Geostatistical models of malaria and associated morbidity among preschool-aged children in Nigeria

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Summary

Malaria remains a threat to the lives of millions of children in tropical and subtropical countries. It is still a disease of public health significance, because of its role as a major cause of morbidity and mortality among the vulnerable group, specifically children under the age of five in the endemic countries. Although, substantial progress has been made in the control and prevention of the disease especially during the past 15 years due to multilateral commitment to malaria control, and this has led to reduction in the burden attributed to the disease. During the same period, financial resources for malaria prevention and control have been like up to twenty-fold increase, which led to widespread scale-up of coverage of the core malaria control interventions: insecticide-treated nets (ITNs), indoor residual spraying (IRS), and prompt treatment of clinical malaria cases with artemisinin-based combination therapy (ACT).

High resolution disease risk distribution is essential information in successful control activities, because of its versatility in cost effective planning, surveillance, and evaluation of such activities. Spatial statistical modelling provides rigorous inferential framework for high resolution disease risk mapping. It is a data-driven approach, which is used to build mathematical relationship between geo-referenced disease data and potential predictors (environmental and socio-demographic factors). Such model always includes the location specific random effect to explain the spatial correlation in the disease data that are due to common exposure in neighbouring locations. Geostatistical model are highly parameterized, nevertheless, a Bayesian geostatistical framework provides flexible and rigorous inferential methods for modelling such data. Computation tools such as simulation based Markov chain Monte Carlo (MCMC) or numerical approximation approach as integrated nested Laplace approach (INLA) are mostly engaged for such model fit.

Nigeria is one of the countries in sub-Sahara Africa with high prevalence of malaria and its related morbidity and mortality among children under the age of five years. Contemporary high resolution estimates of malaria prevalence needed for control activities are lacking. Also the precise nature of malaria transmission and all-cause mortality remains unclear. Furthermore, spatial analysis of the effect of malaria intervention on the risk of the disease at the national and sub-national level is not yet done. Moreover, anaemia prevalence in Nigeria is high; however, its relationship with malaria burden among children under the age of five is not fully understood,

coupled with lack of high resolution estimates of the spatial distribution of the risk in the country.

This thesis aims to address these knowledge gaps by developing data driven Bayesian geostatistical models for analyzing spatially referenced data and also to provide tools for malaria and its related morbidity control programmes in the country. The analysis in this work is based on data from the contemporary nationwide survey which are malaria indicator survey (MIS) and demography and health survey (DHS). Roll back malaria initiative in its global effort of coordinating malaria control developed the MIS to collect malaria related burden data on children under the age of five, and it is always conducted during the high transmission season. MIS is standardized in terms of survey design, questionnaire and implementation time.

In chapter 2, we implemented a Bayesian geo-statistical model to analyze the first nationally representative malaria parasitaemia prevalence data in Nigeria to produce high resolution risk estimates of spatial distribution of malaria prevalence in the country, and also derived number of infected children at the sub-national level. Rigorous Bayesian variable selections were incorporated in the spatial models in order to select the best environmental predictors of malaria and its functional form. The approach identifies important risk factor to build Bayesian model of malaria risk in Nigeria. Also, various interventions coverage indicators were derived to assess their effect on malaria risk. The high resolution estimates show that malaria risk varies between 19.6% and 47.7% in Lagos and Osun state, respectively. However, household coverage indicators of intervention did not indicates association with malaria risk.

Chapter 3, present the assessment of the spatial effect of ITN use by children less than five years on the malaria parasitaemia prevalence at the first administrative, after adjusting for climatic and socio-demographic factors. Bayesian geostatistical model with spatial varying coefficient at the sub-national level was used to explore the malaria risk-intervention relationship. Smooth map of intervention effect was produced based on the parameter estimates of ITN use at the first administrative level.

In chapter 4, we employed a joint Bayesian geo-statistical Cox model with log constant baseline hazard and binomial geostatistical logistic regression models to relate mortality with malaria prevalence, and take into account spatial misalignment between DHS and MIS datasets, to evaluate the contribution of malaria prevalence to all-cause mortality among children less than five year of age. The mortality model was implemented separately for infant 0-6 months, 7-11

months, and older children. The model adjusted for socio-demographic factors known to be associated with risk of death among this vulnerable group. We also produced smooth map of residual variation not accounted for by the factors in our model.

Chapter 5 presents the geostatistical analysis of haemoglobin level/anaemia risk. The study assessed malaria burden on anaemia risk among the children after adjusting for helminthiasis and schistosomiasis, and socio-demographic factors. We make use of some of these factors as available at individual level, and also use the predicted prevalence of those that were not directly obtained with the haemoglobin data, which led to the implementation of Bayesian geostatistical models (Gaussian and logistic) with measurement error, to incorporate the uncertainty in the predicted estimates. The predictive models were used to obtain high resolution estimates of geographical distribution of anaemia risk/haemoglobin level concentration in the country. The population adjusted prevalence show that approximately every 7 out of 10 children under the age of five years are anaemic in the country.

The work in this thesis contributes improved Bayesian statistical methods for generating reliable estimate of disease burden (malaria parasitaemia prevalence, anaemia prevalence and number of infected children) at high spatial resolution. It also adds to the evidence of improve method of evaluating the effect of malaria interventions on disease prevalence. Furthermore, the generated model based risk maps constitute important information to national malaria control programme, because of its resourcefulness in right targeting of high risk area to achieve disease reduction, and eventually elimination. Finally, our work provides essential yardstick on which newer estimates could be compared as new data becomes available and control efforts continue.

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List of Abbreviations

ACT: Artemisinin-based Combination Therapy

ADDS: Africa Data Dissemination Services

AIDS: Acquired Immune Deficiency Syndrome

BCI: Bayesian Credible Interval

CAR: Conditional Auto Regressive

CI: Confidence Interval

CIESIN: Centre for International Earth Science Information

DALY: Disability Adjusted Life Years

DHS: Demographic and Health Survey

EIP: Extrinsic Incubation Period

EIR: Entomological Inoculation Rate

EM: Environmental Management

FCT: Federal Capital Territory, Abuja.

GMRF: Gaussian Markov Random Field

GRUMP: Global Rural Urban Mapping Project

HIV: Human Immunodeficiency Virus

INLA: Integrated Nested Laplace Approach

IPT: Intermittent Preventive Therapy

IRS: Indoor Residual Spraying

ITN: Insecticide Treated Net

LLIN: Long Lasting Insecticide Net

LST: Land Surface Temperature

MAE: Mean Absolute Error

MAP: Malaria Atlas Project

MARA: Mapping Malaria Risk in Africa

MCMC: Markov Chain Monte Carlo

MDG: Millennium Development Goal

ME: Measurement Error

MIS: Malaria Information Survey

NDVI: Normalized Difference Vegetation Index

NMCP: National Malaria Control Programme

NMIS: National Malaria Information Survey

NPC: National Population Commission

OR: Odd Ratio

PCR: Polymerase Chain Reaction

RBM: Roll Back Malaria

RDT: Rapid Diagnostic Test

RDT: Rapid Diagnostic Test

SES: Socio Economic Status

SPDE: Stochastic Partial Differential Equation

SR: Sporozite Rate

STH: Soil Transmitted Helminth

Swiss TPH: Swiss Tropical and Public Health (institute)

UNICEF: United Nation Children Emergency Fund

USAID: United State Agency for International Development

WHO: World Health Organization

Chapter 1 Introduction

1.1 Rationale

Recent years have witnessed exceptional surge in investment for malaria control due to renewed interest among the international health communities and donors on the possibility of the disease elimination. Global finance for malaria control has increased from million to billions of dollars within the last decade as a result of improvement in donation from various donors agencies of the world wealthiest countries coupled with the political willingness on the part of the government of the endemic countries. Intervention coverage is increasing, and also childhood morbidity and mortality is on the decline in so many Asia and sub-Saharan African countries (Crawley et al., 2010).

Achieving high returns on investment in disease prevention and control will necessarily require availability of reliable disease risk estimation. Risk maps represent vital tools in identifying area of high disease prevalence, and can inform for optimal apportionment of control interventions. They are very essential tools that could help control programs fast-track reduction in disease burden, and ultimately disease elimination. This information will find application in various stages of control activities, namely planning, execution, and evaluation of impact of such control program.

Nationwide surveys are mostly designed to produce disease estimates at the country, regional, and first administrative level, but not at local scale appropriate for identification of focal clusters of high risk areas. Spatial statistical modelling, an established rigorous inferential approach can be used to identify important predictors of a particular disease, and as well generate high resolution disease map. The high resolution risk estimates can be overlapped with the population surface, to derive the number of infected persons, at the required administrative level, which could serves a very important input, in the design and implementation of disease control activities.

The thesis focus on the Geostatistical modelling of malaria risk and the effects of control intervention coverage on the disease prevalence, evaluation of malaria burden on anaemia

prevalence, relationship of the parasitaemia prevalence with all-cause mortality. Added to this is the application and development of appropriate methodology for the risk estimations.

1.2 Disease characteristics

1.2.1 Malaria

Malaria is the disease caused by infection with Plasmodium parasites. The parasites are transmitted from an individual to another, through the bite of an infected female mosquito of the genus *Anopheles*. The human malaria parasite needs female mosquito and human to complete its life cycle. The mosquito and human serves as the definitive and intermediate host, respectively.

There are five species of Plasmodium parasite which cause human malaria and they are *P.falciparum , P. Vivax, P. Ovale, P. knowlesi* and *P malariae*, but the two most common are *P.falciparum* and *P. Vivax.* As regard the dominant Plasmodium species in the endemic regions of the world, *P.falciparum* is the most common in sub-Saharan Africa and it is responsible for the most lethal form of the disease; *P. Vivax* is the predominant in Asia and Latin America, and it is associated with chronic but less severe form of the disease.

1.2.1.1 Malaria Vector

The distribution and abundance of different anopheles species determines to a great extent the malaria parasitaemia distribution. More than 400 species of Anopheles mosquitoes are known, however between 30 and 40 of this are considered to be malaria vector of public health significance (http://www.cdc.gov/malaria/about/biology/mosquitoes/index.html). Among these, the most usually associated vectors of malaria transmission in Africa are *An. gambiae* complex, and *An. funestus*. The two most commonly found species of *An. gambiae* complex in the Africa south of Sahara are *An. gambiae senso stricto* and *An. arabiensis*. These species differs in their feeding and resting behaviours, and ecological condition preference. For instance, *An. gambiae s. s.* prefers rain dependent pools and temporary puddles for its breeding site; it rest indoors and feeds on humans. *An. funestus* breed in marshy and swampy areas, a combination of permanent water bodies with vegetation; it also rest indoors, but feed mainly on human either outdoor or indoor. Because of this affinity for large water bodies, increase rainfall also come with rapid increase of vector density, which fall of more slowly as rain ceases (Kweka et al., 2013; Munga et al., 2005). *An. arabiensis* breeds in smaller temporary water, feeds both on human and

animals; it basically feed and rest outside, and it is also able to tolerate dry environment, which makes it the dominant vector at the onset of raining season (Kent et al., 2007; Sogoba et al., 2007). The understanding of this spatial and temporal variation in the distribution of the vector population, which influences malaria transmission dynamics, is very central to malaria control effort and ultimately elimination (Mharakurwa et al., 2012).

1.2.1.2 Global malaria burden

According to the latest world malaria report (World Health Organization et al., 2015a), between 149 and 303 million of malaria cases, and about 438 000 deaths, are estimated globally. Compared with death due to malaria in the year 2000, this estimate represents a 48% decline in global malaria death. The highest percentage (88%) of these cases is homed in sub-Saharan Africa. The bulk (approximately 70%) of malaria deaths occur among children under five. Children under five and pregnant women are at greater risk, due to partial immunity in the former and suppressed immunity in the later. Malaria infection during pregnancy could have undesirable effect on both the mother and fetus.

Malaria still represent major killer of sub-Saharan children due to the fact that a child dies every two minutes as a result of the disease infection in the region (World Health Organization et al., 2015a). Also, the most recent global burden of disease study reports that malaria account for 3.3% of the 2.49 billion estimated global disability adjusted life years (DALYs), which represent an increase of about 19% to the value obtained a decade earlier. Economic-wise, it is estimated that at least $12 million represent the direct cost lost (for instance, illness, treatment and premature mortality) to malaria annually, and the cost due to retarded economic growth is substantially greater than this (https://www.cdc.gov/malaria/malaria_worldwide/impact.html).

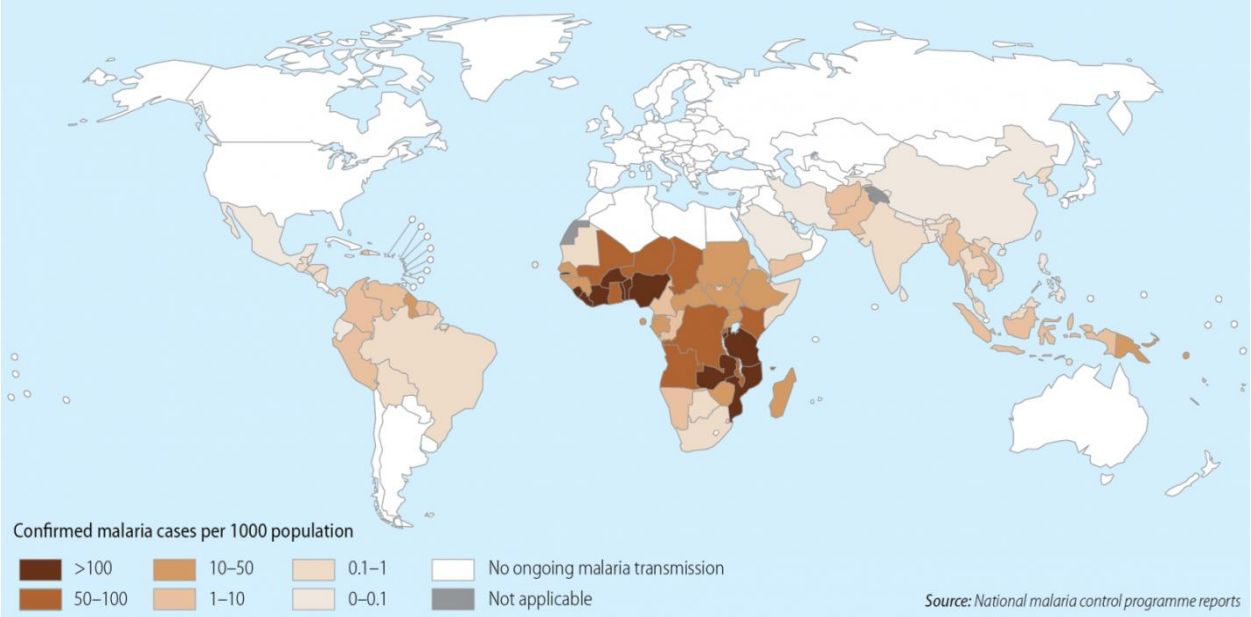

Figure 1.1: Global Malaria distribution 2014 (Source: World malaria report 2014)

1.2.1.3 Diagnosis and Symptom

The symptoms of malaria are very similar to many other febrile illnesses which make the clinical diagnosis to be of lower specificity. This has resulted in over-prescribing of malaria drug with the accompanied drug resistance (Leslie et al., 2014; Yacoub et al., 2005). The gold standard for malaria diagnosis is thin film blood microscopy. Other specialized tests like serology and polymerase chain reaction (PCR) (Wongsrichanalai et al., 2007) are also employed for confirmatory and to determine the parasite species. In the recent times, rapid diagnostic test (RDT) is also being used for diagnosis so that cases can be managed effectively and also with the advantage that it can be use even in remote areas where laboratory facilities are non-existing (D'Acremont et al., 2009).

1.2.1.4 Measures of Transmission

The most widely accessible measure of malaria transmission intensity is the prevalence and it quantifies the risk and endemicity. It is easily estimated through the use of community-based survey data such as malaria information survey (MIS) and demographic health survey (DHS) by calculating the proportion of individuals with positive blood slide. Another measure which is also extensively employed is the entomological inoculation rate (EIR), and it is an estimate of number of infective bite an individual will probably be exposed to over a certain period of time.

It is a product of two rates which are sporozite rate (SR) (proportion of infectious mosquitoes) rate and human biting rate (number of mosquitoes bites a person received per unit time). Sporozite rate denotes fraction of mosquitoes with sporozites in their salivary glands among those dissected and examined. The number of new cases diagnosed to be infected with malaria in a population within a specified period of time known as malaria incidence is another transmission intensity measure but it is difficult to obtain this data. Health management information system (HMIS) which collates data from health facilities often serve as repositories for incidence data, and this data may not reveal the true level of infection in the populace but only a representative of those who can access these facilities.

1.2.1.5 Mapping of malaria transmission

The resourcefulness of disease risk distribution in informed and helpful decision making, and also its importance in the assessment of impact of control programmes have made the map of malaria burden a topic of research for several decades. The first global assessment of malaria endemicity pattern was made by Lysenko and Semashko (Lysenko and Semashko, 1968). This map synthesized data from various disparate sources such as historical records, documents, cartographic records of numerous malariometric indices (disease records, presence and absence of vector, human biting rate, sporozites rate, spleen rates, sickle cell incidence and parasite rates) to archive malaria endemicity during the period between the commencement of 20th century and late 1960's. The synthesized data were interpolated to produce a global malaria risk map by the engagement of heuristic approach such as expert's opinions, global increase and climatic suitability. The map reveals heterogeneity of malaria endemicity in Africa, Americas (central and south), Asia, the Mediterranean region and Oceania. Sequel to this, the Mapping Malaria Risk in Africa (MARA) project initiated in 1997 emphasized the need for the disease risk mapping at continental scale. This initiative led to generation of climatic suitability map (Craig et al., 1999) for sub-Sahara Africa and some model based map (Gemperli et al., 2006; Gosoniu et al., 2009) at sub-continental level.

In furtherance to this, the Malaria Atlas Project (MAP) have sequentially generated two model based map (Gething et al., 2011; Hay et al., 2009) depicting global distribution of *P. falciparum* malaria, which is shown to have predominance in sub-Saharan Africa. Also the availability of data through multilateral initiatives such as Demographic and Health Survey and

Multiple Indicators Cluster Survey in combination with application of spatial statistical models has generated estimates of malaria risk distribution at the national level (Giardina et al., 2012; Riedel et al., 2010). Also, the application of model based techniques to these multiple time point cross-sectional survey data has availed the malaria epidemiologist community the opportunity to map malaria risk both spatially and temporally and thus detecting the changing risk between the time points. Giardina et al. in a model based analysis estimated the changes in malaria risk distribution using two times data for six countries (Angola, Liberia, Rwanda, Mozambique, Senegal and Tanzania) in Sub-Saharan Africa (Giardina et al., 2014). More so, two model-based changing risk maps of *P. falciparum* malaria (Bhatt et al., 2015; Noor et al., 2014) were recently generated for the continent of Africa. These studies which refer to year 2000 as the base year depict the evidence of the malaria parasitaemia decline in all the endemic countries, though there are variations between and within countries.

1.2.1.6 Risk Determinants

1.2.1.6.1 Environmental/climatic factors

Malaria transmission is known to be associated with suitable environmental /climatic conditions which modulate the biological parameters of the vector and also the parasite lifecycles. Environmental factors such as rainfall, temperature, humidity, vegetation, altitude, surface wetness/water bodies are important determinants of the abundance and distribution of parasite and mosquito population. Temperature and humidity influence the developmental period of the parasite in the mosquito also known as extrinsic incubation period (EIP), specifically, the temperature between 25^0C and 30^0C provide best favourable conditions for the EIP, but with decreasing temperature the EIP lengthens, and the cycle will terminate at temperatures below 16^0C. It also affects the time between blood meal and egg-laying known as gonotrophic cycle. More so the rates of developing from the larva to adult mosquito, as well as the survival of the vector at full maturity are influenced by these factors. On average at 31^0C, it takes 7days for mosquito to develop from an egg to an adult while it take approximately 20 days to complete this same cycle at 20^0C.

Rainfall is a very important determinant of malaria transmission because it provides the needed breeding sites for mosquitoes and also the moisture requirements for egg to develop into an adult mosquito, which in effect increase the density of the vectors. However the duration and

also the amount of rain is very crucial in this relationship. A lower bound of around 80mm per month rainfall for five consecutive months is believed (Craig et al., 1999) to be sufficient to sustain transmission in most countries of the sub-Sahara Africa. However, very high intense rainfall could wash away mosquito breeding sites resulting in larval mortality and thereby reducing vectorial capacity and malaria risk. At higher altitudes high extreme rainfall could lead to decrease temperature which might negatively impact malaria transmission.

Vegetation availability is very crucial for malaria transmission because it creates micro-climatic condition in the form of suitable temperature and humidity preferred by the vector. Also it influences the availability of human host which translate to immediacy of blood meal. Altitude (Elevation above sea level) influences malaria transmission indirectly by modulating the temperature. Temperature decreases as altitude increases and it is very difficult for the vector to multiply or the parasite to develop within the mosquito at very high altitude.

Availability of satellite in space gathering environmental information at finer spatial and temporal resolution provides us proxies for these data which are processed using standard geographic information systems. These satellite source data are employed in studying the relationship of these factors with many infectious disease risks such as malaria and soil transmitted helminth (STH) using spatial modelling.

1.2.1.6.2 Socio-Demographic Factors

Malaria transmission is not only influenced by climatic factor; there are non-climatic factors, which plays important role in malaria transmission, such as household socioeconomic status, urbanization, and literacy attainment. Living in well planned urban areas comes with qualities that make the population less vulnerable to malaria risk. Urban dwellers for instance, have higher literacy level, which could translate to better housing and access to control interventions compared to their rural counterparts (Lowe et al., 2013). In addition, the level of pollution in urban area could negatively impact the mosquito habitat and lifecycles. More so, the higher population density in the urban setting might lead to lower biting rates (Robert et al., 2003). In comparison, the materials used in construction of houses among the rural settlers predispose them to higher vulnerability of contact with the disease vector (Mmbando et al., 2011). Malaria is mostly mentioned as disease associated with poverty, because the disease may increase poverty, and poverty could also aggravate malaria transmission. It could increase poverty

because it might prevent the infected from engaging in the means of livelihood and thus paralyzing economic emancipation of the individual. Poverty in turn would increase malaria transmission because access to effective treatment and disease prevention might not be at the reach of the poor. These socioeconomic factor or their proxies are always accommodated in most of the standard disease survey designs such as demographic health and survey (DHS) and malaria indicator survey (MIS).

