Improvement and validation of dynamical malaria models in Africa

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Abstract

Overcoming the serious public health burden of malaria in Africa especially the sub-Saharan Africa requires a detailed understanding of malaria epidemiology in the region. To contribute to this effect, this work embarked on several research steps.
The first part of this study investigated the impact of climatic and environmental factors on seasonal malaria transmission in the Africa. Monthly Entomological Inoculation Rate (EIR_m) data initially gathered from different malaria locations across the region via a literature review was utilized for this purpose. The results revealed that rainfall was the primary climatic determinant of malaria seasonality at markedly seasonal rainfall areas such as Sahel and Eritrea. But its impact at bimodal rainfall distributed and more humid zones was more complex. Temperature was not a limiting factor of malaria seasonality in Africa except for East Africa where it can delay the impact of rainfall. The seasonal peaking characteristics malaria were mostly unimodal. At zones characterised by bimodal rainfall distributions, the peaks were frequently associated with the first rainfall maximum of the year. Seasonal malaria intensity anti-correlated with elevation and population density. Though seasonal malaria transmission is driven mainly by *An. gambiae, An funestus* and *An. arabiensis*, the vectors had competing and complex individual impact on seasonality. The findings of this section have important implications for the disease control especially the spatial and temporal target of malaria interventions and resource allocation. Besides, it provides information regarding future malaria modelling efforts and the validation and evaluation of existing weather-driven malaria models.
The second part of the study validated seasonal malaria transmission in Africa simulated by two malaria models using the observed EIR_m data. The models include the 2010 version of the Liverpool Malaria Model (LMM_{2010}) and the VECtor-borne disease community model of the international centre for theoretical physics,TRIeste (VECTRI). The goal was to determine the accuracy of both models in simulating seasonal malaria transmission in Africa. The validation revealed that LMM_{2010} and VECTRI error ranges were generally within or about the same as the standard deviation of the observed EIR_m data though larger errors were detected for Guinea and some individual monthly minor differences. Both models also agreed with observations that the seasonal peaking behaviour of malaria was predominantly unimodal. However, transmission peaks in the models tend to be delayed by one month in the Sahel and Eritrea area. Both models further agreed with observed values of a seasonality index that the seasonal malaria transmission contrast is closely linked with the latitudinal variation of climatic covariates such as rainfall in Africa. VECTRI revealed a stronger ability in capturing the levels of malaria endemicity in East Africa than LMM_{2010}. The hydrology model in VECTRI poorly captures seasonal malaria transmission at permanent water body locations. Though both models had loopholes, inferences from the validation conclude that they could realistically reproduce the seasonal evolution of the disease in Africa as a function of climate and environment. The findings, therefore,

provides the basis for further review and refinement of the models by their developers to stage them as best fundamental tools for seasonal malaria prediction.
In the third part of this work, a formulated simple model of immunity to malaria and incorporated into VECTRI was evaluated. Also, the section performed a one-at-a-time sensitivity study of VECTRI parameter settings to its output variability. The results revealed that the immunity model enabled VECTRI to simulate different levels of malaria for Africa by reducing transmission rates at increased exposure of humans to malaria. The simple immunity model also substantially improved the seasonal malaria simulations of VECTRI by reducing its output error. The one-at-a-time sensitivity analysis performed on VECTRI parameter settings revealed parameters showing the strongest variation of the model output. The most sensitive parameter settings consisted of survival probabilities (i.e. adult vector and larval survival), threshold temperatures (i.e. minimum temperature for larval survival and that for the sporogonic cycle), degree days (i.e. larvae growth), and hydrological components (i.e. total evaporation and infiltration losses). The new immunity model represents a helpful tool for future malaria modelling effort, and its refinement for consideration in VECTRI is necessary. Parameters contributing most to VECTRI output variability require additional research to strengthen knowledge base to reduce VECTRI output uncertainty.

Zusammenfassung

Nur ein besseres Verständnis der Malariaepidemiologie südlich der Sahara wird es ermöglichen die ernsthafte Belastung der öffentlichen Gesundheit durch diese Krankheit zu überwinden. Die vorliegende Doktorarbeit soll dazu einen Beitrag leisten, indem sie die Malariasaison genauer untersucht. Analysiert wird sowohl die Bedeutung von klimatischen und umgebungsbedingten Antrieben als auch der Einfluss durch unterschiedliche Mückenarten. Außerdem validiert und analysiert sie wetterangetriebene, dynamisch-mathematische Malariamodelle, welche realistische Simulationen von epidemiologischen Malariacharakteristika erstellen.
Diese erste Studie dieser Arbeit untersucht den Einfluss von klimatischen und umgebungsbedingten Faktoren auf die saisonale Verteilung der Malariaübertragung. Hierfür wurde zunächst die Literatur in Bezug auf monatliche Werte der entomologische Inokulationsrate (EIR_m) ausgewertet. Die EIR_m-Werte wurden für unterschiedliche Malariastandorte innerhalb von Subsahara-Afrika zusammengetragen. Für Gebiete mit stark saisonalen Regenfällen hat der Niederschlag den größten klimatischen Einfluss auf die Malariasaison. Für Gebiete, die eine bimodale Regenverteilung aufweisen und feuchter sind, ist der Einfluss komplex. Die Temperatur stellt in Subsahara-Afrika bis auf Ausnahme von Ostafrika keinen limitieren Faktor für die Malariaverbreitung dar. Die Analyse der Spitzen der saisonalen Malariaübertragung zeigt, dass meist unimodale Verteilungen auftreten. Bei bimodaler Niederschlagsverteilung steht die Spitze in der Malariaübertraugung oft in Verbindung mit dem ersten Regenmaximum des Jahres. Die Intensität der Malariasaison ist antikorrelliert mit der Höhenlage und Bevölkerungsdichte. Obgleich die Malariasaison meist durch *An. gambiae, An funestus* und *An. arabiensis* bestimmt wird, besitzen diese Vektoren einen konkurrierenden, komplexen und individuellen Einfluss auf die Saisonalität. Trotzdem die verwendeten Daten einige Unsicherheiten aufweisen hat der erste Teil der vorliegende Arbeit wichtige Implikationen für die zeitliche und räumliche Durchführung von Malariabekämpfungsmaßnahmen und das zur Verfügung stellen von Ressourcen. Die erste Studie hält ebenfalls Informationen in Bezug auf die Validierung und Bewertung von wetterangetriebenen Malariamodellen und für zukünftige Malariamodellierungen bereit.
Die zweite Studie validiert die Ausgabe des LMM_{2010} (Engl.: “2010 version of the Liverpool Malaria Model) und von VECTRI (Engl. “VECtor-borne disease community model of the international centre for theoretical physics,TRIeste”). Die Validierung zeigt, dass die Modelle auf der Basis von Klima- und Umgebungsvariablen in der Lage sind eine realistische Malariasaison zu simulieren. Die Fehler von LMM_{2010} und VECTRI bewegen sich meist innerhalb der Standardabweichung der Beobachtungsdaten. Allerdings wurden für Guinea größere Fehler ausfindig gemacht and es traten ebenfalls kleinere Abweichungen für individuelle Monate auf. Die Charakteristika der Malariaübertragungsspitzen stimmen bei beiden Modellen mit den Beobachtungen überein, bei denen hauptsächlich unimodale Verteilungen auftraten. Die simulierten Spitzen in

der Malariaübertragung treten für den Sahel und Eritrea meist einen Monat später auf als beobachtet. Die Modelle simulieren in etwa den gleichen Malariasaisonalitätsindex wie beobachtet. Letzterer hängt stark von der geographischen Breite und klimatischen Kovariaten wie dem Niederschlag ab. VECTRI trifft die Malariaverhältnisse für Gebiete mit permanentem Wasserangebot nicht sehr gut. Insgesamt zeigen aber die Ergebnisse der zweiten Studie, dass beide Modelle in der Lage sind für Subsahara-Afrika realistische saisonale Malariaübertragungsraten zu simulieren. Diese Studie liefert eine Grundlage für weitere Revisionen und Verbesserungen dieser wetterangetriebenen Modelle, wodurch Werkzeuge entstehen könnten, die eine Malariavorhersage ermöglichen.
Ein neues einfaches Immunitätsmodul von VECTRI wurde abschließend in der dritten Studie der Doktorarbeit untersucht. Dieses Modul ermöglicht VECTRI unterschiedliche Malarianiveaus für Subsahara-Afrika zu simulieren indem die Malariaübertragung reduziert wird, falls Menschen stark der Malaria ausgesetzt sind. Dieses einfache Immunitätsmodul war in der Lage den Modellfehler von VECTRI in Bezug auf saisonale Malariaübertragungsraten zu verkleinern. Eine Sensitivitätsanalyse wurde für die Modellparameter von VECTRI durchgeführt, wobei für jeden Modelllauf immer nur ein Parameter geändert wurde. Die am stärksten sensitiven Parameter stellen Überlebenswahrscheinlichkeiten (Mücken und Larven), Schwellwerttemperaturen (Minimaltemperatur für das Larvenüberleben und für den sporogonischen Zyklus), Gradtage (Larvenentwicklung) und hydrologische Komponenten (Verdunstungs- und Infiltrationsparameter) dar. Die letzte Studie zeigt, dass dieses einfache Immunitätsmodul ein hilfreiches Werkzeug darstellt und dass dieses weiter verbessert werden sollte. Darüber hinaus informiert dieser Teil der Arbeit über weitere Modellparameter, die eingehender erforscht werden müssen.

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Acronyms

EIR	Entomological Inoculation Rate	3
EIR_m	monthly Entomological Inoculation Rate.	3
LMM_{2010}	2010 version of the Liverpool Malaria Model	3
VECTRI	VECtor-borne disease community model of the international centre for theoretical physics, TRIeste	3
Pl.	Plasmodium	6
An.	Anopheles	6
AG	An. gambiae.	25
AF	An. funestus.	25
AA	An. arabiensis	25
AN	An. nili	25
AM	An. moucheti	25
HBR	Human Biting Rate	13
WHO	World Health Organization	13
HLC	Human Landing Catches	14
PSC	Pyrethrum Spray Catches	14
LTC	Light Traps Catches.	14
CSPR	CircumSporozoite Protein Rate.	14
ELISA	Enzyme-Linked Immunosorbent Assay.	14
PCR	Polymerase Chain Reaction.	14
ibpp	infectious mosquito bites per person	19
Pd	Population density.	21
GPDWv3	Gridded Population Density data of the World, version 3	21
PWB	Permanent Water Body	22
ARCv2	African Rainfall Climatology version 2.	19
ERAI	European Centre for Medium-Range Weather Forecasts (ECMWF) Interim Reanalysis	20
SY	Start Year	19
SM	Start Month	19
EY	End Year.	19
EM	End Month	19

CHAPTER 1

Introduction

1.1 The research background

Malaria over the course of history has taken a huge toll on both human life and development in endemic countries (Hay et al. 2010). Some countries in the temperate climate managed to eliminate it (Killeen et al. 2002). Others are engaged in elimination strategies (Feachem et al. 2010). Africa especially the sub-Sahara however, is still occupied with control efforts (Feachem et al. 2010). The disease remains one of the pressing public health problems in the region (Guerra et al. 2008) despite a reduction in its burden over the last decade (WHO 2015). The difficulty in eliminating malaria in the region is due to a complex interplay of many factors (Caminade et al. 2014). The main one being the suitability of climate and environment of the area for malaria transmission (Caminade et al. 2014) that enables the dominance of efficient vectors of the disease (Murray et al. 2012, Sinka et al. 2010). The resistance of malaria parasites to antimalarials (Gregson and Plowe 2005) and malaria vectors to insecticides (Choi et al. 2004, Coetzee and Fontenille 2004) are additional challenges. Other factors include the low socioeconomic status of the region (Tshikuka et al. 1996) and perhaps lack of political will.

Climate and environmental covariates reportedly impact on the development dynamics of both the vectors and parasite (Craig et al. 1999, Gething et al. 2011, Kirby and Lindsay 2009). Their influence trickles further on the behaviour of the vectors, their density and the number of infective mosquito bites a person receives per unit time (Fontenille et al. 1997, Molineaux and Gramiccia 1990). As a result, a temporal and spatial variability of the disease transmission occurs in Africa particularly the sub-Saharan Africa (Mbogo et al. 1995, Robert et al. 2003, Shililu et al. 2003). Another influence of malaria transmission dynamics in the sub-region is linked to the level of immunity acquired by the dwelling population (Molineaux et al. 1988). Due to acquired immunity to malaria, the disease infection moves differentially within the different age groups and gender of the sub-Saharan African population (Doolan et al. 2009, Mandal et al. 2011).

To eliminate malaria in Africa may require a complete trace of the disease progression path. This includes an understanding of the influence of climate and environmental factors including vector type and immune status of the population at stake on the disease seasonality. These, coupled with strengthening health systems, developing infrastructure and poverty reduction, will accelerate the elimination process. Since the systemic interaction of malaria is dynamic, the use of dynamical mathematical malaria models is necessary. These models can provide an explicit framework to understand and analyze the complex transmission pathways of the disease (Dobson and Carper 1992,

Mandal et al. 2011, Patz et al. 2003).

1.2 Statement of the Problem

Studies about the impact of climate and environment including vector type on malaria seasonality in Africa exist. But a comprehensive assessment of the disease in this regard using observed monthly Entomological Inoculation Rate (EIR_m) data across a wide range of different epidemiological settings in the region is scarce. Some previous attempts (Craig et al. 1999, Ermert et al. 2011b, Grover-Kopec et al. 2006, Tanser et al. 2003) relied on model simulated or other surrogates data. Other works that used Entomological Inoculation Rate (EIR) data (Mabaso et al. 2007, Roca-Feltrer et al. 2009) either lumped data from different climate settings or provided no adequate information about the individual influence of climatic and environmental variables. Many other studies (Briet et al. 2008, Giha et al. 2005, Kleinschmidt et al. 2001, Mabaso et al. 2005, Teklehaimanot et al. 2004, Thomson et al. 1999, Yé et al. 2007) relied on prevalence or clinical malaria cases gathered from hospitals or clinics. But prevalence or case data are problematic because they are a cluster of different transmission windows (Reiner Jr et al. 2015). Besides, there are enormous variations in health seeking behaviour of humans and health policies (Afrane et al. 2012). Hence, evidence of the impact of climate and environment on seasonal malaria transmission in Africa especially the sub-Saharan is unconsolidated and require further probe.

Moreover, VECtor-borne disease community model of the international centre for theoretical physics, TRIeste (VECTRI) (Tompkins and Ermert 2013) and 2010 version of the Liverpool Malaria Model (LMM_{2010}) (Ermert et al. 2011a), are weather-driven dynamical mathematical malaria models. They are scientifically sound and found to simulate realistic malaria transmission rates for epidemic and endemic areas in Africa (Ermert et al. 2011a, Tompkins and Ermert 2013). They have contributed to the understanding of malaria transmission dynamics in the region (Caminade et al. 2014, Ermert et al. 2012; 2013, Tompkins and Di Giuseppe 2015). But despite their acceptability and application in the area, their simulation of seasonal malaria patterns for the region has not been extensively validated and evaluated with observed data from many different locations across the region. It means then that their seasonal malaria simulations may not be representative of the local conditions of the area. This applies in particular since most locations of the region are meteorologically different from those that were used during model calibration and validation. For these reasons, their prediction capabilities, accuracy and generality of their simulated malaria seasonality compared to measured values are largely not maximized and indefensible.

The last but not the least, VECTRI is a regionally scaled, high resolution (on the order of 1-5 km) model that innovatively incorporates vector-host interaction and accounts for population density and surface hydrology (Tompkins and Ermert 2013). Despite its novelty and provision of adequate approximations of biological and epidemiological features of malaria in Africa (Caminade et al. 2014, Tompkins and Di Giuseppe 2015), immunity to malaria is missing in its formulations. Since immunity is an important malaria transmission determinant in sub-Saharan Africa (Doolan et al. 2009), its absence in VECTRI suggests the model may be unable to describe the overall malaria transmission dynamics in the region quantitatively. Also, VECTRI parameter settings

have not been optimized to determine their relative importance to malaria outcome. Since parameter settings are most influential on model output (Chitnis et al. 2008), determining their sensitivity to the model outcome is critical for VECTRI validation and guide for future research efforts (Hamby 1994).

1.3 Research questions

To find solutions to the identified problems this research addresses the following questions:

1. Can we use EIR_m data to understand how climate and environment including mosquito type influence seasonal malaria transmission in Africa?
   (a) How do climatic factors such as rainfall and temperature influence seasonal malaria transmission?
   (b) How do hydrological settings such as irrigation and permanent water bodies affect malaria seasonality?
   (c) Is malaria seasonality different at population density domains such as urban, peri-urban and rural areas?
   (d) Does malaria seasonality differ at different elevations?
   (e) How do vector type and their distribution in various climatological settings affect malaria seasonality?
2. Do VECTRI and LMM_{2010} simulate realistic seasonal malaria patterns in Africa as a function of climate and environment?
3. Can a model of immunity to malaria be formulated to understand its impact on seasonal malaria transmission in Africa?
4. Does incorporating immunity into VECTRI make it more realistic and reliable for seasonal malaria study in Africa?
5. How does VECTRI parameter settings influence its seasonal malaria outcome?
   (a) Can we optimize the parameter settings of VECTRI to determine their relative importance to VECTRI simulation of seasonal malaria?
   (b) Which parameters of VECTRI contribute most to its output variability and require additional research to reduce the uncertainty or are insignificant and can be eliminated from the model settings?

1.4 Objectives

The study seeks to achieve the following objectives:

1. Determine the impact of climatic and environmental variables including mosquito species on malaria seasonality in Africa.

2. Verify the accuracy of LMM_{2010} and VECTRI in simulating seasonal malaria transmission in Africa as a function of climate and environment.

3. Evaluate the reliability of a formulated simple model of immunity to malaria in Africa.

4. Improve VECTRI's simulation of seasonal malaria by incorporating the formulated immunity model into its structure.

5. Ascertain the relative importance of VECTRI parameter settings to its seasonal malaria simulations through a sensitivity study.

1.5 Organization of the thesis

The research is organized into the following chapters: In chapter one the motivation to this study encompassing problem statement, research questions, and objectives are presented.
Chapter two reviews the literature on the Plasmodium parasite prevalence, burden, transmission drivers, metrics for estimation malaria transmission, and weather-driven dynamical mathematical malaria models.
In chapter three, the impact of climatic and environmental factors including vector species on seasonal malaria transmission using spatial EIR_m data is presented.
Chapter four uses EIR_m data to validate and evaluate the accuracy of VECTRI and LMM_{2010} in simulating seasonal epidemiological patterns of malaria in Africa.
In Chapter five, the reliability of a formulated simple model of immunity to malaria is evaluated. The chapter also examines whether or not an inclusion of the immunity model into VECTRI structure improved its simulation of seasonal malaria transmission in Africa. Besides, the relative importance of VECTRI parameter settings to its seasonal malaria simulations was examined through a sensitivity study. The thesis is concluded in chapter six with summary, discussions and future outlooks.

CHAPTER 2

Literature review

2.1 Malaria and the Plasmodium parasite

Malaria is a life-threatening vector-borne disease caused by the genus Plasmodium parasite (WHO 2015). Primary route of human infection is through bites of sporozoites infected female Anopheles (An.) mosquitoes during blood meal (Ross 1897). Infection can also take place via shared contaminated sharps (eg. needles, blades, syringes), mother to child during pregnancy and delivery, blood transfusion and organ transplant (WHO 2014). Symptoms may include fever, headache, muscle aches, chills, tiredness, nausea, vomiting and diarrhoea (Laishram et al. 2012, WHO 2000). Complicated symptoms may involve the nervous, respiratory and renal systems (Trampuz et al. 2003). Five species of the parasite causes disease in humans namely Plasmodium (Pl.) *falciparum, vivax, malariae, ovale and knowlesi* (Singh and Daneshvar 2013, WHO 2015).

2.1.1 The genus Plasmodium life cyle

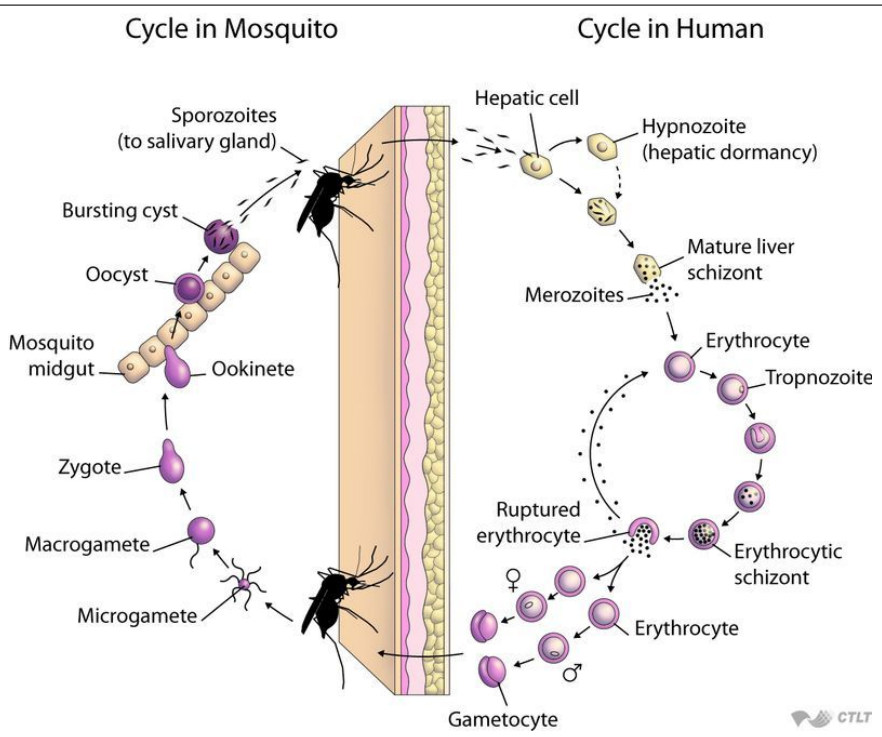

Figure 2.1: The life cycle of the genus Plasmodium parasite. Source: JHSPHOPEN-Courseware (2016)

The parasite's life cycle is reportedly complex, involving sexual and asexual developmental stages and alternates between the female An. mosquito (the vector) and the human host (Aron 1988, Aron and May 1982). The five human species informedly exhibit similar life cycle (Gueirard et al. 2010) as illustrated diagrammatically in Figure 2.1.

During a blood meal, a sporozoite-infected female An. mosquito injects some of the sporozoites (fewer than 100 (Ponnudurai et al. 1991, Rosenberg et al. 1990)) into the human bloodstream. The inoculated sporozoites find their way into the liver and invade the liver cells called hepatocytes (Bailey 1988, Mota et al. 2001). While in the liver, they undergo asexual multiplication (schizogony) for a period (about 9-14 days for Pl. *falciparum*, 12-17 days for Pl. *vivax* and 18-40 days for Pl. *malariae* (Warrell 2002)) to form merozoites (Bousema et al. 2014, Josling and Llinas 2015). Matured merozoites exit the hepatocytes after fracturing them and occupy the red blood cells (erythrocytes). In the blood, they engage in a cycle of erythrocytes invasion and rupture. First, they enlarge into trophozoite after conquering the red blood cell. The trophozoites undergo asexual divisions to form schizonts. Matured schizonts then rupture freeing the newly formed merozoites (about 15 to 30 (Homann 2008)) into the blood that re-invade new erythrocytes (Miller et al. 2002). This cycle repeats about 1-3 days, infecting thousands of red blood cells of the host leading to illness and complications if not treated (Diebner et al. 2000).

Some of the merozoite (<10%) leave the asexual replication cycle and develop into sexual forms of the parasite, called gametocytes (Josling and Llinas 2015). A female An. mosquito having a blood meal on an infected human may ingest these gametocytes. In the mosquito midgut, the gametocytes develop further into male and female gametes which fuse to form diploid zygotes. The Zygotes develop into ookinetes that burrow through the mosquito midgut wall and form oocysts. After a period of growth in the mosquito gut (12 days for Pl. falciparum (Anderson and May 1991, Bruce-Chwatt et al. 1973)), the oocyst bursts and release the newly formed sporozoites into the body cavity of the mosquito. The sporozoites then maneuver their way into the mosquito salivary glands where they remain in wait for another human infection cycle (Bousema et al. 2014, Josling and Llinas 2015).

2.1.2 Epidemiology and burden of malaria

Malaria occurs throughout most of the tropical and subtropical regions of the world (see Figure 2.2). Africa especially the sub-Saharan is, however, the most malaria troubled region (Guerra et al. 2008). For instance, out of about 214 million new cases and 438000 malaria deaths estimated worldwide in 2015, 88% of the cases and 90% of the deaths (especially children under five years) were from the African region (WHO 2015). The disease remains perennial in most parts and one of the major public health concerns of the area (Grover-Kopec et al. 2006), despite a reduction in incidence and mortality rates by 42% and 66% respectively between 2000 and 2015 (WHO 2015). The poorest and marginalised communities are often the most severely affected (Gallup and Sachs 2001).

Of the five human species, Pl. *falciparum and vivax* pose the greatest public health

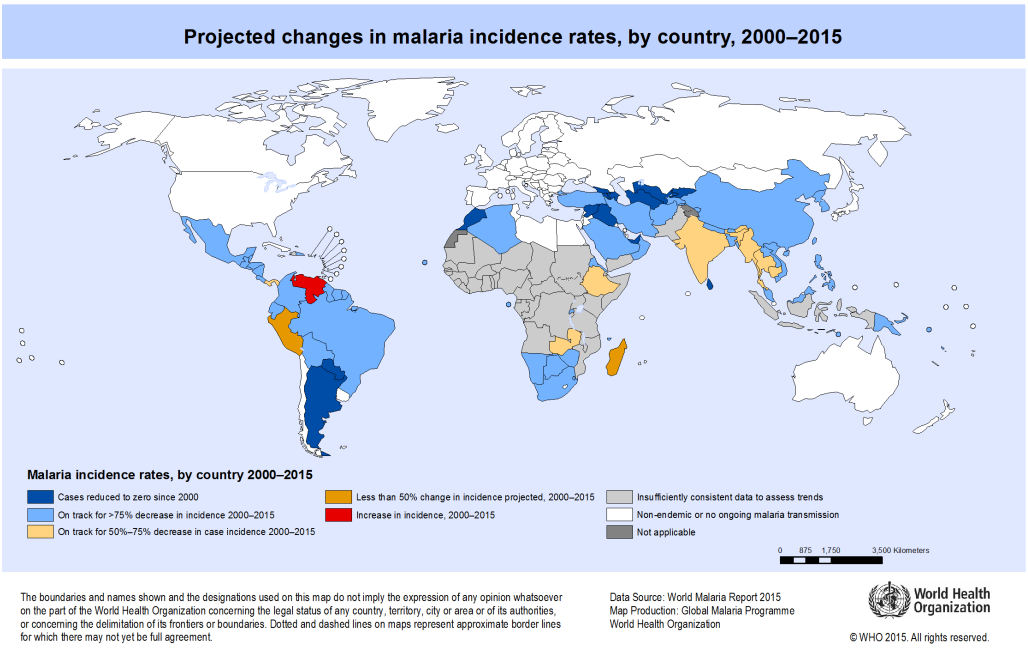

Figure 2.2: Projected changes in malaria incidence rates by country, 2000–2015. Source: (WHO 2015)

challenge (WHO 2015). Pl. *falciparum* is said to be the deadliest and the most widespread in the tropics especially Africa (Guerra et al. 2008, Guyatt and Snow 2001, Hammerich et al. 2002, Hay et al. 2010, McQueen and McKenzie 2004). Pl. *vivax* is supposedly rare in Africa with cases constrained to Madagascar and parts of the Horn (Gething et al. 2012, Mendis et al. 2001). Much of *vivax* (about 80-90%) occur in the Middle East, Asia, and the Western Pacific, with about 10-15% in Central and South America (Mendis et al. 2001). Pl. *vivax* rarely cause death but inflicts debilitating fever, chills, nausea, vomiting, and myalgia (Baird 2004). Pl. *malariae, ovale and knowlesi* contribute a small proportion of malaria infection (Doolan et al. 2009, WHO 2015). Pl. *malariae* is widespread in sub-Saharan Africa, much of south-east Asia, Indonesia and many of the islands of the western Pacific (Collins and Jeffery 2007). Pl. *ovale* is naturally distributed in sub-Saharan Africa and the islands of the western Pacific (Collins and Jeffery 2005). Pl. *knowlesi* (the zoonosis) is widely distributed in south-east especially in Malaysia (Cox-Singh and B 2008, Singh and Daneshvar 2013, White 2008). Sympatric and co-infection of the parasite species have been reported. In Africa, Pl. *malariae* is frequently found in sympatry with Pl. *falciparum* (Collins and Jeffery 2007). In Burkina Faso for instance, Gneme et al. (2013) found Pl. *falciparum* co-existing with *malariae* and *ovale*. Similar co-infection interactions in the sub-region have also been reported in other studies such as McKenzie et al. (2002) and Bousema et al. (2008).

2.2 Malaria transmission drivers

2.2.1 Vector species

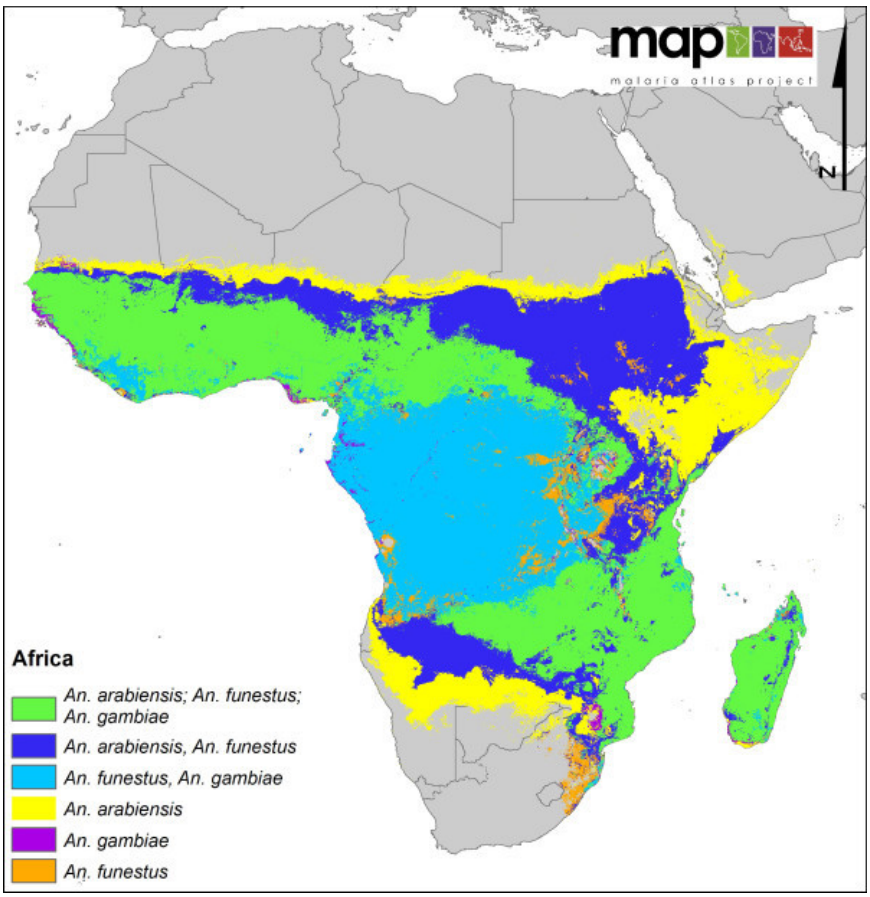

Figure 2.3: The distribution of three most dominant malaria vectors in Africa. Source: Sinka et al. (2012)

The high prevalence, morbidity and mortality rates of malaria in sub-Saharan Africa is partly blamed on the dominance of the most efficient malaria vectors in the region (Guerra et al. 2008, Hay et al. 2009). Reported dominant species include *An. gambiae complex (gambiae ss, arabiensis, melas, merus), funestus, nili and moucheti* (Coetzee et al. 2000, Coetzee and Fontenille 2004, Levine et al. 2004, Lindsay et al. 1998, Murray et al. 2012, Sinka et al. 2010). *An. gambiae complex* class (especially *An. gambiae ss and arabiensis*) and *An. funestus* have been observed as the most efficient vectors in the region(Sinka et al. 2010, White 1974). Their geographic distribution and the sympatric association is displayed in Figure 2.3. Collins and Besansky (1994) indicates that a chunk of malaria cases in Africa are attributed almost entirely to these three vectors. According to Coosemans et al. (1992), they are responsible for most of the malaria cases due to their high anthropophilic behaviour (although *An. arabiensis* is less anthropophilic when cattle feeding opportunity exists). Besides, *An. gambiae and funestus* are long-lived vectors (high longevity).

2.2.2 Meteorological factors

Rainfall

Rainfall has been linked with malaria since the early days of the disease research (Gill 1920). Rainfall reportedly provide the aquatic sites needed by gravid malaria vectors to lay their eggs to develop into adult vector through stages of larvae and pupae (Martens et al. 1995, Molineaux 1988, Reiter 2001). Emerging adults then disperse according to their flight range (Kar et al. 2014). Besides, rainfall informedly provide humidity (at least 60%) suitable for vector survival (Reiter 2001, Thompson et al. 2005). Studies (Craig et al. 1999, Gill 1920) have reported a correlation between the onset of rainy season and an increase in vector abundance. For instance, in a prospective analysis of malaria epidemic associated with El Niñoin in Ugandan highlands, Lindblade et al. (1999) found that rainfall anomaly correlated positively with vector density one month later. Rainfall has also resulted in malaria epidemics at malaria-free zones. For instance, Fontaine et al. (1961) report that the 1958 malaria epidemics outbreak in Ethiopia was a due to an unusually high rainfall amount. Lindsay and Martens (1998) also attributed the 1940 malaria outbreak in Nairobi Kenya to rain. Moderate rain is beneficial for the immature mosquitoes (water-bound stages) to strive and survive. But excessive rain may result in higher water levels, high flow velocities and flooding of water impoundments which are detrimental to their survival (Martens et al. 1995, Paaijmans et al. 2007).

Temperature

Temperature regulates the rate of development and survivorship of both the vector and the parasite (Bayoh and Lindsay 2003; 2004, Beck-Johnson et al. 2013, Martens et al. 1995). According to Craig et al. (1999), the minimum temperature required for the development of *Plasmodium falciparum and vivax* approximates to 18°C and 15°C, respectively. High (low) temperature is reported to shorten (lengthen) the time required for mosquito and parasite maturation (le Sueur and Sharp 1991, Rueda et al. 1990). Teklehaimanot et al. (2004) indicate that larval development may take more than 45 days at 16°C compared to only 10 days at 30°C. Craig et al. (1999) reports that the sporogonic cycle might take about 9 to 10 days at temperatures of 28°C but cease at temperatures below 16°C. Other studies (Bayoh and Lindsay 2003; 2004, Beier 1998) have suggested that the speed of the gonotrophic cycle which determines the feeding frequency of mosquitoes and the proportions of infective mosquitoes is also temperature regulated. Regarding vector survival, Craig et al. (1999) put forward that the daily vector survival is about 90% at temperatures between 16°C and 36°C with peak survival at temperatures between 28°C to 32°C. Kirby and Lindsay (2009) point out that temperatures above 40°C are often fatal to mosquitoes (Kirby and Lindsay 2009).

2.2.3 Environmental factors

Elevation

Malaria transmission intensity varies with altitude due to associated changes in temperature (Drakeley et al. 2005). Cool temperatures at high elevations unlike at low elevations limit malaria transmission. For instance, Bodker et al. (2003) found high malaria transmission intensity at lowlands than at highland areas at six villages in the Usambara Mountains in Tanzania along an altitude transect from 300m to 1700m.

In Papua New Guinea, Attenborough et al. (1997) established that the proportions of mosquitoes with malaria circumsporozoite antigens diminished with increasing altitude along a transect from 170 to 1000m. At different altitudes in western highlands of Kenya, Akhwale et al. (2004) detected that high prevalence of Plasmodium falciparum infection at lowland villages was concomitant with high anaemia than at highland areas. In Tanzania, Balls et al. (2004) found in seven villages located at altitudes between 300m to 1650m a decline in splenomegaly risk with increasing height. Again in Tanzania, Maxwell et al. (2003) found that EIR were 17 times greater at the low-elevated location than at high-elevated areas.

Population density

Population density differentiates malaria transmission intensity between rural, peri-urban and urban settings (Tompkins and Ermert 2013, Vercruysse et al. 1983). Among these settings, a general trend of increasing malaria transmission from urban to peri-urban and to rural centres have been reported (Hay et al. 2005, Keiser et al. 2004, Wang et al. 2005). For instance, in sub-Saharan African cities, Robert et al. (2003) found that the annual mean EIR increased from 7.1 at the city centres to 45.8 at peri-urban areas to 167.7 at rural locations. In Burkina Faso, Modiano et al. (1999) found epidemiological profiles and clinical malaria patterns to be high in rural settings than at urban environments. This pattern is explained by the fact that, the increase in population density from the countryside to cities result in a decrease in biting ratios (Kelly-Hope and McKenzie 2009). Additionally, polluted breedings grounds and access to public health services in urban areas also lowers transmission (Hay et al. 2005).

