Developing Bayesian spatio-temporal models to assess the relation between malaria transmission and mortality in Burkina Faso

Inauguraldissertation
zur
Erlangung der Würde eines Doktors der Philosophie

vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät der
Universität Basel

von
Eric Diboulo
aus Ouagadougou, Burkina Faso

Basel, 2016

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von
Prof. Dr. Jürg Utzinger, PD Dr. Penelope Vounatsou und Prof. Dr. Thomas Junghanss.

Basel, den 21. Juni 2016

Prof. Dr. Jörg Schibler
Dekan

…to my beloved late Father, **DIBOULO Nienfou Anatole Assomption**

Table of contents

List of figures

List of tables

Summary

Background

Malaria control remains a major public health challenge especially in sub-Saharan African countries. In spite of the rapid decline observed in malaria mortality in Africa over the last decade due to scaling up of control interventions and social/economic development, malaria mortality figures remain unacceptably high.

An estimated 198 million cases of malaria worldwide led to nearly 584,000 deaths in 2013. The majority of the illnesses (85%) and the case fatalities (90%) occur in Africa taking its greatest toll among young children under five years of age. Beside the deaths toll, repeated clinical malaria episodes cast an enormous economic burden on households.

Predicting the effectiveness of malaria interventions at a given place requires appropriate information on both mortality and transmission levels in order to ascertain the level of efforts required to achieve a significant reduction in morbidity as well as the number of deaths that could be prevented.

This quantitation is needed for estimating the burden of the disease based on different transmission levels and for building models, which incorporate this relationship in order to predict the likely effects of malaria interventions on mortality. Yet, for many of the sub-Saharan countries, most severely burdened by malaria, these crucial estimates are lacking making it difficult to accurately predict the likely impact of malaria interventions on mortality.

The Malaria Transmission Intensity and Mortality Burden Across Africa, INDEPTH-MTIMBA project was initiated in the 2002 in a number of Health and Demographic Surveillance Systems (HDSS) sites. HDSS are sites that are routinely monitor all life events in a certain area and are used for estimating mortality in the absence of complete registration of deaths and births in many developing countries. The MTIMBA project aimed at assessing the levels of malaria transmission intensity, establishing the relationship between all-cause, malaria-specific mortality and malaria transmission intensity taking into account the effect of disease control interventions. MTIMBA collected georeferenced entomological data, biweekly during a period of 3-4 years. One of the HDSS sites of the MTIMBA project was Nouna in Burkina Faso, however data have not yet been analysed. Previous studies have tried to assess the relation between malaria endemicity and mortality using mortality data from the Demographic Health Surveys (DHS) and malaria data from Malaria Indicator Survey (MIS). In Burkina Faso, the DHS-Multiples Indicator Cluster Survey

(BFDHS-MICS) of 2010 was the first survey that collected georeferenced data of both child mortality and malaria endemicity across the country.

Goal and objectives

The overall goal of the thesis is to assess the association between malaria transmission and mortality at different geographical scales in Burkina Faso. The specific objectives of the research are to (i) obtain time-dependent and spatially explicit estimates of entomological inoculation rate (EIR) within the Nouna HDSS site; (ii) obtain spatially explicit estimates of malaria parasite risk, number of infected children and assess the effects of malaria interventions in Burkina Faso; (iii) assess the relation between infant and under-five mortality and malaria endemicity in Burkina; (iv) assess the relationship between malaria transmission and mortality (all-cause and malaria-specific) across different age groups in Nouna HDSS and (v) assess the ability of verbal autopsies to diagnose malaria as a cause of death using the malaria-transmission relation as a gold standard. We addressed the above objectives by employing Bayesian spatio-temporal models and analysing the Burkina Faso DHS (BFDHS-MICS) 2010, the MTIMBA and the mortality databases from the Nouna HDSS site.

Methods

In chapter 2, the MTIMBA data were analysed to obtain surfaces of malaria transmission across the Nouna HDSS. In particular, Bayesian geostatistical zero-inflated binomial and negative binomial models including harmonic seasonal terms, temporal trends and climatic remotely sensed proxies were applied to assess spatio-temporal variation of sporozoite rate and mosquito density in the study area. Bayesian variable selection was applied to determine the most important climatic predictors and elapsing (lag) time between climatic suitability and malaria transmission. Bayesian kriging was used to predict mosquito density and sporozoite rate at unsampled locations. These estimates were converted to covariate and season-adjusted maps of entomological inoculation rates. The results showed that *Anopheles gambiae* is the most predominant vector (79.3%) and is more rain-dependant than its sibling *Anopheles funestus* (20.7%). Variable selection suggested that the two vector species react differently to different climatic conditions.

Prediction maps of EIR depicted a strong spatial and temporal heterogeneity in malaria transmission risk despite the relatively small geographical extend of the study area.

In chapter 3, Bayesian geostatistical models and BFDHS-MICS 2010 survey data were used to assess the effects of health interventions related to insecticide-treated nets (ITNs), indoor residual spray (IRS), artemisinin-based combinations therapy (ACT) coverage associated with childhood malaria parasite risk at national and sub-national level after taking into account geographical disparities of climatic/environmental and socioeconomic factors. Several ITN coverage measures were calculated and Bayesian variable selection was used to identify the most important ones. Parasitaemia risk surfaces depicting spatial patterns of infections were estimated. The results showed that the population adjusted predicted parasitaemia risk ranges from 4.0 % in Kadiogo province to 82% in Kompienga province. The effect of ITN coverage was not important at national level; however, ITNs had an important protective effect in Ouagadougou as well as in three districts in the western part of the country with high parasitaemia prevalence and low-to-moderate coverage. There was a large variation in ACT coverage between the districts. Although at national level the ACT effects on parasitaemia risk was not important, at sub-national level, 18 districts around Ouagadougou delivered effective treatment.

In chapter 4, we used data form the Burkina Faso first nationally representative household survey focusing on malaria-related indicators, BFDHS-MICS 2010 and apply Bayesian geostatistical Weibull survival models to explore the relationship between malaria and infant/child mortality in Burkina Faso after adjusting for, both individual child and household or family characteristics as well as mother's birth history. There is a significant relationship between malaria endemicty and child survival in urban settings. Children living in the urban settings with endemicity level above 75% are at higher mortality hazards. Other predictors of infants and child survival are those related to biological (birth size, mother age at birth), demographic socioeconomic and antenatal care factors.

In chapter 5, we used entomological data, which, were collected biweekly from 2001-2004, and mortality data extracted from the Nouna HDSS database. We address spatial misalignment between the two data sources by obtaining EIR estimates at the mortality locations using Bayesian spatio-temporal models. Analyses were adjusted for socioeconomic status (SES) and ITN coverage. Time to death was treated at

monthly interval and Bayesian geostatistical logistic regression approximating Cox proportional hazard model and incorporating the predicted EIR as covariate with measurement error were fitted. The mortality rates were highest in 2001, 17 (95% CI: 15.1, 19.1) and 2003, 13.8 (95% CI: 12.95, 14.8). The overall mortality rate over the study period was 11.3 (95% CI: 10.8, 11.7). The highest mortality rates were observed in children and old age groups with the respective rates of 23.9 (95% CI: 22.4, 25.4) and 81.9 (95% CI: 75.8, 88.5). A positive log-natural relationship between mortality and EIR was found among children (1-4 years), while a protective effect was found among adolescents/adults (15-59 years). The highest mortality risk associated with EIR was observed among children (5%).

In chapter 6, we used the same approach as in the previous chapter however focusing the interest on malaria specific mortality in order to assess the relationship between malaria specific mortality and EIR within the Nouna MTIMBA-HDSS site. The sensitivity and specificity of the physician-certified verbal autopsy (PCVA) were also assessed. Results showed that malaria mortality rates were highest in years 2001, 5.4 (95% CI: 4.4, 6.6) and 2003, 4.1 (95% CI: 3.6, 4.7). A significant positive natural logarithmic relationship was found between malaria exposure and mortality among children, with hazard ratio (HR) of 1.06 (95% CI: 1.03, 1.08). The percentage of deaths assigned-malaria as cause in VA was highest in children and adults with respectively 45% and 35.3%. The percentage of deaths attributable to malaria exposure was in old-age group (93.9%). The overall specificity of the PCVA is 0.70

Conclusion/ significance

Results of this work contribute to a better understanding of the interplay between environmental/climatic conditions and malaria transmission, which is important not only for delivering interventions at the right time but also for developing predictive models to support early warning systems (EWS).

The estimated risk and intervention effect maps are valuable tools for identifying high-risk areas and areas with less effective interventions in order to improve malaria control in Burkina Faso. These outputs can serve as benchmarks to evaluate the effectiveness of future control interventions and progress of the efforts towards disease control.

Results from the mortality-malaria transmission analyses improve our understanding of the relationship between malaria transmission, all-cause and malaria specific mortality in Nouna region.

Acknowledgements

I wish to acknowledge a number of people who have contributed to this thesis either directly or indirectly. First and foremost, this thesis would not have materialized without the great scientific support, the mentorship and the patience of my thesis supervisor PD. Dr. Penelope Vounatsou. Thanks for sharing your vast experience with me.

I also like to express my gratitude to Prof. Dr. Tom Smith for accepting me as MSc student in the framework of the MTIMBA project. I appreciate the time we spent together talking about malaria vector bionomics. Special thanks to Prof. Don de Savigny, Prof. Christian Lengeler, PD Dr. Christian Schindler, Dr. Allan Schapira, Prof Guéladio Cissé, Dr. Konstantina Boutsika, Dr. Nakul Chitnis, Dr. Nicolas Maire, Mr. Aurelio Di Pasquale and Dr. Melissa Penny.

Special thanks also go to Prof. Dr. Thomas Junghanss, who was willing to act as the co-referee for this thesis.

Many thanks go to Christine Mensch for her various supports, and to Margrit Slaoui, Zsuzsanna Györffy, Maya Zwygart, Dagmar Batra, Christine Walliser, and Beatrice Wäckerlin. I also like to extend my gratitude to the Informatics and library sections. Thanks Steven Paul for being such a great friend to me. I would like to thank all the Swiss TPH staff for the conducive and supportive environment that enabled me to achieve this work.

Many thanks also go to Prof. Dr. Mitchell Weiss and Prof. Dr. Nino Kunzli for creating a good working environment at the Department of Epidemiology and Public Health (EPH). My heartfelt thanks go to Prof. Marcel Tanner and Prof. Jürg Utzinger for their various supports and kindness.

Many thanks go to the current and former Biostatistics unit members. In particular, I would like to thank Dr. Nadine Schur, Dr. Ronaldo Scholte, Dr. Laura Goşoniu, Dr. Dominic Goşoniu, Dr. Federica Giardina, Dr. Verena Jürgens, Dr. Frédérique Chammartin, Dr. Dimitrios-Alexios Karagiannis-Voules, Sammy Khagayi, Abbas Adigun, Dlamini Sabelo Nick for your friendship and support. To Dr. Astrid Knoblauch, many more

thanks for friendship. Special thanks go to the MTIMBA team: Dr. Simon Kasasa, Dr. Amek Ombek Nyaguara, Dr. Susan Rumisha and Dr. Bernadette Huho. Thanks for your friendship and support.

I enjoyed the friendship of many fellow students and other people I met in Basel. To mention a few, I would like to thank the colleagues. Dr. Henry Mwanyika, Dr. Boniphace Idindili, Dr. Angelina Lutambi, Dr. Bernadette Huho, Dr. Pax Masimba, Simon Vendeline, Dr. Rashid Khatibu, Harris Héritier, Dr. Ikenna Eze, Dr. Youssouf Kanoute, Dr. Henry Owusu, Dr. Henry Ntuku, Dr. Giovanfrancesco Ferrari, Dr. Joëlle Schwarz, Jennie Jaribu, and any whom I may have forgotten. To Mr. Suleiman Jembe, thanks for the brotherhood.

Back in Burkina Faso, my heartfelt thanks go to Dr. Ali SIE, the Director of the Centre de Recherche en Santé de Nouna (CRSN) for his leadership and support during this PhD time. I would also like to extend my gratitude to Dr. Maurice YE, the deputy Director of CRSN and Dr. Coulibaly Aboubacar. I'm deeply indebted to the whole staff of CRSN for their support and collaboration.

I'm forever indebted to my parents, my family for the sacrifices and prayers. May our Lord; the Almighty rewards all your efforts. Thank you Maman for all your efforts and relentless prayers.

I thank the MTIMBA principal investigators (PIs) for conceptualization of the project: Dr. Salim Abdullah, Dr. Ricardo Thompson, Dr. Diadier Diallo, Dr. Seth Owusu-Agyei and Dr. Honorati Masanja.

This thesis is dedicated to my beloved late Father, **DIBOULO Nienfou Anatole Assomption** who has always wished to see me further my studies.

Finally I thank and praise the Lord of hosts, the Almighty for laying his hands on me.

This work was funded by the Swiss National Science Foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286.

Chapter 1: Introduction

1.1 Malaria Burden

Malaria control remains a major public health challenge. An estimated 198 million CI [124; 283] cases of malaria worldwide led to nearly 584,000 CI [367,000; 755,000] deaths in 2013. The majority of illnesses (85%) and case fatalities (90%) occur in Africa taking its greatest toll among young children under five years of age ("WHO | 10 Facts on Malaria" 2015). About 3.2 billion people, almost half of the world's population apportioned in about 105 countries mainly in the tropics and subtropical regions are at risk of infection. Figure 1.1 shows the global distribution of malaria risk.

Malaria represents the leading cause of medical consultation in Burkina Faso. Among children under five years of age, malaria accounted for 61.4% of medical consultations, 77.7% of hospitalizations, and was responsible for almost 80% of deaths in 2011 (INSD 2012).

According the national health statistics, 8,278,408 malaria cases were recorded in the country in 2014, of which 463 774 were severe malaria cases leading to 5632 deaths ("Conseil National de La Statistique" 2016). The overall prevalence of infection in children aged 6-59 months is estimated at 46 % (microscopy test) ("Burkina Faso - Enquête Sur Les Indicateurs Du Paludisme 2014" 2016).

The Disability-adjusted life years (DALYs) quantify both premature mortality (YLLs) and disability (YLDs) within a population. In Burkina Faso, the top three causes of DALYs in 2015 were malaria, diarrheal diseases, and lower respiratory infections ("Global Burden of Disease (GBD)" 2016). Malaria however accounted for the highest premature death in the country with YLLs estimated at 7,623.3 in 2013 ("Global Burden of Disease (GBD)" 2016).

Beside the deaths toll, repeated clinical malaria episodes cast an enormous economic burden on households. Burkina Faso ranks among the world's poorest countries and the food production system relies on rain-fed agriculture. The farming system is still rudimentary and requires massive manpower just to ensure minimum production. The peak of malaria transmission occurs during the rainy season where maximum manpower is needed, therefore casting every year a huge uncertainty on the food security.

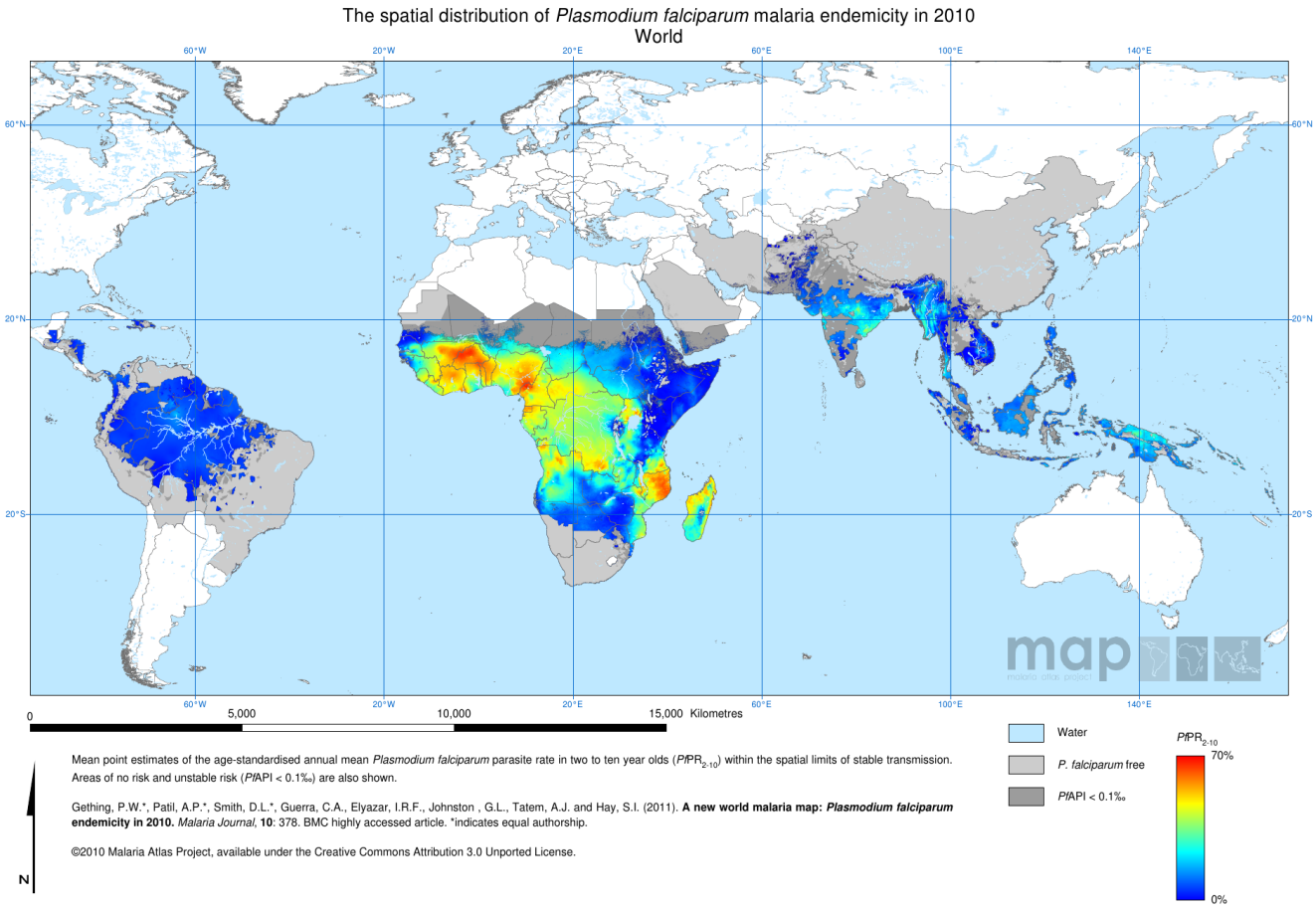


Figure 1.1. Global *Plasmodium falciparum* endemicity

1.2 Malaria disease and transmission

Malaria is a vector-borne infectious disease caused by protozoan parasites of the genus Plasmodium transmitted by a bite from an infective mosquito. There are four malaria parasite species (plasmodia) that cause malaria in humans, namely *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, with *P. falciparum* being the most common species in the tropics including sub-Saharan Africa (SSA) (Rogerson and Carter 2008). The parasite develops into two phases, the asexual phase within the human host and the sexual phase taking place within the mosquito (John C. Beier 1998). Figure 1.2 shows the life cycle of malaria parasite.

The first phase of malaria transmission begins when an infective female (carrying malaria-causing parasites) mosquito injects the parasite (sporozoites) into a human blood stream. The sporozoites then

travel to the liver cells where they rapidly multiply asexually become invasive and transform into merozoites. The duration of this process depends on the species of *Plasmodium*. However some parasites species such as *P. vivax* can remain dormant for a longer period in the liver, causing relapses even several years after the first attack (Krotoski 1989; Cogswell 1992). The liver schizonts become mature and rupture, releasing the merozoites into the blood stream. The merozoites then invade the red blood cells (erythrocytes) after their release and evolve into ring-shaped called trophozoites, which in turn form schizonts where new merozoites develop and are released into the blood stream thereafter.

The simultaneous waves of merozoites escaping and infecting more erythrocytes lead to symptomatic malaria disease and complication of malaria if not treated. Part of the merozoites develops into male and female gametocytes after going into couple of schizogonic cycles.

When a female mosquito bites an infected human, it ingests the gametocytes, which within the mosquito further mature into gametes and sexual replication takes place, producing zygotes. The zygotes further develop into mature oocytes that burst releasing sporozoites, which migrate to salivary glands of the mosquito. These sporozoites are injected when the mosquito take a blood meal on another human and thus begins a new life cycle (Garnham 1988). The life cycles of all human plasmodia species are similar but only vary in the length of time required to complete a particular phase. For instance, the exoerythrocytic cycle takes 43 to 48, 50 and 72 hours respectively for *P. falciparum* and *P. vivax*, *P. ovale* and *P. malariae* infections (Garnham 1988).

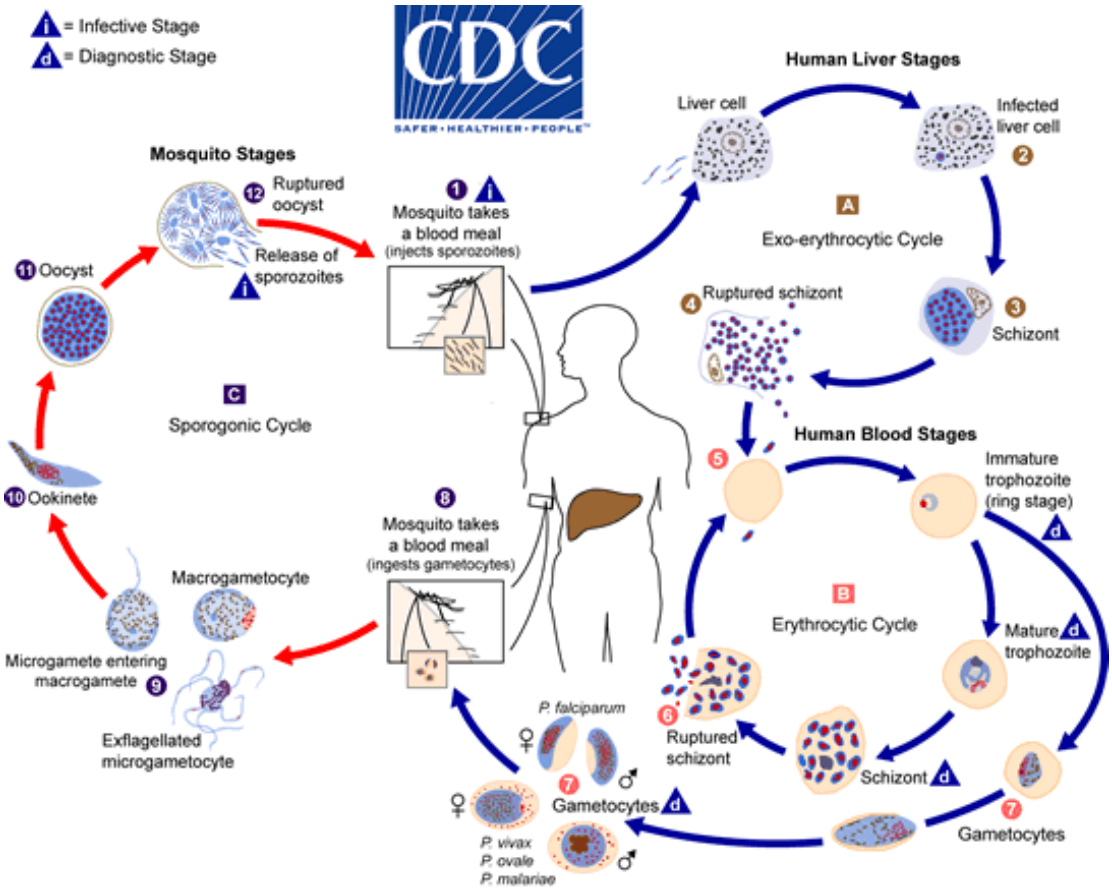


Figure 1.2. Life cycle of malaria parasite

1.3 Malaria vectors

1.3.1 Vectors species

Malaria vectors consist of about four hundred and sixty-two (462) species of Anopheles with unique behaviors associated with ecological factors (Lindsay, Parson, and Thomas 1998). About 50-60 species have the potential of transmitting human malaria (Sinka et al. 2010). From these, *Anopheles gambiae* complex (*An. gambiae* sensu stricto, *An. arabiensis*, *An. quadriannulatus*, *An. bwambae*, *An. merus* and An. *melas*) (Coetzee, Craig, and le Sueur 2000) and *Anopheles funestus* are the main vectors associated with malaria transmission in Africa which bears the highest burden of malaria infection. These vectors, which often co-occur geographically across most sub-Saharan Africa, have different behavioral characteristics and feeding preferences. For instance *Anopheles gambiae sensu stricto*, the most efficient malaria vector, breeds in rice fields, sunlit natural and man-made pools, and puddles. It is mainly endophilic (rest indooors) and endophagic (feed indoors). *An. gambiae* and *An. arabiensis* favour pools produced by rainfall. *An. arabiensis* has similar biting and breeding characteristics except that it tends to

prefer arid areas, bites domestic animals and rests outdoors. *An. funestus* prefers shaded habitats and breeds in permanent waters, especially with vegetation. It bites humans and domestic animals and is both endophilic and exophilic.

In Burkina Faso, malaria transmission occurs throughout the year and is sustained by two sympatric sibling anopheles species: *An. gambiae* and *An. funestus.* It is therefore important to investigate how these species react to the different climatic/environmental conditions.

1.3.2 Entomological inoculation rate

The entomological inoculation rate (EIR) is a commonly used measure of the intensity of malaria transmission. It estimates the number of infective bites an individual receives per unit time. EIR is the product of the "human biting rate" and the sporozoite rate (SR). The SR is the fraction of mosquitoes with sporozoites in their salary glands (J. C. Beier, Killeen, and Githure 1999). The "human biting rate" refers to the number of mosquito bites a person receives per unit time. It is obtained by mosquito collection techniques such as pyrethrum sprays collection, light trap and human landing catch (HLC). The latter is measured by the number of mosquitoes trying to feed on an individual. Although EIR estimates may not be accurate as mosquito density is markedly heterogeneous and sporozoite rates are usually very low even in high endemic areas, it is still considered as the gold standard for estimating the transmission intensity (Drakeley et al. 2005; Ndebele and Musesengwa 2012).

1.4 Factors influencing malaria transmission

1.4.1 Climatic/environmental factors

Malaria transmission and distribution is greatly influenced by environmental and climatic factors. Indeed both the mosquito development and survival as well as incubation period before an infected human develops symptoms of malaria strongly depend on prevailing climatic conditions (Y. Yé 2008; Walker et al. 2013; Knols 2009).

The effects of temperature on the transmission cycle of the malaria parasite are manifold, but its specific effects on sporogonic duration and mosquito survival are the most important (Onori and Grab 1980; Targett 1990). The lower limit of temperature suitability is determined by the number of mosquitoes

surviving the incubation period while parasite development only ceases at 16°C, transmission below 18°C is unlikely because few adult mosquitoes survive the 56 days required for sporogony at that temperature, and because mosquito abundance is limited by long larval duration. At 22°C sporogony is completed in less than three weeks and mosquito survival is sufficiently high (15%) for the transmission cycle to be completed. Thus, temperatures below 18°C were considered unsuitable, and above 22°C, suitable for stable transmission (Craig, Snow, and le Sueur 1999b).

The upper limit of temperature suitability is determined by vector survival, as sporogony takes less than a week. Temperatures of above 32°C have been reported to cause high vector population turnover. Thermal death for mosquitoes occurs around 40–42°C (Haddow 1943) and daily survival is zero at 40°C (Hay, Snow, and Rogers 1998).

There is an apparent ostensibly simple association between particular rainfall and increased abundance of mosquitoes. Studies have demonstrated the relationship between malaria vector abundance and rainfall (J. d. Charlwood et al. 1995; R 1987). Malaria transmission pattern follows the rainfall distribution. Mosquito population increases in the middle of the rainy season and reaches a peak in the early part of the dry season.

The duration of the rainfall season is also important. In regions where temperature is high but rainfall is limited mosquito populations increase rapidly at the onset of rain, because of short developmental cycles (Craig, Snow, and le Sueur 1999b). However, where temperature is limited during the colder season, mosquito populations increase slowly at the onset of rain, with gradually rising temperatures, owing to long developmental cycles.

Altitude also plays a role in malaria transmission. Temperature is directly related to the altitude of an area. Temperature decreases as altitude increases and consequently the mosquito population decreases; Therefore vector species and transmission intensity change with altitude (Kristan et al. 2008).

1.4.2 Interventions

Vector control is the main way to prevent and reduce malaria transmission. A measure of protection is conferred across the community in a place with high coverage of vector control interventions. World Health Organization (WHO) recommended a number of interventions, which reduce malaria transmission.

1.5 Malaria control interventions

1.5.1 Control interventions

Ambitious new goals for control of malaria have been set and significant additional resources for malaria control have been mobilized over the last ten years (de Savigny and Binka 2004). This allowed rapid scaling-up of effective vector control interventions including insecticide-treated nets (ITNs) and indoor residual spraying (IRS), intermittent preventive treatment during pregnancy (IPTp) as well as the development of effective antimalarials in the form of artemisinin-combination therapy (ACTs).

The main building bloc of malaria vector control is mass population coverage with insecticide-treated nets (ITNs). Treatment of mosquito nets with synthetic insecticides began in the 1970s and led to findings of dramatic reductions in mortality and morbidity where they were employed in carefully controlled trials (Alonso et al. 1993; Diallo et al. 2004). New tools for scaling up the impact of malaria control involved the introduction of long-lasting insecticide treated nets (LLINs), the rollout of rapid diagnostic tests (RDTs) in many countries, and the scaling-up of ACTs (Steketee et al. 2008).

1.5.2 Quantification of intervention coverage

Roll Back Malaria Partnership together with MEASURE Evaluation, MEASURE DHS, President's Malaria Initiative, UNICEF and World Health Organization developed in 2013 the household survey indicators for malaria control. Malaria indicator surveys (MIS) rely on household questionnaires to obtain information about insecticide-treated bednets, indoor residual spraying, prompt and effective treatment of fever in young children, prevention of malaria in pregnant women and measurement of malaria parasiteamia and anaemia in children younger than 5 years. This information can be used to construct key coverage indicators in order to quantify coverage of malaria interventions in relation to the Global Malaria Action Plan (GMAP) targets. For instance, the universal access to community case management (CCM) of

malaria can be assessed by measuring the proportion receiving any ACT or first line treatment among children under five years old with fever in the last two weeks. Similarly, progress towards the universal access and utilization of preventive measures can be quantified by measuring the proportion of population with access to an ITN within their household and the proportion of the population that slept under an ITN the night preceding the survey. The universal coverage of vector control intervention can be estimated through the proportion of households sprayed with IRS in the last 12 months.

1.6 Malaria transmission and mortality

A large proportion of childhood deaths in malaria endemic settings are attributed to malaria infection (T. A. Smith, Leuenberger, and Lengeler 2001a). However, the precise nature of the relation between malaria transmission intensity and mortality is still unclear (T. A. Smith, Leuenberger, and Lengeler 2001a; A. Gemperli et al. 2004a). Malaria interventions aim at reducing of the transmission intensity to a level where the disease is no more a public health challenge. However, it is hypothesized that interventions targeting reduction of malaria exposure might delay the acquisition of the natural immunity, thus shifting the burden of the disease to an older age group (Doolan, Dobaño, and Baird 2009; R. W. Snow et al. 1997).

A better understanding of the relationship between malaria transmission intensity mortality is needed for an accurate prediction of the effectiveness of malaria interventions at a given place. This requires appropriate information on both mortality and transmission levels in order to derive the level of reduction in transmission to achieve a significant reduction in morbidity as well as the number of deaths that will be prevented. However, for many of the sub-Saharan countries, most severely burdened by malaria, this crucial information is lacking making it difficult to accurately predict the likely impact of malaria interventions on mortality.

1.7 Verbal autopsy (VA)

Most of the current estimates of malaria-attributable cause of death in sub-Saharan African countries are derived from the verbal autopsy (VA) approaches (França et al. 2011; Byass et al. 2016). VA entails interviewing the main caregiver on the background characteristics of the deceased using structured filter questions on the specific signs and symptoms experienced by the deceased. Information from the VA forms are independently reviewed by at least three experienced physicians (M. Yé et al. 2011b). The underlying cause is defined as the disease or injury that initiated the train of events leading directly to death. Recently alternative computer-coded verbal autopsy (CCVA) methods have gained interest, as ways to improve inter-observer agreement, consistency and comparability, and to make the coding of VAs faster and cheaper. CCVAs can be broadly classified in two groups namely the classic Bayes classifiers and the automated classifiers (Miasnikof et al. 2015).

1.8 Malaria spatio-temporal data

Malaria data (i,e parasitological or entomological) are often collected at fixed locations (e.g. households, villages). They are known as geostatistical data and are often correlated in space because "individuals" at nearby locations share similar exposures and their responses vary in a similar way. Malaria data collected repeatedly over time are also correlated in time and are known as temporal data. Standard statistical methods assume independence of the outcome observations. This assumption does not hold when data are correlated. To avoid wrong inferences correlations should be taken into account when modelling spatio-temporal data. Geostatistical models introduce spatial correlation by a Gaussian process on location-specific random effects. Correlation is often taken to be a function of distance between any pair of locations (Banerjee et al. 2008; Banerjee, Carlin, and Gelfand 2014). These models have large number of parameters and Bayesian formulations are adopted to enable parameter estimation via the powerful Markov chain Monte Carlo (MCMC) simulation methods. Temporal correlation is taken into account by temporal random effects that are modelled via time series models (e.g. autoregressive). Bayesian geostatistical and temporal models have been used to analyse malaria survey data and produce malaria risk maps or assess effects of malaria interventions in space (G. D. Gosoniu 2006; Gosoniu, Veta, and Vounatsou 2010; Laura Gosoniu et al. 2012a; Riedel et al. 2010; Giardina et al. 2012; Giardina et al. 2014) They have been also

applied to entomological data to estimate malaria transmission exposure surface (Amek et al. 2013; Kasasa et al. 2013; Rumisha et al. 2013).

1.9 Objectives of the thesis

The overall goal of the thesis is to assess the association between malaria transmission and mortality at different geographical scales in Burkina Faso.

Specific objectives

1. To obtain time-dependent and spatially explicit estimates of entomological inoculation rate (EIR) within the Nouna HDSS site.
2. To obtain spatially explicit estimates of malaria parasite risk, number of infected children and assess the effects of malaria interventions in Burkina Faso.
3. To assess the relation between infant and under-five mortality and malaria endemicity in Burkina.
4. To assess the relationship between malaria transmission and mortality (all-cause and malaria-specific) across different age groups in Nouna HDSS.
5. To assess the ability of Verbal Autopsies to diagnose malaria as a cause of death using the malaria – transmission relation as a gold standard.

We addressed the above objectives by employing Bayesian spatio-temporal models and analysing known malaria data such as the Burkina Faso Health and Demographic Survey-Multiple Indicator Cluster Surveys of 2010 (BFDHS-MICS 2010), the MTIMBA and the mortality databases from the Nouna HDSS site.

Chapter 2: Bayesian variable selection in modelling geographical heterogeneity in malaria transmission from sparse data: An application to Nouna Health and Demographic Surveillance System (HDSS) data, Burkina Faso

Eric Diboulo[1, 2,3], Ali Sié[3], Diallo D. Diadier[4], Dimitrios A. Karagiannis Voules[1, 2], Yazoume Yé[5], Penelope Vounatsou[1 §]

[1]Swiss Tropical and Public Health Institute, Basel, Switzerland
[2]University of Basel, Basel, Switzerland
[3]Centre de Recherche en Santé de Nouna, Burkina Faso
[4]PATH Malaria Vaccine Initiatives, Senegal
[5]IFC International, Bowie, Maryland, USA

[§]Corresponding author

This paper has been published in *Parasites & Vectors* 2015 8:118

Abstract

Background: Quantification of malaria heterogeneity is very challenging partly because of the underlying characteristics of mosquitoes and also because malaria is an environmentally driven disease. Furthermore in order to assess the spatial and seasonal variability in malaria transmission, vector data need to be collected repeatedly over time (at fixed geographical locations). Measurements collected at locations close to each other and over time tend to be correlated because of common exposures such as environmental or climatic conditions. Non-spatial statistical methods, when applied to analyse such data may lead to biased estimates. We developed rigorous methods for analysing sparse and spatially correlated data. We applied Bayesian variable selection to identify the most important predictors as well as the elapsing time between climate suitability and changes in entomological indices.

Data and Method: Sporozoite and mosquito density data collected over 500 locations in Nouna HDSS during 2001 and 2003 were extracted from the Malaria Transmission Intensity and Mortality Burden in Africa (MTIMBA) database. Bayesian geostatistical zero-inflated binomial and negative binomial models including harmonic seasonal terms, temporal trends and climatic remotely sensed proxies were applied to assess spatio-temporal variation of sporozoite rate and mosquito density in the study area. Bayesian variable selection was employed to determine the most important climatic predictors and elapsing (lag) time between climatic suitability and malaria transmission. Bayesian kriging was used to predict mosquito density and sporozoite rate at unsampled locations. These estimates were converted to covariate and season-adjusted maps of entomological inoculation rates. Models were fitted using Markov chain Monte Carlo simulation.

Results: The results show that *Anopheles gambiae* is the most predominant vector (79.29%) and is more rain-dependant than its sibling *Anopheles funestus* (20.71%). Variable selection suggests that the two species react differently to different climatic conditions. Prediction maps of entomological inoculation rate (EIR) depict a strong spatial and temporal heterogeneity in malaria transmission risk despite the relatively small geographical extend of the study area.

Conclusion: Malaria transmission is very heterogeneous over the study area. The EIR maps clearly depict a strong spatial and temporal heterogeneity despite the relatively small geographical extend of the study area. Model based estimates of transmission can be used to identify high transmission areas in order to prioritise interventions and support research in malaria epidemiology.

Keywords: Bayesian, zero-inflated, negative binomial, stochastic search variable selection, entomological inoculation rate, Burkina Faso, Sub-Saharan Africa, Nouna HDSS, lag time

2.1 Introduction

Malaria is endemic in the majority of sub-Saharan Africa. It is transmitted from human to human via bites of mosquitoes infected with malaria parasites. A favourable environment and a complex system of malaria vectors and parasites maintain this endemicity. The mosquito development and survival strongly depend on prevailing climatic and environmental factors which in turn influence malaria transmission (Y. Yé 2008). The species of vectors and their densities, the species of the malaria parasites, the number of infected bites a human received per night (a parameter known as the entomological inoculation rate, EIR) can change from place to place and according to the season. Therefore, malaria distribution is very heterogeneous within a geographical area and prone to between and within village variation (Greenwood 1989; Carter, Mendis, and Roberts 2000).

There are two main species of malaria vector, the *Anopheles gambiae* and *Anopheles funestus.* They differ in among others things, the type of water bodies in which they lay their eggs, their propensity to bite humans, the length of time for which they survive, the place where they rest after feeding, and time of the day when they bite. *An. gambiae*, the most efficient malaria vector, breeds in rice fields, sunlit pools both natural and man-made, and puddles. It is mainly endophilic (rests indoors) and also endophagic (feeds indoors) and favors pools produced by rainfall. *An. funestus* prefers shaded habitats and breeds in permanent waters, especially with vegetation. It bites humans and domestic animals and is both endophilic and exophilic (Guelbeogo et al. 2009). Understanding the vector species' behavior and their interrelation with the environment is of prime importance in order to develop timely and effective intervention programs.

There is an elapsing time between climatic suitability, abundance of mosquito densities and onset of transmission. Changes in entomological parameters such as EIR depend on lag times and therefore it is important to take lag time into account in order to deliver timely and tailored interventions. A number of studies have used remote sensing (RS) climatic and environment proxies together to identify species-specific climatic predictors however few rigorously incorporate lag times into the analysis. RS data are often summarized by a long term average over a period of time prior to entomological data collection which is often considered as fixed rather than estimated by the data (Rumisha et al. 2014; Amek et al. 2012).

Estimating the lag times is not only important for delivering interventions but also for obtaining good predictive models to assess the distribution of mosquitos' density. Entomological data are sparse and clustered in space and time due to spatial clustering of the environmental exposures and seasonality in transmission. Often the data include a large number of zeros (i.e. mosquito presence and/or infected) especially during the dry season. Zeros with frequencies higher than those expected by the data distribution, (for counts or proportions) often lead to overdispersion and poor fit if they are not taken into account. Zero-Inflated (ZI) models provide a flexible way to address this problem (Hall 2000) by assuming that only a proportion of the zeros arise from the data distribution and the remaining ones are "structural" (i.e. they appear with probability one).

Bayesian geostatistical models have been used to take into account spatio-temporal variation and zero-inflation in entomological data (Rumisha et al. 2014; Amek et al. 2012); however lag times in climatic factors have not been rigorously incorporated into the modelling. Furthermore, selection of the climatic predictors to be included in the model is based on standard variable selection methods, which ignore spatio-temporal correlation. Recently, Bayesian variable selection methods have been used in modelling geostatistical survey data to identify the most important predictors of disease risk (Giardina et al. 2012; Chammartin et al. 2013), however these methods have not been applied in modelling entomological data.
In this study, we apply zero-inflated models and introduce Bayesian variable selection to determine the elapsing time between climate suitability and malaria transmission and develop predictive models of EIR taking into account spatio-temporal heterogeneity and seasonality in terms of mosquito density and infectivity (sporozoite rate) .We also determine the most important climatic predictors associated with the occurrence of the most predominant malaria vector species and transmission using data from the Nouna district in Burkina Faso.

2.2 Data and Methods

The data that motivated the present work were collected at Nouna Health and Demographic Surveillance System as part of the International Network for the Demographic Evaluation of Populations and Their Health-Malaria Transmission Intensity and Mortality Burden across Africa (INDEPTH-MTIMBA) protocol. INDEPTH-MTIMBA was a multi-centre project during 2001-2004 aimed at studying the relationship between the intensity of malaria transmission and all-cause as well as malaria specific mortality taking into account the influence of malaria control activities in each participant site. The Nouna HDSS is run by the Centre de recherche en santé de Nouna (CRSN, Nouna Health Research Center) and located in the Nouna health district's catchment area in northwest Burkina Faso, 300 km away from the capital city, Ouagadougou. Relative to the health district, the HDSS catchment area is located southeast.

The Nouna HDSS area is characterized by a Sub-Saharan climate with a mean annual rainfall of approximately 800mm with fairly constant average daily minimum (20-28.1°C) and maximum temperature (29.5-37.2°C) throughout the year. Rainfall occurs from May to September. The entire region consists of "Plateaux" with gentle slopes and drained by several small semi-permanent streams.
The HDSS area is about 1,775 km^2 with the specificity of covering both rural and semi-urban areas.
The population is about 90,000 residing in 11,750 households across 58 villages and Nouna town. Subsistence farming is the predominant occupation. Malaria is holo-endemic and is known for a seasonal recrudescence during the rainy season, at which time it accounts for the main cause of fever and mortality in the district (Müller et al. 2008). During the dry season, in February and March, lower respiratory infections are the main cause of morbidity, due to the relatively cool temperatures and strong winds, which bring up dust and dirt.

