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„Spatial, temporal, and socioeconomic risk factors of malaria in children from the Ashanti Region, Ghana“

Dissertation

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Contents

List of Publications

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II. Krefis AC, Schwarz NG, Krüger A, Fobil J, Nkrumah B, Acquah S, Loag W, Sarpong N, Adu-Sarkodie Y, Ranft U, May J. Modeling the Relationship between Precipitation and Malaria Incidence in Children from a Holoendemic Area in Ghana. *American Journal of Tropical Medicine & Hygiene* 2011, Feb;84(2):285-291.

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List of Figures

Abbreviations

ACT	Artemisinin-based combination therapy
APT	Agogo Presbyterian Hospital
CI	Confidence interval
DALYs	Disability-adjusted life years
EIR	Entomological inoculation rate
ENVI	Environment for Visualizing Images
ESRI	Environmental System Research Institute
GIS	Geographic information system
GPS	Global Positioning System
IPT	Intermittent preventive treatment
IRS	Indoor residual spraying
ITN	Insecticide-treated net
KCCR	Kumasi Centre for Collaborative Research in Tropical Medicine
LLIN	Long-lasting insecticidal net
MDG	Millennium Development Goals
NDVI	Normalized Difference Vegetation Index
NHIS	National Health Insurance Scheme
OPD	Outpatient department
OR	Odds ratio
PCA	Principal component analysis
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
RR	Relative risk
RS	Remote sensing
UNDP	United Nations Development Programme
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

Chapter 1

Introduction and background

1.1 Malaria – a review

Malaria is the most common vector-borne infectious disease with nearly 250 million estimated clinical cases in 2008 worldwide and approximately one million deaths each year. With a vast majority of cases (85%) Sub-Saharan Africa carries most of the burden. In regions of stable transmission children <5 years of age are at highest risk of becoming infected with malaria. Malaria is caused by an infection with the protozoan *Plasmodium falciparum* transmitted from person to person through the bite of female *Anopheles* mosquitoes [1,2].

Malaria has been described since antiquity where Hippocrates is usually credited with the first clear description of the disease. In the early nineteenth century, an era where miasmatic influences were believed to cause a variety of diseases, Italian scientists hypothesised that malaria is caused by the offensive vapours emanating from the Tiberian marshes [3]. The word “malaria” comes from the Italian, and means verbatim “bad air” (mala aria). Indeed, until the late nineteenth century the cause of the seasonal periodic fevers was not clarified [4]. Among many scientists contributing to the clarification of the disease Laveran was the first to detect the parasite in fresh blood of a patient. The linkage to *Anopheles* mosquitoes as vectors and the characterisation of the complete life cycle was proven by Ross [5,6].

People suffering from malaria generally show symptoms including headache, nausea, fever, vomiting, diarrhoea, and flu-like symptoms. Clinical features for severe malaria include amongst others splenomegaly, convulsions, coma, severe anaemia, spontaneous bleeding from gums, nose etc., thrombocytopenia, hypoglycaemia, pulmonary or renal dysfunction, and neurological changes. In most cases of malaria the incubation period (time from sporozoite inoculation to fever) is approximately one to two weeks [7].

Nowadays malaria is endemic in 108 countries and is restricted to the tropical and subtropical areas and altitudes below approximately 1,500 meters dependent on the climate conditions [1] (Figure 1).

Malaria persists as an important public health problem. Vaccines against malaria infection are still lacking. The number of disability-adjusted life years (DALYs), a measure of disease burden caused by malaria, was estimated at 34 Millions for 2004 worldwide and 31 Millions in Sub-Saharan Africa [8]. Additionally, the disease is one

of the major public health challenges subverting development in the poorest countries in the world: The direct and indirect costs of malaria are very high and the disease has played a significant role in the poor economic performance of Sub-Saharan Africa. Sachs (2002) estimated, that the gross domestic product in these countries would be up to 32% greater today if malaria had been eliminated 35 years ago. Nowadays, malaria costs Africa's economy alone more than US$12 billion annually [9,10].

In contrast to a retrogressive trend in some areas morbidity and mortality from malaria have been increasing in many other areas. Factors such as deteriorating health systems, growing drug and insecticide resistance, failure of water management but also climate, socioeconomic, sociodemographic, and land cover factors are hypothesised to influence the emergence of malaria [11,12].

Therefore, investigations assessing the risk for malaria should evaluate factors influencing the vector population, the human population at risk, and potential factors driving their interaction.