However, some studies reported otherwise. In Libreville, Gabon, Mourou et al. (2012) recorded high EIR in the most central and urbanized quarter than at the peripheral area. At Cotonou in Benin, Wang et al. (2006) reported high prevalence rates of parasitemia (9.0%) in the intermediate than the center (2.6%) and periphery (2.5%). Reasons for this pattern has been blamed on localized differences in environmental settings. According to De Silva and Marshall (2012), high malaria in urban areas may be due to low socioeconomic status and adaptation of malaria vectors to the urban environment. Added, most African cities grow outwards with relatively under-developed or poorly serviced settlements in peri-urban areas (Byrne 2007). Such development activities are accompanied by open pits and burrows which serve as a source of vector breeding leading to high malaria. Some suburban dwellers may engage in agriculture for livelihood which provides breeding grounds for mosquitoes due to the formation of shallow water between seed beds (Adiamah et al. 1993, De Silva and Marshall 2012).

Temporal and permanent water bodies

Temporal and permanent water impoundments supposedly serve as potential habitat for water-bound stages of malaria vectors (Fillinger et al. 2009, Kar et al. 2014). Studies have established the relationship between water bodies and malaria transmission. In Kenya, Zhou et al. (2007) found that Anopheles gambiae and funestus populations decreased with increasing distance from the Yala river. In Ethiopia, Lautze et al. (2007) noted that malaria case rates among people living within 3km of the Koka reservoir was 1.5 times greater than those between 3-6km and 2.3 times higher than those within 6-9km off the reservoir. Temporal breedings sites such as puddles and ponds get water for breeding only in the rainy season. Permanent breeding sites such as rivers, lakes, and

streams contain water year round and tend to support a year-round malaria transmission (Gianotti et al. 2009). Droughts may slow down or stop water flow in permanent water bodies, increasing their ability to support vector breeding (Haque et al. 2010). Flooding of water bodies due to excessive rainfall could alternatively form puddles and ponds at the margins of the impoundment providing a second channel through which the disease-enhancing effect of the reservoir may operate (Lautze et al. 2007). Soil moisture at the surroundings of these permanent water bodies due to rise in groundwater level and reduction in infiltration loss may boost possible breeding grounds by increasing the lifespan of temporary puddles and ponds (Tompkins and Ermert 2013).

Irrigation
Crop irrigation schemes are said to pose considerable risk to malaria especially at epidemic zones (Keiser et al. 2005, Kibret et al. 2014, Muturi et al. 2006). Irrigated fields are known to provide breeding sites for many species of mosquitoes, ideally members of the *An. gambiae complex* such as *An. arabiensis* which prefer to breed in open sunlit pools (Carnevale et al. 1999, Snow 1983, White 1974). Irrigated cultivation may therefore extend the breeding season thereby increasing the annual duration of the diseases transmission. Irrigation may also elevate relative humidity in dry regions aiding vector survival (Ijumba and Lindsay 2001). There is no clear malaria transmission pattern between irrigated and non-irrigated settlements. For instance, Coosemans (985b) found in Burundi that the vectorial capacity of *An. gambiae s. l.* was 150 times higher in rice irrigated scheme than in adjacent areas. In Bobo Dioulasso, Burkina Faso, Robert et al. (1985) determined that the number of infective bites received in a rice growing area was similar to that in a control area. In Tanzania, Ijumba (1997) detected that the number of infective mosquito bites at Lower-Moshi irrigation scheme was 2.6 times lower than at the control village. This suggests that, irrigation may frequently generate high vector numbers but does not necessarily translate into increased risk of exposure to malaria.

2.2.4 Human factors

Immunity
Human immune response to malaria infection is one of the essential features of the disease dynamics in sub-Saharan Africa (Molineaux et al. 1988). Malaria burden is high in children below 5-years of age and pregnant women than adults in the sub-region (WHO 2015). Mandal et al. (2011) explains that the differential burden of the disease is due to their immune status and time spent in the area. Doolan et al. (2009) alludes the reduced risk in older children and adults to acquired protective immunity resulting from the cumulative product of many years of heavy exposure to the antigen. Other studies (Baird et al. 1991; 2003) suggest that the acquisition of immunity by the older folks may be due to intrinsic factors linked with aged that enables a quick immune response than children below 5 years. Unlike endemic areas, the disease burden at epidemic zones where continuous exposure does not occur, cuts across all ages (WHO 2015).

Different stages of immunity to malaria have been reported namely clinical, anti-disease and anti-parasite immunity (Doolan et al. 2009, Filipe et al. 2007). Baird (2004) points out that clinical immunity develops after 5-15 years of continuous expo-

sure to malaria antigens in sub-Saharan Africa. The onset of anti-parasite immunity is however thought to correlate with adolescences (Doolan et al. 2009, Langhorne et al. 2008). In Western Kenya for instance, Kurtis et al. (2001) found the onset of anti-parasite immunity to correlate with puberty from 15years and above. The number of exposure needed to acquire resistance is uncertain. Gupta et al. (1999b) suggest that across a broad range of transmission intensities, one or two malaria infections is enough to acquire immunity. In other works (Baird 1995, Baird et al. 1991, Ciuca et al. 1934), ranges of 4-6 malaria infections is reported as the required number of exposure for immunity develop.
Just as new infections are needed to boost acquired immunity, it is however lost in the absence of exposure to new infections (Aron 1983). For instance, Struik and Riley (2004) and Jennings et al. (2006) found that clinical disease emerged only in migrants from endemic settings who remained away for at least 3-5 years. Filipe et al. (2007) found a half-life of 5 years for clinical immunity but 20 years for anti-parasite immunity. In another study, Färnert et al. (2015) noticed that sub-Saharan African immigrants who lived for more than 15 years in Sweden had a similar risk as non-immune travellers.

Parasite clearance
According to White (2011), parasite clearance is a measure of therapeutic response. Immunity enhances parasite clearance in malaria (Yorke and Macfie 1924). An increase in immunity lowers parasite counts and accelerate parasite clearance. Conversely, a decline in immunity, for example, a reduction in transmission, decelerate parasite clearance rate. Parasite clearance duration is further shortened with the aid of antimalarials (Gomes et al. 2008, White et al. 1989). For instance, Tangpukdee et al. (2008) indicated that antimalarial chemotherapy for uncomplicated and complicated malaria takes three and five days respectively. Pukrittayakamee et al. (2008) found a longer range of about 2-504 hours of gametocyte clearance time which also correlated with the asexual parasite clearance time. The resistance of the parasite to antimalarials may also dictate the clearance time. For example, a drug that will usually clear parasite within 3 days may take longer than that in the case of resistance. Self-clearance (without antimalarials) with antibodies alone may take a longer time (Cohen et al. 1961). In a longitudinal study of recovery rates in Nigeria, Bekessy et al. (1976) noticed a self-clearance time of about 625 and 52 days in infants and adults (> 44) respectively. Added, Macdonald (1950) found an average self-clearance time of about 200 days in a study analysing parasites rates in infants. Similar studies (Eyles and Young 1951, Jeffery and Eyles 1954) in malaria-naive adults found a mean self-clearance duration of about 200-300 days.

2.3 Entomological metrics for malaria transmission

2.3.1 Human Biting Rate

Human Biting Rate (HBR) is defined as the number of mosquito bites a person receives per unit time Tusting et al. (2014). Mathematically, it is expressed as the product of the Anopheline density/capture to people and the average number of persons bitten by one mosquito at a unit time (Baird et al. 2002, Hay et al. 2000, WHO 1975). Standard methods recognised by World Health Organization (WHO) for estimating HBR

in the field include indoor and outdoor Human Landing Catches (HLC), Pyrethrum Spray Catches (PSC), and Light Traps Catches (LTC). Among the methods, HLC is considered the most direct technique as it directly samples human biting mosquitoes (Le Goff et al. 1997, WHO 1975). HLC is, however, both capital and labour intensive, technically difficult to replicate, unethical in areas of drug-resistant malaria, subjected to biases of collectors and their attraction to mosquito (Fontenille et al. 2001, Kilama et al. 2014, Tusting et al. 2014). Unlike HLC, PSC and LTC depend largely on the behaviour of mosquitoes rather than directly feeding on humans (Hay et al. 2000). For this reason, Tusting et al. (2014) note that PSC and HLC may likely overestimate true biting rates, particularly when scores of mosquitoes are biting. Besides, people will often devise ways to avoid a large number of mosquito bites.

2.3.2 CircumSporozoite Protein Rate

CircumSporozoite Protein Rate (CSPR) refers to the proportion of the biting mosquitoes (HBR samples) with sporozoites in their salivary glands (Baird et al. 2002, Hay et al. 2000, WHO 1975). Standard WHO methods for estimating CSPR includes Dissection (of the thorax of the mosquitoes to help reveal potential sporozoites under the microscope), Enzyme-Linked Immunosorbent Assay (ELISA) and Plasmodium-specific Polymerase Chain Reaction (PCR) (Durnez et al. 2011, Hay et al. 2000). According to Durnez et al. (2011), dissection and microscopic examination of the salivary glands of individual mosquitoes are labour intensive and not practical for assaying a high number of mosquitoes. ELISA is considered more advantageous in the sense that the collected mosquitoes can be stored until processed and the method is as well able to distinguish the different human Plasmodium species by species-specific monoclonal antibodies (Burkot et al. 1984, Durnez et al. 2011). Moreover, ELISA techniques are less sensitive compared to Dissection, especially when small numbers of sporozoites are present in the salivary glands (Beier et al. 1990). On the contrary, others studies (Beier et al. 1990, Durnez et al. 2011) have indicated that ELISA techniques could overestimate sporozoite rate since it does not only detect sporozoites in the salivary glands, but also in other mosquito tissues. PCR assays can detect as few as ten sporozoites (Tassanakajon et al. 1993) in contrast to ELISA which requires at least 100 sporozoites (Beier et al. 1987). As put forward by (Durnez et al. 2011), PCR is disadvantageous in that it detects not only the sporozoites but also all the Plasmodium DNA present.

2.3.3 Entomological Inoculation Rate

EIR is expressed as the product of the number of mosquitoes attempting to feed on humans (HBR) and the fraction of the feeding mosquitoes that are actively infective (CSPR) (Bruce-Chwatt 1985, Macdonald 1957). In simple terms, it is the number of infectious mosquito bites a person receives per unit time. EIR is regarded as the gold-standard malariometric (Shaukat et al. 2010, Tusting et al. 2014). First and foremost, it can directly quantify parasite-infected mosquitoes and their propensity to transmit the parasites to humans (MARA 1998, Shaukat et al. 2010). For this reason, it can be used to quantify the impact of vector control and anti gametocytocidal drugs (Shaukat et al. 2010). Secondly, EIR satisfactorily produces an overall estimate of the exposure of a population to malaria parasite (Beier et al. 1999, Takken and Lindsay 2003). It can therefore be used as a legible assessor of malaria endemicity and epidemic risk (Burkot and Graves 1995, Onori and Grab 1980). The last but not the least, Tusting et al. (2014)

argues that EIR estimates are easily interpreted by policymakers and national malaria control program managers alike.

On the contrary, Hay et al. (2000) point out that uncertainties in EIR estimates may be huge since the different methods for determining HBR and CSPR are not standardised. Besides, unskilled labour (few trained specialists) are usually involved during mosquito sampling. The number of sample mosquitoes may, therefore, be largely biased and for that matter may subject estimated EIR to limited precision and accuracy (Fontenille et al. 2001, Kilama et al. 2014, Tusting et al. 2014). Also, estimated EIR does not directly translate into malaria incidence or clinical disease and does not accurately represent exposure when interventions are in place (Tusting et al. 2014). Moreover, it fails to capture local level transmission variability determined by the habits, genetics and physiology of different vector species, spatial heterogeneity of vector habitats, immune status of the local human population or anti-mosquito strategies employed by local communities (Takken and Lindsay 2003).

2.4 Weather-driven dynamical mathematical malaria models

Mathematical modelling of malaria dates back to Sir Ronald Ross (Ross 1915) as the pioneer. Macdonald (1957) and Anderson and May (1991) later reasserted Ross' ideas. Further studies expanded these pioneering models by including factors such as varying population size (Chitnis et al. 2006, Ngwa and Shu 2000, Torres-Sorando and Rodriguez 1997), environment (Parham and Michael 2010), socio-economic, age and immunity (Aron 1988, Filipe et al. 2007, Yang 2000). Generally, mathematical models of malaria transmission have provided an understanding of the disease progression and transmission dynamics (Dobson and Carper 1992, Mandal et al. 2011). According to Parham and Michael (2010), they have helped address multiplicative exposure effects, non-linear feedback pathways, spatiotemporal heterogeneities and complex transmission dynamics of the disease. Models of malaria can be used to quantify both current and future changes in malaria progression (Patz et al. 2003) as well as compare the effects of control strategies used individually or in packages (Chitnis et al. 2008).

Weather-driven dynamical mathematical models of malaria are championing the progress of the disease research. For instance, based on the effect of mean rainfall and temperature on the biology of malaria transmission, Craig et al. (1999) proposed a fuzzy logic model of the distribution of stable malaria transmission in sub-Saharan Africa. Parham and Michael (2010) developed a simple model that allows novel insights into the effects of rainfall and temperature on mosquito population and malaria transmission dynamics. Using a simple mathematical model, Lindsay and Birley (1996) examined the influence of temperature on the ability of Anopheles maculipennis to transmit falciparum vivax. Hay et al. (2002) employed regression approach to investigate reports on long-term meteorological trends in four high-altitude sites in East Africa.
In 2010, some fundamental processes of the weather-driven Liverpool Malaria Model (Hoshen and Morse 2004) were modified by Ermert et al. (2011a) through an extensive literature survey regarding entomological and parasitological malaria variables. The calibration and validation of the modifed verstion of the model herein referred to

as LMM_{2010} are detailed Ermert et al. (2011b). More recently, Tompkins and Ermert (2013) introduced a regional scale, high resolution, dynamical malaria model in 2013 known as VECTRI. The model accounts for the impact of temperature and rainfall variability on the development cycles of both the vector and the parasite as well as environmental factors such as population density and surface hydrology. Bomblies et al. (2008) also introduced a modeling approach that explicitly incorporates hydrologic variability into vector abundance and then malaria incidence. Bomblies et al. (2009) represented the impacts of hydrological variability at the village scale and demonstrated through computer model simulations the importance of high resolution hydrological variability for the prediction of village-scale malaria transmission.

CHAPTER 3

The impact of climatic and environmental factors including mosquito type on seasonal malaria transmission in Africa

Abstract
It is long understood that climate and environment influence malaria transmission in Africa. But there has been no comprehensive assessment in this regard using EIR_m data. Previous attempts mostly relied on malaria prevalence or case data gathered from hospitals. But these metrics unlike EIR are aggregates of different windows of transmission and hence unsuitable for linking climatic and environmental drivers to a malariometric outcome. In this study, the seasonality of EIR_m was analysed with the goal to understand how changes in the conditions of climatic and environmental factors including malaria vector type impacted on seasonal malaria transmission in Africa. A literature search for EIR_m data across different locations over the region enabled the analysis. The results revealed that rainfall was the primary climatic factor explaining malaria seasonality at markedly seasonal rainfall areas such as Sahel and Eritrea. But at bimodal rainfall distributed and more humid zones, its impact was complex. The temperature was not a limiting factor of malaria seasonality in sub-Saharan Africa except for East Africa where it was able to delay the impact of rainfall. The peaking characteristics of seasonal malaria were mostly unimodal. In the case of bimodal rainfall distributions, peaks were frequently associated with the first rainfall maximum of the year. Seasonal malaria intensity was anti-correlated with elevation and population density. Permanent water bodies and irrigation intensified and altered the seasonal transmission pattern from seasonal to perennial in areas of unstable transmission such as Sahel and Eritrea. Though seasonal malaria was collectively driven mainly by AG, AF and AA, they had a competing and complex individual impact on seasonality. The study is a step forward in malaria research as it demonstrated a more detailed analysis compared to existing literature. Though the utilised data was associated with some uncertainties, the findings have important implications for malaria control regarding the spatial and temporal target of malaria interventions and resource allocation. It also informs about future malaria modelling efforts and a guide on the validation and evaluation of the seasonal outcome of existing weather-driven malaria models for the region.

3.1 Background

Malaria transmission in Africa reportedly exhibits seasonality (Mbogo et al. 1995, Shililu et al. 2003). The seasonal fluctuations of the disease are an epitome of endemic and epidemic signals. The disease also varies both temporally and spatially especially between climatic and ecological zones (Kasasa et al. 2013, Kelly-Hope and McKenzie

2009, Okello et al. 2006, Robert et al. 2003, Yeshiwondim et al. 2009). The variability and periodic signatures of malaria are mostly blamed on changes in climatic and environmental covariates over space and time (Beier 1998, Kirby and Lindsay 2009, Onori and Grab 1980, Thompson et al. 2005). Understanding malaria seasonality is, therefore, fundamental for effective planning and implementation of control activities (Molineaux et al. 1988). Knowledge of the influence of climate and environment on seasonal malaria transmission facilitates the measurement and description of geographic patterns, risk and burden of malaria (Gething et al. 2011, Reiner Jr et al. 2015).

Studies on malaria seasonality in Africa exist. Some studies have shown the timings and duration of malaria season (Tanser et al. 2003) or predicted the number of months during which the disease transmission is possible (Craig et al. 1999, Grover-Kopec et al. 2006) using climate suitability in a given month as the hallmark. Many other works used malaria cases or prevalence data gathered from hospitals or clinics as metrics (Briet et al. 2008, Giha et al. 2005, Hay et al. 998a, Kleinschmidt et al. 2001, Mabaso et al. 2005, Teklehaimanot et al. 2004, Thomson et al. 1999, Yé et al. 2007). Others came out with working definitions for malaria seasonality (since there is no precise definition) using EIR (Ermert et al. 2011b) or both EIR and malaria cases (Roca-Feltrer et al. 2009).

But, previous works examining the impact of climatic and environmental factors on seasonal malaria transmission in sub-Saharan Africa using EIR_m as a metric are scarce. Mabaso et al. (2007) came close to this subject but used a seasonality index (Markham 1970) that is deficient in irrigated and bimodal rainfall areas. Besides, they lumped up EIR_m data from different climate settings in their analysis without decoupling their individual effect. Malaria cases or prevalence data on the other hand are unsuitable for linking factors of climate and environment to seasonal malaria since they are aggregates of different temporal transmission windows (Reiner Jr et al. 2015). Besides, health seeking behaviour of humans and health policies differ (Afrane et al. 2012). But unlike clinical cases, EIR directly quantifies parasite-infected mosquitoes and their propensity to transmit the parasites to humans (MARA 1998). Also, EIR determinants (i.e. Human Biting Rate (HBR) and CircumSporozoite Protein Rate (CSPR)) are dependent on the conditions of climate and environment (Appawu et al. 2004, Fontenille et al. 1997, Shililu et al. 2003). EIR estimates, therefore, can directly relate the human-biting activity of Anopheles vectors and the risk of humans to malaria infections to climate and environment (MARA 1998, Vittor et al. 2006).

In this study, spatial EIR_m data were used to examine the impact of climatic and environmental factors including mosquitoes type on seasonal malaria transmission across sub-Saharan Africa. The EIR_m data were gathered from different areas across the region through a literature survey. The study then tested the hypothesis that rainfall is the primary climatic determinant of malaria seasonality and not temperature in the sub-region. The study further demonstrated that seasonal peaking characteristics of malaria have a high tendency towards single maxima than double or any other regime. The work also verified that the influence of elevation and population density on malaria seasonality is much to do with intensity than the timings whiles permanent water bodies and irrigation impacted on both seasonal intensity and duration. The last but not the least, the study showed that seasonal malaria transmission in sub-Saharan Africa is

governed by a sympatric association of AG, AF and AA.

3.2 Materials and methods

3.2.1 Materials

EIR_m data

A review of literature for EIR_m [units: infectious mosquito bites per person (ibpp)] data was conducted. Firstly, the entomological database (unpublished) of Swiss Tropical Institute of Medicine, Basel, Switzerland was consulted. This database consists mainly of EIR_m and other entomological parameters digitised from published articles on entomological surveys in Africa. The EIR_m data obtained therein were verified from their original articles where possible for certainty. Secondly, the compiled entomological and parasitological literature archive of Ermert et al. (2011b) (their additional file 2) was utilised. EIR_m data from articles of Ermert et al. (2011b) database that were unavailable in the Basel database were digitised using an R package (Poisot 2011). Thirdly, an online search for more EIR_m data was explored using search method previously employed by Beier et al. (1999). Badu et al. (2013) also shared their EIR_m data on malaria transmission intensity and dynamics in a mountainous forest region of Ghana.

The EIR_m data gathered were then subjected to a relevancy test previously used by Beier et al. (1999) and Hay et al. (2000). Thus, EIR_m data from a study was relevant if the study 1) employed WHO recommended methods for mosquito sampling and sporozoites detection (see section 2.3.1 a and 2.3.2) 2) period was at least one year with mosquitoes sampled every month or during the transmission season and 3) was conducted at a time where vector control measures were previously not applied.
Figure 3.2 shows the distribution (number of monthly observations in a year) of EIR_m data considered after the relevancy test. The study analysis used EIR_m data between the period 1983-2013 since more observations were within that period. Besides, the rainfall data (African Rainfall Climatology version 2 (ARCv2) dataset) are available from 1983 onwards. The number of locations and length of EIR_m data observed at each zone is displayed in Table 3.1. The geographical locations of the EIR_m data are displayed in Figure 3.1. The classification of the locations into climate zones, hydrology and population density as well as uncertainties pertaining to the observed EIR_m data are detailed in Appendix A. Other details of the locations such as name, longitude, latitude, Start Year (SY), Start Month (SM), End Year (EY) and End Month (EM) are outlined in Table A.1 of Appendix A.

Table 3.1: Number of locations and amount of EIR_m data available at each zone

	Number of locations with n [year] of available data					
Zone	1 [year]	2 [years]	3 [years]	4 [years]	5 [year]	Total number of locations
Sahel	18	6	3	0	1	28
Savanna	16	1	0	0	0	17
Guinea	24	9	0	0	0	33
Cameroon	22	0	0	0	0	22
Eritrea	10	0	0	0	0	10
EEA	39	2	2	0	0	43

Rainfall and temperature timeseries

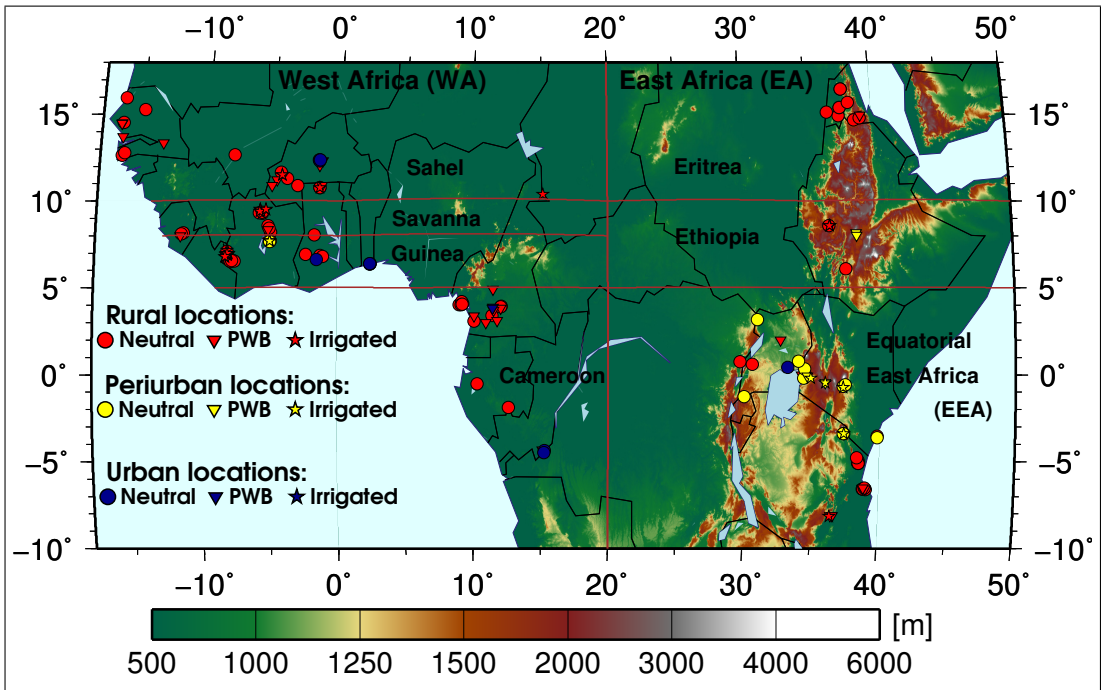

Figure 3.1: The geographical distribution of observed EIR_m data locations in sub-Saharan Africa. The proximity of many sites was so close that they could not be explicitly resolved on the map. Rural: Red coloured locations, Peri-urban: Yellow coloured locations and Urban: Blue coloured locations. Circles: locations devoid of permanent water bodies or irrigation activities (Neutral), Inverted triangles: locations with permanent water bodies (PWB), Star: locations with irrigation.

Local weather station observations in sub-Saharan Africa were consulted for rainfall and temperature data. But these stations were found to have incomplete records, mostly not located at the malaria study locations and were inadequately distributed in the region. For this reason, surrogate data products were utilised.

Regarding rainfall, the ARCv2 dataset (Novella and Thiaw 2013) was utilised. ARCv2 is a gridded daily precipitation estimation dataset centred over Africa at 0.1° spatial resolution and available from 1983 to present. The daily records for each of the malaria location were extracted for the period 1983-2013 using their geographical coordinates. About 3.01% (341 days) of data gaps (same date cutting across all sites) existed due to technical challenges. These shortcomings were replaced with daily climatological values (1983-2013). Monthly values were then estimated from the complete daily records.

Regarding temperature, the daily European Centre for Medium-Range Weather Forecasts (ECMWF) Interim Reanalysis (ERAI) dataset (Dee et al. 2011) was utilised. ERAI is a global atmospheric reanalysis data available from 1979-present at a spatial resolution of 0.75°. Both minimum and maximum temperature were extracted for the period 1983-2013 for each location. Temperature difference resulting from differences in elevation between malaria locations and ERAI heights were corrected. This was done by assuming that, in a standard atmosphere, temperature decreased with altitude at a constant rate of -6.5°C/1000m up to the tropopause as shown in the equation be-

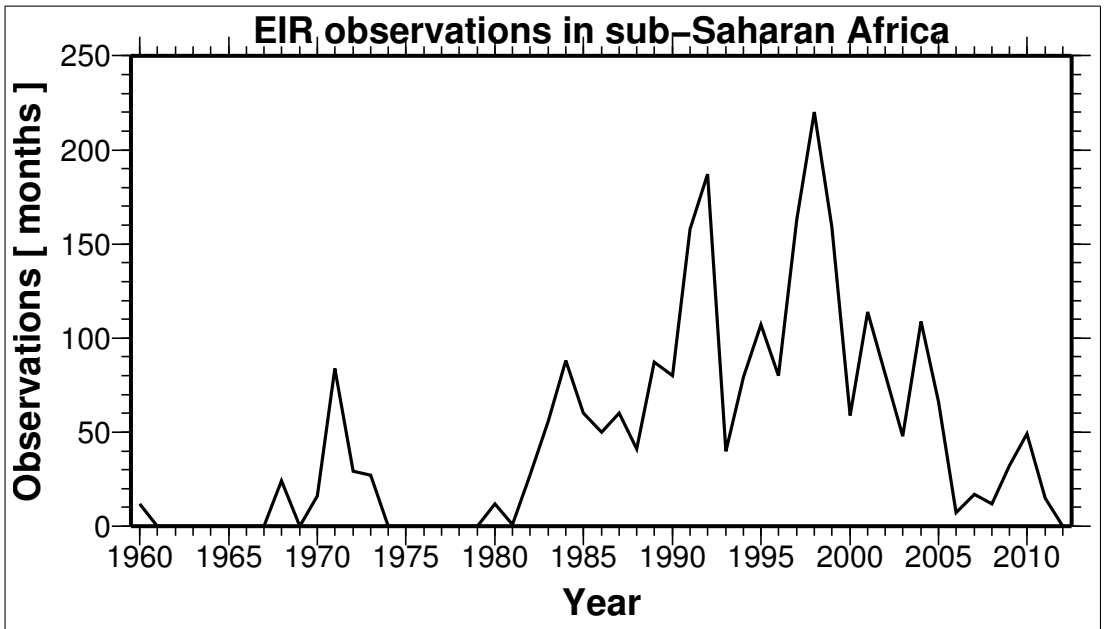

Figure 3.2: Annual distribution of the number of EIR_m observations in sub-Saharan Africa

low:

$$T = T_o - 6.5\frac{h[m]}{1000m} \tag{3.1}$$

where T is the corrected temperature, T_o is the extracted temperature and h is the difference in height between the malaria location height and ERAI height. The mean temperature for each location was then calculated by finding the average between the minimum and maximum values. Monthly values were then estimated for each temperature variable.

The choice of the surrogate data products was based on their reliability, good temporal and spatial resolution, longest daily records for sub-Saharan Africa and as recommended by other works such as (Awange et al. 2016).

Population density (Pd) data
Information regarding whether a malaria location was rural, periurban or urban was missing in most studies. Hence, Pd values for each location was extracted from the Gridded Population Density data of the World, version 3 (GPDWv3) (CIESIN-CIAT 2005) using their geographical longitude and latitude position points. Each location was grouped into rural, peri-urban and urban area using the definition of urbanization by Hay et al. (2005) (see details in appendix A).

3.2.2 Methods

Pair-wise comparism
The seasonal distribution of EIR_m was pair-wise compared with the corresponding monthly series of rainfall and temperature. The goal was to examine any association,

degree of seasonal variability and contrast between the pairs throughout the year. EIR_m data from rural-neutral locations were used (the rest were excluded) to ensure the influence was climate alone as possible.

Like the climatic factors, a pair-wise comparison of EIR_m time series of environmental settings including vector type was made. Regarding hydrology, EIR_m time series of locations with PWB, irrigation and Neutral (used as control check) were contrasted. Regarding population density, EIR_m time series from urban, peri-urban and rural settings were contrasted. Similarly, time series of elevations between 0 and 1500m at intervals of 500m were compared. The limit to 1500m was due to unavailability of EIR_m beyond that height. Concerning vector type, dominant and efficient malaria vectors were identified, and their EIR_m time series contrasted. The comparison was subject to data from the same climate without jeopardising the effects of other environmental variables that may have the potential impact on the output.

EIR peak characteristics

The charateristics of the observed EIR_m regarding the behaviour of peaks in a year were analysed for each zone. On a EIR_m time series, a peak was defined as a local maxima with two points on either side being smaller than it. Two points interval was chosen due to the rather short EIR_m time series length (12 months). At the boundaries of the time series (January and December) where the condition of two points on either side was insufficient, the time series was extended by repeating January and February values to allow for investigation at those boundaries. After peaks had been identified, peak relevancy criterion was further applied. That is, a peak was considered relevant if its amplitude (A) was greater than the sum of the mean (μ) and standard deviation (σ) of the EIR_m of that timeseries (i.e., A > $\mu + \sigma$). Seasonal regimes namely unimodal, bimodal or trimodal malaria transmission were then classified for each zone using the peaks.

Cross-correlation

The EIR_m time series were also cross-correlated with that of rainfall at lags of 0-11 months. The aim was to examine the delay between the onset of suitable rainfall conditions for malaria transmission and malaria season onset. Only lags of positive correlations were examined. The delay period corresponded with the lag(s) with the strongest positive correlation (i.e., one with Pearson's correlation coefficients (R) ≥ 0.5). Permanent Water Body (PWB) and irrigated locations were exempted from the cross-correlation analysis to ensure the influence was climate alone.

3.3 Results

Pair-wise comparism

Figure 3.3 compares the seasonality of EIR_m with that of rainfall and temperature for each climate zone. At Sahel (panel a) and Eritrea (panel e), a short rainfall season with a peak in August was observed. The duration of the EIR season was also notably brief and correlated with rainfall at a late period of about one month (peak in September). The full temperature range was warmer (range: 20°C - 37°C) and anti-correlated with both rainfall and EIR_m. At the rest of the zones (Savanna, Guinea, Cameroon and EEA), seasonal rainfall distributions were mainly bimodal. EIR season at each the

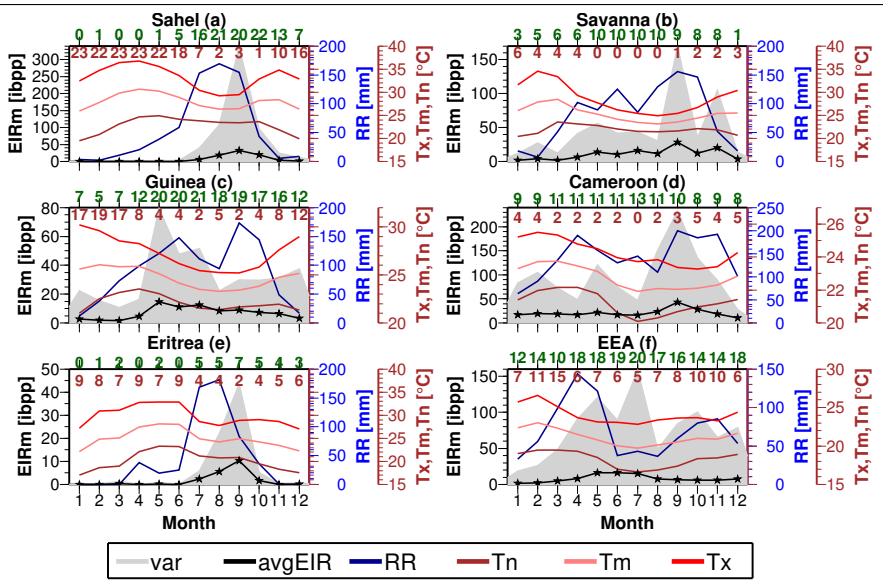

Figure 3.3: Seasonal patterns of EIR_m compared with that of rainfall and temperature over sub-Saharan Africa. Gray shaded area: variability of EIR_m between minimum and maximum. Black star-dotted line: average EIR_m. Rainfall: RR (blue line). Temperature: minimum (Tn, brown), mean (Tm, light red), maximum (Tx, red). Green and brown numbers show number of months suggesting presence and absence of malaria respectively.

zones was mainly year-round and more intense in rainy season (see green numbers). However, EIR peaks were irregular with that of rainfall unlike at Sahel or Eritrea. The temperature at these zones also anti-correlated with EIR_m and rainfall, but was slightly colder at Cameroon and EEA (range: 18°C and 27°C) compared to that of Guinea or Savanna.

Peak characteristics

In Figure 3.4, the seasonal peaking behaviour of EIR_m over sub-Saharan Africa is illustrated. At Sahel (panel a), EIR_m distribution was outrightly unimodal. At the Savanna zone (panel b), both unimodal and bimodal distribution were observed. But peaks were significantly unimodal than bimodal in the area. At Guinea (panel c), observed regimes were unimodal, bimodal and trimodal. However, peaks were again frequently unimodal than the other regimes. Peak characteristics at Cameroon (panel d) and EEA (f) were unimodal, bimodal and no peaks. But the zone was frequently unimodal and less bimodal with insignificant suggestions of no peaks. At Eritrea (panel e) both unimodal and bimodal distribution were found with outstanding unimodal characteristics than bimodal.

Cross-correlation

Figure 3.5 displays the lags and their corresponding Pearson's correlation coefficient between observed EIR_m and rainfall. At Sahel (panel a), positive correlations varied between 0-3 lags with a significant (≥ 0.5) delay at 1 month. At Savanna (panel b), Guinea (panel c), and Cameroon (panel d), positive correlations ranged between delays of 0-2 months but were all insignificant (< 0.5). Positive correlations at Eritrea (panel e) were found between 0-2 lags with significant delay at 1 month like the Sahel. That of EEA (panel f) were observed between 0-3 lags with an insignificant peak at lag 2.

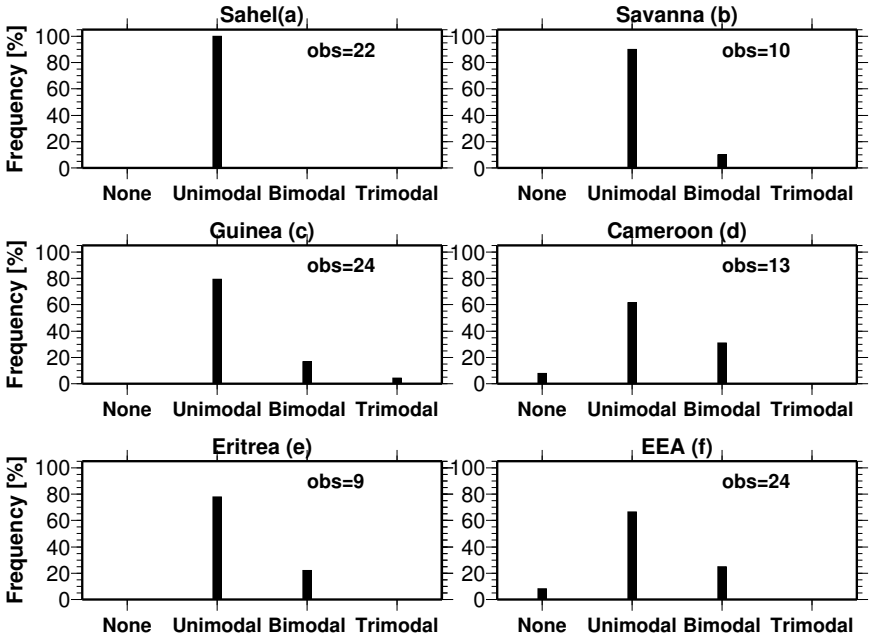

Figure 3.4: Peak characteristics of EIR_m over sub-Saharan Africa. obs: number of observations

Elevation

The relationship between malaria seasonality and elevation are displayed alongside with rainfall and temperature in figure 3.6. Generally, the timings, duration and peak seasons were similar at all elevations, but the intensity differed. EIR intensity was inversely proportional to altitude, i.e., decreased with increasing elevation. Rainfall distribution was similar at all elevations. Temperature range decreased as height increased.