2.2.1 Entomological data

Entomological data were collected using the Center for Disease Control and Prevention (CDC) light traps from 10 randomly selected compounds (from the HDSS database) over two consecutive nights every two weeks during the study period (September 2001- December 2003). In each house, a light trap was hung at about 1.5 m above the floor next to the bed of an index person and mosquitoes were collected for two consecutive nights. The sleeping place was covered with a bed net to protect the index person from

mosquito bites. Other people in the same room without bed nets were also provided with untreated nets for these specific nights. Light traps were operated from dawn to dusk. All *Anopheles* mosquitoes captured were identified morphologically (Wirtz et al. 1987), stored and dried in vials with silica gel until they could be transported to the laboratory for further testing. The head and thorax of each anopheline was tested singly for *P. falciparum* sporozoites using a standard enzyme-linked immunosorbent assay (ELISA) (Wirtz et al. 1987). To assess the seasonal pattern, data were summarized by location and calendar month. This implied that all surveys data collected within the same calendar month from a specific location (compound) were collapsed (mosquito density/tested and positive) into a single observation resulting in 160 and 285 unique locations respectively for sporozoite data of *An. funestus* and *An. gambiae* and 550 unique locations for density data for both species.

2.2.2 Environmental and climatic data

Remote sensing data were used as proxies of climatic and environmental conditions. The predictors used, sources extracted and their spatio-temporal resolution are given in table 2.1.

To account for the environment-lagged effects on changes in mosquito density and infectivity, environmental factors were extracted up to three months prior to the month of mosquito collection for each surveyed location. Based on the biological plausibility (latent periods in the mosquito and parasite life cycle), six lag variables were constructed for each environmental factor (i.e. normalized difference vegetation index (NDVI), day land surface temperature (LST), night LST and rainfall) by averaging its values over the following periods: current month of the mosquito collection (Lag0), one and two month(s) prior to collection (Lag1, Lag2, respectively), average during the current and one previous month (Lag3), average during three months prior to the current one (Lag4) and average during the current and the two previous months (Lag5).

Table 2. 1: Sources of environmental and climatic predictors

Source	Predictor	Period	Spatial Resolution	Temporal Resolution
Moderate Resolution Imaging Spectroradiometer (MODIS) Terra	Day & Night Land Surface Temperature (LST)	2001-2003	$1\times1km^2$	8 days
Moderate Resolution Imaging Spectroradiometer (MODIS) Terra	Normalized Difference Vegetation Index (NDVI)	2001-2003	$0.25\times0.25km^2$	16 days
Africa Data Disseminating Services	Rainfall	2001-2003	$8\times8km^2$	10 days
Health Mapper	Water Bodies (Permanent &semi-permanent)	-	$1\times1km^2$	na

2.3 Description of methods

We followed the approach by (Rumisha et al. 2014) and developed zero-inflated binomial (ZIB) and zero-inflated negative binomial (ZINB) models to model sporozoite rate (proportion of infected mosquitoes) and mosquitoes' densities, respectively. We extended the methodology by introducing Bayesian variable selection to identify the most important climatic factors related to malaria transmission and take into account lag times between climatic suitability and malaria transmission. Four models were fitted separately to *An. funestus* and *An. gambiae* data to obtain species-specific surfaces of mosquito density and sporozoite rate within the study area. The overall EIR estimate at a given location and month is based on the mean number of infected mosquitoes (from both species) multiplied by the conversion factor. Modelling details are given bellow.

2.3.1 Modeling sporozoite rate using zero-inflated binomial (ZIB)

Let $N_{it}, Y_{it}^{(1)}$ be the number of tested and number of positive mosquitoes, respectively at location $i, i = 1,...n$ and month t and $\underset{\sim}{X}_{it}$ is the set of predictors. We consider that $Y_{it}^{(1)}$ arises from a ZIB distribution, that is $Y_{it}^{(1)} \sim ZIB(N_{it}, p_{it}, \pi_{it}^{(1)})$ where p_{it} is the proportion of infected mosquitoes known as the sporozoite rate.

Malaria seasonality introduces a large number of zero infected mosquitoes. The ZIB distribution assumes that a proportion $\pi_{it}^{(1)}$ (i.e. mixing proportion) of those zeros are "structural" (not random) and the remaining ones are present in the data with the frequency defined by the binomial distribution(Hall 2000). We model the relation between the sporozoite rate p_{it} and the environmental predictors via the logistic regression equation, $\log it(p_{it}) = \underset{\sim}{X}_{it}^{T}\underset{\sim}{\beta}^{(1)}$ where $\underset{\sim}{\beta}^{(1)}$ is the set of regression coefficients. We also assume that the mixing proportion of zeros is also influenced by climatic factors $\underset{\sim}{Z}_{it}^{T}$ which we introduce into the modelling by the equation $\log it(\pi_{it}^{(1)}) = \underset{\sim}{Z}_{it}^{T}\underset{\sim}{\gamma}^{(1)}$, where $\underset{\sim}{\gamma}^{(1)}$ is the set of corresponding coefficients.

2.3.2 Modeling mosquito's densities using zero-inflated negative binomial (ZINB)

Let $Y_{it}^{(2)}$ be the number of mosquitoes trapped at location i and time t. We assume that $Y_{it}^{(2)}$ arises from a ZINB distribution, $Y_{it}^{(2)} \sim ZINB(\mu_{it}, r, \pi_{it}^{(2)})$ with μ_{it} and r corresponding to the mean mosquito count and variance of the negative binomial distribution (Vounatsou et al. 2009). $\pi_{it}^{(2)}$ corresponds to the mixing proportion modelling the "excess zeros". As defined above it is considered that a proportion of the zero mosquito counts is "structural" and the remaining $1-\pi_{it}^{(2)}$ arise from the negative binomial distribution. We model the relation between the mean mosquito density μ_{it}, mixing proportion of zeros $\pi_{it}^{(2)}$ and climatic predictors by the equations $\log(\mu_{it}) = \underset{\sim}{X}_{it}^{T}\underset{\sim}{\beta}^{(2)}$ and $\log it(\pi_{it}^{(2)}) = \underset{\sim}{Z}_{it}^{T}\underset{\sim}{\gamma}^{(2)}$ where $\underset{\sim}{\beta}^{(2)}$ and $\underset{\sim}{\gamma}^{(2)}$ the regression coefficients.

2.3.3 Modeling spatio-temporal heterogeneity

We extend the above formulation to include seasonality, spatial and temporal correlation on the sporozoite rates as well as the mosquito density, that is, $\log it(p_{it}) = \underset{\sim}{X}_{it}^{T}\underset{\sim}{\beta}^{(1)} + f_{(1)}(t) + \phi_i^{(1)} + \varepsilon_t^{(1)}$ and $\log(\mu_{it}) = \underset{\sim}{X}_{it}^{T}\underset{\sim}{\beta}^{(2)} + f_{(2)}(t) + \phi_i^{(2)} + \varepsilon_t^{(2)}$, where $f_{(k)}(t)$ captures seasonal patterns, $\phi_i^{(k)}, \varepsilon_t^{(k)}$ model spatial and temporal correlation respectively. The values of the index k correspond to the sporozoite models for *An. funestus* $(k=1)$, *An. gambiae* $(k=2)$ and mosquito density models for *An. funestus* $(k=3)$ and *An.gambiae* $(k=4)$ respectively. We assume a stationary Gaussian spatial process that is, spatial

correlation is considered to be a function of distance only and not of the locations themselves" an autoregressive process of order assuming that temporal correlation is present only between successive time points to capture temporal correlation. Seasonal trends $f_{(k)}(t)$ are modelled via a trigonometric function with a period $T = 12$ months, $f_{(k)}(t) = a_{1k}\cos\left(\frac{2\pi}{T}t\right) + a_{2k}\sin\left(\frac{2\pi}{T}t\right), t = 1,...,12$. The peak months of the wet and dry season are calculated by $t_k = \arctan(a_{1k} / a_{2k}) \times (T / 2\pi)$ and $(t_k + T/2)$, respectively (Stolwijk, Straatman, and Zielhuis 1999).

2.3.4 Determining important predictors and lag times using variable selection

Bayesian variable selection was carried out to determine the most important climatic factors including distance to water bodies and lag variables for each climatic factor (NDVI, day LST, night LST, Rainfall) using a variable selection approach known as stochastic search (George and McCulloch 1993b). In particular, for each predictor $\underset{\sim}{X}_p$ we introduce a binary indicator parameter I_p suggesting presence ($I_p = 1$) or absence ($I_p = 0$) of the predictor from the model. Furthermore, we assume a mixture prior for the corresponding regression coefficient β_p that is $\beta_p \sim (1 - I_p)N(0, \upsilon_0\tau_p^2) + I_p N(0, \tau_p^2)$ proposing a non-informative prior for β_p in case $\underset{\sim}{X}_p$ is included in the model and an informative normal prior with a variance close to zero (i.e. $\upsilon_0 = 10^{-3}$) shrinking β_p to zero if $\underset{\sim}{X}_p$ is excluded from the model. A Bernoulli prior is assumed for the indicator, $I_p \sim Be(0.5)$. For climatic variables with lag effects we introduce a multivariate binary indicator with categories corresponding to the six lag periods and an additional category to allow exclusion of that variable. In this case we consider a multinomial prior for the indicator with equal probabilities among the categories. Variable selection was applied on the climatic factors included in both parts of the models, i.e. the mixing proportion of zeros and the mean parameters of the data distributions. The predictors that are identified as important are those with posterior inclusion probability greater than or equal to 50% (Barbieri and Berger 200406).

Model fit was carried out using Markov chain Monte Carlo simulation. We ran a two-chain Gibbs sampler over 100,000 iterations using a burn-in of 5000 iterations. Convergence was assessed by the Gelman and Rubin diagnostic (Brooks and Roberts 1998) and kernel density plots using the coda routine in R.

Details on remaining prior distribution and implementation are given in the Appendix. The analysis was carried out in OpenBUGS version 3.2.3 (Imperial College and Medical Research Council, London, UK).

2.3.5 Entomological inoculation rate (EIR)

Bayesian kriging (Diggle, Tawn, and Moyeed 1998) was used to predict the mosquito density and the number of infected mosquitoes for each species over a regular grid of 33 605 pixels at 250 x 250m^2 spatial resolution covering the study area. The entomological inoculation rate (EIR) is defined as the product of human biting rate and the sporozoite rate. The human biting rate is the mean number of bites received per host and per night. It is approximated by mosquitoes captured using human landing catches (host-seeking mosquitoes). We used a conversion factor of 1.605 (Lines et al. 1991) to transform light trap catches densities into human landing catches. The light trap density was calculated by dividing the number of mosquitoes caught using the CDC light traps by the number of trap-nights. At a specific pixel *i* and month *t,* a sample of size 1,000 was drawn from the predicted posterior distribution of the species-specific mosquito densities using the zero-inflated negative binomial data distribution. In addition, a sample of the number of infected mosquitoes (from each species) was simulated from the predictive posterior distribution of sporozoite rates based on the zero-inflated binomial with a binomial count equal to the predicted mosquito density. The overall EIR estimate at a given location and month is based on the sample-based mean number of infected mosquitoes (from both species) multiplied by the conversion factor. Bayesian kriging was done in Fortran 95 (Digital Equipment Corporation) using standards numerical libraries (Numerical Algorithms Group Ltd.).

2.3.6 Model validation

Model fit was carried out on a randomly selected locations subset (85%) of the dataset (training set). The remaining 15% was used for model validation (testing test). These subsets were selected by assigning a uniform distribution on the locations. The predictive performance of the models was assessed by calculating the proportion of test locations with the outcome variable included in the credible intervals (CI) with varying probability coverage ranging from 5% to 95% of the posterior predictive distribution and the mean square error between the observed and predicted data (Gosoniu et al. 2006).

2.4 Results

2.4.1 Vectorial density

A total of 13,132 anopheline mosquitoes were trapped in 550 unique locations over the study period. *An.°gambiae* was the predominant vector species representing 79% of the total Anopheles mosquitoes collected. The remaining 21% consisted of *An. funestus*. About 35% of the survey locations had no *An.gambiae* mosquitoes. This percentage reaches 41% for *An. funestus*. The peak collecting period for *An. gambiae* species coincided with the peak of the rainy season (August) while for *An. funestus* it was in September. However the density of *An. funestus* remained comparatively low throughout the study period. The distributions of the species-specific densities and rainfall throughout the study period are given in Figure 2.1.

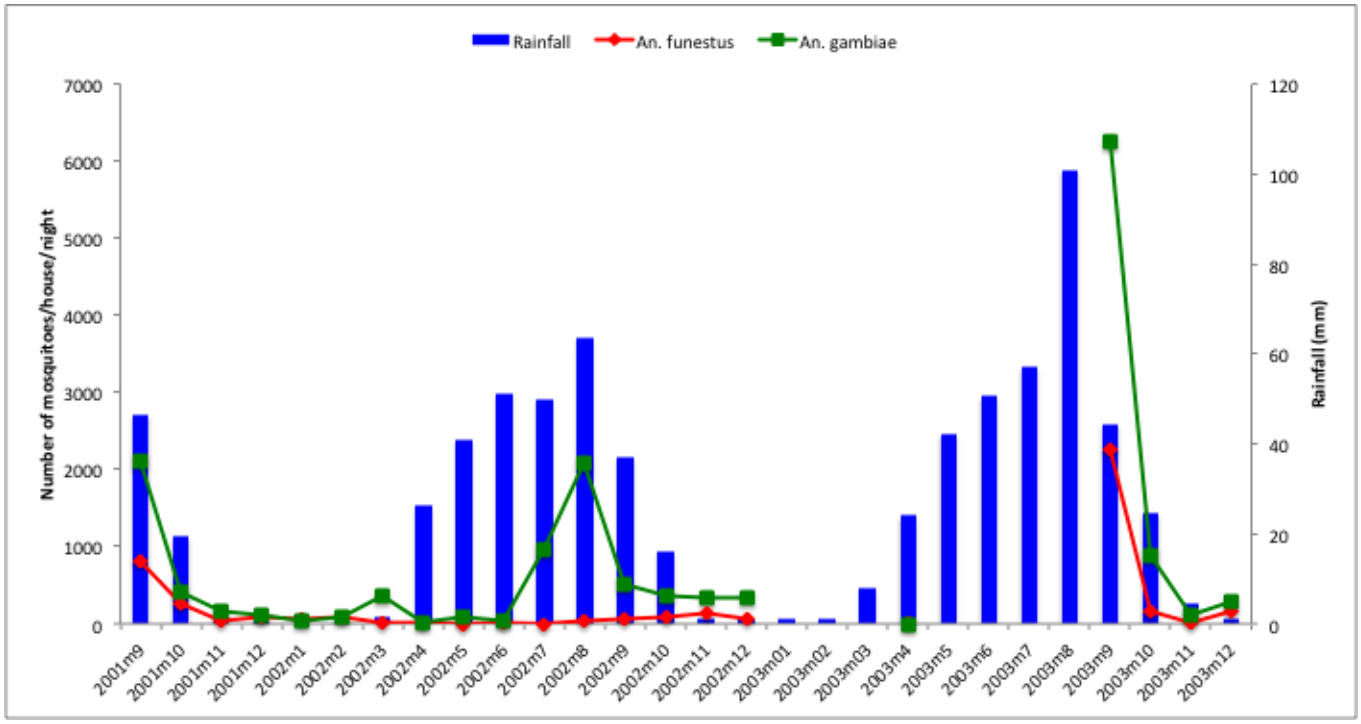


Figure 2. 1: The distributions of the species-specific densities and rainfall throughout the study period

2.4.2 Mosquitos' infectivity

A total of 5,668 mosquitoes were tested for the presence of circumsporozoite antigens out of which 4,230 (74.64%) were *An. gambiae* species. The overall sporozoite rate (SR) was 7.64% (95% CI 7.63-7.65). *Plasmodium falciparum* infection was detected in 9.24% of *An. gambiae* species and 2.92% of *An. funestus* species. Sporozoite rates tend to be higher in the Western part of the study area. Figure 2.3 presents the geographical location of the study area (top left) and surveyed locations with infected and uninfected mosquitoes. The monthly patterns of infected mosquitos and rainfall by species are depicted in Figure 2.2.

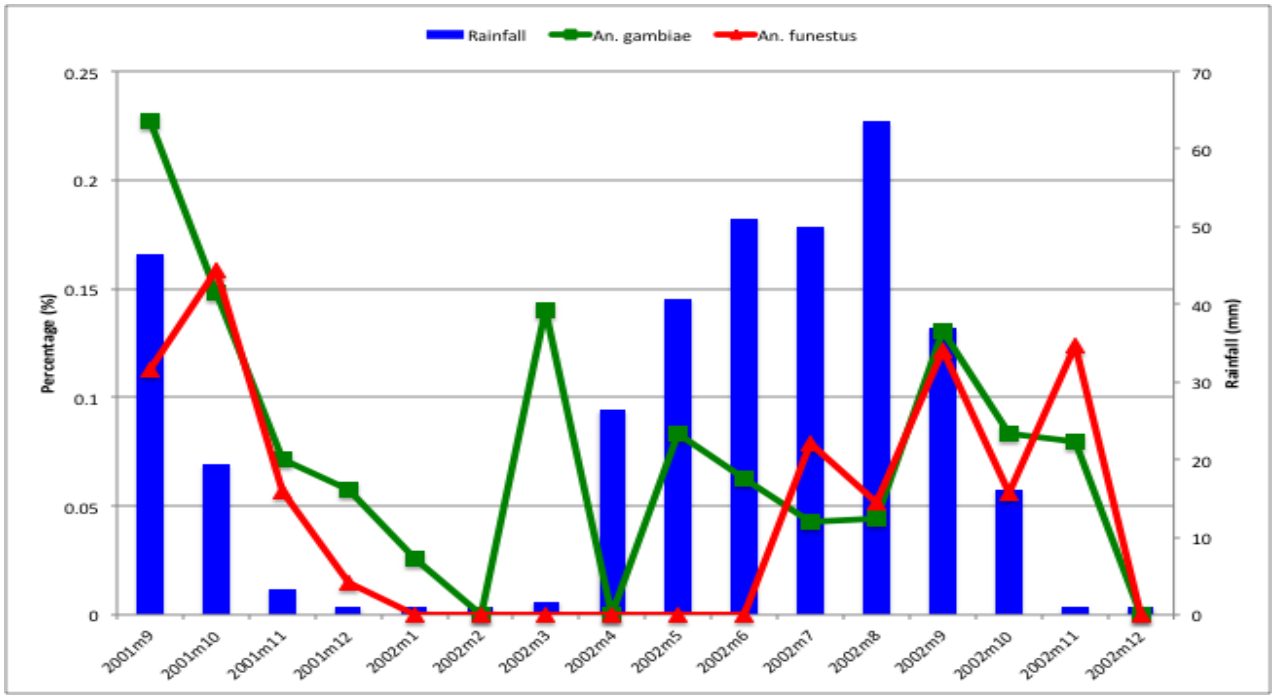


Figure 2. 2: Monthly patterns of species-specific infectivity and rainfall

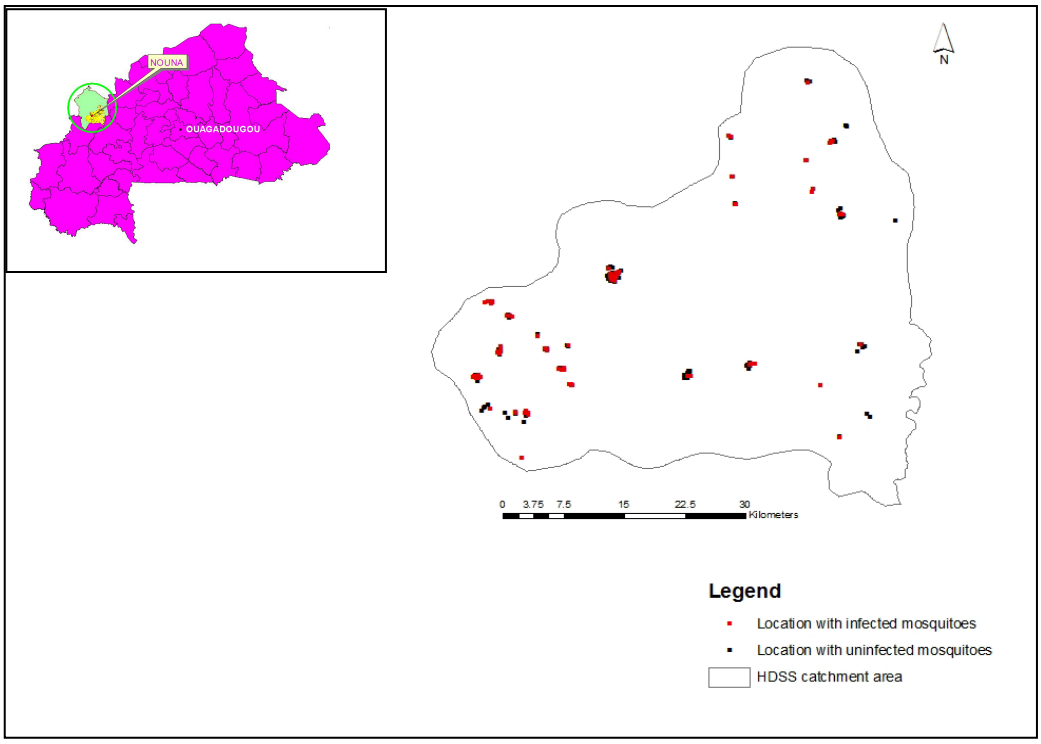


Figure2. 3: Geographical locations (top left) and surveyed locations with infected and uninfected mosquitoes.

2.4.3 Variable selection

Results of the variable selection in Table 2.2 indicate that rainfall and vegetation during the current month (Lag0), and day temperature during the month preceding the collection (Lag1) are important predictors of *An. funestus* density. The rise of *An. gambiae* density depends on suitable climatic conditions over a longer period of time such as rainfall during the current and previous two months and night temperatures during the previous two months. The proportion of "structural" or "excess" zeros is influenced by day and night temperatures for both species. However, for *An. gambiae* densities, the mixing proportion is associated with a longer lag time, that is second month (Lag2) and two previous and current months (Lag5) for day and night temperatures, respectively. Furthermore, distance to water bodies appears to be an important predictor of the mixing proportion of zeros for *An. funestus* densities.

Table 2. 2: Lag times and predictors selected by the variable selection

Model	Zero-inflated Binomial	Zero-inflated Binomial	Zero-inflated negative Binomial	Zero-inflated negative Binomial
Binomial component	*An. funestus*	*An.gambiae*	*An. funestus*	*An.gambiae*
Parameter				
Rainfall	Lag 3	Lag 0	Lag 0	Lag 5
Vegetation (NDVI)	-	-	Lag 0	-
Day temp (LSTD)	Lag 4	Lag 3	Lag 1	-
Night temp (LSTN)	-	Lag 5	-	Lag 4
Distance to water body	Yes	No	No	No
Mixing Proportion				
Rainfall	-	-	-	-
Vegetation (NDVI)	-	-	-	-
Day temp (LSTD)	-	-	Lag 1	Lag 2
Night temp (LSTN)	-	-	Lag 1	Lag 5
Distance to water body	Yes	Yes	Yes	No

Legend:
Lag 0: Average over the current month
Lag 1: Average of the environmental covariate over the previous month
Lag 2: Average of the environmental covariate over second previous month
Lag 3: Average of the environmental covariate over the current and the previous month
Lag 4: Average of the environmental covariate over the previous and the second previous month
Lag 5: Average of the environmental covariate over the current, previous and the second previous month

The most important climatic predictors of the sporozoite rates of *An. funestus* are rainfall during the current and previous month (Lag3) and day temperature during the two previous months (Lag4). Rainfall of the month of collection (Lag0) and more distant lag times for day (Lag3 corresponding to the current and previous month) and night temperatures (Lag5, i.e. current and the two previous months) appear to be the most important predictors of *An. gambiae* sporozoite rates. Distance to water body is the only important predictor of the proportion of "excess" zeros in the sporozoite rates for both species.

2.4.5 Model-based vectorial density

Positive effects of rainfall and vegetation during the current month showed important associations with the density of *An. funestus*. The distance at which the spatial correlation is less than 5% is equal to 10 km (95% Bayesian credible interval (BCI): 3-83 km). The phase of 0.65 radials suggested that the peak of the *An. funestus* density occurs in the month of September and the minimum in the month of March. The effect of predictors associated to the mixing proportion of the zero-inflated distribution was not important. The probability of the excess zeros is highest in the month of November and the lowest in the month of April.

Rainfall (during the current and two previous months) and night temperature (during the two previous months) are important predictors, negatively associated with *An. gambiae* density. Spatial correlation is not important (<0.05) beyond 5 km (95% BCI: 1-35 km). The temporal and the spatial variations are respectively 0.76 (95% BCI: 0.48-1.26) and 0.54 (95% BCI: 0.22-1.13). The maximum *An.gambiae* density occurs in the month of August and the minimum in the month of January. The probability of excess is related positively with the day temperature during the two previous months and negatively with the night temperature during the current and two previous months. The maximum probability of excess zero occurs in November and the minimum in April. Table 2.3 presents the posterior estimates of the ZINB model for both species. Figure 2.4 shows the monthly pattern of observed and fitted density (averaged over spatial locations) respectively for *An. funestus* and *An. gambiae.*

Table 2. 3: Posterior estimates obtained from the geostatistical zero-inflated negative binomial (ZINB) models

Parameters	*An. funestus*	*An.gambiae*
	Median (95% BCI)	Median (95% BCI)
Intercept	-0.38(-1.09, 0.46)	1.85 (-0.11, 3.56)
Year2	0.24 (-0.64,1.07)	-1.01 (-2.75, 0.39)
Rainfall	0.87 (0.021, 1.71)	-2.33 (-4.67, -0.2)
Vegetation (NDVI)	1.12 (0.63, 1.65)	-
Day temp (LSTD)	-0.78 (-1.56, 0.00)	-
Night temp (LSTN)	-	-1.3 (-1.9, -0.64)
Amplitude	3.53(3.50, 3.56)	5.88 (5.83, 5.93)
Shift/phase	0.648 (0.645, 0.653)	-1.159 (-1.163, -1.155)
Dispersion (r)	0.45(0.32, 0.63)	0.93 (0.71, 1.24)
Spatial Variation	0.90(0.33, 2.03)	0.54 (0.22, 1.13)
Range (km)[a]	1 (3, 83)	5 (1, 35)
Temporal variation	-	0.76 (0.48, 1.26)

Parameters	**Mixing proportion**	
	An. funestus	*An.gambiae*
	Median (95% BCI)	Median (95% BCI)
Intercept	-14.42(-27.08, -3.57)	-11.06(-18.80, -3.47)
Year2	0.24 (-0.64, 1.07)	4.42 (-5.67, 11.66)
Distance to water body	-3.52 (-12.43, 3.51)	-
Rainfall	-	-
Vegetation (NDVI)	-	-
Day temp (LSTD)	4.14 (-9.38, 21.23)	3.21(0.89, 5.89)
Night temp (LSTN)	5.13 (-5.08, 14.83)	-1.99 (-5.57, -0.57)
Amplitude	21.92 (21.69, 22.16)	4.03 (3.96, 4.18)
Shift/phase	1.06 (1.05, 1.07)	2.25 (2.22, 2.27)

a: minimum distance in kilometer at which the spatial correlation remains important , BCI=Bayesian Credible Interval

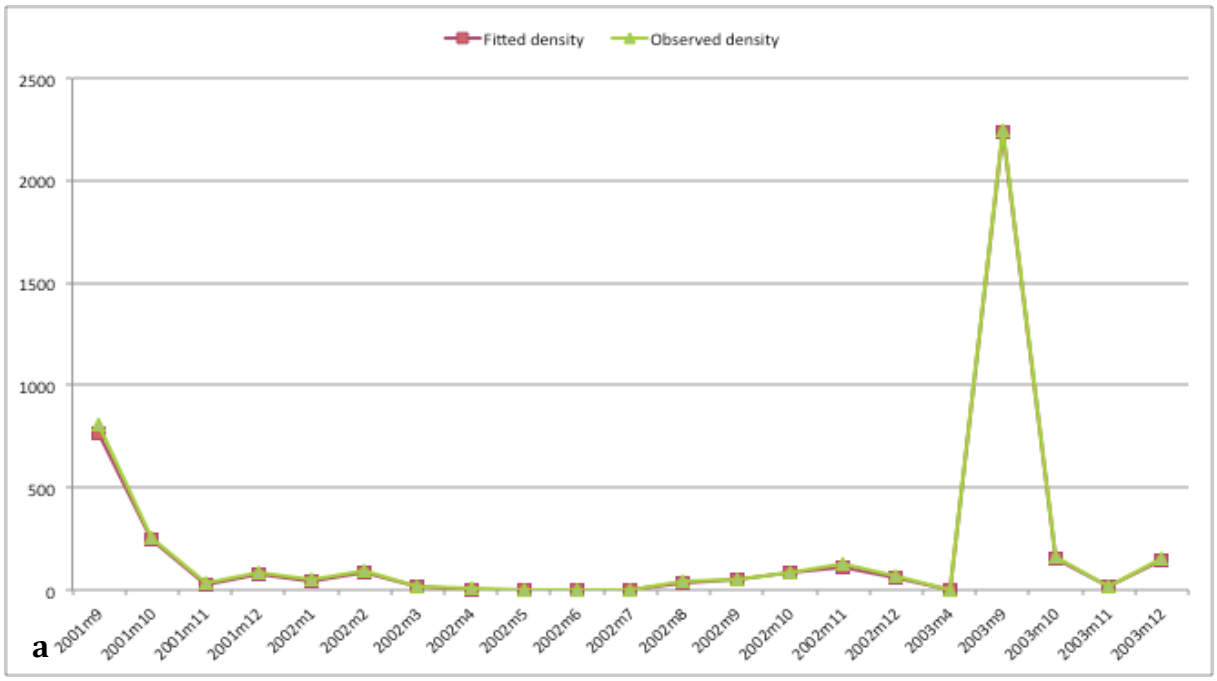


Figure 2.4 (a): 1Monthly patterns of observed and fitted indoor residual densities (averaged over spatial locations) of *An. funestus.*

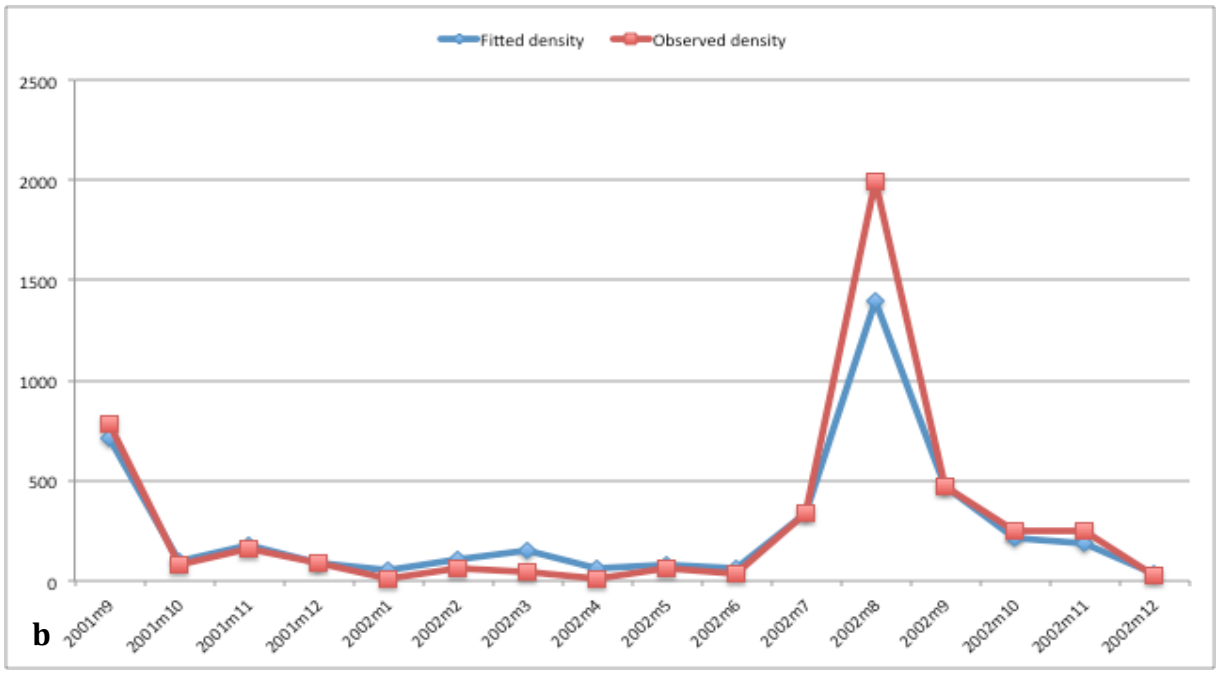


Figure 2.4 (b): 2Monthly patterns of observed and fitted indoor residual densities (averaged over spatial locations) of *An. gambiae.*

2.4.6 Model-based mosquitoes' infectivity

Table 2.4 presents the posterior estimates of the ZIB model for both species. The effects of predictors appeared not to be important for both species. The maximum of *An. funestus* infectivity occurs in the month of August and the minimum in April. Estimates of the seasonality parameters in the mixing proportion indicate that the probability of "structural" zeros is maximum in October and minimum in the month of April.

Table 2. 4: Posterior estimates obtained from the geostatistical zero-inflated binomial (ZIB) models

Parameters	*An. funestus*	*An.gambiae*
	Median (95% CI)	Median (95% CI)
Intercept	-6.65 (-14.8, -1.42)	-1.82 (-4.21, 4.14)
Year2	-0.67 (-3.36, 2.10)	-0.92 (-4.32,1.49)
Distance to water body	0.10(-1.54, 1.83)	-
Rainfall	-1.42 (-4.84, 1.51)	-0.16 (-2.06, 1.94)
Vegetation (NDVI)	-	-
Day temp (LSTD)	-0.25 (-3.53, 2.64)	-0.47(-1.13, 0.08)
Night temp (LSTN)	-	0.05 (-0.72, 0.81)
Amplitude	7.25 (7.12, 7.38)	2.50 (2.45, 2.54)
Shift/phase	-1.89 (-1.94, -1.85)	2.72 (2.68, 2.75)
Spatial Variation	0.67 (0.22, 2.78)	0.51 (0.22, 1.19)
Range (km)[a]	0.05 (0.01, 0.44)	0.05 (0.01, 0.27)
Temporal variation	-	0.99 (0.53, 2.26)
Parameters	**Mixing proportion**	
	An. funestus	*An.gambiae*
	Median (95% CI)	Median (95% CI)
Intercept	-2.96 (-20.12, 11.79)	-11.45 (-26.0, -0.0015)
Year2	1.88 (-17.24, 15.2)	-3.25 (-18.15, 9.07)
Distance to water body	11.5 (-7.67, 27.29)	3.546(-9.625, 11.39)
Rainfall	-	-
Vegetation (NDVI)	-	-
Day temp (LSTD)	-	-
Night temp (LSTN)	-	-
Amplitude	11.09 (10.88, 11.30)	4.03 (3.96, 4.10)
Shift/phase	1.19 (1.15, 1.23)	2.25 (2.22, 2.27)

a: minimum distance in kilometer at which the spatial correlation is significant at 5%, CI=credible interval

Sporozoite rates in *An. gambiae* take the largest and lowest values in November and April, respectively. The probability of "structural" zeros is higher in December and lower in June. Variation in time is larger than the one in space. Furthermore, the distance at which the correlation coefficient falls below 5% (spatial correlation) is deemed unimportant for both *An. funestus* and *An. gambiae* (95% BCI: 1-44 km and 1-27 km, respectively). Figure 2.5 (a)-(b) shows the monthly pattern of observed and fitted sporozoite rate (averaged over spatial locations) respectively for *An. funestus* and *An. gambiae.*

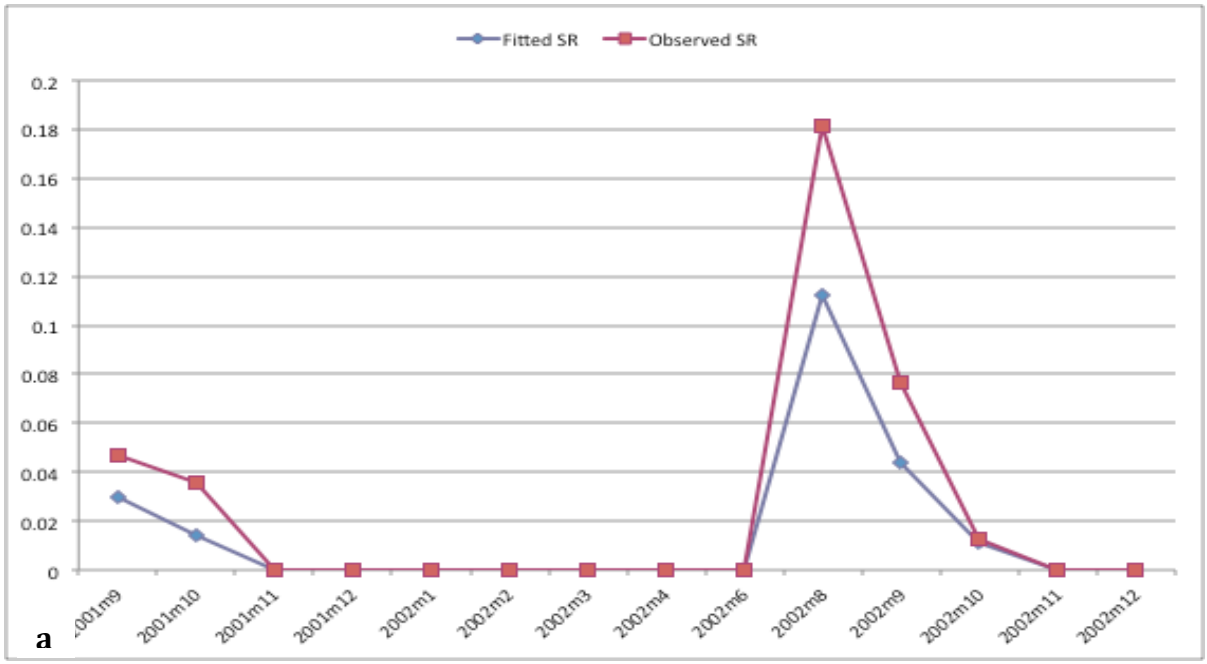


Figure 2.5(a): Monthly pattern of observed and fitted sporozoite rate (averaged over spatial locations) of *An. funestus.*

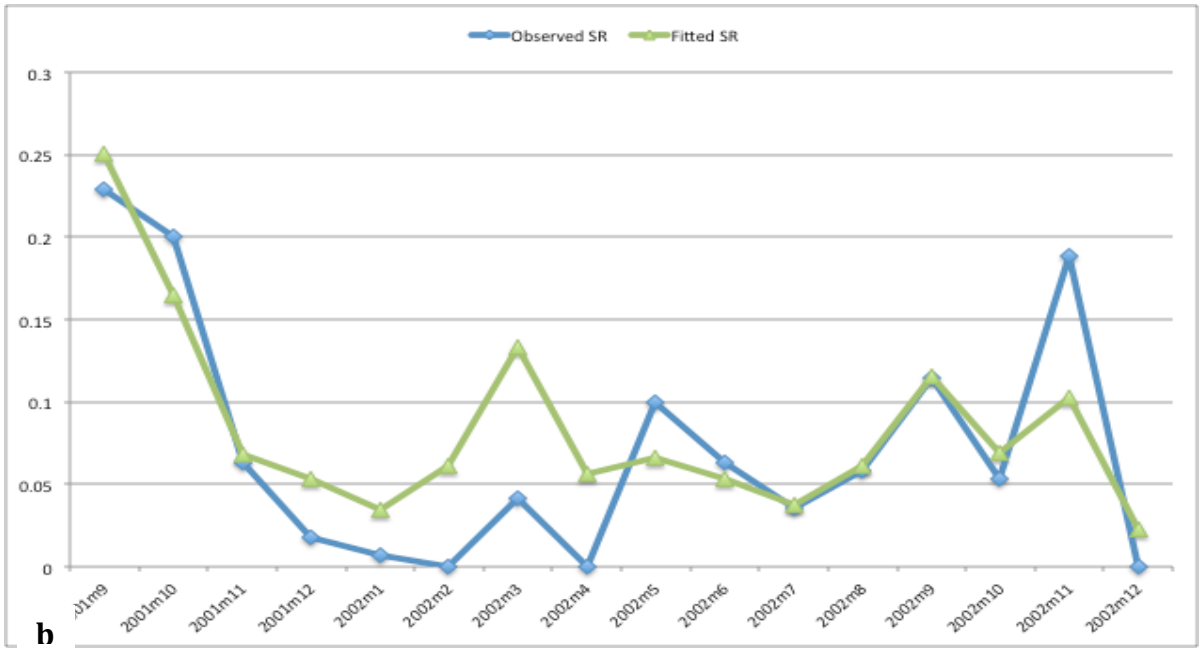
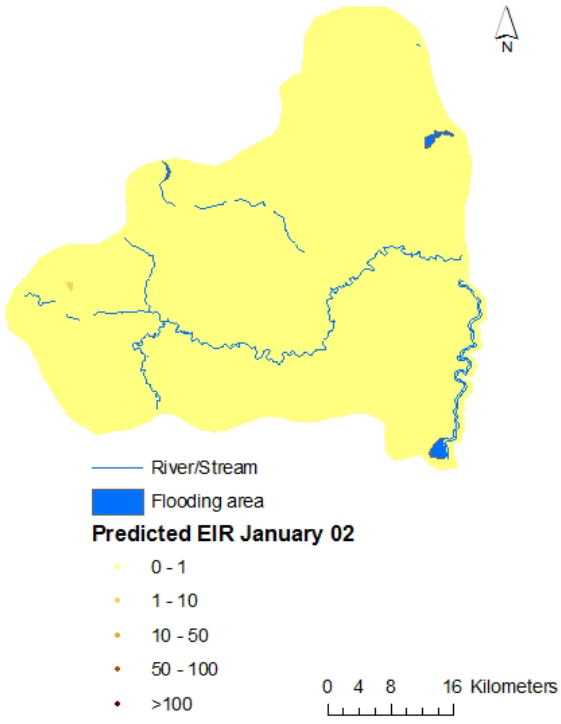
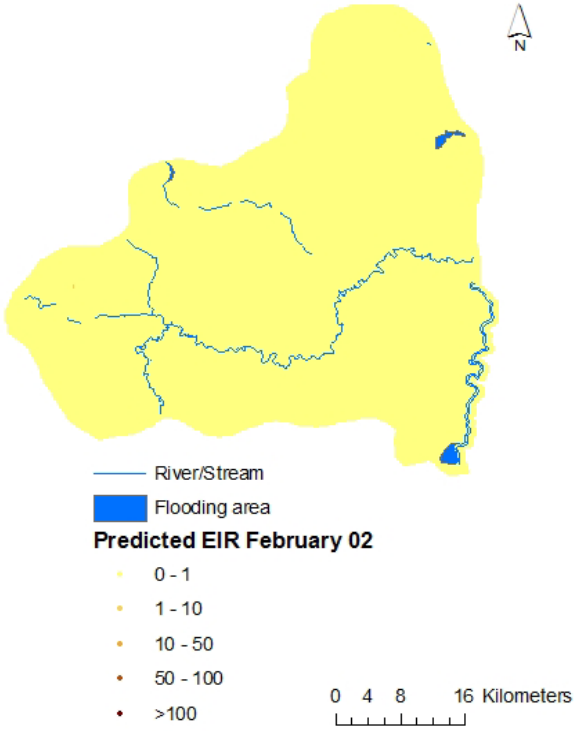