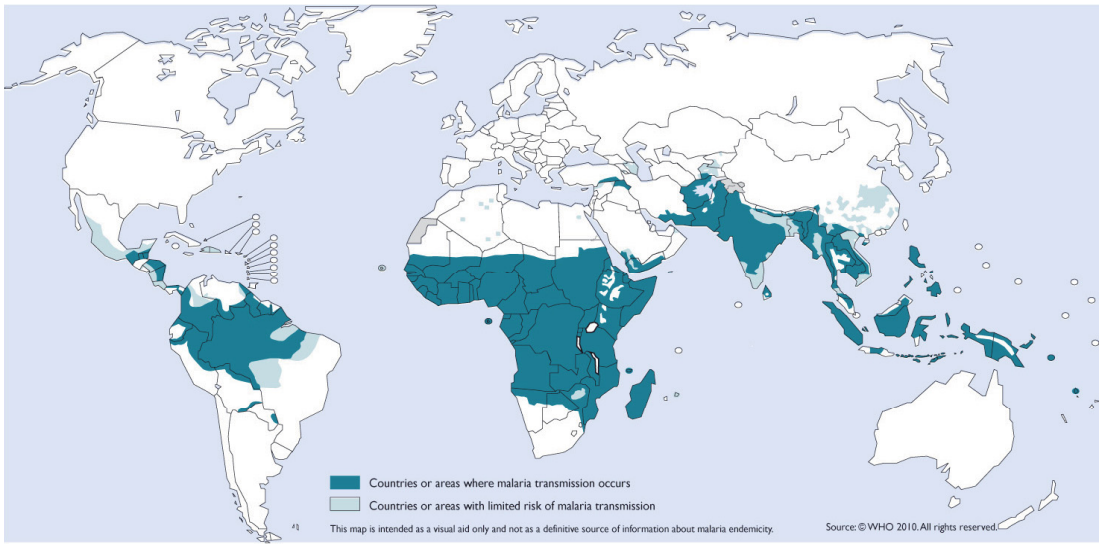

Figure 1: Global distribution of malaria 2009
Source: WHO map. Online available:
http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Malaria_ITHRiskMap.JPG
(accessed 29 September 2010).

1.2 The parasite

The malaria parasite is a mosquito-transmitted protozoan of the genus *Plasmodium*. Plasmodia are sporozoan parasites of red blood cells transmitted to vertebrates by the bites of female mosquitoes [7,13]. Approximately 156 named species of *Plasmodium* infect various species of animals. Formerly four, nowadays five species of the genus *Plasmodium* are known to infect humans: Almost all serious forms of malaria are caused by *P. falciparum.* Malaria caused by *P. vivax, P. ovale,* and *P. malariae* causes milder disease in humans, although on the island of New Guinea *P. vivax* is associated with significant mortality [13,14]. The fifth parasite *P. knowlesi*, a malaria of long-tailed and pig-tailed macaque monkeys, is an important cause of human malaria on the island of Borneo and peninsular Malaysia [15].

The malaria parasite life cycle (Figure 2) involves two hosts and begins when the feeding female anopheline mosquito inoculates plasmodial sporozoites into the human host (1). Inside the human host begins a phase of asexual reproduction. Sporozoites infect liver cells (2) and mature into hepatic schizonts (3), which rupture and release merozoites into the bloodstream (4). This stage lasts on average between 5-6 (*P. falciparum)* and 15 days (*P. malariae)*. In *P. vivax* and *P. ovale* infections a proportion of the intrahepatic parasites do not develop, but instead remain inert as sleeping forms (hypnozoites) in the liver and cause relapses weeks or even years later which characterise infections with these two species. After this initial replication in the liver (exo-erythrocytic schizogony [A]), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony [B]). Merozoites infect red blood cells (5). The ring stage trophozoites mature into schizonts, which rupture releasing merozoites (6). A subpopulation of parasites differentiates into sexual erythrocytic stages (gametocytes) (7). These are the stages which transmit the infection. The phase of asexual multiplication in the red blood cells is approximately 24 h for *P. knowlesi*, 48 h for *P. falciparum, P. vivax* and *P. ovale*, and 72 h for *P. malariae*. The process of gametocytogony takes about 7-10 days in *P. falciparum*. Gametocytogenesis in *P. vivax* begins immediately and takes only four days. One male (microgametocytes) and female (macrogametocytes) are required per mosquito blood meal for infection to occur (8). The parasites´ multiplication inside the mosquito is known as sporogonic cycle [C]. In the mosquito's stomach, the microgametes

penetrate the macrogametes generating zygotes (9). Within 24 h the enlarging zygote becomes motile and this form (the ookinete) penetrates the wall of the mosquito mid-gut where it encysts (as an oocyst) (10 and 11). The oocyst finally bursts to liberate myriads of sporozoites into the coelomic cavity of the mosquito. The sporozoites make their way to the mosquito's salivary glands to await inoculation into the next human host during feeding (12 and 1). The phase of sporogony in the mosquito takes between 8 and 35 days depending on the ambient temperature and species of parasite and mosquito [7,16].

