambo declined tremendously, from 83% (n=74) in 1950 to 14% (n=1115) in 1979 and from 65% (n=35) to 0.1% (n=978), respectively. In the Caprivi district, a pre-control survey in 1966 recorded an overall parasite rate of 32% and this declined to 2% by 1967.

In the Bushu Reserve in Zimbabwe, parasite rates in children between the ages 1-3 years declined from 72% in 1948 to 30% in 1950 following residual spraying, and further to 4.7% in 1952 (Figure 3.1.). The same general pattern was shown by other surveys where

control measures had been introduced (Alves and Blair 1953). Similarly, in the Mazoe Valley when a residual spraying programme with DDT was introduced for the first time in 1945 as part of a pilot project, malaria cases declined from 100 in 1946 to 2 in 1950 at a hospital situated in a sprayed area compared to 62 in 1946 and 68 in 1950 at an adjacent hospital in an unsprayed area (Blair 1951).

Following the introduction of residual spraying with DDT in Maputo, southern Mozambique, in 1946 malaria admissions dropped from 16% to about 8% in 1947 and to a low of 3% and 1% in 1953 and 1954, respectively. In the same region in a rural area in the Limpopo Valley after the introduction of malaria control in 1947, parasite and spleen rates in children under one year declined from 62.7% and 59.4%, respectively, in 1953 to 23.6% and 21% in 1954 and to 17% and 1% in 1955. Only spleen rates were given for children 2-10 years old in 1953, and these stood at 53.2%. They dropped to 26.7 in 1954 and declined further to 13.7% in 1955 (Soeiro 1956). Recently, dramatic reductions in malaria transmission have also been reported in the Maputo region after a year of successful control of vectors by IRS as part of as part of the Lubombo Spatial Development Initiative (LSDI) (Sharp *et al*. 2001).

The application of IRS also greatly altered the entomological situation in the malarious regions of South Africa, Swaziland, Zimbabwe and parts of southern Mozambique. The principal vectors of the *A. gambiae* complex and *A. funestus* were reduced to negligible levels, and while the former could still be found outdoors the latter completely disappeared in certain parts. *A. gambiae* is a species complex initially identified by

Paterson in the early 1960s (Paterson 1963). It was generally presumed that the endophilic and endophagic *A. gambiae s.s.* was well controlled and possibly eradicated over large areas. On the contrary, other members of this complex, namely the exophilic and zoophagic *A. quadriannulatus* (a non vector species) persisted and *A. arabiensis* survived and is currently considered responsible for the remaining malaria transmission in areas under effective IRS (Hansford 1972; Sharp *et al*. 1990).

Malaria situation over time

Over time major gains were made in most countries in the region as a result of large scale and sustained application of IRS. There was a shift in the geographical distribution of malaria coupled by a decline in the level of transmission. In South Africa, malaria is now only found in the northern part of KwaZulu-Natal and in the low altitude areas of Limpopo and Mpumalanga (former Transvaal Province) (Sharp *et al*. 1988; le Sueur *et al*. 1993; Sharp & le Sueur 1996; le Sueur *et al*. 1996). In Swaziland, malaria is now confined to the lowveld area with occasional outbreaks in the middleveld (Ministry of Health 1991). In Botswana and Namibia, malaria still persists in endemic areas albeit at much reduced levels (Ministry of Health 1999; Teklehaimanot *et al*. 1990). In Zimbabwe, malaria was considered eliminated in the plateau area by 1956, and throughout the country transmission was brought down to very low levels (Taylor & Matambu 1986). In Mozambique, although malaria transmission was never interrupted, dramatic reductions in malaria prevalence were achieved between 1960 and 1969, but mainly in the southern parts of the country where malaria control activities had been carried out since 1946 (Schwalbach & de la Maza 1985). Southern Mozambique has also benefited from recent

vector control efforts by IRS (Sharp *et al*. 2001).

Recently collated parasite prevalence database show that parasite rates in the countries under review have been kept at relatively low levels between the 1960 and 1980 (MARA/ARMA, unpublished). Although this success was largely shaped by the quality and extent of IRS programmes, it was also strengthened by the development of good public health infrastructure coupled with effective malaria surveillance activities and improved socio-economic conditions. In addition, South Africa has also developed detailed maps of malaria risk areas to allow authorities to focus their spraying activities, thus facilitating cost-effective control (Sharp and le Sueur 1996; Booman *et al*. 2000; Martin *et al*. 2002).

However, since the mid 1980s these gains were being gradually eroded with malaria epidemics becoming frequent and more severe. In 1996, the entire region experienced one of the most severe epidemics recorded in recent times (le Sueur *et al*. 1996). The recent trend in the reduction of the impact of IRS has been attributed to a number of factors and these include environmental, biological and social constraints. Increased risk has been partly attributed to weather disturbances linked to global climatic events such as El Nino (le Sueur *et al*. 1996). The appearance of *P. falciparum* resistance to chloroquine in the mid-1980s (Deacon *et al*. 1994) and Fansidar resistance in South Africa (Bredenkamp *et al*. 2001) has contributed to an increase in malaria cases as treatment failure increased the pool of malaria infections for the following transmission season. Detection of *A. funestus* resistance to pyrethroids in KwaZulu-Natal, South Africa

(Hargreaves *et al*. 2000) was a further reason for the reduced effectiveness of IRS. Behavioural avoidance of DDT sprayed surfaces by vectors due to its irritating effects also posed an effectiveness problem (Sharp *et al*. 1990). Social resistance to DDT application due to bed bug infestation, as they are resistant to DDT (Newberry and Jansen 1986) and replastering of sprayed walls due to the presence of DDT stains (Mnzava *et al*. 1998) reduced effective IRS coverage. Lack of proper supervision and /or skilled personnel is another mitigating factor because effective application of residual insecticides requires properly trained individuals. Population migration from uncontrolled areas also leads to the deterioration of malaria situation in neighbouring countries that have brought malaria under control (Delfini 1969; Sharp *et al*. 1988).

All these constraints coincide with the renewed interest in the control of malaria in sub Saharan Africa. It is essential therefore that effort be made to ensure that the effectiveness of IRS is not compromised, particularly in areas where it has been proven to work. Continued monitoring and evaluation of its impact is clearly of fundamental importance in this regard. For example, in South Africa this led to the detection of both insecticide and parasite resistance which led to policy change and improved effectiveness of control efforts. We also need to develop climate-based early warning systems to detect climate driven epidemics and improve the impact of control efforts. Inter-country networking and cooperation towards strengthening malaria control programmes across the region is also of vital importance.

Today, with the availability of equally effective alternative intervention such as Insecticide-Treated (mosquito) Nets (ITNs), choosing between IRS and ITNs is a matter of operational feasibility and availability of local resources (Lengeler & Sharp 2003). Appropriate application or integration of IRS with other interventions elsewhere on the continent has to be based on sound scientific research which takes into account the epidemiological setting, organizational capacity, social and financial considerations, as these in turn impact on operational feasibility and sustainability.

Conclusion

Evidence presented in this review confirms that malaria control by IRS has made epidemics less frequent and reduced malaria from hyper- to meso-endemicity and from meso- to hypo-endemicity at the southern fringe of transmission in tropical Africa. The development of large well-organized and well-funded control programmes in these areas led to selective and sustainable application of IRS over time.

Almost all the countries that successfully controlled malaria in southern Africa experienced an acceleration of economic growth immediately following the introduction of effective vector control measures with IRS. Countries that developed national malaria control programmes during this phase and had built up human and organizational resources made significant advances towards malaria control. In addition, most southern African countries developed stronger health systems.

However, with the recent trends in malaria increase and problems of drug and insecticide resistance there is a need to find ways to improve sustainability, both financially and technically, if IRS is to maintain its role as an effective measure against malaria transmission. Already effective supplementary interventions such as ITNs and new drug therapies (artermisinin-based combinations) are now available and the latter has been implemented to good effect in the republic of South Africa. Alternative vector control strategies such as rotational or mixed use of insecticides have also been proposed. South Africa has also recently secured funding to carry out research on feasibility and effect of these strategies. New technologies using GIS as a platform to plan, implement and assess control activities are now available to help rationalize malaria control in time and space and hence minimize cost. To date there is also a renewed interest and political commitment to controlling malaria in Africa through the Roll Back Malaria (RBM) partnership.

Indoor residual spraying is not a magic bullet, and its use in other areas should be planned carefully, after considering the major organizational, technical and financial implications. However, its track record in southern Africa and in many other areas of the world is outstanding and should certainly be considered when planning extended vector control activities in endemic areas.

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Chapter 3: El-Niño Southern Oscillation (ENSO) and annual malaria incidence in Southern Africa

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Abstract

We evaluated the association between annual malaria incidence and ENSO (El Niño Southern Oscillation) as measured by the Southern Oscillation Index (SOI) in five countries in Southern Africa from 1988 to1999. Below normal incidence of malaria synchronized with a negative SOI (El Niño) and above normal with a positive SOI (La Niña), which lead to dry and wet weather, conditions respectively. In most countries there was a positive relationship between SOI and annual malaria incidence, especially where *An. arabiensis* is a major vector. This mosquito breeds in temporary rain pools and is highly sensitive to fluctuations in weather conditions. South Africa and Swaziland have the most reliable data and showed the strongest associations, but the picture there may also be compounded by the moderating effect of other oscillatory systems in the Indian Ocean. The impact of ENSO also varies over time within countries, depending on existing malaria control efforts and response capacity. There remains a need for quantitative studies that at the same time consider both ENSO-driven climate anomalies and non-ENSO factors influencing epidemic risk potential to assess their relative importance in order to provide an empirical basis for malaria epidemic forecasting models.

Introduction

The El Niño Southern Oscillation phenomenon (ENSO) refers to the cyclic warming and cooling of the equatorial Pacific Ocean coupled with changes in the atmospheric pressure across the Pacific. This is the most important climatic cycle that contributes to worldwide interannual 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 regions of the globe and can result in drought in some areas and flooding in others (Nicholls 1993; Bouma *et al*. 1997a; Kovats 2000; Kovats *et al*. 2003).

There is strong evidence that ENSO is associated with heightened risk of malaria in regions of the world where climate is linked to the ENSO cycle (Kovats 2000; Kovats 2003). These include, among others, countries in South Asia and in Latin America (Bouma and van der Kaay 1994 and 1996; Bouma and Dye 1997; Bouma *et al*. 1997b; Poveda *et al*. 2001; Gagnon *et al*. 2002). In Africa, this is supported mostly by studies carried out in the east African highlands of Uganda (Kilian *et al*. 1999; Lindblade *et al*. 1999), Tanzania (Lindsay *et al*. 2000; Wort *et al*. 2004) and Rwanda (Loevinsohn 1994). ENSO also has a strong influence on inter-annual climate variability in Southern Africa (Nicholson 1993; Richard 2000 and 2001; Kovats 2000; Kovats *et al*. 2003) and is the main climatic phenomenon held responsible for some malaria epidemics in the region (Le Sueur *et al*. 1996a; SAMC 2003). However, quantitative analysis of the link between ENSO-related climate anomalies and malaria incidence is limited to a recent study in Botswana (Thomson *et al*. 2005).

In Southern Africa the challenge is that, owing to a long history of malaria control, baseline endemicity has been substantially reduced and in most places immunity is low (Mabaso *et al*. 2004). Under such conditions, seasonal transmission results in high morbidity and mortality if not prevented or contained (SAMC 2003). Consequently, disruption or failure of existing control activities induces epidemics (Mabaso *et al*. 2004; Craig *et al*., 2004a). Thus, climate is not the only factor that has an impact on the epidemic potential and the question is how sensitive malaria transmission is to the impact of ENSO and whether its effects can be separated from other factors influencing epidemic risk in the region. Inter-annual fluctuations in malaria are driven mainly by climate variability; the extent of these fluctuations is indicative of areas prone to epidemics (SAMC, 2003; Craig *et al*. 2004b; Thomson *et al*. 2005).

In this study, we evaluated the association between inter-annual variability in malaria incidence and ENSO from 1989 to 1999 in five countries across Southern Africa in order to determine its relative impact given the different malaria situations in the region.

Materials and methods

Study area

Countries included in the study were Botswana, South Africa, Swaziland, Zambia and Zimbabwe based on the availability of malaria data. In these countries there are many areas with intense seasonal transmission as well as epidemic-prone and malaria-free areas. In Southern Africa, the total population is approximately 145 million people of whom about 92 million live in malarious areas, with approximately 21million cases and 300 000 deaths reported annually (SAMC 2003). The risk of malaria varies considerably both spatially and temporally. Rainfall and temperature are the main limiting climatic factors for transmission of malaria in this region (Craig *et al*. 1999; SAMC 2003).

Data

Malaria

Annual national malaria case data from 1988-1999 and corresponding population estimates were obtained from health information systems and / or annual malaria reports. This period was chosen because of the relative completeness of data from all the selected countries. The data consist of confirmed (Botswana, South Africa and Swaziland) and unconfirmed (Zambia) clinical cases as well a combination of both (Zimbabwe).

ENSO

There is a varying list of indices that can be used to determine ENSO years. In this analysis we use annual averages of the Southern Oscillation Index (SOI) a measure based on the differences in the atmospheric pressure between Tahiti in the eastern equatorial

Pacific and Darwin in Australia (west Pacific), expressed as a standard deviation from the norm and available from the National Oceanic and Atmospheric Administration (NOAA) website (http://www.cdc.noaa.gov/ClimateIndices/List/). SOI is used to quantify the strength of an ENSO event and is negative during El Niño (a warm event) and positive during La Niña (a cold event). In parts of Southern Africa, a strong El Niño event is usually followed by drought, and La Niña by flooding (Nicholls 1993; Richard 2000 and 2001; Kovats 2000; Kovats *et al*. 2003).

Analysis

To display the connection between annual averages of SOI and malaria incidence (per 1000 person-years) in the selected countries, annual standardized incidence anomalies (*SIA*) were calculated using the formula $SIA=(Y-\bar{Y})/\sigma$ where Y denotes the observed incidence in each year, $\bar{Y}$ the long term mean and σ the standard deviation of Y. Scatter plots were used to examine the nature of the relationship between annual averages of SOI and log-transformed annual malaria incidence in each country. A negative binomial regression model with year specific random-effect was used to assess the association between SOI and annual malaria incidence. This model adjusts for overdispersion that may be present in the count data (malaria case data) and used random effects as surrogates for unmeasured factors influencing annual incidence. The analysis was performed in STATA version 9 (Stata Corporation, College Station, TX, USA).

Results

Below normal annual incidence rates synchronized with negative SOI values (El Niño) i.e. dry conditions and above normal incidence with positive SOI values (La Niña) i.e. wet conditions (Figure 3.1.). During the study period the SOI varied from -2.02 to 1.22 with mean = -0.54 and standard deviation = 1.28. Table 3.1. gives summary statistics of malaria incidence for the selected countries.

The SOI showed a positive relationship with annual malaria incidence in Botswana, South Africa, Swaziland and Zimbabwe, but not in Zambia. The negative binomial model (Table 3.2.) confirmed that SOI increases annual malaria incidence in most of the selected countries (suggesting an association with positive SOI values or La Niña) although by a small amount in Zimbabwe, and reduces incidence in Zambia although very slightly. However, these associations were statistically significant only in South Africa and Swaziland.

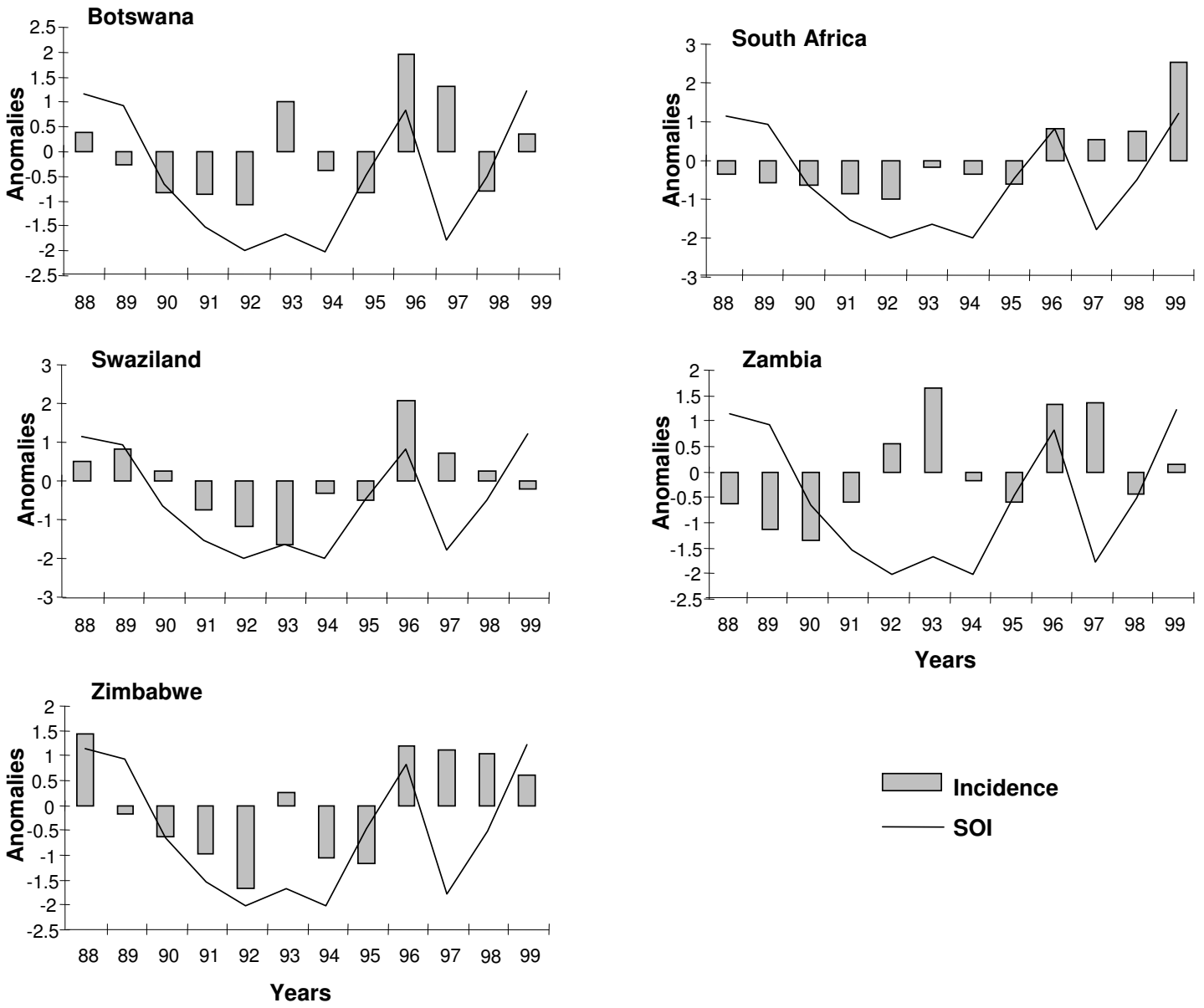

Figure 3.1. Standardised annual malaria incidence and Southern Oscillation Index (SOI) anomalies from selected countries in Southern Africa by year between 1988 and 1999.

Table 3.1. Estimated population in malarious areas, mean incidence (cases per 1000 person years) and standard deviation (SD) in selected countries in Southern Africa from 1988 to 1999.

Country	Population	Mean incidence	SD	Minimum	Maximum
Botswana	620400	5.585	4.906	0.306	15.274
South Africa	4429500	0.363	0.307	0.060	1.139
Swaziland	279300	6.295	3.370	0.716	13.318
Zambia	8690000	323.608	56.248	247.300	415.500
Zimbabwe	5962000	10.721	3.636	5.132	15.527

Table 3.2. Changes in annual malaria incidence (cases per 1000 person years) associated with one unit increase in the Southern Oscillation Index (SOI) in selected countries in Southern Africa.

Country	IRR	95% CI	P-value
Botswana	1.548	0.720, 3.330	0.263
South Africa	1.351	0.976, 1.870	0.070
Swaziland	1.283	0.991, 1.660	0.058
Zambia	0.968	0.895, 1.046	0.409
Zimbabwe	1.073	0.902, 1.276	0.426

IRR, incidence rate ratio; CI, confidence interval estimated from negative binomial model estimated using maximum likelihood.

Discussion

The study period featured a very active ENSO cycle (Kovats 2000; Kovats *et al*. 2003) and therefore offered an ideal opportunity for the evaluation of the relative impact of this phenomenon on malaria incidence in the region. This includes the two major El Niño episodes recorded in 1991 to 1994 and 1997 to 1998 and two La Niña episodes in 1995 to 1996 and 1999. In general, malaria incidence anomalies appeared to be synchronized both with El Niño and La Niña events as described by SOI (Figure 3.1.). Basically,

ENSO events cause rainfall patterns to change and this usually affects mosquito breeding which, in turn, is associated with variation in malaria transmission. However, the impact on malaria incidence may be complicated by non-ENSO factors such as insecticide and drug resistance or failure of malaria control programmes. Hence we used year specific random effects as surrogates for unmeasured factors influencing annual incidence.

In east Africa, ENSO events and in particular El Niño has been linked to changes in optimum climatic condition (i.e. lead to above normal temperature and / or rainfall) and associated increase in epidemic risk (Loevinsohn 1994; Kilian *et al*. 1999; Lindblade *et al*.1999; Lindsay *et al*. 2000; Wort *et al*. 2004). In agreement with others (Nicholls 1993; Kovats 2000; Kovats *et al*. 2003) we found that in most of Southern Africa, ENSO as measured by SOI has the opposite effect during El Niño (dry) conditions and that heightened incidence coincides with La Niña (wet) conditions. A recent study in Botswana (Thomson *et al*. 2005; Thomson *et al*. 2006) demonstrated the predictive value of the association between sea surface temperature (SST), another ENSO index, and rainfall after removing the impact of non-climatic trends and a major policy intervention.

In most of the region, the positive relationship between SOI and annual malaria incidence probably reflects the effect of ENSO on the mosquito vector *Anopheles arabiensis* which breeds in temporary rain pools and is therefore highly sensitive to fluctuations in weather conditions. In Zambia, the lack of an apparent association of SOI with malaria incidence may be due to the lack of effective malaria control and therefore the presence of *Anopheles funestus*. This vector breeds in permanent swamps and streams which are less

dependent on rainfall and therefore less affected by ENSO events. Historical records show that *An. funestus* was responsible for most of the malaria transmission in southern Africa before the advent of DDT (Leeson 1931; De Meillon 1947), resulting in endemic malaria transmission even through the dry winter months. Where effective vector control by IRS with DDT was implemented, *An. funestus* disappeared and *An. arabiensis* took over (Mabaso *et al*. 2005), maintaining levels of transmission that are highly susceptible to rainfall fluctuations. A further reason why malaria cases in Zambia do not appear to correlate with ENSO may be poorer data quality owing to routine inclusion of unconfirmed cases in the official statistics, and this is not accounted for in our models.

South Africa and her closest neighbour Swaziland have the most reliable data and showed the strongest associations of epidemics with ENSO, but the picture there may also be compounded by 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 (i.e. cause rainfall during El Niño) (Richard 2000 and 2001).

There were inconsistencies in the association between ENSO and malaria incidence in Botswana and Zambia in 1993 and in all the countries in 1997, possibly reflecting heterogeneity in the climatic effects of ENSO (Lindsay 2000; Kovats 2000). The impact also varies over time within countries, depending on existing malaria control efforts and response capacity (Gagnon *et al*. 2002; Worrall *et al*. 2004). For example, the 1995 to 1996 epidemic subsided in most countries following the 1997 to 1998 El Niño episode, except in South Africa and Zimbabwe (Figure 1). In South Africa the persistence of the

epidemic was due to problems of insecticide and drug resistance (Hargreaves *et al*. 2000; Bredenkamp *et al*. 2001) and the severity of the epidemics was exacerbated when coupled with the La Niña in 1999. In Zimbabwe socio-economic problems were also beginning to compromise the malaria control programme (DaSilva *et al*. 2004; Kiszewski and Teklehaimanot 2004).

ENSO-induced epidemics are responsive to control where effective antimalarial measures exist, but often not before causing considerable suffering and death (Kiszewski and Teklehaimanot 2004; Worrall *et al*. 2004), and understanding the connection between ENSO related climate anomalies and malaria is important for developing forecasting models to make it possible to plan for this. However, ENSO based climate forecasting models still have to rely on case surveillance for early detection of higher than normal malaria incidence. This surveillance is also influenced by non ENSO factors that should not be dismissed as random error or ignored. There is thus a need for quantitative studies that at the same time consider both ENSO-driven climate anomalies and non ENSO factors influencing epidemic risk potential.

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Chapter 4: Spatio-temporal analysis of the role of climate in inter-annual variation of malaria incidence in Zimbabwe

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Abstract

Background

On the fringes of endemic zones climate is a major determinant of inter-annual variation in malaria incidence. Quantitative description of the space-time effect of this association has practical implications for the development of operational malaria early warning system (MEWS) and malaria control. We used Bayesian negative binomial models for spatio-temporal analysis of the relationship between annual malaria incidence and selected climatic covariates at a district level in Zimbabwe from 1988-1999.