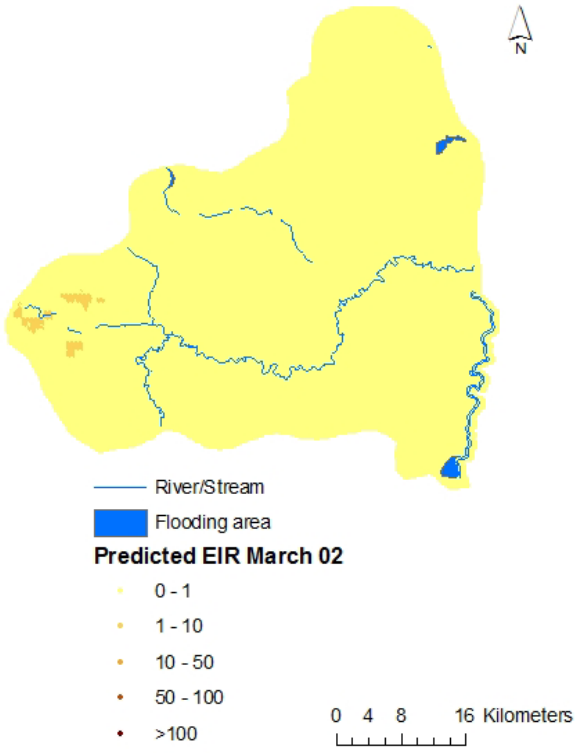
Figure 2.5(b): Monthly pattern of observed and fitted sporozoite rate (averaged over spatial locations) of *An. gambiae*

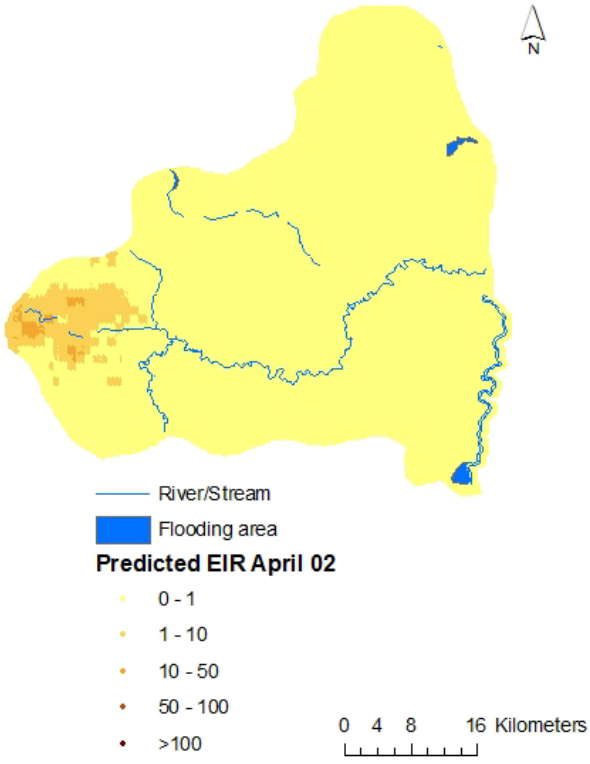
2.4.7 Entomological inoculation rate (EIR)

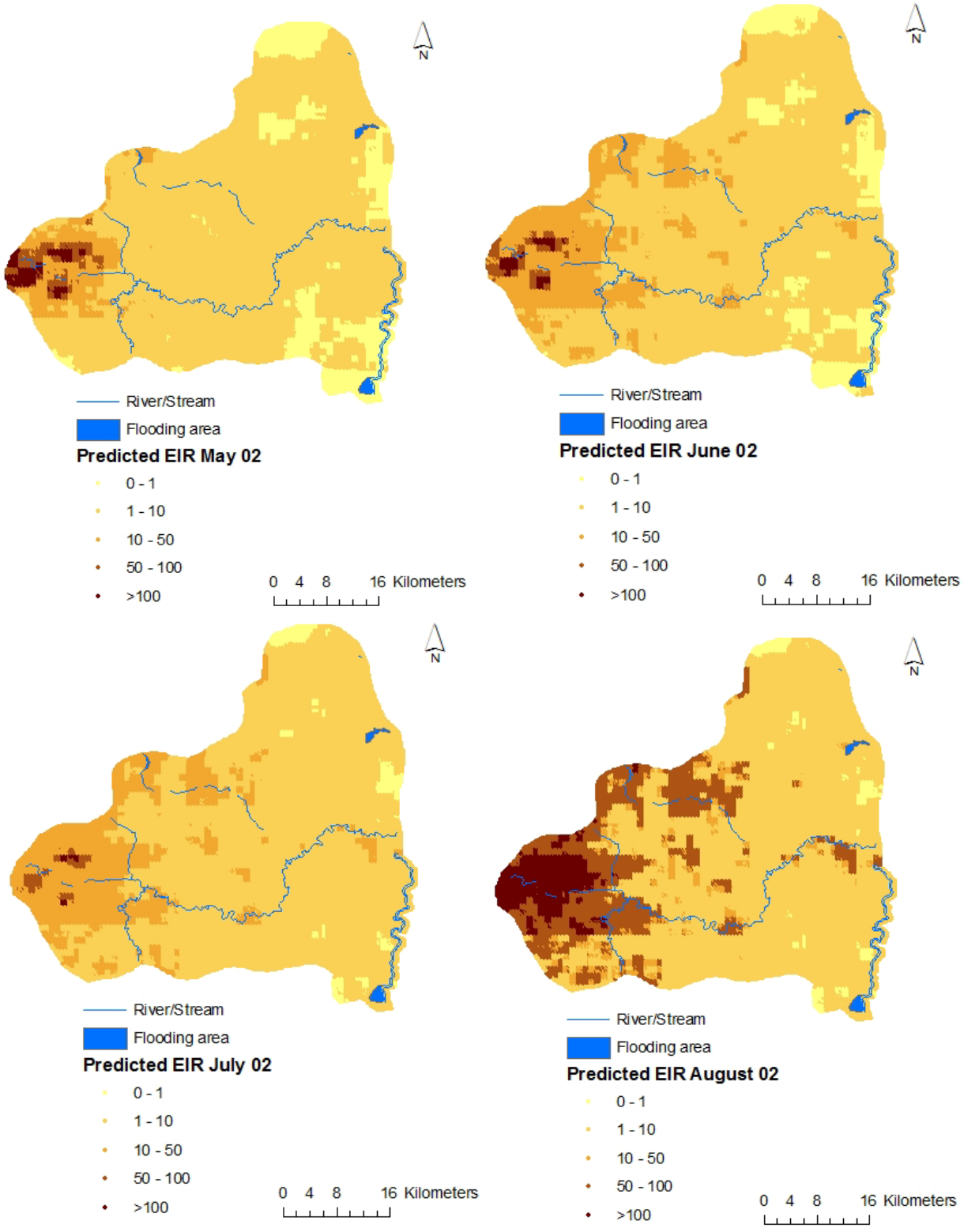
The annual EIR averaged across the area was 131.4 infective bites per person for 2002. Figure 2.6 depicts monthly EIR estimates of the median predictive posterior distribution at 250 by 250 m^2 resolutions within the HDSS site. The high transmission season is during May–October; however there are some "high-transmission" areas in the western part during November. In fact, the western region has the highest EIR estimates across the whole HDSS catchment area.


N
River/Stream
Flooding area
Predicted EIR January 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers


N
River/Stream
Flooding area
Predicted EIR February 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers


N
River/Stream
Flooding area
Predicted EIR March 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers


N
River/Stream
Flooding area
Predicted EIR April 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers


N
River/Stream
Flooding area
Predicted EIR May 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers
N
River/Stream
Flooding area
Predicted EIR June 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers
N
River/Stream
Flooding area
Predicted EIR July 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers
N
River/Stream
Flooding area
Predicted EIR August 02
0 - 1
1 - 10
10 - 50
50 - 100
>100
0 4 8 16 Kilometers

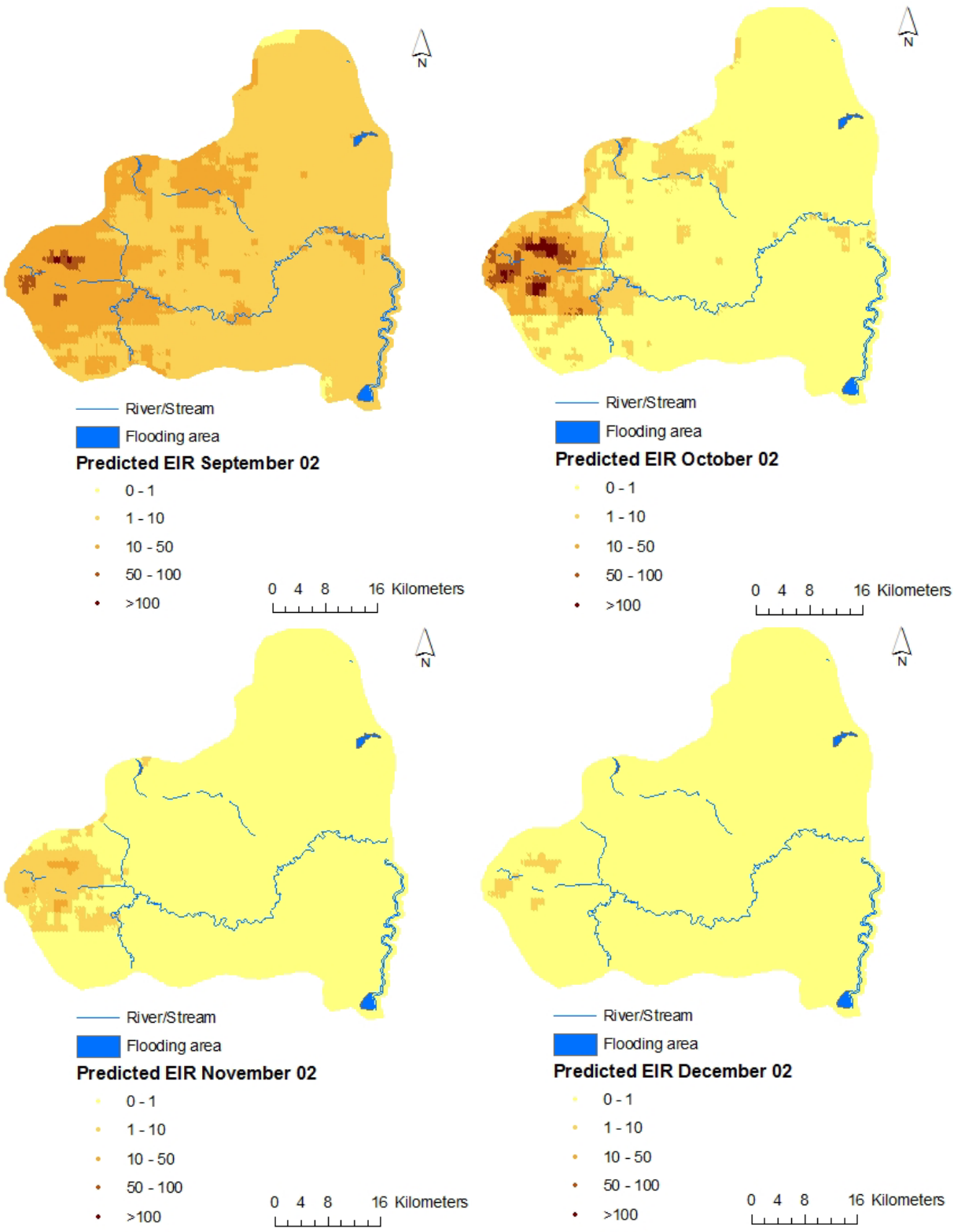
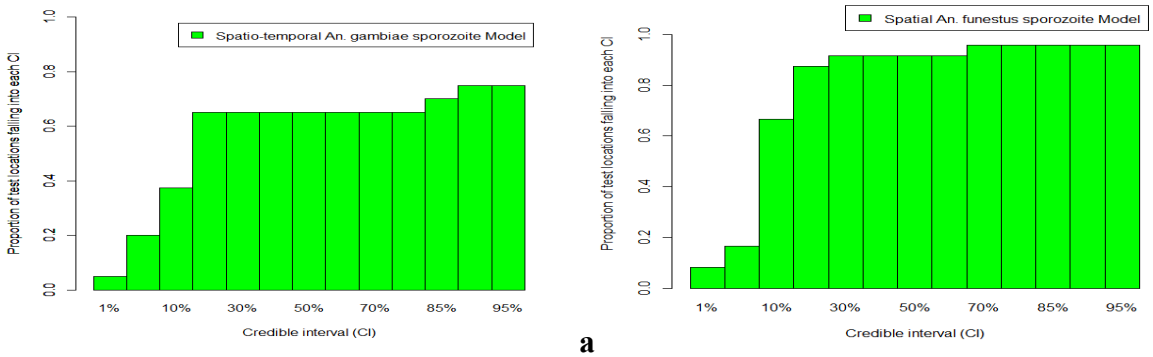


Figure 2.6: Monthly EIR estimates of the median predictive posterior distribution at 250 by 250 m^2 resolutions

2.4.8 Model validation

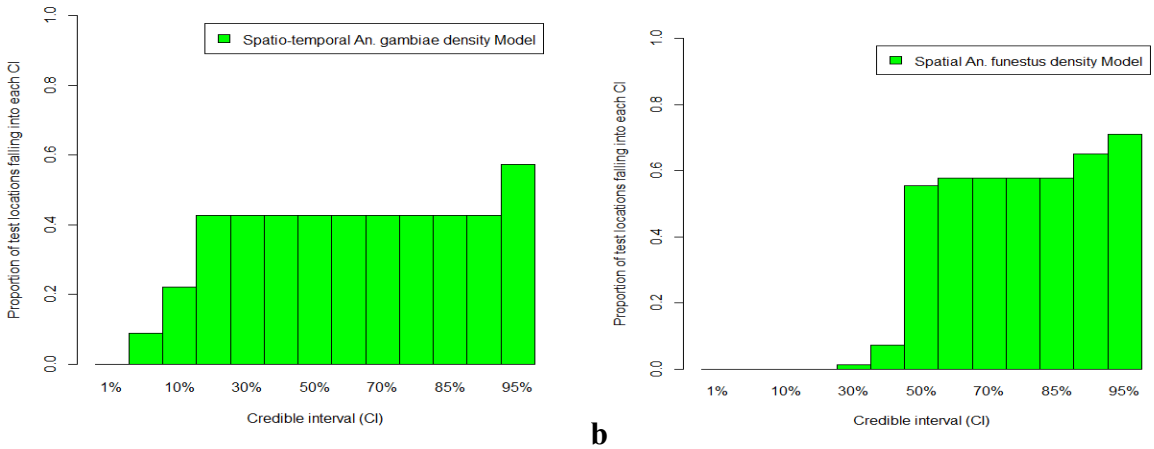
Model validation showed that 92% and 73% of the test locations had sporozoite rate falling within the 95% credible interval estimated from the zero inflated spatial binomial model and zero inflated spatio-temporal model respectively for *An. funestus* and *An. gambiae*.

Density models validation showed that 73% and 58% of the test locations had mosquito densities falling within the 95% credible interval estimated from the zero inflated spatial negative binomial model and zero inflated spatio-temporal negative binomial model respectively for *An. funestus* and *An. gambiae* density models. However the zero inflated spatio-temporal models included higher proportion of test locations in the lowest credible intervals compared to the zero inflated spatial negative binomial. Figure 2.7 (a)-(b) shows the proportions of test locations with respectively sporozoite rate and mosquito density falling in between 5% and 95% credible intervals of the posterior predictive distribution.



a

Figure 2.7(a): 1Proportions of test locations with sporozoite rate falling in between 5% and 95% credible intervals.



b

Figure 2.7(b): 2Proportions of test locations with mosquito density falling in between 5% and 95% credible intervals.

2.5 Discussion

In this study we described and quantified malaria transmission heterogeneity in the Nouna HDSS using a comprehensive entomological dataset and rigorous spatio-temporal models, which include Bayesian variable selection and take into account zero-inflation. The models determine the elapsing time between climate suitability and malaria transmission and estimate spatio-temporal patterns of transmission. Malaria transmission is mainly driven by two efficient vectors namely *Anopheles gambiae* and *An.funestus*, which co-exist geographically across the study area. The transmission fluctuated over the study period indicating seasonal, spatial and temporal variation within such a small geographic extend (1775 km^2). These findings corroborate previous studies concluding a very heterogeneous malaria distribution which is prone to great variations between villages and compounds (Greenwood 1989; Carter, Mendis, and Roberts 2000; N. Amek et al. 2012). Transmission intensity measured by EIR in Nouna HDSS was high (>100 ib/p/y) especially in the rainy season. A seasonal pattern was observed in mosquito densities and in sporozoite rates for both species. The high transmission season starts from May throughout October with the peak transmission occurring in September.

The negative relationship between night temperatures and *An. gambiae* mosquito density in our results possibly imply that although the high temperatures of the study area (average daily minimum: 20-28.1°C, maximum: 29.5-37.2°C) are suitable for stable malaria transmission (Craig, Snow, and le Sueur 1999a), a spell of relief from the heat mainly in the night is also a key determinant for mosquito development and survival.

Rainfall is associated with the densities of both species; however the direction of the effect is different. A negative association with *An. gambiae* density may suggest that although rainfall remains an important factor for the development of this species, consecutive heavy rainfall (over the current and the two previous months as shown by the Lag5 effect) may flush away all suitable *An. gambiae* breeding sites, therefore *An. gambiae* is a rainy-dependant species which favours temporary and shallow breeding sites. A positive association with *An. funestus* density indicates that rainfall is important for the development and survival of this species which predominantly develops in permanent water bodies with emerging vegetation (Dia, Wamdaogo, and Ayal 2013). This result is consistent with the positive important association between NDVI (a proxy measure of vegetation) and *An. funestus* density and the lack of association between NDVI with *An.gambiae* density (NDVI was not identified as a potential predictor of *An.gambiae* density).

The shortest distance at which the spatial correlation was below 5% for sporozoite rate was 5 km for both species. However, for the density it is twice as much for *An. funestus* than that for *An. gambiae* in spite of wide credible intervals associated with both estimates. The negative association between rainfall and sporozoite rate (although not significant) for both species can be explained by the sporogony cycle in relation to mosquito survival. Furthermore, only adult mosquitoes that have successfully taken a blood meal carry sporozoites while many young newly emerged mosquitoes shortly after the onset of the rainy season may reduce the proportion of older ones in the population. Similar results were also found by (N. Amek et al. 2011) and (Kasasa et al. 2013).

The lack of association between distance to water bodies especially *An. gambiae* may be explained by the fact the water bodies considered are mostly large permanent and semi-permanent ones and does not include small breeding sites which are favoured by *An. gambiae*. The zero-inflated (ZI) model formulations that were adopted in our study allow accounting for the structural zeros that may arise due to some factors that have not been considered in the study. For example, vector control interventions targeting adult mosquitoes that are likely to be infective or proximity to temporary water bodies where it is likely to find many young newly emerged (not yet infective) mosquitoes.

Interestingly, high EIR estimates are observed in the western part of the study area, which is located to a large extent in shallows that are extensively used by local populations for rice cultivation. The transmission in this area remained high even during the dry season. Figure 2.2 in the appendix shows the monthly patterns of observed and fitted of sporozoite rate (a,b)-(c,d) and densities (e,f)-(g,h) averaged over spatial locations respectively in high and low EIR regions of the study area and for *An. funestus* and *An. gambiae*. The observed and fitted sporozoite rate and densities plots display similar patterns in both the low and high EIR regions.

The EIR maps clearly depict a strong spatial and temporal heterogeneity despite the relatively small geographical extent of the study area.

These maps are valuable tools in identifying malaria "high-transmission" areas and in prioritizing timely, control interventions. The high spatial resolution EIR estimates are also important in addressing research questions such as the relationship between malaria transmission intensity and mortality.

The lag time analysis indicated short elapsing periods between climatic suitability and rise of *An. funestus* densities as opposed to longer times required by *An. gambiae*. A possible explanation could be that rainfall quickly dries out or it streams into shallows (in case of heavy rainfall) where water is collected for an

extended period thus favouring the development of *An. funestus.* Suitable breeding sites for *An. gambiae* appear only after successive rainfalls that lead to soil saturation. Understanding the lag times between climate suitability and change in malaria transmission is important not only for delivering interventions at the right time but also for developing predictive models to support early warning systems (EWS). In many studies the choice of environmental predictors is based on biological plausibility rather than assessing whether plausibility is supported by the data generated by the study site. However, local conditions influence transmission patterns, therefore rigorous modelling approaches that take into account and estimate lag times in climatic factors are needed to increase model predictive ability.

In this study we used and systematically examined different lag structures through Bayesian variable selection implemented within a geostatistical model. Modelling lag effects via distributed lag models (Almon 1965; A. Gasparrini, Armstrong, and Kenward 2010; Antonio Gasparrini 2011) is an alternative approach to the one used in this paper, however this approach assumes that the different climatic proxies are available on a daily scale or aggregated over a common temporal resolution (e.g. month). We are currently comparing both approaches.

To our knowledge, this is the first effort in estimating and comparing the lag time between climatic suitability and malaria transmission between the two vector species. The results improve our understanding of the dynamics of malaria transmission. However it is worth noticing that the associations found in this study area may not necessarily apply in different eco-climatic zones and further work in the area could clarify how lag effects depend on ecological zone. Model based estimates of transmission can identify high transmission areas in order to prioritise interventions and support research in malaria epidemiology.

Conflicts of interest: The authors declare that they have no competing interests.

Authors Contribution

PV conceived and designed the study. ED analysed the data and drafted the manuscript.

All authors gave intellectual content and critically reviewed the drafts and approved the final manuscript.

Acknowledgments

The authors are grateful to the CRSN and the principal investigator of the INDEPTH-MTIMBA project in Burkina Faso for providing the data. This work was funded by the Swiss National foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286. DAKV was funded by SNSF project no. PDFMP3-137156.

2.6 Appendix

We assume that $\phi_i^{(k)}$'s latent observations from a stationary Gaussian spatial process $N(0,\sigma_{1k}^2 R^{(k)})$. $R^{(k)}$ models spatial correlation as an exponential function of distance d_{ij} between any pairs of locations i and j that is $R_{ij}^{(k)} = \exp(d_{ij};\rho_k)$ and ρ_k is a measure of the rate of the correlation decay with distance. The value $3/\rho_k$ estimates the maximum distance at which the spatial correlation is significant at 5% (Ecker and Gelfand 1997). The σ_{1k}^2 measures the within-location variation. Temporal correlation was introduced by monthly random effects and modelled by autoregressive (AR) process of order 1 that is $\varepsilon_t^{(k)} \sim N(\theta^{(k)}\varepsilon_{t-1}^{(k)},\sigma_{2k}^2)$ and $\varepsilon_t^{(k)} \sim N(0,\sigma_{2k}^2/1-\theta_k)$. σ_{2k}^2 and θ_k are the temporal variance and autocorrelation parameters respectively.

For the regression coefficients we adopt a non-informative normal prior distribution with large variance. We further assumed a normal prior distributions with mean zero and large variance for the coefficients of the seasonal trends, that is a_{1k} and $a_{2k} \sim N(0,10^2)$. For the spatial parameters σ_k^2 and ρ_k we adopt inverse gamma and gamma prior distributions respectively, that is $\sigma_k^2 \sim IG(2.01,1.01)$ and $\rho_k \sim G(0.1,0.1)$. Covariates were standardized in order to acquire better correlation properties and reduce the Markov chain Monte Carlo simulation computational time (Kuo and Mallick 1998a).

Convergence was assessed by Gelman and Rubin diagnostic(Brooks and Roberts 1998) and kernel density plots.

Exploratory analysis was carried out in STATA 11 (Stata Corporation, College Station, Texas, USA).


Observed SR
Fitted SR
Proportion of infected mosquitoes (SR)
a
b
c
d
Observed density
Fitted density
Mosquitoes density
e
f

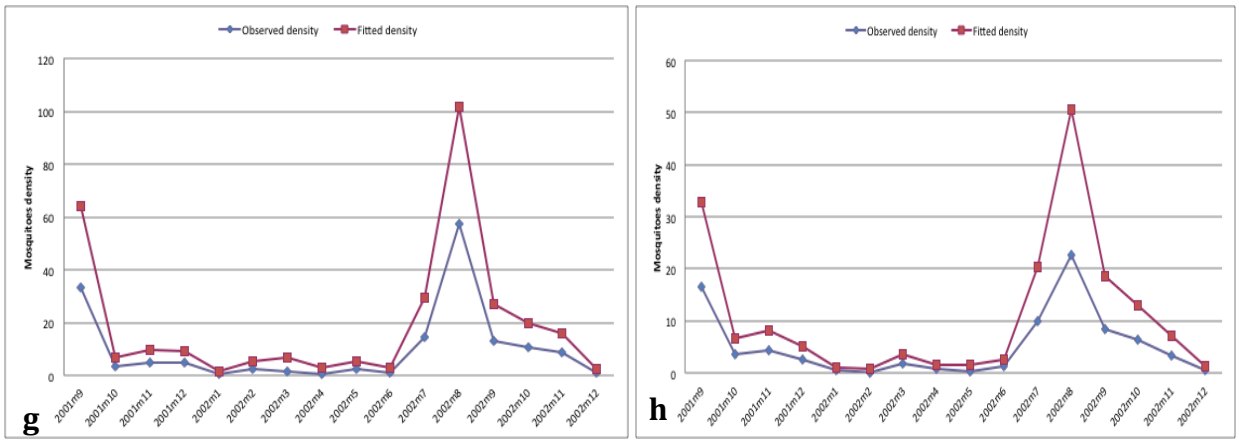


Figure legends

Figure 2.1 (a): Monthly pattern of observed and fitted sporozoite rate of *An. funestus:* averaged over spatial locations in western (high EIR) region of the study area

Figure 2.1 (b): Monthly pattern of observed and fitted sporozoite rate of *An. funestus:* averaged over spatial locations in eastern (low EIR) region of the study area.

Figure 2.1 (c): Monthly pattern of observed and fitted densities of *An. gambiae:* averaged over spatial locations in western (high EIR) region of the study area.

Figure 2.1 (d): Monthly pattern of observed and fitted densities of *An. gambiae:* averaged over spatial locations in western (low EIR) region of the study area.

Figure 2.1 (e): Monthly pattern of observed and fitted densities of *An. funestus:* averaged over spatial locations in western (high EIR) region of the study area.

Figure 2.1 (f): Monthly pattern of observed and fitted densities of *An. funestus:* averaged over spatial locations in western (low EIR) region of the study area.

Figure 2.1 (g): Monthly pattern of observed and fitted densities of *An. gambiae:* averaged over spatial locations in western (high EIR) region of the study area.

Figure 2.1 (h): Monthly pattern of observed and fitted densities of *An. gambiae:* averaged over spatial locations in western (low EIR) region of the study area.

Chapter 3: Assessing the effects of malaria interventions on the geographical distribution of parasitaemia risk in Burkina Faso

Eric Diboulo[1, 2,3], Ali Sié[1], Penelope Vounatsou[1.2 §]

[1]Swiss Tropical and Public Health Institute, Basel, Switzerland
[2]University of Basel, Basel, Switzerland
[3]Centre de Recherche en Santé de Nouna, Burkina Faso

[§]Corresponding author

This paper has been published in *Malaria Journal* 2016 15:228

Abstract

Background: Burkina Faso conducted its first nationally representative household malaria survey in 2010/2011.The survey collected among others, information on malaria interventions, treatment therapies and malaria parasite prevalence in children aged 6-59 months. **Methods**: In this study, we use Bayesian geostatistical models to assess the effects of health interventions related to insecticide treated bed nets (ITN), indoor residual spray (IRS), Artemisinin-based Combinations Therapy (ACT) coverage associated with childhood malaria parasite risk at national and sub-national level after taking into account geographical disparities of climatic/environmental and socio-economic factors. Several ITN coverage measures were calculated and Bayesian variable selection was used to identify the most important ones. Parasitaemia risk surfaces depicting spatial patterns of infections were estimated. **Results**: The results show that the predicted population-adjusted parasitaemia risk ranges from 4.04 % in Kadiogo province to 82% in Kompienga province. The effect of ITN coverage was not important at national level; however ITNs have an important protective effect in Ouagadougou as well as in three districts in the western part of the country with high parasitaemia prevalence and low to moderate coverage. There is a large variation in ACT coverage between the districts. Although at national level the ACT effects on parasitaemia risk was not important, at sub-national level 18 districts around Ouagadougou deliver effective treatment. **Conclusion**: The produced maps show great variations in parasitaemia risk across the country and identify the districts where interventions are being effective. These outputs are valuable tools that can help improve malaria control in Burkina Faso

Keywords: Bayesian, Burkina Faso, Sub-Saharan Africa, effect of malaria interventions, parasitaemia risk, geographical distribution.

3.1 Introduction

Malaria is holoendemic in Burkina Faso with most transmission occurring during or shortly after the rainy season between July to December. Ninety nine percent of infection is attributed to *P. falciparum.* The overall prevalence of infection in children aged 6-59 months is estimated at 66 % (BFDHS-MICS 2010)(Faso) and (USA) 2012). The under-5 severe malaria attributable death has been dropped from 8.1% in 2000 to 3.3% in 2010 ("Plan Stratégique 2011_2015 Palu" 2015). The government has made tremendous efforts to achieve the objectives of the 2006-2010 National Malaria Strategic Plan and implemented special programs such as home-based malaria management in 2008, universal coverage of insecticide treated bed nets (ITN) in 2010, intermittent preventive therapy (IPT) for high-risk groups in 2005, piloting of the indoor residual spray (IRS) in certain health districts since 2010, larval control and sanitation programs, introduction of effective tools for malaria control mainly the rapid diagnostic test (RDT) at all health facilities in 2010 and actual availability of Artemisinin-based Combinations Therapy (ACTs) in health facilities in 2007 ("Plan Stratégique 2011_2015 Palu" 2015).

Burkina Faso carried out the first malaria indicator survey (MIS) in 2010, a nationally representative household survey in the country compiling malaria-related indicators. MIS surveys generate a number of indicators of malaria intervention coverage that can be used to assess progress towards the goals of the global malaria action plan (GMAP) ("Household Survey Indicators for Malaria Control 12b June 2013 (RBM) - Household Survey Indicators for Malaria Control.pdf" 2015). These indicators measure ownership, use and access of ITNs, implementation of IRS, access to ACTs and to Intermittent Preventive Treatment for pregnant women (IPTp). MIS data have been used to assess effects of interventions (Giardina et al. 2012; L Gosoniu et al. 2006; Samadoulougou et al. 2014); Giardina et al. 2014; Riedel et al. 2010). Some studies reported protective effects (Giardina et al. 2012; Giardina et al. 2014) for specific interventions and others did not find any effect (Gosoniu et al. 2012b; Adigun et al. 2015). In the analysis of the Senegal MIS data of 2008, using geostatistical variable selection, we showed that among the various indicators of ITN ownership, only few were able to estimate a protective effect of ITN intervention on parasitaemia risk (Giardina et al. 2012).

Intervention effects are likely to vary in space because there is often geographical variation in the intervention coverage and their effects are related to malaria endemicity (Kobbe et al. 2007; Reid et al. 2012 ; Talisuna et al. 2015). We have recently estimated effects of vector-control interventions on changes

of malaria parasite risk at different spatial resolutions in six sub-Saharan African countries using Bayesian geostatistical models with spatially varying covariates. Results suggested that some interventions may not show any effect when looked upon at national level while they can have a protective effect at sub national level (Giardina et al. 2014).

(Samadoulougou et al. 2014) used the Burkina Faso MIS 2010 data to estimate the spatial distribution of malaria risk among children under-five of age in Burkina. The authors included only ITN use as an intervention-related predictor and estimated an overall effect at country level, which was not statistically significant.

In this study, we analyse MIS data using Bayesian geostatistical models to assess the effects of different malaria interventions at national as well as sub-national level (fifty health districts) in the country. Bayesian variable selection within geostatistical models allowed us to screen different coverage measures for each intervention and spatially structured regression coefficients measured the effects of interventions at district level. We also produce predictive maps of the disease burden adjusted for climatic effects.

3.2 Materials and Methods

3.2.1 Country profile

Burkina Faso lies mostly between latitudes 9° and 15°N and longitudes 6°W and 3°E. It is made up of two major types of countryside. The larger part of the country is covered by a “peneplain”, which forms gently undulating landscapes with, in some areas, a few isolated hills. The southwest of the country forms a sandstone massif bordered with sheer cliffs up to 150 meters high. Burkina is therefore a relatively flat country with an average altitude of around 400 meters. Four main rivers drain the country: the *Mouhoun*, the *Nakambé*, the *Nazinonand* the *Komoé*. The Mouhoun is one of the country's only two rivers which flow year-round, the other being *Komoé*, which flows to the southwest. Burkina Faso has a primarily tropical climate with two very distinct seasons. In the rainy season, the country receives between 600 and 900 millimetres of annual rainfall and malaria is known for a seasonal recrudescence during this period at which it accounts for the main cause of fever and mortality in the country. The rainy season lasts approximately four months, May/June to September, and is shorter in the north of the country. In the dry season, the” harmattan”, a hot dry wind blows from the Sahara carrying dust and dirt that contribute to high morbidity from lower respiratory infections.

3.2.2 Survey Data

The MIS was conducted by the National Institute for Statistics and Demography (INSD) with the technical assistance of ICF Macro from April 2010 to January 2011 using standardized malaria indicator questionnaire. The collected data include information on malaria indicators, education, demographics, and socio-economic characteristics.

A random sample of 574 (176 and 398 respectively in urban and rural settings) clusters and 15,000 households were selected through a stratified two-stage sampling procedure. The clusters were the census units established by INSD in the census carried out in 2006 (Récensement Général de la Population et de l'Habitat, RGPH-2006). At the first stage, 574 clusters were drawn with probability proportional to the number of households in each cluster. The sampling procedure was stratified by area type (urban/rural) of the cluster and by the administrative regions (13 regions). At the second sampling stage, a count of households in each of these 574 clusters provided a list of households from which was derived the final households sample with an equal probability systematic sampling. As part of the final sampling, one in every two households was randomly selected and every child between 6 and 59 months of age was tested for parasitaemia. Two malaria diagnostic tests were performed, namely RDT and blood smear test (microscopy). Analyses in this study are based on the results of microscopic examination since it is considered as the gold standard (Kobbe et al. 2007). Geographic information was collected at the centroid of the clusters. Figure 3.1 shows the observed prevalence reported in 540 survey locations.

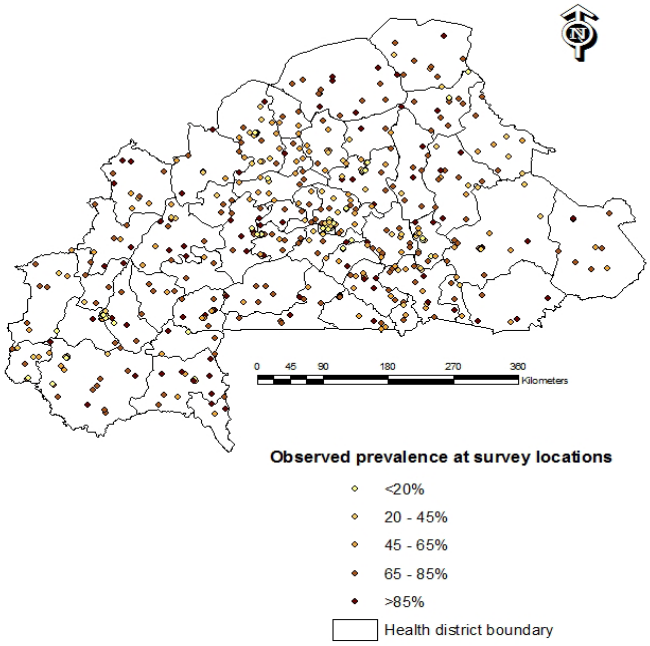


Figure 3. 1: Observed prevalence at survey locations, Burkina Faso MIS 2010.

The MIS data were used to construct intervention coverage measures related to ITN such as the number of ITNs per child under five years (ITNpU5), the proportion of children under five who slept under an ITN the night preceding the survey (ITNsU5) and the total number of ITNs per household member (ITNpPR). An indoor residual spray (IRS) coverage indicator was defined as the proportion of households sprayed with an insecticide within the last 12 months. We also generated a 'case management' coverage measure as a proxy of health system performance. It was defined by the proportion of children under five in the cluster who had received timely a first line ACT out of those reported to have fever 2 weeks prior the survey visit (ratio of ACT per reported recent fever).

Socioeconomic status (SES) was captured by mother's education and wealth index. The latter was calculated as a weighted sum of household assets; the weights were obtained through principal component analysis (Johnson and Rutstein 2004)**.** Socioeconomic quintiles ranging from the poorest to the wealthiest were included as a categorical variable in the analysis.

3.2.3 Climatic data

Malaria transmission is environmentally driven; therefore remotely sensed (RS) climatic and environmental proxies were used as predictors in the models to take into account their potential effects on parasitaemia. In particular, the following climatic and environmental factors were included in the models: land surface temperature day (LSTD) and night (LSTN), rainfall estimates (RFE), normalized difference vegetation index (NDVI), altitude, urban-rural extent, proximity to the rice field (within 5 km radius from the survey locations) and the shortest Euclidean distance to nearest water body calculated in ArcGIS 10 (ESRI; Redlands, CA, USA). Table 2.5 in the appendix indicates the sources of these data as well as their spatial and temporal resolution.

3.3 Bayesian geostatistical modelling

We fitted three Bayesian geostatistical logistic regression models, firstly to estimate the geographical distribution of malaria risk based on climatic predictors (model 1); secondly to assess the effects of malaria related interventions (i.e. ITN, IRS and ACT coverage) at national level after adjusting for climatic and socio-economic (i.e. wealth index, mothers education) confounders (model 2) and thirdly to assess the effects of the above mentioned interventions at the level of the health district (model 3). The climatic model (model 1) was fitted on the number of malaria-infected children at cluster level. The models with intervention effects (models 2 and 3) were applied on the binary outcome indicating the infection status of a child and considering the age of a child (in years) as a covariate. All models included cluster-specific random effects, arising from a Gaussian stationary process with covariance matrix capturing correlation between any pair of cluster locations as a function of their distance. Bayesian geostatistical variable selection was applied in model 1 to identify the most important set of climatic predictors (including their best functional form). In particular, for each climatic predictor an indicator was introduced to estimate the probabilities of excluding or including the predictor into the model in linear or categorical form. The categories of the predictors were defined using their quartiles. The final model included variables and functional forms with inclusion probability of more than 50%. Model 2 contained the most important climatic/environmental predictors selected in model 1 as well as age, SES, ITN, IRS and ACT coverage measures. Geostatistical variable selection was applied to select the best ITN coverage measure (i.e.

ITNpU5, ITNsU5 and ITNpPR) by introducing binary indicators specifying the exclusion or inclusion of each measure from the model.

The effects of malaria interventions (i.e. ITN, IRS and ACT coverage) at sub-national level were estimated from the geostatistical model 3 which includes the intervention coverage measures as spatially varying covariates, following model formulations used by (Giardina et al. 2014). A conditional autoregressive (CAR) prior distribution (Banerjee et al, 2014, Banerjee, Carlin, and Gelfand 2014) was considered to introduce a neighbour-based spatial structure on the regression coefficients related to each intervention effect in the study (Giardina et al. 2014; Haining 2003). Neighbours were defined as the adjacent areas (health districts) of each health district and used to create a matrix of spatial weights taking the value of one for a direct neighbour and zero otherwise. Model 3 utilises the ITN coverage measure, which was selected in model 2.

Bayesian kriging (Diggle, Tawn, and Moyeed 1998) was employed to predict the malaria parasite risk over a regular grid of 226,627 pixels at 1 km^2 resolution covering the entire study area. Population adjusted risk estimates were obtained at district level by combining pixel-level risk estimates with population data of children under 5 years. The analysis was carried out in STATA 13 (Stata corporation, College Station, Texas, USA) and OpenBUGS version 3.2.3 rev 1012 (Imperial College and Medical Research Council, London, UK). Parameter estimates were summarised by their posterior median and the corresponding 95% Bayesian credible interval (BCI). Modelling details are given in the appendix.

The predictive model was validated on a test subset of the data. A randomly selected sample of 432 locations (80% of the data location) was used as a training set for the model fit. The predictive performance of the model was assessed by calculating the proportion of observed prevalence data at the remaining 20% of the test locations, correctly estimated within Highest Posterior Density Intervals (HPDI) of probability coverage ranging from 50 to 95%.

3.4 Results

A total of 5741 children aged between 6 and 59 months from 574 clusters were tested for parasitaemia using blood smear test results. The overall observed malaria parasite prevalence was 65%. Thirty-four (5.92%) clusters had no data thus reducing the actual number of clusters to 540 (figure 3.1).

The ratio of ITN to children under 5 years old ranges from 0.33 in district of Orodara to 1.52 in Nanoro district with 11 out of the 50 districts in the country having a ratio above 1. 80% of the 50 health districts have IRS coverage less than 1%. The maximum IRS coverage of 50% was found in the districts of Diebougou and Toma. The percentage of households falling in the lowest social-economic quintile ranges from 1.6% (in Tenkodogo) to 63.33% (in Gorom-gorom). Table 3.1 gives a summary of the raw coverage measures per health district. The highest proportion of fever cases receiving ACTs is 22% and it is observed in the districts of Tenkodogo in the East central and Koudougou in the Central part of the country. Figures 3.3 (right) depict the ITNpU5, ITNsU5 and ACT coverage at health district level, respectively.