1.2.1.7 Interventions

The mass coverage of the population at risk with insecticide treated net, prompt diagnoses and effective management of cases and indoor residual spraying represents the cornerstone of prevention and control of malaria transmission. Increase in funding support from financing partners such as Global Fund, Gates Foundation, World Bank, Presidential Malaria Initiative has resulted in scaling up of these control interventions in many of the malaria endemic country. Also, the proliferation of nationwide surveys in many of the endemic countries especially the DHS and MIS provide reliable data suitable for the assessment of spatio-temporal effects of these interventions on the malaria morbidity and mortality. To standardize this assessment, the Roll Back Malaria partnership came up with intervention coverage indicators that are derived from household surveys. The derived indicators are related to ITN ownership and use, coverage of household with IRS, and proportion of malaria cases receiving appropriate treatment in the population. Also, therapeutic intervention which targets the definitive host factors necessary for parasite invasion of the erythrocyte is being developed and it has demonstrated potency in humanized mice for all parasites strain tested (Zenonos et al., 2015). More so the RTS S /AS01 *P. falciparum* malaria vaccine is been considered for inclusion in the set of control tools for the disease provided the efficacy it demonstrated in the phase 3 clinical trials is achieved in the large scale implementation project (World Health Organization et al., 2015a)

1.2.1.8 Malaria transmission and mortality

A great proportion of children mortality in high malaria transmission areas is often linked with the malaria parasitaemia infection, to the extent that all-cause mortality rate for children less than five years of age is widely used as an important indicator of the impact of malaria control (Korenromp, 2004). Malaria intervention coverage has been on increase in the recent years, and it has been associated with decline in transmission intensity in many of the endemic countries (Giardina et al., 2014). Also children under five mortality has been declining, but many countries in sub-Saharan and south Asia have not met the MDG target of reducing 1990 mortality value by two-third in 2015 (Unicef, 2015). The accelerated decline could be made possible in these regions also, by increasing the deployment of interventions that target factors attributed to those deaths. Association between variation in malaria transmission intensity and mortality among children has been established in randomized trials (D'Alessandro et al., 1995). However, efforts (Gemperli, 2004; Smith et al., 2001) that has study this relationship using surveys data from diverse sources have been marred with contrasting evidences. It is therefore very important to know if surveys data free from these encumbrances could capture this same relationship demonstrated in the field trial. Malaria information survey data, and mortality data from complete birth history survey such as demographic and health survey, with application of appropriate modeling approach, allows the opportunity to conduct such analysis. The derived information in such analysis will serve a useful tool during malaria control planning and implementation; it will also find applications, in the evaluation of the impact of control activities, and progress towards the MDG.

1.2.2 Anaemia

Anaemia is the health state characterized by sub-optimal healthy red blood cells with accompanied decrease haemoglobin levels and subsequent impairment in meeting the oxygen demands of body tissues.

1.2.2.1 Anaemia Burden

Anaemia affects a quarter of world population (Balarajan et al., 2012). According to a recent estimate (Kassebaum et al., 2014a), it causes annual loss of between 40.98 and 107.54 million DALYs globally. Greater proportion of anaemia burden is concentrated in Africa and Asia with the highest prevalence occurring among preschool-aged children and pregnant women

(Organization and others, 2015). Among children, it is associated with increased risk of death, susceptibility to infection, and impaired growth and cognitive development (De-Regil et al., 2011). With pregnant women, it is often linked with preterm labor, low birthweight, child and maternal death, and impaired immune function (Haider et al., 2013; Peña-Rosas et al., 2015) . Figure 1.2 shows the global distribution of anaemia.

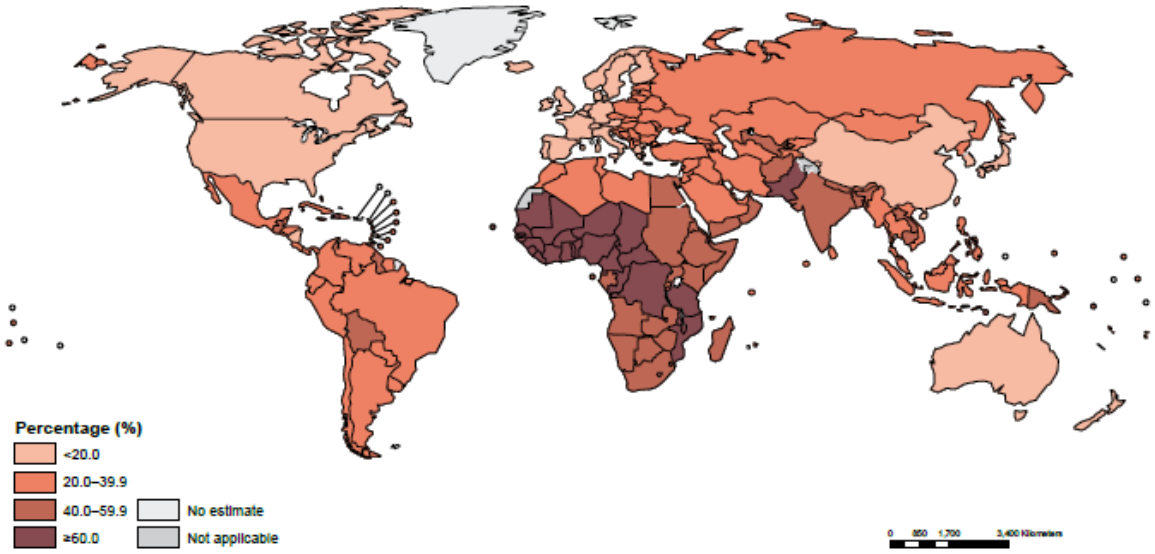

Figure 1.2**:** Global anemia prevalence among preschool children, 2011 (Source: WHO 2015)

1.2.2.2 Risk factors of anaemia

Anaemia has various factors that could independently occur, but usually co-occur, to precipitate its occurrence (McLean et al., 2009). These risk factors could be divided into nutritional, infectious (acute and chronic), genetics, and also socioeconomic. Deficiency of iron, vitamins and minerals (folic acid, vitamin A, vitamin B12 and copper) constitute the nutrition factors. Infectious risk factors includes malaria parasitaemia, soil transmitted helminthiasis that is, hookworm, Ascaris lumbricoides and Trichuris Trichiura infection, Schistosomiasis (hematobium and mansoni infection), Tuberculosis and Human Immunodeficiency Virus infection /Acquired Immune Deficiency Syndrome. The genetic components mainly include those related to sickle cell disorder and thalassaemias.

1.2.2.3 Diagnosis and Assessment of Anaemia

Assessment and diagnosis of anaemia are carried out using various hematological and biomedical indices. Anaemia status can be evaluated through any of the following: haemoglobin concentration, haemoglobin electrophoresis, haematocrit or pack cell volume, mean cell volume, blood film analysis and blood reticulocyte count (Balarajan et al., 2012). Other tests which assess iron status includes corpuscular volume, mean corpuscular haemoglobin, serum ferritin, transferrin saturation, erythrocyte photoporphyrin, transferrin receptors and bone marrow iron stain. Field surveys often employed haemoglobin level measurements obtained through the use of Hemocue Haemoglobinometer (Hemocue AB, Angeholm, Sweden) to determine the population prevalence of anaemia (Crawley, 2004a) . This method is preferred because the testing equipment is field friendly and also economical.

1.2.2.4 Anaemia prevention and control

Control efforts on anaemia are always targeted on the etiology. For instance, improvement in dietary intake, food fortification, supplement with iron and other essential micronutrients are the advocated mitigation strategies for nutritional deficient anaemia (Crawley, 2004a; Soares Magalhães and Clements, 2011). In malaria endemic areas, interventions that reduce malaria transmission such as increasing the population ITN coverage, and case management with ACT are the suggested measures that could reduce anaemia prevalence (World Health Organization et al., 2015a). Periodic application of anti-helminth drugs is the recommended control measure in areas with high prevalence of helminthiasis (World Health Organization, 2010). Added to this, are interventions that could sustain the achievement of preventive chemotherapy such as health education, increased access to safe water, and improved sanitation in the population (Grimes et al., 2015).

1.3 Spatial statistical model

Geostatistical modelling represents the most rigorous inferential approach to deal with spatially structured data. Spatial data are correlated in space because observations at close geographical proximity are likely to share similar exposure which could translate to having comparable risk. Geostatistical models are employed to capture the relationship between disease outcome and the explanatory factors while adjustment is made for spatial dependence in the disease data.

Spatial model are highly parameterized and Bayesian inferential approach provides the appropriate method to handle such because of its flexibility in decomposing the joint model of the data, process and the parameters into different hierarchical levels (Carlin et al., 2009; Gelman, 2014). The available spatial information determines the chosen model of the correlation matrix. For areal data, the covariance matrix is commonly structured as conditional autoregressive (CAR) (Besag et al., 1991) model. In the case of geostatistical data, the correlation structure is modeled as parametric function of Euclidean distance between the observed locations. The parameter function could take the form such as exponential and Matérn suggesting decrease of spatial dependence with increasing distance. When Gaussian priors are assumed for the remaining parameters of fixed component and even the non structured random parts, then we model latent Gaussian process. Analytical solutions of the posterior distribution of Geostatical models parameters are intractable. The simulation based method such as Gibbs sampler and Metropolis- Hasting algorithm refers to as Markov Chain Monte Carlo (MCMC) conducts estimation of model parameters through iterative sampling of the marginal posterior distribution of the parameters. The iterative process in MCMC start at an arbitrary point after which it generate a Markov structure until it reaches a convergence point whose distribution is that of the parameters of interest (Gelfand and Smith, 1990).

Implementing MCMC algorithm for highly parameterized spatial model could be very slow to get to the convergence point, and also it could be computationally demanding due to repeated inversion of matrix involved with the covariance matrix leading to what is generally referred to as big *n* problem, where the *n* represent the number of locations. An approximate Bayesian inferential known as Integrated Nested Laplace approach (INLA) (Rue H. et al., 2009a) is one of the recently developed method to circumvent this problem. The approach consists of representing the likelihood of the latent spatial process, which is a Gaussian Random Field with a Gaussian Markov Random Field (GMRF) through stochastic partial differential equation approach (Lindgren and Rue, 2013). The GMRF are defined by sparse matrices which allow for efficient computational properties. Adopting INLA algorithm to do Bayesian inference on GMRF gives additional computational advantage. Several other methods also exist to overcome the big *n* challenge. The data dimension reduction such as Gaussian predictive process (Banerjee et al., 2008; Finley et al., 2009; Xia and Gelfand, 2005) which project the spatial process to a lower subspace represent one of the methods. Also the covariance tapering (Furrer et al., 2006)

in which zeroes are introduced in the covariance matrix for locations that are almost spatially independent based on a set value is another approach for achieving faster computation. A thorough overview of current state of art methods is given by Lasinio and colleagues (Jona Lasinio et al., 2013).

1.3.1 Misalignment and measurement error

Some epidemiologic studies involves data obtained from diverse sources whose location information do not match such that they represent measures from different samples, but spatial dependency exist in those locations from different sources. In such settings, a simplistic approach will be to use the predicted values of the factor in the outcome-response relationship. Such predictions contain measurement error because the predicted value does not account for uncertainty. However, if measurement error is ignored parameter estimates and confidence interval could be attenuated couple with the fact that loss of power for detecting important signals of connection between variables may result, and significant effects may be mask (Muff et al., 2015). A joint modelling approach that incorporates distribution of prediction would proffer solution in such situation.

1.3.2 Variable Selection

Selection of optimum important predictors from large numbers of available potential covariates is a major step in spatial modelling and needs careful consideration. Disease mapping make use of environmental predictors that are often spatially dependent, and this necessitate use of variable selection approach that gives parsimonious model. The selected model could also determine the accuracy of risk predictions.

In many instances (Clements et al., 2009; Raso et al., 2012; Soares Magalhães et al., 2011) spatial correlation is often neglected when determining variable to be included for final model fit in the process of doing disease mapping. The approach mostly adopted is to do it independently of the spatial model fit. Multivariate stepwise regressions are often used to select covariates to be included in the spatial model fit based on a predefined threshold of significance. This selection method has been faulted by Chammartin and colleague (Chammartin et al., 2013). They demonstrated that it could most likely lead to important predictors' exclusion and wrong covariate estimate. This thesis adopted Bayesian variable selection which account for spatial dependence in the data while exploring all possible models in order to get a parsimonious model.

The hierarchical approach of Bayesian modelling allows incorporation of variable selection component in the prior, likelihood or both depending on the adopted Bayesian variable selection methods. For discussion on available Bayesian variable selection, O Hara et al. (O'Hara and Sillanpää, 2009) provided a well documented review.

1.4 Objectives of the thesis

The overall goal of this thesis is to assess the contribution of malaria burden on children anaemia and mortality in Nigeria, and develop tools to support the disease control.

1.4.1 Specific Objectives:

(i) assess the geographical distribution of malaria risk and calculate the population adjusted prevalence per state in the country.

(ii) obtain spatially explicit estimates of the effects of coverage of control interventions on the geographical distribution of malaria among preschool-aged children.

(iii) evaluate the effects of malaria prevalence on the hazard of mortality among children under the age of five years.

(iv) assess the effects of malaria burden on the spatial distribution of anaemia among preschool-aged children.

Chapter 2 Malaria risk in Nigeria: Bayesian geostatistical modelling of 2010 malaria indicator survey data

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Abstract

Background: In 2010, the National Malaria Control Programme with the support of Roll Back Malaria partners implemented a nationally representative Malaria Indicator Survey (MIS), which assembled malaria burden and control intervention related data. The MIS data were analysed to produce a contemporary smooth map of malaria risk and evaluate the control interventions effects on parasitaemia risk after controlling for environmental/climatic, demographic and socioeconomic characteristics.

Methods: A Bayesian geostatistical logistic regression model was fitted on the observed parasitological prevalence data. Important environmental/climatic risk factors of parasitaemia were identified by applying Bayesian variable selection within geostatistical model. The best model was employed to predict the disease risk over a grid of 4 km^2 resolution. Validation was carried out to assess model predictive performance. Various measures of control intervention coverage were derived to estimate the effects of interventions on parasitaemia risk after adjusting for environmental, socioeconomic and demographic factors.

Results: Normalized difference vegetation index and rainfall were identified as important environmental/climatic predictors of malaria risk. The population adjusted risk estimates ranges from 6.46% in Lagos state to 43.33% in Borno. Interventions appear to not have important effect on malaria risk. The odds of parasitaemia appears to be on downward trend with improved socioeconomic status and living in rural areas increases the odds of testing positive to malaria parasites. Older children also have elevated risk of malaria infection.

Conclusions: The produced maps and estimates of parasitaemic children give an important synoptic view of current parasite prevalence in the country. Control activities will find it a useful tool in identifying priority areas for intervention.

2.1 Introduction

Malaria represents a substantial public health challenge in Nigeria and is a major cause of morbidity and mortality. The country accounts for up to 25% of malaria burden in sub-Saharan Africa, which is globally the highest burden region for malaria (National Population Commission (NPC) [Nigeria], 2012). In terms of morbidity, around 110 million of clinically diagnosed cases, 30 percent of health care facilities admission and 60 percent of outpatient visits are attributed to the disease each year (Mouzin and Global Partnership to Roll Back Malaria, 2012). Malaria is also responsible for 300,000 childhood deaths and 11% maternal deaths annually (Kyu et al., 2013; Mouzin and Global Partnership to Roll Back Malaria, 2012; National Population Commission (NPC) [Nigeria], 2012).

Control of malaria is hinged on key global strategies, which include prompt and effective case management, intermittent preventive treatment (IPT) of malaria in pregnancy and integrated vector management (IVM) comprising the use of insecticide-treated nets (ITN), indoor residual spraying (IRS), and environmental management (EM). The National Malaria Control Programme (NMCP) with the support of Roll Back Malaria (RBM) partners is keying into these strategies which form the basis of its National Malaria Control Strategic plan (2009-2013) (National Population Commission (NPC) [Nigeria], 2012). Long-lasting impregnated net (LLIN) possession was scaled up by mass distribution of more than 24 million LLIN in 14 states of the country as of August 2010 through a campaign supported by the partners (Kyu et al., 2013). Prior to this campaign, more than 600,000 LLINs have been distributed in Cross River State between late 2008 and early 2009 to children under the age of five by the United State Agency for International Development (USAID) and the Canadian Red Cross (Kyu et al., 2013). These efforts contributed to about 42 percent of households having at least one ITN [1]. Between 2008 and 2010, 70 million rapid diagnostic tests (RDTs) were distributed to all heath facilities in the country to allow for free diagnosis of all suspected malaria cases (Mouzin and Global Partnership to Roll Back Malaria, 2012). In 2008, 5% of these cases were screened with RDTs (Mouzin and Global Partnership to Roll Back Malaria, 2012). Pregnant women receiving preventive therapy during their routine antenatal care reached 13 percent in 2010, which may reflect low turnout for antenatal visit and at the same time health care-seeking behaviour. At the end of the same year IRS coverage was two percent in the entire country (Mouzin and Global Partnership to Roll Back Malaria, 2012).

Effective malaria control strategies call for reliable and comprehensive maps of the spatial distribution of the disease risk and estimates of infected people. These are important tools in guiding efficient resource allocation for planning and implementation of intervention programmes and evaluation of their impact (Gemperli et al., 2006; Giardina et al., 2012; Gosoniu et al., 2012, 2010; Riedel et al., 2010). Various maps depicting the geographical distribution of malaria risk in Nigeria are presently available at regional, continental, and global scale. The earlier map of malaria risk in Nigeria was a climatic suitability map estimated by the mapping malaria risk in Africa (MARA) project (Craig et al., 1999). This effort was followed up by empirical mapping using historical survey data from the MARA database to produce a regional map of West Africa (Gemperli et al., 2006). Different Bayesian geostatistical modelling approaches were employed to these historical data attempting to improve the model-based prediction of malaria risk. Sequel to this the Malaria Atlas Project (MAP) in 2007 and 2010 generated a geostatistical model-based global malaria risk map from historical survey data (Gething et al., 2011; Hay et al., 2009). More recently, geostatistical model-based spatio-temporal malaria endemicity maps of Africa were obtained through analysis of data assembled from parasite prevalence surveys adjusting for environmental factors effect (Noor et al., 2014). Analyses that are based on historical survey data suffer from methodological issues due to data heterogeneity that may contribute to less accurate estimates (Giardina et al., 2012; Gosoniu et al., 2012, 2010; Riedel et al., 2010) and do not reflect the current situation of the disease in the country.

In 2010, Nigeria conducted the first nationally representative MIS which assembled information on malaria related burden and the coverage of key interventions among children below the age of five. The survey was implemented by the National Population Commission (NPC) and NMCP with the technical assistance of ICF International and other RBM partners. In this study, the MIS data were analysed in order to identify environmental/ climatic, demographic, and socioeconomic and control intervention factors associated with malaria risk and produce a contemporary risk map of malaria among children under the age of five. Bayesian geostatistical models fitted via Markov Chain Monte Carlo (MCMC) simulation were employed for parameter estimation and predictions. Gibbs variable selection incorporating spatial dependency was used in identifying the most parsimonious model.

2.2 Methods

2.2.1 Study area

Nigeria, the most populous country in Africa, is in the west sub region of Africa with a total land mass of 923,768 square kilometers. The recent census estimates the country population at 140,431,790 people, 32.8% of which are urban settlers (National Population Commission (NPC) [Nigeria], 2012). The country has tropical climate with two seasons (wet and dry season) which are associated with the movement of two dominant winds: the rain bearing south westerly winds, and the cold, dry and dusty north easterly wind generally referred to as the Harmattan. The wet season occurs from April to September, and the dry season from October to March. The annual rainfall ranges between 550mm in some part of the north mainly in the fringes of Sahara desert to 4,000 mm in the coastal region around Niger delta area in the south. The temperature in Nigeria oscillates between 25°C and 40°C. The vegetation that derives from these climatic differences consists of mangrove swamp forest in the Niger Delta to Sahel Savannah in the north. The geographic location of Nigeria makes suitable climate for malaria transmission throughout the country and it is all year round in most part of the country.

The most prevalent malaria parasite species is Plasmodium falciparum (>95%) and it is responsible for most forms of the severe disease (Mouzin and Global Partnership to Roll Back Malaria, 2012; National Population Commission (NPC) [Nigeria], 2012). The other types found are Plasmodium malariae and Plasmodium Ovale (Mouzin and Global Partnership to Roll Back Malaria, 2012). Malaria transmission intensity, duration and seasonality vary among the country's five ecological strata (mangrove swamps, rain forest, guinea savannah, Sudan savannah and Sahel savannah) that extend from south to north(National Population Commission (NPC) [Nigeria], 2012). Considering population density and distribution of risk areas, an estimated 3%, 67% and 30% live in very low to low, moderate, and high to very high transmission intensities area, respectively (Mouzin and Global Partnership to Roll Back Malaria, 2012). Also the duration of transmission season increases from north to south, from approximately three months in the north area bordering Chad to perennial in the most southern part (Mouzin and Global Partnership to Roll Back Malaria, 2012).

2.2.2 MIS Data

The data were collected using the standard malaria indicator questionnaires developed by the RBM and the demographic health surveillance programme. The dataset consists of malariometric information, demographic characteristics and socio-economic status on a nationally representative sample of around 6,000 households from about 240 clusters of which 83 are in the urban areas. These clusters were derived from a stratified two-stage cluster design. Detail description of the sampling strategies is well-documented in the final report of NMIS 2010 (National Population Commission (NPC) [Nigeria], 2012). Blood samples were only taken from 239 clusters due to security challenges in one of the clusters in the north (National Population Commission (NPC) [Nigeria], 2012). Prevalence from two diagnostic methods (RDT and microscopy) were recorded in the data, but the statistical analysis in this work is based on the blood slide microscopy readings which is believed to be the gold standard of malaria diagnosis (Wongsrichanalai et al., 2007). The geographical representation of the clusters involved and observed prevalence in the NMIS is displayed in Figure 2.1.

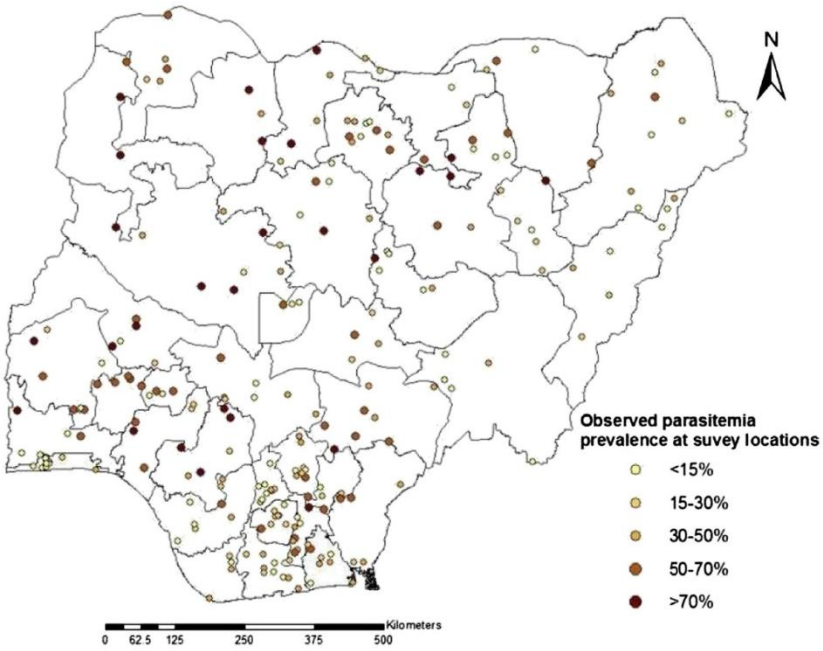

Figure 2.1: Malaria prevalence observed among children less than 5 year at 239 locations of NMIS 2010

2.2.3 Environmental/climatic data

Environmental and climatic predictors were obtained from satellite sources. The acquired factors used in this analysis are Land Surface Temperature (LST), Normalized Difference Vegetation Index (NDVI), altitude, rainfall and distance to permanent water bodies. Weekly and biweekly values of LST and NDVI, respectively, covering the period from October 2009 to October 2010 were extracted from the Moderate Resolution Imaging Spectroradiometer (MODIS) database (http://reverb.echo.nasa.gov/reverb/). Decadal rainfall data for the same period was downloaded from the Africa Data Dissemination Service database (http://earlywarning.usgs.gov/fews/). Annual averages at each location (observed or predicted) were derived for the above predictors. Data on permanent water-bodies was obtained from the HealthMapper database of the World Health Organization (WHO). The minimum distance between the centroid of each cluster to the nearest body of water was calculated in ArcGIS version 9.3 (ESRI; Redlands, CA, USA).