Results

Considerable inter-annual variations were observed in the timing and intensity of malaria incidence. Annual mean values of average temperature, rainfall and vapour pressure were strong positive predictors of increased annual incidence whereas maximum and minimum temperatures had the opposite effects. Our modelling approach adjusted for unmeasured space-time varying risk factors and showed that while year to year variation in malaria incidence is driven mainly by climate the resultant spatial risk pattern may to large extent be influenced by other risk factors except during high and low risk years following the occurrence of extremely wet and dry conditions, respectively.

Conclusion

Our model revealed a spatially varying risk pattern that is not attributable only to climate. We postulate that only years characterized by extreme climatic conditions may be important for developing climate based MEWS and for delineating areas prone to climate driven epidemics. However, the predictive value of climatic risk factors identified in this study still needs to be evaluated.

Background

The risk of malaria infection varies widely according geographic region, season and year (Baird *et al*. 2002; Thomson *et al*. 2003). On the fringes of endemic zones, particularly at the southernmost latitudes in southern Africa, across arid regions of northern Africa and among the highlands of east and central horn of Africa climate is a major determinant of seasonal and inter-annual (year to year) variation in malaria transmission (WHO 2003).

In Southern Africa annual variation in climatic conditions and associated changes in malaria infection affect the timing and intensity of malaria incidence. This has an impact on the effectiveness of interventions (Da Silva *et al*. 2004). As a result there is a need for the development of climate-based malaria early warning systems (MEWS) capable of predicting seasonal to inter-annual variations with a lead time that allows health authorities to respond in a timely manner with preparatory / preventative measures (le Sueur *et al*. 1996a and b). However, despite the fact that climate data are often used to account for spatial, seasonal and inter-annual variation in malaria risk in Africa, there is often little or no consensus about the relative importance and predictive value of different factors involved (Teklehaimanot *et al*. 2004). The disagreements seem to stem from differences in perspective and methods used (Bouma 2003).

In Southern Africa, few studies or models of the relationship between malaria and climatic factors have been published. In a recent meeting of the Southern African Inter-Country Programme on Malaria Control (SAMC) a number of countries acknowledged having poor empirical basis on which to develop and test climate-based early warning

and detection indicators (Da Silva *et al*. 2004). Existing models include a non-spatial model for Zimbabwe which identified temperature as the main determinant of increased malaria risk years (Freeman 1996). Spatial and temporal models which used both temperature and rainfall for analysis and mapping of malaria risk in KwaZulu-Natal, South Africa (Kleinschmidt *et al*. 2001b; Kleinschmidt *et al*. 2002). An exploratory analysis of 30 years worth of data in the epidemic prone area of KwaZulu-Natal, South Africa, which showed that certain aspects of climate appear to drive inter-annual variation of malaria incidence but not its overall level (Craig *et al*. 2004a). In a recent study Thomson *et al*. (2005) showed that rainfall and sea surface temperature (SST) has a potential for application in the development of seasonal forecasts. We also recently developed a space-time seasonality model based on the relationship between monthly clinical malaria case data and environmental factors in Zimbabwe (Mabaso *et al*. 2005).

Year to year predictability of malaria incidence still remains a challenge, and more work is required before malaria climate based forecasting models can realize their full potential in the region. In this study we use Bayesian spatio-temporal analysis to describe year to year variation of malaria incidence data from Zimbabwe in relation to variation in climatic risk factors to enhance our ability of developing an operational MEWS and determine areas prone to climate-driven epidemics.

Methods

Setting

In common with Angola, Namibia, Botswana, Zambia, Mozambique and South Africa Zimbabwe lies at the southern limits of malaria distribution in Africa. Malaria remains a major cause of mortality and morbidity despite more than four decades of sustained national control programme (Makono and Sibanda). Moreover, as a result of reduced level of transmission there is propensity for malaria epidemics unless adequately controlled or prevented. Overall, about 45-50 % of the 12.5 million people of Zimbabwe are at risk of malaria. In 1998, it was estimated that approximately 8 % of all deaths and 12 % of all outpatient cases were due to malaria (http://www.malaria.org/zw/countries/zimbabwe.htm). Recently, substantial socio-economic changes have further compromised the malaria control programme (Da Silva *et al*. 2004).

Climate is another major factor that determines the extent of malaria transmission in Zimbabwe, and its variability may work with or against efforts to bring malaria under control (Hartman et *al*. 2002). The most important factors governing malaria epidemiology in the country are season, altitude, and associated rainfall and temperature changes (Taylor 1985; Taylor and Mutambu 1986; Hartman *et al*. 2002; Mabaso *et al*. 2005). Malaria is found mainly within the low and mid altitude zones and rarely at higher altitude. However, this can vary tremendously from one year to another.

Covariate data

We used normalized difference vegetation index (NDVI) available between 1988 and 1999 from Advanced Very High Resolution Radiometer (AVHRR) sensor onboard the National Oceanic and Atmospheric Administration (NOAA) satellite (http://daac.gsfc.nasa.gov/data/dataset/AVHRR/index.html). We also used mean annual values of rainfall, vapour pressure, minimum, maximum and mean temperature obtained for each district and year for the 12 year period. These were obtained from the climate research unit (CRU) climate surfaces derived from interpolated weather station data as a function of latitude, longitude, and elevation using thin-plate splines (Mitchel 2005).

Malaria data

In Zimbabwe malaria is a notifiable disease and records from hospitals and clinics are compiled at a district, provincial and national levels to describe the malaria situation and trends. We used annual clinical malaria case data for children under the age of five reported in 58 districts covering the whole country between 1988 and 1999 (Ministry of Health and Child Walfare 2000). This is the highest risk group, with relatively little protective immunity and is therefore expected to be more sensitive to changes in malaria transmission. The data included both microscopically confirmed and unconfirmed clinically diagnosed cases. District population projections based on the 1982 and 1992 census were used to calculate incidence rate per 1000 person years (Central Statistics Office 2002).

Analysis

We used the annual proportion of monthly malaria cases and Markham's seasonality index (Markham 1970; McGee 1977) to display between-year variation in the data. The seasonality index has been described in detail elsewhere (Mabaso *et al*. 2005). Briefly, this method calculates the seasonal concentration of the malaria case load and the peak month in a given year.

A preliminary negative binomial regression analysis was carried out in STATA 9.0 (Stata Corp., College Station, TX, USA) to assess the relationship between annual malaria incidence and annual values of each climatic covariate. Thereafter, Bayesian negative binomial models were fitted in WinBUGS (WinBugs 2000) to examine the association between inter-annual variation in malaria incidence and a combination of climatic covariates selected from the preliminary analysis (see the appendix for more details). Basically, spatial random effects were used at a district level to take into account spatial correlation present in the data. Temporal random effects were also used at yearly intervals to account for temporal correlation. Spatial correlation was incorporated by assuming a conditional autoregressive (CAR) process in the random effects. A first order autoregressive process was applied for temporal random effects (Bernardinelli *et al*. 1995).

Markov Chain Monte Carlo simulation (MCMC) was applied to estimate model parameters (Gelfand and Smith 1990). After the initial burn-in of 5000 the number of iterations thereafter depended on convergence which was assessed using ergodic

averages. After convergence a final sample of 5000 was collected to obtain summaries of the posterior distribution of the parameters. The Deviance Information Criterion (DIC) (Spiegelhalter *et al*. 2002) was used for the comparison of model fit. Small values of DIC indicate superior model fit. Model estimates were exponentiated to represent incidence rate ratios (IRR), that is, per unit change in incidence for each covariate.

Results

Figure 4.1.A-D shows that malaria transmission in Zimbabwe is characterized by considerable between and within year variations. The highest malaria incidence recorded during the 12 year period was in 1988 with 15.5 cases per 1000 person years and the lowest was in 1992 with 5.2 cases per 1000 person years (Figure 4.1.A). In addition since 1996, there is a rising trend in annual incidence with reported malaria cases remaining at high levels. The intensity and timing of the seasonal peak also varies from year to year (Figure 4.1.B and C). From 1988 to 1999 the peak month fluctuated between March and April with the exception of 1992 and 1995 which were characterized by peaks in January and May respectively.

High annual malaria incidence coincide with high rainfall and relatively warm conditions while low incidence years coincide only with low rainfall (Figure 4.2.). Vapour pressure and NDVI follow the rainfall pattern. Temperature derived covariates seem to be important only in the presence of sufficient rainfall. The intensity and timing of the seasonal peak in each year appears to follow variability in rainfall.

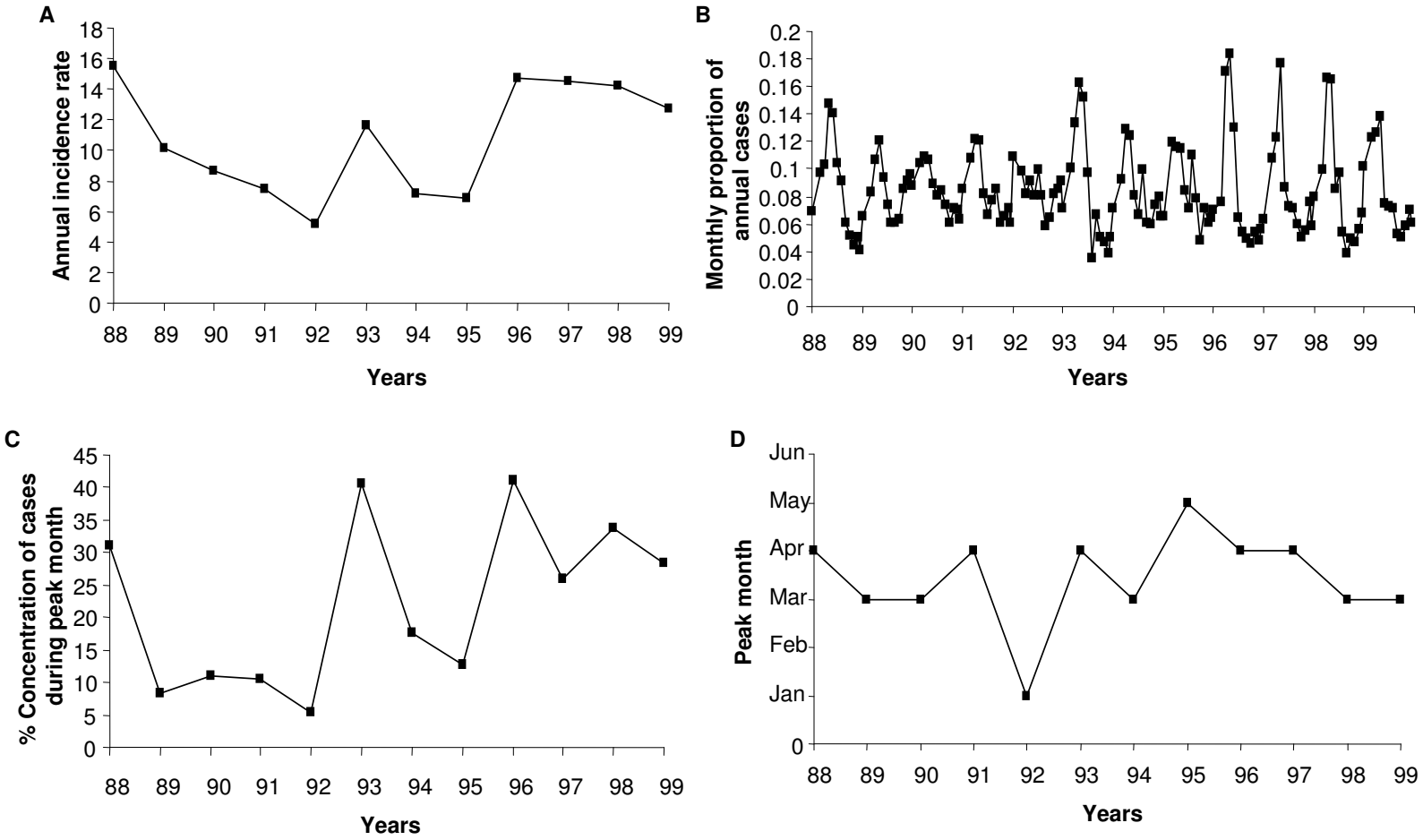

Figure 4.1. (A) Annual malaria incidence rate (cases per 1000 person years) (B) proportion of annual monthly cases (C) percentage concentration of malaria case load during the peak transmission month and (D) peak month during the malaria transmission season in Zimbabwe from 1988-1999.

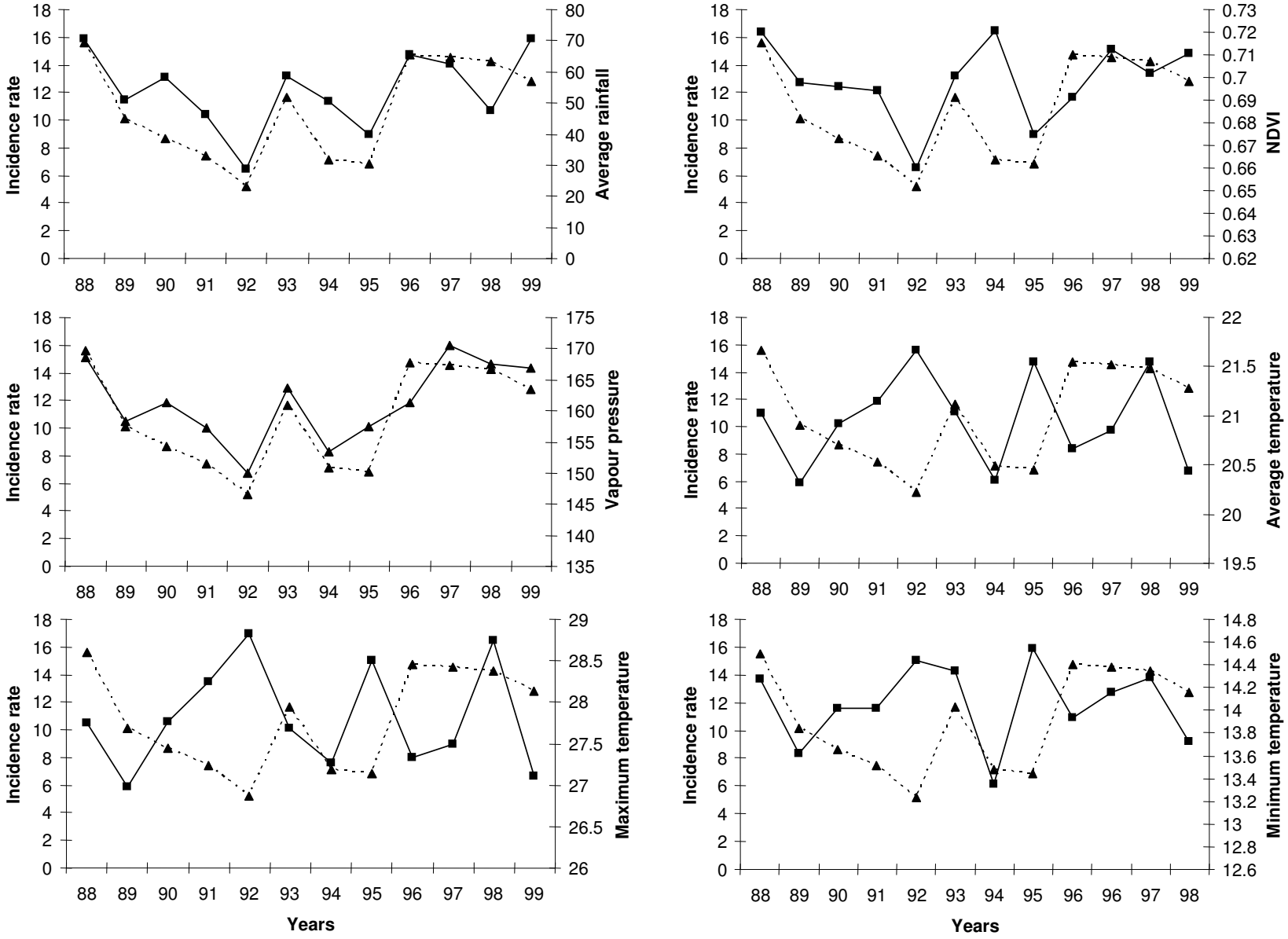

Figure 4.2. Inter-annual variations in malaria incidence rate (cases per 1000 person years), rainfall (mm), vapour pressure (hPa), NDVI (Normalized Difference Vegetation Index), average, maximum and minimum temperatures (°C) in Zimbabwe between 1988 and 1999.

In the bivariate analysis all selected covariates showed a significant relationship ($P < 0.001$) with malaria incidence (Table 4.1.). All models (Table 4.2.) indicated that mean annual temperature, rainfall, vapour pressure and NDVI were strong positive predictors of increased annual incidence rate in contrast maximum and minimum temperature had a reducing effect. However, in the spatial model (model 2) rainfall had no significant effect and in the spatio-temporal model (Model 3) only NDVI was not significant. Model comparison showed that the spatial-temporal model had a small DIC value and therefore was the best fitting model. This model had large spatially correlated random effects.

Table 4.1. Bivariate analysis of the relationship between annual malaria incidence and climatic covariates fitted using negative binomial regression.

Covariates	**Coefficients**	**SE**	**95% CI**	**P-value**
Mean temperature (°C)	0.295	0.024	0.248, 0.341	< 0.001
Maximum temperature (°C)	0.149	0.021	0.107, 0.189	< 0.001
Minimum temperature (°C)	0.439	0.024	0.391, 0.487	< 0.001
Vapour pressure (hPa)	0.046	0.003	0.040, 0.051	< 0.001
NDVI	0.654	0.127	0.405, 0.903	< 0.001
Rainfall (mm)	0.021	0.002	0.016, 0.026	< 0.001

SE – standard error; CI – confidence intervals; NDVI – normalized difference vegetation index

Figure 4.3. show differences in the spatial pattern of modelled malaria incidence during the 12 year study period. In 1988, 1993 and 1996 onwards high to moderate incidence rates were more widespread with the highest incidence rates in the north western and eastern part of the country. In 1992 and 1995 incidence rates were predominantly

moderate to very low levels across the country with pockets of high incidence rates in the districts

Table 4.2. Modelled estimates of the effects of climatic covariates on malaria incidence in the districts of Zimbabwe, including spatial and temporal variance. The smaller value of DIC indicates a better fitting model.

Covariates	**Non spatial Model**	**Spatial Model**	**Spatial-temporal model**
	IRR (95 % CI)	IRR (95 % CI)	IRR (95 % CI)
Mean temperature (°C)	5.332 (4.700, 5.885)	6.533 (4.251, 8.812)	7.634 (6.890, 8.349)
Maximum temperature (°C)	0.440 (0.414, 0.485)	0.363 (0.306, 0.446)	0.291 (0.272, 0.322)
Minimum temperature (°C)	0.700 (0.657, 0.752)	0.479 (0.357, 0.623)	0.500 (0.412, 0.581)
Vapour pressure (hPa)	1.003 (0.998, 1.008)	1.036 (1.020, 1.050)	1.018 (1.005, 1.028)
NDVI	2.700 (2.267, 3.132)	1.478 (1.011, 2.256)	1.375 (0.913, 1.701)
Rainfall (mm)	1.017 (1.012, 1.021)	1.005 (0.999, 1.011)	1.006 (1.000, 1.012)
Spatial variation (σ_{ϕ}^2)		1.346 (1.078, 1.673)	18.620 (15.280, 22.710)
Temporal variation (σ_{ω}^2)			0.004 (0.001, 0.010)
DIC	8414.270	8113.280	7912.610

NDVI – normalized difference vegetation index; DIC – deviance information criterion; IRR – incidence rate ratio; CI – credible intervals

situated along of the Zambezi river system in the north western part and on the border with Mozambique in the eastern part as well as along the Limpopo river system in the south eastern part.

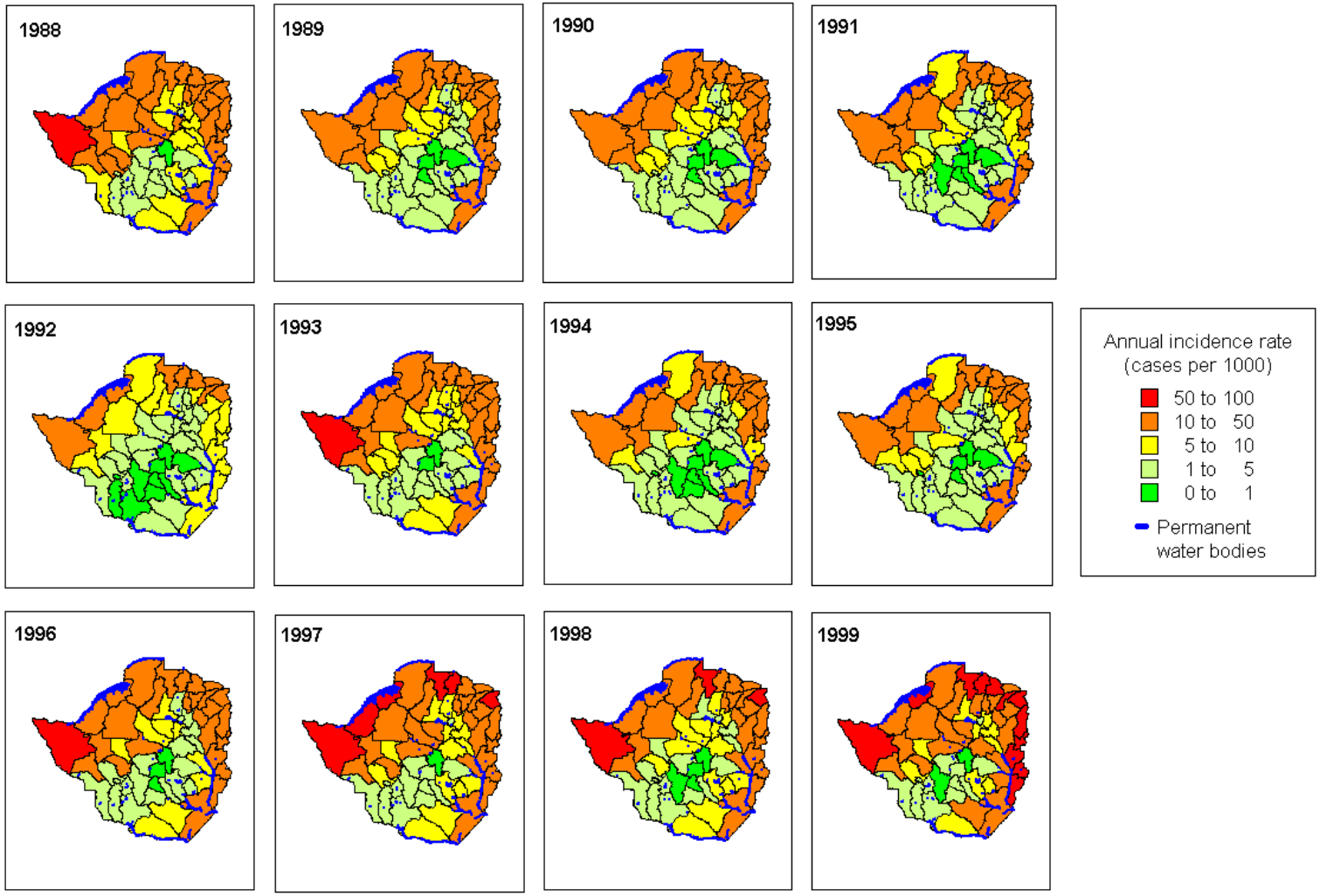

Figure 4.3 Geographic distribution of smoothed malaria incidence (cases per 1000 person years) by year between 1988 and 1999 in Zimbabwe from a spatial-temporal model.

Discussion

Our observations confirm that malaria transmission in Zimbabwe is characterized by substantial inter-annual variation. Incidence rates show a rising, albeit fluctuating, trend with reported cases remaining relatively high after 1996 (Figure 4.1.). The intensity and timing of seasonal transmission also varies from year to year. The highest and lowest risk years were recorded during one of the most wet and severe drought periods in Zimbabwe, respectively (Kovats 2000). From a regional perspective 1988, 1993, 1996 and 1997 were the most serious epidemic years.

Besides the limitation imposed by the effect of misdiagnosis as a consequence of unconfirmed clinically diagnosed cases, which would probably be to smooth over differences since this is not influenced by covariates. There are multiple explanations for the observed trend and it is difficult to identify true causes (Bouma *et al*. 2003). In general, there is more support for non-climatic explanations of recent trends especially in the fringe areas of endemic zones in Africa. These include deterioration of malaria control efforts, development of drug and insecticide resistance and a rise in co-infection with HIV/AIDS (Hay *et al*. 2002a and b; Bouma *et al*. 2003; Craig *et al*. 2004b). In Zimbabwe, none of these have been adequately quantified for inclusion into the modelling framework. Hence our modelling approach adjusts for unmeasured spatially and temporally structured sources of variation while investigating the association between annual malaria incidence and climatic covariates. However, the large residual spatial variation observed in the spatial-temporal model suggests that there are other important covariates not accounted for in the analysis that could explain most of the

spatial variation in malaria incidence. Most of the temporal variation in the data appears to be explained by the selected covariates.