The results of variable selection are presented in Table 3.2. In particular, Bayesian geostatistical variable selection applied in the climatic model 1 indicated that the most important factors related to parasitaemia risk are LSTN (Night Land Surface Temperature) in linear form and the proximity to rice cultivation (categorical) with 74.10% and 74.50% posterior inclusion probabilities, respectively. The place of residence (rural/urban) stood out as one of most important predictors with a posterior inclusion probability of 87.20%. Geostatistical variable selection of the ITN coverage measures (model 2) showed that the proportion of children that slept under a net (U5sITN) had the highest probability (equal to 32.02%) to be included in the model among the ones that were assessed. The inclusion probability of less than 50% indicates that U5sITN is less likely to have an important effect at national scale. We included however U5sITN in model 3 as a spatially varying covariate to assess important effects at sub-national levels and identify health districts that the ITN interventions are associated with the parasitaemia risk.

Table 3. 1: Summary of raw malaria coverage measures per health district.

Health district	Number of clusters	ITNpU5 (%)	ACT (%) (# of fever cases)	IRS (%) (# of clusters)	ITNsU5 (%)	HH in lowest quintile (%)
Banfora	26	109	3 (50)	4 (1)	76	4.37
Barsalogho	6	50	2 (9)	0 (0)	50	23.94
Batie	4	73	1 (7)	0 (0)	38	59.26
Bogande	14	63	1 (26)	0 (0)	54	44.91
Boromo	4	67	0 (16)	0 (0)	56	8.93
Boulsa	9	50	3 (14)	0 (0)	47	13.04
Bousse	6	95	3 (5)	0 (0)	80	24.00
Dande	7	64	1(17)	0 (0)	58	10.00
Dano	12	61	4 (38)	0 (0)	43	47.62
Dedougou	11	73	3 (23)	0 (0)	56	15.53
Diapaga	9	121	0 (6)	0 (0)	63	59.46
Diebougou	4	133	8 (14)	50 (2)	33	14.63
Djibo	15	49	6 (33)	0 (0)	53	39.35
Dori	11	92	2 (11)	0 (0)	60	44.00
Fada N'gourma	17	97	3 (24)	0 (0)	73	28.48
Gaoua	14	109	4 (52)	0 (0)	71	47.76
Gorom-gorom	9	46	11 (14)	0 (0)	38	63.33
Hounde	5	78	0 (21)	0 (0)	50	9.33
Kaya	18	37	12 (4)	0 (0)	39	14.18
Kombissiri	6	46	10 (33)	0 (0)	20	12.50
Kongoussi	10	57	2 (6)	0 (0)	42	23.08
Koudougou	14	68	21 (38)	7 (1)	23	7.24
Koupela	15	84	10 (16)	0 (0)	58	26.04
Leo	7	66	9 (16)	0 (0)	62	14.63
Manga	13	51	2 (34)	0 (0)	21	18.52
Nanoro	4	152	9 (10)	0 (0)	100	14.29
Nouna	10	63	2 (22)	0 (0)	57	13.04
Orodara	9	33	3 (31)	0 (0)	24	20.00
Ouagadougou	36	98	13 (45)	6 (2)	42	1.16
Ouahigouya	24	136	4 (51)	0 (0)	90	15.15
Ouargaye	4	60	1 (4)	0 (0)	17	22.86
Pama	6	86	1 (8)	17 (1)	50	32.95
Po	12	54	4 (18)	0 (0)	42	31.67
Reo	11	75	6 (17)	0 (0)	55	37.23
Sapone	10	60	7 (14)	0 (0)	22	3.28
Sebba	9	87	1 (6)	11 (1)	50	51.11
Secteur 15	13	55	7 (29)	0 (0)	67	7.96
Secteur 22	12	62	8(39)	0 (0)	60	6.84
Seguenega	6	121	1 (25)	0 (0)	53	5.00
Sindou	7	68	2 (31)	0 (0)	63	7.23
Solenzo	8	85	13 (15)	0 (0)	64	20.48
Tenkodogo	18	51	22 (60)	0 (0)	58	1.06
Titao	5	116	1 (20)	0 (0)	58	25.37
To	8	66	5(22)	0 (0)	30	23.46
Toma	4	55	1 (19)	0.5(2)	67	3.64
Tougan	9	56	0 (26)	22 (2)	24	2.02
Yako	10	142	3 (31)	0 (0)	65	19.54
Zabre	4	87	7 (10)	0 (0)	88	52.08
Ziniare	19	104	5 (48)	0 (0)	49	15.00
Zorgho	15	140	11 (74)	7 (1)	91	11.68

Table 3. 2: Results of variable selection for the climatic predictors and ITN coverage measures based on Bayesian geostatistical logistic regression models. Posterior inclusion probabilities larger than 50% indicate an important predictor.

	Posterior inclusion probability (%)	
Variable	**Model 1**	**Model 2**
Altitude	28	
Distance to water body	2	
NDVI	3.30	
LSTD	6.20	
LSTN	74.10	
Rainfall	1.60	
Distance to rice growing area	0.30	
Altitude*	5.70	
Distance to water body*	4	
Area type (urban/rural)*	87.20	
NDVI*	0.20	
LSTD*	4.50	
LSTN*	3.50	
Rainfall*	1	
Distance to rice growing area*	74.50	
ITN coverage		
ITN per person (ITNpPR)	-	0.20
U5 sleep under net (ITNsU5)	-	32.02
ITN per under five years (ITNpU5)	-	2.46

*categorical form.

The predictive performance of the model (model2) is shown in figure 3.2. Eighty two (82%) of test locations were falling into all credible intervals with probability areas greater than 50%.

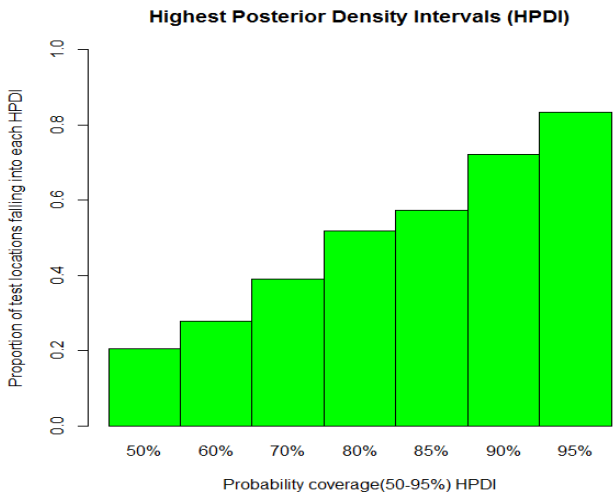


Figure 3. 2: Proportion of test locations falling in the Highest Posterior Density intervals (HPDIs).

Parameter estimates of the three models are given in Table 3.3. In particular the climatic model 1 showed a negative correlation of the parasitaemia risk with LSTN and distance to rice fields. Moreover, living in rural areas increases the odds of being infected by about 3.91 times (95% BCI: 2.88, 5.22). The minimum distance at which the spatial correlation is less than 5% is equal to 10.61km (95% BCI: 2.39-20.82). Model 2 assesses the effects of malaria interventions on parasite risk after adjusting for climatic and socio-economic confounders. Results show that none of the health intervention measure is an important predictor of parasitaemia risk at national level. However, the model indicates that the odds of malaria infection decreases with better socioeconomic conditions reaching a 68% reduction within the least poor group, OR =0.32 (95%BCI: 0.24 -0.43). An increasing gradient of malaria risk was also observed with age with the oldest age group (4-5 years old) having odds of 2.08 times higher than infants. Furthermore, the model reveals a decreasing trend of parasiteamia odds with increasing mother's education level although this decrease is not statistically important. The additional SES and malaria interventions related predictors in model 2 were able to explain some of the spatial correlation in the model. This is reflected in the estimate of the range parameter, which reduced to 3km compared to 10.6 km in model 1.

Table 3. 3: Posterior median and 95% Bayesian Credible Intervals (BCI) of the geostatistical model based on environmental/climatic, malaria intervention coverage and SES predictors.

	Geostatistical Model 1	Geostatistical Model 2	Geostatistical Model 3
Variables	OR (95% BCI)	OR (95% BCI)	OR (95% BCI)
LSTN	0.78 (0.69, 0.88)	0.81(0.72, 0.90)	0.82(0.72, 0.93)
Rice field proximity	0.49 (0.27, 0.81)	0.56 (0.34, 0.98)	0.73 (0.43, 0.99)
No	1.00	1.00	1.00
Yes	0.49 (0.27, 0.81)	0.56(0.34, 0.98)	0.73(0.43, 0.99)
Area type			
urban	1	1	1
rural	3.91(2.88, 5.22)	2.50(1.89, 3.35)	2.36(1.79, 3.13)
SES			
Most poor		1	1
Very poor		0.76(0.61, 0.95)	0.77(0.61, 0.96)
Poor		0.90(0.71, 1.14)	0.92(0.73, 1.16)
Less poor		0.70(0.55, 0.89)	0.71(0.56, 0.90)
Least poor		0.32(0.24, 0.43)	0.33(0.25, 0.45)
Age (yrs)			
0-1		1	1
1-2		1.56(1.23, 1.56)	1.21(0.95, 1.55)
2-3		1.72(1.35, 2.21)	1.71(1.33, 2.19)
3-4		1.88(1.48, 2.41)	1.87(1.47, 2.39)
4-5		2.08(1.62, 2.67)	2.07(1.61, 2.65)
Mother's education			
No education		1	1
Primary		1.08(0.89, 1.31)	0.85 (0.71, 1.03)
Secondary		1.06(0.74, 1.54)	0.88 (0.61, 1.27)
Higher		1.44(0.29, 6.49)-	0.42 (0.05, 2.13)
Case management (ACT)	-	1.45(0.49, 4.21)	0.13 (-1.49, 1.67)
U5 sleep under net (ITNsU5)	-	1.66(0.89, 3.08)	0.25 (-0.37, 0.90)
House Spray (IRS)	-	1.14(0.17, 7.23)	0.11 (-1.75, 1.70)
Variances			
Gaussian process	0.87(0.66, 1.15)	0.6(0.44, 0.80)	0.55(0.39, 073)
Spatially varying ITNsU5			0.57 (0.38, 0.88)*
Spatially varying IRS			0.76 (0.42, 1.75)*
Spatially varying ACT			0.75 (0.42, 1.84)*
Range (km)[a]	10.61(2.39, 20.82)	3.00(0.40, 10.00)	2.70 (0.44, 9.75)

a: minimum distance in kilometer at which the spatial correlation is lower than 5%
Model1 includes only climatic factors,
Model2 includes climatic factors, age, SES , intervention measures
Model3 has spatially varying covariates for IRS, ACT and ITNsU5
*Posterior median

Figures 3.3a-c depict the predicted parasitaemia risk maps (median (a), 2.5th (b) and 97.5th (c) percentiles of the posterior predictive distribution estimated from model 2) in children less than 5 years of age at 1 km^2 spatial resolution in Burkina Faso. Estimates show that malaria parasitaemia risk ranges from 36% to 71% across the country while the median predicted prevalence is 59%. The Southwest, Comoe, Cascade, East, Central-west, Boucle du Mouhoun and the Sahel regions bear the highest prevalence. The central, the North, the east central and regions appear to be the less burdened regions. The total number of infected children under five years old in the country was estimated to be 1,097,296. Table 3.4 presents the population-adjusted and estimated number of infected under five children under 5 years of age per province and region.

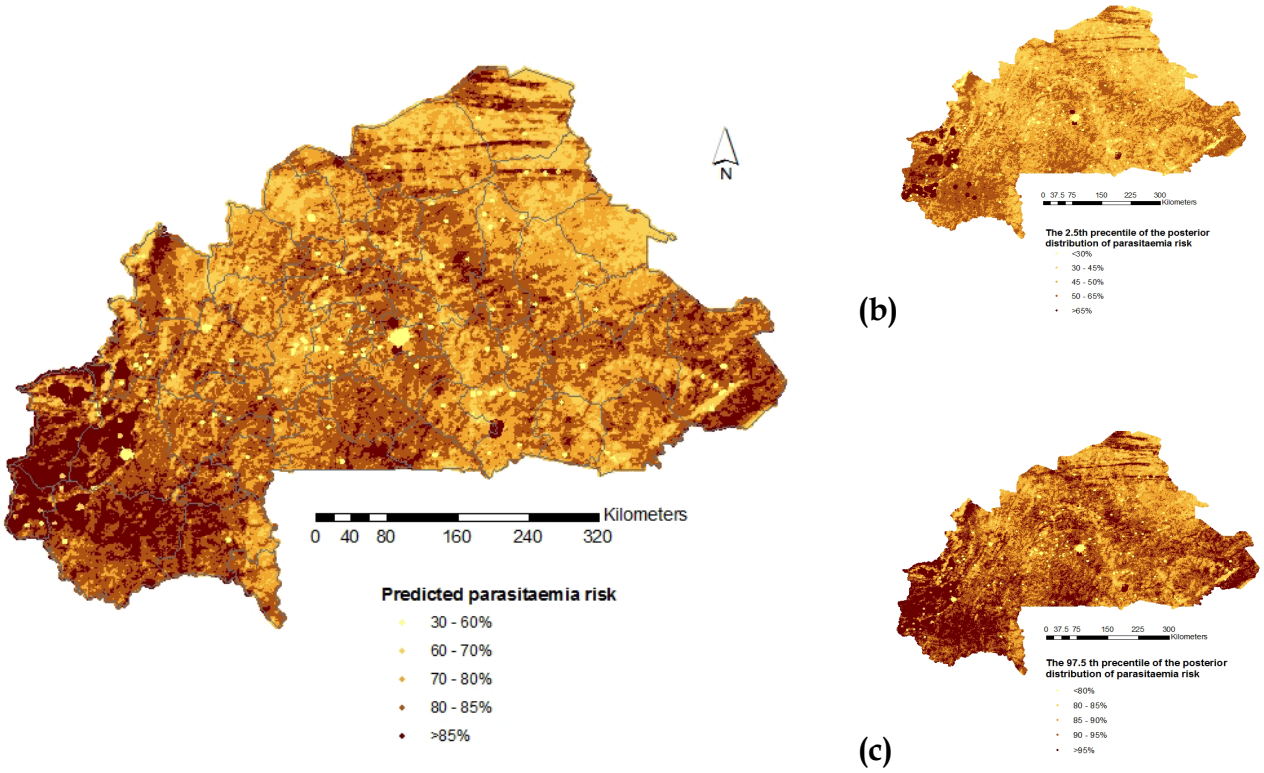


Figure 3. 3: Predicted parasitaemia risk map in children under 5years old based on the (a) median 2.5th percentiles and 97.5th percentiles of the posterior predictive distribution estimated from model 2 at 1 km^2 resolution. Province boundaries are overlaid.

Table 3. 4: Population-adjusted and estimated number of infected children under five years old per province and region.

Region	Province	Observed prevalence (%)	Population of under 5 children	Population adjusted estimated prevalence	Estimated number of infected children
Boucle du Mouhoun	**Bales**	79	37601	17.72	17646
	Banwa	78	47308	16.92	21975
	Kossi	76	48528	28.96	18321
	Mouhoun	74	52335	20.85	21159
	Nayala	81	28425	19.12	13828
	Sourou	63	38168	21.79	18577
Cascades	**Comoe**	59	71772	33.13	32656
	Leraba	55	20765	25.44	8000
Centre	**Kadiogo**	34	243402	4.04	139826
Centre-Est	**Boulgou**	62	98226	10.91	41548
	Koulpelogo	75	47315	18.04	18495
	Kouritenga	52	59702	7.44	24678
Centre-Nord	**Bam**	60	50553	11.46	24229
	Namantenga	78	60409	16.08	27146
	Sanmatenga	62	109630	13.10	46970
Centre-Ouest	**Boulkiemde**	64	87305	8.20	34159
	Sanguie	88	51241	14.39	24188
	Sissili	75	37038	28.00	16542
	Ziro	77	31847	27.71	12820
Centre-Sud	**Bazega**	67	39878	15.11	17614
	Nahouri	71	27251	20.69	11722
	Zounweogo	75	42191	13.65	18243
Est	**Gnagna**	74	78380	18.22	31657
	Gourma	66	59266	33.75	22215
	Komandjari	41	15841	47.24	7041
	Kompienga	73	15690	81.72	5842
	Tapoa	67	67016	38.67	25250
Haut-Bassins	**Houet**	52	148488	10.68	76584
	Kenedougou	65	44522	25.62	20182
	Tuy	75	35504	21.55	18267
Nord	**Loroum**	72	25989	20.06	12062
	Passore	56	57802	9.67	25994
	Yatenga	66	99943	9.80	47657
	Zandoma	60	30413	8.98	13394
Plateau central	**Ganzourgou**	66	56713	10.46	27228
	Kourweogo	52	24218	9.90	11251
	Oubritenga	65	42149	10.15	18400
Sahel	**Oudalan**	72	35453	46.15	14507
	Seno	63	47034	19.54	23291
	Soum	85	62279	31.43	26560
	Yagha	51	28730	34.73	12464
Sud-Ouest	**Bougouriba**	59	17941	24.32	7492
	Ioba	83	33185	15.01	14889
	Noumbiel	87	12456	36.51	5086
	Poni	76	45305	26.78	19638

Spatially structured coefficients of intervention coverage measures obtained by model 3 allowed estimation of the effect of ITN, IRS and ACT at health district level. Figure 3.3 presents the different coverage (right hand side maps) and intervention effects (left hand side maps) for each health district estimated from model 3 with the spatially varying covariates. ACT coverage appears to be an important health system component associated with decreased malaria parasitaemia risk in a number of the health districts. However the strongest effects are observed in the districts of Ouagadougou, Koudougou, Kaya, Zorgho, Koupela and Tenkodogo. ITN usage shows a protective effect in only 4 health districts namely Ouagadougou, Ziniare, Ouahigouya and Sebba. IRS, which, is in a pilot phase in the district of Diebougou (South-west) did not show any effect.

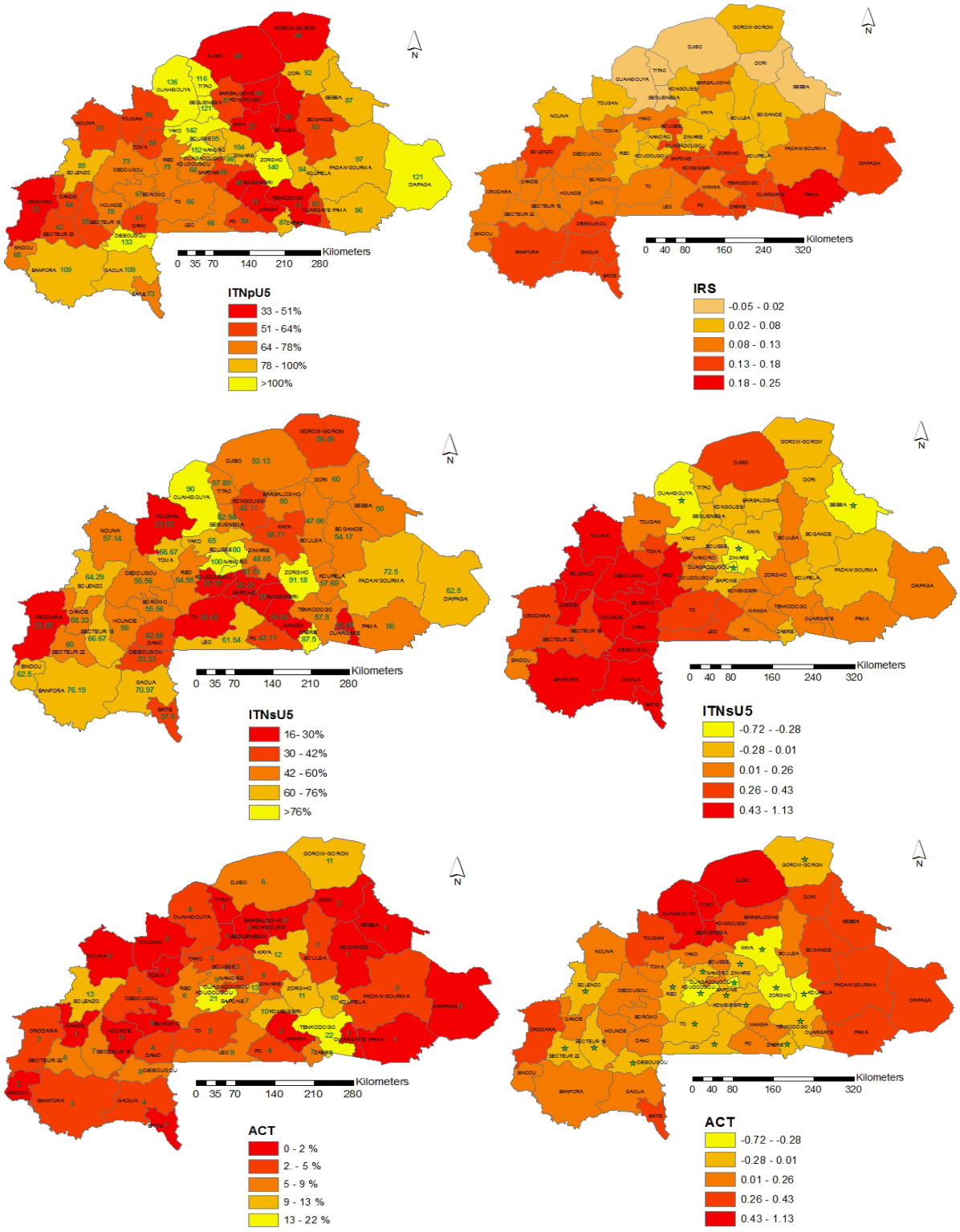


Figure 3. 4: Coverage (right) and intervention effects (left) maps of ITNpU5, ITNsU5, IRS and ACT

Important effects are indicated with (*) and correspond to 95% Bayesian credible intervals that do not include 0.

3.5 Discussion

This is the first study in Burkina Faso, which estimates the spatial effects of malaria interventions on the geographical distribution of parasite risk. We calculated different ITN coverage measures related to bed net use and ownership and studied the effects of ITN, IRS and case management coverage on the spatial pattern of malaria risk after taking into account disease variation due to climatic and socio-economic factors. We also obtained georeferenced estimates of the parasite risk and of the number of infected children. Our study analysed the Burkina Faso MIS survey data of 2010 and employed Bayesian geostatistical models with spatially varying covariates using geostatistical variable selection to identify the most relevant bed net coverage indicators. Our geostatistical variable approach identified a list of the most important climatic and environmental predictors. Weiss (2015) proposed a list potential predictors that could be used to improve malaria modelling (Weiss et al. 2015).

The most important ITN coverage measure was the proportion of children under five years old sleeping under bed net, with however a low posterior probability to be included in the model equal to 32.02% followed by far by the number of ITN per under five (2.46%) and the number of ITN per household member (0.20%). This finding support previous results showing that contingent upon the setting and the prevailing conditions, ITN ownership and ITN use may show different ability in capturing ITN intervention effects on parasitaemia (Giardina et al. 2012).

Overall, the effect of interventions in Burkina Faso was not significantly associated with change in malaria parasitaemia risk at country level. These results are in line with the findings of Giardina (2014) in a multisite study. The lack of statistically important ITN intervention effects may be explained by the fact that at country-level, a sizeable percentage (37.97%) of children under the age of five years still do not sleep under ITN. However when analysed at sub-national level (health district level) some interventions show protective effects in certain districts. For instance ITN use, which appeared to have not an important effect at national level proved to be an effective intervention in four health districts namely Ouagadougou, Ziniare in the central region of the country, Ouahigouya in the North and Seeba in the Sahel region. Among factors that might affect ITN effectiveness feature the inadequate coverage and the uneven distribution of ITN and the usage among households and health districts (“eLife Digest” 2015).

Indeed, malaria is holoendemic in Burkina Faso and the transmission occurs throughout the year. In such settings, even significant reductions in the total exposure would not necessarily warrant substantial

reductions in parasitaemia (Bødker et al. 2006; T. A. Smith, Leuenberger, and Lengeler 2001b; Trape and Rogier 1996; Robert W. Snow and Marsh 1995). Furthermore, there is still an incomplete ITN utilization compliance (62.03%) among children under the age of five years. ITN intervention is expected to be more effective in low transmission settings and with the highest ITN usage (Apinjoh et al. 2015). Districts where ITN usage was found to be protective are located in low to mild transmission settings and ITN usage ranges from 42 to 90% (Prevention 2016).

ACT showed a protective effect in 19 health districts. However it is worth noting that except Gorom-gorom in the Sahel region, Solenzo in the North West (Boucle du Mouhoun), secteur 15 and 22 in the West (Hauts-bassins) and Diebougou in the Southwest, the remaining districts where ACT showed a protective effect are located in the central region. A close inspection of the coverage levels shows that ACT tends to be effective in districts where a minimum level of coverage is achieved (above 5%). This finding supports the hypothesis that the effectiveness of a given intervention is related to both its coverage as well as the transmission levels. Indeed, the ACT effect is presumably limited by very low coverage (Okell et al. 2008). High levels of transmission are also believed to limit the effect of ACT. Findings from a study conducted in Tanzania suggested that the percentage reductions in prevalence of infection and incidence of clinical episodes achieved by ACT were much higher in areas with low initial transmission (Okell et al. 2008). ITN interventions, however, aim at reducing the malaria transmission intensity by reducing the chances that an individual will be bitten by an infective Anopheles mosquito (Eisele, Larsen, and Steketee 2010). However low compliance and actual usage may seriously limit the potential impact of ITNs (Prevention 2016), (Hawley et al. 2003). Therefore conjugate efforts to increase both the ACT coverage (in order to reduce the prevalence) and ITN usage (to further reduce the transmission) are required to warrant a synergetic effect towards a better and effective control of the disease (Fullman et al. 2013). Findings from a continental study that used data from 32 malaria-endemic African countries showed that ITN intervention was the most important and effective malaria intervention accounting for an estimated 68% declines in malaria parasite rate in 2015, followed by ACT (19%) and IRS (13%) (Bhatt et al. 2015). Our study showed an important effect of ITN at some districts, however at country level the effect was not important.

IRS was not associated with malaria parasitaemia risk most probably owing to an extremely low percentage of houses sprayed within the last 12 months (0.92%) prior to the survey.

Malaria is known to be a climate-driven disease and among the most important climatic factors features temperature. The model-based parasitaemia risk map depicts a strong spatial with lower parasitaemia risk estimated in the cities (urban settings) relative to rural settings. Our results show a negative association between increased night temperature and malaria transmission. Laboratory experiments observed the shortest *An. gambiae s.s* larval survival (<7 days) at 10-12°C and 38-40°C and the highest larval mortality occurring between 30-32°C, with death (rather than adult emergence) representing over 70% of the terminal events in mosquitoes originally from Lagos (Nigeria) (Bayoh and Lindsay 2004). In Burkina Faso, the monthly mean temperature in the hottest and driest period (March-May) is constantly well above 31°C. Land surface night temperature, therefore appears to be an important predictor of malaria transmission. Furthermore, the behavioural high temperature avoidance experiment showed that *An. Gambiae,* the most efficient malaria vector species in Burkina Faso, was more sensitive to increased temperatures than its sibling *An. arabiensis* (Bayoh and Lindsay 2004). In nature, this probably results in short distance flights to seek cooler spots, typically the shaded resting sites under vegetation outdoors or cool dark comers indoors. The highly endophilic nature of *An. gambiae* protects the mosquito from the highly variable and more extreme external climate. This may explain the negative association between increased LSTN and the transmission because during the hot night spells local populations rest outdoor thus reducing knowingly or unknowingly the contact human-vector. The authors also found that female temperature avoidance was most pronounced in hungry females (which avoid temperatures above 25°C), less strong in blood-feds (above 30°C) and least strong in newly emerged females (above 32°C). High night temperatures were also found to affect *An. gambiae* (one of the most predominant and effective malaria vector in Burkina Faso) behaviour and vectorial capacity (Cator et al. 2013; Kirby 2005).

A significant negative association between temperature and malaria infection was also found in a previous study in Burkina Faso (Samadoulougou et al. 2014); However the authors did not consider day and night temperatures separately and the climatic data considered in this study do not span the study period (April 2010-January 2011).

Our study estimated a negative association between malaria parasitaemia and proximity with rice growing areas. The rice growing areas used in this study were extracted from the National land use database with cartographic scale coverage of 1/200000 which features only large and economically relatively important rice growing areas. Furthermore, as exposed to an increased risk of malaria infection, surrounding populations receive relatively high attention from the local government including regular sensitization

campaigns (Information Education and Communication). Consequently, as an income generating activity, the local population is relatively well off. This makes it easier to access health care and other protective measures. This effect is known in Burkina Faso as the "paddy paradox" defined as the occurrence of large populations of vectors but low amounts of malaria transmission where irrigated rice is grown. Furthermore it is hypothesized that the "paddy paradox" is due to young pre-gravid mosquitoes dispersing more widely than gravid ones, not necessarily to low survival in the mosquito (J. D. Charlwood et al. 2011). Another reason might be the displacement of the most endophilic and anthropophilic malaria vector *Anopheles funestus* Giles by *An. arabiensis* Patton with lower vectorial capacity, as the latter thrives more than the former in rice fields. Similarly, among members of the *An. gambiae* complex, some cytotypes of *An. gambiae* sensu stricto are more vectorial than others (Ijumba and Lindsay 2001). Furthermore, studies in Burkina Faso, Ghana, Gambia and Tanzania where malaria is stable showed that there is less malaria in irrigated communities than surrounding areas (Ijumba and Lindsay 2001; J. D. Charlwood et al. 2011; Boudin et al. 1991; Lindsay et al. 1991).

The predicted spatial distribution of malaria parasitaemia risk ranges from 36% to 71% across the country while the median predicted prevalence is 59%. Our predicted parasitaemia map shows the higher risks in the Southwest, South-Central and the Eastern region of the country. The above mentioned regions coincide with the regions of country bearing the highest vegetation density and receiving the highest annual rainfall relative to the northern part which receives less rainfall and is more "desertic". Our predicted parasitaemia risk map shows similarities as well as discrepancies with the previous mapping efforts. Compared to the Plasmodium falciparum endemicity map in 2010 in Burkina Faso by the Malaria Atlas Project (MAP) team, common patterns were found especially in the northern and north-eastern parts of country, which appeared to be less burdened (Gething et al. 2011). The two efforts consistently found lower parasitaemia risk in urban settings. However, the highest burden of the disease was found to be in the northwestern part of the country on the MAP endemicity map in 2010, while our predicted parasitaemia risk map placed the highest burden in the southwestern part of the country. Another previous mapping effort indicated the northern part of the country as the most burdened region, whereas the southwestern region appeared among the least burdened region of the country (Samadoulougou et al. 2014). The discrepancies may be explained by the difference in the climatic/environmental and other predictors used in the different models.

This study estimated higher number of infected children in the cities despite the relatively low prevalence observed in the urban settings. This finding is consistent with the results from previous study that used the BFDHS-MICS 2010 data (Samadoulougou et al. 2014). We also observed differences between raw and population-adjusted parasitaemia risk estimates which is explained by the low prevalence observed in densely populated areas. For example the province of Kadiogo, one of the smallest provinces with the highest population density and the lowest population-adjusted raw parasitaemia risk (34%), shows an even lower parasitaemia risk adjustment for the population (4.04%). Similar results were found using Senegal MIS 2008 data (Giardina et al. 2012).

We found an increasing risk gradient with age. Infants had the lowest risk while older children had the highest risk. We also observed an association between socio-economic status and malaria risk with children within the least poor quintile being substantially at reduced risk. Similar results were observed in a previous study in Burkina Faso and in other malaria endemic areas (Giardina et al. 2012; Samadoulougou et al. 2014).

3.6 Conclusions

Our study provides estimates of the effects of malaria interventions at country as well as at local scale. Our estimated risk and intervention effect maps are valuable tools for identifying high-risk areas and areas with less effective interventions in order to improve malaria control in Burkina Faso. These outputs can serve as benchmarks to evaluate the effectiveness of future control interventions and progress of the efforts towards disease control.

Acknowledgment

The authors are grateful to the entire staff of the Centre de Recherche en Santé de Nouna (CRSN), DHS MEASURE Evaluation, the MoH of Burkina Faso and all collaborating institutions whose contributions have enabled this study. This work was funded by the Swiss National foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286 and a European Research Council (ERC) advanced grant

Authors Contribution

PV conceived the study and supported the data analysis. ED analyzed the data and drafted the manuscript. The entire authors gave intellectual inputs, revised the drafts and approved the final manuscript.

Competing Interest: The author have declared no competing interest

3.6 Appendix

Let Y_{ij} indicate the malaria parasitaemia status of child i at location s_j. We assume that Y_{ij} follows a Bernoulli distribution $Y_{ij} \sim Ber(p_{ij})$ and is related to its predictors using a logistic regression model, that is, $\log it(p_{ij}) = \beta_0 + \sum_{k=1}^{K} \beta_k X_{ij}^{(k)} + \phi_j$, where p_{ij} is the risk of child i at location s_j of having malaria parasites, $\boldsymbol{\beta} = (\beta_0, \beta_1, ..., \beta_K)^T$ is the vector of the K regression coefficients. Spatial correlation is taken into account by adding location-specific random effects ϕ_j modelled by a Gaussian process, $\boldsymbol{\varphi} = (\varphi_0, \varphi_1, ..., \varphi_K)^T \sim N(0, \Sigma)$ with variance-covariance matrix related to an exponential correlation function between locations, that is $\sigma^2 \exp(-d_{ij}\rho)$, where d_{ij} is the Euclidian distance between location s_j and s_l, σ^2 is the geographic variability and ρ is a smoothing parameter that controls the rate of correlation decay with increasing distance. Bayesian geostatistical models fitted via Markov Chain Monte Carlo (MCMC) simulation were employed for parameter estimation and predictions. The specification of the Bayesian hierarchical model requires prior distribution for all model parameters. The spatial correlation parameters σ and ρ were assigned an inverse gamma and a gamma prior respectively, $p(\sigma) \sim IG(a_1, b_1)$ and $p(\rho) \sim G(a_2, b_2)$.

Bayesian variable selection was carried out to identify the best set of predictors and their functional form using a variable selection approach known as stochastic search (George and McCulloch 1993a). In particular, for each predictor $\underset{\sim}{X}_p$ we introduce a categorical indicator parameter I_p suggesting exclusion of the predictor from the model ($I_p = 0$), inclusion in linear ($I_p = 1$) or categorical form ($I_p = 2$). I_p has a probability mass function $\prod_{j=0}^{2} \pi_j^{\delta_j(I_p)}$ where π_j are the inclusion probability of functional form j (i.e. $j = 0,1,2$) such that $\sum_{j=0}^{2} \pi_j = 1$ and $\delta_j(\cdot)$ is the Dirac function, $\delta_j(I_p) = \begin{cases} 1 & if \;\; I_p = j \\ 0 & if \;\; I_p \neq j \end{cases}$. Furthermore, we assume a spike and slab prior for the corresponding regression coefficient. For the coefficient β_p of the predictor in linear form we take $\beta_p \sim \delta_1(I_p) N(0, \tau_p^2) + \left(1 - \delta_1(I_p)\right) N(0, \upsilon_0 \tau_p^2)$ proposing a non-informative prior for β_p in case $\underset{\sim}{X}_p$ is included in the model in linear form (slab) and an informative normal prior

shrinking β_p to zero (spike) if $\underset{\sim}{X}_p$ is excluded from the model. Similarly, for the coefficient $\{\beta_{p,l}\}_{l=1,...L}$ corresponding to the categorical form of $\underset{\sim}{X}_p$ with L categories, we assume that $\beta_{p,l} \sim \delta_2(I_p)N(0,\tau^2_{p,l}) + \left(1-\delta_2(I_p)\right)N(0,\upsilon_0\tau^2_{p,l})$. For the inclusion probabilities, we adopt a non-informative Dirichlet distribution with hyper-parameter $\boldsymbol{\alpha} = (1,1,1)^T$ that is,

$\boldsymbol{\pi} = (\pi_0, \pi_1, \pi_2)^T \sim Dirichlet(3, \boldsymbol{\alpha})$.

Age and socioeconomic quintiles were not part of the variable selection. Continuous covariates were standardized in order to acquire better correlation properties and reduce the Markov chain Monte Carlo simulation (MCMC) computational time (Kuo and Mallick 1998b).

We estimate model parameters using Markov chain Monte Carlo simulation (Gibbs sampling) (O'Hara and Sillanpää 2009). Starting with some initial values about the parameters, we run two chains sampler discarding the first 5000 iterations. Convergence was assessed by Gelman and Rubin diagnostic(Brooks and Roberts 1998) and kernel density plots.

Estimating the effect of intervention at sub-national (health district) level

We extend the above model to include intervention coverage measures with spatially varying coefficients as follows: $\log it(p_{ij}) = \beta_0 + \sum_{k=1}^{K}\beta_k X_{ij}^{(k)} + \sum_{m=1}^{M} b_{mj} Z_i^{(m)}(A_j) + \phi_j$, where $Z_i^{(m)}(A_j)$ is the m intervention coverage measure aggregated over the health district A_j of the s_j location, b_{mj} is the corresponding spatially varying coefficient (i.e. effect of intervention at A_j district) and M is the number of spatially varying interventions. We assumed Gaussian conditional autoregressive (CAR) prior distributions for the $\boldsymbol{b}_m$, that is $\boldsymbol{b}_m \sim N(b_{m0}\mathbf{1}, \boldsymbol{\Sigma}_m)$ where b_{m0} is the overall effect of the m intervention at country level and $\boldsymbol{\Sigma}_m^{-1} = \sigma_m^{-2}(D-W)$, D is a diagonal matrix with entries, the sum of the neighbours of each health district, W is a proximity matrix.

Table 3. 5: Environmental and climatic data

Source	Data	Period	Spatial Resolution	Temporal Resolution
Moderate Resolution Imaging Spectroradiometer (MODIS) Terra	Day & Night Land Surface Temperature (LST)	2010-2011	$1\times1km^2$	8 days
Moderate Resolution Imaging Spectroradiometer (MODIS) Terra	Normalized Difference Vegetation Index (NDVI)	2010-2011	$0.25\times0.25km^2$	8 days
Afripop	Population data	2010	$1x1km^2$	na
Africa Data Disseminating Services	Rainfall	2010-2011	$8\times8km^2$	10 days
Digital Elevation Model (Altitude)	Shuttle Radar Topographic Mission (SRTM)	2000	$1\times1km^2$	na
National database of land use	Rice cultivation field	2002	$0.25\times0.25km^2$	na
Health Mapper	Water Bodies	-	$1\times1km^2$	na
Global Rural and Urban Mapping Project	Urban Rural extent	2010	$1\times1km^2$	na

Chapter 4: Bayesian geostatistical modelling of infant and under-five mortality in relation to malaria endemicity: An analysis of Burkina Faso Health and Demographic Survey-Malaria Indicator Cluster Survey (DHS-MICS) data

Eric Diboulo[1, 2, 3], Ali Sié[3], Penelope Vounatsou[1,2 §]

[1]Swiss Tropical and Public Health Institute, Basel, Switzerland
[2]University of Basel, Basel, Switzerland
[3]Centre de Recherche en Santé de Nouna, Burkina Faso

[§]Corresponding author

This manuscript is prepared for submission to *Tropical Medicine & International Health Journal*

Abstract

Background: There has been a remarkable decline in the child deaths over the past quarter of a century worldwide. However in Africa, under-five mortality still remains a major public health problem with malaria still featuring among the top leading causes of hospital consultations and deaths in most Sub-Saharan Africa (SSA) countries.

Data and Method: In this study, we used data form the Burkina Faso first nationally representative household survey focusing on malaria-related indicators, Burkina Faso Demographic and Health Survey-Multiple Indicator Cluster Survey (BFDHS-MICS 2010) and employed Bayesian geostatistical Weibull survival models to explore the relation between malaria and infant/child mortality in Burkina Faso after adjusting for child, household characteristics as well as mother's birth history.

Results: Under five mortality hazard is significantly higher among children born in urban settings where malaria prevalence is above 75%, HR = 3.20 (95% CI: 1.01-10.46). There was no relation between infant and child mortality with malaria in rural settings. No relation was also observed between malaria and infants mortality in the urban settings. The mortality hazard among infants from households in low SES quintiles was significantly higher in both rural and urban settings. Infants born to mothers aged between 20 and 39 years old in rural settings have significantly reduced mortality hazard. Infants born to large households in rural areas have significant higher mortality hazard. Infants born within households with 3 or more under five children in both places of residence are at significantly reduced mortality hazard. This applies to children under five in rural areas. Infants' hazard of death was significant lower among those with average and large birth size in urban settings. This also applies to children under five born with large birth size in rural settings. Children and infants born from a non-singleton outcome had significantly higher mortality hazard.

Conclusion: There is a significant relationship between malaria endemicity and child survival in urban settings. Children living in the urban settings with endemicity level above 75% have higher mortality hazard. Other predictors of infants and child survival are those related to biological (birth size, mother age at birth), demographic socioeconomic and antenatal care factors.

Keywords: Bayesian, geostatistical, malaria, mortality, Demographic and Health Survey, infant, children, Burkina Faso.

4.1 Introduction

Under-five mortality still remains a major public health problem in Sub-Saharan Africa (SSA) despite important efforts over the last decades. An estimated 5.9 million children under five died in 2015 worldwide about half of the deaths occurred in SSA ("WHO | Under-Five Mortality" 2014), ("WHO | Levels and Trends in Child Mortality 2012" 2014). Despite the relatively high rate of under-five mortality in SSA, there are signs of decline with a pace that has increased from 1.8% per year in 1990-2000 to 3.9 per year 2000-2015. However, this progress is slow, and the Millennium Development Goal for child survival (MDG4) target was missed at the global level.

In Burkina Faso, the under-five mortality rate was measured at 89 per 1000 live births in 2015. The leading causes of childhood death are neonatal death (27%), malaria (23%), diarrhea (10%), pneumonia (16%) and injuries (5%) (WHO/CHERG 2012). Malaria features among the top leading under-five causes of death, however the under-5 severe malaria attributable death which is a key indicator of malaria control programs (de Savigny and Binka 2004), declined remarkably over the last ten years from 8.1% in 2000 to 3.3% in 2010. This decline can partly be attributed to the success in a wide range of malaria interventions and control programs such as insecticide treated nets (ITN), actual availability of artemisinin-based combinations therapy (ACTs) in health facilities (2007); launch of home-based malaria management (PECADO) strategy (2008); introduction of the rapid diagnostic test (RDT) as part of malaria case management at all health facilities (2010); universal coverage of ITNs (2010) and intermittent preventive therapy (IPT) for high-risk groups as part of the strategic plan against malaria 2006-2010. Understanding the relationship between malaria endemicity and infant/child mortality is not only important for estimating the burden of clinical malaria but also crucial for predicting and assessing the effectiveness of interventions.