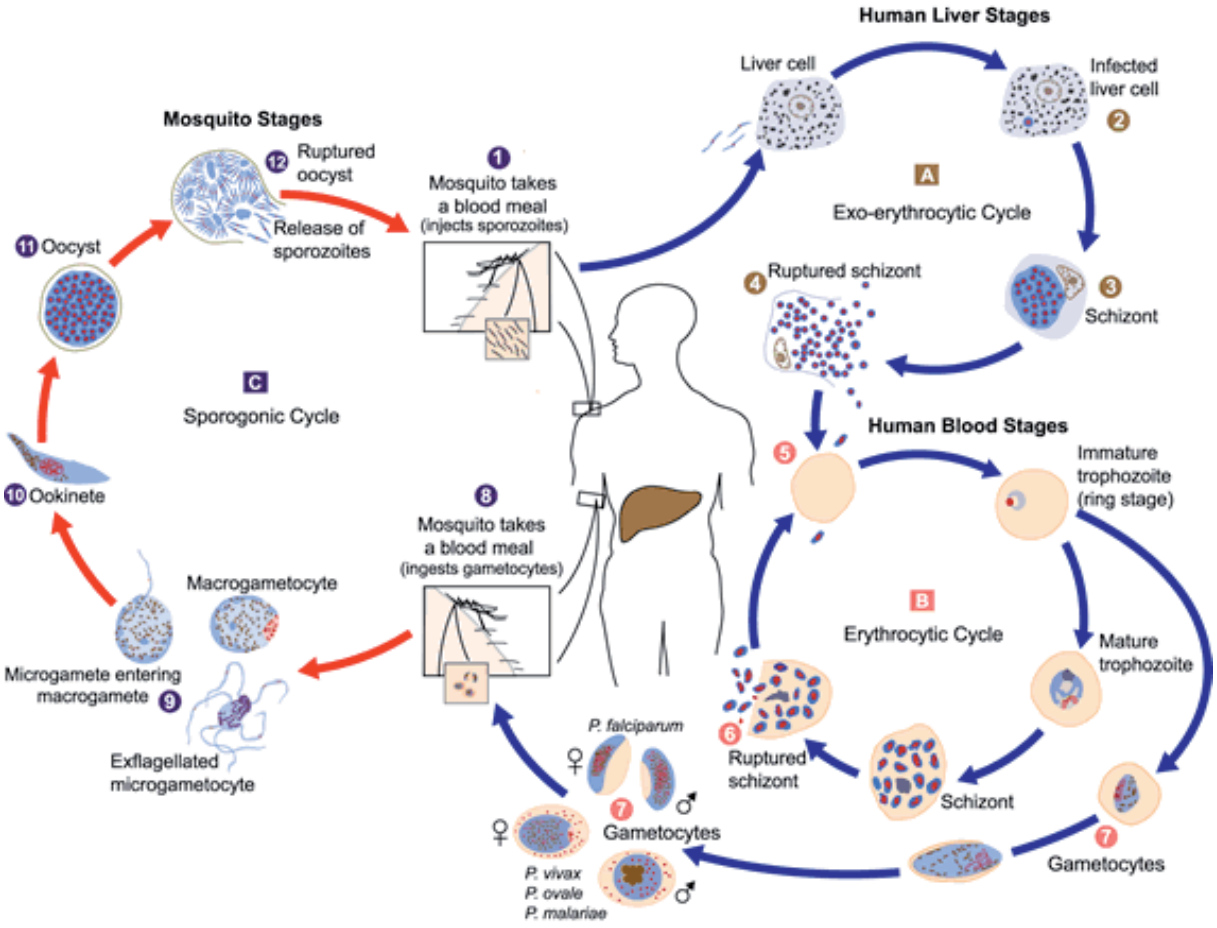

Figure 2: Life cycle of malaria parasite
Source: Centers for Disease Control and Prevention. Online available: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Malaria_il.htm (accessed 30 September 2010).

Nowadays *P. falciparum* is predominant in African countries but also existent in Papua New Guinea and Haiti, whereas *P. vivax* is more common in Central and parts of South America, North Africa, the Middle East, and the Indian subcontinent. In other parts of South America, South-east Asia, and Oceania the prevalence of both species is approximately equal. *P. vivax* is rare in Sub-Saharan Africa, but existent at the horn of Africa. Instead *P. ovale* is common only in West Africa, *P. malariae* is found in most areas, but is relatively uncommon outside Africa. *P. vivax* may also be found in northern China and North Korea [7,13].