Our results showed that annual mean values of temperature, rainfall and vapour pressure are strong positive predictors of increased annual malaria incidence. Annual minimum and maximum temperature had the opposite effects probably due to fact that in an average annual cycle these climatic covariates are associated with the cold dry period (June-August) and hot dry period (August to October), respectively, both of which have low transmission (Mabaso *et al*. 2005). The association between vapour pressure (a measure of humidity) and annual incidence reflect the importance of the interaction between rainfall and temperature which modulates the ambient air humidity which in turn affect the survival and activity of *Anopheles* mosquitoes (Bruce-Chwatt 1980; Molineaux 1888).

Furthermore, the spatio-temporal model (Table 4.2.) showed that while NDVI, a surrogate for the response of vegetation to rainfall, appears to have a positive effect, it had no statistically significant association with annual malaria incidence. This may be due to the fact that vegetation greenness is to a large extent dependant on the amount of rainfall available in a given year (Reid 1957; Ramasdale 1965). Moreover, total annual rainfall in Zimbabwe is characterized by strong variability (Hartman *et al*. 2002). Hence, rainfall is a stronger predictor of malaria incidence at an inter-annual time scale.

The modelled spatial pattern showed that areas in the low lying north-western and south-eastern part of the country have high but less variable incidence, whereas areas of lower incidence in the middle to highland areas showed greater year to year variability. Eco-epidemiological conditions in these areas determine the stability of between year variation in malaria transmission (Reid 1957; Hartman *et al*. 2002; Craig et al. 1999). Our analysis therefore confirms that year to year variation in malaria incidence in Zimbabwe is driven mainly by climatic covariates, and further demonstrates that resultant incidence in a given area may also be a function of other unmeasured risk factors. The spatial effect of climatic conditions during the study period appears to be more evident only during the much reported drought years from 1990-1992 and following heavy rainfall in 1998 (Kovats 2000).

In our previous analysis optimum ranges of climatic risk factors identified in the present study were also significantly associated with malaria transmission at a seasonal time scale (Mabaso *et al*. 2005). It is likely therefore that increase in mean annual temperature, rainfall and humidity is linked to within year changes in average climatic conditions and in turn lead to changes in the full annual cycle of malaria transmission. The magnitude of which probably varies from one year another. For example, Freeman and Bradley (1996) found that higher than average annual mean monthly temperatures during the critical period of malaria transmission (April and September) in the previous year were associated with an increase in the severity of malaria in the following year in some areas. This becomes more pronounced and widespread if both extremes of warm and wet conditions coincide and vice versa as observed during high and low incidence years

(Figure 4.2. and 4.3.). We deduce therefore that extreme climatic events associated with covariates identified in this study may be useful for developing climate based malaria forecasting models operational at both seasonal and inter-annual time scales.

In conclusion, our modelling approach adjusted for unobserved spatial and temporal varying risk factors, and showed that while inter-annual variation in malaria incidence is driven mainly by climatic conditions, the resultant spatially varying risk pattern may also be influenced by other risk factors. Nevertheless, high and low incidence years following the occurrence of extreme climatic conditions may be useful for developing climate based MEWS and for delineating areas prone to climate driven epidemics. However, the predictive value of climatic risk factors identified in this study still needs to be evaluated.

Acknowledgements

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Chapter 5: Towards empirical description of malaria seasonality in southern Africa: the example of Zimbabwe

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Abstract

Quantitative description and mapping of malaria seasonality is important for timely spatial targeting of interventions and for modelling malaria risk. We use Zimbabwe as an example for developing an empirical map of malaria seasonality. We describe the relationship between seasonality in malaria and environmental covariates for the period 1988-1999, by fitting a spatial-temporal regression model within a Bayesian framework to provide smoothed maps of the seasonal trend. We adapt a seasonality concentration index used previously for rainfall to quantify malaria case load during the peak transmission season based on monthly values. Combinations of mean monthly temperature (range 28-32 °C), maximum temperature (24-28 °C) and high rainfall provide suitable conditions for seasonal transmission. High monthly maximum and mean monthly minimum temperatures limit months of high transmission. The intensity of seasonal transmission was highest in the north western part of the country from February-May with the peak in April and lowest in the whole country from July-December. The north western lowlands had the highest concentration of malaria cases (> 25 %) followed by some districts in the north central and eastern part with a moderate concentration of cases (20-25 %). The central highlands and south eastern part of the country had the lowest concentration of malaria cases (< 20 %). This pattern was closely associated to the geographic variation in the seasonality of climatic covariates particularly rainfall and temperature. Our modelling approach quantifies the geographical variation in seasonal trend and the concentration of cases during the peak transmission season and therefore has potential application in malaria control. The use of a covariate adjusted empirical model may prove useful for predicting the seasonal risk pattern across southern Africa.

Introduction

The diverse ecology of sub-Saharan Africa supports a wide range of malaria transmission conditions which vary in terms of their public health effects and necessary responses to control (Macdonald 1957). This is because of the complex interaction, between the malaria parasite, human host, *Anopheles* vector and environmental conditions which vary across different geographic regions in the continent. Understanding the malaria transmission pattern within each region is fundamental for the description of disease risk and control (Molineaux 1988; Bruce-Chwatt 1980). As such a number of different approaches have been used to try and reduce complex malaria situations to a manageable number of types and classes for the purpose of description, planning and development of appropriate control strategies (Mcdonald 1957; Metselaar & Van Theil 1959).

Recently, there has been a considerable interest in developing continental and regional malaria risk maps (Craig *et al*. 1999; Kleinschmidt *et al*. 2001a; Gemperli 2003). Seasonality in transmission is an important but neglected consideration in the mapping of malaria risk. Most malariometric surveys used are deliberately carried out during the peak transmission season, and this introduces a bias in the maps unless it is allowed for (Gemperli 2003). A map of malaria seasonality is also important for timely spatial targeting of interventions, for example, optimizing the timing and frequency of indoor residual spraying with insecticides and / or re-impregnation of insecticide treated bed nets. This is particularly true for regions which experience variation in infection risk due to periodic onset of suitable environmental conditions in a given year. This variation in transmission is reflected in the seasonal fluctuation of vector densities, entomological

inoculation rate and malaria cases (Afari *et al*. 1993; Fontenille *et al*. 1997; Hamad *et al*. 2002; Shililu *et al*. 2003). The challenge is how to translate this variation in the transmission pattern to a quantitative description of malaria seasonality in a given area.

Seasonality in malaria has been described in terms of the timing and length of the transmission period depending on the presence of the period with or without transmission. For example, Tanser *et al*. (2003) used a climate suitability model to describe the duration, start and end of the malaria season based on classifying months dichotomously (i.e. yes or no transmission) according to their suitability of the climate for transmission. Some empirical models also followed a similar approach using the relationship between malaria cases and environmental proxies to predict the number of months during which transmission is possible (Thomson *et al*. 1997; Hay *et al*. 1998a & b; Thomson *et al*. 1999). According to this perspective, malaria is strongly seasonal in areas experiencing transmission over a short period and less so in areas with potentially perennial transmission.

However, although some areas have very little seasonal variation in malaria transmission can be intense with strong seasonal variation, even in areas where it is perennial (Smith *et al*. 1993). Some areas where transmission is limited to a short season have very intense transmission during the peak season, for example in Gambia (Von Seidlein *et al*. 2002), while in other areas transmission is barely measurable even during the peak of the season, for example in eastern Sudan (Theander 1998). Hence the variation in intensity of transmission between months need not be closely linked to the duration of transmission.

Consequently, for the development of empirical maps of malaria seasonality it would be preferable to use seasonality models that predict quantitative variation in intensity of transmission between months, rather than simply classifying them into months of transmission or no transmission.

In this study we use Zimbabwe as an example of mapping malaria seasonality in southern Africa. Zimbabwe has a great variety of malaria transmission situations and fairly reliable recording of clinical malaria episodes at health facilities. It is therefore ideal for this analysis. We describe the relationship between seasonality in the incidence of clinical malaria and environmental factors in order to define spatial variation in seasonality, and to derive a measure of the intensity of seasonality of transmission based on the predicted relationship. A Bayesian analytical framework was employed to account for geographically varying unobserved risk factors and temporal variations (Clayton *et al*. 1993; Knorr-Held & Besag 1998; Lawson *et al*. 1999; Bailey 2001). This provides smooth maps, enabling us to interpret the geographical patterns in seasonality, and to consider the implications for malaria control and the extent to which our approach can be generalized to other areas of southern Africa.

Materials and methods

Study area

Zimbabwe is a landlocked country situated in the south central part of southern Africa approximately between 25°E to 33°E and 16°S to 22°S. Malaria transmission is characterized by regular seasonal fluctuations alternating irregularly with high incidence

periods (Mpofu 1985; Taylor 1985; Taylor & Mutambu 1986). It is estimated that over 5 million people out of a population of 13 million live in malarious areas (SAMC 2003). In 1999 over 740 000 clinical cases and 2 200 deaths from malaria were reported (Ministry of Health and Child Welfare 2000).

The intensity of transmission has been modified by a long history of malaria control. Consequently there is only a small proportion of the population with sufficient immunity to resist malaria infections without seeking treatment. Since the late 1940's Zimbabwe has actively controlled malaria mainly by indoor house spraying with the residual insecticide dichlorodiphenyltrichloroethane (DDT) supplemented by case treatment at all levels of health facility. Initially only low lying areas were sprayed with DDT to prevent the spread of malaria from low to high altitude areas. After independence in 1980 all rural areas, regardless of altitude were included in the spraying programme and in 1988 DDT was replaced by pyrethroids (Taylor 1985; Taylor & Mutambu 1986; Siziya *et al*. 1997; Mabaso *et al*. 2004).

Despite these measures, estimated to cost the country US$ 1 million in 1999 (Lukwa *et al*. 1999), malaria is still a major public health problem in the country. With such a high expenditure on malaria control combined with dwindling resources and a persistently high incidence of clinical malaria there is clearly a need for timely spatial targeting of interventions to improve cost effectiveness.

Data

We used monthly malaria case data collated at a district level by the National Malaria Control Programme (NMCP) between 1988 and 1999 (Ministry of Health and Child Welfare 2000). Only malaria data for the highest risk group i.e. children less than five years old was used in the analysis. The data included both microscopically confirmed and unconfirmed cases symptomatically diagnosed as malaria by trained health workers. Despite this limitation the data give a clear indication of the relative incidence, seasonality and geographical variation of malaria in the country (Mpofu 1985; Taylor & Mutambu 1986). We computed incidence per capita in order to delineate areas of high and low risk in relation to intensity of seasonality using district population projections from the 1982 and 1992 censuses (Central Statistics Office 2002).

Environmental covariates used were mean monthly values of rainfall, vapour pressure, temperature as well as maximum and minimum temperature sourced from the Climate Research Unit (CRU) interpolated climate surfaces with a 0,5 x 0,5° grid resolution about 55 x 55km at the equator (Mitchell et al. 2003). Including, monthly normalized difference vegetation index (NDVI) at 8 x 8 km resolution from Advanced Very High Resolution Radiometer (AVHRR) sensor onboard the National Oceanic and Atmospheric Administration (NOAA) satellite (http://daac.gsfc.nasa.gov/data/dataset/AVHRR/index.html). To account for the time period between the onset of suitable conditions and disease onset which is later, environmental data was lagged two months before disease data based on studies by (Taylor 1985; Taylor & Mutambu 1986). Climate grid cells were calibrated using the

raster GIS software package Idrisi® (http://www.clarklabs.org/) to extract average pixel values of the environmental variables for each district.

Statistical analysis

A Poisson model was fitted in STATA (StataCorp, USA) version 8.0 to analyse the relationship between environmental factors and the number of incident cases (I_{kjt}) in each district (k), year (j) and month (t). All covariates showed significant associations with malaria cases ($p < 0.001$) and were included in the spatial-temporal analysis. Mean temperature and mean maximum temperature showed non-linear relationships with log (I_{kjt}) and were therefore converted to categorical variables for further analysis.

A number of spatial and spatio-temporal models were fitted in WinBUGS (WinBUGS 2000) using the Bayesian approach. Spatial and temporal correlation was taken into account by introducing district and month specific random effects. The full spatio-temporal model assumed that the observed counts of cases I_{kjt} for the k^{th} district (k = 1…58) in the t^{th} month in year j (1988-1999) follow a Poisson distribution with mean (μ_{kjt}), that is,

$$\log(\mu_{kjt}) = \log N_{kj} + \alpha + \boldsymbol{X}^{t}_{kjt}\boldsymbol{\beta} + \phi_k + \omega_{kt}$$

where N_{kj} is the annual total number of cases in district k and year j, α is a measure of the overall incidence, $\boldsymbol{\beta}$ is the vector of regression coefficients, $\boldsymbol{X}_{kjt}$ is the vector of environmental covariates for district k, year j and month t, ϕ_k is the spatial random effect

for district *k* and ω_{kt} is the temporal random effect for month *t* within district *k.* We used a conditional autoregressive (CAR) process to model the spatial correlation in the district specific random effects assuming that each ϕ_k conditional on the neighbouring ϕ_l has a normal distribution with mean the average of ϕ_l and variance inversely proportional to the number of neighbours n_k, that is,

$$\phi_k \mid \phi_l, l \text{ neighbouring of k} \sim \text{Normal}\left(\gamma \sum_{k \neq l} \phi_l / n_k, \sigma_\phi^2 / n_k\right)$$

where γ is a parameter that quantifies the amount of spatial correlation present in the data and σ_ϕ^2 measures the spatial variance. Two CAR models were applied: the CAR(1) which assumed maximum spatial correlation (γ=1) and the CAR(γ) which parameterizes the amount of spatial correlation present in the data. The Deviance Information Criterion (DIC) (Spiegelhalter *et al*. 2002) was applied to select the best fitting model. This is the expected deviance minus the deviance of the posterior expectation of the parameters. It summarizes model fit and complexity defined by the effective number of model parameters. The DIC showed that CAR(1) was more appropriate as indicated in Table 5.1. This model was used in subsequent analyses. An AR (1) process with temporal variance σ_ω^2 was used to model the spatio-temporal interaction parameters ω_{kt} which allow for correlation between consecutive months within district *k* (i.e. assuming that cases at month *t* are influenced by cases in the previous month). We

specified inverse gamma hyper prior distributions for the variance parameters of the spatial and temporal random effects and uniform priors for the regression coefficients as well as the γ parameter (Gelfand *et al*. 1997). Parameter estimation was obtained via Markov chain Monte Carlo simulation (MCMC) employing a single chain algorithm. We considered an initial burn-in of 5000 iterations. Convergence was assessed by plots of ergodic averages of selected parameters of the model and obtained after 20 000 iterations. A further 10 000 iterations were run to avoid false interpretation of convergence to local modes. A final sample of 5000 was then collected to obtain posterior distributions of the parameters.

Table 5.1. Model comparisons using the deviance information criterion (DIC). Smaller values indicate a better fitting model.

MODELS	**TYPE**	**DIC**
(1) $\log(\mu_{kjt}) = \log N_{kj} + \alpha + \boldsymbol{X}^t_{kjt}\boldsymbol{\beta}$	Non spatial	930234
(2) $\log(\mu_{kjt}) = \log N_{kj} + \alpha + \boldsymbol{X}^t_{kjt}\boldsymbol{\beta} + \phi_k$	Spatial CAR(1)	915997
(3) $\log(\mu_{kjt}) = \log N_{kj} + \alpha + \boldsymbol{X}^t_{kjt}\boldsymbol{\beta} + \phi_k$	Spatial CAR(γ)	918118
(4) $\log(\mu_{kjt}) = \log N_{kj} + \alpha + \boldsymbol{X}^t_{kjt}\boldsymbol{\beta} + \phi_k + \omega_{kt}$	Spatial-temporal CAR(1)	759993

As an empirical indicator of the seasonal pattern of disease in district *k* and month *j* we used the proportion of total annual cases occurring in each month, P_{kj}, calculated as:

$\tilde{P}_{kj} = \frac{\sum_t I_{kt}}{\sum_{jt} I_{kjt}}$. We also calculated the smoothed model-based $\tilde{P}_{kj}$ values from the results of the spatio-temporal model.

Measure of seasonality

To derive summary measures of malaria seasonality for each district we applied Markham's concentration index, previously used to quantify seasonality in rainfall (Markham1970; McGee 1977). The method is based on vector representation of mean monthly totals, i.e the malaria incidence in month *t* is represented by a magnitude, $\overline{I}_{kt}$, (equal to the mean over all years of I_{kt}) and a direction, θ_t , corresponding to the month expressed in units of arc. Summation of the 12 monthly vectors gives a vector total $(r_k : \theta_k)$, that is,

$$r_k = \sqrt{(\sum_t \overline{I}_{kt} \sin\theta_t)^2 + (\sum_t \overline{I}_{kt} \cos\theta_t)^2} \text{ and } \theta_k = \tan^{-1} \frac{\sum_t \overline{I}_{kt} \sin\theta_t}{\sum_t \overline{I}_{kt} \cos\theta_t}$$

where r_k is the magnitude of the displacement from a situation of no seasonality, and θ_k is the month of the peak season. The seasonality concentration index, S_i, is given by: $S_i = r_k / \sum_t \overline{I}_{kt}$, usually expressed as a percentage. The index was applied to both smoothed (model based estimates) and raw proportions of cases.

An index of 100 % implies that malaria is concentrated in one month while an index of 0 % indicates a uniform distribution of malaria incidence throughout the year. For comparison between seasonality in malaria and environmental covariates the method was also applied to rainfall, vapour pressure and NDVI. For temperature, annual range (i.e. the difference between the monthly minimum and maximum temperature) was taken as the measure of seasonality.

Results

The broad geographical pattern of malaria risk across the country is shown in Figure 5.1. With the highest incidence from 15 to 46 cases per 1000 person years in the north western lowlands (< 900 m) followed by moderate incidence from five to 15 cases per 1000 person years in the south eastern lowlands (< 600 m), and the lowest incidence from 0.2 to five cases per 1000 person years in the south and central highlands (≥ 1200 m). The highest risk coincides with areas of relatively high rainfall and elevated temperatures and low risk with areas where one or both of these factors are not suitable. However, this pattern was not consistent throughout the country with high incidence recorded in some areas experiencing on average hot and dry and / or wet and cold conditions.

Table 5.2 shows regression coefficients from the spatial-temporal model for the relationship between monthly proportion of cases ratios and environmental conditions. Among temperature derived covariates, both mean monthly temperature range from 28 to 32 °C and maximum temperature range from 24 to 29 °C showed a positive association with malaria incidence. While high monthly maximum and minimum temperatures

showed a negative association. Among other environmental covariates only rainfall and vapour pressure showed a positive association with malaria. NDVI showed a negative association. The modelled seasonal trend showed that on average transmission is most intense from February to May with a peak in April declining rapidly after May and remaining at low levels between June and January (Figure 5.2). Similar trends were observed in all the individual districts in the country (not shown here).

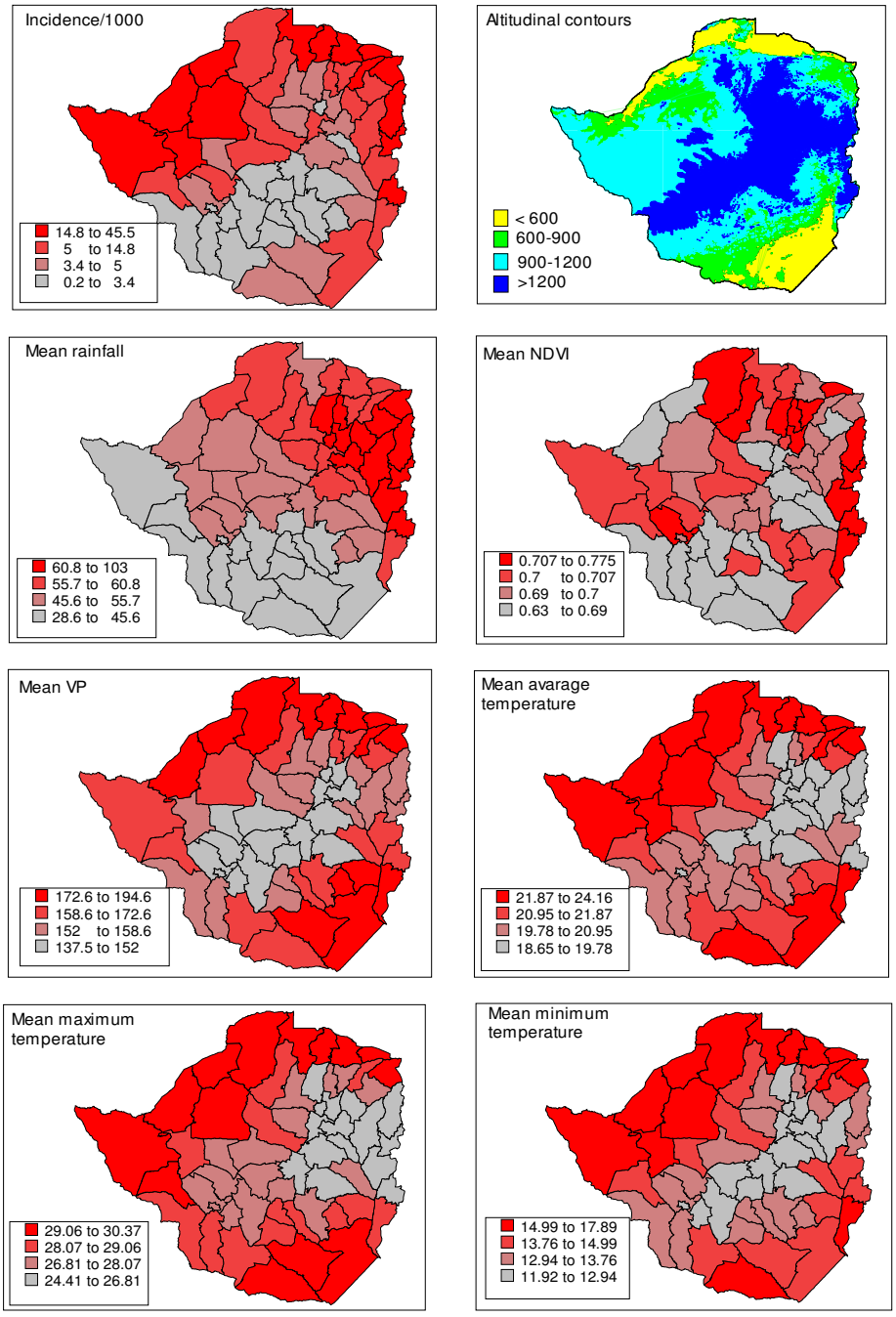

Figure 5.1. Average malaria incidence per thousand person years, altitudinal contours (m) and average climatic conditions [rainfall (mm), NDVI, vapour pressure (hPa), mean average, maximum and minimum temperature (°C)] for 1988-1999 in Zimbabwe. Malaria data from National Malaria Control Programme (Ministry of Health and Child Welfare 2000) and climate data from Climate Research Unit (Mitchel *et al*. 2003).

Table 5.2. Posterior estimates of regression coefficients (β) for environmental covariates and of spatial (σ_ϕ^2) and temporal (σ_ω^2) variances obtained by fitting the spatio-temporal model (Table 5.1. model 4), including 95 % credible intervals.

Variable	Mean	95 % Credible intervals
Spatial variation (σ_ϕ^2)	0.141	(0.110, 0.190)
Temporal variation (σ_ω^2)	0.208	(0.165, 0.251)
Intercept	-2.720	(-2.750, -2.674)
Mean temperature (°C)		
(<18)*		
(18-22)	-0.171	(-0.179, 0.163)
(23-27)	-0.103	(-0.113, -0.093)
(28-32)	0.235	(0.211, 0.258)
Maximum temperature (°C)		
(<24)*		
(24-28)	0.031	(0.023, 0.038)
(29-33)	-0.032	(-0.041, -0.023)
(34-38)	-0.290	(-0.308, -0.274)
Minimum temperature (°C)		
(4-24)	-0.071	(-0.072, -0.069)
Vapour pressure (hPa)		
(72-275)	0.008	(0.008, 0.008)
NDVI		
(0.2-0.9)	-0.216	(-0.257, -0.169)
Rainfall (mm)		
(0-561)	3.61E-05	(3.24E-05, 3.99E-05)

*Temperature range taken as baseline in the analysis.

Smoothed estimates of the proportions of cases revealed a spatial pattern not evident from the maps of raw proportions (Figure 5.3.A and B). The highest intensity of seasonal transmission between February and May is mainly in the north western part of the country followed by some districts in the south eastern part. The lowest intensity of seasonal transmission occurs throughout the country from July to December. The months of January and June appear to be the start and end month for the transmission season, respectively (Figure 5.3.A).