It is worth noting that in the absence of reliable data sources, malaria burden estimates (Murray et al. 2012) in most Sub-Saharan Africa are derived from either hospital-based records (case fatality rates) or rely on fragmented surveillance and assumptions with unknown validity (Bhatt et al. 2015). Furthermore, in most of the SSA countries the health systems provide only a small and distorted picture of the true underlying population level burdens of the disease. The largest proportion of affected population is deflected from the health services by issues including socioeconomic access, geographic and physical access, quality of health services (Don de Savigny 2004) .

Information on malaria prevalence and child mortality can be obtained from Malaria Indicators Surveys (MIS) and Demographic and Health and Surveys (DHS). These data could be used to quantify the malaria related mortality. Furthermore, MIS and DHS surveys are standardized and carried out at a lot more frequent intervals than any other malariology survey.

In the past malaria risk data from the mapping malaria risk in Africa (MARA) project has been linked with DHS data to estimate the relationship between infant and child mortality with malaria endemicity, however no important relation was found, most likely due to age heterogeneities of the historical data across survey locations, and the geographical and temporal misalignment between the MARA and DHS data (Gemperli et al. 2004a).

Recently, Abbas et al. (under review) linked Nigeria and DHS and Malaria Indicator Surveys (MIS) data and showed a significant relationship between malaria endemicity and infant and child mortality. The two surveys however were not aligned in space or in time.

Burkina Faso conducted its first nationally representative household survey focusing on malaria-related indicators in 2010 (DHS-MICS 2010). The survey collected among others, georeferenced information on interventions, case management and malaria parasite prevalence in children aged 6-59 months. Comprehensive birth histories were also collected from female respondents aged 15-49 years. This is the first DHS survey that provides spatially aligned information on malaria endemicity and child mortality.

In this study, Bayesian geostatistical Weibull survival models were employed to explore the relationship between malaria and infant/child mortality while adjusting for both individual child and household or family (bio-social) characteristics as well as mother's birth history.

4.2 Materials and Methods

4.2.1 Country profile

Burkina Faso lies mostly between latitudes 9° and 15°N and longitudes 6°W and 3°E. It has primarily a tropical climate with two very distinct seasons. The country receives between 600 to 900 mm of annual rain. The rainy season lasts approximately four months, May/June to September, and is shorter in the north of the country. During the rainy season, malaria accounts for the main cause of fever and mortality in the

country. In the dry season, the" harmattan", a hot dry wind from the Sahara blows and brings up dust and dirt, lower respiratory infections feature then as the main cause of morbidity. The country is divided in three climatic zones: the Sahel, the Sudan-Sahel, and the Sudan-Guinea. Further details on the country profile are provided by (Diboulo et al., 2016).

4.2.2 Survey Data

The MIS was conducted by the National Institute for Statistics and Demography (INSD) with the technical assistance of ICF Macro from April 2010 to January 2011 using standardized malaria indicator questionnaire. The collected data include information on malaria indicators, education, demographic, and socio-economic characteristics.

A random sample of 574 (176 and 398 respectively in urban and settings) clusters and 15,000 households were selected through a stratified two-stage sampling procedure. The clusters were the census units established by the National Institute for Statistics and Demography (INSD) in the census carried out in 2006 (Récensement Général de la Population et de l'Habitat, RGPH-2006). At the first stage, 574 clusters were drawn with probability proportional to the number of households in each cluster. The sampling procedure was stratified by area type (urban/rural) of the cluster and by the administrative regions (13 regions) where key indicators estimates are available. At the second sampling stage, a count of households in each of these 574 clusters provided a list of households from which was derived the final households sample with an equal probability systematic sampling. As part of the final sampling, one in every two households was randomly selected and every child between 6 and 59 months of age was tested for parasitaemia. Comprehensive birth histories were also collected from all de facto and de jure mothers aged 15-49 years present in the selected household on the night before the survey. Geographic information is available at cluster level. Two malaria diagnostic tests were performed, namely RDT and blood smear test (microscopy). The study population for this analysis includes children born between zero and five years preceding the survey and survived or not the childhood.

4.2.3 Explanatory variables

Malaria endemicity levels in the present analysis were constructed from the microscopy results. The prevalence was categorized into four groups defining different endemicity levels: 0-15%, 15-25%, 25-75%

and above 75%. This categorization was informed by exploratory analyses and some initial categories were combined to gain sufficient number of observations. Furthermore, we used socioeconomic (i.e maternal highest education level, type of place of residence (urban/rural) and wealth index quintiles), demographic (i.e. age of the mother at birth, sex of the child) and biosocial predictors such as birth order, size of child at birth, place of delivery, preceding birth interval (months), number of antenatal visits during pregnancy, numbers of household members, number of children aged 5 and under in household, outcome of the delivery (child is twin).

4.3 Statistical analysis

Separate models were developed for infants (1-11 months) and children (1-5 years) mortality in both rural and urban settings. Bivariate relations were explored using non-spatial Weibull models.
Bayesian geostatistical Weibull survival models were employed to assess the relationship between malaria endemicity and children under-five survival. Spatial correlation was introduced via village-specific random effects, which were assumed to be latent observations from a spatial Gaussian process. We assume a stationary Gaussian spatial process that is, spatial correlation is considered to be a function of distance only and not of the locations themselves. An exponential function was further considered for the correlation matrix.

The analysis was carried out in STATA 11 (Stata Corporation, College Station, Texas, USA) and OpenBUGS version 3.2.3 (Imperial College and Medical Research Council, London, UK). A detailed description of the Bayesian geostaistical formulation is given in appendix.

4.4 Results

The number of individual subjects in the study was 14,152 representing the number of live births born to the interviewed mothers between zero and five years preceding the survey and survived or not the childhood. A total of 1,244 deaths were observed in the study population. The overall mortality rate (MR) is 129 per 1000 live births. The infants' population consisted of 3,610 live births with 842 deaths. The infant mortality rate (IMR) was estimated at 65 per 1000 live births whereas children population of 1 to 4

years old amounted to 10,542 live births with 402 deaths and a MR estimated at 68 per 1000 live births. Mortality rates were calculated using the 5-years (2006-2010) period estimates prior to the survey. One hundred and seventy cluster locations in urban settings against 370 in rural areas had mortality data.

Figure 4.1 and 4.2 show the observed child mortality rates and malaria parasite prevalence map respectively.

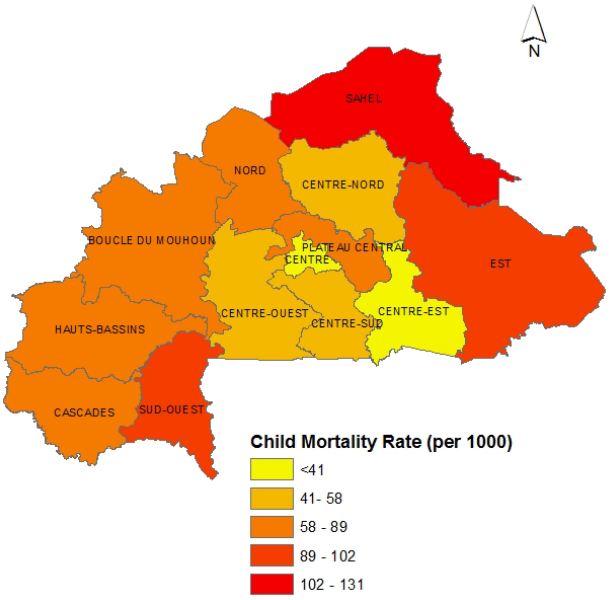


Figure 4. 1: Child mortality map

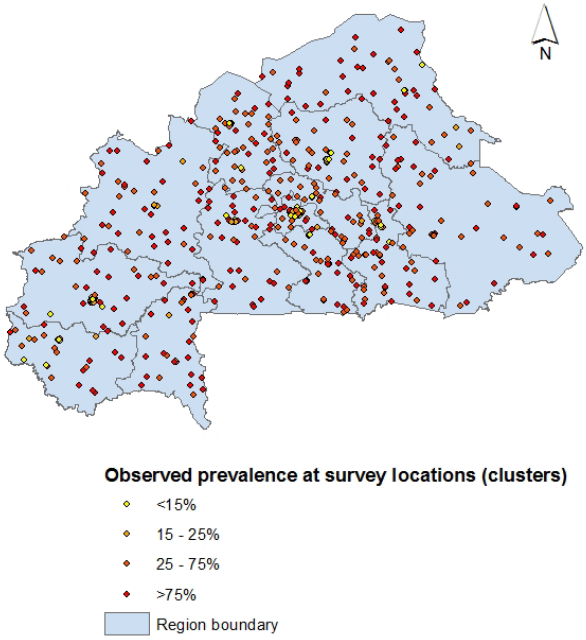


Figure 4. 2: Malaria prevalence map

4.4.1 Non-spatial model-based results

The non-spatial analyses of infant and child mortality stratified by rural and urban areas showed that children living in urban areas with malaria endemicity level above 75% had significantly higher mortality hazard (HR 2.76; 95% CI: 1.08-7.08). There was no relation between malaria endemicity with infant as well as child mortality in rural settings. No relation was also observed between malaria and infants mortality in the urban settings.

4.4.2 Geostatistical models-based results

Table 4.1 presents the hazard ratio (HR) obtained from geostatistical Weibull survival models.

Table 4. 1 Hazard ratio (HR) of predictors of infant and child mortality

		Urban				Rural			
Variable	Category	**Infant** HR (95% CI)	**Freq.**	**Child** HR (95% CI)	**Freq.**	**Infants** HR (95% CI)	**Freq.**	**Child** HR (95% CI)	**Freq.**
Maternal highest education level	No Education	1.00	423	1.00	1377	1.00	2604	1.00	7358
	Educated	0.77(0.50-1.18)	310	0.56(0.27-1.08)	1044	1.02(0.73-1.38)	273	2.05(0.63-5.93)	763
Wealth index	Poorest	1.00	31	1.00	90	1.00	680	1.00	1961
	Poorer	0.97(0.63-1.95)	35	0.83(0.46-1.16)	120	0.96(0.98-1.57)	734	1.02(0.77-1.37)	2050
	Middle	0.89(0.43-1.14)	75	0.57(0.11-1.22)	210	**0.86(0.89-0.94)***	725	0.90(0.65-1.23)	2033
	Richer	0.88(0.34-1.58)	187	0.77(0.22-1.80)	592	**0.77(0.85-0.93)***	605	0.97(0.69-1.36)	1725
	Richest	**0.51(0.57-0.92)***	405	0.88(0.25-1.35)	1409	**0.50(0.52-0.61)***	133	0.60(0.24-1.25)	352
Maternal age at birth	Less than 20 years	1.00	73	1.00	312	1.00	312	1.00	995
	20-29 year	0.85(0.45-1.61)	424	0.96(0.30-3.23)	1352	**0.62(0.47-0.83)***	1466	0.94(0.61-1.43)	4196
	30-39 years	1.11(0.49-2.55)	199	1.61(0.38-6.98)	655	**0.40(0.27-0.59)***	895	0.88(0.52-1.54)	2466
	40 and above	0.93(0.24-3.38)	37	0.54(0.02-7.29)	102	0.61(0.36-1.01)	204	0.84(0.39-1.80)	464
Sex of the child	Male	1.00	378	1.00	1249	1.00	1475	1.00	4113
	Female	0.78(0.53-1.14)	355	0.70(0.38-1.23)	1172	0.98(0.83-1.14)	1402	0.97(0.78-1.19)	4008
Numbers of household members	0-5	1.00	339	1.00	1080	1.00	978	1.00	2471
	6-10	0.85(0.53-1.33)	303	0.66(0.33-1.32)	1057	1.02(0.83-1.26)	1286	0.92(0.69-1.23)	3800
	11-14	0.92(0.35-2.17)	66	1.06(0.27-3.37)	184	**1.37(1.00-1.88)***	394	1.23(0.81-1.86)	1230
	15 or more	3.59(0.91-11.08)	25	1.89(0.37-7.63)	100	1.32(0.88-1.94)	219	1.59(0.95-2.64)	620
Number of under five children	Less than 3	1.00	595	1.00	2014	1.00	1815	1.00	5257
	3 and more	**0.23(0.10-0.48)***	138	0.41(0.13-1.11)	407	**0.47(0.37-0.59)***	1062	**0.49(0.37-0.66)***	2864
Birth interval	First born	1.00	195	1.00	653	1.00	473	1.00	1377
	Less than 23 months	1.35(0.63-2.82)	56	0.75(0.09-4.06)	141	1.23(0.90-1.70)	280	1.50(0.91-2.43)	887
	Between 23-48 months	0.89(0.48-1.66)	313	0.71(1.03-8.36)	1008	**0.59(0.44-0.80)***	1648	1.14(0.73-1.72)	4667

	49 months or more	0.51(0.25-1.04)	169	0.83(0.24-3.06)	619	**0.34(0.23-0.50)***	476	**0.46(0.24-0.83)***	1190
Birth size	Small	1.00	112	1.00	306	1.00	422	1.00	1028
	Average	**0.57(0.36-0.93)***	346	0.65(0.31-1.51)	1192	0.85(0.69-1.05)	1655	0.94(0.69-1.28)	4726
	Large	**0.39(0.23-0.68)***	275	0.63(0.28-1.44)	925	**0.68(0.53-0.89)***	800	**0.66(0.46-0.95)***	2367
Birth order	Order	1.06(0.91-1.23)	733	0.95(0.75-1.22)	2421	**1.12(1.06-1.18)***	2877	1.05(0.97-1.13)	8121
Antenatal visits	0 visit	1.00	88	1.00	230	1.00	571	1.00	3506
	At least 1	**0.07(0.05-0.11)***	645	0.66(0.37-1.21)	2191	**0.12(0.10-0.15)***	2306	**0.69(0.54-0.88)***	4615
Place of delivery	Home	1.00	48	1.00	230	1.00	950	1.00	3201
	Clinic	1.58(0.81-3.20)	685	2.44(0.99-7.86)	2191	0.84(0.70-1.01)	2877	0.81(0.63-1.04)	4920
Child is twin	Single birth	1.00	698	1.00	2333	1.00	2693	1.00	7866
	Multiple birth	1.11(0.52-2.31)	35	0.39 (0.01-2.62)	88	**2.39(1.87-3.04)***	184	**2.23(1.34-3.54)***	255
Malaria endemicity (prevalence)	<15%	1.00	255	1.00	828	1.00	58	1.00	170
	15-25%	1.13(0.64-1.97)	165	1.40 (0.54-3.97)	617	1.38(0.62-3.30)	248	1.56(0.53-6.87)	733
	25-75%	1.02(0.55-1.86)	198	2.13 (0.82-6.54)	655	1.24(0.59-2.86)	1014	1.58(0.56-6.63)	2764
	>75%	1.24(0.62-2.46)	115	**3.20 (1.01-10.46)***	311	1.19(0.57-2.73)	1557	1.24(0.44-5.19)	4454
Weibull shape Parameter (r)		**0.26(0.22-0.23)***		**1.57 (1.24-2.16)***		**0.30(0.28-0.32)***		**1.38(1.23-1.51)***	
Spatial parameters									
Spatial variation		0.27(0.13-0.71)		0.62(0.20-26.38)		0.16(0.10-0.26)		0.36(0.19-1.40)	
Range (Km)[a]		16.42(2.32-47.97)		10.06(1.35-46.75)		12.85(1.47-36.85)		14.57(5.05-47.54)	

a: minimum distance in kilometer at which the spatial correlation is significant at 5%, CI=credible interval
Freq.: Frequency

There was strong association between malaria endemicity levels and children mortality hazard in the urban settings (HR=3.20; 95% CI: 1.01-10.46). Important association has not been confirmed neither for children in rural areas nor for infants (irrespective of setting).

In terms of levels of differentials of infant and child mortality by some socioeconomic and demographic factors and place of residence, there was a significant reduction in the mortality hazard in children born in wealthy households, and this hazard decreases with higher SES status in rural areas while only children born in the richest households (fifth SES quintile) were at significantly reduced mortality hazard in urban areas. Infants born to older mothers as well as those born within large households in rural settings are at significantly reduced mortality hazard. Infants born to large households in rural areas have significant higher mortality hazard (HR=1.37; 95% CI: 1.00-1.88). Infants born within households with 3 or more under five children in urban areas have significantly reduced mortality hazard (HR=0.23; 95% CI: 0.10-0.48); this also applies to both infants and child in rural settings with respectively HR of (0.47; 95% CI: 0.37-0.59) and (0.49; 95% CI: 0.37-0.66). Infants and children born with a large birth interval are less likely to die in rural settings. There was an important negative relation between birth size and the infants' hazard of death in both, rural and urban settings (HR=0.39; 95% CI: 0.36-0.93 and HR=0.68; 95% CI: 0.53-0.89, respectively). This association was also important for children living in rural areas (HR=0.66; 95% CI: 0.46-0.95).

Furthermore, in rural settings, infant mortality hazard increases by 12% for each increase of birth order by 1 child (HR=1.12; 95% CI: 1.06-1.18). The mortality hazard was significantly lower among infants born from mothers who had at least one antenatal visit during pregnancy (HR= 0.77; 95% CI: 0.05-0.11 for rural and HR=0.12; 95% CI: 0.10-0.15 urban areas) and for children in rural settings, HR= 0.69 (95% CI: 0.54-0.88).

Infants and children born from none-singleton outcome had significantly higher mortality hazard in rural settings HR = 2.39 (95% CI: 1.87-3.04) and 2.23 (95% CI: 1.34-3.54).

The mortality hazard is significantly higher among children born in urban settings where malaria prevalence is above 75%, HR = 3.20 (95% CI: 1.01-10.46).

There was a stronger spatial correlation in areas compared to urban.

4.5 Discussion

This study assesses the relationship between malaria endemicity and infant/child mortality after adjusting for socioeconomic factors, individual child and mother as well as household determinants of infant and child death using the Burkina DHS-MICS 2010 data.

The results showed that children living in urban areas where malaria prevalence is above 75% have significantly higher mortality hazard compared to those living in rural areas. The highest malaria prevalence in urban settings is usually observed at the outskirts of the cities. These are slums where underprivileged people live in poor sanitation and hygiene conditions. The analyses were stratified by rural and urban settings as a proxy to low versus high endemicity levels. Urbanisation is generally expected to reduce malaria transmission and endemicity; however the endemicity levels remain high especially at the outskirts of African cities, in some cases even at higher levels than in nearby rural areas (De Silva et al. 2012). The persisting high malaria endemicity in African cities is most probably the consequences of conjugate factors such as uncontrolled urban expansion, urban agricultural practices which are conducive to vector breeding sites. There was no important relationship between malaria endemicity and mortality in rural settings. Potential reasons for this lack of association include the fact that high endemicity levels lead to less mortality. Indeed people living in hyperendemic and holoendemic settings develop much faster and stronger immunity (R. W. Snow et al. 1997; D. Chandramohan et al. 2001). Furthermore, the relationship between malaria endemicity and mortality is not linear (Rowe et al. 2006; Gemperli et al. 2004b) and may reach a plateau after a certain threshold of the transmission intensity. The excess risk of post-neonates mortality in malaria endemic areas was found to be insensitive to the intensity of the transmission over a wide range of endemicity (Ross and Smith 2006).

Overall, the highest mortality rates were observed in the northern (Sahel) and the Southwestern regions of the country.

The study has also identified a number of factors influencing infant and child mortality in terms of levels and differentials between rural and urban settings. We observed a significant reduction in the mortality hazard in infants living in wealthy households. This mortality hazard decreases with higher SES status in both rural and urban areas. Indeed, the socioeconomic status has been found to be one of the most important predictors associated with under-five mortality in many part of the Sub-Saharan Africa (Nattey, Masanja, and Klipstein-Grobusch 2013; N. Fobil et al. 2012). Maternal age at childbirth turned out to be a significant predictor of infant survival especially in rural areas. Infants born to older mothers are less likely

to die. These results are consistent with many studies that have reported higher mortality hazard among infants born to adolescent mothers (Finlay, Özaltin, and Canning 2011; Gubhaju 1985).

In rural areas, infants born in large households had significantly higher mortality hazard. The potential effects of this risk should be put in perspective, indeed, while a larger number of household members could imply higher fertility levels and a fiercer competition for resources, a larger number of potential caregivers residing in an extended household may in fact decrease the mortality hazard. Many studies have investigated the effects of this predictor on infant and child survival (Jamal Uddin 2008; Bank 2004). Our results support the former effects implying higher fertility levels and a competition for resources. This fits well the rural context where family planning campaigns have not yet yielded the expected effects. However, infant in urban areas and both infant and child in rural areas born in households having 3 or more under- five children have significantly reduced mortality hazard. The number of children under five in a given household often reflects the number mothers, therefore the number of potential caregivers in that household, previous studies exploring the effects of the household (number of potential caregivers) size on infant and child mortality reported a significant lower mortality hazard (Jamal Uddin 2008; Bank 2004).

Our results showed that children and infants born after 4 years interval in rural areas had significantly low mortality hazard. These findings are consistent with literature where a short proceeding birth interval has been found to increase the probability of infant mortality in many studies ("WHO | Report of a Technical Consultation on Birth Spacing" 2015).

In the absence of direct measurement for premature delivery, which features among major biological factors causing an increase in the probability of infant and particularly neonatal mortality, birth weight is a good proxy measure assuming premature birth is closely related with low birth weight. Our results showed that infants born with average and large birth size had significantly reduced mortality hazard in urban areas whereas only large birth size was found to be associated with a significantly reduced mortality hazard among both infant and child in rural areas ("WHO | The World Health Report 2005 - Make Every Mother and Child Count" 2015).

Our results showed that higher birth order infants had increased mortality hazard in rural areas. Birth order is also know to play a role in the probability of infant and child mortality (Bank 2004). It has been hypothesized that in intra-household competition, first born children are more likely to capture vital resources such as food and care, thereby reducing their mortality hazard (Bank 2004).

Infants born to mothers who have had at least one antennal visit were less likely to die in both urban and rural areas. However this extended to children in rural areas. Indeed, antenatal visits are expected to improve maternal health and reduce infant mortality hazard("WHO | Antenatal Care in Developing Countries" 2015).

Being born from a non-singleton outcome increases the mortality hazard in both infant and child in rural area. These findings are in line with the results of previous study on the effects of multiple birth on infant mortality (Uthman, Uthman, and Yahaya 2008; Justesen and Kunst 2000; Alam, Van Ginneken, and Bosch 2007). The potential reasons that might explain the higher mortality hazard in infant and child born non-singleton birth involve the place of delivery (by a healthcare professional), mother's personal and biological characteristics, place of residence and household's socioeconomic status (SES).

This study explored the relationship between malaria endemicity and infant/child mortality (while adjusting for socioeconomic factors, individual child, mother as well as household determinants) in Burkina Faso. There was a significantly strong association between high endemicity levels and children mortality especially in urban settings. There was no significant relationship between malaria endemicity and mortality in rural settings. Other important predictors of infants and child survival are those related to biological (birth size, mother age at birth), demographic (number of children under five year-old, household size) socioeconomic and antenatal care factors.

Authors Contribution

PV conceived and designed the study. ED analyzed the data and drafted the manuscript.
All authors gave intellectual content and critically reviewed the drafts and approved the final manuscript.

Acknowledgments

The authors are grateful to the CRSN research team in Burkina Faso. This work was funded by the Swiss National foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286.

4.6 Appendix

Let $s = (s_1, s_2, ..., s_n)^t$ be the set of locations (clusters) with observed mortality data, $t_i(s_j)$ the time to death for infant i at cluster s_j, $X_i(s_j)$ are the covariates associated with infant i at cluster s_j. We assume that $t_i(s_j)$ arises from a Weibull distribution with shape and scale parameters α and λ with α>0. δ_i is an indicator variable taking the value 1 if t_i is failure time and 0 if t_i is right censored. To build the regression, we introduce covariates on a log scale through α and λ_i. That is $t_i \sim dweib(\alpha, \lambda_i)\mathrm{I}\delta_i$

We modeled spatial correlation via cluster-specific random effects ϕ_j (which is considered as latent observations of a spatial Gaussian process) on the log, as $\log(\lambda_i(s_j)) = X_i^T(s_i)\underset{\sim}{\beta} + \phi_j$ where $\underset{\sim}{\beta}$ is the vector of regression coefficients. We assumed $\phi \sim MVN(0, \Sigma)$, Σ is the covariance matrix with elements Σ_{kl} accounting for the covariance between any pair of clusters k and l irrespective of the direction (isotropy). Using an exponential correlation function, the covariance matrix is defined by $\Sigma_{kl} = \sigma^2 \exp(-\rho d_{kl})$ where σ^2 is the spatial variation, d_{kl} is the distance between clusters k and l, and ρ is the rate of correlation decay with increasing distance. The minimum distance at which the spatial correlation is significant at 5% is called range and can be obtained from the value $3/\rho$ (Ecker and Gelfand, 1997).

A Bayesian model formulation requires the specification of prior distributions for all model parameters. In particular, we choose a non-informative normal prior distribution with mean zero and large variance for the $\underset{\sim}{\beta}$ parameters, regression coefficients, an inverse gamma priors for σ_e^2 and σ^2. A gamma prior for ρ, that is $\sigma_e^2, \sigma^2 \sim IG(2.01, 1.01)$ and $\rho \sim G(0.1, 0.1)$, $\alpha \sim G(1.01, 0.001)$.

The model was fitted using Morkov Chain Monte Carlo (MCMC) simulation algorithm in OpenBugs version 3.1.2 (Imperial College and Medical Council, London, UK) to estimate model parameters (Gelfand et al., 2000). Starting with some initials values about the parameters, we run two chains sampler discarding the first 5000 iterations. Convergence was assessed by Gelman-Rubin diagnostic (Gelman, 1992).

Chapter 5: Bayesian geostatistical modelling of all-cause mortality patterns in relation to malaria transmission intensity in Burkina Faso

Eric Diboulo[1, 2, 3], Ali Sié[1], Maurice Yé[1], Pascal Zabé[1], Yazoume Yé[4], Penelope Vounatsou[3 §]

[1]Centre de Recherche en Santé de Nouna, Burkina Faso
[2]Swiss Tropical and Public Health Institute, Basel, Switzerland
[3]University of Basel, Basel, Switzerland
[4] ICF International, Rockville 20850, MD, USA

[§]Corresponding author

This manuscript is prepared for submission to *Acta Tropica*

Abstract

Quantitative estimates of the relationship between malaria transmission intensity and mortality across different levels of transmission are still lacking. These quantitations are needed for improving the estimation of the disease burden and model-based predictions of the effects of interventions on mortality. The Malaria Transmission Intensity and Mortality Burden in Across Africa (MTIMBA) project collected biweekly entomological data from 2001-2004 at household level across a number of selected Health and Demographic Surveillance Systems (HDSS) sites in Africa. In this work we analysed MTIMBA and mortality data from the Nouna HDSS site to assess the relationship between malaria transmission intensity and all-cause mortality.

Data and Method: Entomological data were collected biweekly from 2001-2004 and mortality data extracted from the Nouna HDSS database. We address spatial misalignment between the two data sources by obtaining EIR estimates at the mortality locations using Bayesian spatio-temporal models. The prediction uncertainty was also incorporated into the modeling during estimation of mortality risk. Household asset data were available for only a representative sample of locations. Insecticide-treated net (ITN) coverage was obtained from a onetime survey conducted on a representative sample of HDSS households and was used as a proxy measure of ITN coverage indicator. We employed kriging to estimate the household asset and the ITN coverage indicator at the household with no data. Time to death was treated at monthly interval and Bayesian geostatistical logistic regression approximating Cox proportional hazard model and incorporating the predicted EIR as covariate with measurement error were fitted.

Results: The overall mortality rate over the study period was 11.26 per 1000 (95% CI: 10.81, 11.73). The highest mortality rates were observed in children and old age groups with the respective rates of 23.85 (95% CI: 22.37, 25.42) and 81.92 (95% CI: 75.81, 88.53). A positive log-natural relationship between mortality and EIR was found among children (1-4 years), while a protective effect was found among adults (15-59 years). The excess mortality risk associated with a one-unit increase of the number of infective bites per month was highest among children 1-4 years it was equal to 5%.

Conclusion: Significant relationship between all-cause mortality and malaria transmission was found among children (1-4 years) and adults (15-59 years). This suggests that successful malaria interventions in high malaria endemic areas will not only reduce malaria-related mortality but also other causes-related mortality.

Keywords: Bayesian, geostatistical, malaria, mortality, Burkina Faso, Nouna HDSS, EIR. Socioeconomic status, Insecticide treated nets (ITN).

5.1 Introduction

Recent estimates show that there has been a rapid decline in malaria mortality in Africa; this has been largely attributed to the scaling up of control activities and interventions. In 2015, there were an estimated 438 000 malaria deaths (range 236 000–635 000) worldwide. Most of these deaths occurred in the African Region (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%) ("WHO | Fact Sheet: World Malaria Report 2015" 2016). Ambitious new goals for control of malaria have been set and significant additional resources for malaria control have been mobilized over the last ten years. However, malaria control remains a major public health challenge especially in sub-Saharan African countries.

Successful malaria interventions are expected to reduce the transmission intensity to a level where the disease is no longer a public heath challenge. Assessing the effectiveness of health intervention requires appropriate information on morbidity and cause-specific mortality in order to derive the level of reduction in transmission required to achieve a significant reduction in morbidity and mortality.
However, owing to still embryonic and inadequate vital and civil registration systems, most Sub-Saharan African countries rely on information derived from national censuses and surveys, which are not carried out continuously to assess effectiveness of heath interventions in reducing morbidity and mortality. Understanding the role of transmission intensity in estimating the burden of clinical malaria is crucial in predicting and assessing the effectiveness of interventions.

Many recent studies have investigated the relationship between mortality and malaria transmission intensity from different perspectives such as obtaining direct estimates (Kampe et al. 2015; Larsen et al. 2014 ; Haque et al. 2014; Bi et al. 2013), assessing impact of interventions (Smithson et al. 2015; Aaby et al. 2015; Penny et al. 2015; Louis et al. 2012; Selemani et al. 2015; K'Oyugi 2015), modeling malaria transmission dynamics (Buonomo 2015; Alan Brooks 2012; Penny et al. 2015; Forouzannia and Gumel 2015); Stuckey, Smith, and Chitnis 2014; Okell et al. 2012; Eisele et al. 2012) and forecasting future malaria risk (D. L. Smith et al. 2009; Thomson and Connor 2001; Sriwattanapongse and Prasitwattanaseree 2013). However only few studies have explicitly accounted for differentials in transmission levels in their estimates (Alan Brooks 2012; Stuckey, Smith, and Chitnis 2014; Eisele et al. 2012). The common shortcoming to any of these studies has been the lack of mathematical quantitative estimates describing this

relationship. However, this quantitation is indeed needed for estimating the burden of the disease based on different levels of transmission.

Health and demographic surveillance systems (HDSS) sites and their data have been invaluable in deriving reliable mortality estimates in countries where they exit. The INDEPTH-MTIMBA project aimed at assessing the levels of malaria transmission intensity, establishing the relationship between all-cause, malaria-specific mortality and malaria transmission intensity taking into account the effect of disease control interventions.

Six HDSS sites within five countries namely Burkina Faso, Tanzania, Ghana, Kenya and Mozambique participated in the project and provided comprehensive data. Analyses of data from three MTIMBA sites in Tanzania, Kenya and Mozambique reported a positive log-linear relationship between all-cause mortality and transmission intensity among under-fives, there are differences in the magnitude and direction in mortality risk in other age groups (Rumisha et al. 2014; Amek et al. 2013); Kasasa et al. 2013). Nouna HDSS in Burkina Faso is located in a different agro-ecological zone and has different patterns and levels of malaria transmission from that of the other sites.

In this study, we estimate the relation between all-cause mortality and malaria transmission using the MTIMBA data from the Nouna HDSS. We employed Bayesian geostatistical models to link estimates of malaria exposure (based on EIR) with the HDSS mortality. EIR exposure surfaces were obtained from a separate Bayesian spatio-temporal model (Diboulo et al. 2015). Our mortality model took into account prediction uncertainty in the EIR estimation and adjusted for malaria control interventions and socio-economic factors.

5.2 Material and Methods

5.2.1 Study site

The Nouna health and demographic surveillance system (HDSS) is run by the Centre de Recherche en santé de Nouna (CRSN, Nouna Health Research Center) and located in the Nouna health district's catchment area in northwest Burkina Faso, 300 km away from the capital city, Ouagadougou. Relative to the health district, the HDSS catchment area is located southeast.

The Nouna HDSS area is characterized by a Sub-Saharan climate with a mean annual rainfall of approximately 800mm with fairly constant average daily minimum (20-28.1°C) and maximum temperature (29.5-37.2°C) throughout the year. Rainfall occurs from May to September. The entire region consists of "Plateaux" with gentle slopes and drained by several small semi-permanent streams.

The HDSS area is about 1,775 km2 with the specificity of covering both rural and semi-urban areas. The population is about 90,000 residing in 11,750 households across 58 villages and Nouna town. Subsistence farming is the predominant occupation. Malaria is holo-endemic and is known for a seasonal recrudescence during the rainy season, at which time it accounts for the main cause of fever and mortality in the district (Müller et al. 2008). During the dry season, in February and March, lower respiratory infections are the main cause of morbidity, due to the relatively cool temperatures and strong winds, which bring up dust and dirt.

5.2.2 Mortality Data

The verbal autopsy (VA) technique was used to assign cause of death within the study area. Trained non-medical fieldworkers conducted VA interviews. They interviewed the main caregiver on the background characteristics of the deceased using structured filter questions on the specific signs and symptoms experienced by the deceased. Information from the VA forms are independently reviewed by at least three experienced physicians (M. Yé et al. 2011b). The underlying cause is defined as the disease or injury that initiated the train of events leading directly to death.

5.2.3 Socioeconomic and intervention data

Socioeconomic, household asset-based indicators were collected once during the period of the MTIMBA project in 2004 on a sample of 1000 HDSS households. Principal component analysis was used to construct a household asset (SES) index. The variables used to construct the SES index included in-house assets (motorcycles, bicycle, radio, television, telephone), livestock possession (cattle, sheep, goat pig, guinea fowl), primary source of drinking water, use of improved cooking stoves. SES index was categorized into quintiles ranking households from the poorest (first quintile) to the least poor (fifth quintile). These data were available for only a sample of locations. SES status was estimated for the entire study area by calculating the proportion of households falling into the highest SES quintile per village. The latter estimate was then predicted (on a logit scale) at the villages without data via kriging. Furthermore, we used data from the closest in time insecticide-treated net (ITN) coverage survey to the period of the MTIMBA project, conducted in 2007 to obtain an ITN coverage indicator measuring at village level the proportion of households owning a bed net. The survey was carried out on a representative sample of HDSS households. Kriging was also used to predict bednet coverage (on a log scale) at un-sampled locations.

5.2.4 Entomological inoculation rate (EIR)

Bayesian geostatistical zero-inflated binomial (ZIB) and zero-inflated negative binomial (ZINB) models were developed to model sporozoite rate (proportion of infected mosquitoes) and mosquito densities, respectively. The models included the most important climatic factors related to malaria transmission and took into account lag times between climatic suitability and malaria transmission. Models were fitted separately to *An. funestus* and *An. gambiae* data to obtain species-specific surfaces of mosquito density and sporozoite rate within the study area. The overall EIR estimate at a given location and month are based on the mean number of infected mosquitoes (from both species) multiplied by the conversion factor to adjust for vector collection bias between human bite catch and light trap collection techniques.

5.3 Statistical analysis

Monthly-predicted EIR estimates were available during September 2001 to December 2002, however we analysed mortality 2001-2004 by assuming a transmission (EIR) pattern similar to 2001-2002 throughout the study period. The HDSS population was stratified into different age groups namely neonates (0-28 days), post-neonates (1-11 months), children (1-4 years), school-age (5-14 years) adults (15-59 years) and old age (60 years and above) and separate analyses were carried out for each of those groups. However the neonate group was excluded from the analysis because estimates (number of observations of the outcome variable of interest) were not representative of this sub-group.

Crude mortality rates were calculated by dividing the total number of deaths per age group by the total person-time in that specific age group. The annual mortality rates were expressed per 1000 person-years at risk.

We fitted Cox proportional hazards models with time-dependent covariates approximated by a logistic regression assuming a discrete time to death (Singer and Willett 1993). The models included the following covariates: EIR estimates on the logit scale, proportion of households in the highest SES quintile and bednet ownership. The prediction error of EIR estimates was taken into account by considering EIR as a covariate with measurement error to account for the prediction uncertainty (Armin Gemperli 2003). Bayesian geostatistical models were employed to assess the relationship between malaria transmission intensity and all-cause mortality. Spatial correlation was introduced via village-specific random effects, which were assumed to be latent observations from a spatial Gaussian process. We assume a stationary Gaussian spatial process that is; spatial correlation is considered to be a function of distance only and not of the locations themselves. An exponential function was further assumed for the correlation matrix. Mortality was related to the EIR of the same month. Bayesian models were implemented in OpenBUGS version 3.2.3 (Imperial College and Medical Research Council, London, UK). Parameters were estimated using Markov Chain Monte Carlo (MCMC) simulation algorithm (Gelfand and Smith, 1990). A detailed description of the Bayesian geostatistical formulation is given in appendix.

5.4 Results

The complete mortality database considered over the study period (2001-2004) included 62,132 individuals from 58 villages plus Nouna town. The total time at risk was 207,021.6 person-year (py). A total of 2331 deaths occurred over the study period and were apportioned as follows in the different age groups: 1 death in the neonates group, 67 in the post-neonates or infants group, 941 in the children group, 224 in school-age group, 459 in adults and 639 in old-age group. The mean age at death was 29.93 years (95% CI: 28.65, 31.21) years. Figure 5.1 depicts the EIR pattern and the death count over the study period. The proportion of households falling into the highest SES quintile per village ranged between 0.09 and 0.6; while the proportion of households owning bed nets ranged from 0.25 to 1 in the study area. The predicted annual EIR was 131.4 infective bites per person for year 2002.

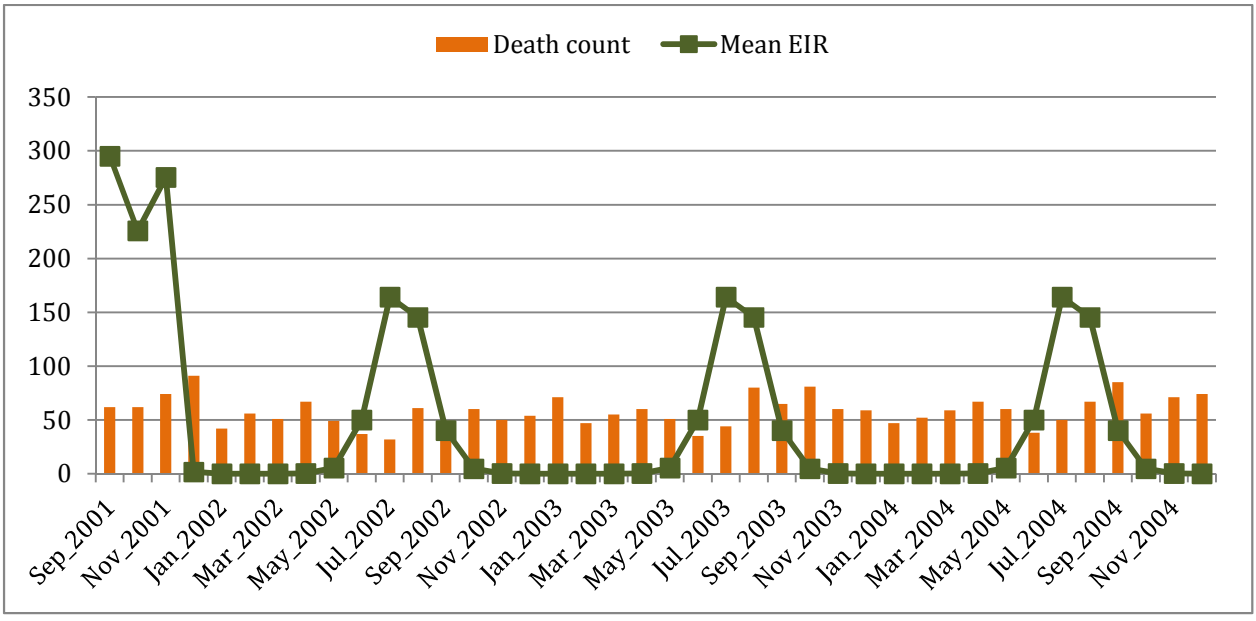


Figure 5. 1: EIR pattern and the death count over the study period

Table 5.1 and 5.2 show the mortality rates per year and the mortality rates per age group respectively over the study period.

Table 5. 1: Mortality rates per year over the study period (2001-2004)

Calendar year	Person-years	Deaths	Rate per 1,000	[95% Conf. Interval]	
2001	17009.68	289	16.99	15.14	19.10
2002	48716.65	554	11.37	10.46	12.36
2003	55247.30	762	13.79	12.85	14.81
2004	86047.98	726	8.44	7.85	9.07
Total	**207021.61**	**2331**	**11.26**	**10.81**	**11.72619**

Table 5. 2: Mortality rates per age group over the study period (2001-2004)

Age group	Person-years	Deaths	Rate per 1,000	[95% Conf. Interval]	
Neonates (0-28 days)	803.00	1	1.25	.18	8.84
Post-neonates (1-11 months)	9336.16	67	7.18	5.65	9.12
Children (1-4 years)	39453.79	941	23.85	22.38	25.42
School-age (5-14 years)	41859.47	224	5.35	4.69	6.10
Adults (15-59 years)	107745.73	459	4.26	3.89	4.67
Old age (60 + years)	7800.13	639	81.92	75.81	88.53
Total	**206998.29**	**2331**	**11.26**	**10.81**	**11.73**

Mortality rates were highest in years 2001, 16.99 (95% CI: 15.14, 19.07) and 2003, 13.79 (95% CI: 12.85, 14.81). The overall mortality rate over the study period was 11.26 (95% CI: 10.81, 11.73).

Infant and old age groups had the highest mortality rates with respectively 23.85 (95% CI: 22.37, 25.42) and 81.92 (95% CI: 75.81, 88.53).

Figure 2 shows crude mortality rates by age groups over the 4-year study period. The death rate was 23.85 in children; it declined with age to reach the lowest at 4.26 in adulthood and increased to its maximum 81.92 in the old-age group.