The Urban-rural extent grid data was acquired from the Global Rural Urban Mapping Project (GRUMP) database. Details about the sources, spatial and temporal resolution of these data is shown in Table 2.1. The coordinates of the clusters in the MIS was used to link malaria data with these datasets.

Table 2.1: Sources, spatial and temporal resolution of model predictors, and population data

Data	Source	Period	Spatial resolution
Land surface temperature (LST) for day and night	MODerate resolution Imaging Spectroradiometer (MODIS) http://reverb.echo.nasa.gov/reverb	2009-2010	1×1 km^2
Normalized difference (NDVI)	MODerate resolution Imaging Spectroradiometer (MODIS) http://reverb.echo.nasa.gov/reverb	2009-2010	0.25×0.25 km^2
Rainfall	Africa Data Disseminating Services http://earlywarning.usgs.gov/fews/	2009-2010	8×8 km^2
Digital elevation model	Shuttle Radar Topographic Mission(SRTM) http://glcfapp.glcf.umd.edu/data/srtm/	2000	1×1 km^2
Urban rural extent	Global Rural and Urban Mapping Project http://sedac.ciesin.columbia.edu/data/set/grump-v1-population/data-download	na	1×1 km^2
Permanent water bodies	Health mapper	na	1×1 km^2
Human population density grid	http://www.worldpop.org.uk/data/	2010	100×100 m^2

2.2.4 Intervention data

Data on measures for preventing malaria, including the possession and use of ITN /LLIN and implementation of IRS were collected in the NMIS. These data were used to generate the following indicators of intervention coverage as recommended by Roll Back Malaria-Measurement and Evaluation Reference Group (RBM-MERG) (DHS, 2013; Kilian et al., 2013) : (i) the proportion with access to ITN in the household, (ii) proportion in every household that slept under an ITN during the previous night to the survey, (iii) proportion of children under 5 who slept under an ITN during the night preceding survey.

2.2.5 Socioeconomic data

Information on socioeconomic status (SES) was measured by a wealth index, which was present in the NMIS. It was derived through Principal Component Analysis as a weighted sum of household assets. SES was included in the analysis as a categorical covariate with categories corresponding to the quintiles.

2.2.6 Population data

Population density grid data for the year 2010 was extracted from Worldpop (http://www.worldpop.org.uk/data/).

Population structure for the same year was obtained from international database of United State census bureau (https://www.census.gov/population/international/data/idb/region.php) to calculate the number of children less than five years.

2.2.7 Bayesian geostatistical modelling

Bayesian geostatistical logistic regression models were applied to identify important predictors of malaria parasite risk, produce a contemporary malaria risk map, and obtain estimates of number of children less than five years old infected with malaria parasites. Variable selection was carried out during the geostatistical model fit. All possible combinations of covariates resulting in 65536 models were fitted to obtain a parsimonious model. Prediction was carried out using Bayesian Kriging (Diggle et al., 2002) based on the model with the best predictive ability. Model validation was performed on the first two models with the highest probability of having generated the data among those considered. In particular, the models were fitted on a random sample of 85% of the locations and used the remaining locations to compare

model-based predictions with observed prevalence by calculating the Mean Absolute Error (MAE). A regular grid of 231,865 pixels at 4 km^2 spatial resolution covering the whole country was generated to predict the parasitaemia risk at un-sampled locations and produce a high-resolution risk map. Population data on the number of children under five years of age was combined with spatially explicitly predicted parasitaemia risk to estimate the number of infected children. The analysis was carried out in Win-BUG1.4 (Imperial College and Medical Research Council London, United Kingdom). Bayesian kriging was implemented in FORTRAN 95 (Compaq Visual FORTRAN Professional 6.6.0) using standard numerical libraries (NAG, The Numerical Algorithm Group Ltd). Details on Bayesian model selection, model fit and validation are provided in Appendix (see subsection 2.6)

2.3 Results

The study included 5,043 children under five years old with complete parasitological and malaria intervention data collected over 239 geo-located clusters. Figure 2.1 show the observed malaria prevalence in the surveyed clusters. The overall prevalence using thick blood smear results was 38%. On average, one ITN is available for every four children or for every five individuals in the household and only 26% of the children less than age of five slept under an ITN during the night preceding the survey. The IRS coverage is 1.02% in the entire country. Table 2.2 shows that the highest model posterior probability was 0.45, that is 45% of the fitted models included rainfall and NDVI in linear forms (Model 1), followed by the one including the above covariates in addition to LST and altitude (posterior probability 0.08).

Model validation results depicted in Table 2.2 indicate that both models have similar MAE estimates in terms of predictive ability, confirming that the LST and altitude did not improve predictions; therefore, inferences were based on Model 1. Posterior estimates of the parameters of (Model 1) as well as the model which includes environmental/climatic, socio-economic, demographic, and intervention covariates (Model 2) are given in Table 2.3. Higher vegetation index is associated with high parasitaemia while increased rainfall reduces malaria risk. A monotone decrease of malaria risk was observed with better socio-economic status which becomes important in the stratum of least poor with an odds ratio of 0.51 (95%BCI: 0.35 – 0.75). Older children have elevated odds of being infected. Moreover, living in rural areas puts children at higher risk. Furthermore, variation in intervention coverage appears not to be associated with

parasitaemia risk. The estimates of the range parameter shows that spatial correlation is present within an ~3.0 km (95% BCI: 1.50 km - 45.00 km) distance which implies that malaria risk at a given location is affected by risk in neighbouring areas up to a distance of approximately 3.0 km. Results of a sensitivity analysis showed that the estimates of the spatial parameters were not sensitive to the choice of the priors. The predicted parasitaemia risk map is depicted in Figure 2.2.

The maps of the lower 2.5% and upper 97.5% credible intervals of the posterior distribution are also displayed in Figure 2.3. The distribution of predicted parasitaemia risk varies in Nigeria between 0.4% and 91%. Parasitaemia prevalence is relatively low in the southern-most and the south-east region of the country particularly in Anambra state where the risk of testing positive to parasitaemia is below 20%. It is only in Abia and Edo states within those regions that the parasitaemia risk respectively went above 30% and slightly above 40%. The south-west, with exception of Lagos state shows relatively higher risk, however the highest prevalence in the country (~48%) was predicted for Osun state within this region. The situation in the central north is similar to the south-west with Kwara and Benue states having the highest (42.4%) and lowest (29.7%) risk in this region, respectively. Most of the state in the north-east and north-west exhibit similar patterns with the exception of Yobe state with parasitaemia risk of approximately 40%. Estimates of the population adjusted prevalence and number of parasitemic children under 5 year aggregated at the state level are given in Table 2.4. Overall 7,104,079 children were estimated to be infected with malaria parasites distributed across regions as follows: 16.5% north-central, 15.6% north-east, 26.7% north-west, 9.80 % south-east, 13.1% southern-most, and 18.4% south-west.

Table 2.2: Model predictive performance in terms of Mean Absolute Error (MAE), based on climatic/environmental factors.

Model	Posterior probability	Mean absolute error
Rainfall and NDVI	45%	0.005
Rainfall, NDVI, LSTN and Altitude	8%	0.005

Table 2.3: Posterior median and 95% Bayesian Credible Intervals (BCI) of Model 1* and Model 2**

	*Model 1	**Model 2
Variables	**OR(95% BCI)**	**OR(95% BCI)**
NDVI	2.01 (1.56, 2.60)	1.56 (1.21, 1.99)
Rain	0.57 (0.44, 0.75)	0.72 (0.57, 0. 91)
Area type		
rural		1
urban		0.43 (0.28, 0.65)
Socioeconomic Index		
Most poor		1
Very poor		1.12 (0.86, 1.44)
Poor		1.19 (0.89, 1.59)
Less poor		1.00 (0.72, 1.39)
Least poor		0.51 (0.35, 0.75)
Age		
0-1		1
1-2		1.35 (1.05, 1.76)
2-3		1.93 (1.50, 2.50)
3-4		2.34 (1.82, 3.02)
4-5		2.76 (2.15, 3.55)
Proportion with access to ITN in the household		0.86(0.51,1.48)
Proportion of children aged 0–59 months who slept under an ITN the night before the survey		0.91(0.57, 1.47)
Proportion of people who slept under an ITN in the night before the survey		0.92(0.50, 1.67)

Spatial Parameters	**Posterior median Model 1**	**95% BCI**	**Posterior median Model 2**	**95% BCI**
σ^2	1.56	(1.20, 2.04)	1.34	(1.02, 1.76)
Range(km)	5.87	(1.54, 60.00)	2.14	(1.12, 45.00)

*Model of malaria risk based on environmental/climatic predictors.

**Model of malaria risk inclusive of intervention after adjusting for climatic/environmental socioeconomic and demographic factors.

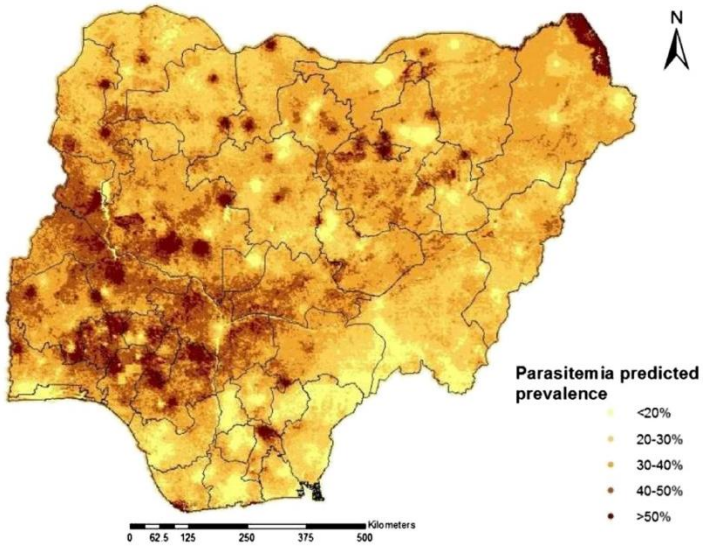

Figure 2.2: Predicted risk map of parasite among children under five years in Nigeria: Estimates are based on model 1 and indicate median posterior distribution over a grid of 231865 pixels.

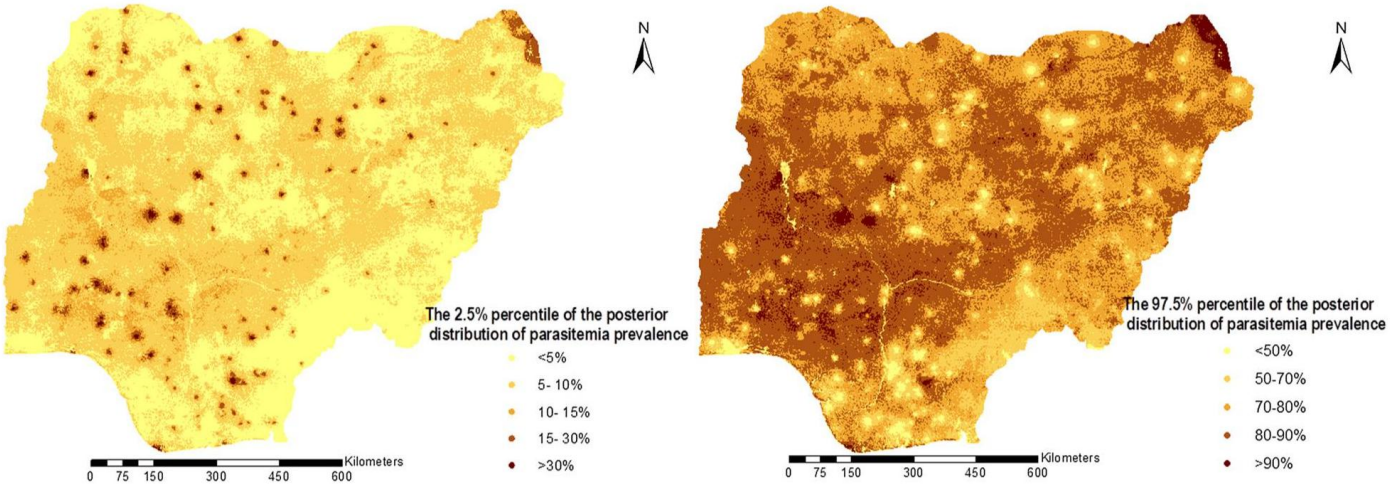

Figure 2.3: The 2.5 % (left) and 97.5 % (right) percentiles of the predicted posterior distribution of malaria prevalence estimated from Model 1.

2.4 Discussion

This work present a geostatistical analysis of the NMIS data to identify important predictors of malaria parasite risk, produce a contemporary malaria risk map, and obtain estimates of number of children less than 5 years old infected with malaria parasites. It is noteworthy that this study generated the first spatially referenced parasitaemia risk estimates and maps in Nigeria from contemporary, geographically-representative data collected in a standardized way across the country. Previous mapping efforts embedded Nigeria within regional, continental and global scale (Gemperli et al., 2006; Gething et al., 2011; Kleinschmidt et al., 2001; Noor et al., 2014) maps making use of historical surveys that may not characterize the current malaria situation in the country. The produced maps and the estimates of the number of infected children illustrate an important synopsis of prevalence of malaria in the country. Therefore they can serve as a resourceful tool in planning interventions and a reference point in evaluating their impact in space and time.

Risk factor analysis was carried out using Bayesian variable selection within a geostatistical setting. This modelling approach identified not only the most import-ant risk factors but also their functional form in order to build a parsimonious model with the best predictive ability. Bayesian variable selection has been implemented in malaria risk modelling by Giardina et al. (Giardina et al., 2012) and Diboulo et al. (Diboulo et al., 2015). Chammartin et al. (Chammartin et al., 2013) introduced Bayesian geostatistical variable selection for identifying functional forms of covariates in modelling neglected diseases however, to our knowledge rigorous modelling of covariate functional forms have not been used in the area of malaria mapping. The result indicated that in Nigeria, rainfall and NDVI are the most important drivers of malaria risk while temperature and altitude do not improve our ability to predict the risk. The geographical distribution of the malaria risk estimates illustrated relatively high prevalence in every region of the country. The geostatistical model predicted higher disease risk (>40%) in some states both in south-west and in north central regions. Both regions have similar rainfall characteristics which create shallow water pockets, suitable breeding sites for Anopheles gambiae, the dominant mosquito vector in the country. Further-more, in both regions there are many water bodies that are surrounded by vegetation, providing suitable habitat for Anopheles funestus, the second

prevalent species in Nigeria. Malaria risk is relatively lower in the southern-most part of the country, which may be due to more rain in the region that could clear away breeding sites of the vector. The distinct heaps of relatively high predicted parasitaemia risk around the survey locations might be explained by the weak spatial correlation in the observed prevalence which resulted in reduced smoothing of the predicted map. The predicted risk map was compared to a previous mapping effort across West Africa by Gemperli, et al. (Gemperli et al., 2006). There were similarities in prevalence for most part of the southern Nigeria with the exception of Lagos where lower prevalence is obtained in this study which might be linked to more urbanization and ongoing interventions. Differences are present in the central north and northwest regions where higher and lower estimates were obtained respectively in this study. The malaria endemicity map produced by the malaria atlas project (MAP) (Gething et al., 2011) shows similar patterns to the present map especially in the north, apart from some areas in the north-east. In the south, MAP predicted higher risk in some parts of the southern-most regions principally around Cross river state. This might be connected to the inclusion of older children (2-10 years) in the MAP analysis. The estimates derived from this study when compared with the recently generated malaria endemicity map of Abdisalan et al. (Noor et al., 2014) shows re-semblance in most part of the country aside the Lake Chad area in the northeast and small fringes of Niger state in the central north where we predicted higher malaria risk.

The study findings indicated an increasing gradient of malaria risk with age, with the older children having the highest risk. The estimated negative association between socioeconomic status and malaria risk also confirms earlier reports (Giardina et al., 2012; Gosoniu et al., 2012, 2010). The analysis showed that variation in the bed net coverage indicators across the country is not related to variation in the parasitaemia risk. However only data from one survey was available, therefore, changes in parasitaemia risk could not be estimated at a given region associated to intervention coverage levels. A limitation of the survey is that it was carried out after the rainy season and, therefore, estimates may not reflect malaria risk during the highest transmission season. Rolling MIS (Roca-Feltrer et al., 2012) that adopt the standard cross-sectional evaluation tool into continuous monitoring can provide timely, accurate, sub-national, and district level burden estimates throughout the year. It was considered as a promising tool for monitoring short-term control progress in the course of its implementation in a district in Malawi; however its feasibility is unclear at national level.

Table 2.4: Estimates of the number of children under five years of age with parasitaemia at state level

Region	State	Prev. A	Population of under 5 children	Estimated number of infected children	95% CI	Prev. B
North Central	**Benue**	29.73%	784875	222340	(200190, 244491)	28.33%
	Kwara	42.37%	449638	151621	(131421, 171821)	33.72%
	Kogi	41.50%	561582	213304	(188056, 238552)	37.98%
	Nasarawa	37.56%	340392	119592	(102802, 136383)	35.13%
	Niger	39.11%	735787	256231	(233893, 278568)	34.82%
	Plateau	31.88%	608271	150934	(142149, 159720)	24.81%
	FCT	34.31%	233252	60270	(53799, 66741)	25.84%
North East	**Adamawa**	28.51%	566017	147375	(135450, 159299)	26.04%
	Bauchi	33.92%	915634	281832	(251864, 311799)	30.78%
	Borno	33. 01%	760560	329545	(318480, 340610)	43.33%
	Gombe	29.74%	415270	108147	(94212, 122082)	26.04%
	Taraba	26.02%	413337	95666	(88832, 102500)	23.14%
	Yobe	39.90%	408299	143671	(117597, 169744)	31.54%
North West	**Jigawa**	32.61%	743497	245984	(201408, 290560)	33.08%
	Kaduna	30.00%	1087823	306971	(274214, 339727)	28.22%
	Kano	32.98%	1661333	413643	(359266, 468019)	24.90%
	Katsina	31.31%	1037799	312991	(269742, 356240)	30.16%
	Kebbi	33.17%	547728	178198	(155795, 200601)	32.53%
	Sokoto	29.23%	758304	241214	(196928, 285499)	31.81%
	Zamfara	30.24%	662075	195519	(167378, 223658)	29.53%
South East	**Abia**	34.34%	552137	170719	(131633, 209805)	30.91%
	Anambra	18.95%	753168	116883	(99151, 134615)	15.52%
	Ebonyi	25.50%	440488	117079	(81696, 152462)	26.58%
	Enugu	28.30%	638279	144983	(120597, 169370)	22.71%
	Imo	24.23%	777127	149944	(116532, 183355)	19.29%
South South	**Akwa Ibom**	24.71%	777083	183459	(148354, 218564)	23.61
	Bayelsa	28.11%	293027	73662	(61359, 85965)	25.14%
	Cross River	21.84%	508781	113384	(94271, 132496)	22.29%
	Delta	25.40%	838073	178389	(153985, 202794)	21.29%
	Edo	41.85%	609027	216539	(190803, 242276)	35.55%
	Rivers	22.39%	835356	160600	(237741, 261026)	19.23%
South West	**Ekiti**	41.24%	522684	175495	(140018, 210972)	33.58%
	Lagos	19.63%	1765136	114114	(94296, 133933)	6.46%
	Ogun	33.50%	778465	180659	(153966, 207352)	23.21%
	Ondo	40.98%	553129	211170	(181103, 241236)	38.18%
	Osun	47.74%	655875	276857	(222237, 331476)	42.21%
	Oyo	38.78%	977540	345095	(291686, 398504)	35.30%

Prev. A: Population unadjusted prevalence; Prev. B: Population adjusted prevalence.

2.5 Conclusion

In conclusion, the predictive prevalence map depicts that malaria morbidity is still high in the entire country and variation in malaria intervention coverage indicators is not associated with variation in parasitaemia risk across the country. The coverage of key malaria interventions is still low and needs scaling up, which requires an increase of health expenditure by the federal government and an increase of awareness by the population on the benefit of bed net use.

Acknowledgement

We would like to acknowledge Measure DHS for making the data available and the financial support of the European Research Council (323180 - IMCCA) and the Swiss National Science Foundation (IZ01Z0-147286).

2.6 Appendix

2.6.1 Geostatistical Model formulation

Let Y_{ij} indicate the malaria parasites status in child i at location s_j ($j=1, \ldots, n$). Y_{ij} is assumed to follow a Bernoulli distribution, that is $Y_{ij} \sim$Be (p_{ij}) , where p_{ij} corresponds to parasitemia risk.

Also let $X_{ij}= (X_{ij}^{(1)}, X_{ij}^{(2)}, \ldots X_{ij}^{(q)})^{T}$ be the vector of predictors observed at location s_j. We model the relationship between malaria risk and its potential predictors on the logit $(p_{ij}) = X_{ij}\beta_j + \varphi_j$, where β_j are the regression coefficients. The spatial dependence was taken into account by location-dependent random effect $\boldsymbol{\varphi}=(\varphi_1, \varphi_2, \ldots \varphi_n)^T$ which were considered to arise from a multivariate normal distribution with mean 0 and variance covariance matrix $\Sigma_{jk}=\sigma_\varphi^2 \exp(-\rho d_{jk})$, where d_{jk} is the Euclidean distance between locations s_j and s_k, σ_φ^2 represent the spatial variance known as partial sill and ρ is a smoothing parameter that controls the rate of correlation decay with increasing distance. The range which defines the minimum distance at which spatial correlation between locations is below 5% is calculated by $3/\rho$. We provide the estimate of the range parameter in km considering that 1 degree corresponds to 111.12km.

Bayesian variable selection(Chammartin et al., 2013; Dellaportas et al., 2002, 2000; Ishwaran and Rao, 2005; O'Hara and Sillanpää, 2009) was used to identify the most important predictors of parasitemia risk after taking into account the spatial correlation in the data at cluster level. This was done by introducing an indicator variable λ_j suggesting the presence or absence of the corresponding X_j covariate that is, $\beta_j = \lambda_j\alpha_j$ where α_j measure the effect size of X_j . We assume a priori equal inclusion probabilities for all variables that is $\lambda_j \sim Be\left(\frac{1}{2}\right)$ and a mixture of normal distribution for α_j that is, $\alpha_j \mid \lambda_j \sim (1-\lambda_j)N(0, \xi v^2) + \lambda_j N(0, v^2)$. The parameter v^2 is a predetermined large variance (i.e. 1000) and ξ is a small constant that shrinks β_j towards zero when the covariate is not selected. We also introduce a separate indicator I_m to select from linear or categorical form of the climatic factors. We assume β_{jm1} and β_{jm2} represent the coefficients corresponding to the linear and categorical forms of the j predictor respectively, that is, $\beta_j = I_m\beta_{jm1} + (1-I_m)\beta_{jm2}$ with I_m assuming a Bernoulli distribution. The selected model was fitted assuming a vague normal prior distribution for β_j that is, $\beta_j \sim$N (0,100).