Until the 1950th malaria was endemic in Europe, northern Asia, and North America, but has been eradicated from these areas.

1.3 The mosquito vector

The most important factors for malaria transmission to man pertain to the mosquito vector, and in particular its longevity. As the phase of sporogony takes more than a week (depending on ambient temperatures) [16], the vector must survive longer than this time span after feeding on a gametocyte-carrying human, if malaria is to be transmitted.

Worldwide nearly 400 species of anopheline mosquitoes are known. Malaria is transmitted by approximately 80 species of anopheline mosquitoes where mosquitoes of the *Anopheles gambiae* complex and *Anopheles funestus* are the main malaria vectors in Sub-Saharan Africa. The optimum conditions for transmission are all-the-year high humidity and an ambient temperature between 20°C and 30°C [17]. Rainfall provides breeding sites for mosquitoes, although excessive rainfall may wash away mosquito larvae and pupae [18].

The epidemiology of malaria is complex and may vary considerably even within relatively small geographical areas [2,19-21]. Malaria transmission intensities (entomological inoculation rate (EIR)) vary from very low (mean of one infectious bite per person every 10 years) to very high (three infectious bites per person per day) [7,20]. Behaviour patterns and specific breeding habitats also vary between vector species. For example, in Africa *A. gambiae* prefers sunlit pools with turbid water with

little or no existent vegetation; *A. funestus* larvae prefer clear water, thriving in irrigation and hydroelectric reservoirs with their frequent changes in water level, around shorelines with vertical, emergent vegetation without organic material or salinity. In rural India, irrigation systems are favoured habitats for the larvae of *A. culcifacies*, whereas in Sri Lanka the vectors prefer riverine pools created by diversion of flow out of riverbeds, breeding primarily in shallow, stagnant surface water exposed to sunlight [22,23].

1.4 The human host

The existence and behaviour of man also plays an important role in the epidemiology of malaria. To transmit the disease there must be a human reservoir of viable gametocytes [7,16]. Additionally, human behaviour is of importance for the emergence of disease. Deforestation is suggested to be one of the most disruptive changes affecting parasitic vector populations. Cleared tropical forests are converted for instance into human settlements which create a need for increased food supply, leading to change in the types and amounts of vegetation and landuse, thereby providing changed ecological niches and conditions for proliferation of newly arriving or adaptive existing vectors and their parasites. Likewise, water bodies in these cleared areas are generally more sunlit and prone to the formation of puddles with more neutral pH, which can favour specific anopheline larvae development [23,24]. During the processes of deforestation and the migration to new settlements, both vectors and humans (non-immune individuals) are exposed to new contacts in new environments. With the larger reservoirs of infection, there is increased parasite transmission and, the humans not only become ill, but also further increase the parasite reservoirs [23-27].

Another factor driving epidemics might be worsening antimalarial drug resistance of humans as well as increasing international air travel.

1.5 Objectives

The objectives of this thesis were to investigate spatial, temporal, and socioeconomic patterns of malaria in children <15 years of age in a holoendemic area in West Africa. Specifically, it was investigated whether malaria is associated with socioeconomic and sociodemographic factors, meteorological conditions, and land cover classes. The following questions were addressed in the papers I-III, respectively, on which this thesis is based:

I. Are there socioeconomic and sociodemographic factors that are correlated to malaria compared to other diseases?
II. Is there a temporal pattern on the occurrence of malaria in relation to precipitation?
III. Can specific land cover determinants be associated with the occurrence of malaria?

1.6 Methods

1.6.1 Study area

In Ghana, where our study was conducted, malaria is prevalent during the entire year and accounts for about 32-42% of all outpatient admissions and for the major inpatient causes of death [28]. Malaria endemicity is traditionally classified in four groups defined in terms of spleen or parasite rates in children aged between 2 and 9 years. The categories are hypoendemic (spleen rate or parasite rate of 0-10%), mesoendemic (spleen or parasite rate of 10-50%), hyperendemic (spleen or parasite rate of 50-75%, adult spleen rate also high) and holoendemic (spleen or parasite rate over 75%, adult spleen rate low) [7]. Our study region can be defined as a hyper- or holoendemic area.

The principal malaria vectors are mosquitoes of the *Anopheles gambiae* complex and *A. funestus* and the predominant *Plasmodium* species is *P. falciparum* (>90%) [29].

This hospital-based survey was accomplished at the Child Welfare Clinic and the Pediatric Ward of the Agogo Presbyterian Hospital (APH), Asante Akim North District, Ashanti Region, central Ghana, West Africa. Agogo town is approximately 80 km northeast of Kumasi, the second largest city of Ghana and the capital of the Ashanti Region. Agogo is 30 km off the main road from Ghana's capital Accra to Kumasi. The tarmac road leading to Agogo is a dead end road.