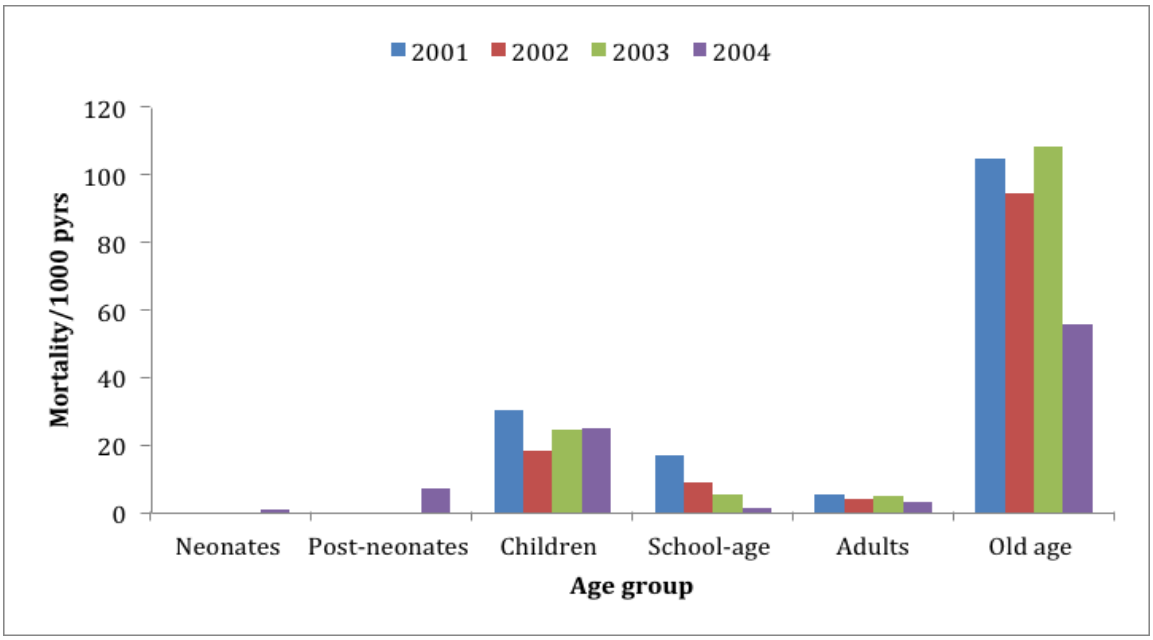


Figure 5. 2: Age specific annual all-cause mortality rates.

Mortality rates for the neonates and the post-neonates could not be estimated for the first 3 years of the study due to an extremely low number of deaths in these specific age groups. However it is noteworthy to mention that the mortality rate declined consistently in all age groups. The highest percentage decline was 90.77 % observed in school age children.

5.4.1 Model-based results

Table 5.3 presents the hazard ratio (HR) of all-cause mortality obtained from geostatistical models adjusted for EIR, ITN and SES. The relationship between mortality and malaria transmission intensity was important in children (1-4 years) and in old age group (15-59 years). In children the HR was estimated at 1.05 (95% BCI: 1.04-1.07) suggesting that for an infective bite (EIR) increase per month the hazard of death increases by 5%. In the old age, a HR of 0.93 (95% BCI: 0.91-0.95) was estimated indicating that a unit increase in EIR reduces the mortality hazard by 7%.

A significant negative association was found between all-cause mortality and socioeconomic (SES) status among adults with the highest protective effects (HR=0.93, BCI: 0.91, 0.95).

The minimum distance, at which the spatial correlation is less than 5% ranges between 4.98 km and 20.42 km across all age groups.

Table 5. 3: Posterior estimates (median and 95% Bayesian credible interval) of the geostatistical model's parameters.

Covariates	Post-neonates HR (95% BCI)	Children HR (95% BCI)	School-age HR (95% BCI)	Adults HR (95% BCI)	Old age HR (95% BCI)
EIR (log scale)	1.02 (0.95, 1.09)	**1.05 (1.04, 1.07)**	1.02 (0.99, 1.05)	0.99 (0.97, 1.01)	**0.93 (0.91, 0.95)**
SES	0.42 (0.01, 1.38)	0.64 (0.69, 1.80)	0.28 (0.04, 1.83)	**0.20 (0.05, 071)**	1.2 (0.33, 4.35)
ITN	1.21 (0.39, 4.80)	0.98 (0.69, 1.46)	1.42 (0.76, 2.58)	1.52 (1.04, 2.29)	1.2 (0.77, 1.83)
Spatial variance	0.38 (0.15, 1.23)	0.18 (0.03, 3.02)	1.05 (0.51, 2.38)	0.56 (0.25,1.79)	0.94 (0.49, 5.34)
Range (km)[a]	14.09 (1.54, 50.22)	7.68 (1.13, 51.63)	4.98 (1.13, 31.93)	20.42 (3.67, 50.55)	5.91 (1.16, 50.39)

a: minimum distance in kilometer at which the spatial correlation remains important , BCI=Bayesian Credible Interval

5.4.2 Effect of EIR on mortality in the different age groups

Figure 5.3 shows the HR of EIR on all-cause mortality estimated from the different age groups. We observe an increase in the risk pattern from early infanthood to childhood where it reaches it maximum. This risk decreases steadily from childhood to elderly age.

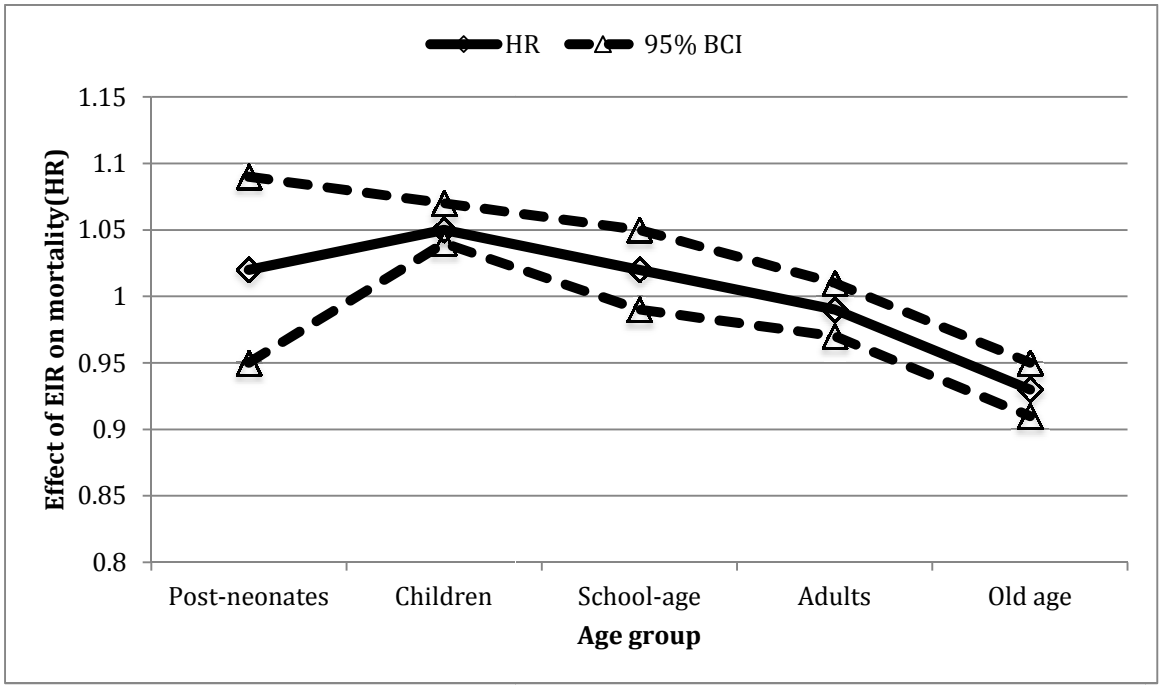


Figure 5. 3: Estimates of HR of EIR on all-cause mortality estimated from the different age groups

5.4.3 Excess mortality attributable to malaria transmission

The excess mortality rate (EMR) was calculated as the difference between the mortality rates (MR) at which the values of EIR is greater than zero and at zero: EMR=MR (EIR>0) - MR (EIR=0). In particular, we computed the probability (P_{ij}) of death for each age group j from the logistic regression model over a range of EIR values between 0.1 and 1200 (with an interval of 0.1) using model coefficients, monthly EIR and midpoint for each age group. A Taylor series approximation was used to obtain probability at zero level of transmission. The probability of death for each age group j was converted to a rate and expressed per 1000 person-years (py), that is $rate = [-\ln(1-P_{ij})]/t$ per 1000 py; where i=EIR interval, j=age group and t=one month.

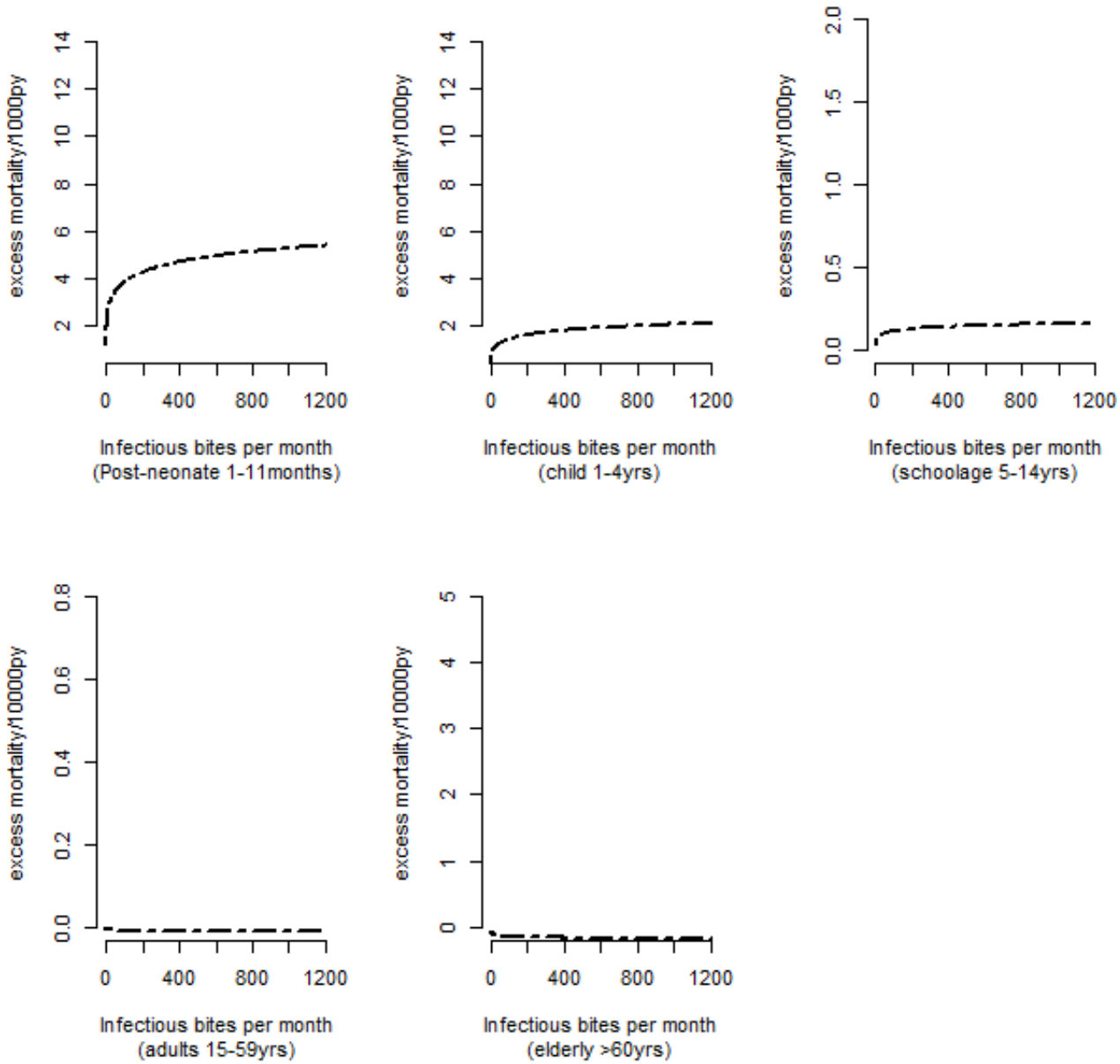


Figure 5. 4: Age-specific patterns of excess mortality by EIR levels.

Post-neonate, children and school age groups show increasing levels of excess mortality with increasing levels of malaria transmission (EIR). The highest rate is observed in post-neonate group.
A protective effect is observed in elderly people. School age group showed a very low excess mortality with increasing levels of transmission.

5.5 Discussion

This study explores the relationship between malaria exposure levels measured via EIR and all-cause mortality in the Nouna HDSS. Malaria transmission intensity was measured by the predicted EIR obtained from separate model at household-level. Vital events were subsequently linked with the transmission levels in order to quantify the malaria exposure-mortality relationship. Separate analyses were carried out for the different age groups where it was possible to assess this relationship, that is, post-neonates, children, school-age, adults and old-age. Overall, our study reports a decline in all-cause mortality rates over the 4-year study period. The largest decline during the study period was observed among school age (5-14 years) 90.77% followed by old-age (60 years and above) 46.74%. Previous studies carried out in the same area reported a decline in all-cause mortality in children aged less than five years (Ramroth et al. 2009; Ndugwa et al. 2008).
Despite the negative temporal trend, the mortality rates remained high among old age and school age with rates of 81.92, (95% CI: 75.81, 88.53) and 23.85, (95% CI: 22.37, 25.42), respectively.
The Bayesian geostatistical models showed a positive and significant log-linear relationship between all-cause mortality and malaria exposure in children (1-4 years). These findings corroborate a positive relationship between mortality and malaria transmission intensity among under-five observed in previous studies carried out in the MTIMBA sites of Rufijii, Kisumu and Manhica (Rumisha et al. 2014; Amek et al. 2013; Kasasa et al. 2013).
Children had a hazard ratio of 1.05 (95% CI: 1.04, 1.07). This effect translates into increasing levels of excess mortality in relation to malaria transmission intensity (EIR) in this age group. This finding is in line with the results from a previous study that used the MTIMBA data from Kisumu HDSS in Kenya, where children appeared to be at higher risk (Amek et al. 2013). However our findings show an increasing pattern of the risk from early infancy to childhood followed by a decreasing trend from childhood to older age.

The highest excess mortality associated with levels of transmission was observed among post-neonates (1-11 months) (figure 3). This may be explained by the fact that this fraction of the population is the most exposed to malaria as they lack or are still building up the immune system.

A significant protective effect was found among elderly people (HR=0.93, 95% CI: 0.91, 085). It might be associated with the development of naturally acquired immunity which is believed to increase with age (Bejon et al. 2009).

ITN use did not show any significant association with all-cause mortality across all age groups, which may be explained by the fact that ITN data was obtained from a onetime survey carried out on a representative sample of Nouna HDSS households.

Higher SES quintiles were protective against all-cause mortality in adults. This implies that adults from well-off households are less likely to die compared to their counterpart in poorer households. These results are consistent with many previous studies which have also reported the effects of socioeconomic disparities on infant and child mortality (Po and Subramanian 2011; Nattey, Masanja, and Klipstein-Grobusch 2013; Sonko et al. 2014). However in the case of adults, this may be explained by the fact that wealthier people have easily access to health care, in the absence of universal health coverage, where the health care financing is still based on the out-of-pocket expenditure.

The minimum distance, at which the spatial correlation is deemed unimportant ranges between 4.98 km and 20.42 km across all age groups, thus suggesting a geographical dependence of mortality.

The analyses also revealed extremely low mortality rates among neonates and post-neonates, which is rather an artifact of the routine data collection system, related to the prevailing socio-cultural practices in the study area. Indeed the verbal autopsy interview is conducted within the three month following any fatal event captured in the HDSS catchment area. In a predominantly Muslim community (about 70%), and owing to some specific cultural practices, it is a common that a newborn have the naming ceremony on the seventh day after birth. This time frame extends up to forty days in some local communities. The death of any newborn before that time frame tends to be silenced and hardly refer to. Newborns that die before their naming date are usually referred to as “passerby”, not full family members; their death is therefore not considered as a major event. One way to overcome that issue in data collection is to ensure a proper registration and follow-up of any pregnant women in the HDSS catchment area.

This study used entomological data, which has been linked to the most comprehensive vital events to assess the relationship between malaria transmission intensity and all-cause mortality adjusted for ITN

coverage and SES in Nouna HDSS. The analyses showed statistically significant relationships between mortality and malaria transmission intensity especially among children (1-4 years) and adults (15-59 years). However these findings can hardly be generalized as the relationship between mortality and transmission intensity depends on the levels of endemicity and malaria distribution is very heterogeneous even within such a small geographical area and prone to between and within village variation (Greenwood 1989; Carter, Mendis, and Roberts 2000).

Authors Contribution

PV conceived and designed the study. ED analyzed the data and drafted the manuscript.
All authors gave intellectual content and critically reviewed the drafts and approved the final manuscript.

Acknowledgments

The authors are grateful to the CRSN and the principal investigator of the INDEPTH-MTIMBA project in Burkina Faso for providing the data. This work was funded by the Swiss National foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286.

5.6 Appendix

Let Y_{ijt} be the mortality (all-cause) status of an individual i at village j and time interval t and N_{ijt} the total number of individuals present at time interval t. X_{ij} is the covariates associated with individual i at location j. We assume that Y_{ijt} arises from a Binomial distribution. That is $Y_{ijt} \sim Bin(N_{ijt}, p_{ijt})$ where, p_{it} is the probability of individual i dying at time interval t. We modeled spatial correlation via village-specific random effects ϕ_j (which is considered as latent observations of a spatial Gaussian process) on the logit, as $\log it(p_{ijt}) = \underset{\sim}{X}_i^T \underset{\sim}{\beta} + \phi_j$ where $\underset{\sim}{\beta}$ is the vector of regression coefficients. EIR is modeled on the log scale as a covariate with measurement errors (because it is estimated by separate Bayesian geostatistical models), that is $\log EIR \sim N(\log \tilde{EIR}_i, \sigma_{ei}^2)$ predicted at the household of child i where $\tilde{EIR}_i$ and σ_{ei}^2 correspond to the mean and variance respectively obtained from posterior prediction distribution of EIR at household i. We assumed $\phi \sim MVN(0, \Sigma)$, Σ is the covariance matrix with elements Σ_{kl} accounting for the covariance between any pair of villages k and l irrespective of the direction (isotropy). Using an exponential correlation function, the covariance matrix is defined by $\Sigma_{kl} = \sigma^2 \exp(-\rho d_{kl})$ where σ^2 is the spatial variation, d_{kl} is the distance between villages k and l, and ρ is the rate of correlation decay with increasing distance. The minimum distance at which the spatial correlation is significant at 5% is called range and can be obtained from the value $3/\rho$ (Ecker and Gelfand, 1997).

A Bayesian model formulation requires the specification of prior distributions for all model parameters. In particular, we choose a non-informative normal prior distribution with mean zero and large variance for the $\underset{\sim}{\beta}$ parameters, regression coefficients, an inverse gamma priors for σ_e^2 and σ^2. A gamma prior for ρ, that is $\sigma_e^2, \sigma^2 \sim IG(2.01, 1.01)$ and $\rho \sim G(0.1, 0.1)$.

The model was fitted using Morkov Chain Monte Carlo (MCMC) simulation algorithm in OpenBugs version 3.1.2 (Imperial College and Medical Council, London, UK) to estimate model parameters (Gelfand et al., 2000). Starting with some initials values about the parameters, we run two chains sampler discarding the first 5000 iterations. Convergence was assessed by Gelman-Rubin diagnostic (Gelman, 1992).

Chapter 6: Estimating the number of malaria-attributable deaths: An application to Nouna Health and Demographic Surveillance Site (HDSS) data, Burkina Faso

Eric Diboulo[1, 2, 3], Ali Sié[1], Maurice Yé[1], Pascal Zabé[1], Yazoume Yé[4], Thomas Smith[2,3], Penelope Vounatsou[2,3 §]

[1]Centre de Recherche en Santé de Nouna, Burkina Faso
[2]Swiss Tropical and Public Health Institute, Basel, Switzerland
[3]University of Basel, Basel, Switzerland
[4] ICF International, Rockville 20850, MD, USA

[§]Corresponding author

This manuscript is prepared for submission to *Malaria Journal*

Abstract

Explicit quantitative estimates of the number of malaria-attributable deaths have been lacking and this has been a common shortcoming of most of malaria-related studies. The Malaria Transmission Intensity and Malaria Burden in Across Africa (MTIMBA) project was initiated to help fill this gap. In this work, estimates of malaria exposure surfaces (EIR surfaces) obtained using MTIMBA data were linked to Nouna Health and Demographic Surveillance Site (HDSS) mortality database in order to estimate the number of malaria-related deaths in Nouna HDSS and assess the performance of the physician-coded verbal autopsy method to correctly identify malaria as the cause of death.

Methods: Bayesian geostatistical logistic regression models approximating Cox proportional hazard model and incorporating the predicted EIR as covariate with measurement error were fitted. EIR estimates were obtained from a separate Bayesian spatio-temporal model; therefore, prediction uncertainty was taken into account during estimation of the mortality hazard. Socioeconomic status (SES) and Insecticide-treated net (ITN) coverage were used as covariates. Time to death was treated at monthly interval. We estimated the number of malaria-attributable deaths across all age groups and assessed the diagnostic performance of the physician-coded verbal autopsy using the estimated malaria-related excess mortality as the gold standard.

Results: The highest malaria-mortality rates were observed in years 2001, 5.41 (95% CI: 4.41, 6.64) and 2003, 4.13 (95% CI: 12.85, 14.81). A significant positive natural logarithmic relationship was found between malaria exposure and mortality among children, with hazard ratio (HR) of 1.06 (95% CI: 1.03, 1.08). Children and adults had the highest percentage of deaths attributed to malaria by VA equal to 44.95% and 35.27%, respectively. The percentage of malaria-related deaths according to the malaria transmission exposure was higher in the old-age group (93.92%). The overall sensitivity and specificity of the physician-certified verbal autopsy (PCVA) were 0.27 and 0.70, respectively.

Conclusion: A significant relationship was found between malaria mortality and malaria transmission among children (1-4 years). This suggests that successful malaria interventions in high malaria endemic areas are likely to further reduce malaria-related mortality in children. The sensitivity and specificity analysis of the physician-certified verbal autopsy (PCVA) indicates an overall moderate specificity but very low sensitivity of this method

Keywords: Bayesian, geostatistical, malaria mortality, Burkina Faso, Nouna HDSS, EIR, physician-certified verbal autopsy, sensitivity and specificity, diagnostic error.

6.1 Introduction

The quantitative relationship between malaria transmission intensity and mortality still remains unclear (T. A. Smith, Leuenberger, and Lengeler 2001a; Rumisha et al. 2014)) partly because of the poor quality data in most endemic countries. Little is therefore known about the minimum reduction in transmission required to achieve a useful health benefits in term of specific reduction in mortality.

Different approaches and data sources have been used to estimate the number of malaria-attributable deaths. These approaches include (i) using data on reported deaths and adjusting them for incomplete reporting and use of public sector facilities (Mendis et al. 2001), (ii) using an estimated number of cases and multiplying by an estimated case fatality rate ("WHO | World Malaria Report 2011" 2016) and (iii) using results of the verbal autopsies (Liu et al. 2012; R. W. Snow et al. 1992).

The main disadvantages associated with the first two approaches lie in the fact that they rely on hospital-based data, which are severely limited and represents only a fraction of the actual burden since a considerable proportion of malaria deaths occur at home (Greenwood et al. 1987)

The INDEPTH-MTIMBA project aimed at assessing the levels of malaria transmission intensity, establishing the relationship between all-cause, malaria-specific mortality and malaria transmission intensity. MTIMBA collected georeferenced entomological data from several Health and Demographic Surveillance Sites (HDSS) in Africa.

In our previous work (Diboulo et al. under review), we used the INDEPTH-MTIMBA and the Nouna HDSS data to assess the relation between malaria transmission and all-cause mortality. Children aged 1-4 years were found to have an increased mortality hazard with increasing levels of transmission while increasing levels of malaria transmission showed a protective effect among old age group.

Recent studies have used data from INDEPTH-MTIMBA project to assess the relationship between malaria transmission and all-cause mortality in Rufiji (Tanzania), Kisumu (Kenya) and Manhiça (Mozambique) (Rumisha et al. 2014; Amek et al. 2013; Kasasa et al. 2013).

One of the main advantages of MTIMBA data resides in the fact that we have the actual estimates of the malaria transmission intensity measured via entomological inoculation rate (EIR) together with the verbal autopsy (VA) data. VA is a tool for obtaining causes of deaths when medical diagnoses are not available. It is based on information about signs and symptoms observed ante mortem by relatives or associates of deceased individuals, and the diagnosis is derived either from a review of questionnaire (which includes an

open section to record the respondent's verbatim account of the subject's final illness and a closed section to probe for specific signs and symptoms) by two or more physicians, or from a set of algorithms.
Different approaches have been used for assessing the sensitivity, specificity and the validity of VA and these approaches include comparing VA diagnoses with reference diagnoses obtained from hospital and used as gold standard (Daniel Chandramohan et al. 1998); comparisons of cause-specific mortality rates between intervention and control groups after an intervention targeted to reduce deaths from a specific cause (Maude and Ross 1997); and using community-based longitudinal demographic surveillance of a population and classifying the cause of death (Deressa, Fantahun, and Ali 2007).

Nouna HDSS in Burkina Faso is a malaria endemic setting where the transmission occurs throughout the year and is sustained by two sympatric sibling anopheles species: *An. gambiae* and *An. funestus*. Malaria is the leading cause of death in the Nouna HDSS catchment area. This offers a unique opportunity to explore the relationship between malaria transmission intensity and malaria cause-specific mortality and to generate quantitative estimates of malaria-attributable deaths. Measuring the magnitude of malaria-attributed deaths is crucial in order to provide decision makers and other relevant stakeholders with the actual burden of the disease.

In this study, we set out to use Nouna HDSS-MTIMBA data to assess the relation between malaria transmission intensity and malaria cause specific mortality and estimate the number of malaria-attributable deaths. Estimates of malaria exposure surfaces (EIR surfaces) obtained using MTIMBA data were linked to Nouna HDSS mortality database. Bayesian geostatistical models incorporating the predicted EIR as covariate (with measurement errors) and adjusting for malaria control interventions were employed to assess the relationship between malaria transmission intensity and malaria cause-specific mortality. We also assessed the diagnostic performance of the physician-coded verbal autopsy (PCVA) using the estimated malaria-related excess mortality as the gold standard.

6.2 Material and Methods

6.2.1 Study site

The Nouna health and demographic surveillance system (HDSS) is run by the Centre de Recherche en santé de Nouna (CRSN, Nouna Health Research Center) and located in the Nouna health district's catchment area in northwest Burkina Faso, 300 km away from the capital city, Ouagadougou. Relative to the health district, the HDSS catchment area is located southeast. Further details on the study site are given in (Diboulo et al., 2015).

6.2.2 Mortality Data

We used Nouna HDSS data to extract mortality data from year 2001 to 2004. The verbal autopsy (VA) technique was used to assign cause of death within the study area. Information from the VA forms are independently reviewed by at least two experienced physicians (M. Yé et al. 2011a). The underlying cause is defined as the disease or injury that initiated the train of events leading directly to death. In this study, all-cause mortality estimates as well as other exposure attributable and not attributable causes of death come from a previous study on all-cause mortality analysis (Diboulo al. 2016c, under review).

6.2.3 Socioeconomic and intervention data

The socioeconomic indicators were collected once during the MTIMBA project period in 2004 on a sample (1000) of HDSS's households. Principal components analysis was used to construct household socioeconomic status (SES) index. SES status was estimated for the entire study area by calculating the proportion of households falling into the highest SES quintile per village (range 0.09-0.6).

Insecticide-treated net (ITN) coverage survey was also conducted in 2007 as part of different study and was used as a proxy measure of ITN coverage indicator (bed nets ownerships). The proportion of households owning bed nets ranges from 0.25 to 1 in the study area. Further details can be found in Diboulo et al. 2016c, under review).

6.2.4 Entomological inoculation rate (EIR)

Bayesian geostatistical zero-inflated binomial (ZIB) and zero-inflated negative binomial (ZINB) models were developed to model sporozoite rate (proportion of infected mosquitoes) and mosquito densities, respectively. The predicted annual EIR was 131.4 infective bites per person for year 2002. Modelling details are provided by (Diboulo et al. 2015).

6.3 Statistical analysis

The analyses included all individuals who were residents and were first restricted to the period from September 2001 to December 2002 where monthly-predicted EIRs are available. We further assumed a similar transmission (EIR) pattern throughout 2002-2004 and extended the study period from September 2001 to December 2004. The HDSS population was stratified into different age groups namely neonates (0-28 days), post-neonates (1-11 months), children (1-4 years), school-age (5-14 years) adults (15-59 years) and old age (60 years and above) and separate analyses were carried out for each of those groups. However the neonate group was excluded from the analysis because estimates (number of observations of the outcome variable of interest) were not representative of this sub-group.

Crude mortality rates were calculated by dividing the total number of deaths in an age group divided by the total person-time in that specific age group. The annual mortality rates were expressed per 1000 person-years at risk. Cox proportional hazards models were fitted using logistic regression assuming a discrete time to death due to the presence of time-dependent covariates (Singer and Willett 1993).

The models included EIR estimates on the logit scale, SES quintiles and ITN coverage indicators. The prediction error of EIR estimates was taken into account by considering EIR as a covariate with measurement error to account for the prediction uncertainty (Gemperli et al. 2003). Bayesian geostatistical models were employed to assess the relationship between malaria transmission intensity and all-cause mortality. Spatial correlation was introduced via village-specific random effects, which were assumed to be latent observations from a spatial Gaussian process. We assume a stationary Gaussian spatial process that is; spatial correlation is considered to be a function of distance only and not of the locations themselves. An exponential function was further assumed for the correlation matrix. Mortality was related to the EIR of the same month.

Bayesian models were implemented in OpenBUGS version 3.2.3 (Imperial College and Medical Research Council, London, UK). Parameters were estimated using Markov Chain Monte Carlo (MCMC) simulation algorithm (Gelfand and Smith, 1990). A detailed description of the Bayesian geostatistical formulation is given in appendix.

6.4 Results

Cause of death was assigned to 81% of the total deaths. Malaria appeared to be the main cause of death over the study period and followed by acute gastro-intestinal infections, pneumonia, HIV/AIDS and coronary heart diseases (CHD). Figure 6.1 and 6.2 show the frequency distribution of deaths by cause and by cause and year. Figure 6.2 shows that malaria, acute gastro-intestinal infections pneumonia, HIV/AIDS and CHDs are consistently the leading causes of death throughout the study period. CHD, acute gastro-intestinal infections and malnutrition are on steady rise overtime.

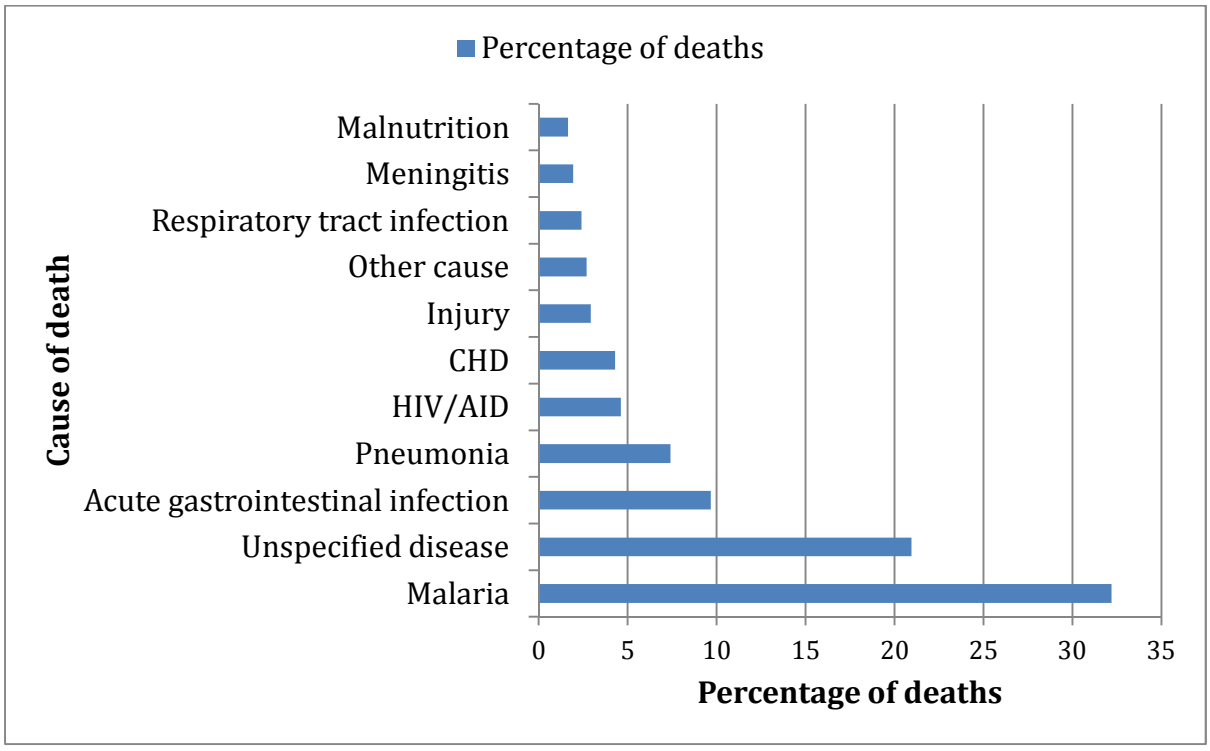


Figure 6. 1: Main causes of deaths

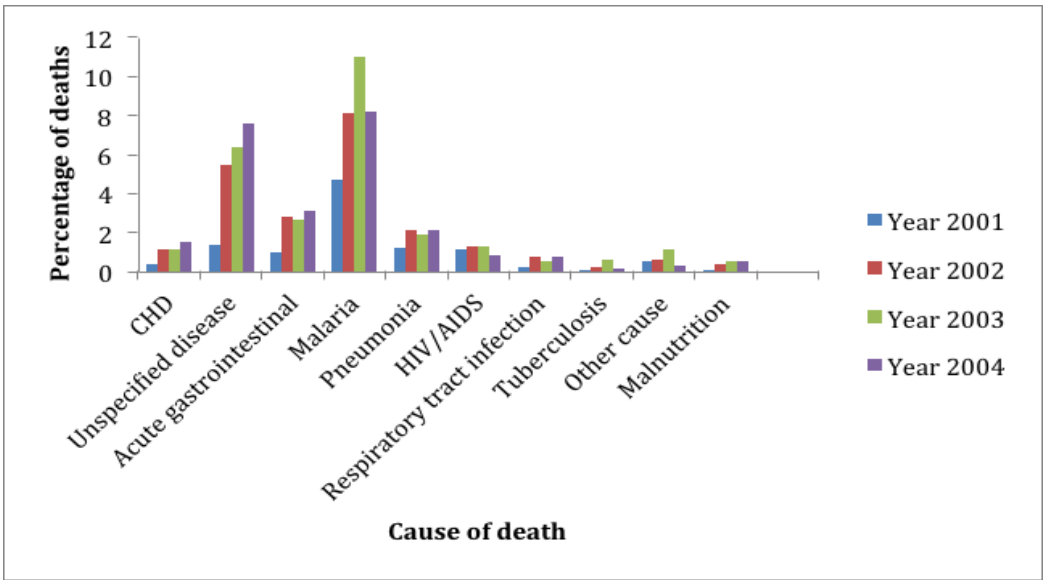
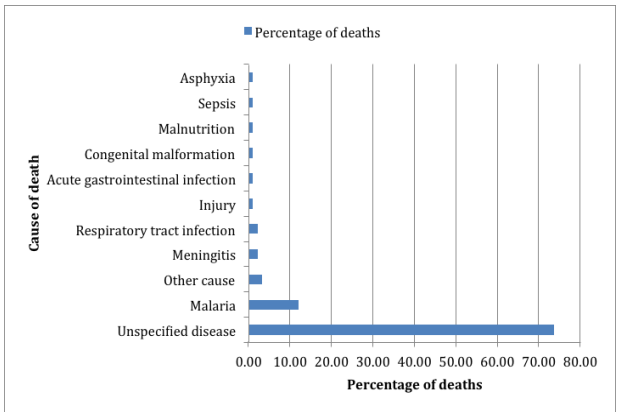
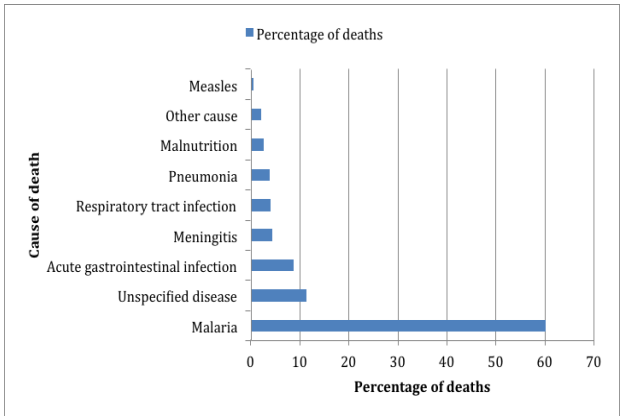


Figure 6. 2: Main causes of deaths per study years

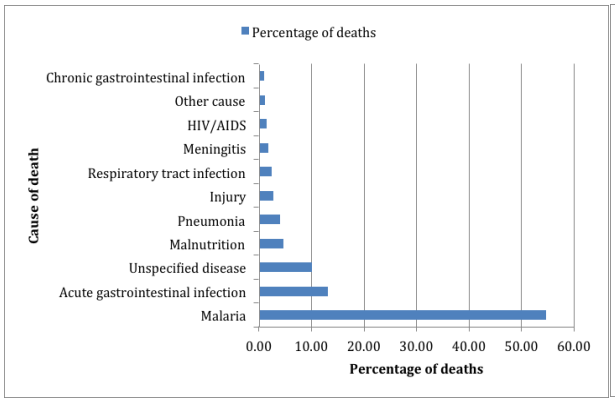
Figures 6.3:1-6 show the leading causes of death among neonates (0-28 days), post-neonates (1-11 months), children (1-4 years), school-age (5-14 years) adults (15-59 years) and old age (60 years and above), respectively. Depending on the age group the proportion of unspecified deaths by verbal autopsy varies from 10% in children to over 70% in neonates. Malaria is the main cause of death up to the school age accounting for around 12%, 60%, 55%, 34% among neonates, post-neonates, children and school age children respectively. Malaria deaths rank 4th among adults with a frequency of 7.35% after HIV/AIDS (18.62%), pneumonia (7.81%) and CHD (7.59%) and become a prominent death cause in the old age.



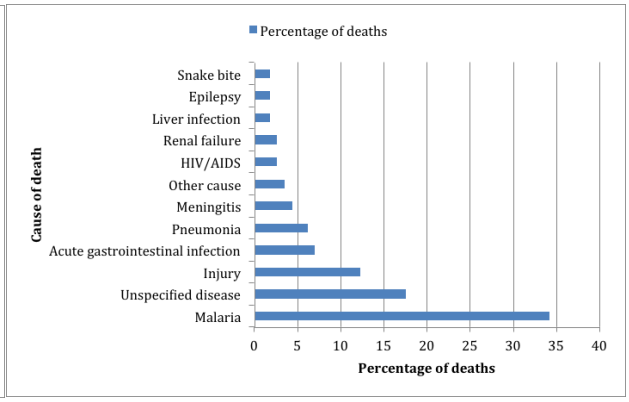
Figures 6.3. 1: Leading causes of death among neonates



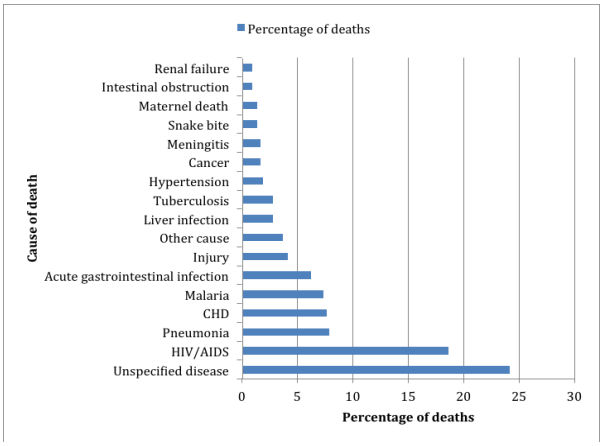
Figures 6.3. 2: Leading causes of death among post-neonates



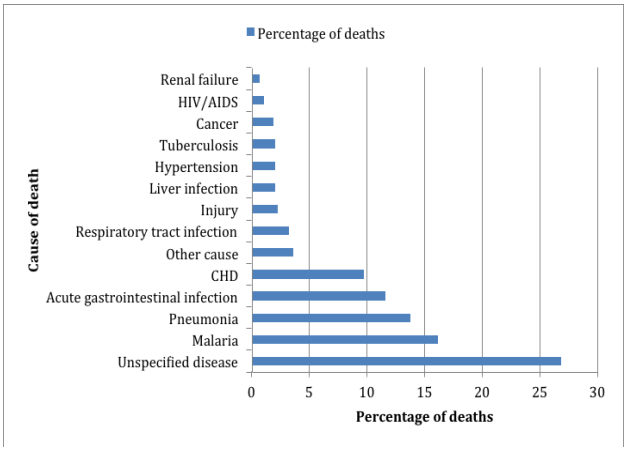
Figures 6.3. 3: Leading causes of death among children



Figures 6.3. 4: Leading causes of death among school age

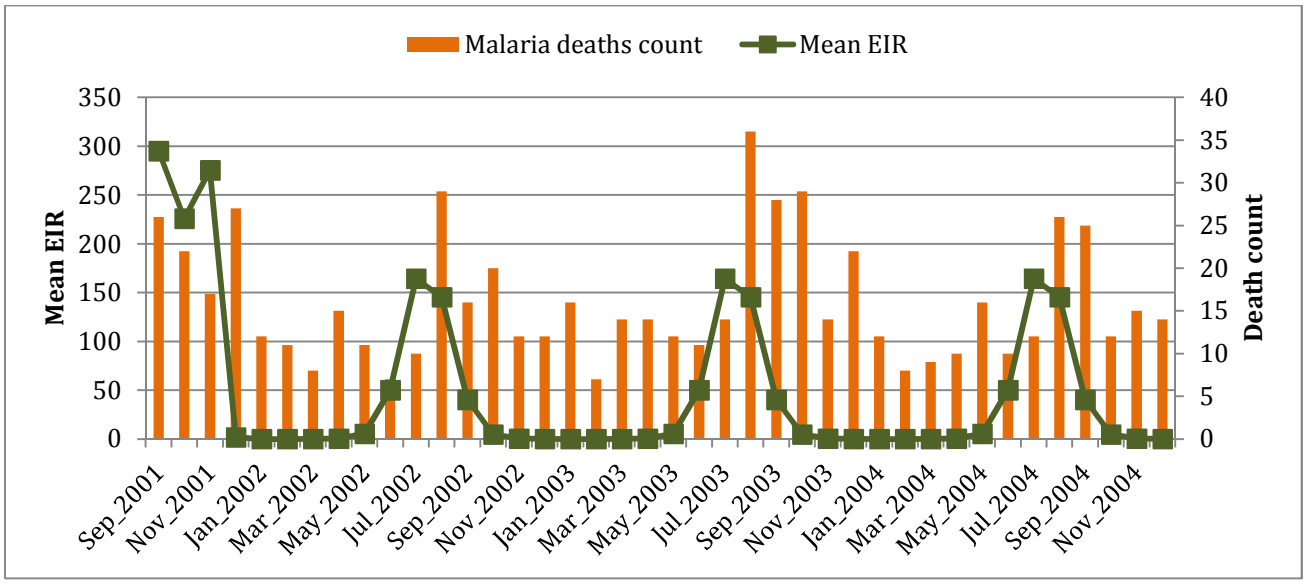


Figures 6.3. 5: Leading causes of death among adults



Figures 6.3. 6: Leading causes of death among old age

The complete mortality database considered over the study period (2001-2004) included 62,132 individuals from 58 villages plus Nouna town. The total time at risk was 207021.6 person-year (py). A number of 641 malaria-related deaths occurred over the study period and were allotted in the different age groups as follows: 0 deaths in the neonates group, 19 in the post-neonates or infants group, 423 in the children group, 79 in school-age group, 30 in adults and 90 in old-age group. The mean age at death was 29.93 (95% CI: 28.65, 31.21) years. Figure 6.4 depicts the EIR pattern and the malaria-related deaths count over the study period. Malaria mortality picks up shortly after the pick of EIR



Figures 6.4 1: EIR pattern and the death count over the study period

Table 6.1 and 6.2 show the malaria mortality per year and per age group respectively over the study period.