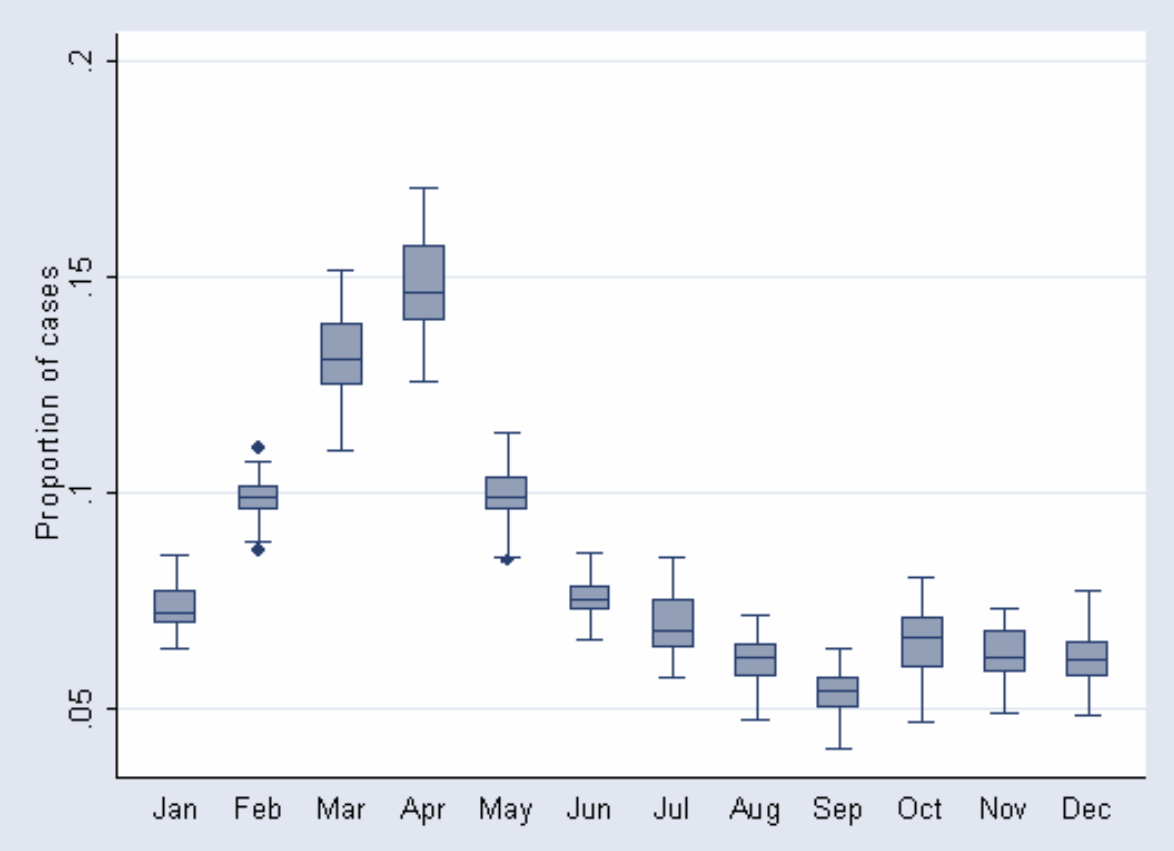

Figure 5.2. Proportion of malaria cases by month averaged over location and year in Zimbabwe between 1988 and 1999 obtained from the spatio-temporal model adjusted for environmental covariates (Table 5.1. model 4). The box represents 2.5th, 50th and 97th quantiles of the posterior distribution of the expected proportion of cases, respectively. The whiskers correspond to the maximum and minimum of the distribution and the dots indicate the outliers.

The mapping of the seasonality concentration index (S_i) from unadjusted proportions of cases showed no clear spatial pattern (Figure 5.4.). The covariate adjusted proportions of cases showed that the percentage concentration of malaria cases was highest (> 25 %) in

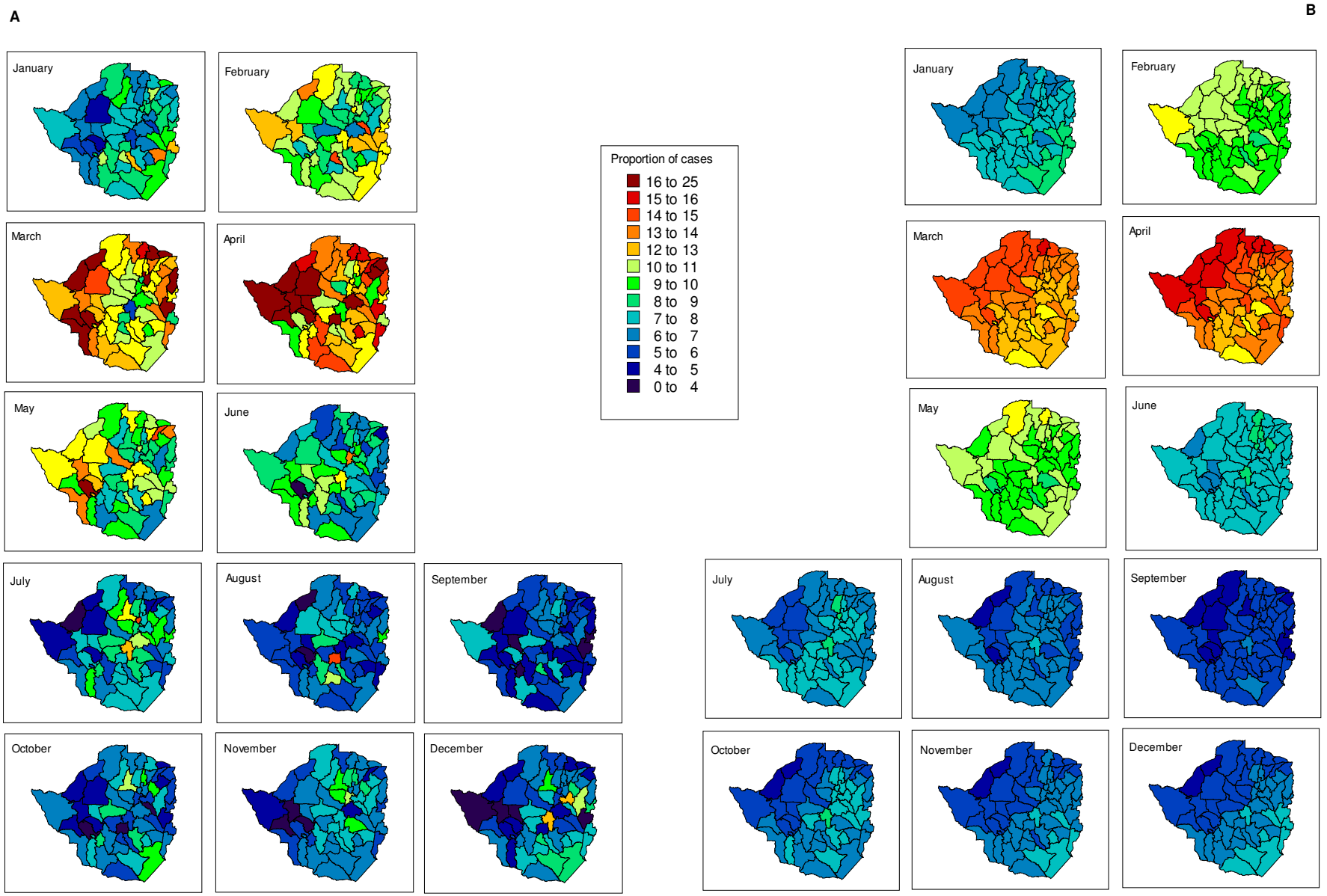

Figure 5.3 Geographical variation in the proportion of A raw and B smoothed malaria cases Table 1 model 4 by month expressed as a Percentage averaged over 1988-1999 in Zimbabwe.

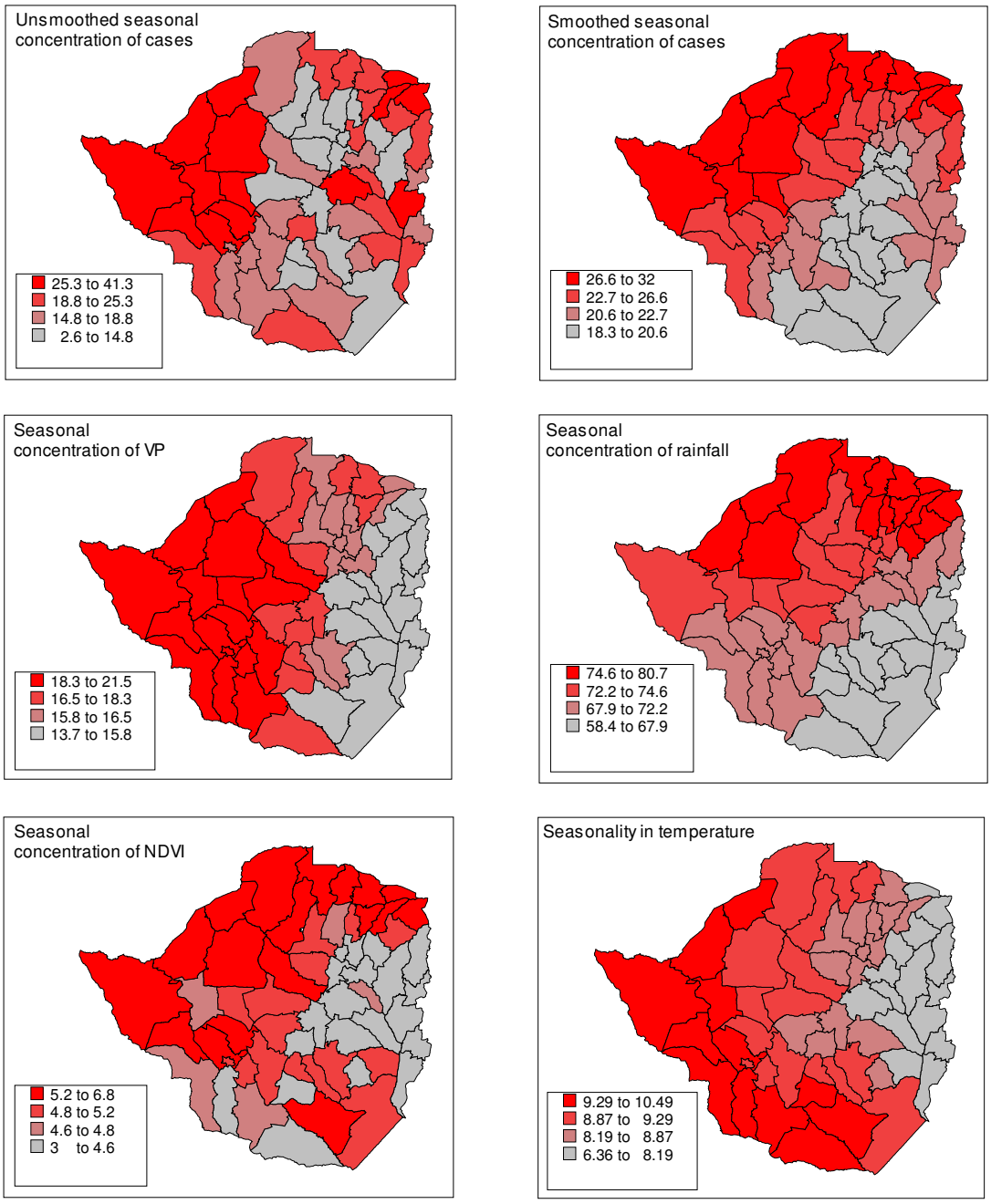

Figure 5.4. Seasonality concentration index (S_i) expressed as a percentage of raw and smoothed malaria cases (Table 1 model 4), rainfall (mm), vapour pressure (hPa), NDVI and seasonality in temperature (°C) [i.e. annual range, derived from the difference between monthly minimum and maximum temperature] averaged over year (1988-1999) and months in Zimbabwe. Malaria data obtained from (Ministry of Health and Child Welfare 2000) and Climate data from Climate Research Unit (Mitchel *et al*. 2003).

the north western lowlands followed by districts in the north central and eastern part of the country (mostly intermediate between lowland and highland areas) with a moderate concentration of cases (20-25 %). The lowest percentage concentration of malaria case (< 20 %) was in the central highlands and parts of the south eastern lowlands. This pattern was closely associated to the geographic variation in the seasonality of climatic covariates particularly rainfall. Seasonality in vapour pressure was also high in the north western lowlands coinciding with warm wet season. Seasonality in NDVI followed that of rainfall in the northern part of the country and to a less extent in southern part.

Discussion

Observed rates of recorded malaria cases in Zimbabwean districts demonstrate how much malaria incidence varies within geographical areas, depending on spatial variation in environmental determinants (Figure 5.1.). However, the observed pattern was not consistent throughout the country. This probably relates to between-district variability (noise, error) in the detection and recording of malaria cases at health facilities (Ray *et al*. 1995), which is determined by other than environmental determinants. Possibly, the population sizes we used as the denominator to calculate malaria incidence rates were incorrect for some districts contributing to error in malaria case rates.

The statistical method employed to quantify the amount of seasonal transmission in each months smoothed unobserved or unmeasured residual variation in malaria case rates between years and districts enabling us to interpret the geographical patterns in seasonality (Figure 5.3.). This work therefore contributes to the evidence for the importance of smoothing for spatial and temporal random effects in the mapping of

malaria (Diggle *et al*. 2002; Kleinschmidt *et al.* 2000; Kleinschmidt *et al.* 2001a & b; Kleinschmidt *et al.* 2002, Gemperli *et al*. 2004).

Our results with regard to the seasonal patterns of malaria transmission confirm what has been shown by other studies of the epidemiology of malaria transmission in Zimbabwe. Taylor (1985) and Taylor and Mutambu (1986) showed that peak in disease incidence is between March and April, and that the overall seasonal trend in the country varied according to the different altitudinal zones. Mpofu (1985) related the observed seasonal trend to the vector population densities. The present analysis showed that the combinations of mean monthly temperature range from 28 to 32 °C, maximum temperature range of 24 to 28 °C and high level of rainfall provides suitable conditions for seasonal transmission. The negative association between malaria incidence and mean monthly temperature range from 23 to 27 °C could be an indication that warmer average conditions are required during months of high transmission (Table 5.2.). Whereas high monthly maximum and minimum temperatures limit seasonal transmission. Surprisingly, NDVI also showed a negative association probably due to colinearity with rainfall which accounts for most variation. Further implications of the performance of NDVI in our analysis are illustrated by the results of the seasonality concentration index as discussed below.

The mapping of smoothed proportions of cases in each month averaged over the 11 year time period visually display the peak months as well as the start and end of seasonal transmission. Modelling and mapping seasonality in this way provides information about

the length of the transmission season based on the predicted relationship between seasonality in malaria and climate without setting any a priori conditions for duration in the model. This modelling approach also quantifies the relative amount of spatial seasonal risk pattern by delineating districts that have high and low proportions of malaria cases in a given time period. However, this requires the visual display of a map for each month. Mapping the seasonality concentration index (S_i) provides a more concise presentation.

The S_i summarizes the spatial seasonal trend observed in Figure 5.3. by displaying the distribution of malaria case load during the peak season across the country (Figure 5.4.). The concentration of cases was highest in the north western lowlands and lowest in the south eastern lowlands and central highlands. This pattern follows the geographic variation in the seasonality of climatic conditions particularly rainfall. For example, the low lying areas have on average elevated temperatures compared to areas at higher altitude. However, these areas are relatively dry and rainfall is strongly seasonal and brings with it intense seasonal transmission. On the contrary, in the south eastern lowlands the seasonal concentration of rainfall is low and as such there is less seasonality in malaria transmission. Nevertheless, perennial transmission in both western and eastern lowlands has been reported along major river systems. In addition, seasons of high rainfall have also been observed to dramatically alter the intensity of seasonal transmission in these areas (Taylor 1985). Seasonality in vapour pressure which is a measure of humidity follows a similar pattern to malaria seasonality. This is biologically plausible since humidity is high where rainfall and temperature are high and such

conditions are conducive to breeding and survival of the vector population and development of the parasite (Molineaux 1988). On the other hand NDVI which has been used to predict the number of months during which seasonal transmission is possible as illustrated by Thomson *et al*. (1997), Hay *et al*. (1998a) and Thomson *et al*. (1999), did not show a similar seasonal pattern to malaria. According to our analysis the greenness is highest in May long after the peak in rainfall and temperature (February-March), and this period coincides with a decline in malaria incidence.

Visual comparison of our model with the seasonality classification by Tanser *et al*. (2003) showed that in Zimbabwe areas with a high seasonality index and therefore high concentration of cases during the peak season fall within potentially perennial transmission areas with 4-6 months of transmission, and low indices within areas with 1-3 months of transmission. It may be that in areas experiencing malaria over a short period transmission is more sporadic and epidemic in nature, and that a greater percentage of recorded cases throughout the year are imported cases and / or false positives due over diagnosis as observed by (Stein and Gelfand 1985; Ray *et al*. 1995; Mharakurwa *et al*. 1997; Siziya *et al*. 1997).

The S_i leads to a quite different classification of areas of high and low seasonality compared to earlier seasonality definitions and maps. In the case of Zimbabwe it shows that strong seasonality tend to be associated with potentially perennial transmission, rather than with shorter annual duration of transmission which was the main determinant of other definitions of seasonality. Moreover, S_i quantifies the concentration of cases and

the peak month in a given year, and the mapping of this index therefore gives information about the intensity transmission during the peak season in a given area. This has potential for application in the timely spatial targeting of malaria interventions. In addition, the use of a covariate adjusted empirical model may prove useful for predicting seasonal risk pattern across the region with validation and / or calibration of the resulting seasonal pattern carried out in areas where fairly reliable malaria case data is available. Further work in this topic will include the investigation of seasonal variation between years and the relationship between the level of transmission and patterns of seasonality.

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Chapter 6: Environmental predictors of the seasonality of malaria transmission in Africa: the challenge

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Abstract

A description of malaria seasonality is important for planning and optimizing malaria control in both time and space but adequate malariological data are not available for many diseases-endemic areas. We analyzed the relationship between seasonality in entomological inoculation rate (EIR) and in environmental factors in sites across sub-Saharan Africa with the objective of predicting seasonality from environmental data. The degree of EIR seasonality in each site was quantified using an index previously used for rainfall. The results showed that seasonality of rainfall, minimum temperature and irrigation are important determinants of seasonality in EIR. Model fit was poor in areas characterized by two rainfall peaks and by irrigation activities. Two rainfall peaks probably dampen seasonality while irrigation creates perennial breeding habitats for vectors independent of rainfall. This complex interplay between the seasonal dynamics of environmental determinants and malaria pose a great challenge and highlights the need for improved models of malaria seasonality.

Introduction

Malaria is one of the most prevalent and devastating public health problems in sub-Saharan Africa (WHO 2003). An important tool for optimizing malaria control over both time and geographical area is a map of malaria seasonality. Such a map would be valuable as a basis for mapping transmission intensity (Gemperli *et al*. 2006). It has long been suggested that assessing the relationship between malariometric indices and environmental factors may be the most effective way of predicting changes in malaria transmission dynamics and thus improve the impact of control efforts (McDonald 1957; Bruce-Chwatt 1980; Molineaux 1988). A number of studies have analyzed this relationship using different approaches and indices in different parts of the continent Thomson *et al*. 1997; Hay *et al*. 2000b; Githeko and Ndegwa 2001; Abeku *et al*. 2004; Zhou *et al*. 2003). However, there is no convincing empirical model of the relationship between seasonality in environmental factors and seasonality in malariometric indices that could be used to map the pattern of seasonality across the continent.

The existing continental model of malaria seasonality is based on climate suitability for malaria transmission in a given month and shows the potential duration, start and end of the malaria season (Tanser *et al*. 2003). This model was validated against parasite prevalence data but these data are not ideal for describing malaria seasonality (Thomson *et al*. 1999; Reiter *et al*. 2004) since at very high transmission levels malaria prevalence is not very seasonal (Smith *et al*. 1993). Clinical malaria case data are more closely related to seasonality in transmission and hence to some environmental proxies for malaria seasonality (Hay *et al*. 1998; Thomson *et al*. 1999). Recently, an empirical

seasonality model that incorporates a combination of clinical malaria data and environmental covariates was used to predict monthly variation in transmission in Zimbabwe (Mabaso *et al*. 2005). A seasonality concentration index previously used for rainfall was applied to the model estimates in order to quantify and map the seasonal risk patterns across the country.

The index quantifies the distribution of the malaria case load during the peak season in a given area and therefore has the potential to be applied to seasonal risk mapping. However, because of the scarcity of reliable clinical malaria case data in large parts of sub-Saharan Africa, the use of other malariometric indices sensitive to malaria seasonality is necessary.

The entomological inoculation rate (EIR) is the definitive measure of malaria challenge and responds to seasonal changes in environmental factors (Rogers *et al*. 2002). EIR relates to both the human-biting activity of Anopheles vectors and the risk to humans of malaria infections (Appawu *et al*. 2004).

In this study we use a seasonality concentration index to model the relationship between seasonality in EIR and environmental factors, in order to identify environmental predictors of malaria seasonality and evaluate the utility of the seasonality index in different sites across sub-Saharan Africa.

Materials and methods

Data

We compiled published and unpublished monthly EIR data from as many different sites across sub-Saharan Africa as we could find (Figure 6.1.). The EIR is the number of infective mosquito bites per human per unit time (McDonald 1957; Molineaux *et al*. 1988). Studies included in the analysis were cross-sectional surveys conducted at least monthly throughout the year prior to the introduction of interventions or where no control methods were in place. These used standard mosquito sampling methods such as human landing catches, pyrethrum spray catches or light traps for estimating biting rates including dissection or enzyme-linked immunosorbent assay (ELISA) for determining the presence of sporozoites and origin of blood meal (Beier *et al*. 1999). Annual and monthly inoculations were derived by multiplying the daily EIR (infective bites per man per night) by 365 and 30 days, respectively.

We used monthly minimum temperature, annual temperature range and rainfall data obtained from the Climate Research Unit (CRU) with a global grid of 0.5 spatial resolution (Mitchel *et al*. 2003). The annual temperature range (the difference between monthly minimum and maximum temperatures) was taken as a measure of seasonality. For EIR and rainfall we applied Markham's seasonality concentration index (Markham1970; McGee 1977) previously used to summarize the seasonal trend in malaria cases by displaying seasonal concentration of cases during the peak transmission season (Mabaso *et al*. 2005). The method is based on vector representation (i.e. give both

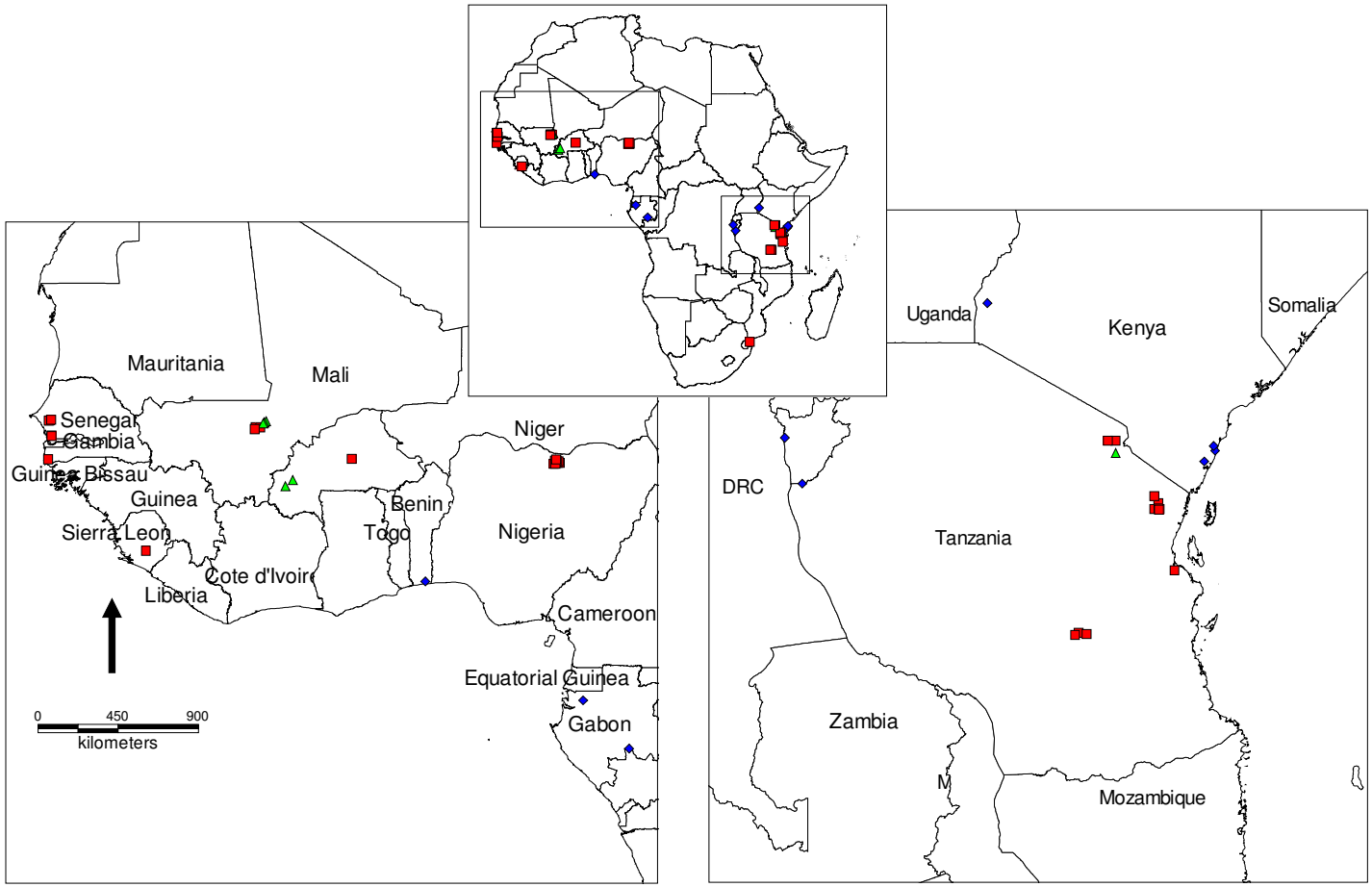


Figure 6.1. Geographic location of EIR study sites, (■) show locations with one rainfall peak and (♦) those with two peaks in a given year, and (▲) show locations with irrigation schemes.

magnitude and direction) of mean monthly values in a given year. The twelve monthly values are added up to give a vector total $(r_t; \theta_t)$, i.e.,

$$r_t = \sqrt{(\sum \bar{r}_i \sin\theta_i)^2 + (\sum \bar{r}_i \cos\theta_i)^2} \text{ and } \theta_t = \tan^{-1} \sum \bar{r}_i \sin\theta_i \Big/ \sum \bar{r}_i \cos\theta_i$$

and the seasonality concentration index C is given by $C = r_t / \sum r_i$ expressed as a percentage, where r_i is the magnitude of the vectors and θ_t is the direction which is the peak month expressed in units of arc. An index of 100 percent implies that value of interest is concentrated in one single month while an index of zero percent means that it is equal in each month of the year.