Population density

In Figure 3.7, the seasonality of malaria at rural, periurban and urban malaria locations are compared. Averagely, EIR season was year-round at all settings. However, the seasonal intensity decreases from rural settings to periurban areas to urban settings.

Effect of hydrology

In Figure 3.8 the temporary differences in malaria between neutral (which served as a control), PWB and irrigated locations are compared. At Sahel (upper row), the length of the season was longer and highly intense at PWB and irrigated sites than at control areas. At the Savanna zone (second row), EIR distribution at control areas was similar to that of irrigated areas though a longer duration and high intensity at PWB locations was observed. At Guinea and Cameroon, year-round transmission was the case at all settings, but EIR intensity was again high at PWB and irrigated locations than at control sites.

Vector type

Figure 3.9 shows the geographical distribution of malaria vectors identified from the

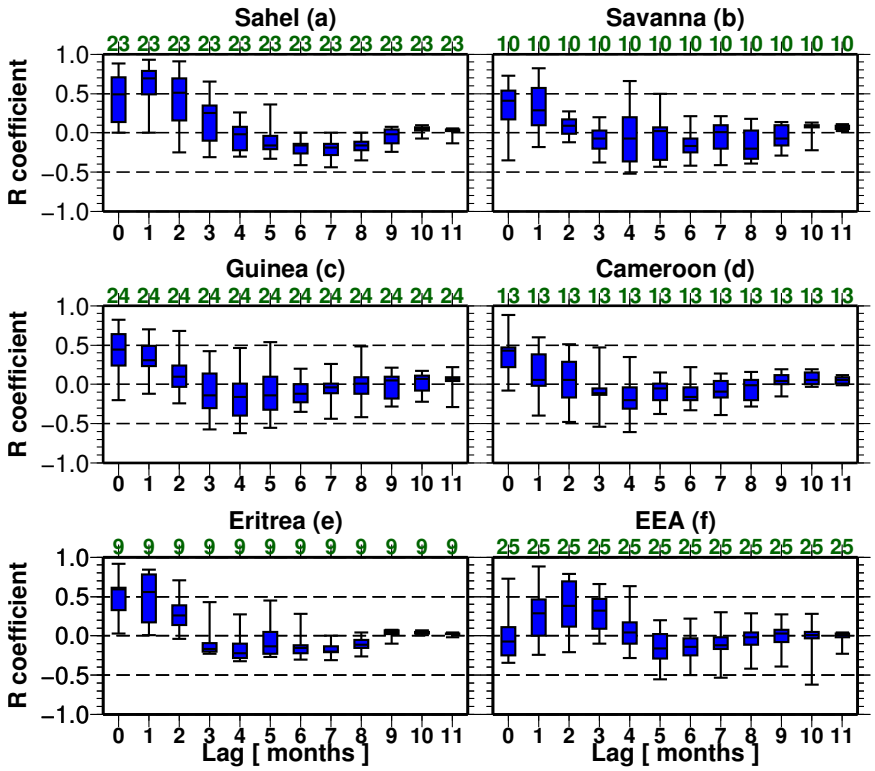

Figure 3.5: Cross correlation between EIR_m and rainfall at lags of 0 to 11 months. Brown numbers (top of panels): number of monthly observations.

publications. They include An. gambiae (AG), An. funestus (AF), An. arabiensis (AA), An. nili (AN) and An. moucheti (AM). Among them, AG, AF and AA were the most dominant and in sympatry. AA was concentrated at areas with highly seasonal rainfall such as the Sahel or the drier Savannah areas in East Africa. AF was limited to relatively humid areas in the West and East. AG was adaptive to all the variable ecology of the sub-region. The AN and AM were confined to moist areas around Cameroon.

Figure 3.10 shows the monthly contribution of AG, AF and AA (the three most dominant malaria vectors) to infectious bites in sub-Saharan Africa. At Sahel (panel a) and Eritrea (panel e), exposure to infectious bites from the sympatric vectors was markedly seasonal with monthly distribution following that of rainfall. EIR_m contribution among the sympatric vectors was also keenly competitive. AG and AF were the sympatric vectors at Savanna (panel b), Guinea (panel c) and Cameroon (panel d). AG inoculations mostly exceeded that of AF at Savanna and Guinea, especially in the rainy season. At Cameroon however, EIR_m contributions from both vectors were highly competitive except in the second rainy season where AF inoculations dominate that of AG for three months. At EEA (panel f), AA inoculations were mostly higher followed by that of AG. Exposure to AF bites was least among the three vectors.

3.4 Discussion

Impact of temperature The pair-wise comparison results revealed the full seasonal temperature window for sub-Saharan Africa to be about 18°C - 37°C. This tempera-

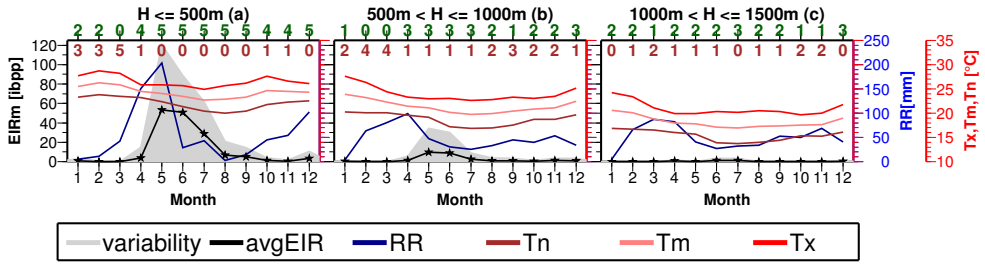

Figure 3.6: Seasonality of EIR_m at different elevations in EEA. Gray shaded area: variability of EIR_m between minimum and maximum. Black star-dotted line: average EIR_m. Rainfall: RR (blue line). Temperature: minimum (Tn, brown), mean (Tm, light red), maximum (Tx, red). Green and brown numbers show the number of months suggesting presence and absence of malaria respectively.

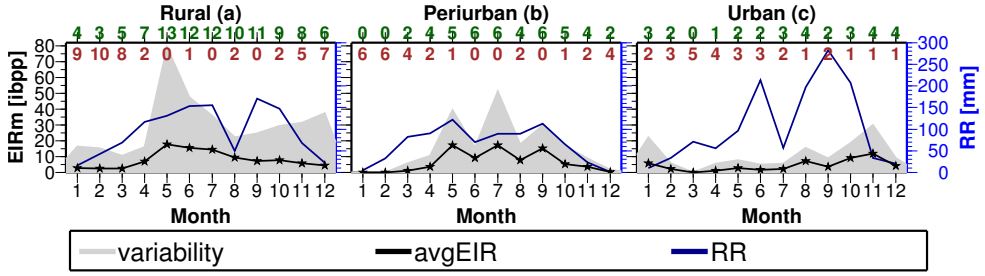

Figure 3.7: Seasonality of EIR_m at different Pd settings at the Guinean zone of West Africa. Gray Shaded area: EIR_m variability between minimum and maximum. Black star-dotted line: average EIR_m. Rainfall: RR (blue line). Green and brown numbers: number of monthly observations suggesting malaria and no malaria respectively.

ture range coincidently falls within the required window (range: 18°C - 40°C, optimum: 22°C - 32°C (Craig et al. 1999)) for malaria transmission. This means that the temperature boundary conditions for gonotrophic and sporogonic cycles (Macdonald 1957) are widely suitable throughout the year in the entire region. Therefore, there may be no possible biological delay between the onset of appropriate temperature conditions and malaria season onset. The anti-correlation between temperature and EIR_m is mainly due to the influence of rainfall on the seasonal distribution of temperature (Collins 2011). In a previous study, Mabaso et al. (2007) found minimum temperature as one of the important determinants of EIR seasonality. In this study, however, all temperature variables were largely within the range of malaria transmission. Moreover, there was little temporal and spatial temperature variation in the entire region. Thus, the impact of temperature may be insignificant since the mosquito and parasite biology are influenced by the extent of the diurnal temperature variation (Paaijmans et al. 2010; 2009). Though the temperature was slightly low at EEA (especially minimum temperature) compared to other zones, the effect may only likely delay the impact of rainfall on vector population at this zone. These findings demonstrate that, though temperature is necessary for malaria transmission, it is essentially not a major player in malaria transmission explaining EIR seasonality in Sub-Saharan Africa.

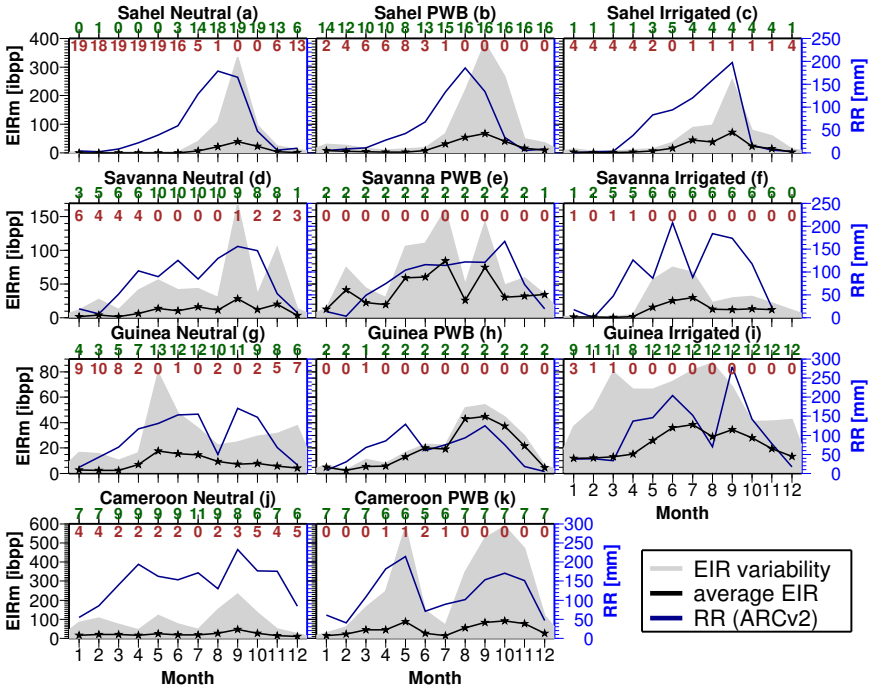

Figure 3.8: Comparison of the seasonal distribution of EIR_m at different settings of hydrology. Involves rural malaria locations only. Left column: Neutral areas (control), Middle column: PWB, and right column: Irrigated: Grey Shaded: EIR variability. Black star-dotted line: average EIR. Blue line: Rainfall (RR). Green and brown numbers indicate the number of monthly observations suggesting presence and no malaria respectively.

Impact of rainfall Regarding rainfall, the results revealed a strong positive relationship between the seasonal distributions of rainfall and EIR_m at each zone. The high correlation clearly manifest that rain mostly controlled the timings, duration and variability of EIR_m seasonality. This applies in particular since rainfall provides the medium for vector breeding (Kar et al. 2014, Molineaux 1988) and essential humidity (at least 60%) for vector survival (Thompson et al. 2005). Moreover, the timings and length of EIR season also strongly correlated with that of rainfall from the northern fringes (such as Sahel and Eritrea) towards equatorial areas (such as Cameroon and EEA). This pattern indicates that the degree of malaria seasonality is closely linked with the latitudinal variation in rainfall in the region. The findings are also comparable to results of previous studies (Craig et al. 1999, Gething et al. 2011, Hay et al. 2009, Kiszewski et al. 2004, MARA 1998) that have used climate variables to developed malaria maps.

The EIR_m peaking behaviour can be attributed to the influence of rainfall on vector persistence. At Sahel and Eritrea, rainfall is highly seasonal (Nicholson 2013) and limits the mosquito population during the long dry season. But transmission bounces back with single peak in the short rainy season when suitable water requirements are met for vector breeding. At bimodal rainfall areas (Savanna, Guinea Cameroon and EEA), mosquito populations do not go through the annual growth and decline cycles like at Sahel and Eritrea. They persist at more stable levels (Craig et al. 1999). The dry period at these zones are short, hence local factors such as water containers, sporadic rain showers and humidity may maintain a greater population of the vectors within

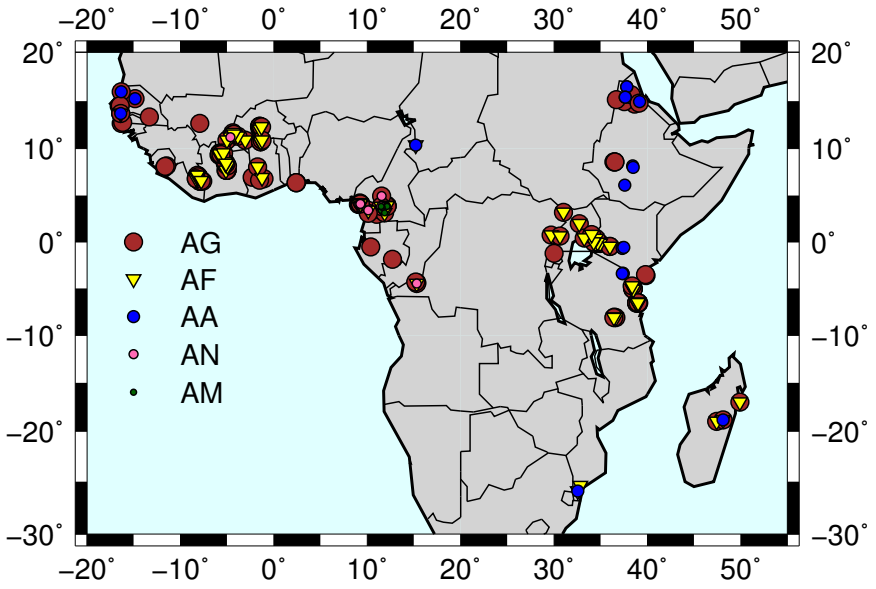

Figure 3.9: Geographical distribution and sympatric association of malaria vectors in sub-Saharan Africa. Malaria vectors contributing to each location EIR_m identified from the articles. The proximity of many sites was so close that the display of the vectors could not be explicitly resolved on the map.

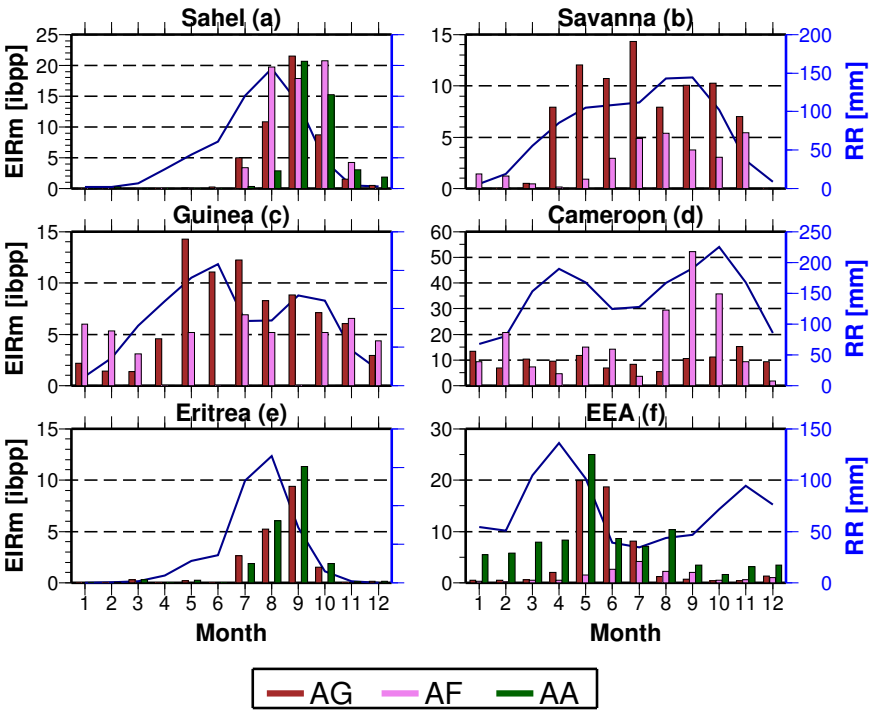

Figure 3.10: Seasonal patterns of EIR_m from three most dominant malaria vectors in sub-Saharan Africa. RR: rainfall (blue line)

this period. Besides, vectors may also adopt mechanisms that may maximise their survival chances during these short dry period (Grover-Kopec et al. 2006, Patz et al. 2003). The onset of the first rainy season will accelerate vector population growth with pronouced peaks in this season. However, vector breeding habitats may become flooded, flushing out and killing some water-bound stage vectors during the second rainy season. This is because the annual rainfall totals are high in these zones and the two rainy seasons consolidate each other in terms of water amount. This will lead to a decline in vector population in the second rainfall season rather than an increase. Besides, over-population of water-bound vector in the second rainy season may also limit available resources for their survival resulting in their death. Hence, the infuence of rainfall on vector persistence may result in high tendency towards unimodal EIR_m distribution than bimodal.

The cross-correlation analysis showed the pause between the onset of suitable rainfall conditions and malaria season onset. The vector persistence phenomena again explain the different lag pattern. The delay of 1 month at Sahel and Eritrea is due to the limiting nature of rainfall on vector population. Since temperature is already warmer and optimum for malaria transmission, the biological delay may not be long when vector population bounces back in the rainy season. This also explains why malaria transmission is markedly seasonal at those locations. At Savanna, Guinea and Cameroon, the lag was predominantly zero suggesting no delay in malaria season onset after rainfall season onset. As highlighted afore, vectors at these zones may persist year-round. The year-round vector persistence additionally explains why malaria transmission at these zones are year-round. On the other hand, the two months maximum lag at EEA was insignificant. This can be attributed to the relatively colder temperature influenced by the complex interplay of topography and large inland water bodies in the area (Indeje et al. 2000). Hence periods at which rainfall temporarily coincides with temperature for transmission to occur takes a longer time. Hence the sporogonic and gonotrophic cycles takes longer days to complete (le Sueur and Sharp 1991, Rueda et al. 1990).

Previous works on cross-correlation analysis using EIR data were scarce for comparison. However studies using malaria cases for cross-correlations reported longer lag period than observed in this study. For instance, Briet et al. (2008) cross-correlated malaria cases with rainfall in Sri Lanka and found that the disease time series were lagging 0-3 months behind rainfall. Again predicting malaria epidemics in the Kenyan highlands using climate data Githeko and Ndegwa (2001) found the association between rainfall (and unusually high maximum temperatures) and the number of inpatient malaria cases 3-4 months later. These longer delays additionally provide information on why malaria case data are not suitable for linking climate variables to malariometric outcome directly.

Altitute

The intensity of EIR_m and temperature were inversely proportional to elevation. Thus, malaria transmission is higher at low altitudes and low/free at higher elevations. The decrease in intensity towards higher elevations is due to the limiting nature of cool temperatures at high elevations on malaria transmission (Drakeley et al. 2005). Previous studies have also reported similar findings. In Tanzania, Maxwell et al. (2003) sampled mosquitoes and found that EIR was about 17 times greater at a lowland than highland

area. In an entomological survey in Papua New Guinea, Attenborough et al. (1997) identified that the proportions of mosquitoes with malaria circumsporozoite antigens were inversely proportional to altitude. In similar studies not using EIR (Akhwale et al. 2004, Balls et al. 2004, Bodker et al. 2003), similar patterns were observed. Though the study was confined within altitudes below 1500m due to insufficient data, the results still demonstrate that altitude is a useful proxy for temperature in malaria transmission. Temperature therefore, is the chief factor controlling the difference in malaria transmission intensity between lowland and highland areas and can, therefore, serve as proxy for elevation and the disease transmission measurements.

Hydrology

The high intensity and longer seasonal duration of EIR_m at PWB and irrigated locations than at control areas is due to the impact of impounded water bodies on vector population. They aid transmission both in dry and wet (more intense) seasons as their existence increases the vector population (Fillinger et al. 2009). This means that inhabitants in areas invaded by PWB or irrigation will be exposed to higher malaria risk than those away. Results from previous studies in this regard that directely used EIR_m were scare for comparison. However surrogates metrics from such studies revealed similar patterns. In an entomological study in Kenya, Zhou et al. (2007) found that An. gambiae and An. funestus populations decreased with increasing distance from the Yala river. In Burundi, Coosemans (985b) found the vectorial capacity of *An. gambiae s. l.* to be 150 times higher in the rice irrigation scheme than in adjacent areas. On the other hand, EIR_m intensity at Savanna (panel f of Figure 3.8) for irrigated areas was lower than that of control locations. This irregularity has also been reported. In Bobo Dioulasso, Burkina Faso, Robert et al. (1985) determined that the number of infective bites received in a rice growing area was similar to that in a control area. In the Lower-Moshi rice irrigation scheme in Tanzania, Ijumba (1997) found that the number of infective bites was 2.6 times lower in an irrigated area than in the control viallage. This irregularity seems to suggest that there is likely no simple relationship between irrigation and seasonal exposure to malaria.

Population density

Observation of the impact of Pd showed a decrease in malaria intensity from rural areas to urban locations. This pattern is because increasing Pd from villages to urban areas results in a reduction in biting ratios (Hay et al. 2005, Kelly-Hope and McKenzie 2009). Additionally, polluted breedings grounds and access to public health services in urban areas also lowers transmission (Hay et al. 2005). Some research has demonstrated this clear conventional trend (Hay et al. 2005, Keiser et al. 2004, Wang et al. 2005). For instance, in a review of malaria transmission in sub-Saharan African cities, Robert et al. (2003) found that annual mean EIRs decreased from the city centres to rural areas (7.1 at city centres, 45.8 in periurban areas, and 167.7 in rural areas). In Burkina Faso, Modiano et al. (1999) found epidemiological profiles and clinical patterns to be high in the countryside than at urban environments.

Vector type

The dominant malaria vectors identified corroborate other works (Coetzee et al. 2000, Lindsay et al. 1998, Sinka et al. 2010). The distribution patterns of their ecological confinements suggest an influence of climatological factors on habitat preference. For

instance the isolation of AA to drier savannah areas may be due to its preference for sunlit breeding sites with relatively limited emergent vegetation (Coetzee et al. 2000, Sinka et al. 2010). The sympatric association of the vectors also validates existing literature. For instance AG reportedly occur in sympatry with AF and AA with all sustaining perenial parasite innoculation (Charlwood et al. 2003, Elissa et al. 2003). Collins and Besansky (1994) indicates that almost all malaria cases in Africa are entirely attributed to these three vectors. The high contribution of these vectors to infectious bites may also be explained largely by their high anthropophilic attitude (Coosemans et al. 1992). The predominance of AG and AF than AA may also be explained by their high longevity (Coosemans et al. 1992). AG and AF are predominant throughout the year with former more in the rainy season and the latter more in the dry season (Adja et al. 2011, Nkuo-Akenji et al. 2006). The longevity of these vectors also accounts for the stability of malaria in parts of Africa where they exist.

3.5 Summary and conclusions

The study examined the seasonality of EIR_m in sub-Saharan Africa with the goal to understand how climatic and environmental factors impacted on seasonal malaria transmission in the sub-region. The work revealed that 1) rainfall is the primary climatic factor limiting malaria seasonality in the Sahel and Eritrea. But its impact on bimodal rainfall distributed and more humid zones was more complicated. 2) Temperature is not a limiting factor of malaria seasonality except at equatorial East Africa where it can delay the impact of rainfall. 3) The peaking characteristics of seasonal malaria (EIR_m) were mostly unimodal. In cases of bimodal rainfall distributions, peak malaria transmission are frequently associated with the first rainfall maximum of the year. 4) The seasonal malaria intensity was anti-correlated with elevation and population density. 5) Permanent water bodies and irrigation intensified and altered malaria transmission pattern from seasonal to perennial especially in areas such as Sahel and Eritrea. 6) Though seasonal malaria was driven mainly by AG, AF and AA, these vectors had a competing and complex individual impact on seasonality.

Though EIR data are scarce (Hay et al. 2005, Kelly-Hope and McKenzie 2009), the study relied on EIR_m data that were within reach and does not claim to have identified all EIR_m data available across sub-Saharan Africa. The study also acknowledges that the observed EIR_m time series were both spatially and temporally limited and unavailable for many settings due to the labour and capital intensive nature involved in its collection. These challenges coupled with inherent uncertainties in EIR_m data during collection (see Appendix A) could have an adverse impact on the outcome of this study. Future EIR_m estimates should, therefore, focus on areas of unavailable data in order to consolidate the spatial homogeneity of EIR data distribution.

Despite the uncertainties in the EIR_m data, the results consolidate evidence of the link between seasonal malaria transmission with climate and environment. It informs our understanding of the impact of climate and environment on vector biology, transmission intensity, clinical disease and mortality risks. The use of EIR_m provided the means to directly relate human risk to infectious mosquito bites to climate and environment. It therefore provides valuable information for improvement and validation of weather-driven dynamical mathematical malaria models for estimation of seasonal malaria in

the area. The study also supplements previous works describing clinical patterns of malaria infection and morbidity. It can help stakeholders establish a robust framework for monitoring, forecasting and control of malaria. Thus, information from this study may aid the spatial targeting of malaria interventions and resource allocation optimisation at locations where climatic and environmental diversity results in seasonal malaria transmission heterogeneity. For instance, year-round malaria chemoprevention in children and pregnant women is cost-effective at perennial transmission settings than at markedly seasonal transmission settings (Cairns et al. 2012). Temperature surveillance and monitoring at highlands areas is necessary since climate change is expected to move malaria to such locations. Elevation can also serve as a proxy for temperature in malaria transmission measurements for an optimum appropriation of control measures. Malaria vector surveillance and monitoring operations are necessary at locations invaded by permanent water bodies and irrigation for appropriate application of control measures. Access to public health services and poverty alleviation in the rural area is needed to curb the high malaria transmission.

CHAPTER 4

The accuracy of VECTRI and LMM_{2010} in simulating seasonal malaria transmission in Africa as a function of climate and environment

Abstract
VECTRI and LMM_{2010} are novel weather-driven dynamical mathematical malaria models that have been applied in Africa to predict epidemic and endemic malaria. But ranges of their seasonal malaria simulations has not been validated with observed data from malaria locations across different climatic and environmental settings in the region. Therefore, information as to whether or not they realistically follow the seasonal evolution of the disease in the region as a function of climate and environment is lacking. In this study, monthly Entomological Inoculation Rate (EIR_m) data was used to validate ranges of seasonal malaria simulated by both VECTRI and LMM_{2010} with the goal of examining their seasonal malaria simulation accuracy. The EIR_m data were gathered from different epidemiological settings across Africa via literature survey. The validation revealed that LMM_{2010} and VECTRI error ranges were generally within or about the same as the standard deviation of the observed data though larger errors were detected for Guinea and some individual monthly minor differences. Both models also agreed with observations that the seasonal peaking behaviour of malaria is predominantly unimodal. However, transmission peaks in the models tend to be delayed by one month in the Sahel and Eritrea area. Both models further agreed with observed values of a seasonality index that the seasonal malaria transmission contrast is closely linked with the latitudinal variation of climatic covariates such as rainfall in Africa. VECTRI revealed a stronger ability in capturing the levels of malaria endemicity in East Africa than LMM_{2010}. The hydrology model in VECTRI poorly captures seasonal malaria transmission at permanent water body locations. Though both had loopholes, the validation revealed they could realistically reproduce the seasonal evolution of the disease in Africa as a function of climate and environment. The findings, therefore, provides the basis for further review and refinement of the models by their developers to stage them as best fundamental tools for seasonal malaria prediction.

4.1 Background

Mathematical models of malaria transmission have provided a framework for understanding the complex transmission dynamics of the disease (Dobson and Carper 1992, Mandal et al. 2011, Parham and Michael 2010). Hence, they are useful in decision-making processes regarding malaria control. For instance, malaria models have helped quantify current and future changes in the disease progression (Patz et al. 2003) and used to evaluate the impact of intervention strategies applied individually or in packages (Chitnis et al. 2008).

The LMM_{2010} (Ermert et al. 2011a) and the VECTRI (Tompkins and Ermert 2013), are such innovative weather-driven dynamical mathematical malaria models. They have been applied in Africa to predict epidemic and endemic malaria for the region. For instance, Ermert et al. (2012) used LMM_{2010} to assess the impact of climate change on disease in Africa. Revisiting a previously assessed potential impact of climate change on the seasonality of malaria in Africa, Ermert et al. (2013) compared data from the Malaria Atlas Project (MAP) and LMM_{2010}. Using ECMWF monthly and seasonal climate forecast, Tompkins and Di Giuseppe (2015) applied VECTRI to predict the potential of malaria in Africa. Caminade et al. (2014) used biased-corrected rainfall and future temperature projections from climate models to compare the metrics of five impact malaria models, among which VECTRI is one, at a global scale for three future time periods of the 2030s, 2050s, and 2080s.

Despite the useful application of both models in understanding malaria transmission in Africa, their seasonal simulation of malaria has not been validated with observed data from different settings of climate and environment across the region. Validation of their seasonal malaria outcome is necessary since the disease locations used during their calibrations are meteorologically different from other areas of the area. The results of the validation will inform about the extent to which their seasonal malaria simulation represent the local malaria conditions of the different epidemiological settings of the region. Thus, the accuracy and generality of seasonal malaria they predict for Africa will be maximised and known. This will assist both model developers in their plans towards refinement as good malaria forecasting tools.

This study validates and evaluates seasonal malaria simulated for sub-Saharan Africa by LMM_{2010} and VECTRI. The goal is to understand whether both models follow the seasonal evolution of the disease in the region as a function of climate and environment to a large extent. Ranges of EIR_m simulated by both models were pair-wise compared with field observed EIR_m data. A review of both model skills enabled the test of the proposition that 1) The error ranges of EIR_m simulated by LMM_{2010} and VECTRI were generally within or about the same as the standard deviation of the observed data. 2) The seasonal peaking behaviour of EIR_m predicted by both models was similar to the observed. 3) The simulated seasonal malaria contrast of LMM_{2010} and VECTRI were akin to that of the observed and linked with the latitudinal variation of climatic covariates such as rainfall. 4) The models were able to capture the different levels of malaria endemicity in East Africa. 5) The hydrology model in VECTRI enabled it to capture seasonal malaria transmission at permanent water body locations very well.

4.2 Data and methods

4.2.1 Data

Observed EIR_m [units: ibpp]
Observed EIR_m data were gathered from many malaria locations across sub-Saharan Africa (see Figure 3.1). Data collection methods, sources and inclusion criteria are detailed in Chapter 3. Inherent uncertainties associated with the field EIR_m data as well as the categorization of data locations into climate zones, hydrology and Pd are described in Appendix A. The study analysis used EIR_m data between the period 1983-

2013 since more observations were within that period (see Figure 3.2). Besides, the rainfall data (ARCv2 dataset) are available from 1983 onwards.

Model input
Continuous daily time series of rainfall and temperature forms the input data for LMM_{2010} and VECTRI. Regarding rainfall, the ARCv2 daily dataset (Novella and Thiaw 2013) was utilised. For temperature, the ERAI daily dataset (Dee et al. 2011) was used. Both the temperature and rainfall time series spanned from 1983-2013. Pd is an extra input data of VECTRI and utilized in the model calculation of mosquito biting ratio (Tompkins and Ermert 2013). The Pd data used was that of the GPDWv3 (CIESIN-CIAT 2005). Details about these input data products and processing steps are described in Chapter 3.

Model output
LMM_{2010} and VECTRI (v1.4) were driven with the daily input data from 1983-2013 for each malaria location (see Figure 3.1). To attain equilibrium, the initial climate forcing of 1983 was repeated in both model simulations for 23 years before passing in the other years. The output of LMM_{2010} and VECTRI comprised of several variables including EIR, HBR, and CSPR. Following the reason, that available field observed data for validation was only EIR_m, the daily EIR simulated by both models were processed to monthly and used for analysis.

4.2.2 Methods

Pair-wise comparism
VECTRI and LMM_{2010} simulated EIR_m were pair-wise compared with the observed. The error contrast between the pairs (i.e. LMM_{2010} vs observed and VECTRI vs observed) was measured with Mean Absolute Error (MAE). The MAE was defined as the arithmetic average of the absolute differences between the observed (O_i) and predicted (P_i) values (Legates and McCabe Jr 1999) of EIR_m:

$$MAE = \frac{1}{n}[\sum_{i=1}^{n} \left|P_i - O_i\right|] \tag{4.1}$$

where n is the number of observations. MAE can range from zero to a large positive value (Moriasi et al. 2007, Willmott et al. 1985). According to Singh et al. (2004), MAE values $\leq$ half the standard deviation (σ) of the observed data are low and appropriate for model evaluation. In this study, Singh et al. (2004) idea of error significance was adapted. Errors of VECTRI and LMM_{2010} in simulating EIR_m were considered low if MAE $\leq \sigma$ of the observed EIR_m. The decision to use full σ instead of half σ was based on the coarse nature of the observed EIR_m (see Appendix A).
Mean Bias Error was also applied to the pairs to measure the tendency of EIR_m simulated by both models to be larger or smaller than the observed counterpart. The MBE was defined as the average of the differences between P_i and O_i pairs (Gupta et al. 1999a, Wilks 1995):

$$MBE = \frac{1}{n}[\sum_{i=1}^{n} \left(P_i - O_i\right)] \tag{4.2}$$

Table 4.1: Seasonality index (SI) of EIR and the corresponding seasonal regime

Seasonal EIR regime	Seasonal Index (SI)
Very equable	≤ 0.19
Equable with a definate EIR season	$0.20 - 0.39$
Rather seasonal with a short period without EIR	$0.4 - 0.59$
Seasonal	$0.6 - 0.79$
Markely seasonal with longer period without EIR	$0.8 - 0.99$
Most EIR in 3 months or less	$1.00 - 1.19$
Extreme, almost all EIR in 1 to 2 months	≥ 1.20

MBE value closed to zero indicates equal distribution between negative and positive errors (Gupta et al. 1999a). Like MAE, the monthly biases of both models were low and acceptable if MBE $\leq \sigma$ of the observed EIR_m. Malaria locations in the vicinity of permanent water bodies and irrigation were excluded in both MAE and MBE calculations.

Peak characteristics

The time series of EIR_m simulated by LMM_{2010} and VECTRI were analysed regarding peak behaviour in a year and compared with that of the observed for each zone. On an EIR_m time series within a year, a peak was defined as a local maximum with two points on either side being smaller than it. Details on how peaks were identified are described in Chapter 3 (see section 3.2.2). The peak analysis was done for each year of available EIR_m of all locations except permanent water bodies and irrigated locations.

Relative seasonality

The seasonal contrasts in malaria amounts within a year rather than whether or not a month had malaria, was assessed. This was done by quantifying the seasonal contrast in EIR_m amount with a seasonality index (SI) (Walsh and Lawler 1981) previously applied to rainfall. The index was defined as the sum of the absolute deviations of EIR_m from the overall monthly mean (EIR_μ), divided by the annual EIR (EIR_a).

$$SI = \frac{1}{EIR_a} \sum_{n=1}^{12} |EIR_m - EIR_\mu|. \tag{4.3}$$

Estimated SI values from both models were then compared with the observed. The choice of this index was due to its advantage of showing differences in relative seasonality even at areas with two seasonal malaria peaks. Ranges of SI values and their corresponding seasonal regimes are presented in Table 4.1. Again malaria locations in the vicinity of permanent water bodies and irrigation were excluded.

Endemicity

The ability of the models to differentiate levels of malaria endemicity in the region was investigated. To achieve this, the definition of endemicity by Beier et al. (1999) was utilized. LMM_{2010} and VECTRI simulated EIR for East Africa were categorized into high (EIR_a > 100), mild (EIR_a between 10-100), low (EIR_a between 1-10), very low (EIR_a between 0-1) and no transmission (EIR_a = 0). These categorized levels of transmission were then contrasted with elevation and validated with the ob-

served. The choice of East Africa was due to the high malaria transmission variability resulting from the complex topography of the area. Malaria locations in the vicinity of permanent water bodies and irrigation were excluded.

Cross correlation
LMM_{2010} and VECTRI simulated EIR_m were cross-correlated with rainfall at lags of 0-11 months and compared with the observed. The aim was to identify whether or not the models were able to determine the delay period between onset of suitable rainfall conditions and malaria season onset. The delay period corresponded with lag(s) at which there exist strong positive correlations between monthly EIR and rainfall. Strong positive correlation was defined as one with Pearson's correlation coefficients (R) ≥ 0.5. Malaria locations in the vicinity of permanent water bodies and irrigation were excluded.

Hydrology
Mean EIR_m time series for malaria locations with PWB and irrigation simulated by VECTRI were compared with the observed. Sites without permanent water bodies or irrigation (Neutral) were used as control check. LMM_{2010} was not included because of the missing hydrology component in its parameterization. The objective here was to examine the representativeness of VECTRI simulates from PWB and Irrigated locations to observed. The Standard Error (SE) of the observed mean EIR_m was calculated and used as uncertainties surrounding the observed mean EIR_m. VECTRI simulated EIR_m were then rated good or acceptable if its mean were about the same or within the uncertainty region otherwise poor. SE of the mean indicate the uncertainty around the estimate of the mean measurement (Altman and Bland 2005) or how much sample means vary from the standard deviation of the sample distribution (Biau 2011, Clark-Carter 2005) and defined as:

$$SE = \frac{\sigma}{\sqrt{N}} \tag{4.4}$$

where N is the sample size.