Prior distributions were assigned to σ_{φ}^2 and ρ to complete the model specification. Inverse Gamma distribution was chosen for spatial correlation parameter σ_{φ}^2 that is, $p\ (\sigma_{\varphi}^2)$ = Gamma (0.001, 0.001). Uniform prior distribution assuming spatial correlation lower than 0.05 as negligible was chosen for ρ, that is $p\ (\rho)$ = Uniform (-log(0.05)/d_{max},-log<(0.05)/d_{min}) where d_{max} and d_{min} are the maximum and mininum (non-zero) Euclidean distance between the survey locations. To assess sensitivity of the estimates to the prior distributions of the spatial parameters, we re-fitted the models using a more informative prior distribution for σ_{φ}^2, that is $p\ (\sigma_{\varphi}^2) \sim$ Gamma (2.01,1.01) and the following prior for ρ, $p\ (\rho)$ = Uniform(-log(0.01)/d_{max},-log<(0.01)/d_{min}).The model was fitted in WinBUG1.4 (Imperial College and Medical Research Council London, United Kingdom) using Markov Chain Monte Carlo (MCMC) simulation. Linear predictors were centered to obtain well-behaved correlation structure and reduce the computation time of MCMC algorithm(Banerjee et al., 2004). The variable selection was carried out only for the environmental/climatic predictors to identify the most important predictors. Assessment of predictive performance of models were made by calculating the Mean Absolute Error (MAE) which provides information on model accuracy using the average of absolute distances between observed and predictive posterior distribution values, that is MAE= $\frac{1}{k}\sum_{i=1}^{k}\sum_{j=1}^{m}\left|\hat{p}_{ij} - p_i\right|$ where k is no of test locations and m is the size of sample drawn from the posterior predictive distribution at the test site. Also $\hat{p}_{ij}$ is the j sample of the predicted posterior distribution at the test site and p_i is the observed prevalence at the test site.

Chapter 3 Assessment of spatial heterogeneity of insecticide treated net use and its effect on malaria risk among children less than five years in Nigeria.

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Abstract

Malaria burden reduction in so many endemic countries of sub-Saharan Africa has been attributed to vector control. However, the coverage of this intervention is not homogeneous even among the different regions of some of these nations, and so also the effect on malaria prevalence. Malaria information survey gathers information on malaria parasitaemia infection and intervention coverage among other things, which can be use in evaluating malaria risk and intervention coverage relationship. We analysed the first national malaria information survey in Nigeria, to assess the effect of coverage of intervention among children under five on parasitaemia prevalence at national and first administrative level of the country. We used Bayesian geostatistical model to estimate the effect of coverage of insecticide treated bednet on the risk of malaria at the national and states level, after controlling for environmental and socio-demographic factors related to malaria parasitaemia prevalence. The result shows that the use of insecticide treated net was not associated with malaria risk when considered nationally. However the analysis at the first administrative level shows intervention coverage to be importantly related to the reduced malaria risk in two states (Adamawa and Taraba) within the north east region, which coincidentally has the highest proportion of insecticide treated net use by the children under five in the country. The produced effect map couple with other epidemiological tool like malaria prevalence map can serve as vital instrument in enhancing malaria control in the country.

3.1 Introduction

The vector control measure, insecticide treated nets, either singly or in combination with other prevention/control strategies has demonstrated to be very efficient and also cost effective against malaria parasite transmission(Giardina et al., 2014; Larsen et al., 2014; Lengeler, 2004). The malaria burden reduction in most of the endemic country of the sub-Saharan Africa has been linked to the extended application of this control intervention. Advocacy for their use have been based on evidence from community based randomized trial (Binka et al., 1998; Phillips-Howard et al., 2003) with confirmation through large scale implementation (D'Alessandro et al., 1995) and systematic reviews(Gamble et al., 2007; Lengeler, 2004).

The roll back malaria partnership in its coordination of global fight against malaria advocated the scaling up of this intervention and others such as, prompt and effective case management, intermittent preventive therapy during pregnancy, and indoor residual spraying, that had proven to bring down malaria transmission (World Health Organization et al., 2015b). It has also developed malaria information survey which gathered malaria related burden data that could provide a clear-cut yardstick to monitor the impact of those control interventions over space and time on malaria risk.

Increase funds for malaria control in the recent years due to overseas development assistance couple with political commitment of the government of the endemic countries has lead to scaling-up of these interventions (Noor et al., 2014, 2009). The massive expansion of ITN distribution in most malaria endemic country of sub-Saharan Africa has shown to be beneficial nationally in many of the countries (Bhatt et al., 2015; Giardina et al., 2014; Mharakurwa et al., 2012; Noor et al., 2014). However, the effect of this intervention on malaria risk across space of some of the country national borders demonstrated spatial heterogeneity even with the same level of coverage (Snow, 2015; Snow and Marsh, 2010) .

Geostatistical models have been employed to study the relationship between vector control intervention and malaria risk with adjustment made for environmental and socio-demographic factors. Some of these studies found effect while others could not found any significant association of ITN intervention coverage with malaria prevalence at the country level. For

instance, an analysis of Angola MIS 2006-2007 data (Gosoniu et al., 2010) relating malaria risk to intervention was able to established decrease malaria prevalence with increased ITN in the household. Also, another study in Senegal (Giardina et al., 2012) found that having one ITN to two people is negatively associated with parasitaemia prevalence. However in Tanzania study (Gosoniu et al., 2012) no apparent relationship could be established between malaria prevalence and the intervention measures.

The effect of intervention coverage on malaria risk might vary in space within a country due to dissimilar level of transmission across the areas in the country. Various measure of coverage has been suggested by RBM-MERG to track the progress of intervention coverage on malaria burden reduction and they can be easily derived from the intervention variables recorded in the MIS. The potential derivative specifically for insecticides treated bednet coverage includes those measuring ownership, and usage by the vulnerable groups.

Recently a study (Giardina et al., 2014) carried out an analysis to study the effect of some intervention coverage in space for six countries in sub-Saharan Africa and found that some of interventions were not importantly related to malaria risk at the national level in four of the countries. However, when considered at sub-national level, by incorporating spatially varying coefficient at the defined areal level, several of the effect became significant at some of the sub-national level. Moreover, another study (Diboulo et al., 2016) deployed the same method to assess the spatial effect of intervention coverage at health district level in Burkina- Faso using MIS data, and demonstrated that malaria prevalence is negatively associated with ITN use by children under the age of five in some of the district. Nigeria, one the country in Africa with high malaria burden, just reach 42% household access to one ITN in 2010 (National Population Commission (NPC) [Nigeria], 2012) . Despite lagging behind in terms of universal coverage; there is also geographical dissimilarity as regard the usage by the highly vulnerable group in different parts of the country.

Model based spatial representation of intervention effect on malaria prevalence is a vital tool that can inform the malaria control programme on how different area of the country is faring regarding malaria control. In our previous work (Adigun et al., 2015), we did an evaluation of household ITN coverage on the risk of malaria at the country level and it appears malaria risk was not associated with any of the indicators considered. However, in this study we assess the

spatial heterogeneity of ITN use by the children and its association with malaria parasitaemia among this vulnerable group across the first administrative level in Nigeria with model formulation that adjusted for environmental and socio -demographic characteristics of the households. We considered the use of ITN only because the value represents the most direct indicator of both individual and communal protection (Killeen et al., 2007) and it is therefore the more useful determinants of epidemiological impact (Korenromp et al., 2003).

3.2 Methods

3.2.1 Country context

The dominant malaria vectors in identified across Nigeria include *An. gambiae s.s, An. arabiensis* and *An. funestus*. Also Plasmodium falciparum represent the most prevalent malaria parasite specie in the country and it is responsible for about 95% of malaria infection in the country. Most area of the country has climate condition that is suitable for malaria transmission throughout the whole year. Administratively, Nigeria is divided into 36 states and the federal capital territory (FCT Abuja) among six geopolitical zones (south-west: 6 states, south-east: 5 states, south-south: 6 states, north-central: 6 states and FCT, north-west: 7 states, and north-east: 6 states. The uptake of ITN in the country has not been very impressive, as at 2003 household access to an ITN was just only 2% and this possession rose to about 17% in 2008 and later to 42% in 2010 due to overseas development assistance in some of the states in the country.

3.2.2 Intervention coverage data

The coverage of bednet intervention at the first administration level were evaluated using the bednet information provided in the MIS following the approach described in Household Survey indicators for malaria control document (DHS, 2013). Proportion of children under five year who slept under ITN during the night before the survey was the indicator of coverage derived for analysis in this study.

3.2.3 Environmental data

In order to control for the effect of environmental factors known to be associated with malaria parasitaemia in the country (Adigun et al., 2015), Rainfall estimates with spatial resolution of 8km×8km and 10 days temporal resolution was obtained from the archives of Africa data dissemination services (ADDS) (http://earlywarning.usgs.gov/fews). Also the measure of

greenness, normalized difference vegetation index data with spatial and temporal resolution of 250m×250m and 16 days, respectively was downloaded from the moderate resolution imagine spectro-radiometer (MODIS) database (http://reverb.echo.nasa.gov/reverb/). The values of these climatic covariates were extracted to the survey coordinates using ArcGIS 10.2 spatial analyst tool (ESRI Redlands, CA). The calculated averages over a year period preceding the survey was used in the analysis.

3.2.4 Socio-demographic data

Clusters were defined as either rural or urban based on the information provided by socio-economic data and applications centre of the centre for international earth science information network (CIESIN) (http://sedac.ciesin.columbia.edu/). The available information in the MIS on household socio economic status in the form of quintiles ranging from poorest to the least poor which was derived from application of principal component analysis on household possession of certain assets was employed in this study. Also the children age in months was classified into five categories with the strata separated by equal interval.

3.2.5 Statistical Analysis

We first fitted a Bayesian geostatistical model to assess the effect of intervention coverage (use of ITN by childrenU5) on malaria parasitaemia prevalence at the country scale, adjusting for the socio-demographic characteristics of the household and climatic factors. Secondly we model the intervention coverage level on malaria parasitaemia prevalence at the states level also adjusting for aforementioned covariates in the initial model fit. These models included the spatial random effect, which account for the correlation in the response variable, and it was assumed to follow a zero-mean multivariate normal distribution with variance-covariance defined as exponential function of the distances between any pair of locations. The spatial correlation at the first administrative level was modeled as conditional autoregressive (CAR) effect. In the CAR model, neighbours are defined as the adjacent areas, and this was used to generate spatial weights matrix, which assigned value one to areas that shares border and zero if they do not. Further details on model formulation are given in the appendix.

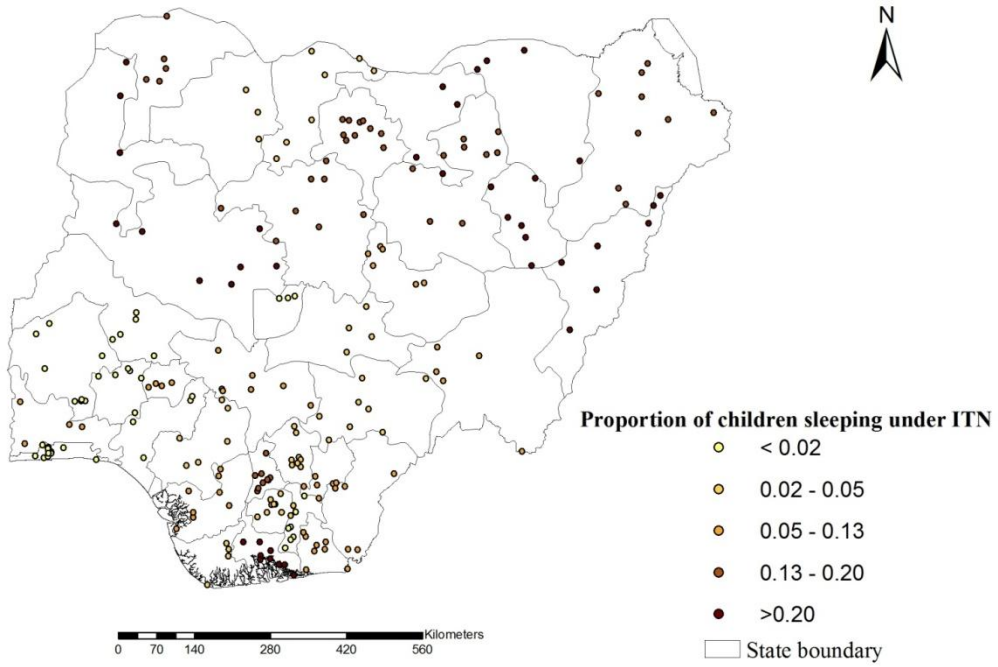

Figure 3.1: Proportion of children under five years of age that sleeps under ITN in the surveyed locations

3.3 Results

The NMIS 2010 was carried out in 239 locations and a total of numbers of 5137 children under the age of five years were examined for malaria parasitaemia by the use of blood smear microscopy. Figure 3.1 shows the proportion of children under that sleeps under ITN in the surveyed clusters of the NMIS. The measure of bednet coverage analysed in this study is proportion of children under five who slept under an ITN in the night preceding the survey. Table 3.1 shows the summary of the ITN use by children less than the age of five years, for the 36 states and the federal capital territory (FCT), Abuja. It shows heterogeneity in various states in the country. Overall the average proportion of children use of ITN in the country is approximately 12% and ranges between 0% in Osun state and FCT, and 25% in Kebbi state. The proportion of ITN use by children under five is relatively very low in all the states of the

southwest region of the country. It ranges between 0% and 11% in Osun and Ogun state, respectively. The south east region shows that Anambra state has highest proportion of use of treated bednet by the children reaching around 16% percent while Abia state has lowest with only 3% of the children using ITN to sleep. In the south-south Bayelsa has the minimum proportion (3%) of children use of ITN while Rivers state, the immediate neighbour has the highest percentage (25%) of usage in this zone. Within the north-central, only Niger state had a little above 20% of children sleeping under ITN while most of other states are having less than 9% of the children to have slept under ITN during the night prior to the survey. Among the states in the northwest Zamfara and Katsina state has very low utilization of ITN by children compare to the other states. The proportion of children that slept under ITN reach at least 20% in most state of the north east with the exception of Bauchi which has slightly lower proportion.

In comparison, the observed malaria prevalence is high in the south west zone with exception of Lagos which has malaria parasitaemia prevalence of about 10%, also Osun state which has 63% parasitaemia prevalence is the highest in this region. In the south east, the observed malaria prevalence is between 14% in Anambra state and 39.8% in Abia state. Among the states in the South- south Edo state has the highest proportion of parasitaemic children which is about 61% while river state has the lowest proportion of malaria infection in this region. The parasitaemia prevalence in most state of the north central zone is high and it ranges between 32 and 66%. Also the states in the northwest zone are generally of high parasitaemic prevalence with only Sokoto having prevalence that is less than 40%. Most states in north east zone have comparatively less malaria prevalence than states in the other zone of the country with the exception of Yobe and Bauchi states that has malaria prevalence above 40%. The analysis shows that, the measure of greenness, NDVI is associated with increased malaria risk, and also higher rainfall has a protective effect on malaria prevalence. The results also show that living in rural area comes with increase risk of malaria infection. In terms of socio-demographic factors, malaria risk is importantly lower among children from the least poor household, and likewise, the odd of malaria infection among the children decreases significantly with the increase level of literacy among mothers. Although the cluster level usage of ITN by the children under five years is negative with malaria risk but this relationship appears not to be important as shown in Table 3.2.

Table 3.1: Summary of observed malaria prevalence and insecticide net use among children by states

States	Number of survey clusters	ITN use by children (%)	Observed malaria prevalence (%)
Lagos	13	2%	10%
Ogun	4	11%	56%
Oyo	8	0.5%	43%
Osun	5	0%	63%
Ondo	5	0.6%	54%
Ekiti	4	8%	40%
Anambra	9	16%	14%
Enugu	8	5%	25%
Imo	10	3%	25%
Abia	7	2%	40%
Ebonyi	6	7%	32%
Edo	6	5%	61%
Delta	8	7%	28%
Bayelsa	4	3%	24%
Rivers	9	25%	20%
Akwa Ibom	8	12%	32%
Cross	5	13%	41%
Kwara	5	2%	59%
Kogi	7	7%	40%
Nasarawa	4	3%	35%
FCT	3	0%	32%
Niger	7	21%	66%
Benue	8	3%	57%
Plateau	6	8%	32%
Sokoto	5	20%	38%
Zamfara	3	4%	67%
Kebbi	3	25%	72%
Kano	10	19%	40%
Katsina	7	3%	52%
Jigawa	4	23%	42%
Kaduna	8	17%	28%
Bauchi	9	19%	44%
Gombe	5	22%	23%
Yobe	5	23%	18%
Borno	9	20%	25%
Adamawa	7	22%	20%
Taraba	5	9%	18%

Table 3.2: Posterior median and 95% Bayesian credible interval (BCI) estimates of ITN use at cluster and state level adjusting for socio-demographic and environmental variables

	Model A	**Model B**
Variables	OR (95% BCI)	OR (95% BCI)
Rainfall	0.84 (0.66, 1.11)	0.77 (0.61, 0.98)
NDVI	1.41 (1.15, 1.75)	1.35 (1.11, 1.65)
Place of residence		
Urban	1	1
Rural	2.27 (1.55, 3.38)	2.36 (1.61, 3.52)
SES		
Most Poor	1	1
Poor	1.12 (0.88, 1.43)	1.11 (0.87, 1.41)
Middle	1.20 (0.91, 1.58)	1.18 (0.90, 1.56)
Richer	1.07 (0.78, 1.47)	1.04 (0.76, 1.41)
Richest	0.64 (0.43, 0.93)	0.60 (0.41, 0.88)
Age categories (Years)		
0-1	1	1
1-2	1.35 (1.06, 1.72)	1.35 (1.06, 1.73)
2-3	1.93 (1.52, 2.46)	1.93 (1.52, 2.45)
3-4	2.25 (1.78, 2.85)	2.25 (1.77, 2.85)
4-5	2.55 (2.02, 3.24)	2.55 (2.02, 3.24)
Literacy level of mother		
Illiterate	1	1
Primary	0.79 (0.64, 0.97)	0.78 (0.64, 0.96)
Secondary	0.78 (0.62, 0.97)	0.77(0.62, 0.96)
Higher	0.37 (0.21, 0.61)	0.36 (0.21, 0.60)
ITN use by childrenU5	0.70 (0.15, 3.77)	
Spatially varying ITN use by childrenU5		0.05(0.004, 0.527)
Spatial Parameters		
Range(km)	32.30 (25.10, 90.27)	22.89 (2.87, 61.12)
Variance	0.76 (0.57, 1.00)	0.85 (0.64, 1.14)

Model A: included ITN use by children at the clusters level

Model B: included ITN use by children as spatially varying at the states level

NDVI: normalized difference vegetation index

SES: socio-economic status

The spatially structured coefficient of intervention estimated from model B allowed the evaluation of the effect of use of ITN at the state level. Figure 3.2 shows the different coverage among the states, and Figure 3.3 depict the effect of this coverage estimated from model B. The result of spatially structured model of malaria risk on children ITN usage, which also adjusted for environmental, and socio-demography factors, shows that increase proportion of children sleeping under net is associated with lower malaria parasitaemia in two neighbouring states Adamawa and Taraba, within northeast region of the country. Likewise, the effect is negative though not significant in most of the other states where the neighbours have comparable level of utilization of ITN by the children.

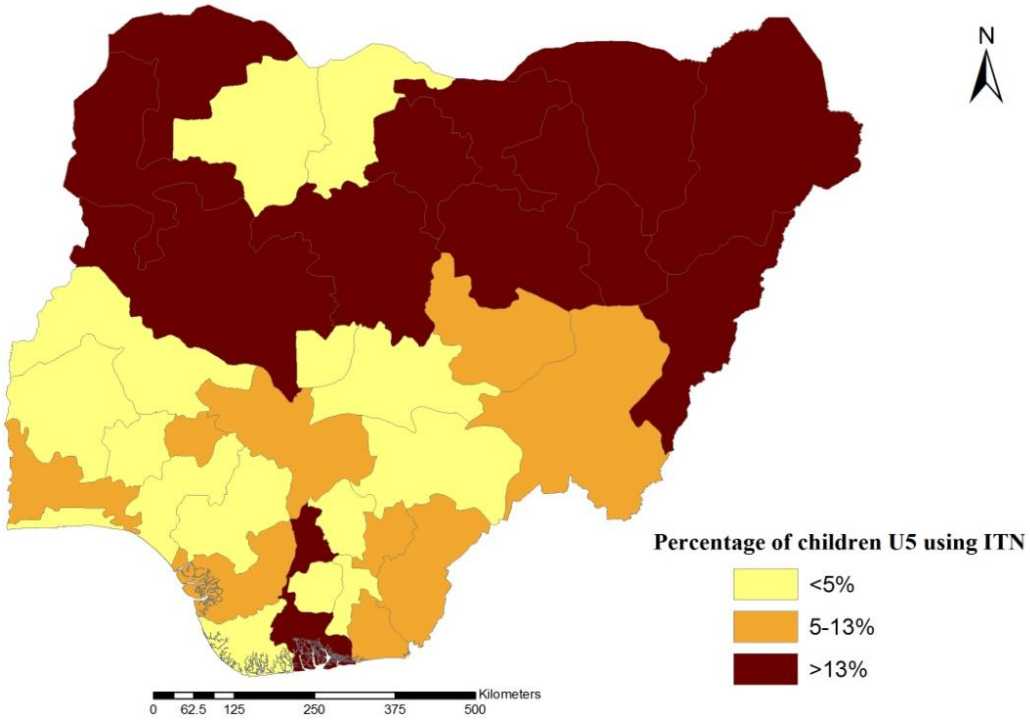

Figure 3.2: Insecticide treated net use by children under five at the state level.

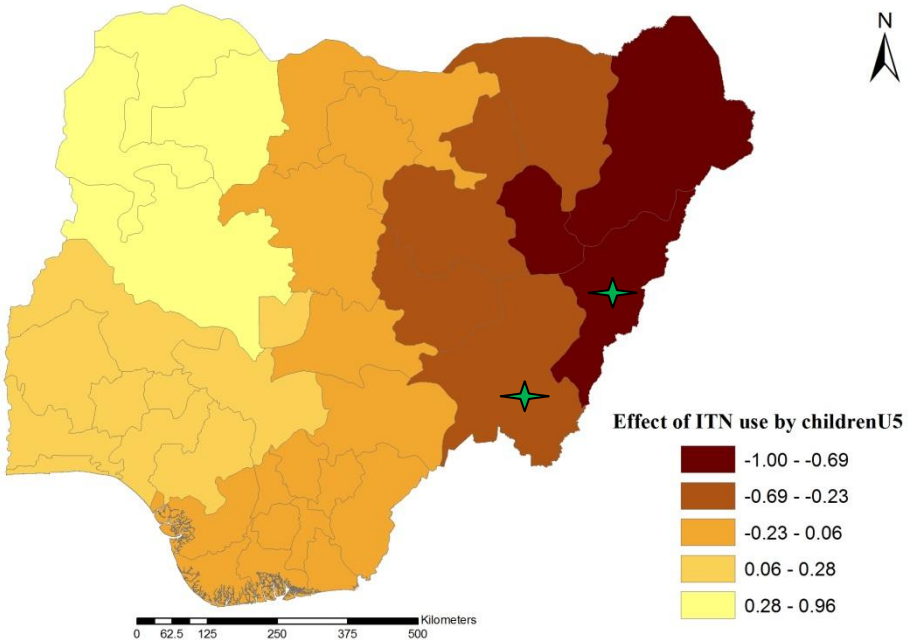

Figure 3.3: Posterior median estimated effect of ITN use intervention.