The effect of anthropogenic environmental change, specifically the presence of irrigation activities in selected localities was also taken into account in the analysis. All types of irrigated agriculture were recorded as either present or absent based on the information available from the literature used.

Statistical analysis

The analysis was carried out in Stata 8.0 (Stata Corporation). We used a Probit transformation to convert the EIR seasonality concentration index into a variable with a normal distribution. A multiple stepwise linear regression analysis was used to describe and model the relationship between the Probit transformed EIR seasonality index and selected explanatory variables in each site (Figure 6.1.), and variables with a *p*-value >

0.2 were removed. Table 6.1. summarizes variables used in the analysis. These variables were

Table 6.1. Mean and SD (standard deviation) of all variables used in the analysis from selected localities (n = 48) in sub-Saharan Africa. Only sites with monthly EIR values were included in the analysis. Where C is the seasonality concentration index expressed a percentage.

		VARIABLES					
		EIR		**Rainfall (mm)**		**Temperature (ºC)**	
		Annual Mean (SD)	C (%) Mean (SD)	Annual Mean (SD)	C (%) Mean (SD)	Minimum Mean (SD)	Annual range* Mean (SD)
Country	**No. of Sites (EIR References)**						
Benin	1 (Akogbeto & Nahum 1996)	4.09	56.45	13536.33	26.65	22.20	3.40
Burkina Faso	3 (Robert *et al*. 1988; Robert & Carnevale 1991; Modiano *et al*. 1996)	80.15 (46.82)	62.79 (28.91)	8621 (1411.17)	73.52 (3.22)	16.20 (0.82)	7.67 (1.85)
Burundi	2 (Coosemans 1985)	43.01 (53.27)	54.24 (0.02)	11281.50 (1085.41)	29.88 (4.13)	13.50 (1.34)	1.86 (0.38)
Gabon	3 (Elissa *et al*. 1999; Elissa *et al*. 2003)	60.549 (41.73)	32.83 (26.97)	20331.61 (3296.17)	26.42 (8.89)	18.90 (0.85)	2.98 (0.76)
Kenya	4 (Mbongo *et a*l. 1993; Mbongo *et al*. 1995; Beier *et al*. 1990)	29.21 (43.42)	55.36 (12.08)	10702.63 (1340.25)	32.30 (13.78	18.83 (2.25)	3.56 (0.97)
Mali	6 (Dolo *et al*. 2004)	146.30 (99.49)	64.24 (27.24)	4782.67 (50.76)	80.73 (0.31)	16.61 (0.15)	9.10 (0.05)
Mozambique	1 (Mendis *et al*. 2000)	153.12	30.05	5570	44.36	10.80	8.73
Nigeria	8 (Molineaux and Gramiccia 1980)	24.88 (26.38)	85.25 (4.65)	5768.19 (800.64)	84.15 (0.56)	13.00 (0.14)	9.58 (0.35)
Senegal	6 (Fontenielle *et al*. 1997; Robert *et al*. 1998)	18.3 (26.38)	66.78 (26.42)	8006.67 (2485.52)	86.10 (1.73)	16.25 (0.78)	4.81 (0.73)
Sierra Leon	1 (Bockarie *et al*. 1994)	13.52	55.58	24216.50	64.00	19.85	2.95
Tanzania	13 (Biro 1987; Smith *et al*. 1993; Premji *et al*. 1997; Charlwood *et al*. 1998; Drakeley *et al*. 2000; Ijumba *et al*. 2002; Bodker *et al*. 2003)	37.5 2 (64.69)	63.28 (56.38)	11222.57 (3114.18)	47.50 (10.74)	15.25 (2.96)	4.47 (0.50)

* Annual range [difference between monthly minimum and maximum temperature] used as a measure of seasonality in temperature

used to see how well they predict seasonal concentration of EIR in the different sites. The performance of climatic predictors was further assessed by fitting the regression model in the presence or absence of irrigation activities, and with or without sites from the tropical zone.

Results

Table 1 shows that there is great variability in the annual EIR values and seasonality among the selected countries (n = 48 sites) and between-sites variation is masked by averaging by country. Only the rainfall seasonality concentration index, minimum temperature and irrigation were selected as potential predictors of the seasonal concentration of EIR (Table 6.2.). Rainfall seasonal concentration showed a positive association with seasonal concentration of EIR while both minimum temperature and irrigation showed a negative association. No evidence of an association was found between annual EIR and either annual rainfall or temperature range.

Table 6.2. Results of multiple stepwise linear regression analysis between EIR seasonality and environmental variables (listed in Table 1) for selected localities in sub-Saharan Africa, and variables with a *p*-value > 0.2 were removed.

Variables	**Coefficients**	**SE**	**p-value**	**95% CI**
Rainfall seasonality index	0.011	0.004	0.006	0.003, 0.019
Minimum temperature (ºC)	-0.057	0.033	0.090	-0.123, 0.009
Irrigation	-0.918	0.236	0.000	-1.393, -0.442

SE, standard error ; CI, confidence intervals.

Model predictions were poor in sites situated in regions with two rainfall peaks (Figure 6.2.). Most of these are in the tropical zone south of the equator (Figure 6.1.) and show very low EIR seasonality indices compared to the rest of the sites. However, we also observed poor model fit in a few sites with one rainfall season. EIR study sites located in the vicinity of irrigation schemes also had low seasonality indices compared to nearby non irrigated sites, for example in Mali with 40.1 percent (3 sites) and 88.3 percent (3 sites) and Tanzania with 26.8 percent (2 sites) and 91.2 percent, respectively.

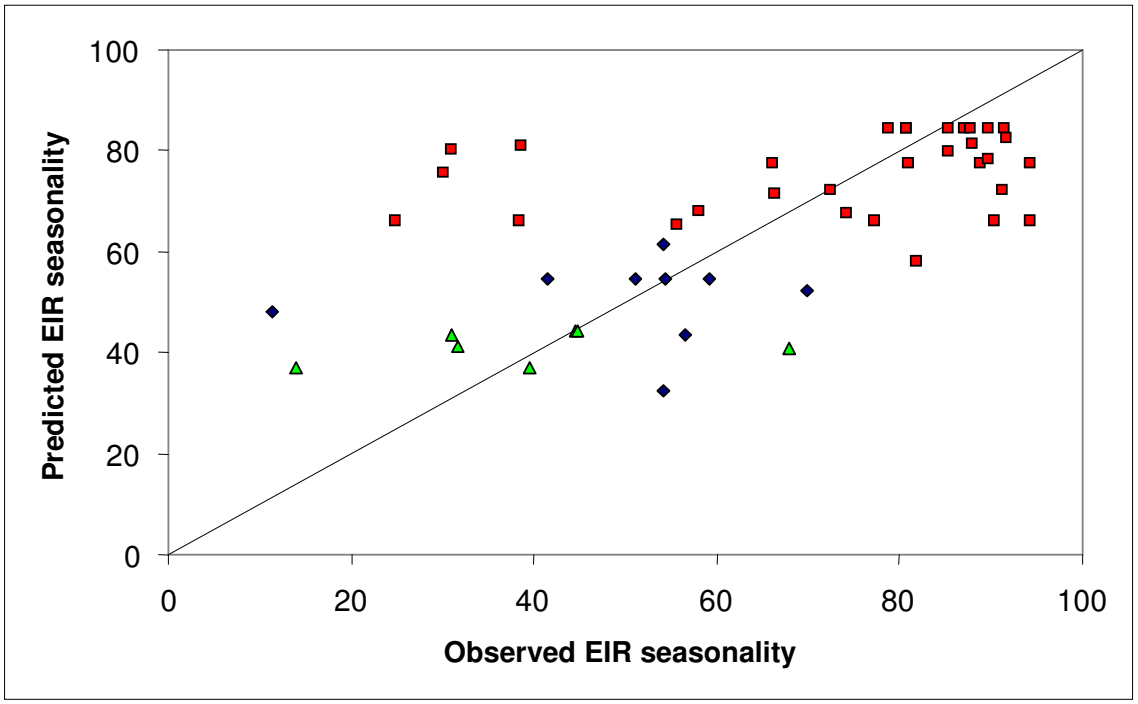


Figure 6.2. Predicted and observed EIR seasonality concentration index from selected sites in sub-Saharan Africa, (!) show locations with one rainfall peak and (∀) those with two peaks in a given year, and (%) show locations with irrigation.

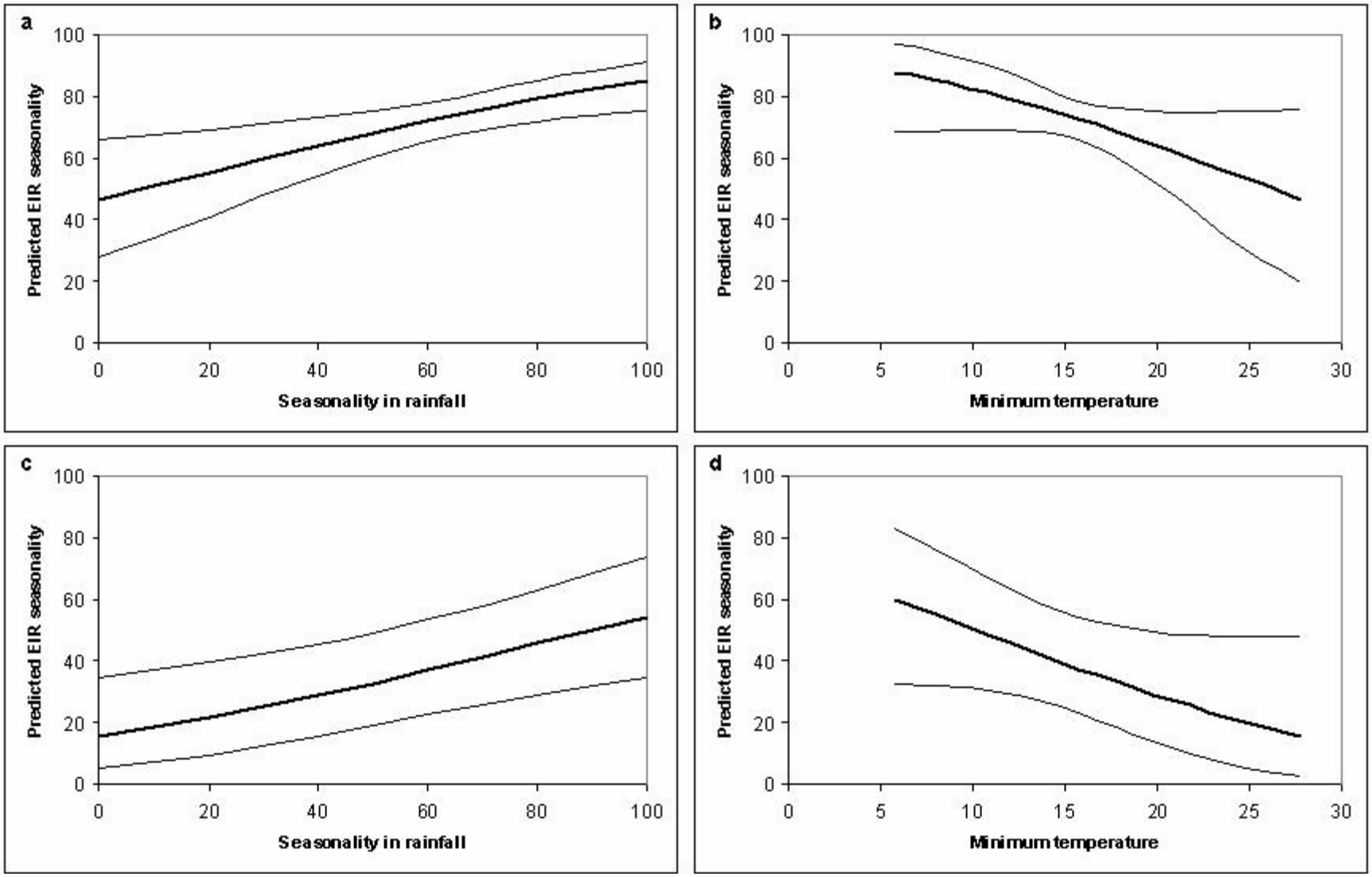


Figure 6.3. EIR seasonality concentration index predicted using rainfall seasonality index and minimum temperature (ºC) including the absence (a, b) and presence (c, d) of irrigation activities with 95 % confidence limit.

Regardless of irrigation activities the seasonal concentration of rainfall remained a better predictor of EIR seasonality than minimum temperature. The predicted EIR seasonality index was higher when irrigated sites were excluded (Figure 6.3.).Conversely, exclusion of study sites from the equatorial tropical zone did not have much effect on the model.

Discussion

Our findings support the claim for a marked heterogeneity in the malaria transmission pattern across the continent (Hay *et al*. 2000c). We further confirm that this variation reflects sub-regional ecological heterogeneity, and is affected by anthropogenic activities such as irrigated agriculture. The analysis showed that rainfall seasonality, and to a lesser extent minimum temperature are important climatic determinants of the intensity of inoculation rate during the peak transmission season. Most of the selected EIR study sites are situated in tropical Africa where seasonality in rainfall drives the seasonal dynamics of malaria transmission. Minimum temperature probably plays little or no role in regulating malaria seasonality in these areas.

The results also showed that irrigation activities have a dampening effect on seasonality of malaria transmission. Elsewhere in Africa irrigation has been shown to alter the transmission pattern from seasonal to perennial especially during the dry season in areas of unstable transmission (Ijumba and Lindsay 2001; Henry *et al*. 2003; Appawu *et al*. 2004; Dolo *et al*. 2004; Sissoko *et al*. 2004). The impact of irrigation on malaria seasonality can vary with the type of irrigation activity and according to the level of endemicity. Increases in the level of transmission in irrigated areas result in more

rigorous control measures usually reflected in the low levels of malaria infection and morbidity (Boudin *et al*. 1992; Ijumba and Lindsay 2001; Ijumba *et al*. 2002; Dolo *et al*. 2004; Sissoko 2004). In the present study, the seasonality of malaria is less in sites with irrigation, irrespective of the effect on overall transmission. However, the effect of minimum temperature and rainfall seasonality still seem to operate in irrigated areas.

The two rainfall seasons in the equatorial tropical zone probably complement each other by intensifying and prolonging the transmission season. The seasonality index seems to work better in areas with unimodal seasonal pattern and this might have had an adverse effect in the analysis in areas with a bimodal seasonal pattern. Poor model fit in a few localities with one rainfall season may be due to the presence of two distinct common African malaria vectors, *Anopheles funestus* and *Anopheles gambiae sensu lato* which have been shown to sustain perennial parasite inoculation given suitable ecological conditions (Elissa *et al*. 1999 and 2003). For example, in some parts of the continent the two main vectors are seasonally with high densities of *An. gambiae* and *An. arabiensis* following the rainy season, and *An. funestus* reaching its peak in the early dry season (Gillies and De Meillon 1968; Cohuet *et al*. 2004).

Urbanization may also be important since it has been shown to produce breeding habitats for malaria vectors by increasing the number of artificial water collection reservoir (Robert *et al*. 2003). However, data used in this analysis was mainly from rural settings and therefore insufficient to explore the impact of urbanization on EIR seasonality. Some of the difficulties we face may be because of chaotic dynamics in the impacts of the

environmental drivers of seasonality on the life histories of both parasite and vector (Altizer 2006).

We have successfully identified environmental predictors of malaria seasonality given the effect of irrigated agriculture across different sites in sub-Saharan Africa. However, we note that the global climate data used is rather coarse and may contain uncertainties that should be borne in mind when dealing with EIR which vary over smaller spatial scales. Remotely sensed environmental proxies may improve model fit. We also acknowledge the need for a seasonality algorithm that captures other components of seasonal variation. Future work will explore the use of improved quantification and modeling of malaria seasonality.

Acknowledgements: We thank Dr. Brian Sharp and Dr. Immo Kleinschmidt for their comments on earlier draft of the manuscript. This work is part of the Mapping Malaria Risk in Africa (MARA) collaboration between the Malaria Research Lead Programme at the Medical Research Council in South Africa and the Swiss Tropical Institute in Basel Switzerland. This work was funded by the Rudolf Geigy Stiftung zu Gunsten des Schweizerischen Tropeninstituts.

Chapter 7: Empirical modelling and mapping of seasonality of malaria transmission by *Anopheles gambiae sensu lato* in Africa

Working paper

Abstract

Seasonal dynamics of malaria transmission as influenced by environmental / climatic conditions have implications for effective implementation of interventions in both space and time, but no analyses have been available of how observed patterns of malaria seasonality vary across the African continent. In this study we used an approximation of the discrete Fourier transformation for both entomological inoculation rate (EIR) due to *Anopheles gambiae s.l.* and meteorological covariates in order to summarise seasonality for 97 sites across sub-Saharan Africa. The empirical relationship between the Fourier coefficients for EIR and for meteorological covariates was used to predict and map the magnitude and timing of the main seasonal cycles. This allowed the estimation of maps of the overall degree of malaria seasonality and the timing and length of seasonal transmission across the continent. The conditions that determine the most infectious periods vary between and within sub-regions along an altitudinal gradient north and south of the equator. These products can be used to account for seasonality in transmission model based mapping of malaria risk at a country, regional and continental level. Model outputs can be further refined as more data become available.

Introduction

In most malaria endemic areas transmission varies strongly with season because of the influence of meteorological conditions that determine the breeding, abundance and survival of the mosquito vectors and the rate of sporogonic development of the parasite (Gillies and De Meillon 1968; Molineaux 1988). Seasonal variations in parasite inoculation rates also affect the acquisition or loss of protective immunity in humans (Fontenille and Simard 2004). The timing of interventions such as the application of indoor residual spraying with insecticides, re-treatment of insecticide impregnated nets (ITNs) (Randolph 1999) and intermittent preventive treatment in infants (IPTi) (Chandramohan *et al*. 2007) need to be coordinated with the malaria transmission season. New intervention strategies such as vaccines may also need to be targeted accordingly and efficiently in both space and time for effectiveness and sustainability (Randolph 1999). There is thus a need for accurate maps of malaria seasonality in endemic areas.

The seasonality of malaria transmission in relation to climatic and environmental covariates is complex (Gemperli *et al.* 2006b; Mabaso *et al*. 2006). Several methods have been used for modelling seasonality in transmission and disease risk. These vary from an assumption of no seasonality, to seasonal adjustment or dichotomously classifying months as with, or without transmission (Abeku *et al.* 2002; Gemperli *et al.* 2006a). Climate based theoretical models have been used to predict the timing and length of the transmission season based temperature or rainfall (Tanser *et al.* 2003; Gemperli *et al.* 2006b). There are also empirical models that fit malaria data to environmental covariates to predict months during which transmission is possible (Thomson *et al.* 1997; Hay *et al.*

1998; Hay *et al.* 1998b; Thomson *et al.* 1998). Most of these models classify months as with or without transmission. However, for including seasonality in models of impact of malaria interventions, it would be preferable to develop empirical models of malaria seasonality that predict quantitative variation between months rather than classifying dichotomously (Mabaso *et al.* 2005). This could also help refining the planning of control interventions.

In this study we use temporal Fourier analysis to estimate the annual cycle of the EIR due to *Anopheles gambiae sensu lato* in relation to meteorological covariates. We use these relationships to map the geographical patterns of seasonality of malaria transmission caused by this vector in the African continent. *An. gambiae s.l.* typically breeds in water bodies and is therefore highly sensitive to temporal meteorological variations (Gillies and De Meillon 1968; Cohuet *et al*. 2004).

Methods

Entomological data

We used the entomological inoculation rate (EIR) for *An. gambiae s.l.*, expressed as average number infective mosquito bites per person per month, disaggregated by calendar month, and averaged over all the years for which data were available from any given site. These data were collated from published and unpublished sources for all 97 geolocated sites in Africa that we could identify, as described in detail in our previous analysis (Mabaso *et al.* 2006). In general, annual values of EIR in tropical Africa vary from as low as one to more than one thousand infective bites per person (Hay *et al.* 2000; Hay *et*

al. 2005). In addition, EIR values vary seasonally, rising and falling with changes in rainfall, temperature and humidity depending on the vector species (Fontenille and Simard 2004; Smith *et al.* 2004).

Meteorological data

We obtained rainfall data from the Climate Research Unit (CRU, Norwich, U.K.) interpolated weather station data at a global resolution of 0.5° grid (Mitchell and Jones 2005). For further analysis we used the $\log_e(R+0.001)$ transform of the average monthly rainfall(R) in millimetres. Other determinants were derived from meteorological satellite sensor data at 8 x 8 km spatial resolution taken from the National Oceanographic and Atmospheric Administration's (NOAA) Advanced Very High Resolution Radiometer (AVHRR) onboard polar-orbiting satellites. These comprised monthly images of normalized difference vegetation index (NDVI), a measure of vegetation greenness / amount of vegetation and a proxy for availability of ground water and therefore a surrogate for mosquito breeding sites, and air temperature (Hay and Lenon 1999; Hay *et al.* 2006).

Site- and time- specific values of these covariates corresponding to the EIR data were extracted using raster geographic information (GIS) software package Idrisi® (http://www.clarklabs.org/). The meteorological data was averaged from 1982 to 2000, which corresponds to time period of the extracted EIR data. The rainfall data were resampled to the same grid as the remote sensed data. Predictions were generated using Idrisi and predicted surfaces were displayed in MapInfo 7.1 (www.mapinfo.com/).

Analysis of malaria seasonality

For each environmental variable and for the $\log_e$ transform of the EIR we approximated the seasonal pattern with the constant, annual and biannual components of the inverse discrete Fourier transform, as described by,

$$Y_{Xt} \approx a_{0X} + a_{1X}\cos\left(\frac{2\pi t}{12}\right) + b_{1X}\sin\left(\frac{2\pi t}{12}\right) + a_{2X}\cos\left(\frac{2\pi t}{6}\right) + b_{2X}\sin\left(\frac{2\pi t}{6}\right), \quad (1)$$

where the subscripts $X = E$ corresponds to the $\log_e$ transform of the EIR; $X = N$ corresponds to NDVI, $X = R$ corresponds to $\log_e$ transform of the rainfall; $X = T$ corresponds to the air temperature. Y_{Xt} then denotes the approximate value of variable X at month t, where $t = 1,2\ldots12$ corresponds to the months of the year. a_{0X} denotes the mean monthly value for variable X, a_{1X}, b_{1X} and a_{2X}, b_{2X} represent the annual and the biannual Fourier coefficients for variable X, respectively. a_{iX} and b_{iX} thus correspond to the real and imaginary parts of the ith Fourier coefficient expressed as a complex number. The values of the Fourier coefficients, for $n = 1, 2$, were obtained using,

$$a_{0X} = \frac{1}{12}\sum_{t=1}^{12} X_t,$$

$$a_{nX} = \frac{2}{12}\sum_{t=1}^{12} X_t \cos\left(\frac{2\pi nt}{12}\right),$$

$$b_{nX} = \frac{2}{12}\sum_{t=1}^{12} X_t \sin\left(\frac{2\pi nt}{12}\right).$$

This approximation of the discrete Fourier transform parameterised the seasonal patterns by reducing the data for each variable for each site to 5 orthogonal terms.