4.3 Results

Pair-wise comparism
Figure 4.1 shows the MAE between monthly pairs of simulated (by LMM_{2010} and VECTRI) and observed EIR_m at each zone. At Sahel (panel a), the monthly MAE of both models were generally about the same as σ except some individual monthly deviations especially in VECTRI. At Savanna (panel b), both models errors were again about the same as the σ but for the last 3 months where the threshold was exceeded. At Guinea (panel c), errors from LMM_{2010} were for the first 5 months within range but exceeded it afterwards. That of VECTRI were generally above the σ. At Cameroon (panel d), unlike Guinea, their MAEs were within the range of σ except some deviations in the second quarter of the season which was much conspicious in LMM_{2010}. At Eritrea (panel e), MAE of VECTRI were significantly higher than desired while that of LMM_{2010} fell within the desired range. At EEA (panel f), both model errors were withing the σ threshold.

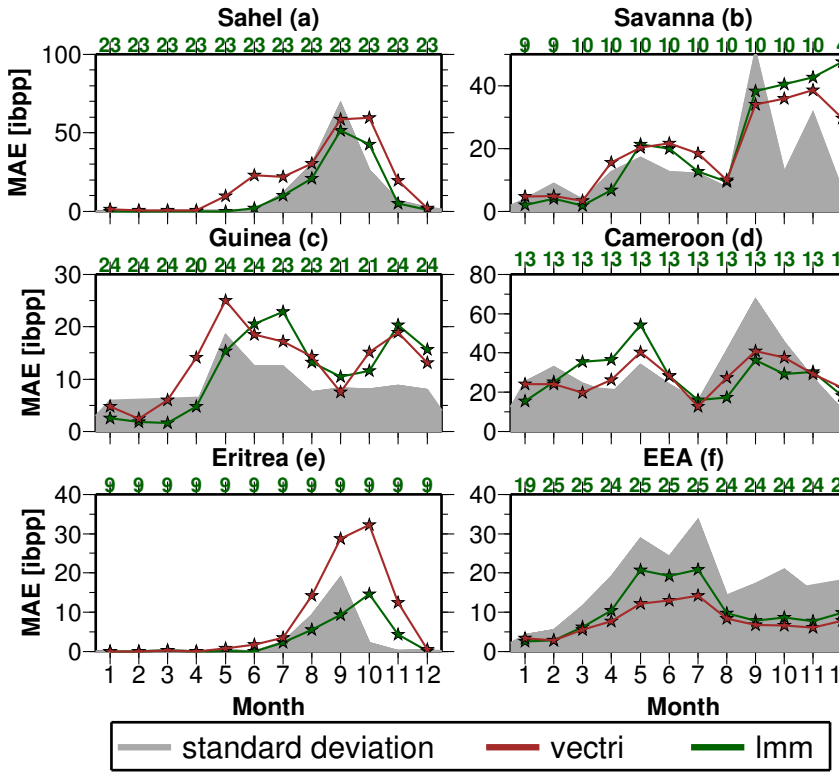

Figure 4.1: Monthly MAE of LMM_{2010} and VECTRI. Grey shaded region: σ of the observed EIR_m. MAE is Low and acceptable if its $\leq \sigma$. Green numbers: number of monthly observations involved.

Figure 4.2 displays the MBE between monthly pairs of simulated and observed EIR_m at each zone. At Sahel (panel a), both models generally over-estimated EIR_m. However, the monthly bias errors were generally within the range of σ except some minor monthly hitches, especially in VECTRI. At the Savanna zone (panel b), LMM_{2010} under- and over-simulated EIR_m towards mid and last 3 months of the season respectively. VECTRI in general over-estimated EIR_m in most parts of the season. However, the bias errors were within ranges of σ of the observed but for the last 3 months of the season. At the Guinean zone (panel c), VECTRI generally over-estimated EIR_m. LMM_{2010}, however, under-simulated EIR_m in first 5 months but over-estimated EIR the rest of the season. VECTRI biases were generally slightly above the σ. LMM_{2010} biases were within the ranges of σ except the last 2 months of the season. At Cameroon (panel d) both models displayed a similar bias pattern. They either over- or under-simulated EIR_m. Bias errors were within ranges of σ. At Eritrea (panel e) VECTRI over-simulated EIR_m with biases outside the ranges of σ of the observed. LMM_{2010} under- and over-estimated EIR_m but its biases fell within ranges of σ. At Equatorial East Africa (panel f), both models under-estimated EIR with biases within ranges of σ of the observed.

Peak characteristics

Figure 4.3 illustrates the seasonal regimes of EIR_m distribution simulated by LMM_{2010} and VECTRI compared to that of observed. At Sahel (panel a), the observed EIR_m distribution unequivocally indicated unimodal distribution. Both model simulates highly agreed with the observed though few observations of both models (quite visible in

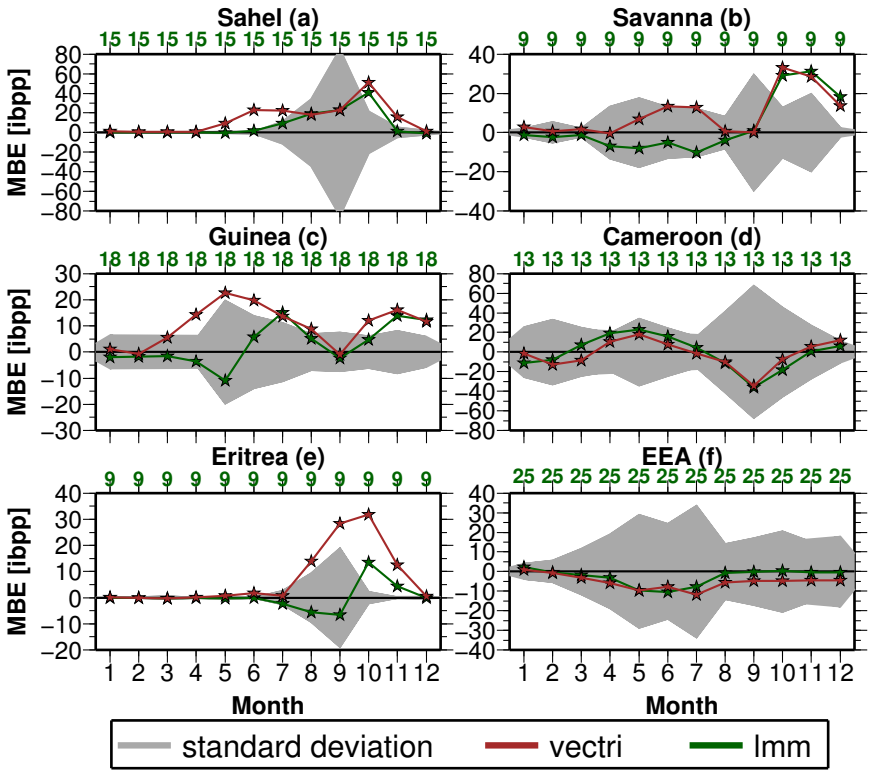

Figure 4.2: Monthly MBE of LMM_{2010} and VECTRI. Same as figure 4.1 but for MBE

VECTRI) suggested bimodality. At Savanna zone (panel b), unimodal and bimodal EIR distribution were suggested by both models and the observed. However, number of observations suggesting bimodality were few compared to unimodality. At Guinea (panel c) uni- and bimodal were conspicuous though there were few suggestions of trimodal by observed data. At Cameroon (panel d) and EEA (f), though few observations suggested no peaks, unimodal and bimodal distribution were suggested with unimodality more pronounced than bimodality. Similar to Savanna, Eritrea (panel e) displayed both uni- and bimodality. But the percentage of observations suggesting bimodal distribution were far too less considering the total number of monthly observations involved. In summary, both models and the observed suggested that the tendency towards unimodal EIR distribution was more likely at all zones than any other regimes. In Figure 4.4 and 4.5, EIR peak months at unimodal and bimodal distributed areas are respectively illustrated. At unimodal areas (Figure 4.4), seasonal peak dates estimated by both models and observed varied widely at all zones. At Sahel (panel a) and Eritrea (panel b), both models and observed peaks were most frequent in September, a month behind rainfall and in October by only both models two months behind rainfall. At the Savanna, peak months widely varied between May and November. At Guinea, peaks mostly varied between May-July and were often earlier than rainfall. At Cameroon and EEA, peak months were more visible in May/June.

At bimodally distributed areas (Figure 4.5) the number of observations for observed EIR_m were too few compared to that of the models. At Sahel, only both models suggested bimodal peaks in July and October. At Savanna, first and second peaks occured in June/July and October/November respectively. At Guinea, Cameroon and EEA, the first season peaks were spread between March and July and the second mostly in October-November. At Eritrea, bimodality was visible in the observed EIR_m, but the number of observations were too few to be considered hence likely fake.

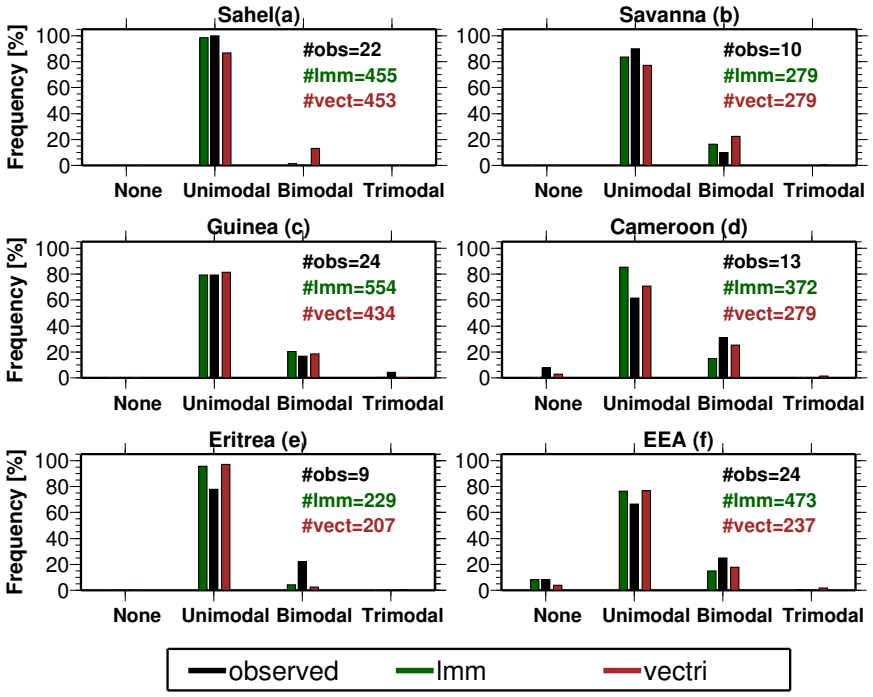

Figure 4.3: Seasonal peaking behaviour of EIR_m over sub-Saharan Africa Number of observations for models and observed are printed in the panel for each zone.

Relative seasonality

The degree of EIR seasonality with respect to latitude simulated by LMM_{2010} and VECTRI are validated with observed and displayed in Figure 4.6. At both regions, simulated (LMM_{2010} and VECTRI) and observed SI values were low at equatorial regions, increased with increasing latitudes towards the northern fringes such as the Sahel and Eritrea where highest SI values were observed. In WA, observed and simulated SI values both ranged between 0.2 at equatorial areas to about 2 in the Sahel. The pattern of LMM_{2010} (panel a) and VECTRI (panel c) simulated SI values were both comparable to that of the observed at WA and EA. Unlike WA where the scatter of SI values were seemingly uniform, SI values in EA were widely dispersed at the equatorial East Africa. In general, the degree of EIR seasonality was closely linked to latitudinal variation in climatic covariates such as rainfall in both West and East Africa, which both models were able to mimic well.

Endemicity

In Figure 4.7, the association between malaria endemicity and elevation are displayed. The field observed data (panel a) showed a decrease in endemicity from low to high elevations. In other words, malaria transmission intensity decreased from high to no transmission at low to high elevations respectively. VECTRI simulates (panel b) were able to mimic similar transmission pattern as the observed. LMM_{2010} simulates (panel c) were patchy.

VECTRI simulated EIR_m cross-correlated with rainfall

Figure 4.8 displays the lags and their corresponding Pearson's correlation coefficient

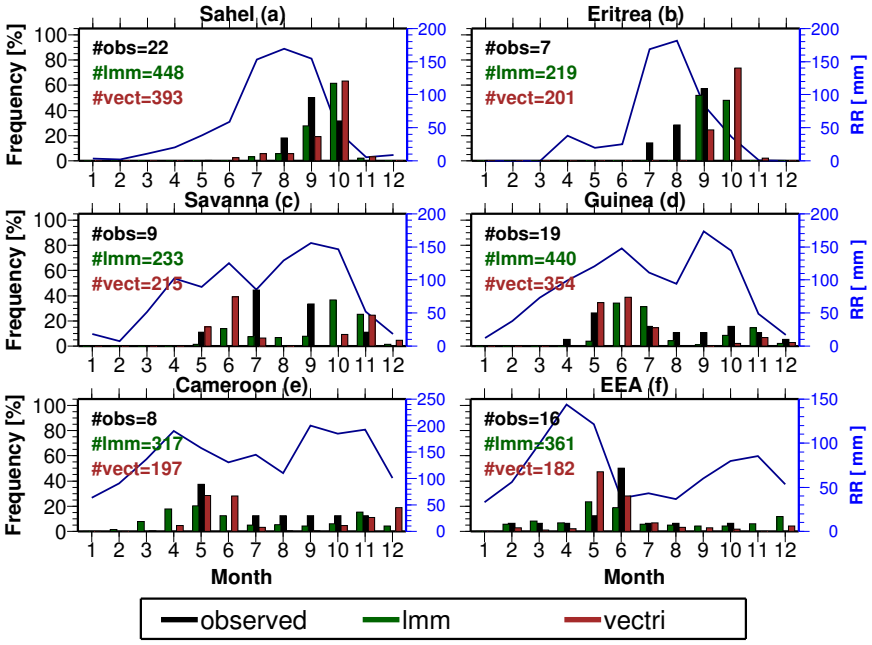

Figure 4.4: EIR peak months at unimodal distributed areas

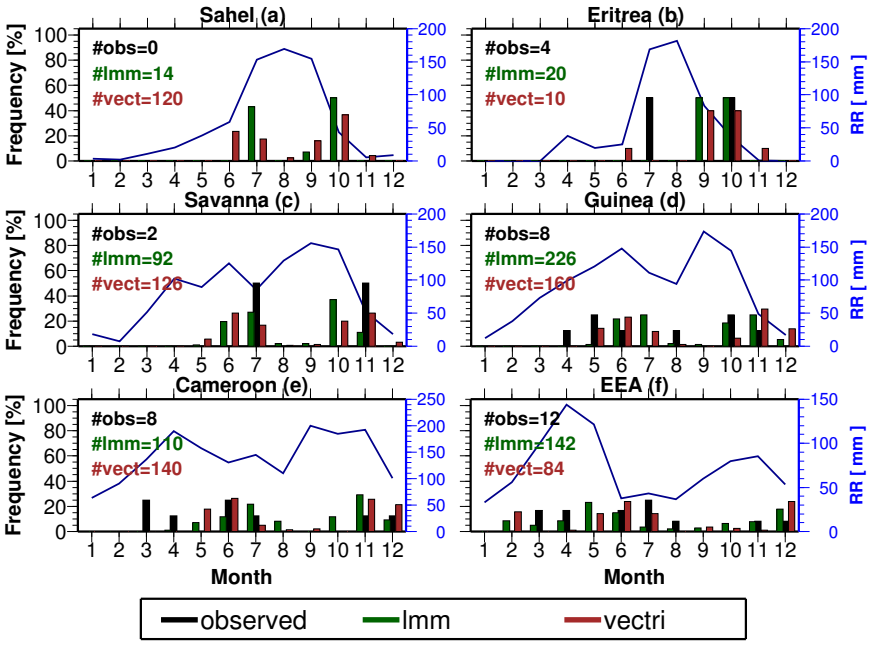

Figure 4.5: Peak months at bimodal EIR distributed areas

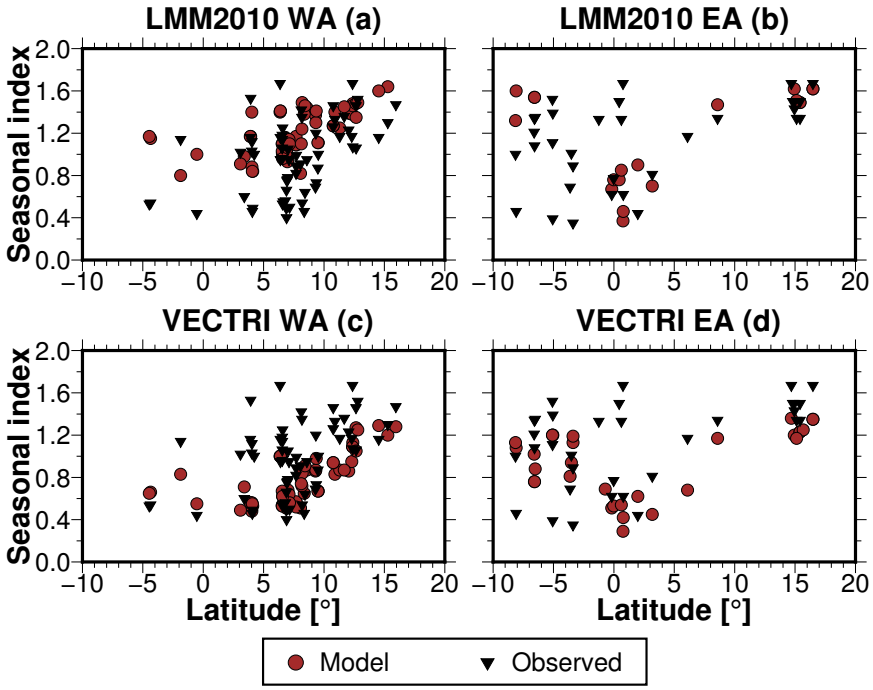

Figure 4.6: Scatter diagram of EIR SI with latitude. Panel a: West Africa (WA), Panel b: East Africa (EA). m is the slope, e is the error in slope and s is the level of significance in slope

from cross-correlation between VECTRI simulated EIR and rainfall compared to observed. At Sahel (panel a), the observed and VECTRI showed positive correlations at 0-3 lags. The observed correlations were significant at 0-2 lags while that of VECTRI were significant at 1-3 lags. At Eritrea (panel b), the observed demonstrated positive correlations at 0-2 lags while that of VECTRI were 0-3 lags. The observed correlations were significant at 0-1 lags while VECTRI were significant at 1-2 lags. At Savanna (panel c) and Guinea (panel d), positive correlations of the observed ranged at 0-2 lags with peak correlation at 0 lag. That of VECTRI ranged from 0-3 lags at Savanna with peaks at 1-2 lags and 0-2 at Guinea with peaks at 0-1 lags. At Cameroon, both observed and VECTRI displayed insignificant positive correlations varying between 0-2 lags with peak at 0 lag for the observed and at lag 1 for VECTRI. At EEA, both observed at VECTRI showed positive correlations at 0-3 lags with peak at 1-2 lags.

LMM_{2010} simulated EIR_m cross-correlated with rainfall

Similar to Figure 4.8, the corresponding cross-correlations of LMM_{2010} output contrasted with the observed are displayed in Figure 4.9. At Sahel (panel a), both the observed and LMM_{2010} showed positive correlations at 0-3 lags. LMM_{2010} correlations were significant at 1-2 lags as that of observed was at 0-2 lags. At Eritrea (panel b), the observed demonstrated positive correlations at 0-2 lags while that of LMM_{2010} were 0-3 lags. The observed correlations were significant at 0-1 lags while LMM_{2010} were significant at 2-3 lags. At Savanna (panel c) and Guinea (panel d), positive correlations of the observed ranged at 0-2 lags with peak correlation at 0 lag. That of LMM_{2010} ranged 0-5 lags at Savanna with peaks at 1-2 lags and 0-3 at Guinea with peak at lag 1. At Cameroon, both observed and LMM_{2010} displayed insignificant positive correlations at 0-2 lags and 0-3 lags respectively with both peaking at lag 0. At

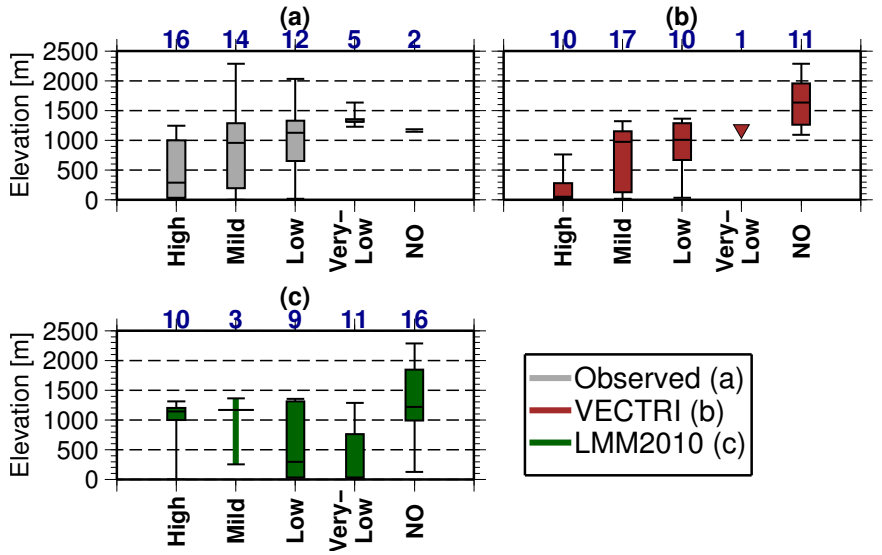

Figure 4.7: Malaria endemicity in East Africa. Excludes all locations in the vicinity of permanent water bodies and irrigation.

EEA, both observed and LMM_{2010} displayed positive correlations at 0-3 lags with peak at 1-2 lags.

Hydrology: Permanent water bodies and irrigation

Figure 4.10 displays the seasonality of VECTRI simulated EIR_m for malaria locations at different settings of hydrology compared with the observed. At Sahel (upper row), the intensity of the simulated EIR_m for PWB and irrigated locations were higher than at control areas. At Savanna, simulations for PWB locations were lower than control sites while that of irrigated areas were higher. Simulations for PWB areas at Guinea and Cameroon were also lower than control areas. However, VECTRI estimations for control and irrigated areas at Guinea were largely over-estimated.

4.4 Discussion

The main aim of this study was to validate and evalute seasonal malaria simulated by VECTRI and LMM_{2010} with the goal to determine whether they realistically predict representative seasonal malaria for Africa as a function of climate and environment. This section provides a detailed discussion of the various aspects investigated with references to results of previous studies where possible.

Pair-wise comparism

The results of MAE and MBE showed that though some individual monthly errors of both models were slightly higher than expected (e.g. at Savanna), majority of the errors were either about the same or within the acceptable range. Of course these individual monthly deviations were expected since it is impossible for the models to be able to define the precise edges of each EIR_m value at each zone. This is because they are not be able to capture all the small scale ecological variability and temporal changes in transmission risk. Besides, both models are still under development and have not

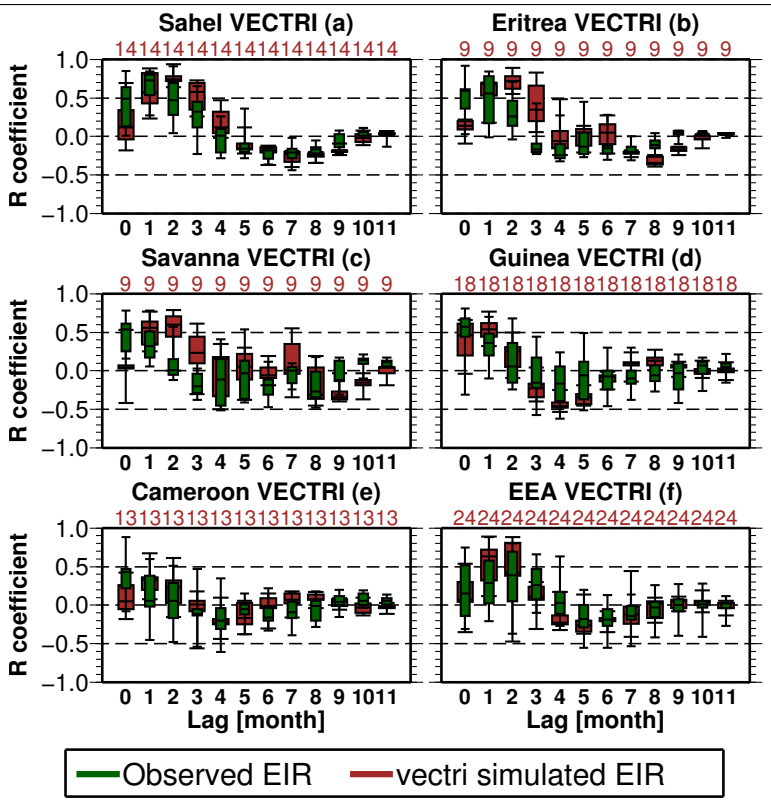

Figure 4.8: Cross correlation between VECTRI simulated EIR_m and rainfall compared to observed. VECTRI: brown box-plots, Observed:green box-plots. Brown numbers (top of panels) indicate the number of monthly observations

incoporated all malaria transmission factors such as immunity, urbanization, socio-economic status and interventions into their algorithsms. Hence, they are not able to currently represent completely the overall transmission pattern. Apart from both model limitations, the observed EIR_m data used for validation had limitations. The observed EIR_m data were too coarse (i.e., EIR_m data were mostly available for shorter period (1year), at different years for the various malaria locations). Again, EIR_m sampling biases during collection (Hay et al. 2000, Shaukat et al. 2010), inhomogeneous distribution of study areas and digitization of EIR_m values from their articles could have a negative impact on the outcome.

The over-estimation of EIR_m by both models at warmer zones (such as Sahel, Eritrea and Savanna) and under-estimation at colder zones (such as Cameroon and EEA) may be due to the use of mean temperature by the models for the simulation. Studies have shown that, the typical approach of using mean temperatures in malaria studies underestimate parasite development under cold conditions and overestimate under warmer conditions Blanford et al. (2013). This is explained by the fact that mosquito and parasite biology are influenced not only by average temperature but also by the extent of the diurnal temperature variation (Paaijmans et al. 2010; 2009).
Besides, the error contrast was higher in VECTRI simulations than that of LMM_{2010} One reason is that VECTRI is likely sensitive to population density used in the calculation of biting ratios. LMM_{2010} uses a fixed population density of 100 persons/km^2 while that of VECTRI depended on the location involved. Sites with density well below 50 persons/km^2 or well above 100 persons/km^2 may results in VECTRI over-

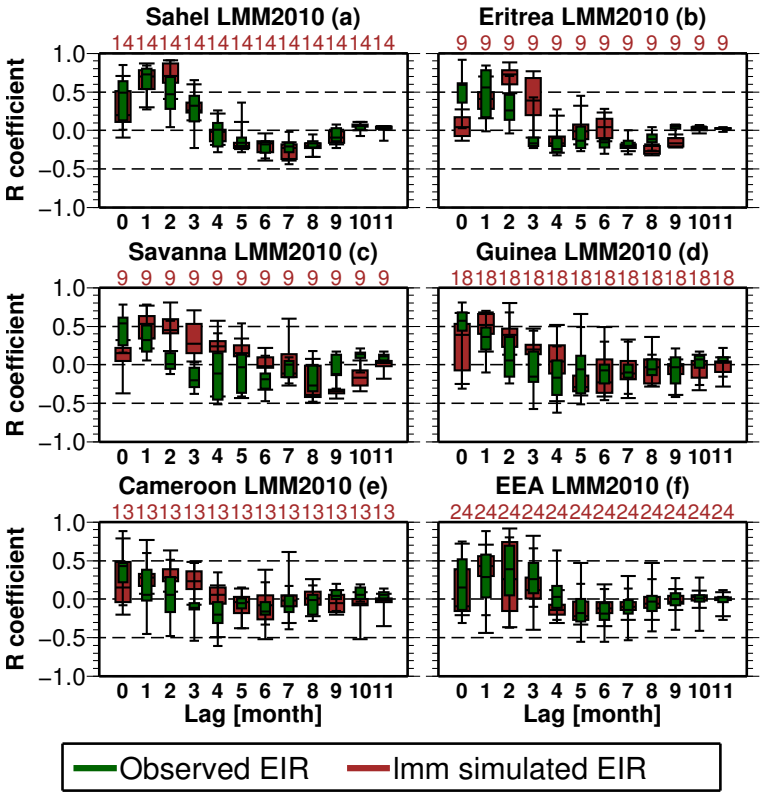

Figure 4.9: Same as figure 4.8 but for LMM_{2010}

estimating or under-estimating EIR_m respectively compared to LMM_{2010}. This pattern was therefore expected since most locations in Sahel and Eritrea have lower density values than at Cameroon and EEA. Another factor that may be responsible for the VECTRI under-estimation at relatively colder areas such as Cameroon and EEA may be due to the water temperature parameterization. The water temperature offset which controls the upper limit of the mean temperature may make it much colder for VECTRI vector resolution compared to LMM_{2010} which has no such parameterization.

On the other hand, the under-estimation of EIR_m by LMM_{2010} most often from the onset towards mid-season may be due to its sensitivity to ideal rain rate value of 1 mm/day for eggs laying. The condition seems not satisfied since rainfall amount is largely low at those times of the year. The ideal value of 1 mm/day in LMM_{2010} is much sensitive to rainfall compared to moderate rain rates of 0 to 20 mm/day in VECTRI. This moderate VECTRI value is likely disadvantageous at highly seasonal rainfall zones like Sahel and Eritrea as it results in the background trasmission during dry periods. Towards the end of the year, both models generally over-estimated EIR_m,particularly in the warmer zones. This may likely be due to higher vector population simulated which appear to be long-lived especially in LMM_{2010} than VECTRI.

Peak characteristics

VECTRI and LMM_{2010} were also able to reproduce the different malaria distribution regimes (no peaks, unimodal, bimodal and trimodal distributions) as identified by the observed at each zone. These regimes are due to the impact that different rainfall distribution patterns in a year have on vector population and their biting activity at a

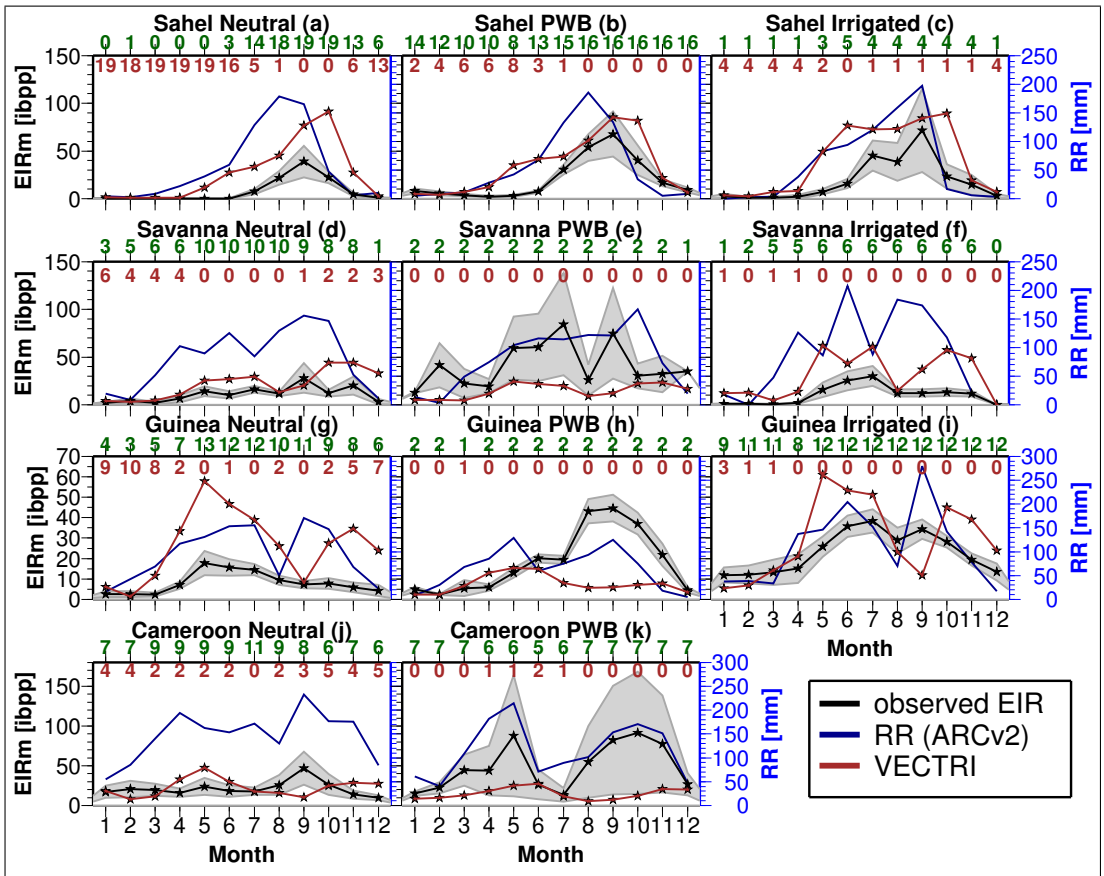

Figure 4.10: Seasonal time series of EIR simulated by VECTRI for different settings of hydrology. Left column:Neutral locations, Middle column: PWB locations, right column: Irrigated locations. Lightgrey shaded area: uncertainty in the observed EIR_m. Green and brown numbers indicate number of months suggesting presence and no of malaria respectively.

location. For instance, sites with markedly seasonal rainfall such as the Sahel displayed unimodal malaria transmission. However, the high tendency of majority of the malaria locations at bimodal rainfall distributed zones (Savanna, Guinea, Cameroon, EEA) towards unimodal malaria distribution instead of bimodal can also be explained by the phenomena of vector persistence. Rainfall seasons at these zones are long and vectors persist at stable levels (Craig et al. 1999). Hence, first rainfall season onset will accelerate their population growth resulting in early peak activity. Since annual rainfall totals are high at these zones (Nicholson 2013) coupled with the fact that the two rainy seasons will consolidate each other regarding water amount, vector breeding habitats may become flooded, flushing out and killing some water-bound stage vectors (Tompkins and Ermert 2013). This will lead to vector population being maintained or decline.

Relative seasonality

Simulated SI values by both models agreed with the observed to a large extent. The low SI values at the equatorial zones suggest that malaria is equable in all months at these regions. The high SI values at areas around Sahel and Eritrea indicate the concentration of malaria in about 1-2 months. The increase in SI values from the equatorial areas towards the Sahel is an indication of seasonal malaria transition from

perennial through to epidemic or malaria free at Sahelian regions. The pattern also suggest that the degree of malaria seasonality is closely linked to latitudinal variation in climatic covariates such as rainfall. The wide spread of SI values in East Africa, especially at EEA, buttresses the fact that seasonal malaria transmission in that region is highly variable.

This approach of quantifying EIR seasonality contrast is scarcely applied in malaria studies hence unique. Previously, Mabaso et al. (2007) applied Markham's concentration index (Markham 1970) in analyzing the relationship between seasonality in EIR and environmental factors in sites across sub-Saharan Africa. They found that seasonality of rainfall, minimum temperature, and irrigation were important determinants of seasonality in EIR. While their approach is entirely different from that applied in this study, the degree of malaria seasonality closely linked to latitudinal variation in climatic covariates as rainfall agrees with their results. However, their index (Markham 1970) is very deficient at locations with two seasonal malaria (Mabaso et al. 2007) unlike the the index applied in this study (Walsh and Lawler 1981).

Endemicity

Evaluating the association between malaria endemicity and elevation showed that endemicity decreased from high endemicity at lower elevations to no transmission at high altitudes. The decrease in intensity towards higher elevations is because cool temperatures at high elevations unlike at low elevations limit malaria transmission (Drakeley et al. 2005). The inability of LMM_{2010} to reproduce similar pattern may be because it was not calibrated with data from East Africa. LMM_{2010} performs better in West Africa where it was calibrated than in East Africa. Previous studies have also reported similar findings. In Tanzania, Maxwell et al. (2003) sampled mosquitoes and found that EIR was about 17 times greater at a lowland than highland area. In an entomological survey in Papua New Guinea, Attenborough et al. (1997) identified that the proportion of mosquitoes with malaria circumsporozoite antigens declined with increasing altitude. In similar studies not using EIR (Akhwale et al. 2004, Balls et al. 2004, Bodker et al. 2003), similar patterns were observed.

Cross-correlation

Significant lags of positive association varied between 0-3 months at all zones, and both model simulates were generally within this range. Though previous works on cross-correlation analysis between EIR and rainfall were scarce, studies using malaria cases in that regard reported similar ranges. For instance, Briet et al. (2008) cross-correlated malaria cases with rainfall in Sri Lanka and found malaria time series lagging between 0-3 months behind rainfall. Again predicting malaria epidemics in the Kenyan highlands using climate data Githeko and Ndegwa (2001) found the association between rainfall (and unusually high maximum temperatures) and the number of inpatient malaria cases 3-4 months later. Despite the fact that simulated lags were within ranges of the observed, significant peak lags differed. Model simulated peak lags were mostly 1 month later than the observed except EEA. This suggests that the vector loading in the models after the onset of suitable climatic conditions are likely slow (slow spin).