✦ Important effect.

3.4 Discussion

We have explored the effect of coverage of intervention in space on the distribution of malaria parasitaemia prevalence among children under the age of five in Nigeria. The analysis was carried out at both national and sub-national level because of the fact that systematic underestimate of the true efficacy of ITN may result if community effect is not considered (Hawley et al., 2003). The assumptions in our modelling approach are that effect of intervention in neighbouring areas should be similar, area located further away from each other should have dissimilar effect due to differing level of endemicity, malaria vector resistance and people's protective behaviour varies in space. We assess the effect of intervention in space using the states in the country as our unit of analysis. Environmental and socio-demographic covariates were adjusted for in our model fit.

Nationally, place of residence (urban/rural), household socioeconomic status and mother education is associated with reduced malaria risk and this is in harmony with well known relationship with malaria parasitaemia. Also increase parasitaemia infection found among older children is in concert with documented evidences (Giardina et al., 2012; Gosoniu et al., 2012; Riedel et al., 2010). Contrariwise, ITN use by under five measured at the cluster level seems not to be associated with parasitaemia risk at the country scale, and this may probably be due to the fact that only small proportion of the children do sleeps under treated bednet. Similar result had been obtained in a study which looks at the effect of intervention coverage on changing malaria risk in six countries of sub-Saharan Africa (Giardina et al., 2014) and also in a similar study in Burkina-Faso (Diboulo et al., 2016) .

Our analysis show that intervention effect varies in different zones of the country. In the north-east, intervention coverage is indicative of negative effect in most states within this zone and only become importantly related with malaria risk in two states of this zone. This result confirm the findings by other studies (Barnes et al., 2005; Chizema-Kawesha et al., 2010) from Africa that higher coverage of intervention in areas with relatively low malaria burden is highly effective in malaria transmission reduction. This might explained the reduced malaria risk associated with relatively higher use of treated bednet among children in these two states of the north-east zone. Moreover most states within the region have comparable proportions of ITN use by children which suggest that communal effect of ITN especially when every area has reasonable level of coverage is stronger than individual area effect (Hawley et al., 2003) .

Studies in various part of Africa have also documented similar evidence found this study. For instance, the multi-country analysis (Lim et al., 2011) of ITN coverage and its effect on malaria risk in seven countries in Africa show intervention coverage was related to malaria risk in four of these countries, and the spatial heterogeneity in the relationship was suggested to be probably due to different level of malaria transmission intensity in the various countries. More so, another study (Apinjoh et al., 2015) in Cameroon show that communities with more possession of ITN have reduced risk of parasitaemia in comparison with other community with lower coverage.

The mechanism through which this increase ITN use confers this community effect is by reducing the mosquitoes' population either by affecting their feeding cycle or killing them and thereby reducing the vectorial capacity, and in effect malaria prevalence.

However, similar effect was not found in any of the states that have comparable coverage like states in the north-east. This might be explained by other factors such as endemicity level prior to scale up of ITN use, emergence of resistance to pyrethroid by the malaria vector, variability in vector composition, and the physical condition of bednet especially presence of holes. More so, most of these states where we could not get important effect of ITN coverage on malaria prevalence would pass for an high transmission settings and it has been shown through mathematical model that in high transmission setting, higher coverage and longer time range will be required to achieve similar gains that could be attained in short space of time with moderate coverage in low prevalence areas (Griffin et al., 2010). The indicated spatial variability regarding the effect of ITN use strengthens the suggestion by Giardina et al. 2014 of the needs to evaluate the effect of intervention coverage on malaria risk at sub-national level.

This study provides an important guide that could be use in intervention planning in the country and the derived intervention effect map could serve a strong empirical basis to inform national strategic plans for the control activities. It shows that most of the states in the country are still far from meeting the target of covering the vulnerable group with the essential tool required to alter the transmission level. However our analysis demonstrate that achieving high coverage of intervention could have great impact in reducing the burden of malaria in the country especially when every states high attained the coverage of this high risk group.

The findings in this work show that recent scale up effort in the country is already paying off, and also support the need for aggressive scale up of ITN in most part of the country. Therefore, continued coordinated effort of all stakeholders in the fight against malaria in the country are required, to make sure that ITNs are reaching all the population at risk of malaria in the country. In addition, there may also be the need for mass drug administration especially in the highly endemic states of the country to bring down parasitaemia prevalence in those places. There may also be the need for targeting of some mosquitoes species that the present intervention is least successful, particularly the *An. arabiensis* responsible for significant proportion of malaria infection in the drier part of the north, which feed mostly outdoor, by killing the developing mosquito at source in their larva habitat. More so a study on pyrethroid resistance in Africa anopheline mosquitoes implicated Nigeria to be one of the countries where *An. gambiae*

populations are developing resistance to the insecticides that is being use in the treatment of bed nets /indoor residual spraying (Awolola et al., 2009; Ranson et al., 2011). Therefore, there may be need to incorporate resistance management into control activities and also non-insecticidal methods should be sought wherever practicable.

Acknowledgement

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3.5 Appendix

3.5.1 Model Formulation

At the locations $S = (s_1, s_2, \ldots s_n)^T$ we consider the binary outcome Y_{ij} which takes value 1 or 0 to indicate that child i at the location s_j is found with malaria parasitaemia or not, respectively. A Bayesian logistic regression was used to relate the malaria risk to its predictors, and it is given as: $logit\,(p_{ij}) = \beta_l \boldsymbol{X}_l + w_k(s_j)$. In the formulation p_{ij} denote the parasitaemia risk, β_l represent the vector of regression coefficient and $\boldsymbol{X}_l$ are the set of covariates. $w = w_k(s_1), w_k(s_2), \ldots w_k(s_n)$ accounts for the spatial correlation in malaria risk and it was assume to have a zero mean multivariate normal distribution that is, $w_{jk} \sim N(0, \Sigma_{jk})$. Σ_{jk} represent the variance-covariance matrix and defines the function which shows decay in correlation between any pair of location with distance. We choose the exponential covariance function in this analysis, that is,$\Sigma_{jk} = \sigma^2 \exp(-\rho\, d(s_j, s_k))$, where σ^2 represent the variance of the spatial process, ρ is the smoothing parameter which control the rate of correlation decay with increasing distance.

We carried out the model fit through the implementation of Markov Chain Monte Carlo simulation. The formulation of this hierarchical Bayesian model was completed by specification of prior distributions for the remaining model parameters. Non informative Normal prior distribution were assigned to the intercept and the regression coefficient, that is, $p(\beta_l) \sim N(0, 1000)$. Inverse gamma distribution was chosen for spatial variance (σ^2) that is, $p(\sigma^2) = IG(a, b)$ with the value of a and b specified such that the distribution has mean of 1 and the precision 0.01. Uniform distribution was assumed for the smoothing parameter (ρ) that is, $(\rho) = (-\log(0.05)/d_{max}\ , -log < (0.05)/d_{min})$. Also d_{min} and d_{max} are the minimum (>0) and maximum Euclidean distance between the survey locations.

In order to evaluate the intervention effect at the first administrative level, the model above was adjusted by introducing the conditional autoregressive structure of the coefficients at area level and it was expressed as: $logit\,(p_{ij}) = \beta_l \boldsymbol{X}_l + b_1(s_j')ITN\_use\_U5(s_j') + w_k(s_j)$ where $b_1(s_j')$ represent the intervention effect at the area s_j' . The Conditional Autoregressive (CAR) spatially random term $b_1(s_j')$ was formulated as composed of two parts with a part capturing homogeneity

across the areas and the other one which capture heterogeneity among areas , that is $b_1(s_j')$ =$(b_1^r(s_j') + \varphi_1)$. The conditional prior distribution $b_1^r(s_j') \,|b_1^r(s_i'), j \neq i,\ v \sim N\left(\frac{1}{n_j}\sum_{j\sim i} b_1^r(s_i'), \frac{v}{n_j}\right)$ was assigned to the first part, where n_j represent the number of neighbours for area j and v is the variance, that is inversely proportional to the number of neighbours. Also the prior $\varphi_1 \sim N(0, \frac{1}{\tau_1})$ was assigned to the other independent random part.

Chapter 4 Geostatistical modeling of mortality hazard and malaria prevalence among preschool-aged children in Nigeria

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Abstract

Estimating the association between malaria prevalence and child mortality is very important for assessing the disease burden from routine survey data. We investigated the relationship of malaria endemicity to all-cause mortality across different age strata in children under the age of five years in Nigeria, linking the two most recent national surveys, the Malaria Indicator Survey (MIS) and the Demographic and Health Survey (DHS). Joint, Bayesian piecewise Cox proportional hazard and binomial geo-statistical models were developed to relate mortality to malaria risk and take into account the spatial misalignment in the survey locations. The results reveal that a unit increase in malaria risk on the logit scale is associated with a 25% and 17% increase in mortality hazard among infants of 7-11 months and children respectively. Malaria endemicity was not associated with mortality during infancy at the first six months of life. These findings indicate that routine MIS data can be used to quantify the malaria related mortality and therefore improve estimate of the disease burden.

Keywords: Bayesian; Cox proportional hazard; geostatistical; INLA; malaria parasitaemia; mortality; spatial misalignment.

4.1 Introduction

Malaria continues to be a threat to survival of children under the age of five in many countries of Sub- Saharan Africa. The most recently available statistics shows that 90% of global malaria deaths occur in this region, out of which 78% were among the children under the age of five (World Health Organization, 2014). Also, in another report, it was estimated that 7% of deaths within this age category in malaria endemic countries are caused by the disease (*World Health Statistics 2015.*, 2015). Apart from being a direct cause of death from an overwhelming acute infection presented as severe malaria, the disease predisposes the children to many other causes of illnesses such as severe anaemia and acute respiratory infection which substantially increase the risk of death (Murphy and Breman, 2001). In addition, low birth weight, which is a risk factor of infant mortality especially in the earlier months of life frequently results from malaria infection in pregnancy (Gemperli, 2003; Murphy and Breman, 2001; Steketee et al., 2001).

Malaria prevalence and all-cause mortality in children remains very high in Nigeria. In 2014, The current global statistics has it that the country alone is responsible for 13% of global under five mortality, which represents the highest in Africa (*World Health Statistics 2015.*, 2015). Also, the National Malaria Information Survey (NMIS) showed a malaria prevalence of around 42% for children less than the age of five (National Population Commission (NPC) [Nigeria], 2012). It is therefore very pertinent to assess malaria-related burden on all-cause children deaths.

Various efforts using different approaches have related malaria transmission with all-cause child mortality and obtained contrasting results. A meta- analysis of all-cause mortality and Entomological Inoculation Rates (EIR) data compiled from reviewing published and unpublished literature found a significant increase in mortality rate with elevated EIR among infants but not any clear trend with children aged between 12 and 59 months in sub-Saharan Africa (Smith et al., 2001). A Bayesian geostatistical model linking Demographic and Health Survey (DHS) dataset with Mapping Malaria Risk in Africa (MARA) historical survey data could not find any apparent relationship between malaria endemicity and all cause mortality among children under five in Mali (Gemperli, 2003). However, the MARA database reports data covering different age group of the population across survey locations. Bhattarai et al. (Bhattarai et al., 2007) analysed data from cross-sectional surveys and hospital records of a district in Tanzania and suggested that the deployment of malaria interventions over years had led to the

decline in all-cause mortality. Kleinschmidt and colleagues (Kleinschmidt et al., 2009) in their estimates of the association of malaria interventions on changes in malaria related health in Bioko island indicated that the reduction in parasite prevalence and the increased child survival could be attributed to an increased deployment of control interventions. A meta-analysis of the relation between reported health impact and coverage of malaria control interventions found a decrease in child mortality as a result of scaling malaria control interventions across Africa (Steketee and Campbell, 2010). A predictive model applied on systematically collated data of key predictors of malaria mortality such as Plasmodium *falciparum* prevalence, vector control and first line anti-malaria drug resistance showed that rapid reduction in malaria mortality in Africa could be ascribed to increased deployment of control interventions in the region (Murray et al., 2012). The Malaria Transmission Intensity and Mortality in Africa (MTIMBA) project collected data on EIR, malaria intervention and some demographics characteristics of households across few health demographic surveillance sites (HDSS) that routinely monitor mortality. Results from an analysis of this data from an HDSS in Tanzania (Rumisha et al., 2014) could not establish any important relationship between all-cause mortality and malaria transmission intensity after adjusting for malaria interventions and spatio-temporal variations in transmission.

The present study, further explores the contribution of malaria risk on all-cause under five child mortality, by analyzing the most recent DHS and NMIS data in Nigeria. The surveys were close in time but the locations were not aligned. This necessitates the use of geostatistical survival and binomial logistic models to link the two datasets and also take into account prediction uncertainty of the malaria risk estimated at the mortality location.

4.2 Methods

4.2.1 Children mortality data

All-cause, under-5 mortality data were obtained from the DHS database. The data was generated from a nationally representative household survey carried out between February and June 2013 in Nigeria. Birth histories on 31,482 children at 862 survey locations with relevant information on maternal demographics (education, mother birth date, interview date, preceding birth interval in months), household characteristics (wealth index quintiles, drinking water source, type of toilet facility, number of children age 5 and under in the household) and individual child factors (age in months, birth order number, size of child at birth, place of

delivery gender and vital status) were obtained. The drinking water source and type of toilet facility were further used to derive indicators of improved drinking water source and sanitation respectively based on definitions provided by the WHO/UNICEF joint monitoring programme (JMP) (UNICEF et al., 2006). Preceding birth intervals and mother's age at birth of the indexed child were grouped into categories with cut-offs chosen based on previous studies (Gemperli, 2003; Rutstein, 2005). Likewise, place of delivery and size of child at birth were regrouped into two (homes and health facilities delivery) and three categories (small, average and large) respectively. Rural-urban gridded data extracted from the Global Rural and Urban Mapping Project (http://sedac.ciesin.columbia.edu/) was used to classify the locations as rural/ urban residence.

4.2.2 Malaria prevalence data

The NMIS implemented between October and December in 2010 collected data over 239 locations using the standard MIS survey design. Malaria parasitaemia was diagnosed using blood slide microscopy and a rapid diagnostic test (RDT). In our study we estimated parasitaemia prevalence using the microscopy results.

4.2.3 Environmental data

The associated factor of malaria risk in Nigeria (Adigun et al., 2015), rainfall and normalized difference vegetation indices (NDVI) were obtained from remote sensing data sources. Decadal rainfall estimates at $8\times8km^2$ spatial resolution, extracted from the African Data Dissemination Service (www. earlywarning.usgs.gov/fews) was used to derive annual averages for both the NMIS and predicted locations. Likewise, biweekly NDVI values, measuring vegetation greenness were obtained at 250×250 m^2 resolution from the Moderate resolution imaging spectro-radiometer (MODIS) database (http://reverb.echo.nasa.gov/reverb/) and summarized by their annual averages at the locations.

4.2.4 Statistical analysis

A Bayesian geostatistical Cox model with piecewise log constant baseline hazard (Breslow, 1974) through data expansion and Poisson regression (Holford, 1980; Laird and Olivier, 1981; Martino et al., 2010) was used to assess the relationship of malaria risk with child mortality after adjusting for household socio-demographic and individual child characteristics. Separate analyses were carried out for different age strata (that is, 0-6 months, 7-11 months and 12-59

months). The malaria prevalence was modeled on the logit scale at the mortality locations via a binomial geostatistical logistic regression model using the environmental predictors of malaria that we identified to be important in our previous work (Adigun et al., 2015). We used a joint modeling formulation, where the logit of malaria risk entered as a covariate in the hazard model.. The use of the joint specification allows appropriate incorporation of the malaria prevalence prediction uncertainty. Approximate Bayesian inference was performed using the integrated nested Laplace approximation(INLA) (Rue H. et al., 2009b) and the stochastic partial differential equations(SPDE) (Lindgren and Rue, 2013) approach using the R-INLA package (available at www.r-inla.org) . Further details are provided in the appendix.

4.3 Results

Table 4.1 provides a summary of malaria prevalence and the number of deaths per thousand at the sub-national level among infant and children less than five years. The unadjusted average malaria prevalence ranges between 10% and 72%. The number of deaths per thousand among infant is between 28 and 121 while is between 13 and 137 among older children. The overall mortality rate (not shown) in children under five years old was 128 per 1000 live births and the infant deaths accounted for 70% of the total deaths. Table 4.2 shows that more than half of the total deaths were recorded in households with mothers lacking formal education, and more than 75% of the children deaths occurred in the rural areas. Children under five mortality risk was higher for women with short preceding inter-pregnancy interval than women with longer inter-pregnancy duration (13% vs. 7%, χ^2=149, P<0.05). Fewer deaths were recorded in households with improved socioeconomic status relative to those in the lower asset index quintile. Additionally, 78% and 57% of the households, where these deaths occurred, do not have access to improved drinking water source and sanitation respectively. Overall, the parasitaemia prevalence estimated by microscopy is 42%. Figure 4.1 shows the observed malaria prevalence at the 239 clusters of the MIS and the crude mortality rate at the 862 DHS clusters. Figure 4.2 (A and B) show the scatter plot and linear fit of the observed malaria prevalence and children mortality rate per thousand.

The frequency distribution of different risk factors, as shown in Table 4.2, does not differ between the three age groups. Parameters estimated from the fitted joint Cox model with piecewise log constant baseline hazard and binomial logistic model are shown in Table 4.2. The

posterior median of the hazard ratio shows that the association between malaria risk and infant mortality is not important during the first six months of life (HR=1.02, 95% Bayesian Credible Interval (BCI) : 0.90, 1.15).

Table 4.1: Malaria prevalence, and infant and children mortality per thousand by first states in Nigeria

	Malaria data			**Children mortality data**				
States	No of clusters	Number of Children Screened	Malaria prevalence %	Number of clusters	Number of infants	Number of infant deaths per thousand	Number of older Children	Number of older children deaths per thousand
Abia	7	98	39	23	136	79	345	36
Adamawa	7	141	20	23	284	90	700	55
Akwa-Ibom	8	205	32	24	143	61	400	22
Anambra	9	134	14	22	119	61	353	26
Bauchi	9	250	44	24	381	88	993	137
Bayelsa	4	123	24	22	198	48	563	39
Benue	8	207	57	24	170	80	475	41
Borno	9	146	25	20	116	27	470	39
Cross river	5	121	41	23	138	44	372	37
Delta	8	184	28	24	162	65	496	27
Ebonyi	6	117	32	23	219	87	492	75
Edo	6	132	61	23	145	33	436	23
Ekiti	4	65	40	23	144	44	367	24
Enugu	8	146	25	22	131	74	367	36
FCT, Abuja	3	53	32	23	106	48	380	31
Gombe	5	151	23	23	299	71	820	88
Imo	10	144	25	24	142	80	318	47
Jigawa	4	104	42	24	348	87	1011	116
Kaduna	8	229	28	24	204	41	656	28
Kano	10	289	40	39	574	72	1438	78
Kastina	7	277	52	24	362	60	999	131
Kebbi	3	93	72	22	339	90	767	97
Kogi	7	125	40	24	117	40	351	32
Kwara	5	85	59	23	176	57	488	24
Lagos	13	107	10	40	249	63	668	18
Nasarawa	4	116	35	22	181	64	453	41
Niger	7	180	66	24	211	52	699	28
Ogun	4	45	56	24	134	60	382	20
Ondo	5	79	54	24	175	71	458	43
Osun	5	62	63	24	132	46	415	13
Oyo	8	127	43	24	160	44	491	36
Plateau	6	121	32	23	178	67	468	26
Rivers	9	192	20	24	134	61	384	31
Sokoto	5	168	38	24	362	82	939	115
Taraba	5	96	17	23	336	78	871	63
Yobe	5	123	42	20	245	60	748	74
Zamfara	3	102	67	23	429	121	908	116

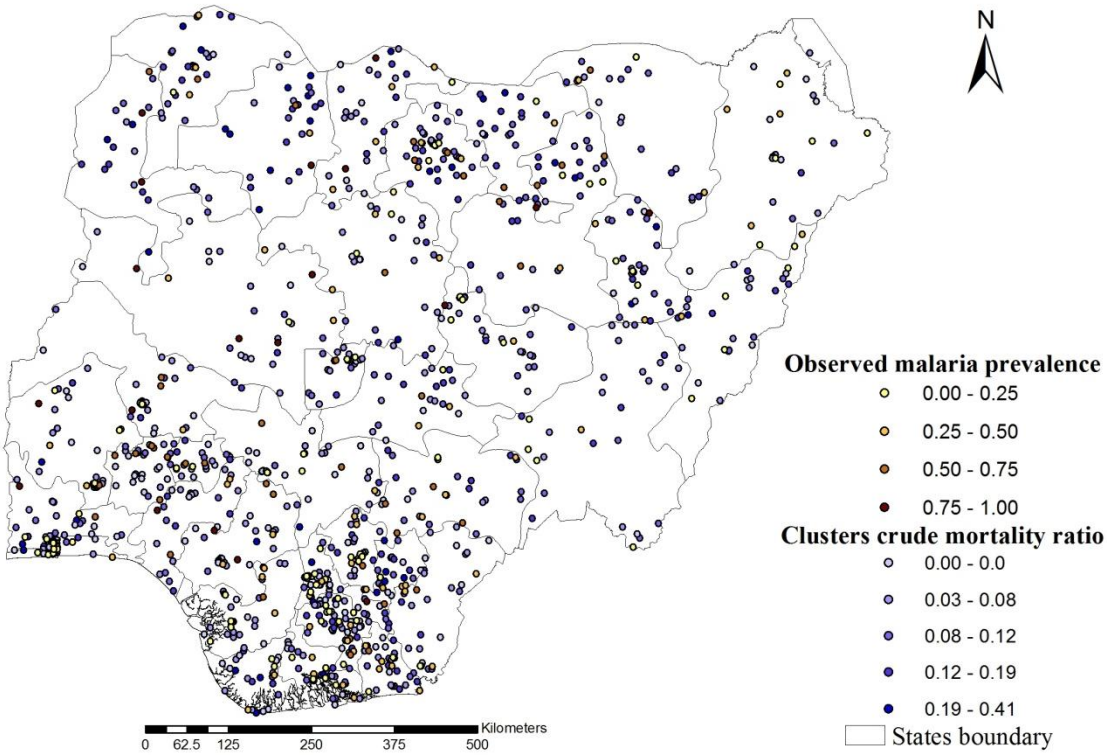

Figure 4.1: Geographical distribution of the observed malaria parasite prevalence and crude mortality ratio

However, infants' 7-11months age experience significantly increased mortality with elevated prevalence of malaria parasitaemia (HR=1.25, 95% BCI: 1.04, 1.50). Moreover, an increase in mortality was associated with an increase in malaria parasite risk among older children (HR=1.02, 95% BCI: 1.17, 1.36). The hazard of mortality is reduced by 62%, 53% and 36% respectively in younger infants, infants aged 7-11 months and children aged 12-59 months for birth intervals of 2 to 5 years and by 69%, 83% and 34% respectively for birth intervals greater than 5years compared to preceding birth interval of less than two years. The mortality hazard rate among children born to mothers with at least secondary education is lower compared to women without formal education. Being female child is associated with important lower mortality rate in

the first six months of life; however this association becomes unimportant with the older children. Having mature mothers in terms of their age at birth is related with lower mortality in infants up to six months old and in children but this relationship becomes not important for older infants (7-11months). Moreover, children and younger infants who were born heavier than average have marked reduced hazard of death, however this association is not important in older infants. Death among younger infants is not related to the socio economic status of the household but the mortality rates are lower for senior infants born in the middle socio economic status households. The mortality hazard for children is lower for household at higher socio-economic level. Rural/ urban disparity appears not to importantly affect the hazard of death among children and infants aged 7-11 months old but living in urban areas significantly reduces the hazard of death among younger infants. Multiple births predispose the children to higher mortality risk. With regards to the number of children under the age of five in the family, the analysis shows that the more the children in the households, the better the survival. Contrariwise, every additional birth into the household predisposes the born child to lower survival across all ages. Improved drinking water source, better sanitation and delivery at health facilities are not associated with child survival. Figures 4.3(A-F) depict the estimated mean of the posterior predictive distribution of spatial random effects and the associated standard deviation in the various age groups.