Modelling of the magnitude and timing of EIR seasonality

The magnitude and timing of the annual and biannual seasonal cycles of the logarithm of the EIR was modelled as a function of the amplitude and phase of meteorological covariates by relating the Fourier coefficients using multiple linear regression. The full multivariate normal model estimated fitted values for each of the Fourier parameters for the log transformed EIR as the system of linear sums,

$$\hat{a}_i = \phi_{i00} + \sum_{j=0}^{2}\left(\phi_{ij1}a_{jN} + \phi_{ij2}a_{jR} + \phi_{ij3}a_{jT}\right) + \sum_{j=1}^{2}\left(\phi_{ij4}b_{jN} + \phi_{ji5}b_{jR} + \phi_{ji6}b_{jT}\right),$$

$$\hat{b}_i = \theta_{i00} + \sum_{j=0}^{2}\left(\theta_{ij1}a_{jN} + \theta_{ij2}a_{jR} + \theta_{ij3}a_{jT}\right) + \sum_{j=1}^{2}\left(\theta_{ij4}b_{jN} + \theta_{ij5}b_{jR} + \theta_{ij6}b_{jT}\right), \qquad (2)$$

where ϕ_{ijk}, and $\theta_{ijk}(k = 0...6)$ are regression coefficients; and $\hat{a}_i$ and $\hat{b}_i$ are estimated by minimising the sum of squared deviations from the values of a_{iE} and b_{iE} for the 97 observed sites.

A backward elimination algorithm was used to eliminate coefficients where $p > 0.2$ (model 1). We also fitted reduced models where only parameters corresponding to the annual cycle ($j < 2$) were included (model 2), a model from which parameters were removed where $i \neq j$ (model 3), and another one for the average levels (model 4). The

Akaike Information Criterion (AIC) was used to select the best fitting models. Statistical analysis was carried out in Stata version 9.0 (StataCorp, USA).

Predicting malaria seasonality

Fourier coefficients for the annual and biannual seasonal components including the annual average were extracted from the predicted surfaces to make predictions of Y_{Et} using equation (2) for each pixel considered to have a climate suitable for malaria transmission in the model of Craig *et al.* (1999).

To describe the predicted seasonal patterns we first exponentiated the fitted values of Y_{Et} to give an annual pattern of the untransformed $Z_t = \exp(Y_{Et})$ scale. We estimated the annual and biannual amplitudes as well as their phases, and the degree of seasonal concentration and peak of Z_t including the annual duration of transmission as described in appendix 2.

Results

Table 7.1 shows summary statistics of the Fourier coefficients for all data used in the analysis.

The best fitting models with smaller AIC values were those that incorporated coefficients of the average and both the annual and biannual cycles as explanatory variables (Table 7.2). The Fourier coefficients for predicting the annual and biannual seasonal components for EIR are given in Table 7.3.

Table 7.1. Distribution of Fourier coefficients for the logarithm of the *An. gambiae s.l.* entomological inoculation rate (EIR) and for meteorological covariates for the 97 sites used in the analysis, SD is the standard deviation.

FOURIER COEFFICIENTS	MEAN	SD	MINIMUM	MAXIMUM
EIR ($\log_e$ (/person per month))				
a_{0E}	-3.37	1.90	-7.67	0.82
a_{1E}	-0.60	0.93	-2.65	2.26
b_{1E}	-0.62	1.49	-3.35	2.93
a_{2E}	-0.05	0.83	-1.87	2.02
b_{2E}	0.10	0.74	-1.40	1.79
Rainfall ($\log_e$ (mm))				
a_{0R}	5.01	1.58	2.43	7.22
a_{1R}	-1.89	1.77	-4.53	1.70
b_{1R}	-1.39	1.92	-5.85	3.48
a_{2R}	-0.20	0.68	-2.55	2.00
b_{2R}	-0.74	0.87	-2.13	1.93
NDVI[†]				
a_{0N}	0.37	0.15	0.13	0.68
a_{1N}	0.00	0.05	-0.13	0.12
b_{1N}	-0.06	0.08	-0.20	0.19
a_{2N}	-0.01	0.05	-0.09	0.11
b_{2N}	-0.01	0.05	-0.20	0.08
Air temperature (˚C)				
a_{0T}	30.83	0.55	29.33	32.11
a_{1T}	-0.06	0.38	-1.12	0.83
b_{1T}	0.52	0.30	0.01	1.12
a_{2T}	-0.14	0.21	-0.60	0.66
b_{2T}	0.02	0.22	-0.37	0.77

[†]NDVI is normalized difference vegetation index

Figure 7.1 compares the observed and fitted Fourier coefficients for the 97 sites with data. The estimated coefficients of the annual average, the annual and biannual amplitude and phase from Model 1 (appendix 3A-E) were used to predict the seasonal pattern for the sampled sites.

Table 7.2. Comparison of models for predicting the magnitude and timing of the logarithm of *An. gambiae s.l.* EIR.

Response variables	Model 1		Model 2		Model 3		Model 4	
	k	AIC	k	AIC	k	AIC	k	AIC
Annual average								
a_{0E}	4	391.5					2	394.04
Annual cycle								
a_{1E}	7	230.1	5	232.9				
b_{1E}	8	303.6	2	327.4				
Biannual cycle								
a_{2E}	9	222.5			5	225.4		
b_{2E}	7	199.6			2	214.9		

Model 1 includes parameters of the annual and biannual cycle including average levels, Model 2 only parameters of the annual cycle, Model 3 only parameters of the biannual cycle and Model 4 only average values. K is the number of parameters included in the different models. The smaller the AIC value the better the model fit. In each case the parameters included in the model were selected using the backward elimination algorithm.

The predicted seasonal pattern

Model predictions of the seasonal pattern (Figure 7.2A-C) compare well with the observed pattern in some sites and not in others. The poor fit in some sites may partly be because the model predictions are based on a long term average and will therefore not necessarily match the site and time specific observed pattern exactly. For example, areas that are sometimes and not too often characterised by a bimodal season pattern in a given year may on average depict a unimodal pattern and vice versa. In addition, the predicted timing of the most infectious period is centred on the average month and the observed pattern may be located within or slightly away from it. Model predictions may also be less accurate in some parts of the continent due to the paucity of data points.

Table 7.3. Parameters retained in Model 1 Table 2.7 of the annual and biannual seasonal pattern for *An. gambiae s.l.* entomological inoculation rate (EIR) with regression coefficients (β) and confidence intervals (CI) estimated using maximum likelihood.

RESPONSE	EXPLANATORY	β	95% CI	
EIR $a0_E$				
	RAIN a_{0R}	-0.47	-0.93	-0.00
	RAIN b_{1R}	0.41	0.09	0.72
	TAIR a_{0T}	-1.14	-2.13	-0.15
	Intercept	34.64	2.78	66.50
EIR $a1_E$				
	RAIN a_{1R}	0.18	0.00	0.35
	RAIN b_{1R}	-0.26	-0.38	-0.13
	RAIN b_{2R}	-0.14	-0.34	0.06
	NDVI a_{1N}	3.75	0.733	6.77
	NDVI a_{2N}	-5.90	-10.53	-1.28
	TAIR a_{0T}	0.42	-0.01	0.84
	Intercept	-13.35	-26.17	-0.52
EIR $b1_E$				
	RAIN a_{2R}	0.40	0.06	0.75
	RAIN b_{2R}	-0.47	-0.76	-0.19
	NDVI b_{1N}	5.18	1.78	8.59
	NDVI b_{2N}	4.27	-1.08	9.61
	TAIR a_{0T}	-0.87	-1.37	-0.37
	TAIR a_{2T}	1.26	0.06	2.47
	TAIR b_{2T}	1.75	0.64	2.85
	Intercept	26.45	11.09	41.81
EIR $a2_E$				
	RAIN b_{1R}	0.14	0.00	0.28
	RAIN a_{2R}	0.34	0.07	0.62
	RAIN b_{2R}	-0.18	-0.36	0.01
	NDVI b_{1N}	-3.14	-5.96	-0.33
	NDVI a_{2N}	5.34	0.76	9.92
	NDVI b_{2N}	-2.28	-5.67	1.12
	TAIR a_{1T}	0.40	-0.10	0.89
	TAIR a_{2T}	-0.65	-1.42	0.12
	Intercept	-0.14	-0.39	0.12
EIR $b2_E$				
	RAIN a_{1R}	-0.13	-0.29	0.04
	RAIN b_{1R}	0.27	0.13	0.41
	RAIN a_{2R}	0.39	0.11	0.67
	NDVI a_{0N}	1.27	-0.34	2.88
	NDVI a_{2N}	-7.32	-11.58	-3.06
	TAIR a_{1T}	-0.64	-1.09	-0.19
	Intercept	-0.27	-1.06	0.52

DVI is normalized vegetation index, TAIR is air temperature.

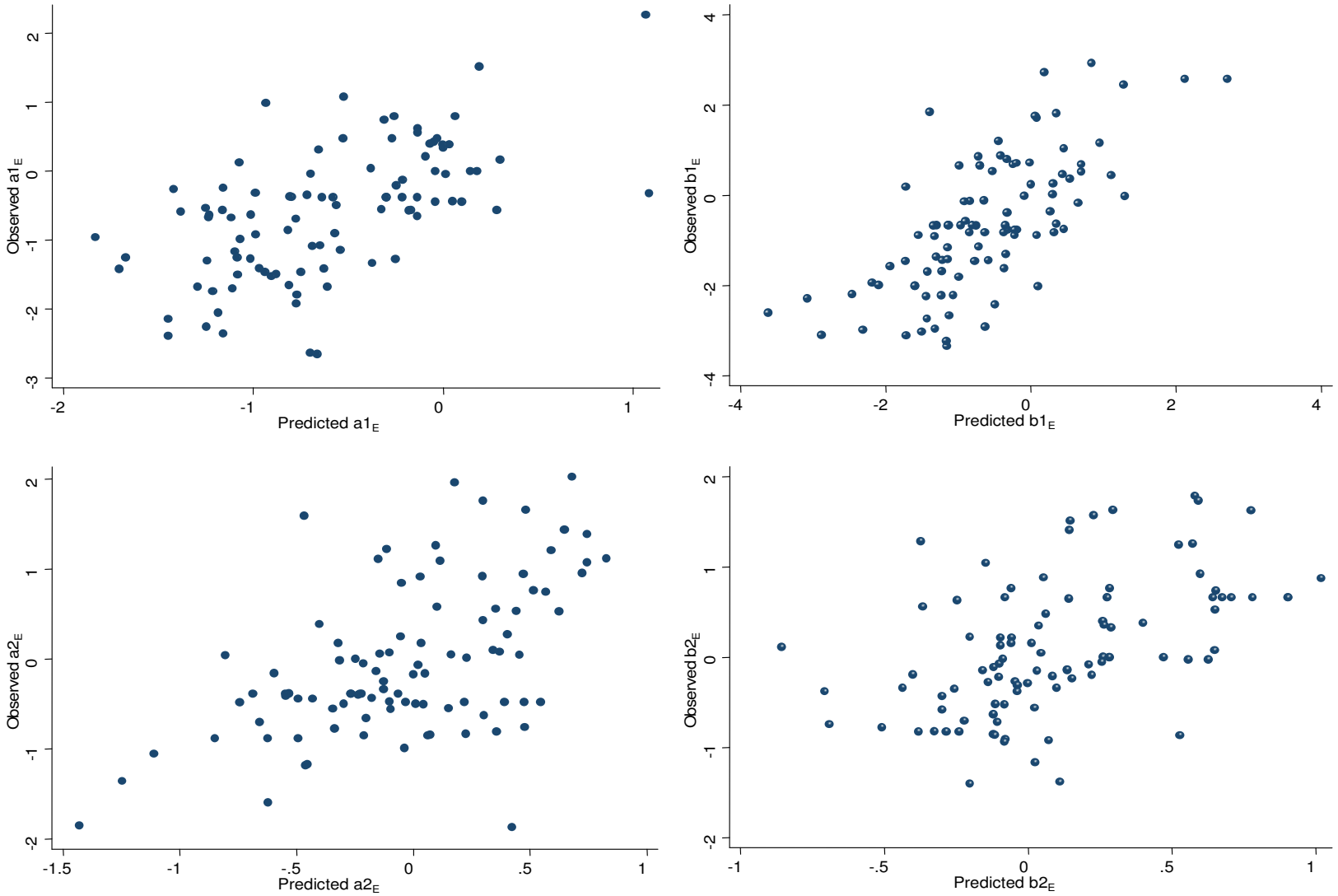
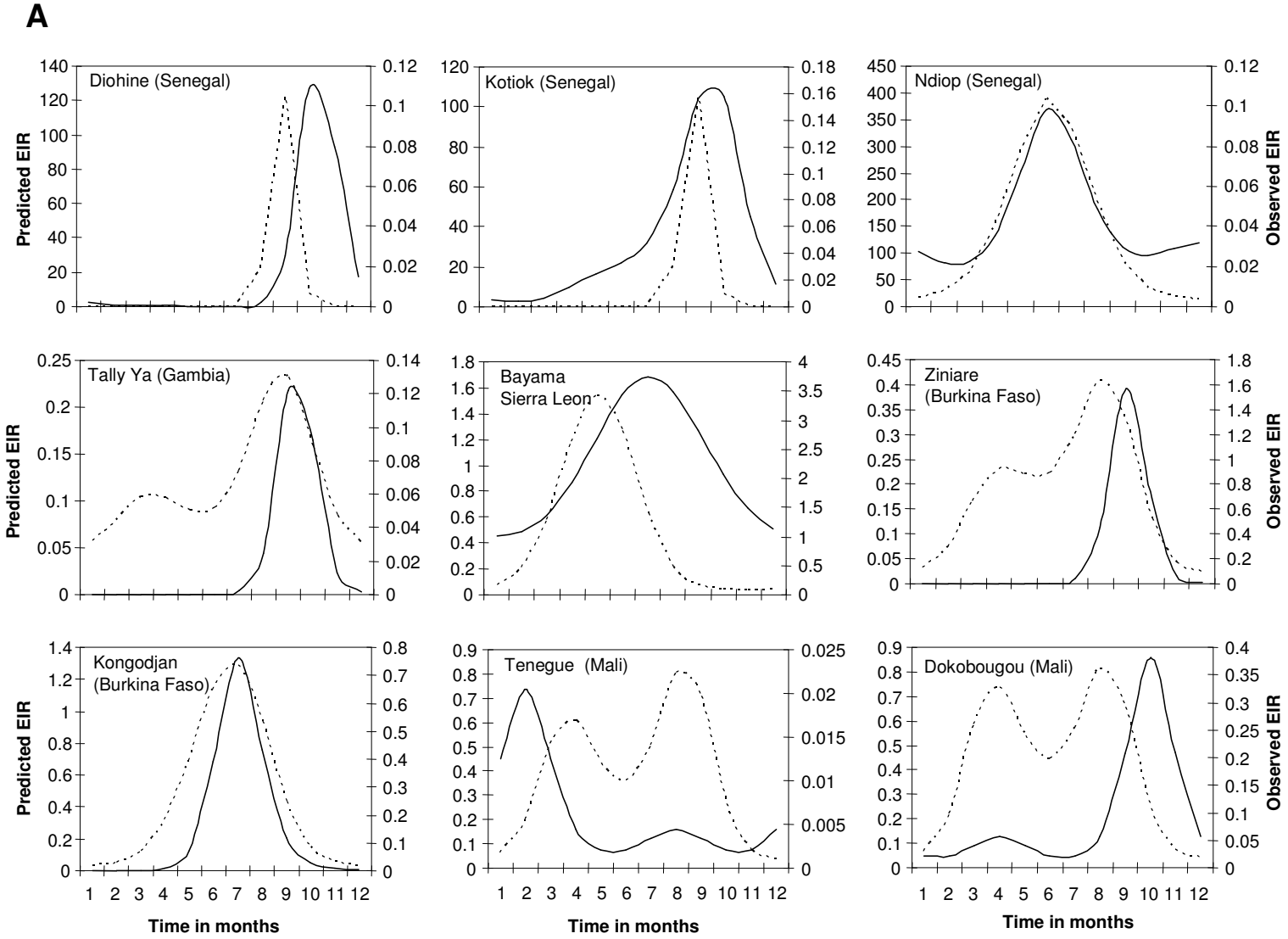
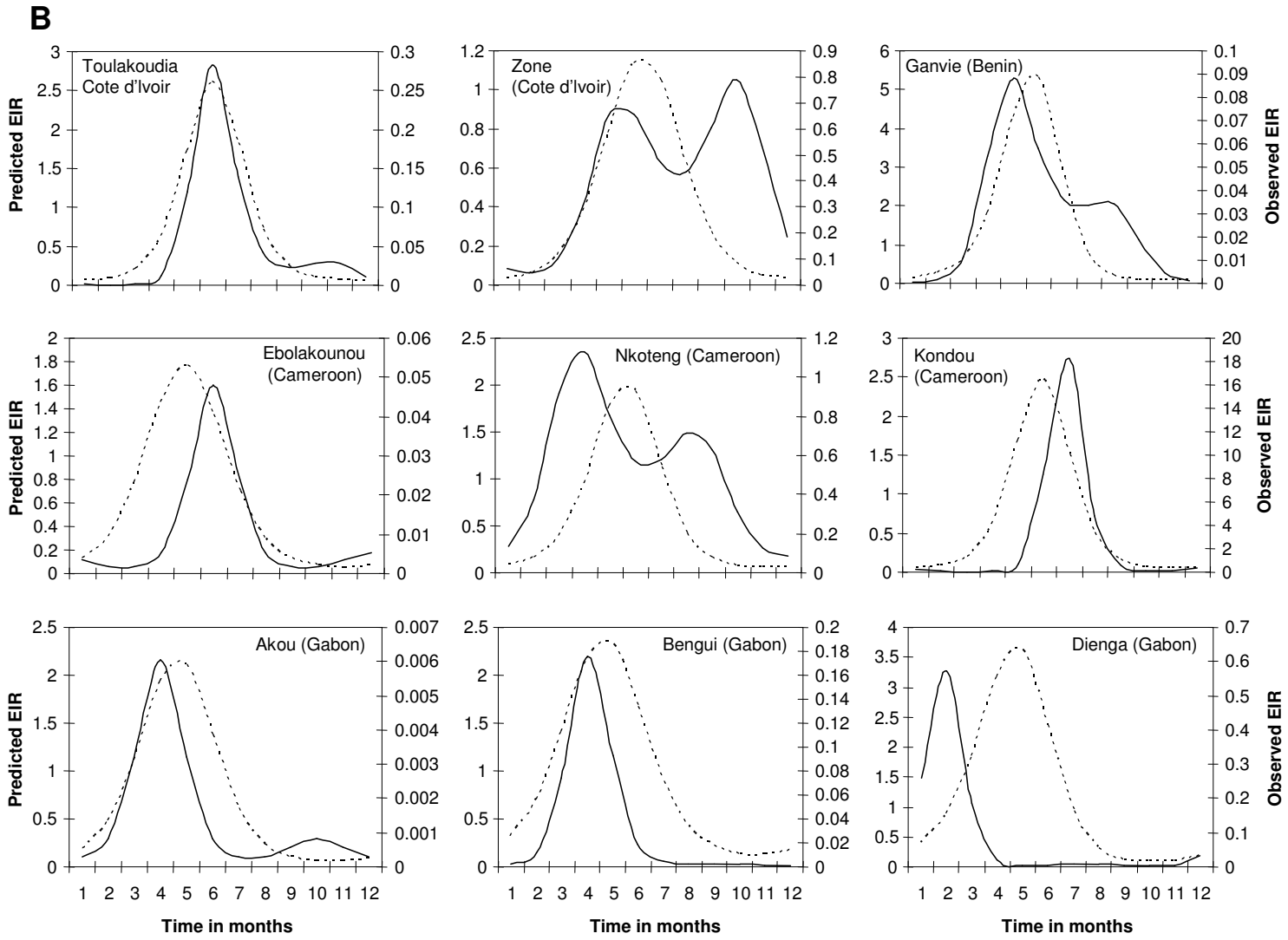


Figure 7.1. Observed versus predicted Fourier coefficients for the logarithm of *An. gambiae s. l.* entomological inoculation rate (EIR) of the annual ($a1_E$, $b1_E$) and biannual ($a2_E$, $b2_E$) cycles.


A
Diohine (Senegal)
Kotiok (Senegal)
Ndiop (Senegal)
Tally Ya (Gambia)
Bayama
Sierra Leon
Ziniare
(Burkina Faso)
Kongodjan
(Burkina Faso)
Tenegue (Mali)
Dokobougou (Mali)
Predicted EIR
Observed EIR
Time in months
1 2 3 4 5 6 7 8 9 10 11 12


B
Toulakoudia
Cote d'Ivoir
Zone
(Cote d'Ivoir)
Ganvie (Benin)
Ebolakounou
(Cameroon)
Nkoteng (Cameroon)
Kondou
(Cameroon)
Akou (Gabon)
Bengui (Gabon)
Dienga (Gabon)
Predicted EIR
Observed EIR
Time in months
1 2 3 4 5 6 7 8 9 10 11 12

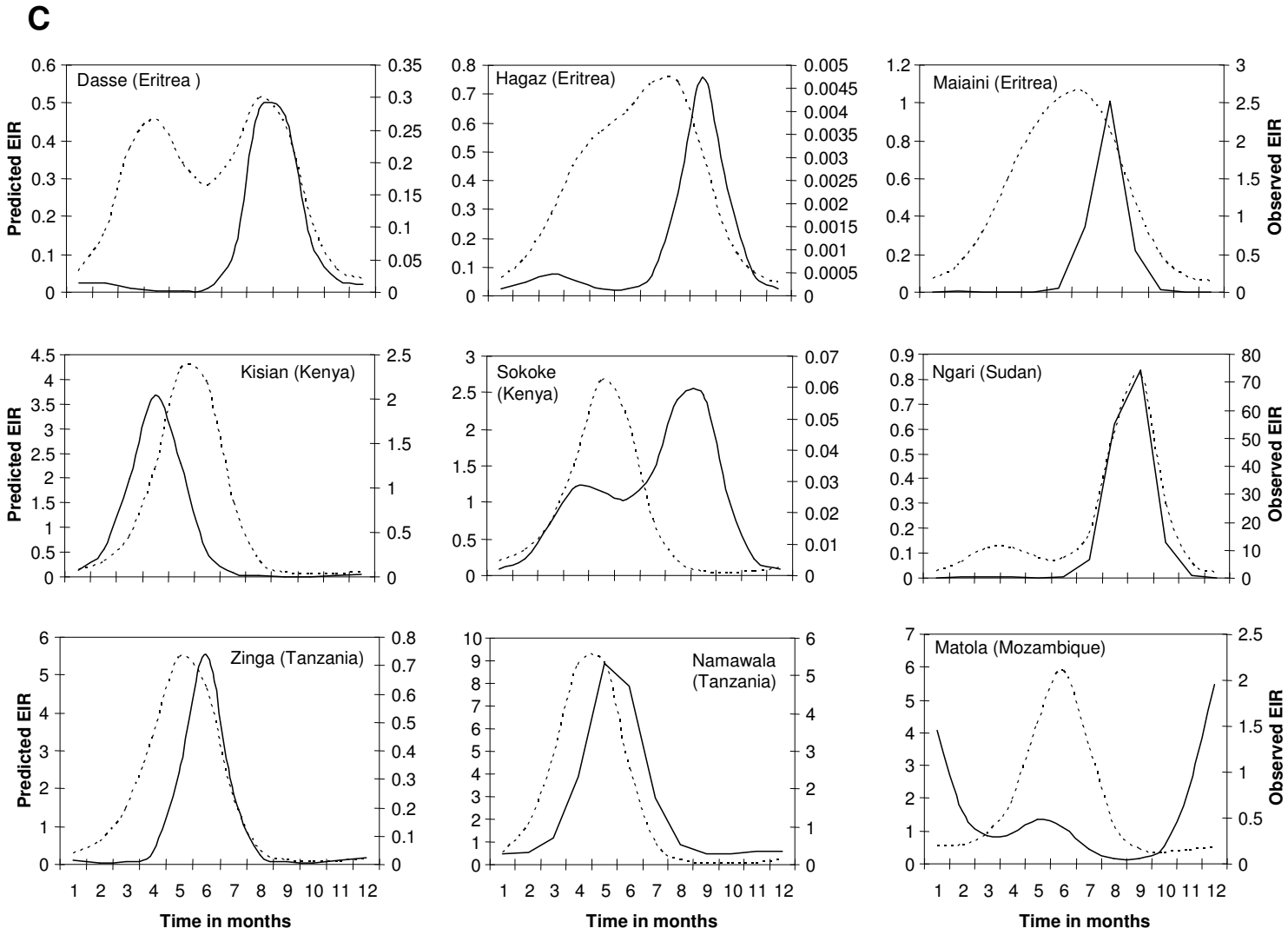


Figure 7.2. Predicted (dotted line) seasonal pattern (Model 1 Table 2.7) versus Fourier approximation of the observed (solid line) seasonal pattern from selected sites in (A) West Africa, (B) west and Central Africa and (B) East Africa.

The predicted degree and timing of malaria seasonality

The parameter estimates from Model 1 were also used to predict the geographical variation of the geometric mean, the timing and phase of the biannual and biannual cycles (Appendix 3A-E). These were in turn used to estimate the degree of malaria seasonality and timing, and the duration of the *An. gambiae* transmission season for the whole of the African continent. For interpretation of predicted surfaces Africa was divided into natural ecological or bioclimatic zones as defined by latitude.