Table 6. 1: Malaria mortality rates per year over the study period (2001-2004)

Calendar year	Person-years	Failures	Rate per 1,000	[95% Conf. Interval]	
2001	17009.68	92	5.41	4.41	6.64
2002	48716.65	151	3.10	2.64	3.64
2003	55247.30	228	4.13	3.63	4.70
2004	86047.98	170	1.98	1.70	2.30
Total	**207021.61**	**641**	**3.10**	**2.87**	**3.35**

Table 6. 2: Malaria mortality rates per age group over the study period (2001-2004)

Age group	Person-	Deaths	Rate per	[95% Conf. Interval]

	years		1,000		
Neonates (0-28 days)	803.00	0	0	-	-
Post-neonates (1-11 months)	9336.16	19	2.02	1.29	3.17
Children (1-4 years)	39453.79	423	10.73	9.76	11.81
School-age (5-14 years)	41859.47	79	1.89	1.52	2.35
Adults (15-59 years)	107745.73	30	.28	.19	.40
Old age (60 + years)	7800.13	90	11.56	9.41	14.22
Total	**207021.61**	**641**	**3.10**	**2.87**	**3.345513**

Malaria mortality rates were among the highest in years 2001, 5.41 (95% CI: 4.41, 6.64) and in 2003, 4.13 (95% CI: 12.85, 14.81) per thousand. The overall mortality rate over the study period was 11.26 (95% CI: 3.63, 4.70). The highest malaria-related mortality was observed in the old-age group (i.e 11.56, 95% CI: 9.40, 14.22) and followed by children (i.e. 10.73, 95% CI: 9.76, 14.22) and post-neonates (i.e. 2.01, 95% CI: 1.29, 3.16).

6.4.1 Model-based results

Table 6.3 presents geostatistical model based estimate the hazard ratio of EIR across the different age groups adjusted for ITN intervention coverage and SES effects. The relationship between malaria exposure (on the logarithmic scale) and mortality was important only in children with a HR=1.06 (95% CI: 1.03, 1.08). The minimum distance at which the spatial correlation is deemed unimportant (i.e. less than 5%) ranges from 11.76 km to 32.5 km.

Table 6. 3: Geostatistical models' posterior estimates for malaria cause specific mortality

Covariates	Post-neonates HR (95% BCI)	Children HR (95% BCI)	School-age HR (95% BCI)	Adults HR (95% BCI)	Old age HR (95% BCI)
EIR (log scale)	0.96 (0.88, 1.05)	**1.06 (1.03, 1.08)**	1.04 (0.99, 1.09)	1.06 (0.99, 1.14)	0.98 (0.94, 1.03)
SES	0.79 (0.001, 1.76)	0.23 (0.05, 1.62)	0.29 (0.02, 3.52)	0.74 (0.02, 1.76)	0.95 (0.10, 1.69)
ITN	1.59 (0.30, 1.98)	1.14 (0.74, 1.75)	1.18 (0.54, 2.62)	1.37 (0.40, 5.31)	0.47 (0.21, 1.00)
Spatial variance	0.17 (0.02, 2.46)	0.30 (0.14, 0.76)	1.23 (0.46, 3.46)	0.50 (0.17, 2.05)	0.54 (0.20, 1.50)
Range (km)[a]	17.26 (1.74, 50.69)	32.5 (5.59, 52.0)	22.65 (4.90, 49.92)	11.76 (1.59, 48.61)	11.78 (1.98, 47.20)

a: minimum distance in kilometer at which the spatial correlation remains important , BCI=Bayesian Credible Interval

6.4.2 Sensitivity and specificity analysis

Table 6.4 shows the number of malaria-related and all-cause deaths recorded at different EIR ranges. The numbers of malaria-related deaths tend to be lower in moderate EIR values (i.e.25 -100 infective bytes per person and year).

Table 6. 4: Distribution of time at risk and deaths by Entomological Inoculation rate (EIR)

		Entomological Inoculation rate (IBPPY)					
		EIR=0	**1-25**	**25-50**	**50-100**	**>100**	**Total**
Post-neonate	Malaria deaths VA	11	4	0	2	2	19
	All-cause deaths	40	14	2	4	7	67
	Person years at risk	5361.13	2472.32	443.15	356.52	703.04	9336.16
Children	Malaria deaths VA	199	110	36	17	61	423
	All-cause deaths	513	219	53	34	122	941
	Person years at risk	22537.41	10112.51	1872.56	1212.84	3671.83	39407.14
School-age	Malaria deaths VA	50	9	5	4	11	79
	All-cause deaths	132	38	11	8	35	224
	Person years at risk	23293.76	13337.85	2079.15	989.59	2159.11	41859.47
Adults	Malaria deaths VA	13	11	1	3	2	30
	All-cause deaths	265	107	27	22	38	459
	Person years at risk	61591.36	30857.32	5870.92	2855.49	6587.29	107762.39
Old-age	Malaria deaths VA	59	14	6	1	10	90
	All-cause deaths	448	91	29	15	56	639
	Person years at risk	4624.77	2132.46	329.87	146.61	549.77	7783.47

Table 6.5 shows the diagnostic performance of VA using the EIR-mortality relationship as gold standard. Malaria exposure-attributable deaths were highest in among children (421) and old-age group (90). The percentage of deaths assigned-malaria as cause in VA was highest in children and school age groups with respectively 44.95% and 35.27%. The percentage of deaths attributable to malaria exposure was high across all age group (>65%). The malaria specific mortality rate ranged from 0.3 in adults to 11.6 in old age group. The highest malaria exposure-attributable mortality rate was observed among adults and old age groups with respectively (106.33 and 112.69 deaths/1000 person-years). The highest sensitivity of the VA were observed among children and school age groups with respectively 0.44 and 0.38, while the highest specificity were observed in adults and old age groups with respective values of 0.96 and 0.92.

Table 6. 5: Diagnostic performance for malaria VA using the EIR-mortality relationship as gold standard

	Post-neonate	Child	School-age	Adults	Old-age	Overall
Estimates of numbers of deaths						
a : Malaria attributable by VA and exposure	15.65	345.4	57.4	26.99	86.71	532.15
b : Malaria attributable by VA only	3.35	77.6	21.6	3.01	3.29	108.85
c: non-malaria attributable by VA and exposure	36.8	437.24	92.43	354.41	513.44	1434.32
d: non-malaria attributable by VA only	11.2	80.76	52.57	74.59	35.56	254.68
Derived quantities						
Overall all-cause mortality rate (deaths/1000 person-years) (from Table 1)	7.18	23.88	5.35	4.26	81.92	11.26
% of deaths assigned malaria as cause in VA (a+b)/(a+b+c+d)	28.36%	44.95%	35.27%	6.54%	14.08%	27.51%
% of deaths attributable to malaria exposure (a+c)/(a+b+c+d)	78.28%	83.17%	66.89%	83.09%	93.92%	84.40%
Malaria specific mortality rate estimated from VAs (deaths/1000 person-years)	2	10.7	1.9	0.3	11.6	3.10
Malaria exposure attributable mortality rate (deaths/1000 person-years)	75.58	88.91	98.65	106.33	112.69	89.04
Sensitivity of VA (a/(a+c))	0.30	0.44	0.38	0.07	0.14	0.27
Specificity of VA (d/(d+b))	0.77	0.51	0.71	0.96	0.92	0.70
Positive Predictive Value of VA (PPV) (a/(a+b))	0.82	0.82	0.73	0.90	0.96	0.83
Negative Predictive Value of VA (NPV) (d/(c+d))	0.23	0.16	0.36	0.17	0.06	0.15

6.5 Discussion

We found a relationship between malaria specific mortality and malaria exposure in children (1-4 years) with a hazard ratio of respectively (HR=1.06, 95% CI: 1.03, 1.08). These findings are in line with those of previous studies based on MTIMBA and HDSS analyses in Kisumu (Amek et al. 2013).

The distribution of time at risk and deaths among the different EIR values showed that the numbers of malaria-related deaths tend to be lower in moderate levels of transmission (i.e. 25-100). This supports findings suggesting that people in areas with moderate transmission intensity tend to develop much faster a stronger natural immunity (Bejon et al. 2009; R. W. Snow et al. 1997).

In this study we considered malaria-attributed deaths derived from the EIR-mortality model as the gold standard and estimated the diagnostic error of VA. The percentage of deaths attributable to malaria exposure was higher in old age group, children and adults with respectively 93.92%, 83.17% and 83.09%.

Results of the diagnostic performance showed that VA had higher specificity than sensitivity across all age groups. The highest specificity was estimated in adults (96%), while the lowest was estimated among

children (51%). The overall specificity is the physician-certified verbal autopsy (PCVA) is found to be 70%.

The diagnostic sensitivity of VA was among the highest in post-neonates, children and school-age groups with values of 30%, 44% and 38%, respectively. VA had the lowest probability to correctly diagnose malaria deaths in adults (i.e. 7%). Furthermore the PCVA proved to be very good at confirming malaria related deaths (PPV=83%); it did however correctly identify overall 27% of all malaria related deaths (sensitivity). The negative predictive value (NPV) which, expresses the ability of the PCVA at reassuring that a death is not malaria-related, is estimated at 15%. Many studies found reasonable validity of the PCVA in determining the cause of death (Soofi et al. 2015; Winbo 1998; Engmann et al. 2012; Leitao et al. 2014).

The PCVA has often been criticized, as it tends to overestimate malaria burden due to poor sensitivity and specificity in distinguishing fevers caused by malaria and those, which are not (Adjuik et al. 2006; Ndugwa et al. 2008; Todd et al. 1994). Our results however showed an overall poor performance of the PCVA in detecting malaria-attributable deaths (sensitivity of 27%). A study in Kenya assessed the diagnostic performance of the PCVA by comparison with a prospective survey of childhood deaths at a district hospital where medically confirmed diagnoses were available. Common causes of death were detected by PCVA with specificities greater than 80%. Sensitivity of the PCVA technique was greater than 75% for measles, neonatal tetanus, malnutrition, and trauma-related deaths; however, malaria, anaemia, acute respiratory-tract infection, gastroenteritis, and meningitis were detected with sensitivities of less than 50% (R. W. Snow et al. 1992).

The specificity and the sensitivity are two estimates of the divergence that may exist between the actual cause of death and the cause diagnosed by VA, since this discrepancy may have a major impact on cause-specific mortality rates (Maude and Ross, 1997). However, unlike certain diseases, malaria has no specific pathognomonic symptoms (Rogier et al. 2005) and symptoms such as fever, anaemia, coma, respiratory distress and neurological disturbances associated with malaria also overlap with many other tropical diseases (Marsh et al. 1996; Berkley et al. 1999).

The VA may therefore be less reliable for diagnosing malaria deaths. Many other previous studies have compared VA diagnoses with hospital-based diagnoses concluded that VA had low sensitivity and moderate specificity (Rowe 2005; Anker et al., 1999; Todd et al. 1994; R. W. Snow et al. 1992).

This study found an association between malaria transmission and malaria-mortality in children (1-4 years). This suggests that successful malaria interventions in high malaria endemic areas are likely to further reduce malaria-related mortality. The sensitivity and specificity analysis of the physician-certified verbal autopsy (PCVA) indicates an overall poor performance of this method. However, further investigations using larger VA datasets are needed to confirm these findings.

Authors Contribution

PV conceived and designed the study. ED analyzed the data and drafted the manuscript.
All authors gave intellectual content and critically reviewed the drafts and approved the final manuscript.

Acknowledgments

The authors are grateful to the CRSN and the principal investigator of the INDEPTH-MTIMBA project in Burkina Faso for providing the data. This work was funded by the Swiss National foundation (SNSF) Swiss Programme for Research on Global Issues for Development (R4D) project no. IZ01Z0-147286.

6.6 Appendix

Let Y_{ijt} be the malaria-specific mortality status of an individual i at village j and time interval t and N_{ijt} the total number of individuals present at time interval t. X_{ij} is the covariates associated with individual i at location j. We assume that Y_{ijt} arises from a Binomial distribution. That is $Y_{ijt} \sim Bin(N_{ijt}, p_{ijt})$ where, p_{it} is the probability of individual i dying at time interval t. We modeled spatial correlation via village-specific random effects ϕ_j (which is considered as latent observations of a spatial Gaussian process) on the logit, as $\log it(p_{ijt}) = \underset{\sim}{X}_i^T \underset{\sim}{\beta} + \phi_j$ where $\underset{\sim}{\beta}$ is the vector of regression coefficients. EIR is modeled on the log scale as a covariate with measurement errors (because it is estimated by separate Bayesian geostatistical models), that is $\log EIR \sim N(\log \tilde{EIR}_i, \sigma_{ei}^2)$ predicted at the household of child i where $\tilde{EIR}_i$ and σ_{ei}^2

correspond to the mean and variance respectively obtained from posterior prediction distribution of EIR at household i. We assumed $\phi \sim MVN(0,\Sigma)$, Σ is the covariance matrix with elements Σ_{kl} accounting for the covariance between any pair of villages k and l irrespective of the direction (isotropy). Using an exponential correlation function, the covariance matrix is defined by $\Sigma_{kl} = \sigma^2 \exp(-\rho d_{kl})$ where σ^2 is the spatial variation, d_{kl} is the distance between villages k and l, and ρ is the rate of correlation decay with increasing distance. The minimum distance at which the spatial correlation is significant at 5% is called range and can be obtained from the value $3/\rho$ (Ecker and Gelfand, 1997).

A Bayesian model formulation requires the specification of prior distributions for all model parameters. In particular, we choose a non-informative normal prior distribution with mean zero and large variance for the $\underset{\sim}{\beta}$ parameters, regression coefficients, an inverse gamma priors for σ_e^2 and σ^2. A gamma prior for ρ, that is $\sigma_e^2, \sigma^2 \sim IG(2.01,1.01)$ and $\rho \sim G(0.1,0.1)$.

The model was fitted using Morkov Chain Monte Carlo (MCMC) simulation algorithm in OpenBugs version 3.1.2 (Imperial College and Medical Council, London, UK) to estimate model parameters (Gelfand et al., 2000). Starting with some initials values about the parameters, we run two chains sampler discarding the first 5000 iterations. Convergence was assessed by Gelman-Rubin diagnostic (Gelman, 1992).

Chapter 7: General discussion

In this thesis, we assess the relationship between malaria transmission and mortality across all age groups and at different geographical scales in Burkina Faso. The results of this research contribute to the field of malaria epidemiology with i) knowledge on the malaria transmission-mortality relationship ii) up-to-date, nationwide, spatially explicit estimates of malaria risk and number of infected children under five years and iii) estimates of infant and under-five mortality in relation to malaria endemicity in Burkina Faso iv) estimates of the performance of verbal autopsy to diagnose malaria as the cause of death.

The work is structured around 7 chapters, which form the thesis. Chapter 2 corresponds to a manuscript, which has been already published in Parasites & Vectors. Chapter 3 has been published in Malaria Journal. Chapter 4 has been prepared for submission to Tropical Medicine & International Health Journal. Chapters 5 and 6 will be submitted to Acta Tropica and Malaria journal, respectively. For each chapter, detailed discussion and conclusion are provided. In this section, we summarise the main findings and their significance, discuss limitations and propose extensions of the work.

7.1 Significance of the work

7.1.1. Epidemiological methods

In chapter 2, we followed the approach by (Rumisha et al. 2014) and developed spatio-temporal models of EIR by fitting zero-inflated binomial (ZIB) and zero-inflated negative binomial (ZINB) models to sporozoite rates (proportion of infected mosquitoes) and mosquito densities, respectively. We extended the methodology by introducing Bayesian variable selection to identify the most important climatic factors related to malaria transmission and take into account lag times between climatic suitability and malaria transmission. Four models were fitted separately to *An. funestus* and *An. gambiae* data to obtain species-specific surfaces of mosquito density and sporozoite rate within the study area. The overall EIR estimate at a given location and month is based on the mean number of infected mosquitoes (from both species) multiplied by a conversion factor.

To our knowledge, this is the first effort for estimating and comparing the lag time between climatic suitability and malaria transmission between the two vector species (*An. gambiae* and *An. funestus*) using

rigorous modelling approaches. The results improve our understanding of the dynamics of malaria transmission in relation to the two species and are useful in timing control interventions.

We also assess the diagnostic performance of the physician-coded verbal autopsy (PCVA) using the estimated malaria-related excess mortality as the gold standard. Children and adults had the highest percentage of deaths attributed to malaria by VA equal to 44.95% and 35.27%. The percentage of malaria-related deaths according to the malaria transmission exposure was higher in old-age group (93.92%). The overall specificity of the physician-certified verbal autopsy (PCVA) was 0.70

The sensitivity and specificity analysis of the physician-certified verbal autopsy (PCVA) indicate an overall good performance of this method. This confirms that malaria still ranks among the leading causes of deaths and the acceptable diagnostic performance of the PCVA.

7.1.2 Malaria epidemiology

Results of this work contribute to a better understanding of the interplay between environmental/climatic conditions and malaria transmission, which is important not only for delivering interventions at the right time but also for developing predictive models to support early warning systems (EWS).

The estimated risk and intervention effect maps are valuable tools for identifying high-risk areas and areas with less effective interventions in order to improve malaria control in Burkina Faso. These outputs can serve as benchmarks to evaluate the effectiveness of future control interventions and progress of the efforts towards disease control.

Results from the mortality-malaria transmission analyses improve our understanding of the relationship between malaria transmission, all-cause and malaria specific mortality in Nouna region.

In chapter 2, model-based high-resolution maps depicting monthly malaria transmission pattern in Nouna HDSS catchment area were produced at 250m by 250 m spatial resolution using rigorous Bayesian geostatistical and temporal models. The potential strength of these maps lies in the fact that they account for small scale and species-specific spatio-temporal variation of malaria transmission within the Nouna HDSS catchment area. This is of particular importance since malaria transmission is mainly driven by two efficient vectors namely *Anopheles gambiae* and *An.funestus*, which co-exist geographically across the study area. Interestingly, high EIR estimates are observed in the western part of the study area, which is

located to a large extent in shallows that are extensively used by local populations for rice cultivation. The transmission in this area remained high even during the dry season. Therefore special targeted interventions focusing on these areas can be carried out continuously.

The prediction maps of entomological inoculation rate (EIR) surfaces depict strong spatial-temporal heterogeneity. Our results contribute to better understanding of the interplay between environmental/climatic conditions and malaria transmission, which is important not only for delivering interventions at the right time but also for developing predictive models to support early warning systems (EWS).

In chapter 3, we analyze MIS data using Bayesian geostatistical models to assess the effects of different malaria interventions at national as well as sub-national level in the country. Bayesian variable selection within geostatistical models allowed us to screen different coverage measures for each intervention and spatially structured regression coefficients measured the effects of interventions at district level. We also produce predictive maps of the disease burden adjusted for climatic effects at 1 km^2 spatial resolution covering the entire country. We also obtained maps of the effects of malaria interventions at health district level, which enabled us to identify districts where interventions are less likely to be effective. This is of policy relevance, as it will guide the choice of intervention with regard to their respective likelihood of success in a given place. While in districts where single interventions are less likely to be effective, a combination of interventions should be delivered in order to achieve synergistic effects.

In this thesis, we also assessed the relationship between malaria endemicity and infant/child all-cause mortality in Burkina Faso using Burkina Faso Demographic and Health Survey-Multiple Indicator Cluster Survey (BFDHS-MICS 2010) data. We employed Bayesian geostatistical Weibull survival models to explore malaria and infant/child mortality relationship in Burkina Faso while adjusting for individual and household characteristics as well as mother's birth history. There was a significantly strong association between high endemicity levels and children mortality especially in urban settings. No significant relationship was found between malaria endemicity and mortality in rural settings. Previous studies in other settings have investigated the relationship between child/infant all-cause mortality and malaria endemicity using Demographic and Health Survey data and reached different conclusions. Indeed while (Gemperli et al. 2004a) did not find any relation between malaria endemicity and mortality in Mali; (Kimani-Murage et al. 2014) using Demographic and Health Survey data collected between 1993 and 2008 in Kenya found

more rapid and statistically significant decline in infant, child and under five mortality rate in rural areas but not in urban areas.

Previous studies using MTIMBA data found a positive log-linear relationship between all-cause mortality and malaria exposure in infant and child in Navrongo (Ghana), Kisumu (Kenya) HDSS (Amek et al. 2013; Kasasa et al. 2013). Our analyses in the Nouna HDSS confirmed this finding. We found that overall, malaria transmission and all-cause mortality risk increases from early infanthood to childhood where it reaches its maximum; it then decreases steadily from childhood to elderly age. However, the EIR was negatively correlated with all-cause mortality in elderly population (60+ years). The same finding was obtained from the analyses in Kisumu HDSS (Amek et al. 2013) and it may be explained by the fact that elderly people have over time acquired natural immunity against the disease (Doolan, Dobaño, and Baird 2009). Higher SES quintiles were protective against all-cause mortality in adults. This implies that adults from well-off households are less likely to die compared to their counterpart in poorer households.

A significant positive log-linear relationship was also found between EIR and malaria mortality in children (Chapter 6). This suggests that successful malaria interventions in malaria endemic areas are likely to further reduce malaria-related mortality.

7.2 Limitations and challenges

7.2.1 Intervention and socioeconomic data in the MTIMBA project

The MTIMBA project was primarily designed to gather comprehensive entomological, demographic as well as malaria-related interventions data. However the Nouna HDSS site by then was not routinely monitoring ITN and SES information. The ITN coverage estimates used in this thesis were extracted from a survey conducted in 2007, as part of another study on a sample of the HDSS households. The socioeconomic indicators were also collected once during the period of the MTIMBA project in 2004 on a sample of 1000 HDSS households. Principal components analysis was then used to construct household socioeconomic status (SES) index categorized into quintiles ranking households from the poorest (first quintile) to the least poor (fifth quintile). These data were therefore available for a sample of locations. SES status was estimated for the entire study area by calculating the proportion of households falling into the highest SES quintile per village. The lack of ITN and SES information at households with mortality data and the temporal misalignment between the ITN data used in the modeling may bias the malaria-mortality estimates.

7.2.2 Nouna HDSS mortality data

Extremely low mortality rates were observed among neonates and post-neonates in the Nouna HDSS. This finding may be associated with the routine data collection system, especially the mortality data and the prevailing socio-cultural practices in the study area. Indeed the verbal autopsy interview is conducted within the three months following any fatal event captured in the HDSS catchment area. Owing to some specific cultural practices, it is a common practice that a newborn has the naming ceremony on the seventh day after birth. This time frame extends up to forty days in some local communities. The death of any newborn before that time frame tends to be silenced and hardly refer to. One way to overcome that issue in data collection is to ensure a proper registration and follow-up of any pregnant women in the HDSS catchment area.

7.2.3 Environmental/climatic predictors and la analysis

The environmental and climatic predictors used in this thesis were extracted from satellite data sources. These data were obtained in a continuous scale at different temporal and spatial resolutions. However, MTIMBA data were collected biweekly and aggregated at monthly intervals in our analyses. Covariates were also summarized over months (current and previous ones in the lag analyses). The summarized values are linked to the study outcome to assess the time interval that best explains the variation in the data. Aggregating of the data could have resulted in masking variation in the data and subsequently led to biased parameter estimates.

7.3 Extension and future research

The models used to obtain georeferenced estimates of malaria risk based on the 2009 MIS data can be applied to analyse the most recent MIS data of 2014 dataset to produce comparative estimates in order to monitor changes of the malaria situation in the country. These estimates and intervention effect maps will be valuable tools for identifying priority areas and areas with less effective interventions in order to improve malaria control in Burkina Faso. Further analyses of the malaria-mortality relation using

complementary data e.g. incidence should be conducted to confirm our findings on the relationship between malaria endemicity and children under five of age mortality.

In this thesis we used and systematically examined different lag structures through Bayesian variable selection implemented within a geostatistical model. Future research should explore lag effects via distributed lag models as an alternative approach to the one used in this work (Almon 1965; Gasparrini, Armstrong, and Kenward 2010; Gasparrini 2011). However it is worth noting that this approach assumes that the different climatic proxies are available on a daily scale or aggregated over a common temporal resolution (e.g. month).

Bibliography

Aaby, Peter, Amabelia Rodrigues, Poul-Erik Kofoed, and Christine Stabell Benn. 2015. "RTS,S/AS01 Malaria Vaccine and Child Mortality." *The Lancet* 386 (10005): 1735–36. doi:10.1016/S0140-6736(15)00693-5.

Adigun, Abbas B., Efron N. Gajere, Olusola Oresanya, and Penelope Vounatsou. 2015. "Malaria Risk in Nigeria: Bayesian Geostatistical Modelling of 2010 Malaria Indicator Survey Data." *Malaria Journal* 14 (1): 156. doi:10.1186/s12936-015-0683-6.

Adjuik, Martin, Tom Smith, Sam Clark, Jim Todd, Anu Garrib, Yohannes Kinfu, Kathy Kahn, et al. 2006. "Cause-Specific Mortality Rates in Sub-Saharan Africa and Bangladesh." *Bulletin of the World Health Organization* 84 (3): 181–88. doi:/S0042-96862006000300012.

Alam, Nurul, Jeroen K. Van Ginneken, and Alinda M. Bosch. 2007. "Infant Mortality among Twins and Triplets in Rural Bangladesh in 1975–2002." *Tropical Medicine & International Health* 12 (12): 1506–14. doi:10.1111/j.1365-3156.2007.01959.x.

Alan Brooks, Olivier J. T. Briët. 2012. "Simulated Impact of RTS,S/AS01 Vaccination Programs in the Context of Changing Malaria Transmission." *PloS One* 7 (3): e32587. doi:10.1371/journal.pone.0032587.

Almon, Shirley. 1965. "The Distributed Lag Between Capital Appropriations and Expenditures." *Econometrica* 33 (1): 178–96. doi:10.2307/1911894.

Alonso, P. L., S. W. Lindsay, J. R. Armstrong Schellenberg, K. Keita, P. Gomez, F. C. Shenton, A. G. Hill, P. H. David, G. Fegan, and K. Cham. 1993. "A Malaria Control Trial Using Insecticide-Treated Bed Nets and Targeted Chemoprophylaxis in a Rural Area of The Gambia, West Africa. 6. The Impact of the Interventions on Mortality and Morbidity from Malaria." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 87 Suppl 2 (June): 37–44.

Amek, Nyaguara, Nabie Bayoh, Mary Hamel, Kim A Lindblade, John E Gimnig, Frank Odhiambo, Kayla F Laserson, Laurence Slutsker, Thomas Smith, and Penelope Vounatsou. 2012. "Spatial and Temporal Dynamics of Malaria Transmission in Rural Western Kenya." *Parasites & Vectors* 5: 86. doi:10.1186/1756-3305-5-86.

Amek, Nyaguara, Nabie Bayoh, Mary Hamel, Kim A Lindblade, John Gimnig, Kayla F Laserson, Laurence Slutsker, Thomas Smith, and Penelope Vounatsou. 2011. "Spatio-Temporal Modeling of Sparse Geostatistical Malaria Sporozoite Rate Data Using a Zero Inflated Binomial Model." *Spatial and Spatio-Temporal Epidemiology* 2 (4): 283–90. doi:10.1016/j.sste.2011.08.001.

Amek, Nyaguara Ombek. 2013. "Bayesian Spatio-Temporal Modelling of the Relationship between Mortality and Malaria Transmission in Rural Western Kenya." http://core.ac.uk/display/18262461.

Amek, Nyaguara Ombek. 2013. "Bayesian Spatio-Temporal Modelling of the Relationship between Mortality and Malaria Transmission in Rural Western Kenya." doi:10.5451/unibas-006166981.

Apinjoh, Tobias O., Judith K. Anchang-Kimbi, Regina N. Mugri, Delphine A. Tangoh, Robert V. Nyingchu, Hanesh F. Chi, Rolland B. Tata, Charles Njumkeng, Clarisse Njua-Yafi, and Eric A. Achidi. 2015. "The Effect of Insecticide Treated Nets (ITNs) on Plasmodium Falciparum Infection in Rural and Semi-Urban Communities in the South West Region of Cameroon." *PLoS ONE* 10 (2). doi:10.1371/journal.pone.0116300.

Banerjee, Sudipto, Bradley P. Carlin, and Alan E. Gelfand. 2014. *Hierarchical Modeling and Analysis for Spatial Data*. Crc Press.

http://books.google.com/books?hl=en&lr=&id=WVHRBQAAQBAJ&oi=fnd&pg=PP1&dq=info:sbZW01DLddwJ:scholar.google.com&ots=Anx_xpSKq0&sig=fg6t8ffxR0QN-vv1tllvVubukQU.

Banerjee, Sudipto, Alan E. Gelfand, Andrew O. Finley, and Huiyan Sang. 2008. "Gaussian Predictive Process Models for Large Spatial Data Sets." *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 70 (4): 825–48. doi:10.1111/j.1467-9868.2008.00663.x.

Bank, The World. 2004. "Background Papers." 28911. The World Bank. http://documents.worldbank.org/curated/en/2004/11/5525106/ecuador-creating-fiscal-space-poverty-reduction-fiscal-management-public-expenditure-review-vol-2-2-background-papers.

Barbieri, Maria Maddalena, and James O. Berger. 200406. "Optimal Predictive Model Selection." *The Annals of Statistics* 32 (3): 870–97. doi:10.1214/009053604000000238.

Bayoh, M. N., and S. W. Lindsay. 2004. "Temperature-Related Duration of Aquatic Stages of the Afrotropical Malaria Vector Mosquito Anopheles Gambiae in the Laboratory." *Medical and Veterinary Entomology* 18 (2): 174–79. doi:10.1111/j.0269-283X.2004.00495.x.

Beier, J. C., G. F. Killeen, and J. I. Githure. 1999. "Short Report: Entomologic Inoculation Rates and Plasmodium Falciparum Malaria Prevalence in Africa." *The American Journal of Tropical Medicine and Hygiene* 61 (1): 109–13.

Beier, John C. 1998. "Malaria Parasite Development in Mosquitoes." *Annual Review of Entomology* 43 (1): 519–43. doi:10.1146/annurev.ento.43.1.519.

Bejon, Philip, Edna Ogada, Norbert Peshu, and Kevin Marsh. 2009. "Interactions between Age and ITN Use Determine the Risk of Febrile Malaria in Children." *PLoS ONE* 4 (12). doi:10.1371/journal.pone.0008321.

Berkley, J. A., I. Mwangi, F. Mellington, S. Mwarumba, and K. Marsh. 1999. "Cerebral Malaria versus Bacterial Meningitis in Children with Impaired Consciousness." *QJM: Monthly Journal of the Association of Physicians* 92 (3): 151–57.

Bhatt, S., D. J. Weiss, E. Cameron, D. Bisanzio, B. Mappin, U. Dalrymple, K. E. Battle, et al. 2015. "The Effect of Malaria Control on Plasmodium Falciparum in Africa between 2000 and 2015." *Nature* 526 (7572): 207–11. doi:10.1038/nature15535.

Bi, Yan, Wenbiao Hu, Henling Yang, Xiao-Nong Zhou, Weiwei Yu, Yuming Guo, and Shilu Tong. 2013. "Spatial Patterns of Malaria Reported Deaths in Yunnan Province, China." *American Journal of Tropical Medicine and Hygiene* 88 (3): 526–35. doi:10.4269/ajtmh.2012.12-0217.

Bødker, René, Hamisi A. Msangeni, William Kisinza, and Steve W. Lindsay. 2006. "Relationship Between the Intensity of Exposure to Malaria Parasites and Infection in the Usambara Mountains, Tanzania." *The American Journal of Tropical Medicine and Hygiene* 74 (5): 716–23.

Boudin, C., J. Lyannaz, M. F. Bosseno, P. Carnevale, and P. Ambroise-Thomas. 1991. "Epidemiology of Plasmodium Falciparum in a Rice Field and a Savanna Area in Burkina Faso: Seasonal Fluctuations of Gametocytaemia and Malarial Infectivity." *Annals of Tropical Medicine and Parasitology* 85 (4): 377–85.

Brooks, Stephen P., and Gareth O. Roberts. 1998. "Convergence Assessment Techniques for Markov Chain Monte Carlo." *Statistics and Computing* 8 (4): 319–35. doi:10.1023/A:1008820505350.

Buonomo, Bruno. 2015. "Analysis of a Malaria Model with Mosquito Host Choice and Bed-Net Control." *International Journal of Biomathematics* 8 (6): 1550077. doi:10.1142/S1793524515500771.

"Burkina Faso - Enquête Sur Les Indicateurs Du Paludisme 2014." 2016. Accessed March 8. http://microdata.worldbank.org/index.php/catalog/2521/get_microdata.

Byass, Peter, Kobus Herbst, Edward Fottrell, Mohamed M. Ali, Frank Odhiambo, Nyaguara Amek, Mary J. Hamel, et al. 2016. "Comparing Verbal Autopsy Cause of Death Findings as Determined by

Physician Coding and Probabilistic Modelling: A Public Health Analysis of 54 000 Deaths in Africa and Asia." *Journal of Global Health* 5 (1). Accessed February 11. doi:10.7189/jogh.05.010402.

Carter, R, K N Mendis, and D Roberts. 2000. "Spatial Targeting of Interventions against Malaria." *Bulletin of the World Health Organization* 78 (12): 1401–11.

Cator, Lauren J, Shalu Thomas, Krijn P Paaijmans, Sangamithra Ravishankaran, Johnson A Justin, Manu T Mathai, Andrew F Read, Matthew B Thomas, and Alex Eapen. 2013. "Characterizing Microclimate in Urban Malaria Transmission Settings: A Case Study from Chennai, India." *Malaria Journal* 12 (March): 84. doi:10.1186/1475-2875-12-84.

Chammartin, Frédérique, Ronaldo GC Scholte, Luiz H Guimarães, Marcel Tanner, Jürg Utzinger, and Penelope Vounatsou. 2013. "Soil-Transmitted Helminth Infection in South America: A Systematic Review and Geostatistical Meta-Analysis." *The Lancet Infectious Diseases* 13 (6): 507–18. doi:10.1016/S1473-3099(13)70071-9.

Chandramohan, Daniel, Laura C. Rodrigues, Gillian H. Maude, and Richard J. Hayes. 1998. "The Validity of Verbal Autopsies for Assessing the Causes of Institutional Maternal Death." *Studies in Family Planning* 29 (4): 414–22. doi:10.2307/172253.

Chandramohan, D., B. Greenwood, J. Cox, R. Mswia, and P. Setel. 2001. "Relationship between Malaria Endemicity and Acute Febrile Illness Mortality in Children." *Bulletin of the World Health Organization* 79 (4): 375–76.

Charlwood, J.d., J. Kihonda, S. Sama, P.f. Billingsley, H. Hadji, J.p. Verhave, E. Lyimo, P.c. Luttikhuizen, and T. Smith. 1995. "The Rise and Fall of Anopheles Arabiensis (Diptera: Culicidae) in a Tanzanian Village." *Bulletin of Entomological Research* 85 (01): 37–44. doi:10.1017/S0007485300051993.

Charlwood, J D, E V E Tomás, P Salgueiro, A Egyir-Yawson, R J Pitts, and J Pinto. 2011. "Studies on the Behaviour of Peridomestic and Endophagic M Form Anopheles Gambiae from a Rice Growing Area of Ghana." *Bulletin of Entomological Research* 101 (5): 533–39. doi:10.1017/S0007485311000125.

Coetzee, M., M. Craig, and D. le Sueur. 2000. "Distribution of African Malaria Mosquitoes Belonging to the Anopheles Gambiae Complex." *Parasitology Today* 16 (2): 74–77. doi:10.1016/S0169-4758(99)01563-X.

Cogswell, F B. 1992. "The Hypnozoite and Relapse in Primate Malaria." *Clinical Microbiology Reviews* 5 (1): 26–35.

"Conseil National de La Statistique." 2016. Accessed March 3. http://www.cns.bf/spip.php?id_rubrique=17&page=publdetails.

Craig, M H, R W Snow, and D le Sueur. 1999a. "A Climate-Based Distribution Model of Malaria Transmission in Sub-Saharan Africa." *Parasitology Today (Personal Ed.)* 15 (3): 105–11.

Craig, M. H., R. W. Snow, and D. le Sueur. 1999b. "A Climate-Based Distribution Model of Malaria Transmission in Sub-Saharan Africa." *Parasitology Today* 15 (3): 105–11. doi:10.1016/S0169-4758(99)01396-4.

Cressie, Noel. 1993. *Statistics for Spatial Data*. Revised Edition. Wiley-Interscience.

Deressa, Wakgari, Mesganaw Fantahun, and Ahmed Ali. 2007. "Malaria-Related Mortality Based on Verbal Autopsy in an Area of Low Endemicity in a Predominantly Rural Population in Ethiopia." *Malaria Journal* 6 (September): 128. doi:10.1186/1475-2875-6-128.

de Savigny, Don, and Fred Binka. 2004. "Monitoring Future Impact on Malaria Burden in Sub-Saharan Africa." *The American Journal of Tropical Medicine and Hygiene* 71 (2 Suppl): 224–31.

De Silva, Prathiba M., John M. Marshall, Prathiba M. De Silva, and John M. Marshall. 2012. "Factors Contributing to Urban Malaria Transmission in Sub-Saharan Africa: A Systematic Review, Factors Contributing to Urban Malaria Transmission in Sub-Saharan Africa: A Systematic Review." *Journal of Tropical Medicine, Journal of Tropical Medicine* 2012, 2012 (October): e819563. doi:10.1155/2012/819563, 10.1155/2012/819563.

Dia, Ibrahima, Moussa Wamdaogo, and Diego Ayal. 2013. "Advances and Perspectives in the Study of the Malaria Mosquito Anopheles Funestus." In *Anopheles Mosquitoes - New Insights into Malaria Vectors*, edited by Sylvie Manguin. InTech. http://www.intechopen.com/books/anopheles-mosquitoes-new-insights-into-malaria-vectors/advances-and-perspectives-in-the-study-of-the-malaria-mosquito-anopheles-funestus.

Diallo, D. A., S. N. Cousens, N. Cuzin-Ouattara, I. Nebié, E. Ilboudo-Sanogo, and F. Esposito. 2004. "Child Mortality in a West African Population Protected with Insecticide-Treated Curtains for a Period of up to 6 Years." *Bulletin of the World Health Organization* 82 (2): 85–91.

Diboulo, Eric, Ali Sié, Diallo A. Diadier, Dimitrios A. Karagiannis Voules, Yazoume Yé, and Penelope Vounatsou. 2015. "Bayesian Variable Selection in Modelling Geographical Heterogeneity in Malaria Transmission from Sparse Data: An Application to Nouna Health and Demographic Surveillance System (HDSS) Data, Burkina Faso." *Parasites & Vectors* 8 (1): 118. doi:10.1186/s13071-015-0679-7.

Diggle, P. J., J. A. Tawn, and R. A. Moyeed. 1998. "Model-Based Geostatistics." *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 47 (3): 299–350. doi:10.1111/1467-9876.00113.

Don de Savigny, Fred Binka. 2004. "Monitoring Future Impact on Malaria Burden in Sub-Saharan Africa." *The American Journal of Tropical Medicine and Hygiene* 71 (2 Suppl): 224–31.

Doolan, Denise L., Carlota Dobaño, and J. Kevin Baird. 2009. "Acquired Immunity to Malaria." *Clinical Microbiology Reviews* 22 (1): 13–36. doi:10.1128/CMR.00025-08.

Drakeley, C. J., P. H. Corran, P. G. Coleman, J. E. Tongren, S. L. R. McDonald, I. Carneiro, R. Malima, et al. 2005. "Estimating Medium- and Long-Term Trends in Malaria Transmission by Using Serological Markers of Malaria Exposure." *Proceedings of the National Academy of Sciences of the United States of America* 102 (14): 5108–13. doi:10.1073/pnas.0408725102.

Ecker, Mark D., and Alan E. Gelfand. 1997. "Bayesian Variogram Modeling for an Isotropic Spatial Process." *Journal of Agricultural, Biological and Environmental Statistics* 2: 347–69.

Eisele, Thomas P., David A. Larsen, Neff Walker, Richard E. Cibulskis, Joshua O. Yukich, Charlotte M. Zikusooka, and Richard W. Steketee. 2012. "Estimates of Child Deaths Prevented from Malaria Prevention Scale-up in Africa 2001-2010." *Malaria Journal* 11 (March): 93. doi:10.1186/1475-2875-11-93.

Eisele, Thomas P., David Larsen, and Richard W. Steketee. 2010. "Protective Efficacy of Interventions for Preventing Malaria Mortality in Children in Plasmodium Falciparum Endemic Areas." *International Journal of Epidemiology* 39 (suppl 1): i88–101. doi:10.1093/ije/dyq026.

"eLife Digest." 2015. *eLife*, December. doi:10.7554/eLife.09672.002.

Engmann, C, A Garces, I Jehan, J Ditekemena, M Phiri, M Mazariegos, E Chomba, et al. 2012. "Causes of Community Stillbirths and Early Neonatal Deaths in Low-Income Countries Using Verbal Autopsy: An International, Multicenter Study." *Journal of Perinatology* 32 (8): 585–92. doi:10.1038/jp.2011.154.

Eric Diboulo, Ali Sié. 2015. "Bayesian Variable Selection in Modelling Geographical Heterogeneity in Malaria Transmission from Sparse Data: An Application to Nouna Health and Demographic

Surveillance System (HDSS) Data, Burkina Faso." *Parasites & Vectors* 8 (1). doi:10.1186/s13071-015-0679-7.