Hydrology
The attempt in this section was geared towards the assessment of how well the elaborate hydrology model in VECTRI can replicate EIR seasonality at PWB and irrigated areas. At Savanna, Guinea and Cameroon where EIR_m values from PWB locations were lower than control locations was due to VECTRI's sensitivity to population density. Sites involved in these areas had population density greater than 200 persons per km^2. As elaborated in the previous sections, VECTRI largely underestimates biting ratios for locations with population density well above 100 persons per km^2. The water temperature offset as elaborated afore coupled with the traditional use of mean temperature may also have contributed to the low values at Cameroon. Despite these hitches (which are refineble), VECTRI performance at Sahel and irrigated areas at Savanna and Guinea were comparable to the observed though over-estimations were obvious.

4.5 Summary and conclusions

Ranges of EIR_m simulated by LMM_{2010} and VECTRI for sub-Saharan Africa were validated with observed EIR_m data gathered from different climatic and environmental settings across Africa. The goal was to determine whether or not the models could realistically simulate characteristic seasonal malaria patterns in Africa as a function of climate and environment.

LMM_{2010} and VECTRI error ranges were generally within or about the same as the accepted standard deviation of the observed data. It is, however, worth noting that, larger errors were detected for Guinea and some individual monthly minor differences occurred. Besides, both models agreed with the observed on speculations regarding malaria peaking characteristics that, malaria distribution was predominantly unimodal. However, it was noted that maximum malaria transmission peaks in the models tend to be delayed by one month in the Sahel and Eritrea area. Both models further agreed with the observed values of a seasonality index that the disease progression was closely linked with the latitudinal variation of climatic covariates such as rainfall. VECTRI revealed a stronger ability in capturing the levels of malaria endemicity in East Africa than LMM_{2010}. VECTRI does not capture very well malaria transmission at permanent water body locations.

The comparability of LMM_{2010} and VECTRI error ranges to standard deviations of the observed EIR_m coupled with their agreement with the validated steps in general, confirmed the hypothesis that they could reproduce realistic EIR_m for the African region. It is therefore concluded that both models could mimic the seasonal malaria transmission dynamics in Africa as a function of climate and environment to a large extent. While both models in their current state can be used as early malaria warning system, VECTRI has more advantage at highland areas in East Africa than LMM_{2010} since it was able to mimic malaria endemicity pattern correctly. The identified loopholes in both models provide the basis for further review and refinement of the models by their developers to stage them as best fundamental tools for seasonal malaria prediction.

The sparsity and paucity of the observed EIR_m both in time and space could have had an adverse impact on both model output. Future studies should focus on using more condensed and homogeneously distributed EIR_m data for validation. Moreover, while

the conventional use of mean temperatures by the models to simulate EIR_m might be appropriate under certain conditions, it may likely over- or under-estimate EIR_m at warmer and colder zones respectively. Future developments should therefore focus on the use of diurnal daily temperature ranges rather than mean. This is important since the biology of the malaria vectors and parasite is influenced by both average temperature and the extent of the diurnal temperature variation that occurs throughout the day. In addition, optimizing the parameter settings of both models through a sensitivity study is important in order to determine their relative importance to model output. This has the advantage of resolving their simulation hitches resulting from parameter settings. Besides, inclusion of other transmission factors such as immunity, urbanization and interventions into their algorithms is necessary. It will enable the models to describe the overall malaria transmission dynamics in the region quantitatively. These recommendations forms the focus of the next chapter.

CHAPTER 5

An evaluation of a simple model of immunity to malaria and sensitivity of VECTRI paramter settings to the spread of malaria in Africa

Abstract
VECTRI model has provided adequate approximations to biological and epidemiological features of malaria in Africa. But immunity to malaria which is an important determinant of the disease in the region is missing in its formulations. Besides, the sensitivity of VECTRI parameter settings to its output variability has also not been analyzed. Thus, VECTRI is currently unable to describe the overall malaria transmission dynamics in the region quantitatively and qualitatively. This study utilized a new simple model of immunity in VECTRI and performed a one-at-a-time sensitivity study of VECTRI parameter settings to its output variability. The findings revealed that the immunity model enabled VECTRI to simulate different levels of malaria for Africa by reducing transmission rates at increased exposure of humans to malaria. The simple immunity model also substantially improved the seasonal malaria simulations of VECTRI by reducing its output error. The one-at-a-time sensitivity analysis performed on VECTRI parameter settings revealed parameters that show the strongest variation of the model output. The most sensitive parameters include the adult vector survival probability, the minimum temperature for larval survival, larvae growth degree days, the minimum temperature for sporogonic cycle, base daily larval survival rate, and total evaporation and infiltration losses. The new immunity model represents a helpful tool for future malaria modelling effort, and its refinement for consideration in VECTRI is necessary. Parameters contributing most to VECTRI output variability require additional research to strengthen knowledge base to reduce VECTRI output uncertainty.

5.1 Background

Human immune response to malaria infection is one of the essential features of the disease's dynamics in Africa (Molineaux et al. 1988). The differential movement of infection among different age groups and gender in the region is attributed to their immune status (Mandal et al. 2011). Children below 5-years of age and pregnant women are the most burdened by malaria due to their lack of protective immunity (WHO 2015). Older children (> 5years) and adults have reduced risks due to acquired protective immunity. The build-up of protective immunity is due to the cumulative product of many years of heavy exposure to malaria (Doolan et al. 2009). Additional reasons are associated with intrinsic factors linked with aged that enables a quick immune response of older children and adults (Baird et al. 1991; 2003). But due to lack of continuous exposure to malaria at epidemic zones, the disease burden cuts across all ages (WHO 2015).

Some malaria models (Aron 1988, Filipe et al. 2007, Gatton and Cheng 2004) have incorporated immunity into their algorithms. Incorporating immunity into malaria models makes them more realistic especially regarding their prediction of malaria and evaluation of the outcome of vaccination programmes (Koella 1991). Since presumed base values of model parameters are usually not error-free, other models (Chitnis et al. 2008) have optimized their parameter settings to determine their sensitivity and robustness to malaria outcome (Hamby 1994).
The VECTRI is a weather-driven dynamical mathematical malaria model. It has provided adequate approximations of biological and epidemiological features of malaria in Africa (Caminade et al. 2014, Tompkins and Di Giuseppe 2015). But the immune response of human subjects to malaria is missing in its formulations. The absence of immunity in the model presupposes that VECTRI is currently unable to describe the overall malaria transmission dynamics in the region quantitatively. This is evident since immunity is an important malaria transmission determinant in Africa (Doolan et al. 2009). Also, VECTRI parameter settings have not been optimized to determine their relative importance to model output. Since parameter settings are most influential on a model result (Chitnis et al. 2008), a study of parameter sensitivity to model results is critical for model validation and guide for future research efforts (Hamby 1994).

In this study, a new simple model of immunity to malaria was used in VECTRI with the aim of understanding the effect of immunity to inform future malaria modelling efforts. An additional goal was to determine whether inclusion of immunity into VECTRI improved its malaria prediction capability for Africa. Moreover, the parameter settings of VECTRI were optimized through a sensitivity study with the aim of determining parameters that contributed most to VECTRI output variability. The study outcome will reveal how the simple immunity module enabled VECTRI to simulate different levels of malaria for Africa as well as improved the seasonal malaria simulations errors in VECTRI. The study will further show how a one-at-a-time sensitivity analysis performed on VECTRI parameter settings revealed parameters that show the strongest variation of the model output and require additional research to reduce VECTRI output uncertainty.

5.2 Methods

5.2.1 Brief description of VECTRI

When a pathogen invades a population, it categorises the population into compartments based on infection status (Crompton et al. 2014). Following this ideology, VECTRI formulated malaria parasite progression in the vector and host populations using an array of bins approach. The various stages of explicit resolution are depicted schematically in Figure 5.1.

The larvae life cycle is divided into fractional bins. Vectors lay eggs into the first bin. The eggs advance a number of bins at a fractional growth rate dependent on the local water temperature to the last bin where they develop into adult mosquitoes. At the adult stage, a two-dimensional array of bins consisting the gonotrophic and sporogonic cycles are resolved. The first gonotrophic bin consists of gravid vectors searching for a blood meal. Successful vectors advance regarding egg development to the final bin

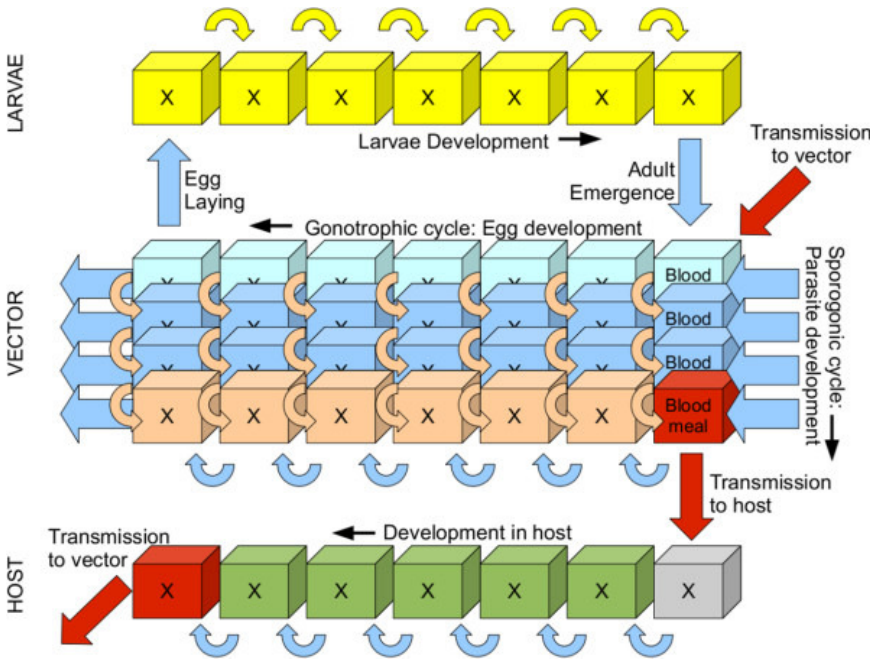

Figure 5.1: The structural layout of VECTRI model. The top row shows the larvae status divided into a series of bins representing the fractional development state. The 'X' in each bin represents the density of larvae in a specific fractional growth stage. The middle block represents the vector state in two dimensions: the egg development within the female and the infective state. The lower row models the host infective state. The curved arrows represent the progression direction of the larvae, vector and host state, while the straight red arrows mark the parasite transmission pathways between host and vector. Source:Tompkins and Ermert (2013)

(where new eggs are laid) at a rate dependent on ambient temperature. The vector is recycled to the first meal-searching bin upon becoming gravid again. During the blood meal, a proportion of the biting vectors become infected by an infective host and progress in the sporogonic dimension at a rate also determined by temperature. Upon reaching the last bin, they become infective to humans and remain so untill death. In the human host population, the first bin represents the fraction of the host population Susceptible (S) to malaria infection. Upon getting infected, the susceptibles progresses a number of bins representing the Exposed (E)-fraction incapable of passing on the infection to others though infected, and the Infectious (I)- capable of infecting the susceptible individuals via vectors that feed on them. The set of equations and parameterization associated with each of the stages are detailed in the original article Tompkins and Ermert (2013).

5.2.2 Modelling immunity to malaria

Incorporation of immunity into malaria models One way to incorporate immunity into malaria models is to consider a separate immune compartment in human host population (Chitnis et al. 2006, Dietz et al. 1974, Laneri et al. 2010, Ngwa and Shu 2000, Yang 2000). Another way is to use immunity functions (Cairns et al. 2011, Filipe et al. 2007, Okell et al. 2008). The former approach was applied in VECTRI since it is a compartmental model. Thus, immunity was implemented by extending the compartmental classes of the human host population to include those that Recovered (R) from

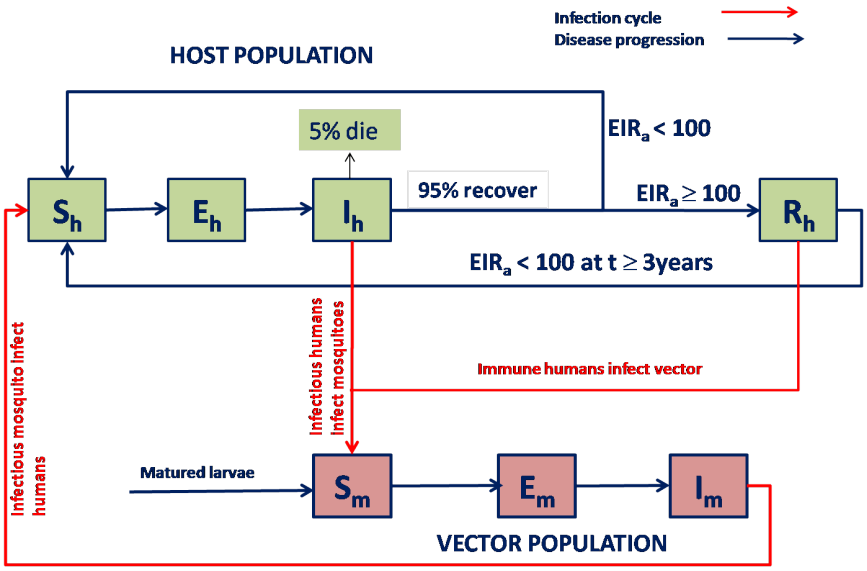

Figure 5.2: Schematic diagram of the simple immunity model incorporated into VECTRI

infections. The schematic representation of the compartmental extension is displayed in Figure 5.2 and Fortran programmed by Dr. Adrian Tompkins (the original author of VECTRI). Human subjects leaving the infectious class gained permanent, temporal or no immunity (Ngwa and Shu 2000, Yang 2000). Thus, it was considered that infectious humans (I_h) that recovered from infections joined the recovered compartment (R_h) if partial immunity was attained. Otherwise, they move directly back to the susceptible class (S_h). It was also assumed that about 95% of the infected individuals subsequently recovered from infections and acquired temporal protection to severe disease. The rest of the 5% either recovered without immunity and returned directly to the susceptible class or died of the infection.

Acquisition of immunity

Precise onset of immunity is yet unknown. Some studies suggest it is developed after 5-15 years of continuous and heavy exposure to infections (Baird 2004). Others indicate only one or two successful malaria infections accross a broad range of transmission intensities is necessary (Gupta et al. 1999b). Ranges of 3-6 malaria episodes have also been reported (Baird 1995, Baird et al. 1991, Ciuca et al. 1934). In this work, the acquisition of partial immunity depended on the number of infectious mosquito bites (EIR) the recovering group accumulated in a year (EIR_a) (see Figure 5.2). Thus, they gained immunity and moved to the R_h class if the EIR_a is at least 100 ibpp, else they joined S_h group. The choice of 100 ibpp in a year was to reflect the slow build up of immunity to parasitaemia (Baird 1995). The duration of building effective immunity was right after recovery from the disease. It was considered that exposure to new infections by the R_h class boosted the immunity they acquired (Doolan et al. 2009). The mathematical formulation of the rate of acquisition of immunity, q, was given as:

$$q = \exp \frac{-EIR_a}{tau} \tag{5.1}$$

where

$$tau = \frac{-100}{\ln(0.05)} \tag{5.2}$$

Immuned individuals infect biting mosquitoes with a lower probability than non-immune subjects since acquired immunity decrease the infectivity of gametocytes to mosquitoes (Buckling and Read 2001, Drakeley et al. 2006). As a result, it was considered that the recovered group still infected vectors at a low rate. The infection probability of 0.04 was adapted from Ermert et al. (2011a).

Loss of acquired immunity

The acquired immunity was assumed temporal and lasted only for T years in the absence of new infections (Doolan et al. 2009). Reported period of decay of acquired immunity to malaria varies. Clinical immunity is reported to have a half-life of at least 3-5 years (Filipe et al. 2007, Jennings et al. 2006, Struik and Riley 2004). Anti-parasite immunity which develops later in life has been found to last more 15 years (Filipe et al. 2007, Färnert et al. 2015). Since the study focus regards temporal protection against severe disease, a shorter half of 3 years was chosen. Thus, it was considered that individuals of the R_h class lost the acquired immunity after 3 years of unable to accummulate atleast 100 ibpp. Once the immunity is lost, they moved back directly to the Susceptible class (see Figure 5.2). The duration of loss was expressed in days as:

$$T = \frac{-X * 365}{\ln(0.05)} \tag{5.3}$$

where X is the duration of the acquired immunity in years.

Parasite clearance

The study assumed that treatment is sought by patients since people will most likely seek treatment for clinical symptoms of malaria. With antimalarials clearance time is shorter (Gomes et al. 2008, White et al. 1989) though depends on the therapy used. Artimisinin based therapies may take about 2-7 days (Baird 2005, Brandts et al. 1997). Antimalarial chemotherapy for uncomplicated and complicated malaria found about 3 and 5 days respectively (Tangpukdee et al. 2008). Plasmodium Vivax gametocyte clearance time which correlated with asexual parasite clearance time lasted up to 21 days (Pukrittayakamee et al. 2008). Since it may take several days before treatment is sought, the study assumed a maximum of 20 days clearance time. For instance, young children and adults seeking treatment at formal sectors reported mean duration of 6 and 6.4 days of fever (Mota et al. 2009). The reciprocal of the clearance time gave the rate of clearance.

Additional considerations

The utilized immunity model was simple with minimal parameters. The reason was due to the fact that many details of acquired immunity are unknown and are thus difficult to parameterize (Baird et al. 2003). The primary goal was to reproduce observed epidemiological malaria trends in Africa. The age dependency features of immunity (Karp and Auwaerter 2007, Mandal et al. 2011, Yamana et al. 2013) was exempted by assuming a homogeneously mixed population of humans. The various types and

stages of development of immunity (Filipe et al. 2007, Gupta et al. 1999b, Yang et al. 1997) were exempted. Though the interaction of the mosquito immune system affects *Plasmodium* parasites (Crompton et al. 2014), this was not considered in the vector population since they do not recover from infections but are regulated by mortality (Chitnis et al. 2006). Parameter values of the immunity model were taking from literature where possible otherwise assumptions were made based on the current understanding of immunological processes in the host population.

5.2.3 Evaluation of the immunity model

Evaluation of the immunity model VECTRI (v1.4) was driven with daily timeseries of rainfall and temperature from 1983-2013 for malaria locations accross sub-Saharan Africa (see Figure 3.1). The ARCv2 daily dataset (Novella and Thiaw 2013) was utilized as the rainfall product. In terms of temperature, the ERAI dataset (Dee et al. 2011) was used. Details on these input products are given in chapter 3. Equilibrium runs by VECTRI was achieved by repeating the 1983 climate forcing data for 23 times before passing on the rest of the 29 years (1984-2013).

Simulated annual malaria cases and exposure to infectious bites (EIR_a) were then contrasted with time to determine the influence of immunity on the pattern of clinical cases. Sensitivity of the immunity parameters to seasonal malaria cases was additionally evaluated. The baseline parameter values of the immunity model were varied using values gathered from literature and observed the associated changes in seasonal clinical malaria cases.

To examine whether the incorporated immunity improved VECTRI's malaria predictive capability or not, an evaluation of VECTRI seasonal malaria outcome was carried out. Observed $\mathrm{EIR_m}$ gathered from malaria sites across sub-Saharan Africa were pairwise compared with VECTRI simulated $\mathrm{EIR_m}$. The error contrast between them was then measured with Mean Absolute Error (MAE). VECTRI errors were considered low if its MAE was within the standard deviation (SD) of the observed $\mathrm{EIR_m}$. The statistical formulations of these error indices are given in Chapter 4.

5.3 Sensitivity of VECTRI parameter settings

The impact of VECTRI parameter settings to its malaria outcome was performed through a sensitivity study. The essence was to discover parameters that had high impact on the VECTRI predicted malaria outcome. Several methods of parameter sensitivity analyses utilized for various modelling situations exist (Downing et al. 1985, Hamby 1994). In this work, a one-at-a-time design was applied. The method involved varying each parameter value independently by a factor (e.g. $\pm 20\%$ (Hamby 1995) or $\pm$SD (standard deviation) (Downing et al. 1985)) while holding all others constant (O'Neill et al. 1980). Here, baseline values of malaria model parameter settings were gathered from literature where possible and evaluated the sensitivity at their minimum and maximum values. Parameters where further information about other base value distribution were scare, the sensitivity was evaluated at $\pm 50\%$ of their base values. Details of VECTRI baseline parameters settings, the gathered ranges and the associated $\pm 50\%$ are presented in Table 5.1. The associated changes in annual EIR EIR_a

Table 5.1: VECTRI default parameters and their dimensions. Inclusive are ranges of parameter base values and 50% change when ranges were scarce. References (Ref) to the ranges: A: Tompkins and Ermert (2013); B: Ermert et al. (2011a); C: Chitnis et al. (2008); D: as refereced in text and E: Craig et al. (1999)

Parameter	Description	Unit	Value	Range	Ref	±50%	+50%	-50%
N_{egg}	Eggs laid per female vector	eggs	80	5 - 290	B	-	290	5
D_{egg}	Days for egg hatching	days	1.0	-	-	0.5	1.5	0.5
D_{pupae}	Days for pupae stage	days	1.0	-	-	0.5	1.5	0.5
$K_{L,Craig}$	Larvae growth degree days	Kday	5.54e-3	-	-	2.77e-3	8.31e-3	2.77e-3
$T_{L,max}$	Maximum water temperature for larvae survival	°C	38.0	34.0 - 38.0	A	-	38.0	34.0
$T_{L,min}$	Minimum water temperature for larvae survival	°C	16.0	16.0 - 18.0	A	-	18.0	16.0
K_{flush}	Minimal daily survival of L1 larvae	-	1.0	-	-	0.5	1.5	0.5
τ_{flush}	Larvae-flushing rainfall e-folding factor	mm/day	20	-	-	10.0	30.0	10.0
M_{L4}	Larval mass constant	mg	0.45	-	-	0.225	0.675	0.225
$M_{L,max}$	Larvae biomass carry capacity of pools	mg/m^2	300	-	-	150	450	150
P_{Lsurv}	Base daily larval survival rate	-	0.987	0.527 - 0.987	A,B	-	0.987	0.527
K_w	Pond growth rate factor	m^{-1}	1e-3	-	-	5e-4	1.5e-3	5e-4
E+I	Total evaporation and infiltration losses	mm/day	250	-	-	125	375	125
W_{fmax}	Max default water fraction	-	0.2	-	-	0.1	0.3	0.1
T_{wat}	Water temperature offset to air temperature	K	0.5	-	-	0.25	0.75	0.25
$V_{t,indoor}$	Proportion of time spent indoor resting	-	0.5	-	-	0.25	0.75	0.25
$V_{success}$	Blood meal success rate per day	-	0.5	-	-	0.25	0.75	0.25
τ_{zoo}	Zoophilicity rate	Km^{-2}	30.e-6	-	-	15e-6	45.e-6	15.e-6
τ_{anthro}	Minimum anthropophilic bite rate	-	0.05	-	-	0.025	0.075	0.025
H_{clear}	Host parasite clearance rate	days	20	3 - 21	D	-	21	3
P_{ihv}	Transmission probability from host to vector	-	0.2	0.064 - 0.8	B	-	0.8	0.064
$\mathbf{P}_{rhv}$	**Transmission probability from immune host to vector**	-	0.04	-	-	0.02	0.06	0.02
P_{ivh}	Transmission probability from vector to host	-	0.3	0.01 - 0.46	B	-	0.46	0.01
$\mathbf{R}_{imm}$	**Infectious bites needed to acquire immunity**	year^{-1}	100	-	-	50	150	50
$\mathbf{R}_r$	**loss of acquired immunity**	days	365	365 - 609	D	-	609	365
T_{gono}	Minimum temperature for gonotrophic cycle	°C	7.7	4.5 - 9.9	A,B	-	9.9	4.5
D_{gono}	Gonotrophic cycle degree days	days	37.1	36.5 - 65.4	A,B	-	65.4	36.5
T_{sporo}	Minimum temperature for sporogonic cycle	°C	16.0	14.2 - 19.0	A,B	-	19.0	14.2
D_{sporo}	Sporogonic cycle degree days	days	111.0	111.0 - 204.4	B	-	204.4	111.0
$T_{V,min}$	Minimum temperature below which vector dies	°C	5.0	4.0 - 6.0	E	-	6.0	4.0
$T_{V,max}$	Maximum temperature above which vector dies	°C	39.9	39.9 - 42.0	E	-	42.0	39.9
P_{Vsurv}	Vector survival probability	-	0.96	0.45 - 0.99	B	-	0.99	0.45
H_{latent}	Latent period in host	days	20	9 - 26	A,B,C	-	26	9
H_{detect}	Malaria detection in host blood	days	9	-	-	4.5	13.5	4.5
H_{mdeath}	Malaria induced host death rate	days^{-1}	0.02	-	-	0.01	0.03	0.01

was then measured using a sensitivity coefficient (ϕ) defined as:

$$\phi_i = \frac{\%\Delta Y}{\%\Delta X_i} \tag{5.4}$$

where Δ X is the percentage change in parameter value at i while Δ Y is the associated percentage change in output (EIR_a). The choice of this method was based on its computational ease and practicality (Hamby 1995).

5.4 Results and discussion

5.4.1 The simple immunity model

Figure 5.3 displays simulated annual malaria cases and exposure to infectious bites (EIR_a) for malaria locations subjected to different climate conditions in Africa. In the first place, a strong inter-annual signal in both simulated malaria cases and EIR_a was observed in all zones. The high variability is expected since Africa supports substantially heterogeneous ranges of malaria risk which vary temporally and spatially (Mbogo et al. 1995).

Among the climatologically different zones, simulated malaria cases differed. Simulated cases without immunity (red line) are higher at all zones than simulated cases

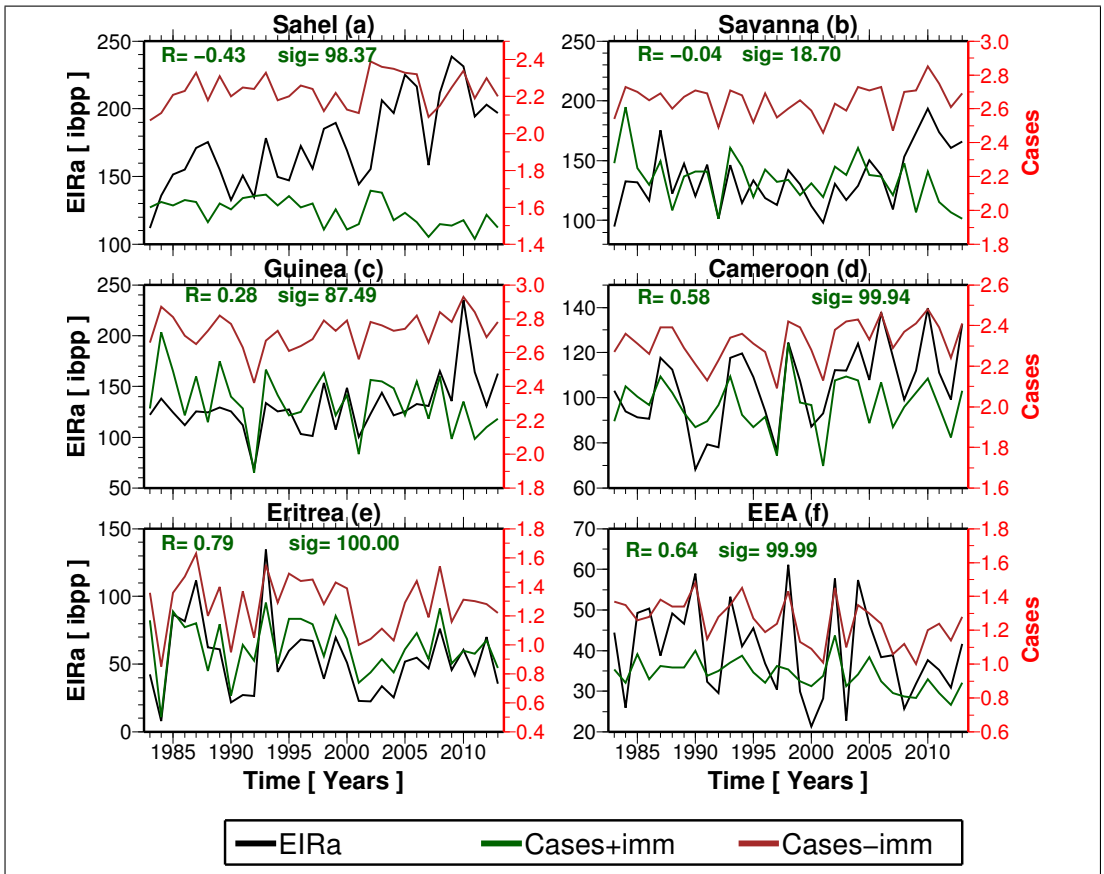

Figure 5.3: Simulated annual malaria cases and EIR_a for sub-Saharan Africa. Simulated EIR_a:black line, simulated malaria cases with incorporated immunity model:Green line, simulated cases without the immunity model:red line. Green printed numbers:Correlation between EIR_a and malaria cases with incorporated immunity model.

when immunity was introduced (green line). This means that the proposed immunity was able to dampen the effect of increased exposure to infectious bites. Moreover, malaria cases were high at Sahel (panel a), Savanna (panel c), Guinea (panel d) and partly low at Cameroon (panel e) than observed at Eritrea (panel e) and EEA (panel f). At zones of higher malaria cases, EIR_a were mostly $\geq$100 ibpp but ranged between 10-100 ibpp at Eritrea and EEA. This pattern corroborates reports of areas of intense and moderate malaria transmission in Africa (Beier et al. 1999) respectively. Thus, the model is apparently able to distinguish between probable areas of stable and unstable malaria spots in the region. The annual cases at Cameroon are low (which should not be the case) because the model is under-simulating infectious inoculations rates for the area (see details in Chapter 4).

Regarding the correlation between cases (green line) and EIR_a (black line), it can be observed that correlation coefficient are low at Sahel, Savanna and Guinea. This again is a confirmation of locations with the highest impact of immunity due to the exposure of inhabitants to severe infectious mosquito bites. At these zones, initial malaria cases were usually high but decreased with increasing exposure to infectious bites as time progressed. This pattern is a clear manifestation of the build up of immunity. In the first instance, those areas exhibit intense transmission which satisfies the condition

($EIR_a \geq 100$) to acquire immunity. At the beginning of exposure to infectious bites, cases are high since the human subjects had no immunity (which need time to be activated). As exposure to infectious bites intensified, immunity is activated and boosted by the sustained high infectious bites. Hence, the downward movement of cases is the consequence of the effect of the slow build up of immunity that reduced subjects that would have suffered from clinical disease. The relatively low malaria cases at Sahel(panel a) compared to other high transmission zones (panel b and c) is attributed to the highly seasonal nature of malaria due to the markedly seasonal nature of rainfall in the area (Nicholson 2000).

However, at zones of low transmission (panel e and f), the progression of cases with time rather correlated strongly with infectious bites confirming low or lack of immunity. This behaviour is because the annual exposure to infectious bites were not intense enough ($EIR_a < 100$ ibpp) for subjects to acquire any sustainable immunological memory in order to suppress clinical disease. Some individual year exposure may result in the acquisition of immunity but may decay fast due to lack of continuous intense infection. Studies have reported malaria transmission at such zones as low, stable endemic risk or epidemic prone zones (Craig et al. 1999, Shililu et al. 2003). Low or lack of immunity at such areas is therefore not surprising. An occurrence of epidemics in those regions may have devastating consequences such as high risk of stillbirths (Wort et al. 2006).

The outcome of this model confirms known reports that human subjects at stable malaria transmission zones acquired immunity due to continuous heavy exposure than those at unstable areas (Doolan et al. 2009, Langhorne et al. 2008, Mandal et al. 2011). The immunity model also demonstrated that zones of greater acquired resistance resulting from exposure to high inoculations rendered the inhabitants more resilient and less vulnerable to malaria epidemics that may be associated with climate anomalies than areas with low or no immunity. Hence the risk of a location to clinical malaria cases depended on the level of acquired immunity. These deductions suggest that the immunity model is able to mimic the general pattern of observed malaria transmission in Africa.

Immunity parameter sensitivity

The sensitivity of seasonal malaria case outcome to immunity model parameter settings are displayed in Figure 5.4. Panel (a) shows the results of the settings to different infectious bites needed to acquire immunity. Without immunity (black line), cases were high. When immunity was included (Green line, default), cases lowered. This was expected because infected subjects acquired some form of protection against clinical disease resulting in the reduction of prevailing malaria cases. Lowering the default threshold condition to gaining immunity (red) further reduced cases. This suggest that a build up an active immunity in those who recover from the disease when exposed to least infections could reduce the number of cases. Hence for areas of intense transmission, clinical cases will be far lower. But, prevailing malaria cases increased when the default threshold was increased (brown). This is because the exposure amount and time required for acquired protection against clinical disease was lengthened thereby lowering the immunological memory.

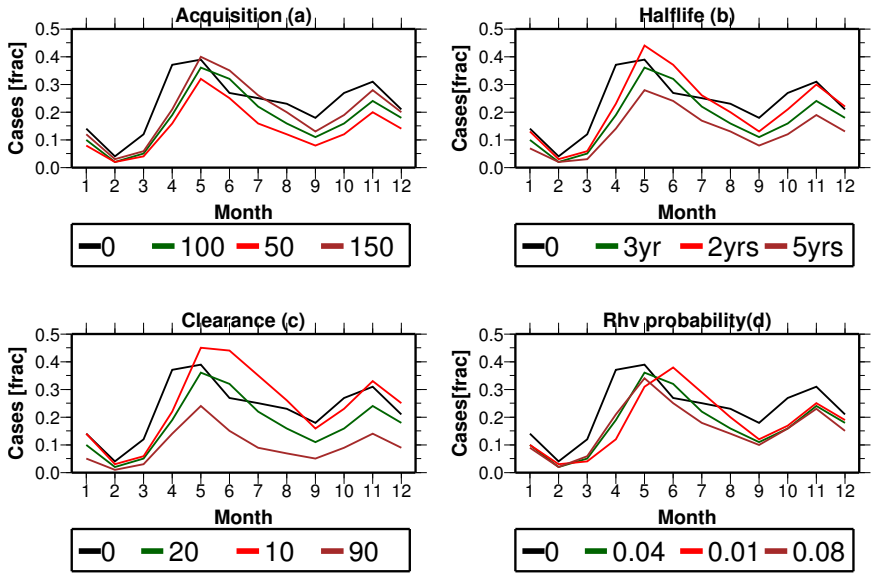

Figure 5.4: Sensitivity of immunity parameter settings to seasonal malaria outcome. Panel a): EIR_a at which immunity is acquired, b): durations at which the acquired immunity is lost, c): days of parasite clearace by non-immuned subjects and d): probabilities that immuned subjects infected the vector mosquito. Black shows cases without immunity. Green is the default setings, Red and brown are for settings below and above default respectively.

Panel (b) displays the behaviour of seasonal malaria cases when the half-life of immunity was reduced from 3yrs(green) to 2yrs(red) and increased from 3yrs to 5yrs(brown). Reducing the decay period of acquired immunity increased cases and increasing it decreased cases substantially. The pattern was expected because, shortening the half-life meant a reduction in immunological retention memory of the host, resulting in higher clinical cases. The vice versa is applicable when the threshold was increased.

Similar to panel (b), panel (c) showed that malaria cases were on the high when clearance time was reduced from 20 to 10 days (red) but on the low when clearance time was increased to 90 days (brown). The 90 days clearance time reflects somewhat the idea that immunity is build at a slow rate (Day and Marsh 1991). Delayed clearance time allowed sufficient time for host memory receptive to recognise parasites strains, hence the acquisition of immunity and lower clinical cases. The faster clearance time (10days) assumed the fact that individuals sort treatment when sick and so will clear infections in a matter of few days. High cases however suggest that though individuals may be exposed to substantial transmission, clearance of infections in few days via antimalarials may not result in the acquisition of immunity. This applies in particular to individuals without prior exposure to infections.

In panel (d) changes in the probability of immune subjects to infect the mosquito is presented. Unlike other cases, there was no substantial change in seasonal cases when the probability was varied. This was expected because immuned subject infection rates are far lower than that of the infectious and for that matter will not result in any substantial change.