The model predictions (Figure 7.3) suggested that overall the concentration index for the EIR is highest (2.49-3.24) in the Savannah-Sahelian zone between 10˚-20˚ N, 15˚ W-40˚ E and the Greater Horn of Africa (15˚S-25˚ N, 30˚-55˚ E) as well as parts of the eastern and southern tropical and subtropical regions. A moderate degree of seasonality (2.00-2.49) was also predicted in these regions including the West African forest belt 15˚ W and 10˚ E). The lowest degree of seasonality (0.25-1.50) is predicted in the in Sudano-Savannah region approximately 10˚-15˚ N, 15 W˚-40˚ E and in the central equatorial tropical rain forest and its margins (5˚-10˚S, 10˚-30˚E).

Figure 7.4 shows that the predicted peak of transmission in the Savannah-Sahelian region is predominantly in August / September. In the West African coastal zone and forest belt stretching to the Savannah region (5˚ and 10˚ N) the peak is centred on June. In the central equatorial zone the predicted peak is in May. In the greater Horn of Africa there is variation between April to June depending on the location and in the southern tropical and subtropical regions the timing of the peak is in mainly in April or in May.

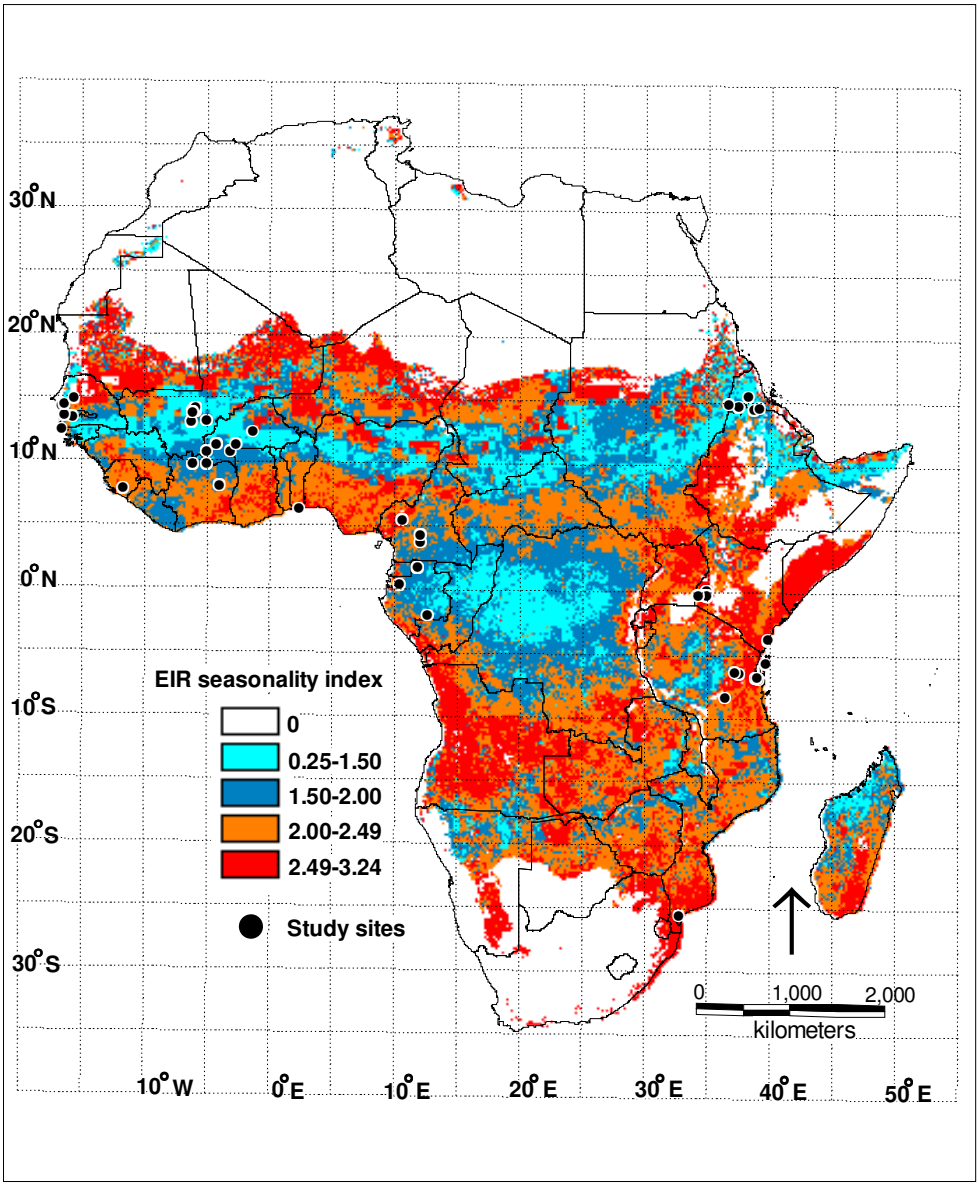


Figure 7.3. Estimated concentration index (CI) of the *An. gambiae s.l.* entomological inoculation rate from Model 1 Table 2.7. Black dots are study sites (n=97).

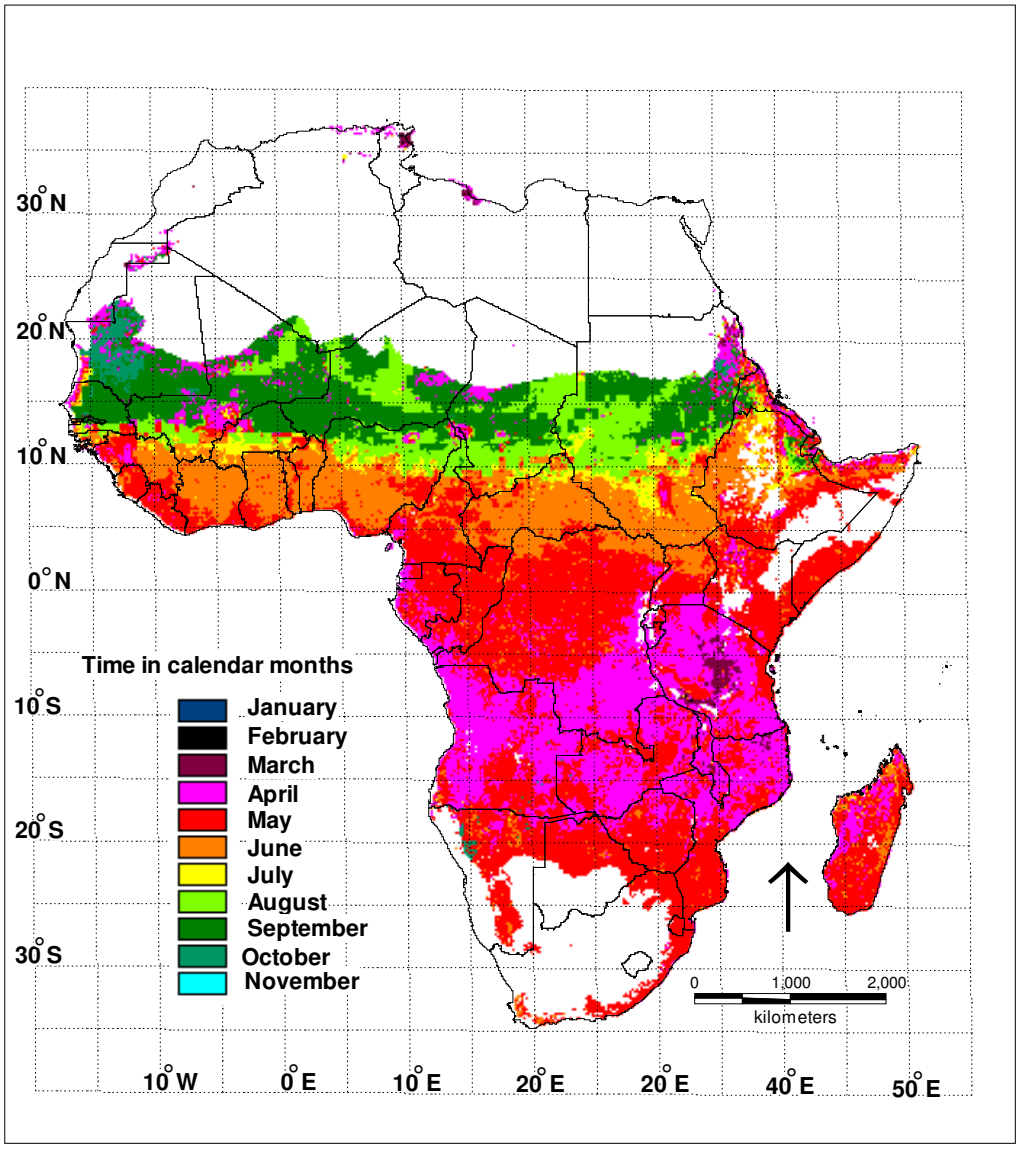


Figure 7.4. Estimated peak month of the *An. gambiae s.l.* entomological inoculation rate (Model 1 Table 2.7).

The predicted duration of seasonal transmission

As one would expect the map of the predicted length of the transmission season (Figure 7.5) suggests that the central equatorial zone and the savannah region have the longest transmission season (8 to 10 months). The shortest transmission season occurs in the Sahel 15˚ and 20˚ N as well as in the eastern and southern parts of the tropical and subtropical regions (1 to 4 months) depending on the location. Intermediate between these regions are areas with the duration of seasonal transmission roughly between four and seven months. Surprisingly, the model predicts shorter transmission season in the West African forest belt than in Savannah areas to the north. Generally, the predicted length of the malaria transmission season compares well with classifications derived using climate based models (Tanser *et al*. 2003).

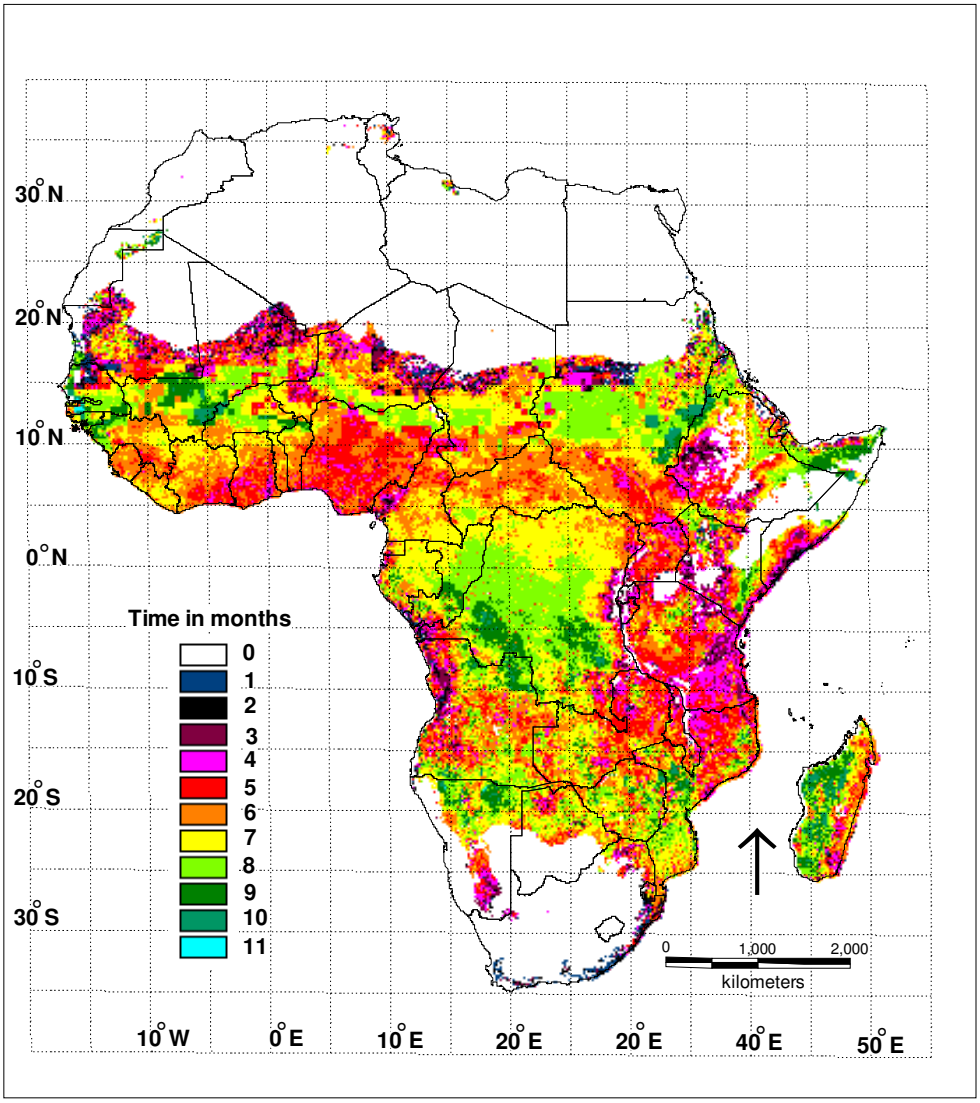


Figure 7.5. Estimated average length of the malaria transmission season by *An. gambiae s.l.* (Model 1 Table 2.7) showing number of months during which transmission is possible defined as the number of months with 95 % of transmission in a given year.

Discussion

In sub-Saharan Africa heterogeneity in malaria epidemiology reflects the complex interaction of many factors including seasonal dynamics as influenced by environmental / climatic conditions (Gillies and De Meillon 1968; Molineaux 1988, Small *et al.* 2003). Improved understanding of the seasonal dynamics of malaria transmission is important for the optimal design of malaria control and prevention strategies. In this study we use an approximation of the discrete Fourier transform for EIR and environmental covariates to describe the amplitude and phase of the annual and biannual seasonal components. This approach allowed us to predict the main seasonal patterns as functions of the empirical relationships between EIR and prevailing climatic / environmental conditions, and thus for the first time to produce maps of the degree of seasonality in malaria transmission and of the period of the year when it peaks.

Seasonal changes in rainfall and air temperature are major determinants of the seasonal characteristics of malaria transmission in the continent. These either limit or trigger seasonal transmission depending on the time of the year and the location. (Craig *et al*. 1999; Hay *et al*. 2000; Tanser *et al*. 2003; Hoshen and Morse 2004; Grover-Kopec et al. 2005). The length of the transmission season is determined by the coincident occurrence and duration of suitable rainfall and optimum temperature conditions as well as terrain and vegetaion (Gillies and De Meillon 1968; Molineaux 1988). In this analysis the predicted seasonal transmission of *An.gambiae s.l.* reflects the heterogeneity in ecological conditions that varies with latitude or altitude across the continent (Reiter *et al*. 2004).

Model predictions show that overall the degree of seasonality is highest in northern and southern parts of the continent towards the limits of malaria distribution with a peak in August / September and April / May, respectively. The nothern margins including parts of the Greater Horn of Africa are charactrized by the shortest transmsion season. In the southern parts of the tropical and subtropical Africa the picture is more complex with a mixture of both long and short transmission season. In the northern part seasonal transmission is set off into wet and dry periods since there is very little variation in temperature, and in the southern parts this includes the onset of elevated temperatures. These include the desert fringe in the north and the semi-arid southern margins as well as highlands areas where seasonal epidemics are the rule (Craig *et al.* 1999; Tanser *et al.* 2003; Hoshen and Morse 2004; Grover-Kopec *et al.* 2005). On the other hand the model suggests that the degree of seasonality is lowest in the Savannah-Sudano region as well as in the central equatorial rainforest zone with a peak in August / September and May, respectively. The duration of seasonal transmission is basically longer in the savannah region and in the central equatorial rainforest zone. In the Savannah-Sudano region the rainfall is more seasonally distributed but transmission continues for the greater parts of the year with considerable seasonal variation. In parts of Savannah the bimodal peak in rainfall including the presence of both wet and dry season vectors may also serve to prolong seasonal transmission (Fontenille and Simard 2004). The central equatorial rainforest region is characterized by optimum temperature and rainfall regimes for the greater part the year, and malaria transmission is perennial but seasonal in nature (Craig *et al.* 1999; Tanser *et al.* 2003; Fontenille and Simard 2004).

The comparison of the fitted seasonal pattern against the observed appears to be reasonably accurate in some parts and less so in other parts of the continent. This is to be expected since the model predictions are based on a long term average and will therefore not necessarily match the site and time specific observed pattern exactly. The magnitude and timing of the most infectious period follows the onset of suitable conditions after an appropriate lag representing vector breeding, their densities, feeding frequency, survival and the extrinsic incubation period of the parasites in the vector mosquitoes (Gillies and De Meillon 1968; Molineaux 1988). The conditions that determine the seasonal cycles of transmission vary between and within sub-regions along a latitudinal gradient north and south of the equator. This may vary from one year to another with the possibility of wide seasonal variation in transmission intensity and timing.

Most study sites used in the analysis do not separate *An. gambiae sensu stricto* from *An. arabiensis* or the salt water species *An. melas* in West Africa and *A. merus* in East Africa. The salt water species show different seasonality and are likely to be important in coastal areas. Model predictions may also be confounded by the presence of *Anopheles arabiensis* which has been shown to sustain all year round transmission even during the dry season in parts of the continent (Trape *et al.* 1994; Lindsay *et al.* 1998; Bayoh *et al.* 2001; Fontenille and Simard 2004). Different chromosomal form of *An. gambiae s.s.* the Savannah, Bamako and Mopti are important west Africa (della Torre *et al*. 2002; della Torre *et al*. 2005). The frequency of these vectors change seasonally (Coluzzi *et al.* 1979), and the accuracy of model prediction will vary in accordance with the predominance of one of the vector species in a given location.

It is important to also acknowledge the limitations of our models and maps since these were derived from sparsely distributed point data collected at a local level and aggregated at a continental level to model average conditions of seasonal transmission. Hence, model predictions may not necessarily match locally derived estimates. The observed seasonal pattern can also change over time. The measure of length of season does not take into account the overall level of transmission so that 5% of the annual transmission in a marginal area might be negligible, while 5% in a high transmission area might be considerable. It follows that if we define seasons of transmission and no transmission there should be a greater contrast between high and low transmission areas than we see in our map.

The EIR are not an unbiased sample of the situation on the ground. The data certainly over represent high transmission sites. On the other hand seasonal geometric mean may be higher in places with short intense seasonal transmission than in places with perennial transmission (appendix 3A). All these underscore the difficulty inherent in trying to model seasonal dynamics of malaria transmission given sparse data in the face of time- and space-dependant potential confounders.

Nevertheless, our models are a starting point for seasonality modelling. We therefore, for the first time, empirically predict and map the degree and timing of malaria seasonality as well as the duration of transmission across sub-Saharan Africa by one of the major malaria vector species. These products can be used to account / calibrate for seasonality

in transmission model based mapping of malaria risk at a country, regional and continental level. Models and maps produced in this work can be refined and / or improved for application at a sub-national level as more malaria and high resolution environmental data becomes available. There is a need for studying together all main vectors, human infectivity and incidence.

Chapter 8: GENERAL DISCUSSION AND CONCLUSIONS

Since the availability of effective tools for malaria control and prevention the geographical description of malaria risk has been high on the research agenda. The availability of new datasets, novel analytical tools and innovative statistical and mathematical models in recent years presents new possibilities for improving existing information and knowledge base. This work is part of the MARA/ ARMA (http://www.mara.org.za/) project, which was motivated by these developments to establish an atlas of malaria risk for Africa. We focus mainly on temporal variations in malaria risk with the aim of developing an empirical model and map of malaria seasonality for sub-Saharan Africa to facilitate optimization of malaria control and / or interventions in both space and time.

The first part of this work focuses on Southern Africa since this is the only region with long-time series of fairly reliable clinical malaria data. The review of malaria control mainly by IRS with insecticides in this region showed that countries that developed national malaria control programmes and had built up human and organizational resources made significant advances towards malaria control. For example, malaria was reduced from high to very low in the different parts of the region. However, IRS is not a magic bullet, and its use in other areas should be planned carefully, after considering the major organizational, technical and financial implications. From this work it is also clear that besides changes ecological diversity as influenced by climatic and environmental factors the extent of malaria control efforts can also alter the level of endemicity.

Consequently, variability observed in our analysis may not be attributable only to climatic / environmental factors as observed elsewhere in the continent (Hay *et al*. 2002a and b; Bouma *et al*. 2003; Craig *et al*. 2004b). It is therefore important to adjust for other potential sources of variation in the observed data.

In the subsequent analysis where we examined the temporal effect of ENSO events on annual malaria incidence in selected countries in Southern Africa, we used year specific random effects as surrogates for unobserved factors influencing annual incidence. The analysis showed that in this region increased incidence follows La Nina (cold event) which leads to wet conditions and that El Nino (warm event) which leads to dry conditions has the opposite effect. This is contrary to observations in East Africa where El Nino has been shown to lead warm-wet conditions and therefore heightened incidence (Loevinsohn 1994; Kilian *et al*. 1999; Lindblade *et al*. 1999; Lindsay *et al*. 2000; Wort *et al*. 2004). However, we also found that the impact of ENSO on malaria incidence in Southern Africa varies over time within and between countries, partly due to existing malaria control efforts and response capacity but also because of spatial variability in climatic conditions over time.

The spatial and temporal variability of annual malaria incidence was investigated using malaria case data from Zimbabwe. A Bayesian statistical modelling framework was used to account for unmeasured spatially and temporary varying potential risk factors. This analysis confirmed that while inter-annual variation in malaria incidence is driven mainly by climatic conditions, the spatial pattern is influenced by factors other risk factors. The

exception was during high and low risk years following the occurrence of extremely dry and wet conditions, respectively. Overall, low lying areas showed less year to year variability in malaria while highland areas showed greater variability. The latter is typical of areas characterized by stable seasonal transmission and the former by unstable seasonal transmission (Craig *et al*. 1999; Tanser *et al*. 2003). This provides useful information for delineating areas prone to climate driven epidemics and for developing climate based seasonal forecasting models. The description of the average seasonality of malaria in a given area is thus important for laying the basis for monitoring seasonal change and variability in transmission / disease risk.

In our initial attempt towards the development of an empirical model of malaria seasonality we used Zimbabwe and the Bayesian space-time statistical approach. The analysis employed the proportion of annual cases occurring in each month as a relative measure of the amount of seasonal transmission occurring in each month. The modelled covariate-adjusted, smoothed monthly estimates enabled us to interpret geographical variation in malaria seasonality which was not apparent in the observed data. This approach quantifies seasonal transmission between months differently from previous studies that classified months as either suitable or not suitable for transmission based on climatic conditions (Thomson *et al*. 1997; Hay *et al*. 1998a & b; Thomson *et al*. 1999; Tanser *et al*. 2003). Most importantly a seasonality concentration index was adapted to summarize the modelled seasonal trend. The index quantifies the concentration of malaria case load and the peak month during the transmission season, and therefore can be used for timely spatial targeting of malaria intervention. This work also raised prospects for

the application of the seasonality index in the modelling and mapping of malaria seasonality across sub-Saharan Africa.

To evaluate the potential application of the seasonality concentration index in the description of malaria across the continent we used the relationship between seasonality in EIR and environmental covariates. The results showed that the rainfall seasonality index and minimum temperature are important predictors of the intensity of inoculation rate during the peak transmission season. However, model fit was poor in areas characterized by bimodal rainfall patterns and irrigation activities though the effect of minimum temperature and rainfall seasonality still seem to operate in irrigated areas. In addition, the seasonality index performed better in areas characterized by a single peak in transmission compared to areas with two peaks. The presence of both *A. gambiae s.l.* (predominant in the wet season) and *A. funestus* (predominant in the dry season) in a given area could have also confounded the analysis. Since the two vector mosquitoes have been shown to sustain potentially perennial transmission or lead to biannual seasonal pattern (Gillies and De Meillon 1968; Elissa *et al*. 1999 and 2003; Cohuet *et al*. 2004). These findings highlighted the need for improved quantification of malaria seasonality in order to capture the complex interplay between the seasonal dynamics of environmental determinants of malaria transmission across the continent.

To improve on this approach we used an approximation of the discrete Fourier transformation for both malaria and environmental data in order to capture important seasonal characteristics of malaria transmission across sub-Saharan Africa. We found that

conditions that determine the most infectious periods vary between and within sub-regions along an altitudinal gradient north and south of the equator. Our models for the first time predict and map the degree and timing of malaria seasonality as well as the duration of transmission across the continent based on the empirical relationship between seasonality in EIR and meteorological determinants. We also estimated the average seasonal pattern based on our model predictions, and although these matched reasonably well with observed data in some study sites, overall the pattern varied depending on the geographical location. This may largely be due to the comparison of long term average model estimates to year specific observed EIR data. Inconsistencies in model predictions especially in the dry regions may be due to the presence of *A. arabiensis* which has also been shown to sustain all year round transmission even during the dry season, and therefore contribute to complexity of the seasonal dynamics of malaria transmission (Trape *et al*. 1994; Lindsay *et al*. 1998; Bayoh *et. al.* 2001). This is case since most study sites used in the analysis do not separate *A. gambiae s.s*. from *A. arabiensis*. However, our models can be refined and / or improved as more detailed malaria and meteorological data become available. The model outputs can be used to calibrate for malaria seasonality in transmission based models for mapping malaria risk at a country, regional and continental level.