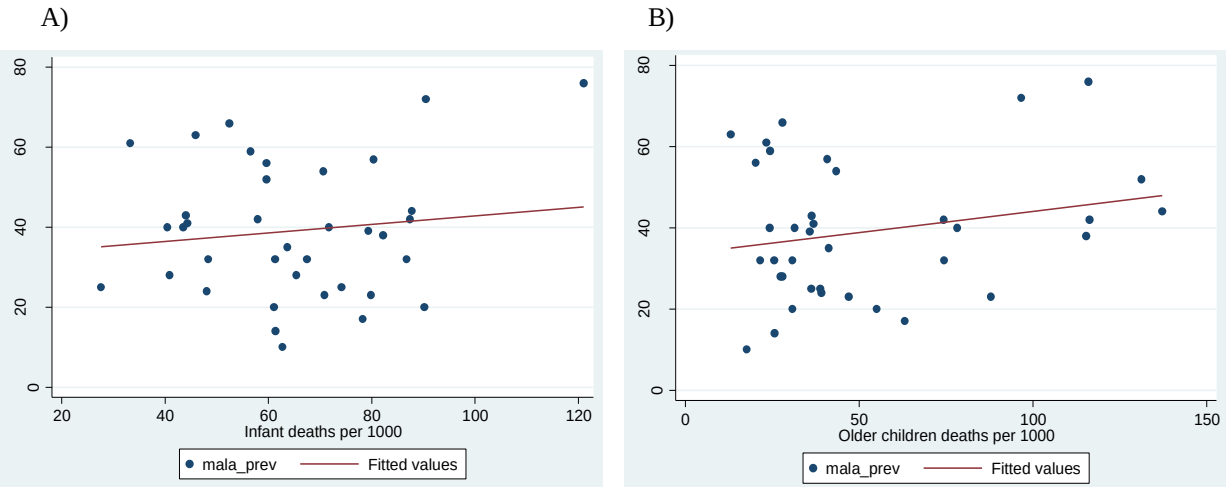

Figure 4.2: Scatter plots and linear fit of the observed malaria prevalence with the number of deaths per 1000 for infant (A) and 12-59months (B)

Table 4.2: Raw data frequency and parameter estimates (posterior median and 95% BCI) of a joint geostatistical Bayesian piecewise constant Cox proportional hazard and binomial logistic model.

Variables	Infants 0-6 months (N=5,099)			Infants 7-11 months (N=2,947)			Children 12-59 months (N=22,381)		
	Freq.(%)	HR	95% BCI	Freq.(%)	HR	95% BCI	Freq.(%)	HR	95% BCI
Malaria Risk (logit scale)		1.02	0.90, 1.15		1.25	1.04, 1.50		1.17	1.02, 1.36
Gender									
Female	51.9	1.00		49.0	1.00		50.6	1.00	
Male	48.1	1.33	1.19 ,1.48	51.0	1.02	0.81, 1.28	49.4	1.13	0.98, 1.30
Place of delivery									
Homes	63.9	1.00		61.5	1.00		63.2	1.00	
Health Facilities	36.1	1.05	0.90, 1.21	38.5	0.82	0.58, 1.16	36.8	0.82	0.65, 1.02
Multiple birth									
Single	93.8	1.00		97.3	1.00		97.1	1.00	
Twin	6.2	9.39	7.62, 11.57	2.7	2.30	1.30, 4.09	2.9	2.14	1.52, 3.00
Size at birth									
Smaller than average	18.8	1.00		14.9	1.00		13.8	1.00	
Average	40.4	0.88	0.76, 1.02	41.0	0.97	0.70, 1.35	41.7	0.85	0.69, 1.03
Bigger than average	40.8	0.71	0.61, 0.83	44.1	0.76	0.54, 1.06	44.5	0.75	0.62, 0.92
Mother Education									
No formal education	47.1	1.00		45.7	1.00		47.2	1.00	
Primary	20.4	1.05	0.90, 1.24	18.3	0.58	0.40, 0.84	20.7	0.92	0.74, 1.14
Secondary	26.7	0.63	0.52, 0.76	30.0	0.40	0.25, 0.63	26.0	0.73	0.55, 0.97
Post Secondary	5.9	0.58	0.41,0.83	5.9	0.60	0.27, 0.63	6.5	0.31	0.14, 0.70
Preceding birth interval									
<2years	17.2	1.00		14.0	1.00		19.3	1.00	
2-5years	54.7	0.38	0.33, 0.44	57.3	0.47	0.36, 0.62	54.7	0.64	0.54, 0.75
>5years	8.0	0.31	0.24, 0.40	7.9	0.17	0.08, 0.37	6.9	0.66	0.46, 0.93
Firstborn	20.1	0.88	0.72, 1.08	20.8	0.54	0.35, 0.84	19.1	0.77	0.59, 1.00
Mother age at birth									
<=19years	10.5	1.00		11.8	1.00		12.5	1.00	
20-29years	49.9	0.58	0.48,0.70	53.1	0.67	0.45, 0.99	51.8	0.70	0.55, 0.88
30-39years	32.7	0.53	0.41,0.68	29.6	0. 61	0.37, 1.04	30.4	0.61	0.44, 0.84
40-49years	7.0	0.52	0.37,0.73	5.5	0.47	0.21, 1.05	5.4	0.62	0.39, 0.98
Socio-Economic Status									
Poorest	22.8	1.00		22.4	1.00		22.4	1.00	
Poorer	25.4	0.96	0.81, 1.13	22.3	0.99	0.73, 1.33	23.3	1.13	0.95, 1.36
Middle	19.9	0.96	0.78, 1.19	20.1	0.53	0.35, 0.80	19.9	0.71	0.55, 0.92
Richer	17.9	1.17	0.91, 1.51	19.1	0.65	0.39, 1.07	18.6	0.70	0.50, 0.97
Richest	14.0	1.12	0.81, 1.55	16.1	0.56	0.27, 1.13	15.8	0.59	0.37, 0.94
Birth order		1.10	1.06, 1.13		1.08	1.01, 1.16		1.07	1.02, 1.15

Continue on next page

	Infants 0-6 months			Infants 7-11 months			Children 12-59 months		
	Freq.(%)	**HR**	**95% BCI**	**Freq.(%)**	**HR**	**95% BCI**	**Freq.(%)**	**HR**	**95% BCI)**
Children less than the age of five									
< = 3	86.8	1.00		87.5	1.00		87.1	1.00	
> 3	13.2	0.27	0.21, 0. 34	12.5	0.45	0.29, 0.67	12.9	0.46	0.36, 0.58
Residence									
Rural	69.2	1.00		67.0	1.00		67.0	1.00	
Urban	30.8	0.76	0.61, 0.93	33.0	1.40	0.98, 2.00	33.0	0.80	0.63, 1.0
Improved Water Source									
No	75.7	1.00		74.7	1.00		74.8	1.00	
Yes	24.3	0.95	0.83, 1.10	25.3	0.96	0.69, 1.32	25.2	0.99	0.82, 1.20
Improved Sanitation									
No	53.8	1.00		50.3	1.00		51.4	1.00	
Yes	46.2	1.05	0.90, 1.21	49.7	1.19	0.90, 1.55	48.6	1.04	0.88, 1.23
Spatial Parameters									
$\sigma^2(\boldsymbol{variance})$		0.64	0.44, 0.95		0.07	0.01, 0.29		0.12	0.05, 0.25
Range (km)		15.56	8.49, 25.88		70.42	18.27, 337.37		165.91	34.26, 890.35

Abbreviations: HR: Hazard Ratio; BCI: Bayesian Credible Interval

These maps indicate the estimates of the geographical variation in the mortality hazard that is not captured by the adopted socio-demographic covariates. They therefore represent the marginal burden of mortality among children under five that may be due to other unmeasured ecological variables. There are striking differences in the maps across the ages especially in the smoothness as we traverse the categories.

The map of early infant life shows very weak smoothness, however, the smoothness improves with the senior infants. These maps avail us the opportunity to identify high mortality hazard areas, specifically in the south-east extending to some part in the south-south and in the northwest as well as some areas in the north-east which share border with Cameroon. Also the map of children shows the region with distinct lower survival that extends from Sokoto State in the northwest region to Gombe including fringes of Borno State in the northeast. More so, in the south, higher mortality hazard is found in the south-eastern states. Estimates of the prediction error illustrate lower uncertainty at those areas of close proximity to the observed mortality data.

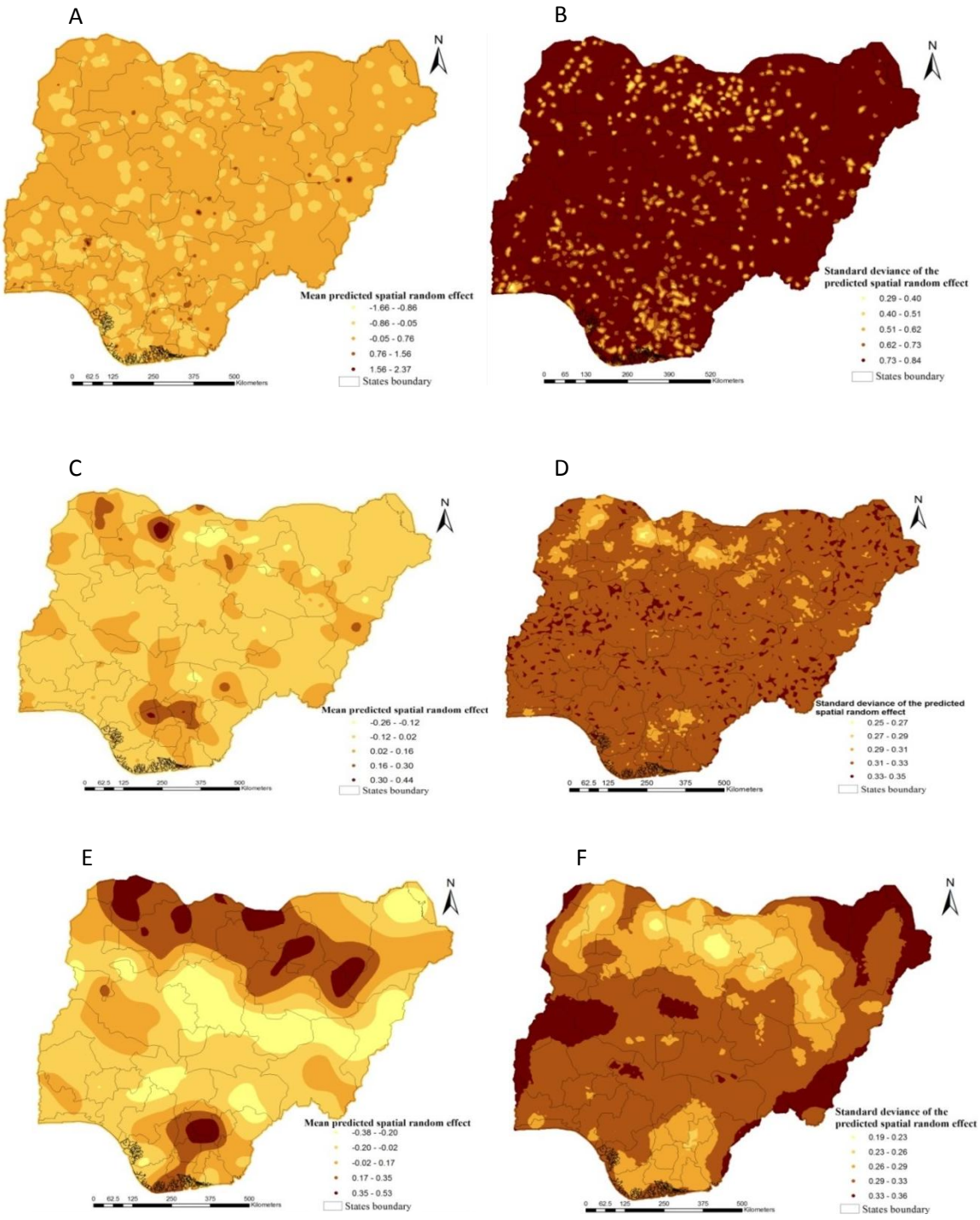

Figure 4.3: Predictive posterior distribution of the spatial random effect: posterior mean (left) and standard deviation (right)

A and B Infants 0-6months

C and D Infants 7-11months

E and F Child 12-59months

4.4 Discussion

The study represents the first effort that linked MIS and DHS data to assess the contribution of malaria parasitaemia prevalence to all-cause mortality across the different age strata in children less than five years. We developed a rigorous Cox model with piecewise log constant baseline hazard geostatistical model which relates mortality to malaria risk, adjusts for socio-demographic and child characteristics and takes care of the spatial misalignment in the datasets. Separate analyses were conducted for infants 0 to 6 months, 7 to 11 months and children to capture the varying relationship with age (Kanté et al., 2014).

Our analysis shows that malaria risk is associated with increased hazard of death among children whose age are at least seven months, after taking into account the individual child and maternal characteristics. The study results also appear to indicate that malaria risk is not related to early infant death in the country. This lack of association between malaria risk and younger infants mortality may be due to the latent transferred immunity and physiologic protection during the earlier months of life (Kazembe et al., 2007). Another reason might be other unmeasured competing risk factors especially birth asphyxia, preterm birth complications and infectious diseases such as pneumonia, sepsis and meningitis (Black et al., 2010; Liu et al., 2012) that could have stronger associations than malaria risk. Nevertheless, we cannot rule out the indirect consequences of malaria on the mortality hazard of this age group mostly known to manifest in low birth weight and preterm delivery which are often associated with maternal malaria in pregnancy (Desai et al., 2007).

The estimated fixed effects of the mortality hazard confirmed well-known factors linked to child mortality. The positive association between lower birth weight and increased risk of death especially in the earlier months of life confirmed previous findings (Akinyemi et al., 2015; Class et al., 2014). In the same vein, mother's education is known to negatively impact child mortality because some appreciable level of educational attainment could probably bring on considerable health awareness, higher purchasing power perhaps through better paid employment and utilization of health facilities which might transform to the improvement in childhood survival (Kanté et al., 2014; Kazembe et al., 2007; Liu et al., 2012). Previous studies (Althabe et al., 2012; Hong, 2006) have also linked multiple births to higher early childhood death especially when the births are pre-termed coupled with low birth weight and birth defects. Moreover urban / rural survival disparities especially among the younger infants might be linked to variation in

the availability of basic medical services and health care provision in which the rural infants are disadvantaged (Jimenez-Soto et al., 2014; Van de Poel et al., 2009). Likewise, lack of survival advantage among the children born in the health facilities compare to those in various homes could be explained by a considerable frequency of high risk deliveries in the health facilities. The reported protective advantage of longer birth spacing on children survival strengthens the existing knowledge on this relationship from previous study (Kozuki and Walker, 2013; Ronsmans, 1996). More so, the findings of higher mortality hazards for younger infants born to teenage mothers is not at variance with existing literature and this has been mostly associated with physiologic immaturity, premature birth complications and lack of experience on caring for newborn (Selemani et al., 2014; Sharma et al., 2008). The non-important association between socio economic status and survival advantage of the younger infants is already reported in literature. At this stage of age, mortality is rather influenced by endogenous factors and less likely by exogenous ones such as the household socio economic status (Sartorius et al., 2010). Nevertheless, the importance of this association among the older age could be due to externally derived factors which the parent can substantially manipulate to reduce the hazards of mortality (Manda, 1999).

The map of spatial random effects reveals the higher foci of unexplained correlation in the mortality which coincides with areas of low uptake of immunization in some parts of the north (data not shown) and that of relatively low consultation of health care provision for the management of childhood illness in some states in the south east and partly south-south. This calls for intensification of health education through various media on the importance of child immunization against the aforementioned vaccine preventable diseases and also on programmes that could improve health care seeking behavior. The study uses mortality data, which is not cause-specific; however, this is the first study showing a relation between malaria endemicity and mortality across different age groups of children under five years old. These results indicate the potentials of using MIS data to estimate the malaria related burden on child mortality.

Acknowledgement

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4.5 Appendix

4.5.1 Mortality model

Let the locations of the observed mortality be $\boldsymbol{s} = (s_1, s_2, \ldots s_L)^t$ and the exposure time that each child j in location s_i lived before death or censored be divided into piecewise continuous k time intervals t_{ijk}. We also consider the death indicator d_{ijk} , where $d_{ijk} = 1$ if the child j dies in interval k and d_{ijk}=0 otherwise. We fitted a piecewise proportional hazards model as if d_{ijk} are independent Poisson observations with means μ_{ijk}=$t_k\lambda_{ijk}$ where λ_{ijk} is the hazard for child j at location s_i in the interval .

We modeled $log(\mu_{ijk}) = log(t_k) + p_0 + \boldsymbol{X}_j^t(s_i)\boldsymbol{\alpha_1} + \beta Z(s_i) + W_i$, where $\log(t_k)$ is the known offset in the model, p_k is the log of baseline hazard at interval k which is assumed piecewise constant that is, $p_k = p_0 = log(\lambda_0)$, $Z(s_i)$ is the malaria prevalence on the logit scale and $\boldsymbol{X}_j(s_i)$ represent row vectors of associated covariates, $\boldsymbol{\alpha_1}$ are the coefficients of the individual specific covariates. β is the coefficient of the malaria prevalence covariate. The spatial correlation was incorporated into the model via location specific spatial random term $\boldsymbol{w} = (w_1,\ldots, w_L)$ where W_i= log w_i . $\boldsymbol{w}$ is assumed to arise from multivariate Gaussian that is, $\boldsymbol{w} \sim MVN(0, \Sigma)$ with Matérn covariance matrix Σ_{ij}=$\sigma_w^2\left(\kappa d_{ij}\right)^v K_v(\kappa d_{ij})/(\Gamma(v)2^{1-v})$. σ_w^2 represent the spatial process variance, v is the smoothing parameter with the value fixed to 1 in this application, κ is the scaling parameter, K_v is the modified Bessel function of second kind and order v, d_{ij} is the Euclidean distance between two locations i and j, The spatial range ρ =$\sqrt{8}/\kappa$ is the distance in which correlation become negligible (<0.1).

4.5.2 Malaria prevalence model and prediction at mortality locations

We assume $\boldsymbol{s}' = (s_1', s_2', \ldots, s_k')$ are the locations with observed malaria data different from observed mortality locations. Also let Y_i and N_i be the number found with malaria parasite and number examined respectively at location s_i'. Y_i is typically assumed to have come from binomial distribution with probability p_i at location s_i' that is $Y_i \sim Bn(N_i, p_i)$. The relation between $\boldsymbol{p}(s_i')$ and $\boldsymbol{\phi}(s_i')$, the vectors of location specific environmental/climatic covariates is modeled through $logit(p(s_i')) = \boldsymbol{\alpha}\phi^{\boldsymbol{t}}(s_i') + u(s_i')$ where u_i is the spatial random effect which is assumed to

arise from a multivariate Gaussian process as specified in the mortality model that is $u(s_i') \sim MVN(0, \Sigma_{u'})$,where $(\Sigma_{u'})_{i',j'}=\sigma_u^2\left(\kappa d_{i',j'}\right)^{v} K_v(\kappa d_{i',j'})/(\Gamma(v)2^{1-v})$.

Let $\phi(\boldsymbol{s}) =(\phi(\boldsymbol{s_1}), \phi(\boldsymbol{s_2}), \dots, \phi(\boldsymbol{s_L}))^{\boldsymbol{t}}$ be the malaria environmental covariates at the mortality location. The predicted malaria prevalence $Z(\boldsymbol{s}) = \left(Z(s_1), Z(s_2), \dots, Z(s_L)\right)^t$ at the mortality location conditional on $u(\boldsymbol{s}')= (u(s_1'), u(s_2'), \dots, u(s_K'))^t$ and on the covariance parameters of the malaria spatial process at those locations could be written as $Z(s_i)=\phi^t(s_i)\boldsymbol{\alpha} + w_i$ where w_i is a vector of the predicted malaria random effects at the mortality locations s_i . To complete the Bayesian model specification, we adopt priors for the models parameter. We specify non informative Gaussian distribution priors for regression coefficients, that is $\boldsymbol{\alpha_1}$ $\boldsymbol{\alpha}$ and $\beta \sim N(0, 1000)$, log-normal priors were used for hyperparameters κ and τ_w that is log $(\kappa) \sim lognormal(0,100)$ and log $(\tau_w) \sim lognormal(0,100)$, with $\sigma_w^2 = 1/(4\pi\kappa^2\tau_w^2)$ and $\rho = \sqrt{8}/\kappa$.

Chapter 5 Geostatistical analysis of anaemia risk factors among preschool-aged children in Nigeria

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This paper is going to be submitted to *Parasites and vectors.*

Abstract

Background: Anaemia burden in Nigeria among children under five year of age is high, but the contribution of various risk factors is not fully understood. Also, estimates at high spatial resolution appropriate for control are non- existing. We aimed to provide the model based estimate of anaemia risk and the number of anaemic children per state.

Methods: We implemented hierarchical Bayesian measurement error model, using the nationally representative malaria burden dataset, the predicted estimates (on logit scale) of soil transmitted helminth, Schistosoma, and nutritional indicators, to determine associated anaemia risk factor and generate high resolution map of haemoglobin level and anaemia risk.

Findings: The analysis reveals that exposure to increase prevalence of Ascaris lumbricoides is associated with increase anaemia risk. It also shows that malaria infection and relatively low socio-economic status predisposes the children to elevated anaemia risk. More so, the population adjusted prevalence of anaemia in the country is approximately 64% (95% Bayesian Credible Interval 47 to 79), and the estimated number of anaemic children is around 17 million (95% Bayesian Credible Interval: 12 to 21 million). Adamawa state in the northeast has the lowest population adjusted prevalence, which is 46.9% (95% Bayesian Credible Interval: 26.8, 67.5), and Jigawa state in the northwest with population adjusted estimate of 84.8% (95% Bayesian Credible Interval: 69.7, 93.1) was the highest.

Conclusion: We provide estimates of spatial distribution of anaemia risk, contributing factors, and number of children affected, which can help programme managers in proficient allocation of interventions.

5.1 Introduction

Globally, anaemia represents a public health problem (McLean et al., 2009). About a quarter (1.62 billion) of the world population is at risk, importantly the children under five and pregnant women are susceptible to higher risk (Balarajan et al., 2011). The recent world health organization(WHO) reports estimated that about two-third (67.6%) of children under five years of age, and around 57.1% pregnant women are anaemic in Sub-Saharan Africa (Balarajan et al., 2011; De Benoist et al., 2008). Anaemia in the early childhood especially during the age between birth and the first 59 months of life could have an unfavorable long term effects. Anaemia is being implicated in increased susceptibility to infection, defective cognitive development, retarded growth and increased mortality among the preschool and school-going age children (Crawley, 2004b; Kassebaum et al., 2014b; Soares Magalhães and Clements, 2011).