The vegetation of the study area mainly consists of semi-deciduous forest with major vegetation types of open forest, closed forest and wooded savannah. The climate is tropical with a mean annual temperature of 26°C and two rainy seasons: the first occurs from May to July and the second from September to November with monthly rainfall up to 400 millimeters. The harmattan (a dry and dusty West African trade wind) season occurs during December to April and is associated with drought conditions. The topography of the district is mainly undulating with the lowest area near the Volta Lake (152 meters) and the highest area at the Akwapim-Mampong range (up to 762 meters). Agriculture is the predominant major occupation among people; main staple food crops produced in the district include maize, cassava, plantain, cocoyam and yam [30].

The overall study included 14 villages which were summarised into four village clusters ("Greater Agogo" (Agogo city and Hwidiem), "Greater Konongo" (Konongo and Odumasi), "West of Agogo" (Akutuase, Amantena and Wioso), and "Near Street" (Domeabra, Juansa, Kyekyebiase, Nyaboo, Obenimase, Patriensah and Pekyerekye) (Figure 3). The total population of all villages was 61,346 inhabitants (census data 2004) where the population ranged from 890 inhabitants in the smallest village to 15,383 in the largest (see Appendix 1). The main ethnic groups in this area are tribes from Akan origin, the Ewe, and tribes from northern Ghana, which have the same language origin (e.g. Konkonba, Dagarti, Moshi or Dagomba) [30].