Improvement

Figure 5.5 displays the MAE indices of immunity incorporated VECTRI (v1.4) simu-

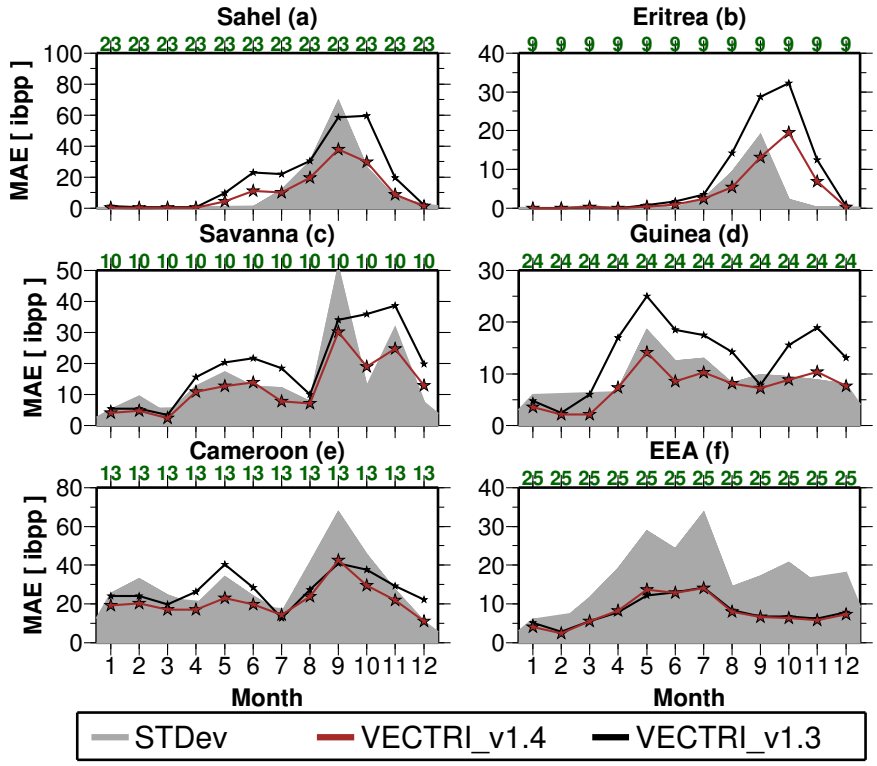

Figure 5.5: Mean Absolute Error of model simulated EIR_m to the observed. The grey shaded region is the standard deviation of the observed EIR_m. The black line is MAE of VECTRI without immunity and red with immunity.

lated EIR_m and that of VECTRI without immunity (v1.3). The error significance were measured using the standard deviation (SD) of the observed EIR_m. MAE was considered high (low) if above (within) the SD of the observed. The figure revealed that error indices of VECTRI incorporated immunity were mainly lower and within the SD of the observed at all the climatologically different zones of sub-Saharan Africa than VECTRI without immunity. This clearly validates that inclusion of immunity into the structure of VECTRI model improved its seasonal simulation of malaria outcome substantially. The inclusion of immunity makes VECTRI more realistic and reliable for malaria study in the African region. As identified in Chapter 4, the fact that the model did not include all transmission factors in its algorithms is one the challenges regarding output certainty. Though it is impossible for the model to be able to define the precise edges of each EIR_m value, an inclusion of other missing factors will reduce VECTRI simulation error as revealed in this test study.

5.4.2 Sensitivity test

Figure 5.6 displays the sensitivity of EIR_a to the different parameters of VECTRI. The sensitivity coefficient, ϕ shows the factor of change in EIR_a when the corresponding parameter was evaluated at their minimum range/-50% (green line) and at maximum range/+50% (red line) of their baseline values. The maximum/+50% and minimum/-50% ranges are indicated in Table 5.1.

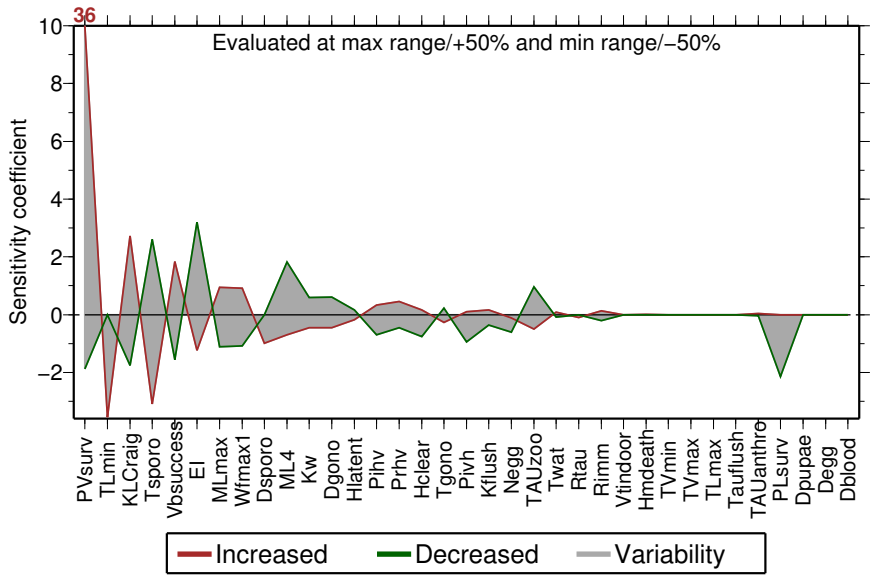

Figure 5.6: Sensitivity of VECTRI simulated EIR_a to its parameters settings Parameter base values evaluated at maximum range/+50% (red line) and at minimum range/-50% (Green line). Grey shade: variability of the parameter at maximum and minimum. The brown number 36 is the maximum sensitive coefficient for PVsurv

VECTRI simulated EIR_a was sensitive to quite a number of parameters. However, the most sensitive parameter was P_{Vsurv}, the underlying adult vector survival probability. Increasing P_{Vsurv} translates to increasing the adult vector lifespan and for that matter their population leading to higher inoculations. The default probability value (See Table 5.1) is too high making the vectors to be long-lived than expected. However, when P_{Vsurv} was evaluated at the minimum range, the output coefficient was low. Hence, increasing the survivial probability will results in model overestimation. Moreover, T_{Lmin} (Minimum water temperature for larvae survival) was found to be a sensitive parameter. This parameter impacts on the fractional growth rate of larvae which follows a degree day concept based on a linear function of water temperature (T_{wat}). Optimum water temperature accelerates larvae growth rate but below T_{Lmin} larvae growth ceases. In VECTRI, this fractional growth rate is directly proportional to T_{wat}-T_{Lmin}. Therefore, increasing T_{Lmin} meant lowering Water temperature, hence slowing down larvae growth rate. This will lead to a reduction in the number of maturing vectors joining the biting population. Exposure to infectious inoculations will then be reduced in effect.

Other parameters include larvae growth degree days, minimum temperature for sporogonic cycle, base daily larval survival rate, and total evaporation and infiltration losses. In general, the sign of the computed sensitivity coefficient (i.e. whether EIR_a increased (decreased) when a parameter was (increased(decreased)) for all the parameters agreed with the intuitive expectation. It was also observed that most sensitive parameters were related to vectors (water-bound and adults). One can, therefore, link the relative importance of these parameters to malaria transmission and prevalence through their impact on mosquito biting rates. This suggests strategies towards control of vector population e.g. insecticide-treated bed nets and indoor residual spraying which have proven useful in previous studies (Hawley et al. 2003, Sharma et al. 2005).

5.5 Summary and conclusions

A simple model of immunity to malaria (with limited parameters though captured many of the important aspects of the role of immunity in malaria transmission) was utilized in VECTRI. This allowed for simulation of clinical malaria case and observation of the effects of acquired immunity to malaia at climatologically different malaria zones in Africa. The sensitivity of the parameter settings of VECTRI were additionally analyzed through a one-at-a-time sensitivity analysis by evaluating the sensitivity coefficient of EIR_a to model parameters.

The analysis showed that the simple immunity module enabled VECTRI to simulate different levels of malaria for sub-Saharan Africa by reducing transmission rates at increased malaria exposure of humans. The immunity module also substantially improved the seasonal malaria simulations of VECTRI by reducing its error. The sensitivity analysis revealed parameters that show the strongest variation of the model output. The most sensitive parameter settings consisted of the adult vector survival probability, minimum temperature for larval survival, larvae growth degree days, minimum temperature for sporogonic cycle, base daily larval survival rate, and total evaporation and infiltration losses.

It can, therefore, be concluded that areas with high immunity rendered the inhabitants more resilient and less vulnerable to malaria epidemics that may be associated with e.g. climate anomalies than areas with low or no immunity. This has important implications for control and future malaria modelling efforts. The substantial reduction of the models' simulation errors makes it more reliable and better tool for malaria forecast and control in Africa. Parameters contributing most to VECTRI output variability require additional research to strengthen knowledge base to reduce VECTRI output uncertainty, especially at Cameroon and EEA. These parameters are also critical when validating and using VECTRI as a guide for future research.

CHAPTER 6

Conclusions, recommendations and future outlook

6.1 Summary and discussions

Malaria burden in Africa especially the sub-Saharan Africa remains a serious complex public health problem despite its reduction over the last decade (WHO 2015). Overcoming malaria challenges in the region requires advancing our understanding of malaria epidemiology in the area. This thesis contributes to this effect by investigating the impact of climatic and environmental drivers including malaria vector type on seasonal malaria transmission dynamics in Africa. The study further validated and analyzed weather-driven dynamical mathematical malaria models that are used to provide adequate approximations of seasonal epidemiological features of malaria in the area.

Regarding the impact of climatic and environmental factors on seasonal malaria transmission, the study found rainfall as the primary climatic factor limiting malaria seasonality in the region. This applies in particular to markedly seasonal rainfall areas such as the Sahel and Eritrea but not necessarily at bimodal rainfall distributed or more humid zones which were more complex. These findings were contrary to literature e.g. Mabaso et al. (2007). Again disagreeing with literature (Mabaso et al. 2007), temperature was not a limiting factor of malaria seasonality in Africa except for East Africa where it was able to delay the impact of rainfall. Unlike this work, most studies (Mabaso et al. 2007, Roca-Feltrer et al. 2009) do not explicitly delineate the influence of the differing climatic zones and environmental settings as applied in this study but sort of lump information which is problematic.
This work also revealed that the peaking characteristics of seasonal malaria were mostly unimodal. In the case of bimodal rainfall distributions, the malaria transmission peak was frequently associated with the first rainfall maximum of the year. Most studies have concentrated on showing the start, end and duration of malaria season (Craig et al. 1999, Ermert et al. 2011b, Grover-Kopec et al. 2006, Tanser et al. 2003) but peak characteristics are scarce. The finding consolidates this research gap indicating a significant forward step in malaria studies. Seasonal malaria intensity was anti-correlated with elevation and population density which corroborates literature. Though seasonal malaria was driven mainly by *An. gambiae, An funestus, An. arabiensis*, these vectors have a competing and complex individual impact on seasonality.
Studies using EIR_m to investigate malaria seasonality are scarce due to lack of standardized and geolocated EIR data (Hay et al. 2005, Kelly-Hope and McKenzie 2009). For this reason, numerous studies have relied on malaria cases which are not suitable metric since cases or prevalence are different aggregated temporal windows of transmission (Reiner Jr et al. 2015). But, unlike the traditional use of malaria case data,

the conscious effort in gathering EIR_m through literature survey has enabled us to directly relate the risk of humans to malaria infections (due to the human-biting activity of Anopheles vectors) to climate and environment.

In the second part, the study validated and evaluated the seasonal ranges of EIR_m simulated by LMM_{2010} and VECTRI for Africa with observed EIR_m data. The goal was to examine their seasonal malaria simulation accuracy. Findings of the study revealed that both models could reproduce realistic seasonal malaria transmission rates for Africa. For instance, LMM_{2010} and VECTRI simulation error ranges were generally within or about the same as the standard deviation of the observed EIR_m data despite the significant deviations detected for Guinea and some individual monthly minor differences. Concerning peak characteristics, both models agreed with observations that the malaria distribution was predominantly unimodal. However, the maximum malaria transmission peaks in the models tend to be delayed by one month especially in the Sahel and Eritrea area. Both models further agreed with observed values of an index of the malaria seasonality, which was closely linked to the latitudinal variation of climatic covariates such as rainfall.
Malaria seasonality varies at highland areas especially East Africa (Drakeley et al. 2005). For instance, Maxwell et al. (2003) sampled mosquitoes and found that EIR was about 17 times greater at lowland than highland area. VECTRI revealed a stronger ability in capturing the levels of malaria endemicity in at such zones than LMM_{2010}. LMM_{2010} performed better in West Africa where it was calibrated than in East Africa. The inability of LMM_{2010} to reproduce similar pattern in East Africa may be because it was not calibrated with data from the area. Also, unlike VECTRI, it lacks components such as population density and hydrology. The hydrology model in VECTRI does not capture very well malaria transmission at permanent water body locations and needs further review. Despite these hitches, findings of this study maximize the seasonal malaria prediction accuracy, generality and reliability of both models.

The utilized simple immunity model enabled VECTRI to simulate different levels of malaria for Africa. It was able to reduce transmission rates at increased exposure of humans to malaria. It also substantially improved the seasonal malaria simulations of VECTRI by reducing its error. The outcome was expected because malaria burden differ in Africa (Mandal et al. 2011) following the immune status of inhabitants based on exposure intensity and age (Mandal et al. 2011, Molineaux et al. 1988). Though the immunity model was not age-structured, its ability to mimic similar malaria patterns represent a significant improvement and a helpful tool. A refinement of this model is necessary for full implementation in VECTRI.
The one-at-a-time sensitivity analysis performed on VECTRI parameter settings revealed parameters that show the strongest variation of the model output. The most sensitive parameter settings consisted of the adult vector survival probability, the minimum temperature for larval survival, larvae growth degree days, the minimum temperature for sporogonic cycle, base daily larval survival rate, and total evaporation and infiltration losses. This finding provides information about parameters that needs additional research for improvement of model output variability. The sensitive parameters were found to be related to vectors both at the water bound stages and adults. One can, therefore, link the relative importance of these parameters to malaria transmission and prevalence through their impact on mosquito biting rates. This suggest vector control

strategies such as insecticide-treated bed nets and indoor residual spraying which have proven useful in previous studies (Hawley et al. 2003, Sharma et al. 2005).

6.2 Study weakness

The sparsity and paucity of accurate measurement of EIR_m data were the primary challenges of this study. Standardized and geolocated EIR_m data are scarce because its measurements are both labour and capital intensive (Hay et al. 2005, Kelly-Hope and McKenzie 2009). For this reason, the field observed EIR_m data used were sparse spatially and temporally (see Table 3.1). For instance, the spatial distribution of data locations was inhomogeneous, abundant in some countries and very sparse in others (see Figure 3.1). This characteristic can provide limiting and misleading results of approaches of statistical applications such as computation of averages. Moreover, the time series of the observed EIR_m surveillances were rarely available in the long-term for many settings. Monthly values of about a year and on rare occasions above a year were mostly available (see Table 3.1) and differed in SY and SM of records between locations (see Table A.1). Again, the rather short nature of the EIR_m time series limited the investigation of year-year variations in malaria seasonality which is particularly important for naturally seasonal malarious areas such as the Sahel. Thus, surveys carried out during epidemic years, may not give a realistic view of those conducted in non-epidemic years (MARA 1998). Details of the data weakness are outlined in Appendix A.

Meteorological time series of local weather station observations located at the malaria locations are usually ideal for this kind of study. But these observation stations were inadequately distributed in the area, contained incomplete records and mostly not located at the malaria study locations. For this reason, the study relied on surrogate meteorological data products such as ARCv2 and ERAI. The use of the surrogate products may likely over-estimate or under-estimate rainfall and temperature records of locations which will have adverse consequence especially on the LMM_{2010} and VECTRI output.

6.3 Conclusions and study significance

Findings of the study regarding the impact of climatic and environmental factors including malaria vector type on seasonal malaria transmission seasonality have important implications for malaria control and possible elimination in Africa. It suggests that temporal and spatial target of malaria interventions and resource allocation optimization should focus on the rainy seasons. Areas of seasonal transmission severity identified will aid the choice and cost effectiveness of an intervention. For instance, year-round malaria chemoprevention in children and pregnant women is cost-effective at perenial transmission settings such as Savanna, Guinea and Cameroon than at markedly seasonal transmission settings such as Sahel and Eritrea.
The findings of this work also consolidate evidence of the link between seasonal malaria transmission patterns and climate and environment. Our understanding of the impact of climate and environment on vector biology, transmission intensity, clinical disease and mortality risks has been widely informed. The outcome also supplement previous works describing clinical patterns of malaria infection and morbidity that will

help stakeholders establish a robust framework for monitoring, forecasting and controll. EIR_m can, therefore, be used as the gold-standard metric for evaluating seasonal malaria outcome of weather driven dynamical mathematical malaria models as a function of climate and environment.
Following to the impact of climate change on temperature suitability for malaria transmission at highland areas (Alemu et al. 2011, Parham and Michael 2010), temperature surveillance and monitoring at elevated areas is necessary to curb the prolifiration of malaria vectors. Elevation measurements can also serve as proxy for temperature in malaria transmission measurements which can be usefull for optimum appropriation of control measures. Malaria vector surveillance and monitoring operations are also necessary at malaria locations invaded by permanent water bodies and irrigation for appropriate application of control tools. Access to public health services and poverty alleviation at rural areas is needed to curb the high malaria transmission.

The work on the accuracy of LMM_{2010} and VECTRI in simulating seasonal malaria for Africa has maximized our convictions on their reliability. It is therefore concluded that, both models can realistically mimic seasonal malaria transmission dynamics in Africa as a function of climate and environment to a large extent. While both models in their current state can be used as early malaria warning system, VECTRI may have more advantage in highland areas such as East Africa over LMM_{2010}. The findings of this work therefore provide the basis for further review and refinement of both models by their developers regarding identified hitches and inclusion of other missing malaria transmission factors.

The immunity model widened our understanding of the impact of immunity on malaria seasonality in Africa and informed about future malaria modelling efforts in the region. The study indicated that locations with high immunity rendered the inhabitants more resilient and less vulnerable to malaria risk. Hence, monitoring of climate anomalies at areas with low immunity is needed to prepare for associated malaria epidemics in those areas. Moreover, the sensitivity of VECTRI output depended on the choice of parameter values and assumptions upon which it operates. It is, therefore, important that VECTRI output and its parameter values be tested against field observations when using the model for public policy and health decision makings. Parameters contributing most to VECTRI output variability are critical when validating and using VECTRI as a guide for future research. They require additional research to increase their knowledge base for adjustment.

6.4 Recommendations and future outlook

An examination of the map of the geographical distribution of EIR_m study sites (Figure 3.1) showed that, data locations were spatially inhomogeneous across sub-Saharan Africa. This pattern seems to suggest a preferential selection of study sites, especially locations where malaria is recognized as either a local health problem or has a strong historical basis. Future EIR_m surveillance should spread to parts of the region without observations. It should also seek to extend the EIR_m timeseries of already observed locations though costly and labour intensive. Moreover, a team of international network with the mandate to map EIR_m data via standard methods in a grid-based system in needed to record the spatial distribution of malaria transmission in Africa more

closely(Hay et al. 2000).

A political will by African governments and efforts to building a dense network of ground meteorological station measurement across Africa is necessary. This could be deployed on a pilot basis until areas are covered. Resolving issues with meteorological measurements will aid immensely not only in malaria research but also other vector-borne diseases such as dengue fever, yellow fever and zika virus. Future studies look forward to reconstructing meteorological time series for the EIR_m data locations using data from available station measurements. This can be used for similar studies in comparison with surrogate observations.

Malaria vector type, their behaviour and distribution are one of the important factors of seasional malaria transmission. *An. gambiae, funestus and arabiensis* were identified as the most dominant,treacherous, sympathric and overall malaria causing vectors in Africa. Both VECTRI and LMM_{2010} formulations are limitted to literature on *An. gambiae complex* only. Future modeling efforts should therefore include that of *An. funestus*. Future works should also explicitly identify and include the anthropohilic behaviour of these three primary vectors and presence of animals such as cattle at a malaria location. The inclusion of these malaria vector dynamics may improve model estimation of malaria seasonality in the region.

Although the simple immunity model utilized in VECTRI improved its seasonal simulations substantially, its refinement to include age-structure is necessary. This is important since malaria infection moves differentially within age groups in endemic areas. Since infections are higher in children than in adults (Baird et al. 2003), the age-structured model should involve different transmission probabilities of gametocytes from children, immune and non-immune adults to mosquitoes. Besides, the interaction of the mosquito immune system affects *Plasmodium* parasites transmission to the host (Crompton et al. 2014). The inclusion of immune processes of the vector into models is very useful.

While the conventional use of mean temperatures by the models to simulate EIR_m might be appropriate under certain conditions, it may likely over- or under-estimate EIR_m at warmer and colder zones respectively. This characteristic was evident in this study. Future developments should, therefore, focus on the use of diurnal daily temperature ranges rather than mean. This is important since the biology of the malaria vectors and parasite is influenced by both average temperature and the extent of the diurnal temperature variation that occurs throughout the day.

To conclude, information from the impact of climatic and environmental factors on seasonal malaria transmission, model validation and improvement for effective seasonal malaria prediction are valuable. This information coupled with strengthening health systems, developing infrastructure and poverty reduction in sub-Saharan Africa may contribute immensely to maximum control and ultimate elimanation of malaria.

Appendix A

Appendix

A.1 Categorization of data locations

First, the malaria locations were grouped into zones of similar climate (see Figure 3.1). The purpose was to decouple and avoid lumping data from climates of dissimilar characteristics. The step was important since different climate settings impact on seasonal malaria transmission differently. The sub-Saharan Africa was first and foremost divided into two broad sections: the West (longitudes $\leq 20°$) and the East (longitudes > 20°). Using the climate information of Omotosho and Abiodun (2007), the West was subgrouped into latitudinal bands of Sahel (latitudes $\geq 10°$), Savanna (8° <= latitudes < 10°), Guinea (5° <= latitudes <8°) and Cameroon area (latitudes < 5°). East Africa has a sophisticated climate unlike the West due to the existence of complex topography and large inland water bodies (Indeje et al. 2000). For this reason and as a matter of simplicity, the East was crudely subdivided into Eritrea (latitudes $\geq 10°$), Ethiopia (5° <= latitudes < 10°) and Equatorial East Africa (latitudes < 5°). It was then assumed that climate variation within each sub-division was meagre to result in any significant differences in seasonal malaria transmission. The analysis of malaria seasonality was then limitted to each zone.

Secondly, each malaria location was identified as either rural (R), peri-urban (PU) or urban (U) setting. The approach was necessary because malaria transmission especially intensity reportedly depends on Pd type of the location (Kelly-Hope and McKenzie 2009, Tompkins and Ermert 2013, Vercruysse et al. 1983). In the articles from which data were digized, the Pd status of most of the locations were unavailable and difficult to identify. Hence, the identification of the Pd status of each location was based on the following steps. 1) the Pd values for each site were extracted from the GPDWv3 (CIESIN-CIAT 2005) using their geographical longitude and latitude position points. But the GPDWv3 data were available for only 1990, 1995 and 2000. This meant that locations where surveys are conducted outside these dates, had no Pd data (though available for 1990, 1995 and 2000). To find Pd values for such locations, the annual rate of change in density per location was calculated from the available dates (1990,1995 and 2000). The determined rate of change was then used to estimate the Pd value for such locations. 2) Using the definition of urbanisation by Hay et al. (2005) each location was classified as rural (Pd ≤ 250), peri-urban (250<pd$\leq$1000) and urban (Pd > 1000). See table A.1

Thirdly, water impoundments and irrigation provide potential habitat for water-bound stages of malaria vectors (Fillinger et al. 2009, Kar et al. 2014). They pose considerable risk to malaria especially at epidemic zones (Keiser et al. 2005, Muturi et al. 2006). For this reason, each malaria location was identified as either Neutral (N), Irrigated (I)

or Permanent Water Body (PWB) depending on the type of hydrology pertaining the location. The hydrology information of each location was obtained from the respective articles from data were digitized. Locations characterised by water bodies such as rivers, streams, dams, swamps, marshland and lakes were said to be pwb. Those with ongoing irrigation activities and double croping associated with crops such as rice and sugarcane were regarded as irrigated. Locations without irrigation and PWBs were regarded as neutral. See table A.1.

A.2 Observed EIR_m data uncertainties

Inherent uncertainties may characterise observed EIR_m data as a result of errors emanating from the estimation of HBR and CSPR (Shaukat et al. 2010). Note that EIR in simple terms is the product of HBR and CSPR.
First, the different mosquito sampling methods (HLC, PSC and LTC) are not standardized (Fontenille et al. 2001, Githeko et al. 1996). Estimated HBR from each method and for that matter EIR may differ and may not accurately represent the levels of exposure experienced by individuals in a study community (Kilama et al. 2014). For instance, the most direct mosquito sampling technique is HLC (Tusting et al. 2014, WHO 1975) as it directly samples human biting mosquitoes (Le Goff et al. 1997). But, PSC and LTC depend largely on the mosquito behaviour rather than directly feeding on humans (Hay et al. 2000). They may therefore likely overestimate true biting rates (Mboera 2005) since mosquitoes are collected off human baits.

Secondly, estimates of HBR and CSPR need to be repeated every day of the month for at least a year or a complete transmission season (Hay et al. 2000). But due to the capital and labour intensive nature of the methods, HBR and CSPR estimates are conducted in few days (most often one or two days) of the month and the average daily value is determined. The product of the average daily value and the number of days of the month yield the monthly estimate. The insufficient sampling days can be problematic especially in areas where mosquitoes are rare or are rarely infected. Besides, few trained specialist are mostly involved, and the sampling is subjected to collector skills, collector attraction to mosquitoes as well as instrumental errors. These biases may limit the precision and accuracy of estimated EIR_m (Fontenille et al. 2001, Kilama et al. 2014, Tusting et al. 2014).

Thirdly, long-term EIR_m surveillances were rarely available for many settings. Monthly time series of about a year and on rare occasions above a year were mostly available (see Table 3.1) and differed in SY and SM of records between locations (see Table A.1). Thus, surveys carried out during epidemic years, may not give a realistic view of those conducted in non-epidemic years (MARA 1998).

The fourth uncertainty is the inhomogeneous distribution of data locations (see Figure 3.1), abundant in some countries and very sparse in others. The entomological surveys appeared to be concentrated mainly in areas where malaria is known to be prevalent (MARA 1998). These characteristics in effect can be very limiting and sometimes be misleading regarding the application of statistical approaches such as computing average values.

The last but not the least, the EIR_m data used in this study were manually digitised from figures of articles in which they were published using an R package (Poisot 2011). The accuracy of the digitised EIR values will also then be subject to the precision of the individual digitising the data.

Table A.1: Malaria locations and their characteristics

Country	site	lon	lat	elevation	Pd	Hydrology	SY	SM	EY	EM	Ref
Benin	Gbegame	2.41	6.36	6	U	N	1987	1	1987	12	Akogbeto et al. (1992)
Benin	Ladji	2.43	6.39	2	U	N	1987	1	1987	12	Akogbeto et al. (1992)
Benin	St. Ritha Nord	2.40	6.38	4	U	N	1987	1	1987	12	Akogbeto et al. (1992)
Burkina Faso	Balonguen	-1.49	12.04	343	R	N	2000	12	2001	11	Ilboudo-Sanogo et al. (2010)
Burkina Faso	Dande	-3.08	10.90	275	R	N	1983	1	1984	12	Robert et al. (1985)
Burkina Faso	Guinghin Nord	-1.55	12.37	305	U	N	1984	3	1985	2	Rossi et al. (1986)
Burkina Faso	Karangaso	-4.63	11.22	366	R	pwb	1988	3	1989	2	Robert et al. (1988)
Burkina Faso	Kologh-Naba	-1.54	12.38	292	U	N	1984	3	1985	2	Rossi et al. (1986)
Burkina Faso	Kongodjan	-5.02	10.90	480	R	pwb	1983	1	1984	12	Robert et al. (1985)
Burkina Faso	Lena	-3.88	11.30	307	R	N	1999	1	2001	12	Dabire et al. (2008)
Burkina Faso	Nongremassm	-1.50	12.30	310	U	N	1984	3	1985	2	Rossi et al. (1986)
Burkina Faso	St. Camille	-1.50	12.36	299	U	N	1984	3	1985	2	Rossi et al. (1986)
Burkina Faso	Tago	-4.38	11.67	308	R	N	1983	1	1983	12	Robert et al. (1985)
Burkina Faso	Tensobtenga	-1.30	12.30	295	R	pwb	2000	12	2001	11	Ilboudo-Sanogo et al. (2010)
Burkina Faso	VK4	-4.27	11.52	288	R	I	1983	1	1984	12	Robert et al. (1985)
Burkina Faso	VK6	-4.27	11.52	288	R	I	1983	1	1984	12	Robert et al. (1985)
Cameroon	Nkol-Bikok	11.52	3.87	728	U	pwb	1989	3	1990	2	Fondjo et al. (1992)
Cameroon	Nkol-Bisson	11.00	3.00	760	R	pwb	1989	4	1990	3	Fondjo et al. (1992)
Cameroon	Ebogo	11.47	3.40	659	R	N	1991	4	1992	3	Njan Nloga et al. (1993)
Cameroon	Ebolakounou	12.13	3.93	701	R	N	1997	6	1998	5	Meunier et al. (1999)
Cameroon	Ekombitie	11.83	3.12	693	R	pwb	2007	1	2007	12	Fils et al. (2010)
Cameroon	Esuke-camp	9.31	4.10	279	R	N	2004	10	2005	9	Tanga et al. (2011)
Cameroon	Idenau	9.05	4.02	359	R	N	2001	8	2002	7	Bigoga et al. (2007)
Cameroon	Koundou	12.12	3.90	705	R	N	1997	6	1998	5	Meunier et al. (1999)
Cameroon	Likoko	9.23	4.22	1933	R	N	2002	10	2003	9	Tanga and Ngundu (2010)
Cameroon	Limbe	9.18	4.03	185	R	N	2001	8	2002	7	Bigoga et al. (2007)
Cameroon	Mbebe	10.12	3.38	70	R	pwb	1989	4	1990	3	Le Goff et al. (1997)
Cameroon	Ndogpassi	10.13	3.08	72	R	N	2011	1	2011	12	Antonio-Nkondjio et al. (2012)
Cameroon	Nsimalen Ekoko	12.12	3.82	699	R	pwb	1991	4	1992	3	Manga et al. (1995)
Cameroon	Nsimalen Mefou	11.57	3.70	680	R	pwb	1991	4	1992	3	Manga et al. (1995)
Cameroon	Sanaga	11.52	4.92	474	R	pwb	1989	4	1990	3	Carnevale et al. (1992)
Cameroon	Simbock-Block6	11.50	3.83	717	U	pwb	1999	1	1999	12	Antonio-Nkondjio et al. (2002)
Cameroon	Tiko	9.28	4.07	182	R	N	2001	8	2002	7	Bigoga et al. (2007)
Chad	Goulmoun	15.20	10.39	324	R	I	2006	6	2007	5	Kerah-Hinzoumbé et al. (2009)
DRC	Kimbangu	15.31	-4.36	295	U	N	1988	9	1989	8	Coene (1993)
DRC	Kwamutu	15.28	-4.47	346	U	N	1988	9	1989	8	Coene (1993)
DRC	Mbansale	15.17	-4.33	289	R	pwb	1990	5	1991	4	Karch et al. (1993)
Eritrea	Adibosqual	38.65	14.69	1482	R	N	1999	1	1999	12	Shililu et al. (2003)
Eritrea	Anseba-Adiboqual	37.81	16.48	894	R	N	1999	10	2000	9	Shililu et al. (2004)
Eritrea	Anseba-Hagaz	37.81	16.48	894	R	N	1999	10	2000	9	Shililu et al. (2004)
Eritrea	Dasse	37.50	14.93	916	R	N	1999	1	1999	12	Shililu et al. (2003)
Eritrea	Debub-Mai-Aini	39.15	14.95	1809	R	N	1999	10	2000	9	Shililu et al. (2004)
Eritrea	Gash-Barka-Dasse	37.64	15.41	610	R	N	1999	10	2000	9	Shililu et al. (2004)
Eritrea	Gash-Hiletsidi	37.64	15.41	610	R	N	1999	10	2000	9	Shililu et al. (2004)
Eritrea	Hagaz	38.27	15.68	883	R	N	1999	1	1999	12	Shililu et al. (2003)
Eritrea	Hiletsidi	36.66	15.13	586	R	N	1999	1	1999	12	Shililu et al. (2003)
Eritrea	Maiaini	39.09	14.81	1554	R	N	1999	1	1999	12	Shililu et al. (2003)
Ethiopia	Baka-Boro	36.52	8.58	1316	R	I	2010	2	2011	1	Jaleta et al. (2013)
Ethiopia	Chano	37.58	6.10	1211	R	N	2009	5	2010	4	Massebo and Lindtjørn (2013)
Ethiopia	Dirama	38.42	8.17	2031	PU	PW	2008	7	2010	6	Animut et al. (2013)
Ethiopia	Hobe	38.48	8.02	1834	PU	PW	2008	7	2010	6	Animut et al. (2013)
Ethiopia	Machara	36.42	8.58	1351	R	N	2010	2	2011	1	Jaleta et al. (2013)
Ethiopia	Wama-Kusaye	36.49	8.59	1319	R	I	2010	2	2011	1	Jaleta et al. (2013)
Gabon	Benguia	10.37	-0.53	37	R	N	2003	5	2004	4	Elissa et al. (2003)
Gabon	Dienga	12.68	-1.87	772	R	N	2003	5	2004	4	Elissa et al. (2003)
Ghana	Abotanso	-1.28	6.88	374	R	N	2004	9	2005	8	Badu et al. (2013)
Ghana	Gyidim	-1.08	6.80	408	R	N	2003	11	2005	10	Badu et al. (2013)
Ghana	Hwidiem	-2.35	6.93	186	R	N	2003	11	2005	10	Badu et al. (2013)
Ghana	Kintampo	-1.73	8.06	354	R	N	2003	11	2005	10	Dery et al. (2010)
Ghana	KND-Irrigated	-1.44	10.76	212	R	I	2001	6	2002	5	Appawu et al. (2004)
Ghana	KND-Lowland	-1.44	10.76	212	R	N	2001	6	2002	5	Appawu et al. (2004)
Ghana	KND-Highland	-1.44	10.76	212	R	N	2001	6	2002	5	Appawu et al. (2004)
Ghana	LowCost	-1.55	6.63	250	U	N	2003	11	2005	10	Badu et al. (2013)
Ghana	NHDSS	-1.29	10.89	287	R	pwb	2001	11	2004	10	Kasasa et al. (2013)
Ivory Coast	Alloukoukro	-5.15	7.69	334	R	pwb	1991	1	1992	12	Dossou-Yovo et al. (1995)
Ivory Coast	Batouapleu	-8.32	6.79	243	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Beoue	-7.87	6.55	268	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Bepleu	-8.05	7.00	285	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Bietouo	-8.13	6.90	283	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Binguebougou	-5.81	9.53	357	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Dar-es-Salam	-5.01	7.71	325	PU	N	1991	1	1992	12	Dossou-Yovo et al. (1998)
Ivory Coast	Bouake-Kennedy	-5.01	7.69	351	PU	N	1991	1	1992	12	Dossou-Yovo et al. (1998)
Ivory Coast	Bouake-Sokoura	-5.05	7.68	361	PU	N	1991	1	1992	12	Dossou-Yovo et al. (1998)
Ivory Coast	Tolakouadiokro	-5.04	7.73	331	PU	I	1991	1	1992	12	Dossou-Yovo et al. (1998)
Ivory Coast	Bouake-Zone	-5.06	7.70	367	PU	I	1991	1	1992	12	Dossou-Yovo et al. (1998)
Ivory Coast	Bouenneu	-8.23	6.93	251	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Danta	-8.16	7.02	272	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Douandrou	-7.92	6.54	237	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Douedy-Guezon	-7.75	6.57	266	R	N	1998	4	1999	3	Briët et al. (2003)

Table A.2: Table A.1 continuou

Country	site	lon	lat	elevation	pd	Hydrology	SY	SM	EY	EM	Ref
Ivory Coast	Fapaha	-5.83	9.49	361	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Finneu	-8.15	7.00	274	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Folofonkaha	-5.21	8.58	328	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Gbahouakaha	-5.41	9.50	345	R	I	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Gbontegleu	-8.24	6.97	257	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Glopaoudy	-7.63	6.54	234	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Kabolo	-4.99	8.19	268	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Kaforo	-5.67	9.29	329	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Kombolokoura	-5.88	9.33	366	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Meantouo	-8.14	6.89	277	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Nanbekaha	-5.69	9.29	320	R	I	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Nombolo	-5.83	9.41	379	R	I	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Nongotchenekaha	-5.40	9.52	332	R	I	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Ounandiekaha	-5.17	8.36	286	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Pepleu	-8.20	6.95	256	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Petionara	-5.12	8.43	277	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Pohan	-7.93	6.54	249	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Seileu	-8.17	7.10	337	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Tioroniaradougou	-5.64	9.36	361	R	N	1996	12	1997	11	Briët et al. (2003)
Ivory Coast	Vetouo	-8.12	6.96	280	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Yotta	-8.19	7.15	340	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Zeale	-8.16	6.99	265	R	I	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Ziglo	-7.80	6.57	256	R	N	1998	4	1999	3	Briët et al. (2003)
Ivory Coast	Zoleu	-8.31	6.81	236	R	I	1998	4	1999	3	Briët et al. (2003)
Kenya	Ahero	34.92	-0.18	1152	PU	I	1989	8	1990	7	Githeko et al. (1993)
Kenya	Asembo	34.40	-0.18	1148	PU	N	1988	3	1989	2	Taylor et al. (1990)
Kenya	Kameichiri	37.30	-0.65	1188	PU	N	2004	4	2005	3	Muturi et al. (2008)
Kenya	Kilifi	39.85	-3.63	18	PU	N	1990	12	1991	11	Mbogo et al. (1993)
Kenya	Kisian	34.67	-0.07	1246	PU	pwb	1985	10	1988	9	Beier et al. (1990)
Kenya	Loboi	35.98	-0.47	2285	PU	pwb	1994	1	1994	12	Aniedu (1997)
Kenya	Mbuinjeru	37.32	-0.72	1141	PU	N	2004	4	2005	3	Muturi et al. (2008)
Kenya	Mumias	34.49	0.34	1311	PU	I	1995	5	1996	4	Shililu et al. (1998)
Kenya	Murinduko	37.45	-0.57	1311	PU	N	2004	4	2005	3	Muturi et al. (2008)
Kenya	Perkerra	35.98	-0.47	2285	PU	I	1994	1	1994	12	Aniedu (1997)
Kenya	Saradidi	34.24	-0.02	1221	R	N	1985	10	1988	9	Beier et al. (1990)
Kenya	Sokoke	39.82	-3.52	125	R	N	1990	12	1991	11	Mbogo et al. (1993)
Madagascar	Manarintsoa	47.42	-19.00	1290	R	I	1988	10	1989	9	Lepers et al. (1991)
Madagascar	Saharevo	48.10	-18.82	873	R	pwb	2003	10	2004	9	Andrianaivolambo et al. (2010)
Madagascar	Ambodifotatra	49.88	-17.00	3	R	pwb	1988	11	1989	10	Lepers et al. (1991)
Mali	Sotuba	-7.91	12.66	323	R	N	1998	1	1998	12	Sagara et al. (2002)
Mozambique	CdSLCMPC	32.57	-25.92	35	PU	N	1985	1	1985	12	Zharov (1992)
Mozambique	Manhica	32.81	-25.40	20	R	I	2001	10	2002	9	Aranda et al. (2005)
Senegal	Affiniam-Diagobel	-16.37	12.65	12	R	N	1985	1	1986	12	Faye et al. (1994)
Senegal	Barkedji	-14.88	15.28	349	R	N	1994	6	1996	5	Lemasson et al. (1997)
Senegal	Dielmo	-16.42	13.72	32	R	PWB	1990	4	1995	3	Fontenille et al. (997a)
Senegal	Diohine	-16.52	14.50	8	R	pwb	1995	1	1995	12	Robert et al. (1998)
Senegal	Kotiokh	-16.56	14.49	7	R	pwb	1995	1	1995	12	Robert et al. (1998)
Senegal	Ndiop	-16.36	15.95	6	R	N	1993	5	1996	4	Fontenille et al. (997a)
Senegal	Ngayokheme	-16.43	14.53	11	R	N	1995	1	1995	12	Robert et al. (1998)
Senegal	Takeme-Ousseuk	-16.20	12.80	21	R	N	1985	1	1986	12	Faye et al. (1994)
Senegal	Wassadou	-13.33	13.35	26	R	pwb	1992	9	1993	8	Faye et al. (1995)
Sierra Leone	Bayama	-11.67	8.00	102	R	pwb	1990	11	1991	10	Bockarie et al. (1995)
Sierra Leone	Mendewa	-11.48	8.17	325	R	N	1990	1	1990	12	Bockarie et al. (1994)
Sierra Leone	Nyandeyama	-11.62	8.12	118	R	N	1990	1	1990	12	Bockarie et al. (1994)
Tanzania	Bagamoyo	38.44	-5.07	1093	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Balangai	38.46	-4.93	1230	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Chasimba	38.82	-6.58	36	R	N	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Chekereni	37.36	-3.38	763	PU	I	1994	7	1995	6	Ijumba et al. (2002)
Tanzania	Idete	36.48	-8.10	295	R	N	1992	7	1994	6	Charlwood et al. (1998)
Tanzania	Kerege	39.03	-6.57	36	R	pwb	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Kisangasangeni	37.39	-3.39	759	PU	N	1994	7	1995	6	Ijumba et al. (2002)
Tanzania	Kongo	38.83	-6.53	19	R	pwb	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Kwameta	38.47	-5.08	671	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Kwamhanya	38.46	-5.06	596	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Magundi	38.47	-5.09	671	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Mapinga	39.07	-6.60	59	R	N	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Matimbwa	38.87	-6.50	21	R	pwb	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Michenga	36.63	-8.12	258	R	pwb	1989	5	1991	4	Lyimo (1993)
Tanzania	Milungui	38.36	-4.76	1636	R	N	1995	10	1996	9	Bodker et al. (2003)
Tanzania	Mvuleni	37.33	-3.39	786	PU	N	1994	7	1995	6	Ijumba et al. (2002)
Tanzania	Namawala	36.40	-8.15	289	R	N	1990	8	1991	7	Smith et al. (1993)
Tanzania	Yombo	38.85	-6.57	36	R	N	1992	1	1992	12	Shiff et al. (1995)
Tanzania	Zinga	38.98	-6.52	22	R	N	1992	1	1992	12	Shiff et al. (1995)
Uganda	Apac-Olami	32.72	1.98	1053	R	N	2001	6	2002	5	Okello et al. (2006)
Uganda	Arua-Cilio	31.02	3.18	976	PU	N	2001	6	2002	5	Okello et al. (2006)
Uganda	Jinja-School	33.22	0.43	1166	U	N	2001	6	2002	5	Okello et al. (2006)
Uganda	Kabale-villages	30.00	-1.25	1888	PU	N	1997	10	1998	9	Lindblade et al. (1999)
Uganda	Kanungu-Kihihi	29.70	0.75	758	R	N	2001	6	2002	5	Okello et al. (2006)
Uganda	Kyenjojo-Kasiina	30.62	0.62	1361	R	N	2001	6	2002	5	Okello et al. (2006)
Uganda	Tororo-Namwaya	34.02	0.77	1143	PU	N	2001	6	2002	5	Okello et al. (2006)

Bibliography

Adiamah, J. H., Koram, K. A., Thompson, M. C., Lindsay, S. W., Todd, J., and Greenwood, B. M. (1993). Entomological risk factors for severe malaria in a peri-urban area of the gambia. *Ann Trop Med Parasitol*, 87(5):491–500.