As it is with many public health problem, anaemia has been well reported to be of multi-factorial aetiology which are often interrelated (Balarajan et al., 2011; Brooker et al., 1999; Schellenberg et al., 2003), and the contributory factors stratifies into infectious, and non-infectious causes. Infectious causes include malaria, intestinal helminth and HIV/AIDS while the non-infectious causes comprise nutritional deficiency (iron, vitamin A, vitamin C, vitamin B12 and folic acid), and genetic characteristics (heamoglobinopathies and thalassaemias) (Balarajan et al., 2011; Brooker et al., 1999; Crawley, 2004b).

Anaemia control is often targeted on its aetiology. For instance, improvement of dietary intake, food fortification, supplement with iron and other essential micronutrients are being advocated for nutritional deficiency anaemia (Crawley, 2004b; Soares Magalhães and Clements, 2011). Also, the control strategies for malaria promotes the application of proven measures discussed elsewhere (Balarajan et al., 2011; Crawley, 2004b; Soares Magalhães and Clements, 2011), which has noticeably contributed to the reduced burden of the diseases, and in effect anaemia. Likewise, quarterly deworming of the vulnerable group is the recommended strategy, in area of higher prevalence of intestinal helminthes. Also, a study in West Africa (Soares Magalhães and Clements, 2011) suggested that control of infectious diseases such malaria and intestinal helminthes, and given of micronutrient supplements to the people in high risk area could contribute to reduction in anaemia burden.

Nigeria, one of the country in the sub-Sahara Africa with high burden of anaemia (De Benoist et al., 2008), is also having high malaria parasitaemia prevalence (World Health Organization et al., 2015a). Furthermore, intestinal helminthes still represent public health problem in the country (Lai et al., 2015; Oluwole et al., 2015). Moreover, malnutrition prevalence among children under five years extracted from nationally representative surveys (DHS 2008 and 2013) is shown to range between 3 and 31 % in the country. More so, the country bears the greatest burden of sickle cell disorder in sub-Saharan Africa. The carrier prevalence is between 20 and 30%, while the disease prevalence is between 2 to 3% in the populace (Adewoyin, 2015).

However, no study has looked at the relationships of anaemia with malaria, malnutrition, STH, and Schistosoma among children under the age of five years in Nigeria. Also, high resolution estimates depicting the geographical variation of anaemia risk, and the number of children affected in the country is not available.

Gayawan et al. (Gayawan et al., 2014) used the national malaria information survey (NMIS) (National Population Commission (NPC) [Nigeria], 2012) data, to examine the socio-demographic factors associated with haemoglobin concentration and anaemia risk. Fever within two weeks prior to the survey was use as proxy of malaria infection in their analysis, and they generated residual spatial variation estimates of anaemia risk among children under five years, at the first administrative level in the country. More so, another attempt (Adebayo et al., 2016) employed the same data, to study the influence of socio-demographic factors on malaria and anaemia risk among children under five years of age in Nigeria. However, exposure to Schistosoma/helminth parasite which may contribute to increase anaemia risk was not considered in any of this study. More so, while the residual spatial variation estimates derived from their analyses could be employ for control activities, a finer resolution estimate will improve better targeting of area with high anaemia prevalence, due to high heterogeneity in the risk that might exist within the first administrative level.

In this study, we aimed to assess the infectious determinants, socio-demographic, and malnutrition correlates of haemoglobin concentration and anaemia risk, in addition, predict the spatial distribution of anaemia risk, and mean haemoglobin concentration, and as well provide estimates of number of anaemic children under the age of five years per state in the country.

We made use of the assembled malaria burden information, which includes haemoglobin concentration and socio-demographic characteristics derived from the NMIS, the Kriged malnutrition proxy from the demographic and health survey, and the distribution of risk surfaces of Schistosoma and soil transmitted helminthes obtained from geostatistical analysis of Nigeria data (Lai et al., 2015; Oluwole et al., 2015). Because of misalignment in the datasets, we implemented hierarchical Bayesian classical measurement error model, in relating the haemoglobin concentration and anaemia risk to the socio-demographic characteristics, malaria parasitaemia, and the risk surfaces of the ecological factors (intestinal helminth, and malnutrition proxy), to account for uncertainties in the employed ecological covariates.

5.2 Methods

5.2.1 Data sources

Haemoglobin concentration, malaria parasitaemia, and socio-economic data were obtained from the Nigeria 2010 Malaria Indicator Survey (MIS) (National Population Commission (NPC) [Nigeria], 2012) which was carried out at 239 locations across the country. The survey used the hemocue blood haemoglobin test to assess the haemoglobin level in the capillary blood sample obtained by heel prick of the children. The malaria infection data we extracted were based on the microscopy test. We used as a socio-economic proxy, the household asset index which was available in the MIS. Estimates of *S. mansoni* and *S. haematobium*, hookworm, *Trichuris Trichiura* and *Ascaris lumbricoides* risk at a given location were extracted from disease risk surfaces obtained from geostatistical analyses described in (Oluwole et al., 2015) and (Lai et al., 2015). Information on age, weight and height was extracted from the Demographic Health Surveys (DHS) of 2003, 2008 and 2013 and used to generate nutritional indices (z-score of weight adjusted for age (WAZ), an indicator of underweight; z-score of weight adjusted for height (WHZ), an indicator of wasting; and z-score of height adjusted for age (HAZ), an indicator of stunting). The anthropometric z-scores were calculated in Stata 12.1 software (Statacorp.) using the zscore06 module which is based on the 2006 WHO child growth standards (Onis, 2006; Weltgesundheitsorganisation et al., 2006). The population proportion of children younger than the age of five and the gridded human population per $100m \times 100m$ spatial resolution for the year 2010 were obtained from the international database of United States census bureau (https://www.census.gov/population/international/data/idb/region.php) and the

Worldpop database respectively (www.worldpop.org.uk). The gridded human population data was aggregated to the pixel size of the predicted anaemia prevalence using the aggregate module of spatial analyst extension in ArcGIS 10.2.1. Information on the type of geographical location (i.e. urban/rural) was based on extracted gridded data from Global and Urban Rural Mapping Project (http://sedac.ciesin.columbia.edu/data/collection/grump-v1).

5.2.2 Geostatistical modelling

Bayesian geostatistical models were fitted on the haemoglobin concentration and anaemia status of each child. The included predictors are individual level information on demographic characteristics (i.e. age, gender) and Malaria parasitaemia status, household socio-economic status, and location type, as well as estimates of malnutrition, hookworm, *Ascaris lumbricoides*, *Trichuris Trichiura*, *Schistosoma mansoni* and *Schistosoma hematobium* prevalence at the cluster level of geographical location. Apart from the location type data, other location level information were misaligned (i.e. available at different set of locations) than the outcome data. To address the misalignment, a joint modelling formulation was considered between a geostatistical Gaussian model of hemoglogin outcome and geostatistical binomial models for the prevalence-type predictors at the misaligned locations. These formulations allowed geostatistical binomial models to be fitted on the predictors and then use their predictions at the outcome locations as covariates with measurement error. The spatial correlation in the data was modeled using isotropic Matern covariance correlation function of distance between two points.

Approximate Bayesian inference was performed using the integrated nested Laplace approximation(INLA) and the stochastic partial differential equations(SPDE) (Lindgren and Rue, 2013) approach implemented in the R-INLA package (available at www.r-inla.org). Supplementary Appendix provides comprehensive model formulation.

Children were classified as either anaemic or not based on the available altitude adjusted continuous haemoglobin concentration level. Specifically, a child was defined as being anaemic when the Hb level is less than 11g/dl.

The models were employed to predict the haemoglobin concentration and anaemia risk on a $2 \times 2km^2$ grid of 229123 pixels covering the country. The predicted anaemia risk surface was spatially joined with the population of children less than five years of derived from the gridded population density and the census based population proportion to calculate the population adjusted prevalence.

5.2.3 Model Validation

The model was fitted on a random subset of around 85% of the locations and the predictive performance was assessed using the hold out dataset by calculating the Mean Absolute Error (MAE) applying $\frac{1}{N}\sum_{k=1}^{N}|\gamma_k - \hat{\gamma}_k|$, where γ_k and $\hat{\gamma}_k$ respectively indicates the observed and median of the posterior distribution of anaemia prevalence at the test location k. In addition, the proportion of observations being correctly predicted within the 95% Bayesian credible intervals (BCI) of the posterior predictive distribution was also calculated.

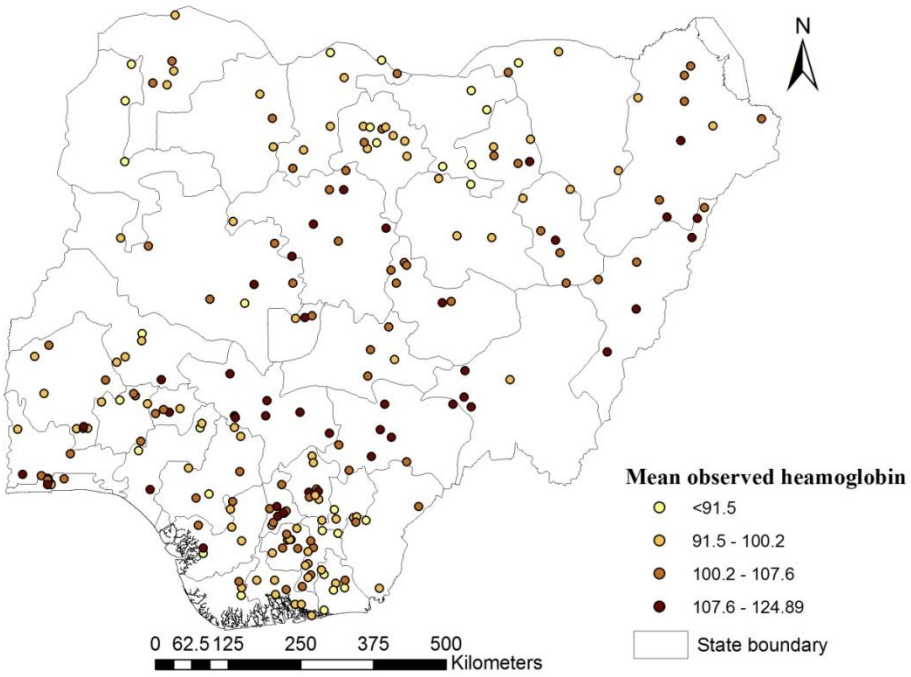

Figure 5.1: The spatial distribution of the observed mean haemoglobin concentration

5.3 Results

5.3.1 Descriptive analysis

The dataset analysed has complete information on 4597 children within 227 surveyed clusters, which include individual characteristics (haemoglobin measurements, malaria parasitaemia, demographic and socio-economic factors) and the model based estimates of STH, Schistosoma and malnutrition proxy. The spatial distribution of the observed clusters mean heamoglobin is depicted in Figure 5.1. The mean altitude adjusted haemoglobin concentration among the study population was estimated to be 9.96 g/dl (95% CI: 9.92, 10.01). Overall, 71% of

the children had some degree of anaemia that further stratifies into 4.52% severe, 41.61% moderate, and 29.12% mild condition, based on WHO cut-off classification for defining anaemia. The model based prevalence of hookworm, Ascaris lumbricoides, and Trichuris Trichuria was 7% (CI: 1 - 23%), 4% (CI: 0.1 - 75%), and 0.1% (0.01 - 1%), respectively. Likewise, estimated prevalence of Schistosoma heamatobium and Schistosoma mansoni was 14% (0.02 - 53%) and 1.3% (CI: 0.01 - 33%), respectively. Also, the estimated malnutrition prevalence among children under the age of five was 9.3% (2.7- 31%).

5.3.2 Bayesian hierarchical regression model of haemoglobin concentration with measurement error

The result of Geostatistical Bayesian regression model of haemoglobin level is presented in Table 5.1. Haemoglobin concentration level has important relationship with all the individual level covariates considered in the model. Specifically, our analysis indicates that testing positive to malaria parasitaemia decreases mean haemoglobin concentration level to about 0.80 g/dl (95% CI: 0.67, 0.86). Likewise being a male child is associated with reduced haemoglobin level of 0.17 g/dl (95% CI: 0.08, 0.26) compare to their female counterpart. Also, the analysis indicates that children mean haemoglobin level gets enhanced with increase age. Likewise, the result demonstrated that children mean haemoglobin level gets better with improved living conditions in the household.

Surprisingly, exposure to different prevalence of STH and Schistosoma appears not to have an important relationship with disparity in haemoglobin levels among the children. In the same way variation in malnutrition risk does not suggest association with heterogeneity in haemoglobin level among the study population.

We obtained the MAE value of 4.76 for the mean haemoglobin model validation, based on 15% subset of the locations; also, about 65% of the observed mean haemoglobin concentrations are contained in the 95% BCI of the predictive distribution of the estimated haemoglobin.

Table 5. 1: Parameter estimates of the model of haemoglobin concentration

Variable	Median	95% Bayesian credible interval
Intercept	107.65	(104.27, 111.02)
Gender		
Male(versus Female)	-1.71	(-2.67, -0.82)
Age in months	0.22	(0.19, 0.25)
Malaria Infection		
Infected(Not Infected)	-7.56	(-8.59, -6.53)
SES Quintiles(versus least poor)		
Less poor	-3.26	(-4.82, -1.69)
Middle	-4.79	(-6.60, - 2.99)
Poorer	-4.81	(-6.82, -2.79)
poorest	-5.16	(-7.40, -2.93)
Schistosoma Hematobium risk	-1.06	(-3.15, 1.01)
Schistosoma Mansoni risk	-0.70	(-2.82, 1.73)
Hookworm risk	-0.18	(-2.40, 2.15)
Ascaris lumbricoides risk	-1.10	(-2.80, 0.78)
Trichuris Trichiura risk	1.12	(-1.11, 3.34)
Malnutrition risk	1.23	(-0.98, 3.58)
Spatial random effect		
Range(km)	145.33	(84.93, 235.69)
Variance	44.42	(27.83, 64.79)

Figure 5.2 (a) and (b) shows the map of posterior predicted mean haemoglobin level and standard deviation of the predicted error generated from the model with wealth-index estimates and malaria risk, which are covariates shown to be importantly related to the haemoglobin concentration among the children.

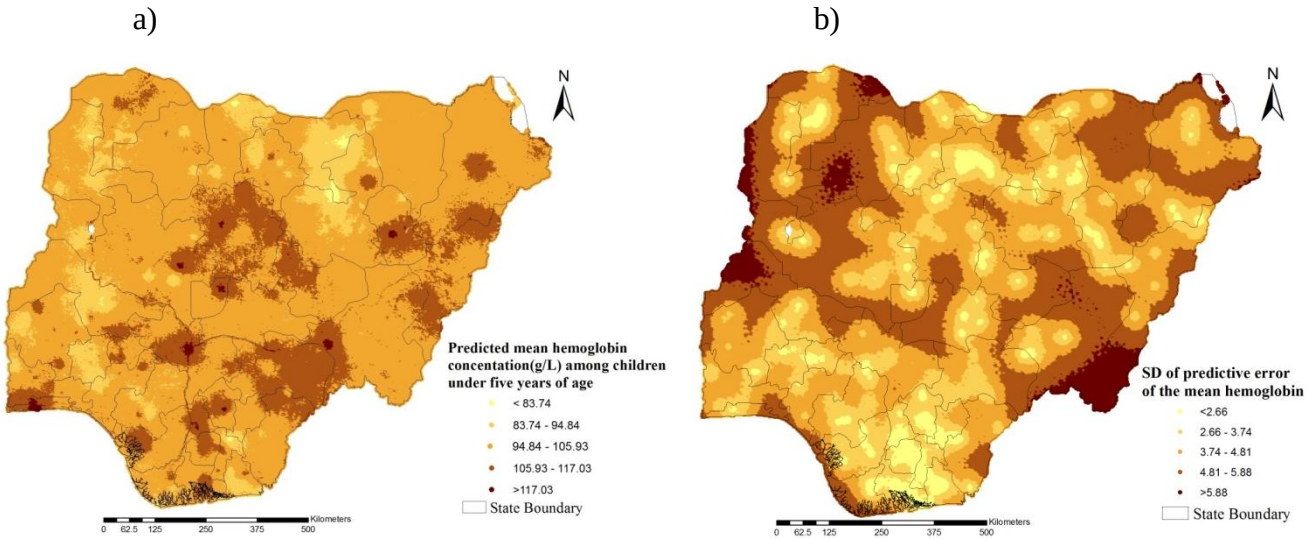

Figure 5.2: Estimates of the geographical distribution of mean haemoglobin level (a), and standard deviation of the predictive error (b).

5.3.3 Bayesian logistic measurement error model of anaemia risk

Table 5.2 presents the hierarchical Bayesian logistic measurement error model of anaemia risk. It shows that all the individual level covariates are importantly associated with the risk of anaemia. Malaria infection and socio-economic status are positively related to increase anaemia risk. Conversely, our analysis reveals that decreasing anaemia risk was associated with increasing age. We also noted that the risk of anaemia among the male children is higher than their female counterpart. With respect to the ecological covariates, only exposure to increase Ascaris lumbricoides risk is associated with increase prevalence of anaemia. However, heterogeneity in the risk surfaces of the other soil transmitted helminth and Schistosoma covariates appear not to have important relationship with anaemia risk. More so, the range of spatial correlation distances of the anaemia risk covers between 81.0km and 234.0km.

Table 5. 2: Parameter estimates of the logistic model of anaemia risk

Variable	Coefficients	95% Bayesian Credible Interval
Intercept	-0.146	(-0.547, 0.255)
Gender		
Female	-	
Male	0.286	(0.137, 0.426)
Age in months	-0.028	(-0.033, -0.024)
Malaria Infection		
Not Infected	-	
Infected	0.978	(0.811, 1.145)
Wealth Quintiles		
Least Poor	-	
Less poor	0.436	(0.210, 0.661)
Middle	0.634	(0.381, 0.894)
Poorer	0.630	(0.347, 0.914)
Poorest	0.690	(0.382, 0.997)
Schistosoma Hematobium risk	0.146	(-0.151, 0.380)
Schistosoma Mansoni risk	-0.308	(-0.575, 0.064)
Hookworm risk	0.129	(-0.133, 0.523)
Ascaris lumbricoides risk	0.287	(0.040, 0.514)
Trichuris Trichiura risk	0.126	(-0.070, 0.301)
Malnutrition	0.081	(-0.113, 0.232)
Spatial random effects		
Range(km)	144.75	(104.20, 202.28)
Variance	0.31	(0.21, 0.50)

The model validation based on 15% of the survey locations resulted in MAE of 0.10. Also it reveals that around two-third (71%) of the of the observed anaemia prevalence were appropriately estimated within 95% BCI of the predicted posterior distribution of anaemia.

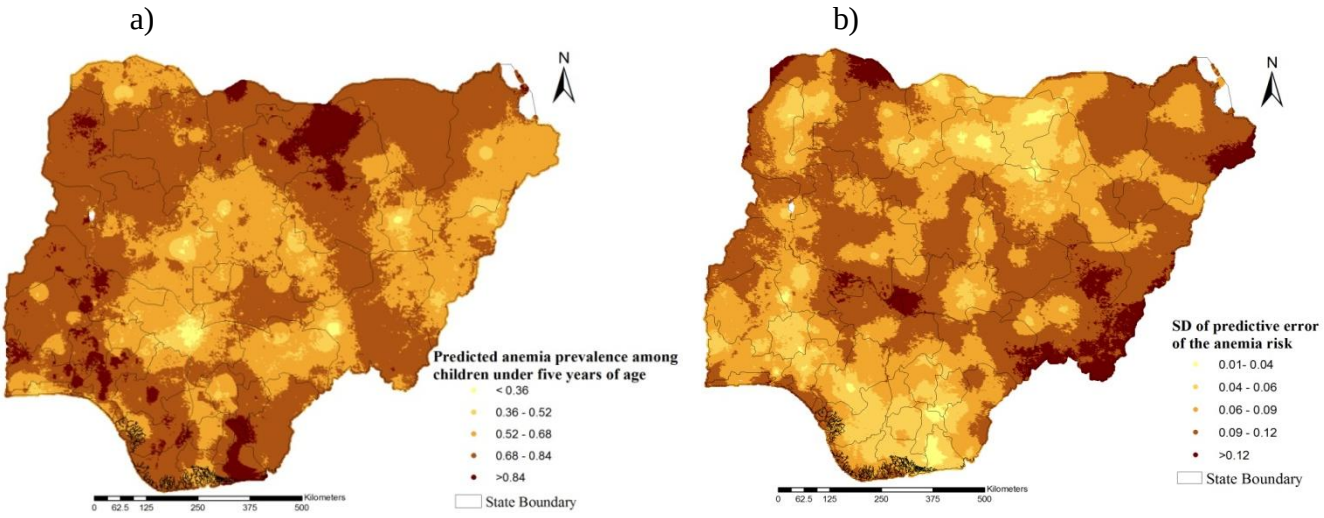

Figure 5.3: Estimates of the geographical distribution of anemia risk (a), and standard deviation of the predictive error (b).

The map of anaemia risk estimates as shown in Figure 5.3(a) reveals that prevalence is high in the entire country with extended higher risk cluster in the most part of Jigawa, some part of Kebbi and Kano in the Northwest , central part of Kwara in the North central. In the Southwest elongated foci of higher predicted risk were found in Osun, Ondo, and Ogun States. In the Southernmost part of country, Akwa-Ibom has the larger foci of higher risk.

Moreover, the population adjusted predicted estimate of the anaemia stratified by state is presented in Table 5.3. The estimated population adjusted median anaemia risk varies between 47% (95% BCI: 27, 68) in Adamawa State to 85% (95% CI: 70, 93) in Jigawa State. Overall, there are about 17 million children under the age of five (95% BCI: 12, 21) that are anaemic, in the country.

Table 5. 3: Population Adjusted prevalence of anaemia risk and the number of anaemic children.