Faso), Institut National de la Statistique et de la Démographie (Burkina, and ICF International (USA). 2012. *Enquête Démographique et de Santé et à Indicateurs Multiples Du Burkina Faso 2010 (EDSBF-MICS IV)*. Ouagadougou (BFA); Calverton, Maryland (USA): INSD; ICF International.

Finlay, Jocelyn E., Emre Özaltin, and David Canning. 2011. "The Association of Maternal Age with Infant Mortality, Child Anthropometric Failure, Diarrhoea and Anaemia for First Births: Evidence from 55 Low- and Middle-Income Countries." *BMJ Open* 1 (2): e000226. doi:10.1136/bmjopen-2011-000226.

Forouzannia, Farinaz, and A. Gumel. 2015. "Dynamics of an Age-Structured Two-Strain Model for Malaria Transmission." *Applied Mathematics and Computation* 250 (January): 860–86. doi:10.1016/j.amc.2014.09.117.

França, Elisabeth, Deise Campos, Mark DC Guimarães, and Maria de Fátima M Souza. 2011. "Use of Verbal Autopsy in a National Health Information System: Effects of the Investigation of Ill-Defined Causes of Death on Proportional Mortality due to Injury in Small Municipalities in Brazil." *Population Health Metrics* 9 (August): 39. doi:10.1186/1478-7954-9-39.

Fullman, Nancy, Roy Burstein, Stephen S. Lim, Carol Medlin, and Emmanuela Gakidou. 2013. "Nets, Spray or Both? The Effectiveness of Insecticide-Treated Nets and Indoor Residual Spraying in Reducing Malaria Morbidity and Child Mortality in Sub-Saharan Africa." *Malaria Journal* 12: 62. doi:10.1186/1475-2875-12-62.

Garnham, P.C.C. 1988. "History of Discoveries of Malaria Parasites and of Their Life Cycles." *History and Philosophy of the Life Sciences* 10 (1): 93–108.

Gasparrini, A., B. Armstrong, and M. G. Kenward. 2010. "Distributed Lag Non-Linear Models." *Statistics in Medicine*. doi:10.1002/sim.3940.

Gasparrini, Antonio. 2011. "Distributed Lag Linear and Non-Linear Models in R: The Package Dlnm." *Journal of Statistical Software* 43 (8): 1–20.

Gemperli, Armin. 2003. *Development of Spatial Statistical Methods for Modelling Point-Referenced Spatial Data in Malaria Epidemiology*.

Gemperli, A., P. Vounatsou, I. Kleinschmidt, M. Bagayoko, C. Lengeler, and T. Smith. 2004a. "Spatial Patterns of Infant Mortality in Mali: The Effect of Malaria Endemicity." *American Journal of Epidemiology* 159 (1): 64–72.

George, Edward I., and Robert E. McCulloch. 1993a. "Variable Selection via Gibbs Sampling." *Journal of the American Statistical Association* 88 (423): 881–89. doi:10.1080/01621459.1993.10476353.

Gething, Peter W., Anand P. Patil, David L. Smith, Carlos A. Guerra, Iqbal R. F. Elyazar, Geoffrey L. Johnston, Andrew J. Tatem, and Simon I. Hay. 2011. "A New World Malaria Map: Plasmodium Falciparum Endemicity in 2010." *Malaria Journal* 10: 378. doi:10.1186/1475-2875-10-378.

Giardina, Federica, Laura Gosoniu, Lassana Konate, Mame Birame Diouf, Robert Perry, Oumar Gaye, Ousmane Faye, and Penelope Vounatsou. 2012. "Estimating the Burden of Malaria in Senegal: Bayesian Zero-Inflated Binomial Geostatistical Modeling of the MIS 2008 Data." *PLoS ONE* 7 (3). doi:10.1371/journal.pone.0032625.

Giardina, Federica, Simon Kasasa, Ali Sié, Jürg Utzinger, Marcel Tanner, and Penelope Vounatsou. 2014. "Effects of Vector-Control Interventions on Changes in Risk of Malaria Parasitaemia in Sub-Saharan Africa: A Spatial and Temporal Analysis." *The Lancet Global Health* 2 (10): e601–15. doi:10.1016/S2214-109X(14)70300-6.

"Global Burden of Disease (GBD)." 2016. Accessed March 3. http://www.healthdata.org/gbd.

Gosoniu, Gabriel Dominic. 2006. *Bayesian Spatial Modeling of Malaria Transmission Parameters in Rufiji, Tanzania*. University of Neuchâtel - Facultof Economics - Institute of Statistics.

Gosoniu, Laura, Amina Msengwa, Christian Lengeler, and Penelope Vounatsou. 2012a. "Spatially Explicit Burden Estimates of Malaria in Tanzania: Bayesian Geostatistical Modeling of the Malaria Indicator Survey Data." *PLoS ONE* 7 (5). doi:10.1371/journal.pone.0023966.

Gosoniu, Laura, Andre Mia Veta, and Penelope Vounatsou. 2010. "Bayesian Geostatistical Modeling of Malaria Indicator Survey Data in Angola." *PLoS ONE* 5 (3): e9322. doi:10.1371/journal.pone.0009322.

Gosoniu, L, P Vounatsou, N Sogoba, and T Smith. 2006. "Bayesian Modelling of Geostatistical Malaria Risk Data." *Geospatial Health* 1 (1): 127–39.

Greenwood, B M. 1989. "The Microepidemiology of Malaria and Its Importance to Malaria Control." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 83 Suppl: 25–29.

Greenwood, B. M., A. K. Bradley, A. M. Greenwood, P. Byass, K. Jammeh, K. Marsh, S. Tulloch, F. S. Oldfield, and R. Hayes. 1987. "Mortality and Morbidity from Malaria among Children in a Rural Area of The Gambia, West Africa." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 81 (3): 478–86.

Gubhaju, B. B. 1985. "Effects of Birth Order and Maternal Age on Infant and Child Mortality in Rural Nepal." *Biology and Society: The Journal of the Eugenics Society* 2 (1): 15–22.

Guelbeogo, Wamdaogo, N'Fale Sagnon, Olga Grushko, Malgaouende Yameogo, Daniela Boccolini, Nora Besansky, and Carlo Costantini. 2009. "Seasonal Distribution of Anopheles Funestus Chromosomal Forms from Burkina Faso." *Malaria Journal* 8 (1): 239. doi:10.1186/1475-2875-8-239.

Haddow, A. J. 1943. "Measurements of Temperature and Light in Artificial Pools with Reference to the Larval Habitat of Anopheles (Myzomyia) Gambiae, Giles, and A. (M.) Funestus, Giles." *Bulletin of Entomological Research* 34 (02): 89–93. doi:10.1017/S0007485300023609.

Haining, Robert P. 2003. *Spatial Data Analysis: Theory and Practice*. Cambridge, UK ; New York: Cambridge University Press.

Hall, D B. 2000. "Zero-Inflated Poisson and Binomial Regression with Random Effects: A Case Study." *Biometrics* 56 (4): 1030–39.

Haque, Ubydul, Hans J. Overgaard, Archie C. A. Clements, Douglas E. Norris, Nazrul Islam, Jahirul Karim, Shyamal Roy, et al. 2014. "Malaria Burden and Control in Bangladesh and Prospects for Elimination: An Epidemiological and Economic Assessment." *Lancet Global Health* 2 (2): E98–105.

Hawley, William A., Penelope A. Phillips-Howard, Feiko O. Ter Kuile, Dianne J. Terlouw, John M. Vulule, Maurice Ombok, Bernard L. Nahlen, et al. 2003. "Community-Wide Effects of Permethrin-Treated Bed Nets on Child Mortality and Malaria Morbidity in Western Kenya." *The American Journal of Tropical Medicine and Hygiene* 68 (4 suppl): 121–27.

Hay, S. I., R. W. Snow, and D. J. Rogers. 1998. "Predicting Malaria Seasons in Kenya Using Multitemporal Meteorological Satellite Sensor Data." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 92 (1): 12–20.

"Household Survey Indicators for Malaria Control 12b June 2013 (RBM) - Household Survey Indicators for Malaria Control.pdf." 2015. Accessed July 20. http://www.malariasurveys.org/documents/Household%20Survey%20Indicators%20for%20Malaria%20Control.pdf.

Ijumba, J. N., and S. W. Lindsay. 2001. "Impact of Irrigation on Malaria in Africa: Paddies Paradox." *Medical and Veterinary Entomology* 15 (1): 1–11.

INSD. 2012. "Burkina Faso Enquête Démographique et de Santé et à Indicateurs Multiples (EDSBF-MICS IV), Institut National de La Statistique et de La Démographie (INSD) Ministère de l'Économie et Des Finances, Ouagadougou, Burkina Faso et ICF International, Calverton, Maryland, USA: 501."

Jamal Uddin. 2008. "Predictors of Infant Mortality in a Developing Country." *Asian Journal of Epidemiology*, January, 1–16. doi:10.3923/aje.2008.1.16.

Johnson, Kiersten, ORC Macro MEASURE/DHS+ (Programme), and Shea Oscar Rutstein. 2004. *The DHS Wealth Index*. Calverton, Md: ORC Macro, MEASURE DHS+.

Justesen, A., and A. Kunst. 2000. "Postneonatal and Child Mortality among Twins in Southern and Eastern Africa." *International Journal of Epidemiology* 29 (4): 678–83.

Kampe, Eveline Otte Im, Olaf Mueller, Ali Sie, and Heiko Becher. 2015. "Seasonal and Temporal Trends in All-Cause and Malaria Mortality in Rural Burkina Faso, 1998-2007." *Malaria Journal* 14 (August): 300. doi:10.1186/s12936-015-0818-9.

Kasasa, Simon. 2013. *Assessing Malaria Attributed Mortality in West and Southern Africa*. Basel: s.n.

Kasasa, Simon, Victor Asoala, Laura Gosoniu, Francis Anto, Martin Adjuik, Cletus Tindana, Thomas Smith, Seth Owusu-Agyei, and Penelope Vounatsou. 2013. "Spatio-Temporal Malaria Transmission Patterns in Navrongo Demographic Surveillance Site, Northern Ghana." *Malaria Journal* 12 (1): 63. doi:10.1186/1475-2875-12-63.

Kimani-Murage, E. W., J. C. Fotso, T. Egondi, B. Abuya, P. Elungata, A. K. Ziraba, C. W. Kabiru, and N. Madise. 2014. "Trends in Childhood Mortality in Kenya: The Urban Advantage Has Seemingly Been Wiped out." *Health & Place* 29 (September): 95–103. doi:10.1016/j.healthplace.2014.06.003.

Kirby, Matthew J. 2005. "Why Does Anopheles Arabiensis Predominate over An. Gambiae Sensu Stricto in Hot and Arid Conditions?" Thesis, NonPeerReviewed.

Knols, Bart GJ. 2009. "Review of 'Environmental Factors and Malaria Transmission Risk: Modelling the Risk in a Holoendemic Area of Burkina Faso' by Yazoume Yé, Osman Sankoh, Bocar Kouyaté and Rainer Sauerborn." *Parasites & Vectors* 2 (1): 14. doi:10.1186/1756-3305-2-14.

Kobbe, Robin, Samuel Adjei, Christina Kreuzberg, Benno Kreuels, Benedicta Thompson, Peter A. Thompson, Florian Marks, et al. 2007. "Malaria Incidence and Efficacy of Intermittent Preventive Treatment in Infants (IPTi)." *Malaria Journal* 6 (December): 163. doi:10.1186/1475-2875-6-163.

K'Oyugi, Boniface O. 2015. "Effects of Bed Nets and Anti-Malaria Drugs Use on Childhood Mortality in Kenya's Malaria Endemic and Epidemic Areas." *Bmc Public Health* 15 (January): 34. doi:10.1186/s12889-015-1398-x.

Kristan, Mojca, Tarekegn A. Abeku, James Beard, Michael Okia, Beth Rapuoda, James Sang, and Jonathan Cox. 2008. "Variations in Entomological Indices in Relation to Weather Patterns and Malaria Incidence in East African Highlands: Implications for Epidemic Prevention and Control." *Malaria Journal* 7 (1): 231. doi:10.1186/1475-2875-7-231.

Krotoski, W. A. 1989. "The Hypnozoite and Malarial Relapse." *Progress in Clinical Parasitology* 1: 1–19.

Kuo, Lynn, and Bani Mallick. 1998a. "Variable Selection for Regression Models." *Sankhyā: The Indian Journal of Statistics, Series B (1960-2002)* 60 (1): 65–81. doi:10.2307/25053023.

Larsen, David A., Paul Hutchinson, Adam Bennett, Joshua Yukich, Philip Anglewicz, Joseph Keating, and Thomas P. Eisele. 2014. "Community Coverage with Insecticide-Treated Mosquito Nets and Observed Associations with All-Cause Child Mortality and Malaria Parasite Infections." *American Journal of Tropical Medicine and Hygiene* 91 (5): 950–58. doi:10.4269/ajtmh.14-0318.

Leitao, Jordana, Nikita Desai, Lukasz Aleksandrowicz, Peter Byass, Pierre Miasnikof, Stephen Tollman, Dewan Alam, et al. 2014. "Comparison of Physician-Certified Verbal Autopsy with Computer-Coded Verbal Autopsy for Cause of Death Assignment in Hospitalized Patients in Low- and

Middle-Income Countries: Systematic Review." *BMC Medicine* 12 (February): 22. doi:10.1186/1741-7015-12-22.

Lindsay, S W, L Parson, and C J Thomas. 1998. "Mapping the Ranges and Relative Abundance of the Two Principal African Malaria Vectors, Anopheles Gambiae Sensu Stricto and An. Arabiensis, Using Climate Data." *Proceedings of the Royal Society B: Biological Sciences* 265 (1399): 847–54.

Lindsay, S. W., H. A. Wilkins, H. A. Zieler, R. J. Daly, V. Petrarca, and P. Byass. 1991. "Ability of Anopheles Gambiae Mosquitoes to Transmit Malaria during the Dry and Wet Seasons in an Area of Irrigated Rice Cultivation in The Gambia." *The Journal of Tropical Medicine and Hygiene* 94 (5): 313–24.

Lines, J.d., C.f. Curtis, T.j. Wilkes, and K.j. Njunwa. 1991. "Monitoring Human-Biting Mosquitoes (Diptera: Culicidae) in Tanzania with Light-Traps Hung beside Mosquito Nets." *Bulletin of Entomological Research* 81 (01): 77–84. doi:10.1017/S0007485300053268.

Liu, Li, Hope L. Johnson, Simon Cousens, Jamie Perin, Susana Scott, Joy E. Lawn, Igor Rudan, et al. 2012. "Global, Regional, and National Causes of Child Mortality: An Updated Systematic Analysis for 2010 with Time Trends since 2000." *Lancet (London, England)* 379 (9832): 2151–61. doi:10.1016/S0140-6736(12)60560-1.

Louis, Valérie R., Joëlle Bals, Justin Tiendrebéogo, Mamadou Bountogo, Heribert Ramroth, Manuela De Allegri, Corneille Traoré, et al. 2012. "Long-Term Effects of Malaria Prevention with Insecticide-Treated Mosquito Nets on Morbidity and Mortality in African Children: Randomised Controlled Trial." *Tropical Medicine & International Health* 17 (6): 733–41. doi:10.1111/j.1365-3156.2012.02990.x.

Marsh, K., M. English, J. Crawley, and N. Peshu. 1996. "The Pathogenesis of Severe Malaria in African Children." *Annals of Tropical Medicine and Parasitology* 90 (4): 395–402.

Maude, G. H., and D. A. Ross. 1997. "The Effect of Different Sensitivity, Specificity and Cause-Specific Mortality Fractions on the Estimation of Differences in Cause-Specific Mortality Rates in Children from Studies Using Verbal Autopsies." *International Journal of Epidemiology* 26 (5): 1097–1106. doi:10.1093/ije/26.5.1097.

Mendis, K., B. J. Sina, P. Marchesini, and R. Carter. 2001. "The Neglected Burden of Plasmodium Vivax Malaria." *The American Journal of Tropical Medicine and Hygiene* 64 (1-2 Suppl): 97–106.

Miasnikof, Pierre, Vasily Giannakeas, Mireille Gomes, Lukasz Aleksandrowicz, Alexander Y. Shestopaloff, Dewan Alam, Stephen Tollman, Akram Samarikhalaj, and Prabhat Jha. 2015. "Naive Bayes Classifiers for Verbal Autopsies: Comparison to Physician-Based Classification for 21,000 Child and Adult Deaths." *BMC Medicine* 13 (1): 1–9. doi:10.1186/s12916-015-0521-2.

Müller, Olaf, Manuela De Allegri, Heiko Becher, Justin Tiendrebogo, Claudia Beiersmann, Maurice Ye, Bocar Kouyate, Ali Sie, and Albrecht Jahn. 2008. "Distribution Systems of Insecticide-Treated Bed Nets for Malaria Control in Rural Burkina Faso: Cluster-Randomized Controlled Trial." *PLoS ONE* 3 (9): e3182. doi:10.1371/journal.pone.0003182.

Murray, Christopher J. L., Lisa C. Rosenfeld, Stephen S. Lim, Kathryn G. Andrews, Kyle J. Foreman, Diana Haring, Nancy Fullman, Mohsen Naghavi, Rafael Lozano, and Alan D. Lopez. 2012. "Global Malaria Mortality between 1980 and 2010: A Systematic Analysis." *Lancet (London, England)* 379 (9814): 413–31. doi:10.1016/S0140-6736(12)60034-8.

Nattey, Cornelius, Honorati Masanja, and Kerstin Klipstein-Grobusch. 2013. "Relationship between Household Socio-Economic Status and under-Five Mortality in Rufiji DSS, Tanzania." *Global Health Action* 6 (January). doi:10.3402/gha.v6i0.19278.

Ndebele, P, and R Musesengwa. 2012. "Ethical Dilemmas in Malaria Vector Research in Africa: Making the Difficult Choice between Mosquito, Science and Humans." *Malawi Medical Journal : The Journal of Medical Association of Malawi* 24 (3): 65–68.

Ndugwa, Robert P., Heribert Ramroth, Olaf Müller, Momodou Jasseh, Ali Sié, Bocar Kouyaté, Brian Greenwood, and Heiko Becher. 2008. "Comparison of All-Cause and Malaria-Specific Mortality from Two West African Countries with Different Malaria Transmission Patterns." *Malaria Journal* 7 (1): 1–12. doi:10.1186/1475-2875-7-15.

N. Fobil, Julius, . Wibke Loag, . Norbert Schwarz, . Frederick Rodrigues, . Christian G. Meyer, . Alexander Kraemer, and . Juergen May. 2012. "Area-Based Socioeconomic Conditions and Urban Malaria and Diarrhea Mortalities in Accra, Ghana." *International Journal of Tropical Medicine* 7 (1): 6–16. doi:10.3923/ijtmed.2012.6.16.

O'Hara, R. B., and M. J. Sillanpää. 2009. "A Review of Bayesian Variable Selection Methods: What, How and Which." *Bayesian Analysis* 4 (1): 85–117. doi:10.1214/09-BA403.

Okell, Lucy C., Chris J. Drakeley, Teun Bousema, Christopher J. M. Whitty, and Azra C. Ghani. 2008. "Modelling the Impact of Artemisinin Combination Therapy and Long-Acting Treatments on Malaria Transmission Intensity." *PLOS Med* 5 (11): e226. doi:10.1371/journal.pmed.0050226.

Okell, Lucy C., Lucy Smith Paintain, Jayne Webster, Kara Hanson, and Jo Lines. 2012. "From Intervention to Impact: Modelling the Potential Mortality Impact Achievable by Different Long-Lasting, Insecticide-Treated Net Delivery Strategies." *Malaria Journal* 11 (September): 327. doi:10.1186/1475-2875-11-327.

Onori, E., and B. Grab. 1980. "Indicators for the Forecasting of Malaria Epidemics." *Bulletin of the World Health Organization* 58 (1): 91–98.

Penny, Melissa A, Katya Galactionova, Michael Tarantino, Marcel Tanner, and Thomas A Smith. 2015. "The Public Health Impact of Malaria Vaccine RTS,S in Malaria Endemic Africa: Country-Specific Predictions Using 18 Month Follow-up Phase III Data and Simulation Models." *BMC Medicine* 13 (1). doi:10.1186/s12916-015-0408-2.

"Plan Stratégique 2011_2015 Palu." 2015. Accessed July 20. http://www.sante.gov.bf/index.php/quotidien/actualites/210-plan-strategique-20112015-palu.

Po, June Y. T., and S. V. Subramanian. 2011. "Mortality Burden and Socioeconomic Status in India." *PLoS ONE* 6 (2): e16844. doi:10.1371/journal.pone.0016844.

Prevention, CDC-Centers for Disease Control and. 2016. "CDC - Malaria - Malaria Worldwide - How Can Malaria Cases and Deaths Be Reduced? - Insecticide-Treated Bed Nets." Accessed March 11. http://www.cdc.gov/malaria/malaria_worldwide/reduction/itn.html.

R, Akhtar. 1987. *Health and Disease in Tropical Africa*. CRC Press.

Ramroth, Heribert, Robert P. Ndugwa, Olaf Müller, Yazoume Yé, Ali Sié, Bocar Kouyaté, and Heiko Becher. 2009. "Decreasing Childhood Mortality and Increasing Proportion of Malaria Deaths in Rural Burkina Faso." *Global Health Action* 2 (April). doi:10.3402/gha.v2i0.1909.

Reid, Heidi L., Ubydul Haque, Shyamal Roy, Nazrul Islam, and Archie C. A. Clements. 2012. "Characterizing the Spatial and Temporal Variation of Malaria Incidence in Bangladesh, 2007." *Malaria Journal* 11 (May): 170. doi:10.1186/1475-2875-11-170.

Riedel, Nadine, Penelope Vounatsou, John M Miller, Laura Gosoniu, Elizabeth Chizema-Kawesha, Victor Mukonka, and Rick W Steketee. 2010. "Geographical Patterns and Predictors of Malaria Risk in Zambia: Bayesian Geostatistical Modelling of the 2006 Zambia National Malaria Indicator Survey (ZMIS)." *Malaria Journal* 9 (February): 37. doi:10.1186/1475-2875-9-37.

Rogerson, Stephen J, and Richard Carter. 2008. "Severe Vivax Malaria: Newly Recognised or Rediscovered?" *PLoS Med* 5 (6): e136. doi:10.1371/journal.pmed.0050136.

Rogier, C, T. Fusaï, B. Pradines, and Jean-Francois Trape. 2005. "Comment évaluer la morbidité attribuable au paludisme en zone d'endémie ?" *Revue d'Epidémiologie et de Santé Publique* 53 (3): 299–309. doi:10.1016/S0398-7620(05)84607-3.

Ross, Amanda, and Thomas Smith. 2006. "The Effect of Malaria Transmission Intensity on Neonatal Mortality in Endemic Areas." *The American Journal of Tropical Medicine and Hygiene* 75 (2 suppl): 74–81.

Rowe, Alexander K. 2005. "Should Verbal Autopsy Results for Malaria Be Adjusted to Improve Validity?" *International Journal of Epidemiology* 34 (3): 712–13. doi:10.1093/ije/dyi087.

Rowe, Alexander K., Samantha Y. Rowe, Robert W. Snow, Eline L. Korenromp, Joanna RM Armstrong Schellenberg, Claudia Stein, Bernard L. Nahlen, Jennifer Bryce, Robert E. Black, and Richard W. Steketee. 2006. "The Burden of Malaria Mortality among African Children in the Year 2000." *International Journal of Epidemiology* 35 (3): 691–704. doi:10.1093/ije/dyl027.

Rumisha, Susan Fred. 2013. "Modelling the Seasonal and Spatial Variation of Malaria Transmission in Relation to Mortality in Africa." Phd, University_of_Basel. http://edoc.unibas.ch/diss/DissB_10515.

Rumisha, Susan Fred, Thomas Smith, Salim Abdulla, Honorath Masanja, and Penelope Vounatsou. 2014. "Modelling Heterogeneity in Malaria Transmission Using Large Sparse Spatio-Temporal Entomological Data." *Global Health Action* 7 (0). doi:10.3402/gha.v7.22682.

Rumisha, Susan F., Thomas A. Smith, Honorati Masanja, Salim Abdulla, and Penelope Vounatsou. 2014. "Relationship between Child Survival and Malaria Transmission: An Analysis of the Malaria Transmission Intensity and Mortality Burden across Africa (MTIMBA) Project Data in Rufiji Demographic Surveillance System, Tanzania." *Malaria Journal* 13 (1): 124. doi:10.1186/1475-2875-13-124.

Samadoulougou, Sekou, Mathieu Maheu-Giroux, Fati Kirakoya-Samadoulougou, Mathilde De Keukeleire, Marcia C. Castro, and Annie Robert. 2014. "Multilevel and Geo-Statistical Modeling of Malaria Risk in Children of Burkina Faso." *Parasites & Vectors* 7 (1): 350. doi:10.1186/1756-3305-7-350.

Samadoulougou, Sekou, Mathieu Maheu-Giroux, Fati Kirakoya-Samadoulougou, Mathilde De Keukeleire, Marcia C. Castro, and Annie Robert. 2014. "Multilevel and Geo-Statistical Modeling of Malaria Risk in Children of Burkina Faso." *Parasites & Vectors* 7 (1): 350. doi:10.1186/1756-3305-7-350.

Selemani, Majige, Sigilbert Mrema, Amri Shamte, Josephine Shabani, Michael J. Mahande, Karen Yeates, Amina S. Msengwa, Maurice C. Y. Mbago, and Angelina M. Lutambi. 2015. "Spatial and Space-Time Clustering of Mortality due to Malaria in Rural Tanzania: Evidence from Ifakara and Rufiji Health and Demographic Surveillance System Sites." *Malaria Journal* 14 (September): 369. doi:10.1186/s12936-015-0905-y.

Singer, Judith D., and John B. Willett. 1993. "It's About Time: Using Discrete-Time Survival Analysis to Study Duration and the Timing of Events." *Journal of Educational and Behavioral Statistics* 18 (2): 155–95. doi:10.3102/10769986018002155.

Sinka, Marianne E, Michael J Bangs, Sylvie Manguin, Maureen Coetzee, Charles M Mbogo, Janet Hemingway, Anand P Patil, et al. 2010. "The Dominant Anopheles Vectors of Human Malaria in Africa, Europe and the Middle East: Occurrence Data, Distribution Maps and Bionomic Précis." *Parasites & Vectors* 3 (December): 117. doi:10.1186/1756-3305-3-117.

Smith, David L., Simon I. Hay, Abdisalan M. Noor, and Robert W. Snow. 2009. "Predicting Changing Malaria Risk after Expanded Insecticide-Treated Net Coverage in Africa." *Trends in Parasitology* 25 (11): 511–16. doi:10.1016/j.pt.2009.08.002.

Smithson, Paul, Lia Florey, S. Rene Salgado, Christine L. Hershey, Honorati Masanja, Achuyt Bhattarai, Alex Mwita, and Peter D. McElroy. 2015. "Impact of Malaria Control on Mortality and Anemia among Tanzanian Children Less than Five Years of Age, 1999-2010." *Plos One* 10 (11): e0141112. doi:10.1371/journal.pone.0141112.

Smith, T. A., R. Leuenberger, and C. Lengeler. 2001a. "Child Mortality and Malaria Transmission Intensity in Africa." *Trends in Parasitology* 17 (3): 145–49.

Snow, Robert W., and Kevin Marsh. 1995. "Will Reducing Plasmodium Falciparum Transmission Alter Malaria Mortality among African Children?" *Parasitology Today* 11 (5): 188–90.

Snow, R. W., J. R. Armstrong, D. Forster, M. T. Winstanley, V. M. Marsh, C. R. Newton, C. Waruiru, I. Mwangi, P. A. Winstanley, and K. Marsh. 1992. "Childhood Deaths in Africa: Uses and Limitations of Verbal Autopsies." *Lancet (London, England)* 340 (8815): 351–55.

Snow, R. W., J. A. Omumbo, B. Lowe, C. S. Molyneux, J. O. Obiero, A. Palmer, M. W. Weber, et al. 1997. "Relation between Severe Malaria Morbidity in Children and Level of Plasmodium Falciparum Transmission in Africa." *Lancet (London, England)* 349 (9066): 1650–54. doi:10.1016/S0140-6736(97)02038-2.

Sonko, Sheriff T., Malanding Jaiteh, James Jafali, Lamin BS Jarju, Umberto D'Alessandro, Abu Camara, Musu Komma-Bah, and Alieu Saho. 2014. "Does Socio-Economic Status Explain the Differentials in Malaria Parasite Prevalence? Evidence from The Gambia." *Malaria Journal* 13 (1): 449. doi:10.1186/1475-2875-13-449.

Soofi, Sajid Bashir, Shabina Ariff, Ubaidullah Khan, Ali Turab, Gul Nawaz Khan, Atif Habib, Kamran Sadiq, et al. 2015. "Diagnostic Accuracy of WHO Verbal Autopsy Tool for Ascertaining Causes of Neonatal Deaths in the Urban Setting of Pakistan: A Hospital-Based Prospective Study." *BMC Pediatrics* 15 (October). doi:10.1186/s12887-015-0450-4.

Sriwattanapongse, Wattanavadee, and Sukon Prasitwattanaseree. 2013. "MALARIA MORTALITY MODELING IN THAILAND." *Southeast Asian Journal of Sciences* 2 (1): 12.

Steketee, Richard W., Naawa Sipilanyambe, John Chimumbwa, James J. Banda, Abdirahman Mohamed, John Miller, Suprotik Basu, Simon K. Miti, and Carlos C. Campbell. 2008. "National Malaria Control and Scaling up for Impact: The Zambia Experience through 2006." *The American Journal of Tropical Medicine and Hygiene* 79 (1): 45–52.

Stolwijk, A M, H Straatman, and G A Zielhuis. 1999. "Studying Seasonality by Using Sine and Cosine Functions in Regression Analysis." *Journal of Epidemiology and Community Health* 53 (4): 235–38.

Stuckey, Erin M., Thomas Smith, and Nakul Chitnis. 2014. "Seasonally Dependent Relationships between Indicators of Malaria Transmission and Disease Provided by Mathematical Model Simulations." *Plos Computational Biology* 10 (9): e1003812. doi:10.1371/journal.pcbi.1003812.

Talisuna, Ambrose O., Abdisalan M. Noor, Albert P. Okui, and Robert W. Snow. 2015. "The Past, Present and Future Use of Epidemiological Intelligence to Plan Malaria Vector Control and Parasite Prevention in Uganda." *Malaria Journal* 14 (1): 158. doi:10.1186/s12936-015-0677-4.

Targett, G. a. T. 1990. "Malaria. Principles and Practice of Malariology, Vols 1 and 2. Ed. W. H. Wernsdorfer and I. McGregor. 2048 Pages. ISBN 0 443 024170. Churchill Livingstone, Edinburgh, 1988. £195 (two Volumes)." *Parasitology* 100 (03): 499–499. doi:10.1017/S0031182000078811.

Thomson, M. C., and S. J. Connor. 2001. "The Development of Malaria Early Warning Systems for Africa." *Trends in Parasitology* 17 (9): 438–45. doi:10.1016/S1471-4922(01)02077-3.

Todd, J. E., A. De Francisco, T. J. O'Dempsey, and B. M. Greenwood. 1994. "The Limitations of Verbal Autopsy in a Malaria-Endemic Region." *Annals of Tropical Paediatrics* 14 (1): 31–36.

Trape, J. F., and C. Rogier. 1996. "Combating Malaria Morbidity and Mortality by Reducing Transmission." *Parasitology Today (Personal Ed.)* 12 (6): 236–40.

Uthman, Olalekan A, Mubashir B Uthman, and Ismail Yahaya. 2008. "A Population-Based Study of Effect of Multiple Birth on Infant Mortality in Nigeria." *BMC Pregnancy and Childbirth* 8 (September): 41. doi:10.1186/1471-2393-8-41.

Vounatsou, P, G Raso, M Tanner, E K N'goran, and J Utzinger. 2009. "Bayesian Geostatistical Modelling for Mapping Schistosomiasis Transmission." *Parasitology* 136 (13): 1695–1705. doi:10.1017/S003118200900599X.

Walker, Martin, Peter Winskill, María-Gloria Basáñez, Joseph M. Mwangangi, Charles Mbogo, John C. Beier, and Janet T. Midega. 2013. "Temporal and Micro-Spatial Heterogeneity in the Distribution of Anopheles Vectors of Malaria along the Kenyan Coast." *Parasites & Vectors* 6 (1): 311. doi:10.1186/1756-3305-6-311.

Weiss, Daniel J., Bonnie Mappin, Ursula Dalrymple, Samir Bhatt, Ewan Cameron, Simon I. Hay, and Peter W. Gething. 2015. "Re-Examining Environmental Correlates of Plasmodium Falciparum Malaria Endemicity: A Data-Intensive Variable Selection Approach." *Malaria Journal* 14 (1): 1–18. doi:10.1186/s12936-015-0574-x.

"WHO | 10 Facts on Malaria." 2015. *WHO*. Accessed January 14. http://www.who.int/features/factfiles/malaria/en/.

"WHO | Antenatal Care in Developing Countries." 2015. *WHO*. Accessed November 23. http://www.who.int/maternal_child_adolescent/documents/9241590947/en/.

"WHO | A Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children." 2016. *WHO*. Accessed July 5. http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_4/en/.

"WHO | Fact Sheet: World Malaria Report 2015." 2016. *WHO*. Accessed June 2. http://www.who.int/malaria/media/world-malaria-report-2015/en/.

"WHO | Levels and Trends in Child Mortality 2012." 2014. *WHO*. Accessed August 8. http://www.who.int/maternal_child_adolescent/documents/levels_trends_child_mortality_2012/en/.

"WHO | Report of a Technical Consultation on Birth Spacing." 2015. *WHO*. Accessed November 20. http://www.who.int/maternal_child_adolescent/documents/birth_spacing05/en/.

"WHO | The World Health Report 2005 - Make Every Mother and Child Count." 2015. *WHO*. Accessed November 23. http://www.who.int/whr/2005/en/.

"WHO | Under-Five Mortality." 2014. *WHO*. Accessed August 8. http://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/.

"WHO | World Malaria Report 2011." 2016. *WHO*. Accessed June 6. http://www.who.int/malaria/world_malaria_report_2011/en/.

Winbo, I. 1998. "NICE, a New Cause of Death Classification for Stillbirths and Neonatal Deaths. Neonatal and Intrauterine Death Classification according to Etiology." *International Journal of Epidemiology* 27 (3): 499–504. doi:10.1093/ije/27.3.499.

Wirtz, R. A., F. Zavala, Y. Charoenvit, G. H. Campbell, T. R. Burkot, I. Schneider, K. M. Esser, R. L. Beaudoin, and R. G. Andre. 1987. "Comparative Testing of Monoclonal Antibodies against

Plasmodium Falciparum Sporozoites for ELISA Development." *Bulletin of the World Health Organization* 65 (1): 39–45.

Wongsrichanalai, Chansuda, Mazie J. Barcus, Sinuon Muth, Awalludin Sutamihardja, and Walther H. Wernsdorfer. 2007. "A Review of Malaria Diagnostic Tools: Microscopy and Rapid Diagnostic Test (RDT)." Text. December. http://www.ncbi.nlm.nih.gov/books/NBK1695/.

Yé, Maurice, Eric Diboulo, Louis Niamba, Ali Sié, Boubacar Coulibaly, Cheik Bagagnan, Jonas Dembélé, and Heribert Ramroth. 2011a. "An Improved Method for Physician-Certified Verbal Autopsy Reduces the Rate of Discrepancy: Experiences in the Nouna Health and Demographic Surveillance Site (NHDSS), Burkina Faso." *Population Health Metrics* 9: 34. doi:10.1186/1478-7954-9-34.

Yé, Yazoumé. 2008. *Environmental Factors and Malaria Transmission Risk: Modelling the Risk in a Holoendemic Area of Burkina Faso*. Ashgate Publishing, Ltd.

Curriculum vitae

Name: Eric Diboulo
Date and place of birth: 02nd October 1972, Ouagadougou
Nationality: Burkinabe
Official Address: P.O. BOX: O2, Nouna, Burkina Faso
Cell: (+226) 70140926
E-mail: diboulоeric@yahoo.fr
Skype: diboulo_eric

1. Education background

PhD: Epidemiology, Swiss Tropical and Public Health Institute (Swiss TPH) and University of Basel, Switzerland. 2016. Title: Developing Bayesian spatio-temporal models to assess the relation between malaria transmission and mortality in Burkina Faso.

Master Degree: Infection Biology and Epidemiology, Swiss Tropical and Public Health Institute (Swiss TPH) and University of Basel, Switzerland, February 2010

Master Degree: Applied computer Sciences and Geomatic; Major: GIS and Remote Sensing, International Institute for Water and Environmental Engineering, Ouagadougou, Burkina Faso, 2007

Diploma: Rural Development Engineer: Agronomy, Institute of Rural Development, Polytechnic University of Bobo- Dioulasso, Burkina Faso. June 1999.

Bachelor of Science: Chemistry-Biology, Faculty of the Sciences and engineering (FA.S.T) University of Ouagadougou, Burkina Faso 1996

High School: Science major, High school " *Lycée Bogodogo de Ouagadougou*", Burkina Faso, 1993

2. Professional Experience

Since November 2012: Associated facilitator of a **TropED**-accredited course on: "Climate change and human health: Health impacts and policy implications in Africa", jointly organized by CRSN and Institute of Public Health, University of Heidelberg, Germany

September 2010: Epidemiologist/Biostatistician at CRSN (Centre de Recherche en Santé de Nouna), in charge of statistical analyses and modelling of epidemiological data; Burkina Faso.

March 1st, 2010- June 2010: Internship in the unit of Biostatistics and Computational Sciences at Swiss Tropical and Public Health institute (SwissTPH); Switzerland

September 2008 -February 2010: Design and implementation of a Global database for malaria vector Bionomics with a GIS interface at Swiss TPH, Basel, Switzerland.

February 2002-September 2008: In charge of the design, implementation and management of the GIS (Geographic Information System) unit at the Centre National de Recherche et de Formation sur le Paludisme (C.N.R.F.P) unit; Burkina Faso.

July 2004-November 2005: In charge of the design, implementation and management of Saponé HDSS (Health and Demographic Surveillance System) at the Centre National de Recherche et de Formation sur le Paludisme (C.N.R.F.P); Burkina Faso.

June 2000-January 2002: Head of the Agricultural department and the applied GIS unit for natural resources management at Nouhao Valley Development Project; Burkina Faso.

January - June 2000: GIS and Remote sensing Assistant at G.I.D (Geographic Investigation for Development) Society, Burkina.

3. Computer Skills

Familiar with the following software:

- **Statistics and Spatial analyses software**:

CRIMSTAT, STATSCAN, EPIANALYST, S-PLUS, SPATIALSTAT

- **Statistics and data processing software**: R, Stata, SPSS - Epi info - **Winbugs**, OpenBugs EXCEL
- **Software development and programming Language**: **V**isual **B**asic (VB), Pendragon 5.1 For PDAs (Personal Digital Assistant), EpiSurveyor, Fortran
- **Database Systems Management (DBSM):** ACCESS, SQL Server, SQLite
- **G.I.S (Geographic Information System) and images processing software**: PC ARCINFO - ARCVIEW 3.x - WINCHIPS - COREL PHOTO PAINT - **HEALTH MAPPER** - ArcGIS 10.x – StarGIS – GEOIMAGE – Manifold - ER MAPPER – ENVI – ERDAS- **GRASS – QGIS - gvSIG**
- **Topographic data processing software**: SURFER 32
    - Concepts with the following software: ATLAS GIS – ILWIS- IDRISI
- **Word processing software**: WORD - WINWORD -WORDART.

4. Language Skill

Speaking: French (fluent) – English (fluent)
Writing: French (fluent) – English (fluent)
Reading: French (fluent) – English (fluent)

5. Peer reviewed publications

Diboulo, E. Ali Sié, Diallo A. Diadier, Dimitrios A. Karagiannis Voules, Yazoume Yé, Penelope Vounatsou. Bayesian variable selection in modeling geographical heterogeneity in malaria transmission from sparse data: an application to Nouna Health and Demographic Surveillance System (HDSS) data, Burkina Faso. Parasit. Vectors 8, 118 (2015).

Maurice Yé, **Eric Diboulo**, Louis Niamba, Ali Sié, Boubacar Coulibaly, Cheik Bagagnan, Jonas Dembélé, and Heribert Ramroth: An improved method for physician-certified verbal autopsy reduces the rate of discrepancy: experiences in the Nouna Health and Demographic Surveillance Site (NHDSS), Burkina Faso. Population Health Metrics 2011, 9:34 doi:10.1186/1478-7954-9-34

Eric Diboulo, Ali Sié, Joacim Rocklov, Louis Niamba, Maurice Yé, Cheik Bagagnan, Rainer Sauerborn: Weather and Mortality: a 10 years retrospective analysis of the Nouna Health and Demographic Surveillance System (HDSS), Burkina Faso. Global Health Action, 2012.

Schoeps A, Souares A, Niamba L, **Diboulo E**, Kynast-Wolf G, Müller O, Sié A, Becher H. Childhood mortality and its association with household wealth in rural and semi-urban Burkina Faso. Trans R Soc Trop Med Hyg. 2014 Oct;108(10):639-47. doi: 10.1093/trstmh/tru124. Epub 2014 Aug 16.

Streatfield PK, Khan WA, Bhuiya A, Hanifi SM, Alam N, **Diboulo E**, Niamba L, Sié A, Lankoandé B, et al. Mortality from external causes in Africa and Asia: evidence from INDEPTH Health and Demographic Surveillance System Sites. Glob Health Action. 2014 Oct 29;7:25366. doi: 10.3402/gha.v7.25366. eCollection 2014.

Maurice Yé, **Eric Diboulo**, Moubassira Kagoné, Ali Sié, Rainer Sauerborn and Svetla Loukanova. Health worker preferences for performance-based payment schemes in a rural health district in Burkina Faso. Glob Health Action 2016, 9: 29103 - http://dx.doi.org/10.3402/gha.v9.29103

Giovanfrancesco Ferrari, Henry M. Ntuku, Sandro Schmidlin, **Eric Diboulo**, Antoinette K. Tshefu and Christian Lengeler. A malaria risk map of Kinshasa, Democratic Republic of Congo. Malaria Journal 2016, 15:27 doi:10.1186/s12936-015-1074-8

Diboulo, E. Ali Sié, Penelope Vounatsou Assessing the effects of malaria interventions on the geographical distribution of parasitaemia risk in Burkina Faso. Malaria Journal 2016 15:228
DOI: 10.1186/s12936-016-1282-x

6. Award

- **Health Sciences Days of Bobo-Dioulasso, Burkina Faso (JSSB, 2012)**: Young researcher award.