Adja, A. M., N'Goran, E. K., Koudou, B. G., Dia, I., Kengne, P., Fontenille, D., and Chandre, F. (2011). Contribution of an. funestus, an. gambiae, and an. nili (diptera:culicidae) to the perenial malaria transmission in the southern and western forest areas of cote d'ivoire. *Ann Trop Med Parasitol*, 105(1):13–24.

Afrane, Y. A., Githeko, A. K., and Yan, G. (2012). The ecology of anopheles mosquitoes under climate change: case studies from the effects of environmental changes in east africa highlands. *Annals of the New York Academy of Sciences*, 1249:204–210.

Akhwale, W. S., Lum, J. K., Kaneko, A., Eto, H., Obonyo, C., Björkman, A., and Kobayakawa, T. (2004). Anemia and malaria at different altitudes in the western highlands of kenya. *Acta Tropica*, 91(2):167–175.

Akogbeto, M., Modiano, D., and Bosman, A. (1992). Malaria transmission in the lagoon area of cotonou, benin. *Parassitologia*, 34(1-3):147–154.

Alemu, A., Abebe, G., Tsegaye, W., and Golassa, L. (2011). Climatic variables and malaria transmission dynamics in jimma town, south west ethiopia. *Parasit Vectors*, 4(30).

Altman, D. G. and Bland, J. M. (2005). Standard deviations and standard errors. *BMJ*, 331:903.

Anderson, R. M. and May, R. M. (1991). *Infectious diseases of humans: dynamics and control*. Oxford University Press, London.

Andrianaivolambo, L., Domarle, O., Randrianarivelojosia, M., Ratovonjato, J., Le Goff, G., Talman, A., Ariey, F., and Robert, V. (2010). Anthropophilic mosquitoes and malaria transmission in the eastern foothills of the central highlands of madagascar. *Acta tropica*, 116(3):240–245.

Aniedu, I. (1997). Dynamics of malaria transmission near two permanent breeding sites in baringo district, kenya. *The Indian journal of medical research*, 105:206–211.

Animut, A., Balkew, M., Gebre-Michael, T., and Lindtjørn, B. (2013). Blood meal sources and entomological inoculation rates of anophelines along a highland altitudinal transect in south-central ethiopia. *Malaria journal*, 12(1):1.

Antonio-Nkondjio, C., Awono-Ambene, P., Toto, J.-C., Meunier, J.-Y., Zebaze-Kemleu, S., Nyambam, R., Wondji, C. S., Tchuinkam, T., and Fontenille, D. (2002). High malaria transmission intensity in a village close to yaounde, the capital city of cameroon. *Journal of medical entomology*, 39(2):350–355.

Antonio-Nkondjio, C., Defo-Talom, B., Tagne-Fotso, R., Tene-Fossog, B., Ndo, C., Lehman, L. G., Tchuinkam, T., Kengne, P., and Awono-Ambene, P. (2012). High mosquito burden and malaria transmission in a district of the city of douala, cameroon. *BMC infectious diseases*, 12(1):1.

Appawu, M., Owusu-Agyei, S., Dadzie, S., Asoala, V., Anto, F., Koram, K., Rogers, W., Nkrumah, S., Hoffman, S. L., and Fryauff, D. J. (2004). Malaria transmission dynamics at a site in northern ghana proposed for testing malaria vaccines. *Trop Med Int Health*, 9:164–170.

Aranda, C., Aponte, J. J., Saute, F., Casimiro, S., Pinto, J., Sousa, C., Rosario, V. D. O., Petrarca, V., Dgedge, M., and Alonso, P. (2005). Entomological characteristics of malaria transmission in manhica, a rural area in southern mozambique. *Journal of medical entomology*, 42(2):180–186.

Aron, J. L. (1983). Dynamics of acquired immunity boosted by exposure to infection. *Math Biosci*, 64(2):249–259.

Aron, J. L. (1988). Mathematical modelling of immunity to malaria. *Math Biosci*, 90(1-2):385–396.

Aron, J. L. and May, R. M. (1982). *The population dynamics of malaria, in population dynamics of infectious disease (R. M. Anderson ED.)*. Chapman and Hall, London.

Attenborough, R. D., Burkot, T. R., and Gardner, D. S. (1997). Altitude and the risk of bites from mosquitoes infected with malaria and filariasis among the mianmin people of papua new guinea. *Trans R Soc Trop Med Hyg*, 91:8–10.

Awange, J. L., Ferreira, V. G., Forootan, E., Khandu, Andam-Akorful, S. A., Agutu, N. O., and He, X. F. (2016). Uncertainties in remotely sensed precipitation data over africa. *International Journal of Climatology*, 36:303–323.

Badu, K., Brenya, R. C., Timmann, C., Garms, R., and Kruppa, T. F. (2013). Malaria transmission intensity and dynamics of clinical malaria incidence in a mountaneous forest region of ghana. *Malaria World Journal*, 4(14):4–14.

Bailey, N. T. J. (1988). *The Biomathematics of malaria, in: Malaria: Principles and Practice of Malariology*. Oxford Uni. Press, London.

Baird, J. K. (1995). Host age as a determinant of naturally acquired immunity to plasmodium falciparum. *Parasitol Today*, 11(3):105–111.

Baird, J. K. (2004). Chloroquine resistance in plasmodium vivax. *Antimicrob. Agents Chemother*, 48(11):4075–4083.

Baird, J. K. (2005). Effectiveness of antimalarial drugs. *N Engl J Med*, 352(15):1565–77.

Baird, J. K., Bangs, M. J., Maquire, J. D., and Barcus, M. J. (2002). *Epidemiological Measure of Risk of Malaria. In Methods in Molecular Medicine. Malaria Methods and Protocols*. Humana Press, Inc, Totowa, N J, 72 edition.

Baird, J. K., Jones, T. R., Danudirgo, E. W., Basri, H., Annis, B. A., Bangs, M. J., Wiady, I., and Masbar, S. (1991). Age-dependent acquired immunity against plasmodium falciparum among people with 2 years exposure to hyperendemic malaria. *Am J Trop Med Hyg*, 45(1):65–76.

Baird, J. K., Krisin, Barcus, M. J., Elyazar, I. R. F., Bangs, M. J., Maguire, J. D., Fryauff, D. J., Richie, T. L., Sekartuti, and Kalalo, W. (2003). Onset of clinical immunity to plasmodium falciparum among javanese migrants to indonesian papua. *Ann Trop Med Parasitol*, 97(6):557–564.

Balls, M. J., Bodker, R., Thomas, C. J., Kisinza, W., Msangeni, H. A., and Lindsay, S. W. (2004). Effect of topography on the risk of malaria infection in the usambara mountains, tanzania. *Trans R Soc Trop Med Hyg*, 98:400–408.

Bayoh, M. N. and Lindsay, S. W. (2003). Effect of temperature on the development of the aquatic stages of anopheles gambiae sensu stricto (diptera: Culicidae). *Bull Entomol Res*, 93(5):375–381.

Bayoh, M. N. and Lindsay, S. W. (2004). Temperature-related duration of aquatic stages of the afrotropical malaria vector mosquito anopheles gambiae in the laboratory. *Med Vet Entomol*, 18:174–179.

Beck-Johnson, L. M., Nelson, W. A., Paaijmans, K. P., Read, A. F., Thomas, M. B., and Bjornstad, O. N. (2013). The effect of temperature on anopheles mosquito population dynamics and the potential for malaria transmission. *PLoS One*, 8(11):e79276.

Beier, J. C. (1998). Malaria parasite development in mosquitoes. *Annu Rev Entomol*, 43:519–543.

Beier, J. C., Killen, G. F., and Githure, J. I. (1999). A short report: Entomologic inoculation rate and plasmodium falciparum malaria prevalence in africa. *Am. J. Trop. Med. Hyg*, 61(1):109–113.

Beier, J. C., Perkins, P. V., Koros, J. K., Onyango, F. K., Gargan, T. P., Wirtz, R. A., Koech, D. K., and Roberts, C. R. (1990). Malaria sporozoite detection by dissection and elisa to assess infectivity of afrotropical anopheles (diptera: Culicidae). *Journal of Medical Entomology*, 27:377–384.

Beier, J. C., Perkins, P. V., Wirtz, R. A., Whitmire, R. E., Mugambi, M., and Hockmeyer, W. T. (1987). Field evaluation of an enzyme-linked immunosorbent assay (elisa) for plasmodium falciparum sporozoite detection in anopheline mosquitoes from kenya. *Am J Trop Med Hyg*, 36:459–468.

Bekessy, A., Molineaux, L., and Storey, J. (1976). Estimation of incidence and recovery rates of plasmodium falciparum parasitaemia from longitudinal data. *Bull World Health Organ*, 54(6):685–693.

Biau, D. J. (2011). Standard deviation and standard error. *Clin Orthop Relat Res*, 469:2661–2664.

Bigoga, J. D., Manga, L., Titanji, V. P. K., Coetzee, M., and Leke, R. G. F. (2007). Malaria vectors and transmission dynamics in coastal south-western cameroon. *Malaria Journal*, 6(1):1.

Blanford, J. I., Blanford, S., Crane, R. G., Mann, M. E., Paaijmans, K. P., Schreiber, K. V., and Thomas, M. B. (2013). Implications of temperature variation for malaria parasite development across africa. *Sci Rep*, 3(1300).

Bockarie, M. J., Barnish, G., Maude, G. H., Greenwood, B. M., et al. (1994). Malaria in a rural area of sierra leone. iii. vector ecology and disease transmission. *Annals of tropical medicine and parasitology*, 88(3):251–262.

Bockarie, M. J., Barnish, G., Touré, Y. T., et al. (1995). Vectorial capacity and entomological inoculation rates of anopheles gambiae in a high rainfall forested area of southern sierra leone. *Tropical medicine and parasitology: official organ of Deutsche Tropenmedizinische Gesellschaft and of Deutsche Gesellschaft fur Technische Zusammenarbeit (GTZ)*, 46(3):164–171.

Bodker, R., Akida, J., Shayo, D., Kisinza, W., Msangeni, H. A., Pedersen, E. M., and Lindsay, S. W. (2003). Relationship between altitude and intensity of malaria transmission in the usambara mountains, tanzania. *J Med Entomol*, 40(5):706–717.

Bomblies, A., Duchemin, J.-B., and Eltahir, E. A. B. (2008). Hydrology of malaria: model development and application to a sahelian village. *Water Resources Research*, 44.

Bomblies, A., Duchemin, J.-B., and Eltahir, E. A. B. (2009). A mechanistic approach for accurate simulation of village scale malaria transmission. *Malaria Journal*, 8(223).

Bousema, J. T., Drakeley, C. J., Mens, P. F., Arens, T., Houben, R., Omar, S. A., Gouagna, L. C., Schallig, H., and Sauerwein, R. W. (2008). Increased plasmodium falciparum gametocyte production in mixed infections with p. malariae. *Am. J. Trop. Med. Hyg*, 78(3):442–448.

Bousema, T., Okell, L., Felger, I., and Drakeley, C. (2014). Asymptomatic malaria infections: detectability, transmissibility and public health relevance. *Nature Reviews Microbiology*, 12(12):833–840.

Brandts, C. H., Ndjave, M., Graninger, W., and Kremsner, P. G. (1997). Effect of paracetamol on parasite clearance time in plasmodium falciparum malaria. *Lancet*, 350(9079):704–709.

Briët, O. J. T., Dossou-Yovo, J., Akodo, E., Van De Giesen, N., and Teuscher, T. M. (2003). The relationship between anopheles gambiae density and rice cultivation in the savannah zone and forest zone of cote d'ivoire. *Tropical Medicine & International Health*, 8(5):439–448.

Briet, O. J. T., Vounatsou, P., and Amerasinghe, P. H. (2008). Malaria seasonality and rainfall seasonality in sri lanka are correlated in space. *Geospatial Health*, 2(2):183–190.

Bruce-Chwatt, L. J. (1985). *Essential malariology*. Heinemann, London, 2nd edition.

Bruce-Chwatt, L. J., Draper, C. C., and Konfortion, P. (1973). Seroepidemiologic evidence of eradication of malaria from mauritius. *Lancet*, 2:547–551.

Buckling, A. and Read, A. F. (2001). The effect of partial host immunity on the transmission of malaria parasites. *Proc Biol Sci*, 268(1483):2325–2330.

Burkot, T. R. and Graves, P. M. (1995). The value of vector-based estimates of malaria transmission. *Annals of Tropical Medicine and Parasitology*, 89:125–134.

Burkot, T. R., Williams, J. L., and Schneider, I. (1984). Identification of plasmodium falciparum infected mosquitoes by a double antibody enzyme-linked immunosorbent assay. *American Journal of Tropical Medicine and Hygiene*, 33:783–788.

Byrne, N. (2007). Urban malaria risk in sub-saharan africa: where is the evidence? *Travel Medicine and Infectious Disease*, 5(2):135–137.

Cairns, M., Ghani, A., Okell, L., Gosling, R., Carneiro, I., Anto, F., and et al (2011). Modelling the protective efficacy of alternative delivery schedules for intermittent preventive treatment of malaria in infants and children. *PLoS ONE*, 6(4):e18947.

Cairns, M., Roca-Feltrer, A., Garske, T., Wilson, A. L., Diallo, D., Milligan, P. J., Ghani, A. C., and Greenwood, B. M. (2012). Estimating the potential public health impact of seasonal malaria chemoprevention in african children. *Nature Communications*, 3(881).

Caminade, C., Kovats, S., Rocklov, J., Tompkins, A. M., Morse, A. P., Colon-Gonzalez, F. J., Stenlund, H., Martens, P., and Lloyd, S. J. (2014). Impact of climate change on global malaria distribution. *PNAS*, 111(9):3286–3291.

Carnevale, P., Goff, G., TOTO, J.-C., and Robert, V. (1992). Anopheles nili as the main vector of human malaria in villages of southern cameroon. *Medical and veterinary entomology*, 6(2):135–138.

Carnevale, P., Guillet, P., Robert, V., Fontenille, D., Doannio, J., Coosemans, M., and Mouchet, J. (1999). Diversity of malaria in rice growing areas of the afrotropical region. *Parassitologia*, 41:273–276.

Charlwood, J. D., Smith, T., Lyimo, E., Kitua, A. Y., Masanja, H., Booth, M., Alonso, P. L., and Tanner, M. (1998). Incidence of plasmodium falciparum infection in infants in relation to exposure to sporozoite-infected anophelines. *The American journal of tropical medicine and hygiene*, 59(2):243–251.

Charlwood, J. D., Thompson, R., and Madsen, H. (2003). Observations on the swarming and mating behaviour of anopheles funestus from southern mozambique. *Malaria Journal*, 2(2).

Chitnis, N., Cushing, J. M., and Hyman, J. M. (2006). Bifurcation analysis of a mathematical model for malaria transmission. *SIAM J Appl Math*, 67(1):24–45.

Chitnis, N., Hyman, J. M., and Cushing, J. M. (2008). Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. *Bulletin of Mathematical Biology*, 70:1272–1296.

Choi, K. S., Christian, R., Nardini, L., Wood, O. R., Agubuzo, E., Muleba, M., Munyati, S., Makuwaza, A., Koekemoer, L. L., Brooke, B. D., Hunt, R. H., and Coetzee, M. (2004). Insecticide resistance and role in malaria transmission of anopheles funestus populations from zambia and zimbabwe. *Parasites and Vectors*, 7(464).

CIESIN-CIAT (2005). Gridded population of the world, version 3 (gpwv3): Population density grid. palisades, ny: Nasa socioeconomic data and applications center (sedac). http://dx.doi.org/10.7927/H4XK8CG2. Assessed:20-05-2015.

Ciuca, M., Ballif, L., and Chelarescu-Vieru, M. (1934). Immunity in malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 27(6):619–622.

Clark-Carter, D. (2005). *Standard error. In: Everitt BS, Howell D, eds. Encyclopedia of Statistics in Behavioral Science. Vol 4. Hoboken.* NJ: John Wiley and Sons, Ltd.

Coene, J. (1993). Malaria in urban and rural kinshasa: the entomological input. *Medical and veterinary entomology*, 7(2):127–137.

Coetzee, M., Craig, M., and le Sueur, D. (2000). Distribution of african malaria mosquitoes belonging to the anopheles gambiae complex. *Parasitology Today*, 16(2):149–151.

Coetzee, M. and Fontenille, D. (2004). Advances in the study of anopheles funestus, a major vector of malaria in africa. *Insect Biochem Mol Biol*, 34:599–605.

Cohen, S., McGregor, I. A., and Carrington, S. (1961). Gamma-globulin and acquired immunity to human malaria. *Nature*, 192:733–737.

Collins, F. H. and Besansky, N. J. (1994). Vector biology and the control of malaria in africa. *Science*, 264(5167):1874–5.

Collins, J. M. (2011). Temperature variability over africa. *Journal of Climate*, 24:3649–3666.

Collins, W. E. and Jeffery, G. M. (2005). Plasmodium ovale: parasite and disease. *Clin Microbiol Rev*, 18(3):570–581.

Collins, W. E. and Jeffery, G. M. (2007). Plasmodium malariae: parasite and disease. *Clin Microbiol Rev*, 20(4):579–592.

Coosemans, M., Wéry, M., Mouchet, J., and Carnevale, P. (1992). Transmission factors in malaria epidemiology and control in africa. *Memorias do Instituto Oswaldo Cruz, Rio de Janeiro*, 87(Suppl. III):385–391.

Coosemans, M. H. (1985b). Comparison de l'endemie malarienne dans une zone de riziculture et dans une zone de cultture de coton dans la plaine de la rusizi, burundi. *Annales de la Societe Belge de Medecine Tropicale*, 65(2):187–200.

Cox-Singh, J. and B, S. (2008). Knowlesi malaria: newly emergent and of public health importance? *Trends in Parasitology*, 24(9):406–410.

Craig, M. H., Snow, R. W., and le Seur, D. (1999). A climate-based distribution model of malaria transmission in sub-saharan africa. *Parasitology Today*, 15(3):105–111.

Crompton, P. D., Moebius, J., Portugal, S., Waisberg, M., Hart, G., Garver, L. S., Miller, L. H., Barillas, C., and Pierce, S. K. (2014). Malaria immunity in man and mosquito: insights into unsolved mysteries of a deadly infectious disease. *Annu Rev Immunol*, 32:157–187.

Dabire, K., Diabate, A., Pare-Toe, L., Rouamba, J., Ouari, A., Fontenille, D., and Baldet, T. (2008). Year to year and seasonal variations in vector bionomics and malaria transmission in a humid savannah village in west burkina faso. *Journal of Vector Ecology*, 33(1):70–75.

Day, K. P. and Marsh, K. (1991). Naturally acquired immunity to plasmodium falciparum. *Immunol Today*, 12(3):A68–71.

De Silva, P. M. and Marshall, J. M. (2012). Factors contributing to urban malaria transmission in sub-saharan africa: a systematic review. *Journal of Tropical Medicine*, 2012.

Dee, D. P., Uppala, S. M., Simmons, A. J., Berrisford, P., Poli, P., Kobayashi, S., and et al (2011). The era-interim reanalysis: configuration and performance of the data assimilation system. *Quarterly Journal of the Royal Meteorological Society*, 137(656):553–597.

Dery, D. B., Brown, C., Asante, K. P., Adams, M., Dosoo, D., Amenga-Etego, S., Wilson, M., Chandramohan, D., Greenwood, B., and Owusu-Agyei, S. (2010). Patterns and seasonality of malaria transmission in the forest-savannah transitional zones of ghana. *Malaria journal*, 9(314).

Diebner, H. H., Eichner, M., Molineaux, L., Collins, W. E., Jeffery, G. M., and Dietz, K. (2000). Modelling the transmission of asexual blood stages of plasmodium falciparum to gametocytes. *J Theor Biol*, 202(2):113–127.

Dietz, K., Molineaux, L., and Thomas, A. (1974). A malaria model tested in the african savannah. *Bull World Health Organ*, 50(3-4):347–357.

Dobson, A. P. and Carper, R. J. (1992). *Global warming and potential changes in host-parasite and disease vector relationships. Pages 201–217 in R. Peters and T. Lovejoy, eds. Global warming and biodiversity*. Yale University Press, New Haven, Conn.

Doolan, D. L., Dobano, C., and Baird, J. K. (2009). Acquired immunity to malaria. *Clinical Microbiology Reviews*, 22(1):13–36.

Dossou-Yovo, J., Doannio, J., Diarrassouba, S., and Chauvancy, G. (1998). Impact d'aménagements de rizières sur la transmission du paludisme dans la ville de bouaké, côte d'ivoire. *Bull Soc Pathol Exot*, 91(4):327–33.

Dossou-Yovo, J., Doannio, J., Riviere, F., and Chauvancy, G. (1995). Malaria in cote d'ivoire wet savannah region: the entomological input. *Tropical medicine and parasitology: official organ of Deutsche Tropenmedizinische Gesellschaft and of Deutsche Gesellschaft fur Technische Zusammenarbeit (GTZ)*, 46(4):263–269.

Downing, D. J., Gardner, R. H., and Hoffman, E. O. (1985). An examination of response-surface methodologies for uncertainty analysis in assessment models. *Technometrics*, 27(2):151–163.

Drakeley, C., Sutherland, C., Bousema, J. T., Sauerwein, R. W., and Targett, G. A. T. (2006). The epidemiology of plasmodium falciparum gametocytes: weapons of mass dispersion. *Trends Parasitol*, 22(9):424–430.

Drakeley, C. J., Carneiro, I., Reyburn, H., Malima, R., Lusingu, J. P. A., Cox, J., Theander, T. G., Nkya, W. M. M. M., Lemnge, M. M., and Riley, E. M. (2005). Altitude-dependent and -independent variations in plasmodium falciparum prevalence in northeastern tanzania. *Journal of Infectious Diseases*, 191:1589–1598.

Durnez, L., Bortel, W. V., Denis, L., Roelants, P., Veracx, A., Trung, H. D., Sochantha, T., and Coosemans, M. (2011). False positive circumsporozoite protein elisa: a challenge for the estimation of the entomological inoculation rate of malaria and for vector incrimination. *Malaria Journal*, 10(195).

Elissa, N., Migot-Nabias, F., Luty, A., Renaut, A., Toure, F., Vaillant, M., Lawoko, M., Yangari, P., Mayombo, J., Lekoulou, F., et al. (2003). Relationship between entomological inoculation rate, plasmodium falciparum prevalence rate, and incidence of malaria attack in rural gabon. *Acta tropica*, 85(3):355–361.

Ermert, V., Fink, A. H., Jones, A. E., and Morse, A. P. (2011a). Development of a new version of the liverpool malaria model. i. refining the parameter settings and mathematical formulation of basic processes based on literature review. *Malaria Journal*, 10(35).

Ermert, V., Fink, A. H., Jones, A. E., and Morse, A. P. (2011b). Development of a new version of the liverpool malaria model. ii. calibration and validation for west africa. *Malaria Journal*, 10(62).

Ermert, V., Fink, A. H., Morse, A. P., and Paeth, H. (2012). The impact of regional climate change on malaria risk due to greenhouse forcing and land-use changes in tropical africa. *Environmental Health Perspectives*, 120:77–84.

Ermert, V., Fink, A. H., and Paeth, H. (2013). The potential effects of climate change on malaria transmission in africa using bias-corrected regionalised climate projections and a simple malaria seasonality model. *Climatic Change*, 120:741–754.

Eyles, D. E. and Young, M. D. (1951). he duration of untreated or inadequately treated plasmodium falciparum infection in the human host. *J Natl Malaria Soc*, 10(4):327–336.

Faye, O., Gaye, O., Faye, O., and Diallo, S. (1994). La transmission du paludisme dans des villages éloignés u situés en bordure de la mangrove au sénégal. *Bulletin de la Société de pathologie exotique*, 87(3):157–163.

Faye, O., Gaye, O., Fontenille, D., Sy, N., Konate, L., Hébrard, G., Hervé, J.-P., Trouillet, J., Diallo, S., and Mouchet, J. (1995). Comparaison de la transmission du paludisme dans deux faciès épidémiologiques au sénégal: la zone côtière sahélienne et la zone méridionale soudanienne. *Dakar Médical*, 40(2):201–207.

Feachem, R. G. A., Phillips, A. A., Hwang, J., Cotter, C., Wielgosz, B., Greenwood, B. M., Sabot, O., Rodriguez, M. H., Abeyasinghe, R. R., Ghebreyesus, T. A., and Snow, R. W. (2010). Shrinking the malaria map: progress and prospects. *Lancet*, 376(9752):1566–1578.

Filipe, J. A. N., Riley, E. M., Drakeley, C. J., Sutherland, C. J., and C, G. A. (2007). Determination of the processes driving the acquisition of immunity to malaria using a mathematical transmission model. *Plos Comput Biol*, 3(12):e255.

Fillinger, U., Sombroek, H., Majambere, S., van Loon, E., Takken, W., and Lindsay, S. W. (2009). Identifying the most productive productive sites breeding sites for malaria mosquitoes in the gambia. *Malaria Journal*, 8(62).

Fils, E. M. B., Ntonga, P. A., Belong, P., and Messi, J. (2010). Contribution of mosquito vectors in malaria transmission in an urban district of southern cameroon. *Journal of Entomology and Nematology*, 2(2):13–17.

Fondjo, E., Robert, V., Le Goff, G., Toto, J., Carnevale, P., Kalema, M., and Hughlett, S. (1992). Le paludisme urbain à yaoundé (cameroun). ii: Etude entomologique dans deux quartiers peu urbanisés. commentaire. *Bulletin de la Société de pathologie exotique*, 85(1):57–63.

Fontaine, R. E., Najjar, A. E., and Prince, J. S. (1961). The 1958 malaria epidemics in ethiopia. *Am J Trop Med Hyg*, 10(6):795–803.

Fontenille, D., Lochouarn, L., Diagne, N., Sokhna, C., Lemasson, J., Diatta, M., Konate, L., Faye, F., Rogier, C., and Trape, J. F. (1997). Malaria transmission in urban sub-saharan africa. *Am. J. Trop. Med. Hyg.*, 56:247–253.

Fontenille, D., Lochouarn, L., Diatta, M., Sokhna, C., Dia, I., Diagne, N., Lemasson, J.-J., Ba, K., Tall, A., Rogier, C., and Trape, J.-F. (1997a). Four years entomological study of the transmission of seasonal malaria in senegal and the bionomics of anopheles gambiae and a. arabiensis. *Am. J. Trop. Med. Hyg.*, 91(6):647–652.

Fontenille, D., Meunier, J. Y., Nkondjio, C. A., and Tchuinkam, T. (2001). Use of circumsporozoite protein enzyme-linked immunosorbent assay compared with microscopic examination of salivary glands for calculation of malaria infectivity rates in mosquitoes (diptera: Culicidae) from cameroon. *Journal of Meidical Entomology*, 38:451–454.

Färnert, A., Wyss, K., Dashti, S., and Naucler, P. (2015). Duration of residency in a non-endemic area and risk of severe malaria in african immigrants. *Clin Microbiol Infect*, 21(5):494–501.

Gallup, J. L. and Sachs, J. D. (2001). The economic burden of malaria. *Am. J. Trop. Med. Hyg*, 64:85–96.

Gatton, M. L. and Cheng, Q. (2004). Modeling the development of acquired clinical immunity to plasmodium falciparum malaria. *Infect Immun*, 72(11):6538–6545.

Gething, P. W., Elyazar, I. R. F., Moyes, C. L., Smith, D. L., Battle, K. E., and et al (2012). A long neglected world malaria map: Plasmodium vivax endemicity in 2010. *PLoS Negl Trop Dis*, 6(9):e1814.

Gething, P. W., Patil, A. P., Smith, D. L., Guerra, C. A., Elyazar, I., Johnston, G. L., Tatem, A. J., and Hay, S. I. (2011). A new world malaria map: Plasmodium falciparum endemicity in 2010. *Malaria Journal*, 10(378):1475–2875.

Gianotti, R. L., Bomblies, A., and Eltahir, E. A. B. (2009). Hydrologic modelling to screen potential environmental management methods for malaria vector control in niger. *Water Resour Res*, 45:W08438.

Giha, H. A., El-Ghazali, G., A-Elgadir, T. M. E., A-Elbasit, I. E., Eltahir, E. M., Baraka, O. Z., Khier, M. M., Adam, I., Troye-Blomberg, M., Theander, T. G., and Elbashir, M. I. (2005). Clinical pattern of severe plasmodium falciparum malaria in sudan in an area characterized by seasonal and unstable malaria transmission. *Trans R Soc Trop Med Hyg*, 99(4):243–251.

Gill, C. A. (1920). The relationship between malaria and rainfall. *Indian J Med Res*, 37:618–632.

Githeko, A., Mbogo, C., Atieli, F., Juma, F., et al. (1993). Plasmodium falciparum sporozoite and entomological inoculation rates at the ahero rice irrigation scheme and the miwani sugar-belt in western kenya. *Annals of tropical medicine and parasitology*, 87(4):379–391.

Githeko, A. K., Mbogo, C. N. M., Curtis, C. F., Lines, J., and Lengeler, C. (1996). Entomological monitoring of large-scale vector-control interventions. *Parasitology Today*, 12:127–128.

Githeko, A. K. and Ndegwa, W. (2001). Predicting malaria epidemics in kenyan highlands using climate data: a tool for decision makers. *Glob Change Hum Health*, 2:54–63.

Gneme, A., Guelbeogo, W. M., Riehle, M. M., Tiono, A. B., Diarra, A., Kabre, G. B., Sagnon, N., and Vernick, K. D. (2013). Plasmodium species occurrence, temporal distribution and interaction in a child-aged population in rural burkina faso. *Malar J*, 12(67-10):1186/1475–2875–12–67.

Gomes, M., Ribeiro, I., Warsame, M., Karunajeewa, H., and Petzold, M. (2008). Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. *BMC Infectious Diseases*, 8(39):10.1186/1471–2334–8–39.

Gregson, A. and Plowe, C. V. (2005). Mechanisms of resistance of malaria parasites to antifolates. *Pharmacol Rev*, 57:117–145.

Grover-Kopec, E. K., Blumenthal, M. B., Ceccato, P., Dinku, T., Omumbo, J. A., and Connor, S. J. (2006). Web-based climate information resources for malaria control in africa. *Malaria Journal*, 5(38).

Gueirard, P., Tavares, J., Thiberge, S., Bernex, F., Ishino, T., Milon, G., Franke-Fayard, B., Janse, C. J., Menard, R., and Amino, R. D. (2010). Development of the malaria parasite in the skin of the mammalian host. *Proc Natl Acad Sci U S A*, 107(43):18640–5.

Guerra, C. A., Gikandi, P. W., Tatem, A. J., Noor, A. M., Smith, D. L., Hay, S. L., and Snow, R. W. (2008). The limits and intensity of plasmodium falciparum transmission: implications for malaria control and elimination worldwide. *Plos Med*, 5:e38.

Gupta, H. V., Sorooshian, S., and Yapo, P. O. (1999a). Status of automatic calibration for hydrologic models: Comparison with multilevel expert calibration. *Journal of Hydrology Engineering*, 4(2):135–143.

Gupta, S., Snow, R. W., Donnelly, C. A., Marsh, K., and Newbold, C. (1999b). Immunity to non-cerebral severe malaria is acquired after one or two infections. *Nat Med*, 5(3):340–343.

Guyatt, H. L. and Snow, R. W. (2001). The epidemiology and burden of plasmodium falciparum-related anemia among pregnant women in sub-saharan africa. *Am. J. Trop. Med. Hyg*, 64(1,2):36–44.

Hamby, D. M. (1994). A review of techniques for parameter sensitivity analysis of environmental models. *Environmental Monitoring and Assessment*, 32:135–154.

Hamby, D. M. (1995). A comparison of sensitivity analysis techniques. *Health Phys*, 68(2):195–204.

Hammerich, A., Campbell, O. M., and Chandramohan, D. (2002). Unstable malaria transmission and maternal mortality experiences from rwanda. *Trop Med Int Health*, 7(7):573–576.

Haque, U., Hashizume, M., Glass, G. E., Dewan, A. M., Overgaard, H. J., and Yamamoto, T. (2010). The role of climate variability in the spread of malaria in the bangladeshi highlands. *PLoS ONE*, 5:e14341.

Hawley, W. A., ter Kuile, F. O., Steketee, R. S., and et al (2003). Implications of the western kenya permethrin-treated bed net study for policy, program implementation, and future research. *Am J Trop Med Hyg*, 68(4):168–73.

Hay, S I Cox, J., Rogers, D. J., Randolph, S. E., Stern, D. I., Shanks, G. D., Myers, M. F., and Snow, R. W. (2002). Climate change and the resurgence of malaria in the east african highlands. *Nature*, 415(6874):905–9.