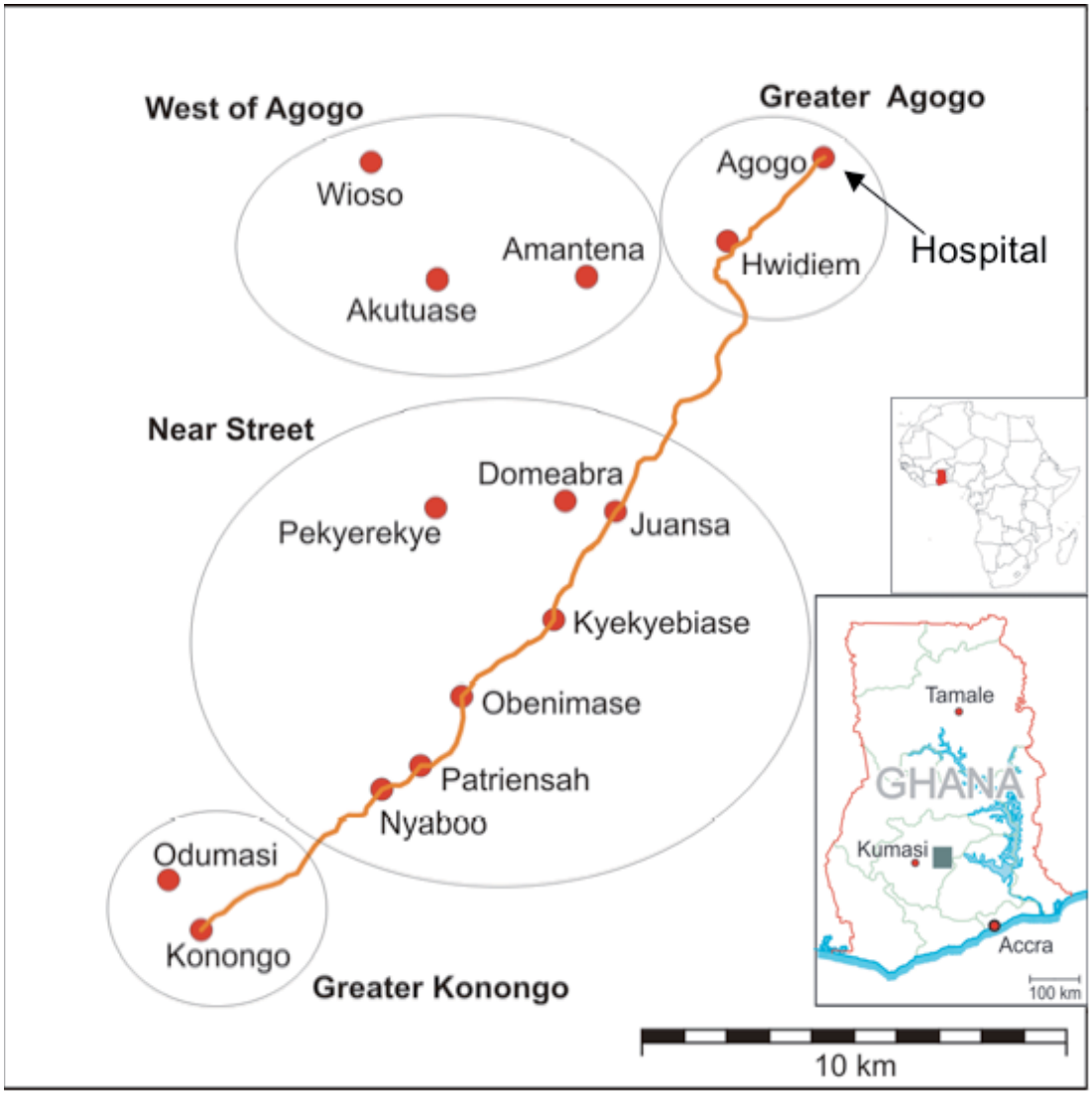

Figure 3: Study area
Map of the 14 included villages and village clusters in the Asante Akim North District, Ashanti Region, central Ghana, West Africa. Red dots indicate villages; the solid line indicates the main road.

1.6.2 Malaria cases and malaria incidence in children

The overall study was carried out during May 2007 to August 2009 (duration 26 months). Children up to 14 years of age, who were presented to the hospital, were eligible for the study and diagnostic assessments were integrated into the hospital routine. Aims and principles of the study were explained in detail to participants and parents or guardians and informed consent was obtained by signature or thumb print by the caregiver. The study design and the informed consent form were approved by

the Committee on Human Research, Publications, and Ethnics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

The case definition for malaria was fulfilled, if the axillary temperature was ≥37.5°C and a *P. falciparum* parasitaemia with >0 parasites/μL was detected in the thick or thin smears. Microscopic parasite examination was done according to quality-controlled standardized procedures [31].

Additionally, we computed weekly (see Appendix 3 and Paper II) and yearly (see Appendix 1 and Paper III) malaria incidences (new disease cases) per 1,000 children <15 years of age, respectively. Due to the fact that the clinical assessment in the outpatient department (OPD) finished in November 2008 incidences were computed for the study period of 18 months (end of May 2007 to end of November 2008). Malaria cases that presented within 21 days after the initial malaria diagnosis were considered as a relapse and not counted as a new case. The reference population was corrected for the following: it was estimated that 42% of the total population was <15 years of age [32] and after comparing our study population with the hospital admission records we assumed that 70% of all hospital admissions were included into the study. Furthermore, we computed the proportion of people from each village attending the APH, when looking for professional medical care using information from a community survey, which had been carried out in 2007 (see Appendix 1). STATA/SE software version 10 (StataCorp LP, College Station, TX) was used for all calculations in this thesis.

1.6.3 Data collection and analysis on personal or family characteristics

During the whole study period of 26 months information on personal or family characteristics with a potential influence on malaria and information about factors possibly describing the family's financial situation was collected through interviewing the parent or the guardian, who accompanied the child to the hospital using a structured questionnaire (see Appendix 2 and Paper I).

To classify the family's economic status, several socioeconomic indicator variables were considered to enter a principal component analysis (PCA). PCA is a multivariate statistical technique used to reduce a number of variables in a data set into a

smaller number of “dimensions”. Factor scores for each included variable were calculated and used as weights to compute a new variable, which described the economic situation of each household. Variables, which showed relevant contributions (>10%) to the combined socioeconomic status score factor, entered the PCA [33]. We used the factor of the PCA with the highest eigenvalue as the variable, which describes sufficiently the socioeconomic status of a household. The respective factor scores were categorized in terciles with the lowest 33% of households according to the economic status variable classified as poor, the highest 33% as rich, and the rest as average economic status, and were used in the regression analysis [34]. First, we calculated the odds ratio (OR) for each potential risk factor of acquiring malaria and tested the significance of association by the chi-square test. Second, by using multivariate logistic regression for all potential risk factors, together with the newly created variable describing the socioeconomic status we estimated adjusted ORs to assess their independent effect on malaria risk.

1.6.4 Precipitation data and time series analysis

The Ghana Meteorological Agency provided data on daily precipitation in Agogo and Konongo during March 2007 to November 2008. For both areas weekly means of the factor precipitation were calculated (see Appendix 3 and Paper II).

Associations between precipitation and malaria incidence during March 2007 to November 2008 in the two village clusters Greater Agogo and Greater Konongo were modeled by linear regression analysis using the logarithm of the weekly incidence. We analysed the cross-correlation functions between the time series of the weekly precipitation and the log-transformed weekly malaria incidence to assess time lags with peak correlations between the course of malaria incidence and the course of precipitation. These time lags were used in a linear model of the regression of precipitation on log-transformed malaria incidence for each village cluster, respectively. To account for autoregression of the incidence time series, an autoregressive term of white noise was included in the regression models. Finally, the two regression models were applied to estimate expected incidences.