Limitations of this work also need to be acknowledged. Firstly, the quality of malaria control efforts and notification data might vary over time, and it is difficult to quantify the potential impact of any such variation in our models. Secondly, in addition to climatic and environmental covariates used in the analysis there are other important potential sources

of variation as alluded to in the respective chapters and simply treating these as random effects might not be enough. We also note that interpolated climate data used is coarse and therefore contain uncertainties that should be borne in mind when dealing with smaller spatial scales. The complex interplay between the different vectorial systems found in Africa with their distinct ecological and behavioural characteristics (Trape *et al*. 1994; Lindsay *et al*. 1998; Bayoh *et. al.* 2001), presents another constraint in our analysis since few studies separate even the most important *A. gambiae* sibling species.

Conclusion

The Bayesian analytical framework used in this study enhanced our ability to evaluate the relationship between malaria and environmental factors, and improved considerably the identification of important associations and covariates. In the final analysis an approximation of the discrete Fourier transformation used removes noise from the original time series and therefore allowed us to model the main seasonal variation in both malaria and meteorological covariates.

This work presents the first step towards the development of improved models of malaria seasonality. While there is still scope for further refining the models as more relevant data become available, model outputs can be used as inputs in transmission models for mapping malaria risk. The seasonality maps produced are also important for determining the most effective moment and geographical position for control efforts to be applied throughout sub-Saharan Africa. In addition, climatic and associated environmental determinants of seasonal and between year-variation in malaria including the impact of

ENSO provide valuable information for the development of empirical seasonal forecasting models.

APPENDICES

Appendix 1: statistical model

We assumed that the observed counts of malaria cases Y_{it} in district i (i = 1,…, 58) and year t (1988-1999) follow a negative binomial distribution with parameters p_{it} and r, that is, $Y_{it} \sim NB(p_{it}, r)$, where p_{it} relates to average number of cases via the formula $(\mu_{it}) = p_{it}/r$ and r is the overdispersion parameter. We modelled average number of new cases (μ_{it}) as a function of potential risk factors as follows:

(1) $\log(\mu_{it}) = \log N_{it} + \alpha + \boldsymbol{X}_{it}^T \boldsymbol{\beta}$ (non-spatial model)

(2) $\log(\mu_{it}) = \log N_{it} + \alpha + \boldsymbol{X}_{it}^T \boldsymbol{\beta} + \phi_i$ (spatial model)

(3) $\log(\mu_{it}) = \log N_{it} + \alpha + \boldsymbol{X}_{it}^T \boldsymbol{\beta} + \phi_i + \omega_{it}$ (spatio-temporal model)

N_{it} denotes population at risk in district i and year t, α is the incidence rate when all covariates have zero value, $\boldsymbol{X}_{it}$ is a vector of climatic covariate effect in district i and year t, $\boldsymbol{\beta}$ a vector of the regression coefficients, ϕ_i is the spatial random effect for district i and ω_{it} is the temporal random effect for year t and district i. District specific random effects were modelled via a conditional autoregressive (CAR) process, which implies that each ϕ_i conditional on the neighbour ϕ_j follows a normal distribution with mean equal to the average of neighbouring ϕ_j and variance inversely proportional to the number of neighbours n_i, that is, $\phi_i \mid \phi_j, j$ neighbouring of $i \sim$ Normal $(\gamma \sum_{i \neq j} \phi_j / n_i, \sigma_\phi^2 / n_i)$ where γ is a parameter that quantifies the amount of spatial correlation present in the data and σ_ϕ^2

measures the spatial variance. The temporal effects were modelled by first order autoregressive process with temporal variance σ_{ω}^{2}, which allows correlation between consecutive time periods for each district and year. We assumed inverse gamma hyper-prior distributions for the variance parameters of the spatial and temporal random effects, non-informative Uniform prior distributions $U(-\infty,\infty)$ for the regression coefficients $\boldsymbol{\beta}$, and a Uniform distribution $U(a,b)$ for γ, with limits *a* and *b* specified as described in Gelfand and Vounatsou (2003).

Appendix 2: Estimating the magntitude and timing of malaria seasonality

We approximated the discrete Fourier transform of Z_t in order to derive statistics describing the seasonal pattern for each pixel, again using average, annual and biannual components, so that for n=1,2:

$$a_0 = \frac{1}{12}\sum_{t=1}^{12} Z_t,$$

$$a_n = \frac{2}{12}\sum_{t=1}^{12} Z_t \cos\left(\frac{2\pi nt}{12}\right),$$

$$b_n = \frac{2}{12}\sum_{t=1}^{12} Z_t \sin\left(\frac{2\pi nt}{12}\right).$$

The annual component of the Fourier transform has one peak, while the biannual component has two peaks. Each of these peaks may be represented as a complex number. We represent the two sums of the peaks of the annual and biannual cycles as,

$$\begin{aligned} z_1 &= r_1 e^{i\psi_1} + r_2 e^{i\psi_2/2}, \\ z_2 &= r_1 e^{i\psi_1} + r_2 e^{i(\psi_2/2+\pi)}, \end{aligned} \tag{3}$$

where,

$$\begin{aligned} r_1 &= |a_1 + ib_1|, \\ r_2 &= |a_2 + ib_2|, \\ \psi_1 &= \mathrm{Arg}(a_1 + ib_1), \\ \psi_2 &= \mathrm{Arg}(a_2 + ib_2), \end{aligned} \tag{4}$$

and $i = \sqrt{-1}$ is the unit imaginary number

The overall amplitude of the seasonal variation is then:

$$A = \mathrm{Max}\left(|z_1|, |z_2|\right), \tag{5}$$

To describe the degree of concentration of the seasonal pattern we used a modified version of Markham's seasonality concentration index (Markham1970; McGee 1977) that

incorporates both seasonal cycles, corresponds to the amplitude divided by the average of Z_t:

$$CI = \mathrm{Max}\left(|z_1|,|z_2|\right)/a_0 . \tag{6}$$

The peak of the transmission season is then given by,

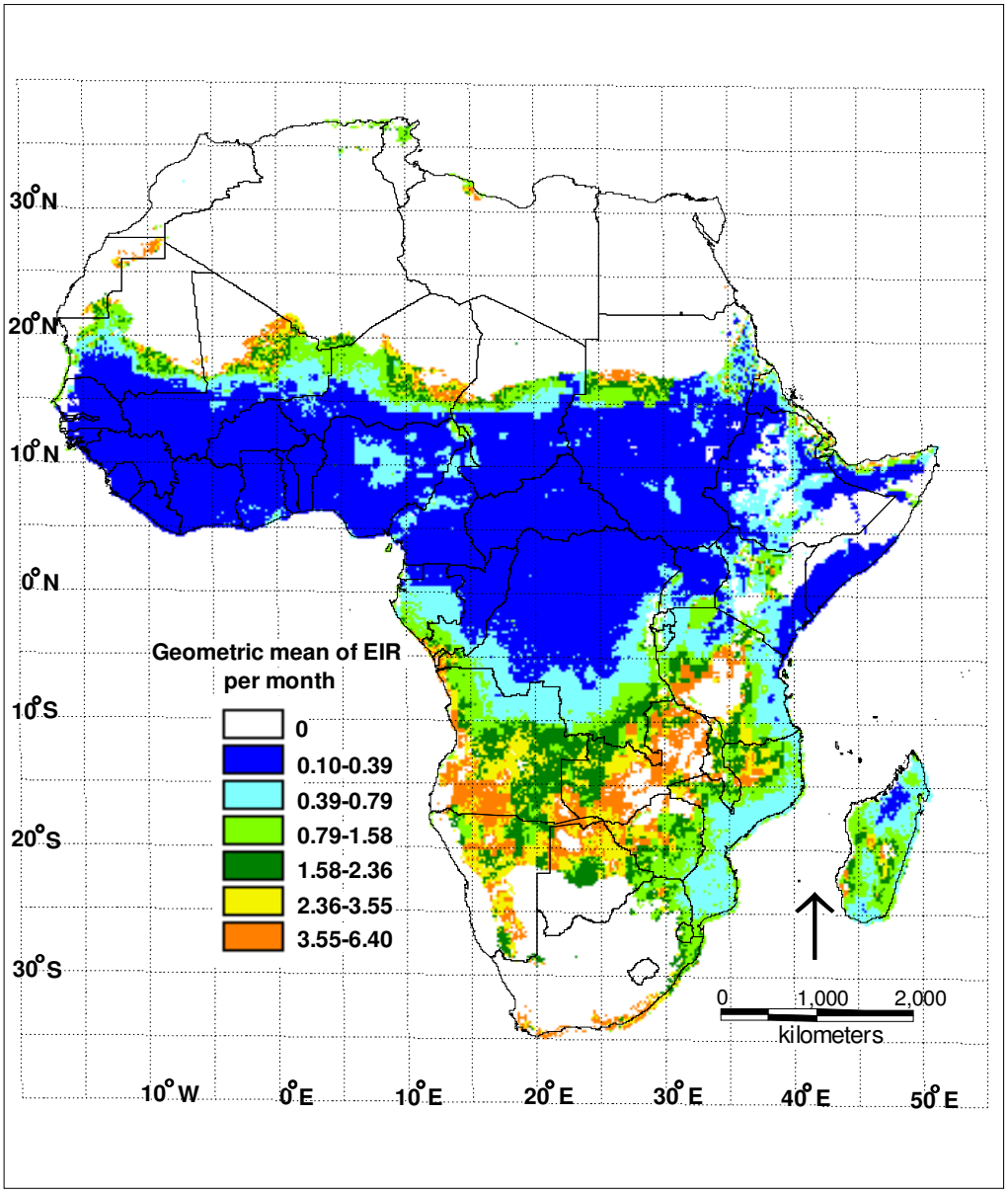
$$CI_\psi = \begin{cases} \mathrm{Arg}(z_1) & |z_1| \geq |z_2| \\ \mathrm{Arg}(z_2) & |z_1| < |z_2| \end{cases}, \tag{7}$$

and the annual duration of transmission, *L*, defined as the number of months accounting for 95% of the estimated EIR, which was calculated by dividing the year into 1000 equal time intervals, for each of which $f(\tau)$ was calculated at τ equal to the midpoint of the intervals. The time intervals were then ranked in descending order of $f(\tau)$ and, *L* estimated by the proportion of intervals (cumulated in rank order) required in order to include 95% of $\int_0^{12} f(\tau)\, d\tau$, where

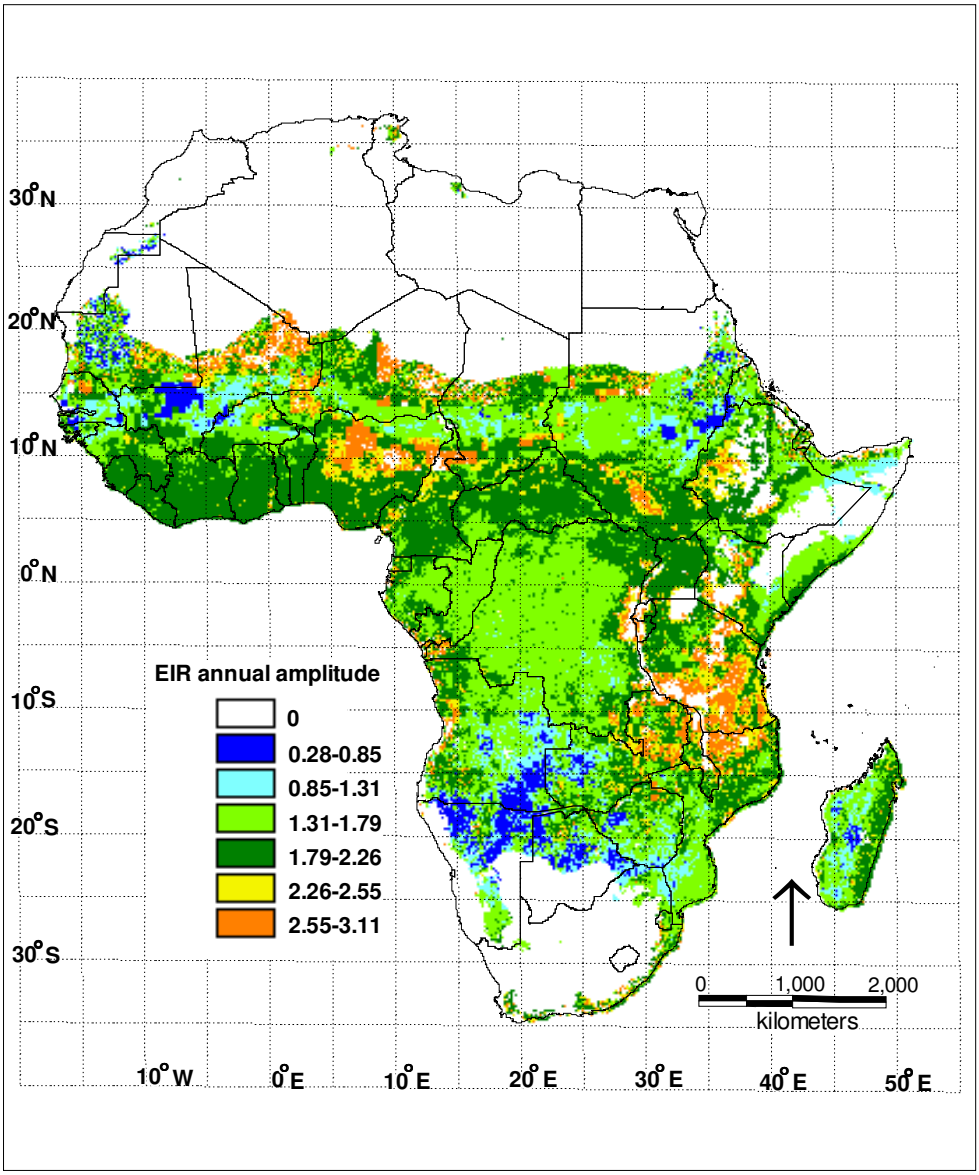
$$f(\tau) = a_0 + a_1 \cos\left(\frac{2\pi\tau}{12}\right) + b_1 \sin\left(\frac{2\pi\tau}{12}\right) + a_2 \cos\left(\frac{2\pi\tau}{6}\right) + b_2 \sin\left(\frac{2\pi\tau}{6}\right) \tag{8}$$

and τ represents the time of year and varies continuously from 0 to 12.

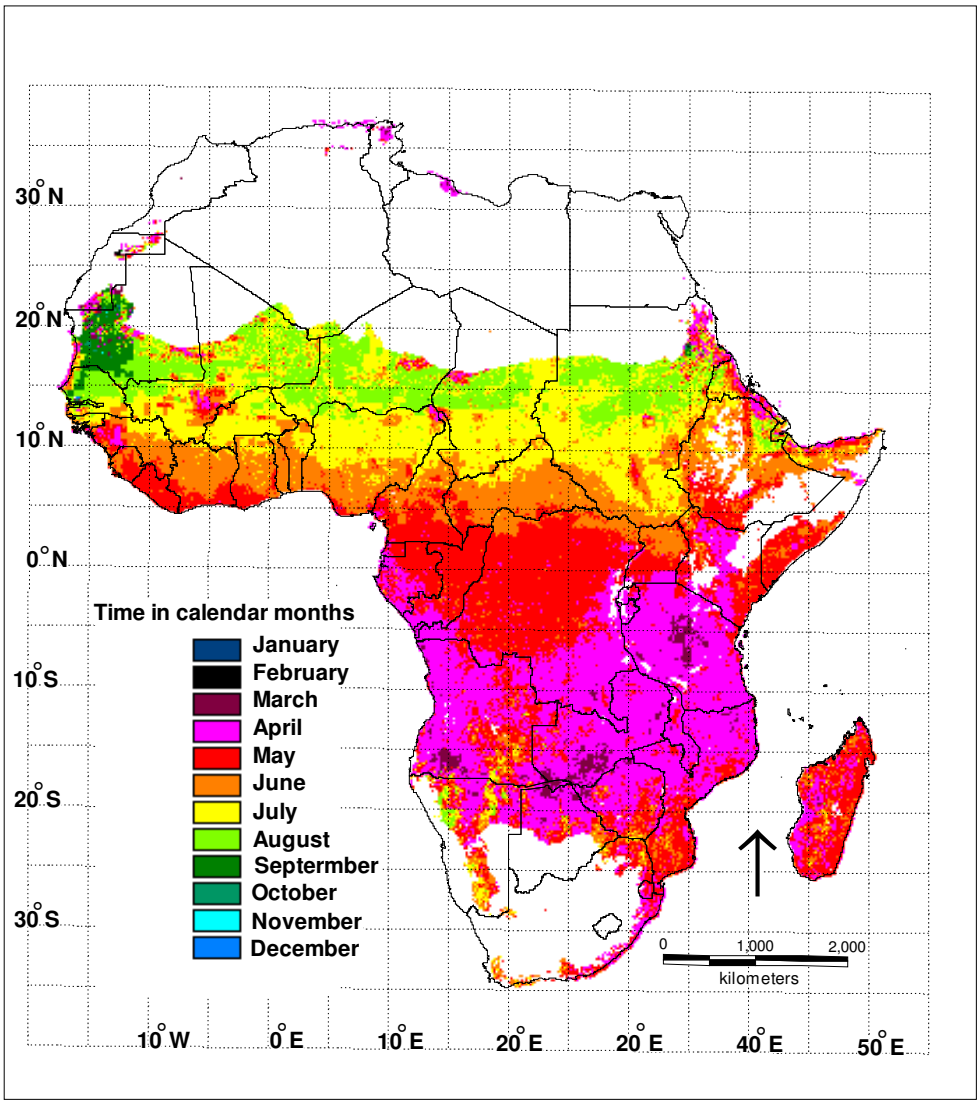
Appendix 3A: Predicted *An. gambiae s.l.* geometric mean of predicted monthly EIR (Model 1 Table 2.7).



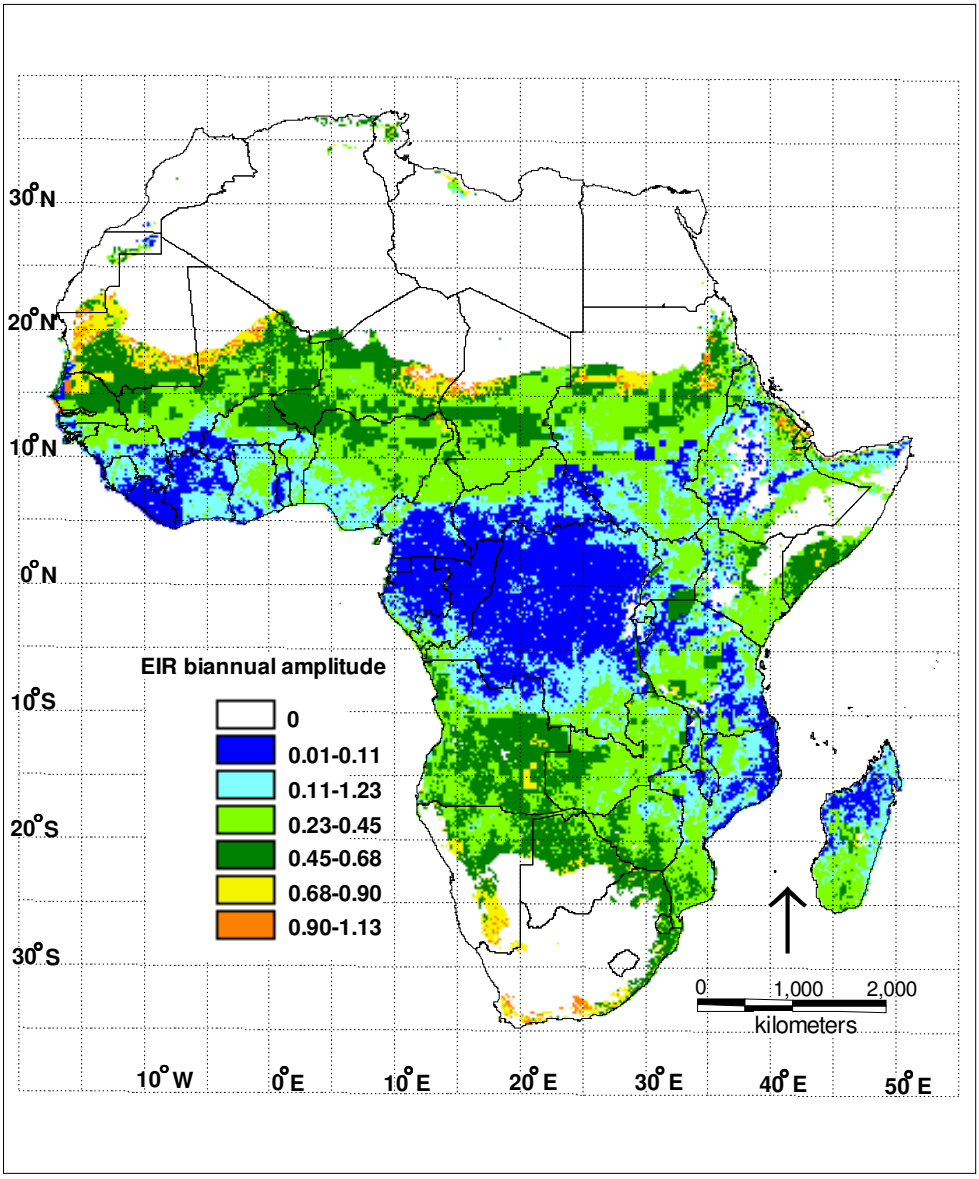
Appendix 3B: Predicted amplitude of the annual component for *An. gambiae s.l.* EIR on a log scale (Model 1 Table 2.7).



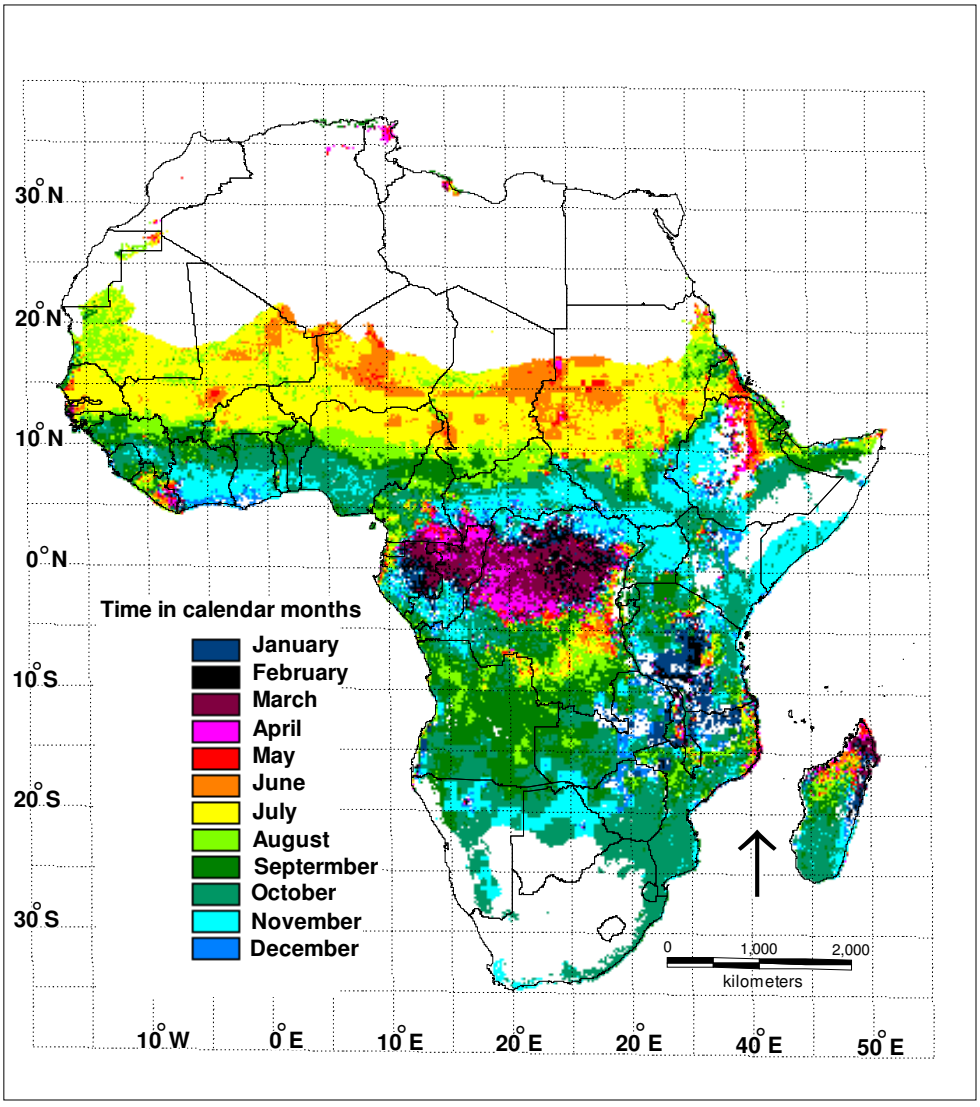
Appendix 3C: Predicted phase of the annual component of the amplitude for *An. gambiae s.l.* EIR (Model 1 Table 2.7).



Appendix 3D: Predicted amplitude of the biannual component for *An. gambiae s.l.* EIR on a log scale (Model 1 Table 2.7).



Appendix 3E: Predicted phase of the biannual component of the amplitude for *An. gambiae s.l.* EIR (Model 1 Table 2.7).



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