Hay, S. I., Guerra, C. A., Tatem, A. J., Atkinson, P. M., and Snow, R. W. (2005). Urbanization, malaria transmission and disease burden in africa. *Nat Rev Microbiol*, 3(1):81–90.

Hay, S. I., Rogers, D. J., Toomer, J. F., and Snow, R. W. (2000). Annual plasmodium falciparum entomological inoculation rates(eir) across africa: literature survey, internet access and review. *Trans R Soc Trop Med Hyg.*, 94(2):113–127.

Hay, S. I., Snow, R. W., and Rogers, D. J. (1998a). Predicting malaria seasons in kenya using multitemporal meteorological satellite sensor data. *Trans R Soc Trop Med Hyg*, 92(1):12–20.

Hay, S. L., Guerra, C. A., Gething, P. W., Patil, A. P., Tatem, A. J., and Noor, A. M. e. a. (2009). A world malaria map: plasmodium falciparum endemicity in 2007. *Plos Med*, 6(3):e1000048.

Hay, S. L., Okiro, E. A., Gething, P. W., Patil, A. P., Tatem, A. J., Guerra, C. A., and Snow, R. W. (2010). Estimating the global clinical burden of plasmodium falciparum malaria in 2007. *Plos Med*, 7:e1000290.

Homann, M. V. (2008). *Human genetic factors involved in immunity to Plasmodium falciparum infection*. PhD thesis, Department of Immunology, The Wenner-Gren Institute, Stockholm University, Sweden.

Hoshen, M. B. and Morse, A. P. (2004). A weather-driven model of malaria transmission. *Malaria Journal*, 3(32).

Ijumba, I. N. (1997). *The impact of rice and sugarcane irrigation on malaria transmission in the Lower Moshi area in northern Tanzania*. PhD thesis, Danish Bilharziasis Laboratory, University of Copenhagen.

Ijumba, J. N. and Lindsay, S. W. (2001). Impact of irrigation on malaria in africa: paddies paradox. *Med Vet Entomol*, 15:1–11.

Ijumba, J. N., Shenton, F. C., Clarke, S. E., Mosha, F. W., and Lindsay, S. W. (2002). Irrigated crop production is associated with less malaria than traditional agricultural practices in tanzania. *Trans R Soc Trop Med Hyg*, 96(5):476–80.

Ilboudo-Sanogo, E., Tiono, B. A., Sagnon, N., Cuzin Ouattara, N., Nébié, I., and Sirima, S. (2010). Temporal dynamics of malaria transmission in two rural areas of burkina faso with two ecological differences. *Journal of medical entomology*, 47(4):618–624.

Indeje, M., Semazzi, F. H. M., and Ogallo, L. J. (2000). Enso signals in east african rainfall seasons. *International Journal of Climatology*, 20:19–46.

Jaleta, K. T., Hill, S. R., Seyoum, E., Balkew, M., Gebre-Michael, T., Ignell, R., and Tekie, H. (2013). Agro-ecosystems impact malaria prevalence: large-scale irrigation drives vector population in western ethiopia. *Malaria journal*, 12(1):1.

Jeffery, G. M. and Eyles, D. E. (1954). The duration in the human host of infections with a panama strain of plasmodium falciparum. *Am J Trop Med Hyg*, 3(2):219–224.

Jennings, R. M., De Souza, J. B., Todd, J. E., Armstrong, M., Flanagan, K. L., and et al (2006). Imported plasmodium falciparum malaria: are patients originating from disease-endemic areas less likely to develop severe disease? a prospective, observational study. *Am J Trop Med Hyg*, 75(6):1195–1199.

JHSPHOPEN-Courseware (2016). Life cycle of the malaria parasite from epidemiology of infectious diseases. `http://ocw.jhsph.edu`. Copyright © Johns Hopkins Bloomberg School of Public Health. Creative Commons BY-NC-SA. Accessed: March 26, 2016.

Josling, G. A. and Llinas, M. (2015). Sexual development in plasmodium parasites: knowing when it's time to commit. *Nature Reviews Microbiology*, 13(9):573–587.

Kar, N. P., Kumar, A., Singh, O. P., Carlton, J. M., and Nanda, N. (2014). A a review of malaria transmission dynamics in forest ecosystems. *Parasites and Vectors*, 7(265).

Karch, S., Garin, B., Asidi, N., Manzambi, Z., Salaun, J. J., and Mouchet, J. (1993). Moustiquaires imprégnées contre le paludisme au zaïre. In *Annales de la Société belge de Médecine tropicale*, volume 73, pages 37–53.

Karp, C. L. and Auwaerter, P. G. (2007). Coinfection with hiv and tropical infectious diseases. i. protozoal pathogens. *Clin Infect Dis*, 45(9):1208–13.

Kasasa, S., Asoala, V., Gosoniu, L., Anto, F., Adjuik, M., Tindana, C., Smith, T., Owusu-Agyei, S., and Vounatsou, P. (2013). Spatio-temporal malaria transmission patterns in navrongo demographic surveillance site, northern ghana. *Malaria Journal*, 12(63).

Keiser, J., Caldas De Castro, M., Maltese, M. F., Bos, R., Tanner, M., Singer, B. H., and Utzinger, J. (2005). Effect of irrigation and large dams on the burden of malaria on a global and regional scale. *Am. J. Trop. Med. Hyg.*, 72(4):392–406.

Keiser, J., Utzinger, J., Caldas De Castro, M., Smith, T. A., Tanner, M., and Singer, B. H. (2004). Urbanization in sub-saharan africa and implication for malaria control. *American Journal of Tropical Medicine and Hygiene*, 71(2):118–127.

Kelly-Hope, L. A. and McKenzie, F. E. (2009). The multiplicity of malaria transmission: a review of entomological inoculation rate measurements and methods across sub-saharan africa. *Malaria Journal*, 8(19).

Kerah-Hinzoumbé, C., Péka, M., Antonio-Nkondjio, C., Donan-Gouni, I., Awono-Ambene, P., Samè-Ekobo, A., and Simard, F. (2009). Malaria vectors and transmission dynamics in goulmoun, a rural city in south-western chad. *BMC infectious diseases*, 9(1):1.

Kibret, S., Wilson, G. G., Tekie, H., and Petros, B. (2014). Increased malaria transmission around irrigation schemes in ethiopia and the potential of canal water management for malaria vector control. *Malaria Journal*, 12(360).

Kilama, M., Smith, D. L., Hutchinson, R., Kigozi, R., Yeka, A., Lavoy, G., Kamya, M. R., Staedke, S. G., Donnelly, M. J., Drakeley, C., Greenhouse, B., Dorsey, G., and Lindsay, S. W. (2014). Estimating the annual entomological inoculation rate for plasmodium falciparum transmitted by anopheles gambiae s.l. using three sampling methods in three sites in uganda. *Malaria Journal*, 13(111).

Killeen, G. F., Fillinger, U., Kiche, I., Gouagna, L. C., and Knols, B. G. (2002). Eradication of anopheles gambiae from brazil: lessons for malaria control in africa? *Lancet Infect Dis*, 2:618–627.

Kirby, M. J. and Lindsay, S. W. (2009). Effect of temperature and inter-specific competition on the development and survival of anopheles gambiae sensu stricto and anopheles arabiensi larvae. *Acta Trop*, 109(2):118–123.

Kiszewski, A., Mellinger, A., Spielman, A., Malaney, P., Sachs, S. E., and Sachs, J. (2004). A global index representing the stability of malaria transmission. *Am J Trop Med Hyg*, 70(5):486–498.

Kleinschmidt, I., Sharp, B. L., Clarke, G. P., Curtis, B., and Fraser, C. (2001). Use of generalized linear mixed models in the spatial analysis of small-area malaria incidence rates in kwazulu natal, south africa. *Am J Epidemiol*, 153(12):1213–21.

Koella, J. C. (1991). On the use of mathematical models of malaria transmission. *Acta Trop*, 49(1):1–25.

Kurtis, J. D., Mtalib, R., Onyango, F. K., and Duffy, P. E. (2001). Human resistance to plasmodium falciparum increases during puberty and is predicted by dehydroepiandrosterone sulfate levels. *Infect Immun*, 69(1):123–128.

Laishram, D. D., Sutton, P. L., Nanda, N., Sharma, V. L., Sobti, R. C., Carlton, J. M., and Joshi, H. (2012). The complexities of malaria disease manifestations with a focus on asymptomatic malaria. *Malaria Journal*, 11(29).

Laneri, K., Bhadra, A., Ionides, E. L., Bouma, M., Dhiman, R. C., Yadav, R. S., and et al. (2010). Forcing versus feedback: Epidemic malaria and monsoon rains in northwest india. *PLoS Comput Biol*, 6(9):e1000898.

Langhorne, J., Ndungu, F. M., Sponaas, A. M., and Marsh, K. (2008). Immunity to malaria: more questions than answers. *Nat Immunol*, 9(7):725–732.

Lautze, J., McCartney, M., Kirshen, P., Olana, D., Jayasinghe, G., and Spielman, A. (2007). Effect of a large dam on malaria risk: The koka reservoir in ethiopia. *Tropical Medicine and International Health*, 12(8):982–989.

Le Goff, G., Carnevale, P., Fondjo, E., and Robert, V. (1997). Comparison of three sampling methods of man-biting anophelines in order to estimate the malaria transmission in a village of south cameroon. *Parasite*, 4:75–80.

le Sueur, D. and Sharp, B. L. (1991). Temperature-dependent variation in anopheles merus larval head capsule width and adult wing length: implications for anopheline taxonomy. *Med Vet Entomo*, 5:55–62.

Legates, D. R. and McCabe Jr, G. J. (1999). Evaluating the use of "goodness-offit" measures in hydrologic and hydroclimatic model validation. *Water Resources Research*, 35(1):233–241.

Lemasson, J.-J., Fontenille, D., Lochouarn, L., Dia, I., Simard, F., Ba, K., Diop, A., Diatta, M., and Molez, J.-F. (1997). Comparison of behavior and vector efficiency of anopheles gambiae and an. arabiensis (diptera: Culicidae) in barkedji, a sahelian area of senegal. *Journal of Medical Entomology*, 34(4):396–403.

Lepers, J. P., Fontenille, D., Rason, M. D., Chougnet, C., Astagneau, P., Coulanges, P., and Deloron, P. (1991). Transmission and epidemiology of newly transmitted falciparum malaria in the central highland plateaux of madagascar. *Annals of tropical medicine and parasitology*, 85(3):297–304.

Levine, R. S., Peterson, A. T., and Benedict, M. Q. (2004). Geographic and ecologic distributions of the anopheles gambiae complex predicted using a genetic algorithm. *Am J Trop Med Hyg*, 70(2):105–109.

Lindblade, K. A., Walker, E. D., Onapa, A. W., Katungu, J., and Wilson, M. L. (1999). Highland malaria in uganda: prospective analysis of an epidemic associated with el nino. *Trans R Soc Trop Med Hyg*, 93(5):480–487.

Lindsay, S. W. and Birley, M. H. (1996). Climate change and malaria transmission. *Ann. Trop Med Parasit*, 90(6):573–88.

Lindsay, S. W. and Martens, W. J. M. (1998). Malaria in the africa highlands: past present and future. *Bull World Health Organ*, 76(1):33–45.

Lindsay, S. W., Parson, L., and Thomas, C. J. (1998). Mapping the ranges and relative abundance of the two principal africa malaria vectors, anopheles gambiae sensu stricto and an. arabiensis, using climate data. *Proc. R. Soc. Lond. B*, 265:847–854.

Lyimo, E. O. K. (1993). *Bionomics of the malaria mosquito Anopheles gambiae sensu lato in southeast Tanzania*.

Mabaso, M., Craig, M., Vounatsou, P., and Smith, T. (2005). Towards empirical description of malaria seasonality in southern africa: the example of zimbabwe. *Trop Med Int Health*, 10:909–918.

Mabaso, M. L. H., Craig, M., Ross, A., and Smith, T. (2007). Environmental predictors of the seasonality of malaria transmission in africa: the challenge. *Am. J. Trop. Med. Hyg.*, pages 33–38.

Macdonald, G. (1950). The analysis of malaria parasite rates in infants. *Trop Dis Bull*, 47(10):915–938.

Macdonald, G. (1957). *The Epidemiology and Control of Malaria*. Oxford University Press, London.

Mandal, S., Sarkar, R. R., and Sinha, S. (2011). Mathematical models of malaria - a review. *Malaria Journal*, 10(202).

Manga, L., Toto, J., and Carnevale, P. (1995). Malaria vectors and transmission in an area deforested for a new international airport in southern cameroon. In *ANNALES-SOCIETE BELGE DE MEDECINE TROPICALE*, volume 75, pages 43–43. INSTITUTE OF TROPICAL MEDICINE.

MARA (1998). Towards an atlas of malaria risk in africa. towards an atlas of malaria transmission in africa: First technical report of the mara/arma. Technical Report 30, South African Medical Research Council, IDRC, Canada and Wellcome Trust, UK.

Markham, C. G. (1970). Seasonality of precipitation in the united states. *Ann. Ass. Am. Geogr.*, 60:593–597.

Martens, W. J. M., Niessen, L. W., Rotmans, J., Jetten, T. H., and Mcmichael, A. J. (1995). Potential impact of global climate-change on malaria risk. *Environ Health Persp.*, 103(5):458–464.

Massebo, F. and Lindtjørn, B. (2013). The effect of screening doors and windows on indoor density of anopheles arabiensis in south-west ethiopia: a randomized trial. *Malaria journal*, 12(1):1.

Maxwell, C. A., Chambo, W., Mwaimu, M., Magogo, F., Carneiro, I. A., and Curtis, C. F. (2003). Variation of malaria transmission and morbidity with altitude in tanzania and with introduction of alphacypermethrin treated nets. *Malaria Journal*, 2(28).

Mboera, L. E. G. (2005). Sampling techniques for adult afrotropical malaria vectors and their reliability in the estimation of entomological inoculation rate. *Tanzania Health Research Bulletin*, 7:117–124.

Mbogo, C. M., Snow, R. W., Khamala, C. P., Kabiru, E. W., Ouma, J. H., Githure, J. I., Marsh, K., and Beier, J. C. (1995). Relationships between plasmodium falciparum transmission by vector populations and the incidence of severe disease at nine sites on the kenyan coast. *Am. J. Trop. Med. Hyg.*, 52:201–206.

Mbogo, C. N., Snow, R. W., Kabiru, E. W., Ouma, J. H., Githure, J. I., Marsh, K., and Beier, J. C. (1993). Low-level plasmodium falciparum transmission and the incidence of severe malaria infection on the kenyan coast. *Am J Trop Med Hyg*, 49:245–253.

McKenzie, F. E., Jeffery, G. M., and Collins, W. E. (2002). Plasmodium malariae infection boosts plasmodium falciparum gametocyte production. *Am. J. Trop. Med. Hyg*, 67(4):411–414.

McQueen, P. G. and McKenzie, F. E. (2004). Age-structured red blood cell susceptibility and the dynamics of malaria infections. *Proc. Natl. Acad. Sci*, 101(24):9161–9166.

Mendis, K., Sina, B. J., Machesini, P., and Carter, R. (2001). The neglected burden of plasmodium vivax malaria. *Am. J. Trop. Med. Hyg*, 64S:97–106.

Meunier, J. Y., Safeukui, I., Fontenille, D., and Boudin, C. (1999). [malaria transmission in an area of future vaccination in equatorial forest of south cameroon]. *Bulletin de la Societe de pathologie exotique (1990)*, 92(5):309–312.

Miller, L. H., Baruch, D. I., Marsh, K., and Doumbo, O. K. (2002). The pathogenic basis of malaria. *Nature*, 415:673–9.

Modiano, D., Sirima, B. S., Sawadogo, A., Sanou, I., Paré, J., Konaté, A., and Pagnoni, F. (1999). Severe malaria in burkina faso: urban and rural environment. *Parasitologia*, 41(1-3):251–254.

Molineaux, L. (1988). *The epidemiology of human malaria as an explanation of its distribution, including some implications for its control*, volume 2. Churchill Livingstone, Edinburgh.

Molineaux, L. and Gramiccia, G. (1990). The garki project : research on the epidemiology and control of malaria in the sudan savanna of west africa. Technical report, World Health Organization, Geneva.

Molineaux, L., Muir, D. A., Spencer, H. C., and Wernsdorfer, W. H. (1988). *The epidemiology of malaria and its measurement. In Malaria: principles and practice of malariology (Wernsdorfer, W.H. and McGregor, I., eds)*, volume 2. Churchill Livingstone, Edinburgh.

Moriasi, D. N., Arnold, J. G., Van Liew, M. W., Bingner, R. L., Harmel, R. D., and Veith, T. L. (2007). Model evaluation guidelines for systematic quantification of accuracy in watershed simulations. *Trans. ASAE*, 50(3):885–900.

Mota, M. M., Pradel, G., Vanderberg, J. P., Hafalla, J. C., Frevert, U., Nussenzweig, R. S., Nussenzweig, V., and Rodriguez, A. (2001). Migration of plasmodium sporozoites through cells before infection. *Science*, 291(5501):141–144.

Mota, R. E., Lara, A. M., Kunkwenzu, E. D., and Lalloo, D. G. (2009). Health seeking behavior after fever onset in a malaria-endemic area of malawi. *Am J Trop Med Hyg*, 81(6):935–943.

Mourou, J. R., Coffinet, T., Jarjaval, F., Cotteaux, C., Pradines, E., Godefroy, L., Kombila, M., and Pages, F. (2012). Malaria transmission in libreville: results of a one year survey. *Malaria Journal*, 11(40).

Murray, C. J., Rosenfeld, L. C., Lim, S. S., Andrews, K. G., Foreman, K. J., Haring, D., Fullman, N., Naghavi, M., Lozano, R., and Lopez, A. D. (2012). Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet*, 379:413–31.

Muturi, E., Shililu, J., Jacob, B., Gu, W., Githure, J., and Novak, R. (2006). Mosquito species diversity and abundance in relation to land use in riceland agroecosystem in mwea, kenya. *J Vector Biol*, 31:129–137.

Muturi, E. J., Muriu, S., Shililu, J., Mwangangi, J., Jacob, B. G., Mbogo, C., Githure, J., and Novak, R. J. (2008). Effect of rice cultivation on malaria transmission in central kenya. *The American journal of tropical medicine and hygiene*, 78(2):270–275.

Ngwa, G. A. and Shu, W. S. (2000). A mathematical model for endemic malaria with variable human and mosquito populations. *Math Comput Model*, 32(7-8):747–763.

Nicholson, S. E. (2000). The nature of rainfall variability over africa on time scales of decades to millenia. *Global and Planetary Change*, page 137–158.

Nicholson, S. E. (2013). The west african sahel: a review of recent studies on the rainfall regime and its interannual variability. *ISRN Meteorol*, 2013:1–32.

Njan Nloga, A., Robert, V., Toto, J., and Carnevale, P. (1993). Anopheles moucheti, vecteur principal du paludisme au sud-cameroun. *Bulletin de Liaison et de Documentation-OCEAC*, 26(2):63–67.

Nkuo-Akenji, T., Ntonifor, N. N., Ndukum, M. B., Kimbi, H. K., Abongwa, E. L., Nkwescheu, A., Anong, D. N., Songmbe, M., Boyo, M. G., Ndamukong, K. N., and Titanji, V. P. K. (2006). Environmental factors affecting malaria parasite prevalence in rural bolifamba, south-west cameroon. *African Journal of Health Sciences*, 13:40–46.

Novella, N. S. and Thiaw, W. M. (2013). African rainfall climatology version 2 for famine early warning systems. *Journal of Aplied Meteorology and Climatology*, 52:588–606.

Okell, L. C., Drakeley, C. J., Bousema, T., Whitty, C. J., and Ghani, A. C. (2008). Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity. *PLoS Med*, 5(11):e226.

Okello, P. E., Van Bortel, W., Byaruhanga, A. M., Correwyn, A., Roelants, P., Talisuna, A., D'Alessandro, U., and Coosemans, M. (2006). Variation in malaria transmission intensity in seven sites throughout uganda. *Am J Trop Med Hyg*, 75(2):219–225.

Omotosho, J. B. and Abiodun, B. J. (2007). A numerical study of moisture build-up and rainfall over west africa. *Meteorol Appl*, 14:209–225.

O'Neill, R. V., Gardner, R. H., and Mankin, J. B. (1980). Analysis of parameter error in a nonlinear model. *Ecological Modelling*, 8:297–311.

Onori, E. and Grab, B. (1980). Indicators for the forecasting of malaria epidemics. *Bulletin of the World Health Organisation*, 58(1):91–98.

Paaijmans, K. P., Blanford, S., Bell, A. S., Blanford, J. I., Read, A. F., and Thomas, M. B. (2010). Influence of climate on malaria transmission depends on daily temperature variation. *Proc Natl Acad Sci USA*, 107(33):15135–15139.

Paaijmans, K. P., Read, A. F., and Thomas, M. B. (2009). Understanding the link between malaria risk and climate. *Proc Natl Acad Sci USA*, 106(33):13844–13849.

Paaijmans, K. P., Wandago, M. O., Githeko, A. K., and Takken, W. (2007). Unexpected high loses of anopheles gambiae lavae due to rainfall. *PLoS One*, 2(11):e1146.

Parham, P. E. and Michael, E. (2010). Modeling the effects of weather and climate change on malaria transmission. *Environmental Health Perspectives*, 118(5):620–626.

Patz, J. A., Githeko, A. K., McCarty, J. P., Hussein, S., Confalonieri, U., and de Wet, N. (2003). *Climate change and infectious diseases. In: McMichael AJ, Campbell-Lendrum DH, Corvalan CF, Ebi KL, Githeko AK, editors. Climate change and human health: risks and responses*. World Health Organization, Geneva.

Poisot, T. (2011). The digitize package: extracting numerical data from scatterplots. *The R Journal*, 3(1).

Ponnudurai, T., Lensen, A. H. W., Van Gemert, G. J., Bolmer, M. G., and Meuwissen, J. H. (1991). Feeding behaviour and sporozoite ejection by infected anopheles stephensi. *Trans. R. Soc. Trop. Med. Hyg*, 85(2):175–180.

Pukrittayakamee, S., Imwong, M., Singhasivanon, P., Stepniewska, K., Day, N. J., and White, N. J. (2008). Effects of different antimalarial drugs on gametocyte carriage in p. vivax malaria. *Am J Trop Med Hyg*, 79(3):378–384.

Reiner Jr, R. C., Geary, M., Atkinson, P. M., Smith, D. L., and Gething, P. W. (2015). Seasonality of plasmodium falciparum transmission: a systematic review. *Malaria Journal*, 14(343).

Reiter, P. (2001). Climate change and mosquito borne diseases. *Environmental Health Perspectives*, pages 223–234.

Robert, V., Dieng, H., Lochouarn, L., Traore, S., Trape, J.-F., Simondon, F., and Fontenille, D. (1998). La transmission du paludisme dans la zone de niakhar, sénégal. *Tropical Medicine & International Health*, 3(8):667–677.

Robert, V., Gazin, P., Boudin, C., Molez, J. F., Oudreaogo, V., and Carnevale, P. (1985). La transmission du paludisme en zone de savane arboree et en zone rizicole des environs de bobo dioulasso (burkina faso). *Annales de la Societe Belge de Medecine Tropicale*, 65(2):201–214.

Robert, V., Macintyre, K., Keating, J., Trape, J. F., Duchemin, J. B., Warren, M., and C, B. J. (2003). Malaria transmission in urban sub-saharan africa. *Am J. Trop. Med. Hyg.*, 68(2):169–176.

Robert, V., Ouari, B., Ouedraogo, V., and Carnevale, P. (1988). Etude écologique des culicidae adultes et larvaires dans une rivière en vallée du kou, burkina faso. *Acta tropica*, 45(4):351–359.

Roca-Feltrer, A., Schellenberg, J. R. M. A., Smith, L., and Carneiro, I. (2009). A simple method for defining malaria seasonality. *Malaria Journal*, 8(276).

Rosenberg, R., Wirtz, R. A., Schneider, I., and Burge, R. (1990). An estimation of the number of malaria sporozoites ejected by a feeding mosquito. *Trans R Soc Trop Med Hyg*, 84(2):209–212.

Ross, R. (1897). On some peculiar pigmented cells found in two mosquitos fed on malarial blood. *British Medical Journal*, 2:1786–1788.

Ross, R. (1915). Some priori pathometric equations. *Br Med J*, 1:447–546.

Rossi, P., Belli, A., Mancini, L., and Sabatinelli, G. (1986). [a longitudinal entomologic survey on the transmission of malaria in ouagadougou (burkina faso)]. *Parassitologia*, 28(1):1–15.

Rueda, L. M., Patel, K. J., Axtell, R. C., and Stinner, R. E. (1990). Temperature-dependent development and survival rates of culex quinquefasciatus and aedes aegypti(diptera: Culicidae). *Journal of Medical Entomology*, 27:892–898.

Sagara, I., Sangaré, D., Dolo, G., Guindo, A., Sissoko, M., Sogoba, M., Niambélé, M. B., Yalcoué, D., Kaslow, D. C., Dicko, A., et al. (2002). A high malaria reinfection rate in children and young adults living under a low entomological inoculation rate in a periurban area of bamako, mali. *The American journal of tropical medicine and hygiene*, 66(3):310–313.

Sharma, S. N., Shukla, R. P., Raghavendra, K., and Subbarao, S. K. (2005). Impact of ddt spraying on malaria transmission in bareilly district, uttar pradesh, india. *J Vector Borne Dis*, 42(2):54–60.

Shaukat, A. M., Bremen, J. G., and McKenzie, F. E. (2010). Using the entomological inoculation rate to assess the impact of vector control on malaria parasite transmission and elimination. *Malaria Journal*, 9(112).

Shiff, C. J., Minjas, J. N., Hall, T., Hunt, R. H., Lyimo, S., and Davis, J. R. (1995). Malaria infection potential of anopheline mosquitoes sampled by light trapping indoors in coastal tanzanian villages. *Medical and veterinary entomology*, 9(3):256–262.

Shililu, J., Ghebremeskel, T., Mengistu, S., Fekadu, H., Zerom, M., Mbogo, C., Githure, J., Novak, R., Brantly, E., and Beier, J. C. (2003). High seasonal variation in entomologic inoculation rates in eritrea, a semi-arid region of unstable malaria in africa. *Am. J. Trop. Med. Hyg.*, 69(6):607–613.

Shililu, J., Ghebremeskel, T., Seulu, F., Mengistu, S., Fekadu, H., Zerom, M., Asmelash, G., Sintasath, D., Mbogo, C., Githure, J., et al. (2004). Seasonal abundance, vector behavior, and malaria parasite transmission in eritrea. *Journal of the American Mosquito Control Association*, 20(2):155–164.

Shililu, J., Maier, W., Seitz, H., and Orago, A. (1998). Seasonal density, sporozoite rates and entomological inoculation rates of anopheles gambiae and anopheles funestus in a high altitude sugarcane growing zone in western kenya. *Tropical Medicine and International Health*, 3(9):706–710.

Singh, B. and Daneshvar, C. (2013). Human infections and detection of plasmodium knowlesi. *Clinical Microbiology Reviews*, 26(2):165–184.

Singh, J., Knapp, H. V., and Demissie, M. (2004). Hydrologic modeling of the iroquois river watershed using hspf and swat. Technical Report ISWS CR 2004-08, Department of Natural Resources and the Illinois State Geological Survey, Illinois State Water Survey.

Sinka, M. E., Bangs, M. J., Manguin, S., Coetzee, M., Mbogo, C. M., Hemingway, J., Patil, A. P., Temperley, W. H., Gething, P. W., Kabaria, C. W., Okara, R. M., Van Boeckel, T., Godfray, H. C. J., Harbach, R. E., and Hay, S. I. (2010). The dominant anopheles vectors of human malaria in africa, europe and middle east: Occurrence data, distribution maps and bionomic precis. *Parasites and Vectors*, 3(117).

Sinka, M. E., Bangs, M. J., Manguin, S., Rubio-Palis, Y., Chareonviriyaphap, T., Coetzee, M., Mbogo, C. M., Hemingway, J., Patil, A. P., Temperley, W. H., Gething, P. W., Kabaria, C. W., Burkot, T. R., Harbach, R. E., and Hay, S. I. (2012). A global map of dominant malaria vectors. *Parasites and Vectors*, 4(5:69).

Smith, T., Charlwood, J. D., Kihonda, J., Mwankusye, S., Billingsley, P., Meuwissen, J., Lyimo, E., Takken, W., Teuscher, T., and Tanner, M. (1993). Absence of seasonal variation in malaria parasitaemia in an area of intense seasonal transmission. *Acta tropica*, 54(1):55–72.

Snow, F. (1983). Mosquito production and species succession from an area of irrigated rice felds in the gambia, west africa. *Journal of Tropical Medicine and Hygiene*, 86:237–245.

Struik, S. S. and Riley, E. M. (2004). Does malaria suffer from lack of memory? *Immunol Rev*, 201:268–290.

Takken, W. and Lindsay, S. W. (2003). *Ecological aspect for application of genetically modified mosquitoes*. Kluwer academic publishers, Netherlands.

Tanga, M. C. and Ngundu, W. I. (2010). Ecological transition from natural forest to tea plantations: effect on the dynamics of malaria vectors in the highlands of cameroon. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 104(10):659–668.

Tanga, M. C., Ngundu, W. I., and Tchouassi, P. D. (2011). Daily survival and human blood index of major malaria vectors associated with oil palm cultivation in cameroon and their role in malaria transmission. *Tropical Medicine & International Health*, 16(4):447–457.

Tangpukdee, N., Krudsood, S., Srivilairit, S., Phophak, N., Chonsawat, P., Yanpanich, W., Kano, S., and Wilairatana, P. (2008). Gametocyte clearance in uncomplicated and severe plasmodium falciparum malaria after artesunate-mefloquine treatment in thailand. *Korean J Parasitol*, 46(2):65–70.

Tanser, C. F., Brian, S., and le Sueur, D. (2003). Potential effect of climate change on malaria transmission in africa. *Lancet Infect Dis*, 362:1792–1798.

Tassanakajon, A., Boonsaeng, V., Wilairat, P., and Panyim, S. (1993). Polymerase chain reaction detection of plasmodium falciparum in mosquitoes. *Trans R Soc Trop Med Hyg*, 87:273–275.

Taylor, K. A., Koros, J. K., Nduati, J., Copeland, R. S., Collins, F. H., and Brandling-Bennett, A. D. (1990). Plasmodium falciparum infection rates in anopheles gambiae, an. arabiensis, and an. funestus in western kenya. *The American journal of tropical medicine and hygiene*, 43(2):124–129.

Teklehaimanot, H. D., Lipsitch, M., Teklehaimanot, A., and Schwartz, J. (2004). Weather-based prediction of plasmodium falciparum malaria in epidemic-prone regions of ethiopia i. patterns of lagged weather effects reflects biological mechanisms. *Malaria Journal*, 3(41).

Thompson, M. C., Mason, S. J., Phindela, T., and Connor, S. J. (2005). Use of rainfall and sea surface temperature monitoring for malaria early warning in bostwana. *Am J Trop Med Hyg*, 73(1):214–221.

Thomson, M. C., Connor, S. J., D'Alessandro, U., Rowlingson, B., Diggle, P., Cresswell, M., and Greenwood, B. (1999). Predicting malaria infection in gambian children from satellite data and bed net use surveys: the importance of spatial correlation in the interpretation of results. *Am J Trop Med Hyg*, 61(1):2–8.

Tompkins, A. M. and Di Giuseppe, F. (2015). Potential predictability of malaria in africa using ecmwf monthly and seasonal climate forecast. *Journal of applied meteorology and climatology*, 54:521–540.

Tompkins, A. M. and Ermert, V. (2013). A regional-scale, high resolution dynamical malaria model that accounts for population density, climate and surface hydrology. *Malaria Journal*, 12(65).

Torres-Sorando, L. and Rodriguez, D. J. (1997). Models of spatio-temporal dynamics in malaria. *Ecol Model*, 104:231–240.

Trampuz, A., Jereb, M., Muzlovic, I., and Prabhu, R. M. (2003). Clinical review: Severe malara. *Critical Care*, 7(4):315–323.

Tshikuka, J. G., Scott, M. E., Gray-Donald, K., and Kalumba, O. N. (1996). Multiple infection with plasmodium and helminths in communities of low and relatively high socio–economic status. *Annals of Tropical Medicine and Parasitology*, 90:277–293.

Tusting, L. S., Bousema, T., Smith, D. L., and Drakeley, C. (2014). Measuring changes in plasmodium falciparum transmission: precission, accuracy and cost of metrics. *Advance Parasitol*, 84:151–208.

Vercruysse, J., Jancloes, M., and van de Velden, L. (1983). Epidemiology of seasonal falciparum malaria in an urban area in senegal. *Bull World Health Org*, 61:821–831.

Vittor, A. Y., Gilman, R. H., Tielsch, J., Glass, G., Shields, T., Lozano, W. S., Pinedo-Cancino, V., and Patz, J. A. (2006). The effect of deforestation on the human-biting rate of anopheles darlingi, the primary vector of falciparium malaria in the peruvian amazon. *Am. J. Trop. Med. Hyg*, 74(1):3–11.

Walsh, R. P. D. and Lawler, D. M. (1981). Rainfall seasonality spatial patterns and change through time. *Weather*, 36:201–208.

Wang, S. J., Lengeler, C., Smith, T. A., Vounatsou, P., Akogbeto, M., and Tanner, M. (2006). Rapid urban malaria appraisal (ruma) iv: epidemiology of urban malaria in cotonou (benin). *Malaria Journal*, 5(45).

Wang, S. J., Lengeler, C., Smith, T. A., Vounatsou, P., Diadie, D. A., Pritroipa, X., Convelbo, N., Kientga, M., and Tanner, M. (2005). Rapid urban malaria appraisal (ruma) i: epidemiology of urban malaria in ouagadougou. *Malaria Journal*, 4(43).

Warrell, D. A. (2002). *Clinical features of malaria. Essential Malariology. Edited by: Warrell, D A, Gilles, H M*. Oxford University Press, New York.

White, G. B. (1974). Anopheles gambiae complex and disease transmission in africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene.*, 68:278–302.

White, N. J. (2008). Plasmodium knowlesi:the fifth human malaria parasite. *Clinical Infectious Diseases*, 46:172–173.

White, N. J. (2011). The parasite clearance curve. *Malaria Jour*, 10(278).

White, N. J., Krishna, S., Waller, D., Craddock, C., Kwiatkowski, D., and Brewster, D. (1989). Open comparison of intramuscular chloroquine and quinine in children with severe chloroquine-sensitive falciparum malaria. *Lancet*, 2(8675):1313–1316.

WHO (1975). *Manual on Practical Entomology. Part II. Methods and Techniques*. World Health Organization, Geneva.

WHO (2000). Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene.*, 94(S1).

WHO (2014). World malaria report. *Transactions of the Royal Society of Tropical Medicine and Hygiene*.

WHO (2015). World malaria report. Technical report, World Health Organization.

Wilks, D. S. (1995). *Statistical Methods in Atmospheric Sciences*. Academic Press, San Diego.

Willmott, C. J., Ackleson, S. G., Davis, R. E., Feddema, J. J., Klink, K. M., Legates, D. R., O'Donnel, J., and Rowe, C. M. (1985). Statistics for the evaluation and comparison of models. *Journal of Geophysical Research*, 90(c5):8995–9005.

Wort, U. U., Hastings, I., Mutabingwa, T. K., and Brabin, B. J. (2006). The impact of endemic and epidemic malaria on the risk of stillbirth in two areas of tanzania with different malaria transmission patterns. *Malaria Journal*, 5(89).

Yamana, T. K., Bomblies, A., Laminou, I. M., Duchemin, J. B., and Eltahir, E. A. (2013). Linking environmental variability to village-scale malaria transmission using a simple immunity model. *Parasites Vectors*, 6(226).

Yang, H. M. (2000). Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector). *Revista de Saúde Pública*, 34(3):223–231.

Yang, H. M., Coutinho, F. A. B., and Massad, E. (1997). Acquired immunity on a schistosomiasis transmission model-fitting the data. *J Theor Biol*, 188(4):495–506.

Yeshiwondim, A. K., Gopal, S., Hailemariam, A. T., Dengela, D. O., and Patel, H. P. (2009). Spatial analysis of malaria incidence at the village level in areas with unstable transmission in ethiopia. *Int J Health Geogr*, 8(5).

Yorke, W. and Macfie, J. W. S. (1924). Observations on malaria made during treatment of general paralysis. *Trans R Soc Trop Med Hyg*, 18:13–44.

Yé, Y., Louis, V. R., Simboro, S., and Sauerborn, R. (2007). Effect of meteorological factors on clinical malaria risk among children: an assessment using village-based meteorological stations and community-based parasitological survey. *BMC Public Health*, 7(101).

Zharov, A. A. (1992). Observations on malaria vectors in mozambique. i. the status of anopheles populations before the start of mosquito control. *Meditsinskaia parazitologiia i parazitarnye bolezni*, (3):23.

Zhou, G., Munga, S., Minakawa, N., Githeko, A. K., and Yan, G. (2007). Spatial relationship between adult malaria vector abundance and environmental factors in western kenya highlands. *Am J Trop Med Hyg*, 77:29–35.

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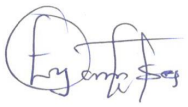
Declaration

I hereby declare that this thesis is my own work towards the PhD and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

Cologne, 25th October 2016.



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