1.6.5 Analysis of remote sensing data

This part of the study included the 12 villages Agogo, Hwidiem, Akutuase, Amantena, Wioso, Domeabra, Juansa, Kyekyebiase, Nyaboo, Obenimase, Patriensah, and Pekyerekye. In order to map land cover, we used two multispectral Ikonos images with 4-meter spatial resolution and four broad spectral bands (blue, 0.45-0.52 µm; green, 0.52-0.59 µm; red, 0.62-0.68 µm; and near-infrared, 0.77-0.86 µm), along with one panchromatic band with 1 m pixels, acquired May 4, 2009 and November 26, 2009. No images were available for the two southernmost villages Konongo and Odumasi.

By using the software ENVI 4.4 (ITTVIS, 2009) a Normalized Difference Vegetation Index (NDVI) (NDVI = [NIR – red] / [NIR + red]) image was calculated, which is a commonly used measure of vegetation productivity [35]. To improve classification accuracy, the spatial relationship of pixels was likewise considered by calculating a set of eight textural measures (contrast, homogeneity, angular second moment, variance, mean, dissimilarity, entropy, and correlation) based on a grey level co-occurrence matrix, leading to a new textural image for each measure [36,37]. Finally, the textural images were combined with the NDVI image and the four spectral bands for further analysis.

In March 2010 field sampling was conducted by direct inspection of approximately 500 points randomly selected in the vicinity of the included villages defining the land cover pattern for each point. We marked the points using a Garmin eTrex®H Global Positioning System (GPS) and took notes on the dominant vegetation or crop type and photographs.

By using the ENVI software, these reference areas were digitised as regions of interest and were used to represent one of the following land cover classes: banana or plantain, cacao, palm trees, oranges, swampy area, water, deforested area and roads, built-up areas (houses), and forest.

The combined bands were classified using the supervised maximum likelihood classifier. With the assumption that the distribution of class samples is normal the statistical distribution of classes in multivariate feature space were modeled and determined by class means and variance-covariance matrices [38]. Therefore, a random subset of 70% of the pixels for each of the classes was chosen for a basic

analysis (“training data”) and 30% were used for assessment of accuracy (“validation data”). Additionally, we applied a majority/minority analysis for generalisation of the classification image to minimise “salt and pepper effects” (existence of dark pixels in bright regions and bright pixels in dark regions) and evaluated for accuracy using the overall accuracy computed from a confusion matrix.

The final image was transferred to ArcGIS version 9.3, developed by Environmental System Research Institute (ESRI, 2008). Taking into account that adult mosquitoes remain generally up to 2 km of their breeding side [39-41] a radius of 2 km (from the village centre) around each village was created and the percentage of various land covers in each radius was computed. Due to the particular size of the village Agogo an oval-shaped radius of 2 km was used. In order to test the validity of the analysis additional radii of 0.5 km, 1 km, and 1.5 km around each village were used.

Poisson regression modeling with adjustment for overdispersion was applied to quantitatively assess the associations between the land covers as well as human population density, and the incidence of malaria. By using Spearman rank correlation the cross correlation between all potential determinants for malaria was computed. Land cover proportions were analysed as continuous variables and human population density as per 1,000 inhabitants. The approximated interquartile range was used as unit increase for the continuous variables.

In a first step, the influence of each potential determinant was assessed separately in a univariate Poisson regression. The measure of association between a variable and malaria incidence was defined as the relative risk (RR) and complemented by a 95% confidence interval (CI) and p-value. In a second step as sensitivity analysis and to account for confounding, the high correlated determinants with a p-value less than 0.05 were included in a bivariate Poisson regression analysis.

Chapter 2

Principal component analysis of socioeconomic factors and their association with malaria in children from the Ashanti Region, Ghana

Principal component analysis of socioeconomic factors and their association with malaria in children from the Ashanti Region, Ghana

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Malaria Journal 2010, 9:201

Background

The socioeconomic and sociodemographic situation are important components for the design and assessment of malaria control measures. In malaria endemic areas, however, valid classification of socioeconomic factors is difficult due to the lack of standardised tax and income data. The objective of this study was to quantify household socioeconomic levels using principal component analyses (PCA) to a set of indicator variables and to use a classification scheme for the multivariate analysis of children <15 years of age presented with and without malaria to an outpatient department of a rural hospital.