States	Children Population	Number Anaemic (95% BCI)	Population adjusted prevalence (95%BCI)
Abia	541743	406997 (341583, 457322)	0.75 (0.63, 0.84)
Adamawa	525969	246608 (140840, 355088)	0.47 (0.27, 0.68)
Akwa-Ibom	713030	589458 (507753, 644401)	0.83 (0.71, 0.90)
Anambra	777794	458974 (352566, 557050)	0.59 (0.45, 0.72)
Bauchi	883761	588060 (427456, 715830)	0.67 (0.48, 0.81)
Bayelsa	312545	238927 (183175, 274625)	0.76 (0.59, 0.88)
Benue	804607	442624 (281805, 593741)	0.55 (0.35, 0.74)
Borno	744032	390739 (223833, 545863)	0.53 (0.30, 0.73)
Cross-River	550349	397641 (299189, 469824)	0.72 (0.54, 0.85)
Delta	766769	526169 (408142, 619833)	0.69 (0.53, 0.81)
Ebonyi	394455	292807 (234447, 335977)	0.74 (0.59, 0.85)
Edo	653789	476174 (377235, 551814)	0.73 (0.58, 0.84)
Ekiti	425077	244764 (177976, 306159)	0.58 (0.42, 0.72)
Enugu	597748	374963 (293293, 446646)	0.63 (0.49, 0.75)
FCT	242101	129795 (83663, 1736630)	0.54 (0.35, 0.72)
Gombe	474525	226028 (144987, 306658)	0.48 (0.31, 0.65)
Imo	725800	507076 (422467, 577397)	0.70 (0.58, 0.80)
Jigawa	824515	698959 (574441, 767510)	0.85 (0.70, 0.93)
Kaduna	1135155	588644 (377160, 789271)	0.52 (0.33, 0.70)
Kano	1748004	1268813(102612, 1454044)	0.73(0.59, 0.83)
Katsina	1076591	806165 (621841, 933152)	0.75 (0.58, 0.87)
Kebbi	632264	494812 (353157, 575720)	0.78 (0.56, 0.91)
Kogi	634682	309438 (191677, 425389)	0.49 (0.30, 0.67)
Kwara	456922	304940 (206135, 378913)	0.67(0.45, 0.83)
Lagos	1883622	905553 (607499, 1209897)	0.48 (0.32,0.64)
Nassarawa	354094	221757(149472, 281527)	0.63(0.42, 0.80)
Niger	729654	434941 (278050, 562663)	0.60(0.38, 0.77)
Ogun	670347	414118 (282360, 524360)	0.62(0.42, 0.78)
Ondo	622839	443066 (327524, 528188)	0.71(0.53, 0.85)
Osun	730224	477923 (354801, 580574)	0.65 (0.48, 0.80)
Oyo	1134624	711672 (516417, 875548)	0.63(0.46, 0.77)
Plateau	597910	292356 (175026, 405622)	0.49(0.29, 0.68)
Rivers	881090	618099 (501286, 712842)	0.70 (0.57, 0.81)
Sokoto	675491	458480 (322192, 558022)	0.68 (0.48, 0.83)
Taraba	425162	225755(118521, 319910)	0.53 (0.28, 0.75)
Yobe	437165	295997 (196731, 367846)	0.68(0.45, 0.84)
Zamfara	602236	440149 (304070, 527735)	0.73 (0.50, 0.88)

5.4 Discussion

We have conducted an analysis of the contribution of individual, household, and cluster level factors on the mean haemoglobin concentration and anaemia risk among children less than five years of age in Nigeria, through the implementation of rigorous geostatistical hierarchical Bayesian measurement error model. The modelling approach adopted in our analysis accounted for uncertainties in the covariates obtained at the cluster level. The method was chosen because of the fact that if measurement error in the ecological effects are disregarded, important effect of the covariates measured either with or without uncertainty may not be detected (Muff et al., 2015). More so, we estimated the model based finer resolution anaemia risk and haemoglobin concentration, and as well calculated population adjusted prevalence, which we aggregated to produce estimates for the states in the country. The estimated prevalence shows that anaemia is still a severe public health problem in the country, according to World Health Organization grouping of anaemia prevalence.

The spatial analysis reveals that malaria infection plays a very pivotal role in the increased prevalence of anaemia. The relation between malaria parasitemia with reduced Hb level/anaemia risk is well documented (Foote et al., 2013; Glinz et al., 2015; Kassebaum et al., 2014a; Koukounari et al., 2008; Magalhães et al., 2013; Ngesa and Mwambi, 2014; Pullan et al., 2013). Likewise household socioeconomic status that was associated with elevated anaemia risk in this study broadens confidence in earlier studies (Goswmai and Das, 2015; Schellenberg et al., 2003) which explained that purchasing capacity of the household is linked to affordability of preventive and curative measures. Previously, increased anaemia risk has been associated higher ascaris lumbricoides infection in a rural setting of Nigeria (Osazuwa et al., 2011). The mechanism through which this occur has been suggested that Ascaris lumbricoides infection often leads to reduced appetite, nutrient uptakes and mal-absorption of Vitamin A and other nutrients which could predispose to being anaemic (Staudacher et al., 2014). The gender difference in anaemia risk which favors the female children in terms of having lower risk has also been observed in other studies and attributed it to genetics factors (El Kishawi et al., 2015).

Clear association of anaemia risk /haemoglobin level with hookworm exposure was not identified in this study. Although studies which assessed this relationship has hitherto yielded non-consensus results, with some demonstrating association while some could not suggest relationship. For instance, a study among Kenya school children indicated that hookworm

infection was not associated with anaemia risk/ haemoglobin level and low intensity of hookworm in that area was given as the very likely reason why clear relationship could not be established. Also in another study (Adish et al., 1999) among preschool Ethiopian children, where hookworm parasite prevalence was around 0.4%, the result of the analysis could not show a clear association between anaemia risk and hookworm infection among the studied population. Another study that examine iron status between pre and post treatment with anti-helminth drug among school age children in Ivory coast demonstrated that hookworm infection does not reduce dietary iron absorption or the systemic iron utilization (Glinz et al., 2015) and in effect was not associated with anaemia risk in that population. In contrast, a study in Mozambique demonstrated an inverse relationship between haemoglobin level and hookworm infection, however, the level of parasitaemia in that setting reach above 30% of the school children examined. In addition, the study in the three contiguous West Africa state (Ghana, Burkina-Faso, Mali) using spatial analytical approach also positive anaemia risk relationship with increased hookworm prevalence, however the estimated prevalence in that study is higher than our setting. We opine that generally low hookworm burden in the country might be a reason why anaemia risk was not associated with hookworm prevalence in this study.

Likewise, Trichuris Trichiura prevalence which does not suggest association with anaemia risk/ haemoglobin level in this study could probably be linked to its generally very low prevalence in the country (Pullan et al., 2014) and this finding is not at variance with similar earlier studies using ecological approach (Magalhães et al., 2013) and as an individual level factor (Koukounari et al., 2008). Also, the association of Trichuris Trichiura with lower haemoglobin level/anaemia is often related to intensity of infection/endemicity in the population. Most studies (Ezeamama et al., 2008; Osazuwa et al., 2011; Sorensen et al., 2011) that have found no evidence have also demonstrated low prevalence in the study settings while those that indicated association (Quihui-Cota et al., 2010; Ramdath et al., 1995; Robertson et al., 1992) also reported moderate to high infection intensity/high prevalence.

Similarly, our model has not identified important relationship between anaemia risk and the model based exposure surface of Schistosoma mansoni and Schistosoma heamatobium; this might be related to possibly the low prevalence (Ekpo et al., 2013) in most part of the of the country. Related evidence that was observed in an extensive study (Befidi-Mengue et al., 1993)

carried out among school children in Cameroon, to assess the effect of Schistosoma hematobium infection on anaemia, also documented low parasite load among the studied population . In comparison, studies (Ayoya et al., 2009; Bustinduy et al., 2013; Koukounari et al., 2007) which had demonstrated important relationship between anaemia risk and these intestinal helminth also reported heavy infection / high parasite prevalence among the group studied. Also, Schistosoma mansoni is often linked with iron deficiency anaemia (IDA) especially with heavy infection (Butler et al., 2012), but the data we have analyzed is not IDA specific and this might also be a reason why Schistosoma mansoni is not associated with anaemia risk in this study. More so, the predicted risk surfaces used in our model fit are derived from age heterogeneous data and it may not be representatives of the risk among preschool children. Also, the tendency of children in this age range to have less exploration of their environment, which could result in limited contact with infective materials, might also be a reason why most of the Schistosoma prevalence relationship with anaemia risk appears not to be significant in this study.

Moreover, the positive association between haemoglobin and age can probably be linked to childhood physiology of balance between iron ingestion and requirement (Ewusie et al., 2014; Gao et al., 2013), that is, as the children advances in age, the iron intakes and requirement increases and reduces, respectively.

Undernutrition effects might be better captured at smaller scale, because large within to between cluster variation could confound haemoglobin and malnutrition relationship. Consequently, the programme planners need to make optimum use of the MIS platform by ensuring that information on all components of nutrition indicators are taken during the collection of MIS data, to allow assessment of between individual variations of this measure to the risk of anaemia.

Our work extends the evidence on the contribution of exposure to malaria parasitaemia and Ascaris lumbricoides to the prevalence of anaemia, and also generated important epidemiological resources that could be adopted for targeted control of anaemia in the country. The predicted risk estimates provides the public health managers with important decision-support instrument that could be used to guide the allotment of control interventions based on severity of prevalence among this susceptible group in various part of the country. Added to this is that the control

managers could utilize the predicted map in future surveys planning and as well employ it as the reference in the assessment of effectiveness of control programme.

The computational challenge of the measurement error modeling approach restricted us to the use of median predictive prevalence of the important parasite exposure instead of their distribution that was used in the model fitting which could have probably improved the precision of predicted estimates of the anaemia risk/ mean haemoglobin. Also, we could not estimate the population attributable fraction of anaemia, contributed by important infectious factors (malaria parasitaemia and Ascaris lumbricoides) in our model, because the risk surface of the latter was used on logit scale in our anaemia risk modelling.

Despite all the limitation of using ecological factor, the study suggest that in the absence of individual level covariates, we can resort to ecological proxy, and combine with appropriate modelling strategy, to identify important determinants and area with high anaemia risk.

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5.5 Appendix

5.5.1 Anaemia Measurement Error Model

The anaemia status Y_{ij} of child i at the location j considered as 1 if the child was anaemic and 0 otherwise is assumed to have arise from Bernoulli distribution, that is Y_{ij}~$Bern(p_{ij})$. The probability of being anaemic is given as: $logit(p_{ij})$ =β_0+$\boldsymbol{\beta_x X}$+$\mathbf{Z}\boldsymbol{\beta_z}$+ Ψ_j where β_0 denote the intercept, **Z** are the vectors of observed covariates and $\boldsymbol{\beta_z}$ are the corresponding coefficient. Instead of the true covariates $\boldsymbol{X}$**,** the surrogates **W** were sampled distribution of the Schistosoma, soil transmitted helminthes and nutrition proxy on the logit scale , such that **W**= $\boldsymbol{X + U}$**,** where $\boldsymbol{U}$ represent the error vector and are assumed to be Gaussian with 0 mean and precision τ_u. We assumed classical homoscedastic measurement error with independent exposure model (that is $\boldsymbol{X}$ is independent of observed **Z)** for the unobserved $\boldsymbol{X}$ and the first level of our model involve three models:

$logit(p_{ij})$ =β_0+$\boldsymbol{\beta_X X}$+$\mathbf{Z}\boldsymbol{\beta_z}$+ Ψ_j

0= -X+$\boldsymbol{\alpha_0 1}$ **,** $\boldsymbol{X}$~ N ($\boldsymbol{\alpha_0 1}$, $\tau_X I$) , and

W= $\boldsymbol{X + U}$ **W** | $\boldsymbol{X}$, **θ** ~ MVN ($\boldsymbol{X}$, $\tau_u I$) which are regression, exposure and error model respectively. **W** is the stacked vectors of sampled distributions. I is of the dimension 50×n. The second level of the model formulation is the latent field $\boldsymbol{\theta}_1$= $(\beta_0, \boldsymbol{\beta_z}, \boldsymbol{\alpha_0}, \boldsymbol{X^T})^{\mathrm{T}}$ and the unknown hyperparameters $\boldsymbol{\theta}_2$= ($\boldsymbol{\beta_X}, \tau_u, \tau_X, \boldsymbol{\theta}_3$) where $\boldsymbol{\theta}_3$ represent all additional parameters of the regression models. Prior distribution were assigned to the components of $\boldsymbol{\theta}_1$, specifically β_0 , $\boldsymbol{\beta_z}$, $\boldsymbol{\beta_X}$~ $N(0, 0.01)$. Also $\boldsymbol{\alpha_0}$ was fixed at mean 0 and precision 1 because of the centering of **W**. More so for hyperparameters τ_X and τ_u , we specified τ_X~ Ga(1,0.622) and τ_u~Ga(1,0.622) as suggested in Roos et al. (Roos and Held, 2011).

The spatial random effect Ψ was modeled as multivariate normal distribution with mean zero and Matérn covariance function between two locations, that is Ψ_j~ MVN(0, Σ) where

Σ_{s_m,s_n} = $\sigma_\Psi^2\left(\kappa d_{s_m,s_n}\right)^v K_v(\kappa d_{s_m,s_n})$/ ($\Gamma(v)2^{1-v}$) , σ_Ψ^2 is the spatial process variance, d_{s_m,s_n} is the distance between locations s_m and s_n, κ is the scale parameter and K_v is the modified Bessel function of second kind and order v.

5.5.2 Haemoglobin level model

The notation is as detailed in the anaemia model and it is only the distribution of the response variable that changed, that is: The haemoglobin level Y_{ij} of child i at the location j is assumed to come from normal distribution, that is, $Y_{ij} \sim \text{N}ormal(\mu_{ij}, \tau)$. The mean haemoglobin level is given as: $\mu_{ij} = \beta_0 + \boldsymbol{\beta_x X} + \mathbf{Z}\boldsymbol{\beta_z} + \Psi_j$. Also we specify Gamma prior for the precision τ that is, $\tau = \text{Ga}(1, 0.622)$.

Chapter 6 Discussion and Outlook

This PhD thesis contributes to the field of malaria epidemiology with data-driven Bayesian statistical methods for the analysis of spatio-temporal survey data, and provides a better understanding of the effects of malaria interventions coverage on the geographical distribution of the disease risk and of the relation between malaria burden with child mortality and anaemia risk in Nigeria. This thesis is organized in journal-article format and four manuscripts are produced. Each chapter provides detailed methodologies, results and discussion. In this section we report a summary of most important contributions and findings of our work, the implications for the disease control, and give suggestions for further extensions.

6.1 Significance of the work

6.1.1 Contribution to spatial modelling of malaria and its related co-morbidity risk

A number of environmental, socio-economic, intervention and health system related factors can predict the geographical distribution of malaria risk and they are often correlated. Selection of parsimonious models with the best predictive ability is an important step in risk mapping. In chapter 2 we extended the geostatistical variable selection to the inclusion of the functional form of the environmental covariates. To our knowledge, this is the first attempt to introduce the functional form of the covariates in the selection of predictors in malaria risk modelling.

Measurement error (ME) can sometimes occur in epidemiologic studies linking data from different sources. In the mortality-malaria hazard model considered in chapter 4, the mortality and malaria data were observed at dissimilar spatial locations. The approach that is often used is to predict the covariate at the location of the outcome and employ the mean/median predicted value in the model fit without adjusting for uncertainty in the prediction. In such circumstance where ME is not considered, estimated parameters and confidence interval could suffer serious biases (Carroll, 1998; Muff et al., 2015) . Also, important effect of some other covariates measured with or without error may not be detected. To address this we developed a joint model formulation in order to allow for prediction uncertainty of malaria risk in the assessment of mortality hazard-malaria prevalence relation. Implementation of survival model with measurement error is computationally demanding and the widely used Markov Chain Monte

Carlo algorithms are known to converge slowly. We employed integrated nested Laplace approach (INLA) (Rue H. et al., 2009b) and stochastic partial differential equation (SPDE). The SPDE approach approximates the spatial process, a Gaussian Field by Gaussian Markov random field (GMRF). The GMRF are defined by sparse matrix, which enjoy numerical computational properties (Cameletti et al., 2013) and this allows INLA to estimate model parameters at a very pragmatic computational time. This has been applied in chapter 4 to assess malaria-mortality relation, and estimate malaria burden on the geographical distribution of anaemia in chapter 5.

6.1.2 Contribution to malaria epidemiology and implication for control interventions

Our work provides important tools for the activities of the national malaria control programmes in the country by obtaining contemporary high spatial resolution estimates of malaria (Chapter 2) and anaemia risk (Chapter 5) in the country. The generation of these risk estimates was motivated by the availability of the first nationwide malaria information survey that could provide more accurate estimates and the actual disease distribution in the country and the first high resolution map of anaemia risk. These maps are based on national survey data collected using the same methods and including the same age groups of the population. These survey data are free of encumbrances (collection over different season, diverse diagnostic procedures/tools, overlapping age-group across study sites) of historical surveys data that have been employed in some of the previous maps (Gemperli et al., 2006; Gething et al., 2011; Gosoniu et al., 2009) of malaria risk. The model based malaria risk estimates (Chapter 2) indicates vital information that most states of the country are in the intermediate risk envelope (between 5% and 40%). The produced model based malaria distribution map will aid in effectiveness of malaria control in the country because it delineates areas at high risk, which could guide efficient spatial allocation of control/prevention resources. Our findings which indicate that household level coverage of ITN is not associated with malaria risk in the country could possibly due to small proportion of children sleeping under impregnated nets.

We further explored the community effect of ITN use on the prevalence of malaria in the country in chapter 3 of this thesis. Though our model indicated that the proportion of ITN use is not associated with malaria risk at the country level, however a spatially varying coefficient model assessing the effects of ITN use in space show that ITN use is associated with the reduced risk of malaria in two neighbouring states that is (Adamawa and Taraba) within the north east

part of Nigeria. This increases our confidence that the ongoing scaling up of control interventions is already yielding positive results. It is therefore important for the country to strive to meet the target of universal coverage of core malaria interventions for all population at risk.

A clear understanding of factors associated with anaemia risk and knowledge of its geographical distribution is important in developing effective strategies for anaemia control and prevention. In chapter 5, we provided the first high resolution estimates of the spatial distribution of anaemia risk in Nigeria. The model based estimates show that overall; approximately every 7 out of 10 children under the age of five years are anaemic. It shows that Jigawa state in the northwest has the highest prevalence (85%) of anaemia in the country, and Lagos, Adamawa, Gombe, Kogi and Plateau have the lowest levels which are close to 50%. Our findings show that malaria infection and Ascaris lumbricoides prevalence are the main infectious factors associated with anaemia prevalence; furthermore economically disadvantaged children are at increased risk of anaemia. Our estimated anaemia risk map can guide national control managers a decision support tool for delivery of ancillary micronutrient supplementation and fortified food with the aim of reducing iron deficiency anaemia. Likewise, it could be use in evaluation of impact of intervention programmes.

Understanding of the relation between malaria prevalence and mortality among the vulnerable group in the population is essential in measuring the impact of malaria control. In chapter 4, we assessed the contribution of malaria prevalence to all-cause mortality among children under five in Nigeria after adjusting for socio-demographic factors mostly linked to mortality in this age group. Several efforts (Gemperli, 2004; Smith et al., 2001) have been made to evaluate the above mentioned relation. However, those attempts in various parts of the malaria endemic region of sub-Sahara Africa have not been able to draw a general pattern on the malaria risk and mortality relationship among children, possibly due to some shortcoming such as the data used and methodology limitation. We embraced joint model formulation so that uncertainties are incorporated in the predicted malaria prevalence at the mortality locations, because the two data sets we used are spatially misaligned. Our finding shows that malaria prevalence is associated with increased mortality hazard for children above the age of six months. The modelling approach and the datasets employed give us the confidence that the result of our analysis may reflect malaria risk and all-cause mortality relationship in Nigeria.

All this affirms that malaria is still of public health significance in the country and that the country need to aggressively scale up the coverage of malaria interventions.

6.2 Limitations

Malaria transmission is mostly affected by prevailing environmental/climatic conditions and the prevalence is known to vary by season, because the vector population which transmits the parasite is determined by the climatic condition during the various season of the year. The cross-sectional nature of MIS data analysed in this work could not allow us explore seasonality in malaria transmission in the country. The estimates of the relative contribution of various risk factors of anaemia are very important to determine the optimum combination of interventions that can maximally reduce the disease burden. In our anaemia risk analysis, the soil transmitted helminthiasis, schistosomiasis, and malnutrition data were available on the logit scale at the cluster level that could not be used to derive the odd of anaemia associated with these risk factors, which is an input in the calculation of attributable fractions. Therefore, we could not calculate the proportion of anaemia that could have been averted if those factors associated with anaemia risk in our model is reduced to the alternative exposure level. Also in this same study the effect of risk factors were assumed not to vary over the areas. However, the disease-risk factor relationship may exhibit variation across space probably due to some unmeasured factors such as heterogeneous intervention level, and disparities in health-system performance across regions/states in the country. Spatially varying coefficient model could have been be used to assess the effect of the risk factors at sub-national scale.

The malaria prevalence and mortality relationship is often assumed to be non-linear. It is believed that mortality hazard associated with malaria is higher at intermediate transmission level and plateau or even reduced at higher transmission (Snow et al., 1999). However, the joint modelling approach employed in our geostatistical model of malaria risk-mortality hazard relation, in order to incorporate prediction uncertainty in the predicted malaria prevalence could not allow the assessment of the non-linearity in this relationship.

The MIS locations are always displaced from the initial collection points to keep some anonymity so that individual privacy of health information is maintained and it is not well known whether this have impact on the parameter estimate and the interpolated surfaces .

The assumption of the latent spatial process in the models used in this work has been that of stationarity and isotropy, by which the underlying spatial process only depends on distance between locations, and not on direction and geographic position. However, some factors like ecological variation, heterogeneous coverage of control effort in space and inequality in health system effectiveness can introduce local spatial dependency which will violate this assumption especially in disease-risk factor relation analysis over large geographical area. The application of a non-stationary model to malaria-risk factor analysis especially in regions with large disparities in environmental conditions has been suggested to give more accurate result than their stationary counterparts (Gosoniu and Vounatsou, 2011; Lawson et al., 2016) but these models are computationally intensive especially when the area of study is large.

6.3 Extension of this work

Contemporary malaria information surveys are available for many other malaria endemic countries in sub-Saharan Africa. The methodology generated in this thesis can be applied to those data in order to also produce contemporary risk estimates for these countries. Additionally the high resolution estimates generated in this thesis can also serve an input in the burden of disease estimation.

The measure of malaria transmission used in this work has been based on prevalence because it is the most readily available complete data. However parasite prevalence measures suffer from the setback of being subject to seasonal variation (O'Meara et al., 2007). The health management information system data, which are collated monthly, can be modeled also using appropriate methodology and compare with the estimates from this work. It would also enabled temporal variation in malaria transmission to be assessed, and incidence maps to be produced can guide control activities in timelier manner.

Also the newly conducted MIS data, when it is made available, can be combined with the data used in this work, to see the change in malaria risk over time and also the effect of interventions on this change can also be study.

Furthermore, the Bayesian Geostatistical models with measurement error applied to spatially misaligned data in this thesis can be further applied to others diseases.

6.4 Conclusion

The past decades has witness exceptional surge in international funding and political commitment for malaria control. Coverage with existing control interventions is increasing and various endemic countries are recording decline in malaria related morbidities and mortality. This decline has led to renew interest in malaria elimination and eradication, however many of the endemic countries need high resolution estimates of contemporary prevalence that can be used to track the impact of intervention over time. This PhD thesis was born out of the need for a better understanding of malaria burden effects on children health and mortality risk in Nigeria. We have evaluated the effects of intervention on malaria risk distribution, assessed the malaria burden relationship with children mortality, and provided the model based high spatial resolution estimates of malaria risk and anaemia prevalence in Nigeria. The derived estimates can serve as a benchmark in the monitoring of the impact of ongoing control intervention on malaria related morbidities and mortality.

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2000- 2001	Master of Science (M.Sc.) in Biostatistics at the Faculty of Public Health, University of Ibadan. Thesis: Pattern of mortality among individuals aged 65 and above in a rural community, Nigeria. (Advisor: Prof. Dr. E. A. Bamgboye)
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PROFESSIONAL EXPERIENCE AND TEACHINGS

2004- Till now	Statistician National centre for remote sensing, Jos, Nigeria.
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PUBLICATIONS

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