Methods

In total, 1,496 children presenting to the hospital were examined for malaria parasites and interviewed with a standardised questionnaire. The information of 11 indicators of the family's housing situation was reduced by PCA to a socioeconomic score, which was then classified into three socioeconomic status (poor, average, and rich). Their influence on the malaria occurrence was analysed together with malaria risk co-factors, such as sex, parent's educational and ethnic background, number of children living in a household, applied malaria protection measures, place of residence, and age of the child and the mother.

Results

The multivariate regression analysis demonstrated that the proportion of children with malaria decreased with increasing socioeconomic status as classified by PCA ($p<0.05$). Other independent factors for malaria risk were the use of malaria protection measures ($p<0.05$), the place of residence ($p<0.05$), and the age of the child ($p<0.05$).

Conclusions

The socioeconomic situation is significantly associated with malaria even in holoendemic rural areas where economic differences are not much pronounced. Valid classification of the socioeconomic level is crucial to be considered as confounder in intervention trials and in the planning of malaria control measures.

Background

Malaria is one of the major public health challenges subverting development in the poorest countries in the world. The direct and indirect costs of malaria are very high and the disease has played a significant role in the poor economic performance of Sub-Saharan Africa. Sachs (2002) estimated, that the gross domestic product in these countries would be up to 32% greater today if malaria had been eliminated 35 years ago [1]. In contrast to a retrogressive trend of malaria morbidity and mortality in many areas malaria burden has been increasing in other areas [2]. Factors such as deteriorating health systems, growing drug and insecticide resistance, failure of water management but also socioeconomic, land-use factors, and climate are hypothesised to influence the emergence of malaria [3,4].

In Ghana, where the study was conducted, malaria is prevalent during the entire year and accounts for about 32-42% of all outpatient admissions and for major in-patient causes of death [5]. Sociodemographic factors such as ethnic group, parent's education and occupation, use of protective measures, and living standard of the family are suggested to be important risk factors for malaria and malaria epidemics [6-8]. The impact of socioeconomic factors, namely the family's financial situation, is difficult to assess due to the lack of standardised economic data of income and tax. The use of single indicators for the household's economical situation reduces the available information and may imperfectly set the focus point on the selected parameters. Additional socioeconomic factors assessed in the Demographic and Health Survey 2008 and not considered here are marital status and religion, which we did not found appropriate in the context of the study.

The aim of the presented study was to investigate the association between the socioeconomic status of families classified with a number of indicators as a PCA-based score and their association with childhood malaria.

Methods

Study area

This survey was accomplished at the Child Welfare Clinic and the Pediatric Ward of the Agogo Presbyterian Hospital, Asante Akim North District (Ashanti Region) in central Ghana, West Africa. Recruitment area included 14 villages which were summarised into four clusters ("Greater Agogo" (Agogo city and Hwidiem), "Greater Kononogo" (Kononogo and Odumasi), "West of Agogo" (Akutuase, Amantena and Wioso), and "Near Street" (Domeabra, Juansa, Kyekyebiase, Nyaboo, Obenimase, Patriensah and Pekyerekye) (Figure 1). The study area covers approximately 345 km^2; the coverage population of the study hospital was 61,346 inhabitants (census data 2004) where the population ranged from 890 inhabitants in the smallest village to 15,383 in the largest.

The vegetation of the study area is mainly semi-deciduous forest with major vegetation types of open forest, closed forest and wooded savannah. The climate is tropical with a mean annual temperature of 26°C and two rainy seasons: a first rainy season from May to July and a second from September to November. The dry harmattan season occurs between December and April and is associated with drought conditions. The topography of the district is generally undulating and the altitude variation is 226 meters between the lowest (227 meters) and the highest (453 meters) village included in our study. Agriculture is the predominant major occupation among people; main staple food crops produced in the district include maize, cassava, plantain, cocoyam and yam [9]. The principal malaria vectors are mosquitoes of the *Anopheles gambiae* complex and *Anopheles funestus*. Malaria is hyper-/holoendemic in this area with intense perennial transmission and seasonal peaks and the predominant *Plasmodium* species is *Plasmodium falciparum* (>90%) [10]. Entomological evaluation during the study period indicated approximately 400 infective bites per person-year (EIR) (unpublished data). Subsidised insecticide-treated bed nets were available, and their use was encouraged.

The study was carried out between May 2007 and August 2009 (duration 26 months). Diagnostic assessments were integrated into the hospital routine. In total, 1,496 children up to 14 years of age, who visited the hospital for medical care, were included in the study. The case definition for malaria was fulfilled if the axillary tempe-

rature was ≥37.5°C and a *P. falciparum* parasitaemia count of >0 parasites/μL was detected in the thick or thin smears. Parasite examination was done according to quality-controlled standardised procedures described elsewhere [11].

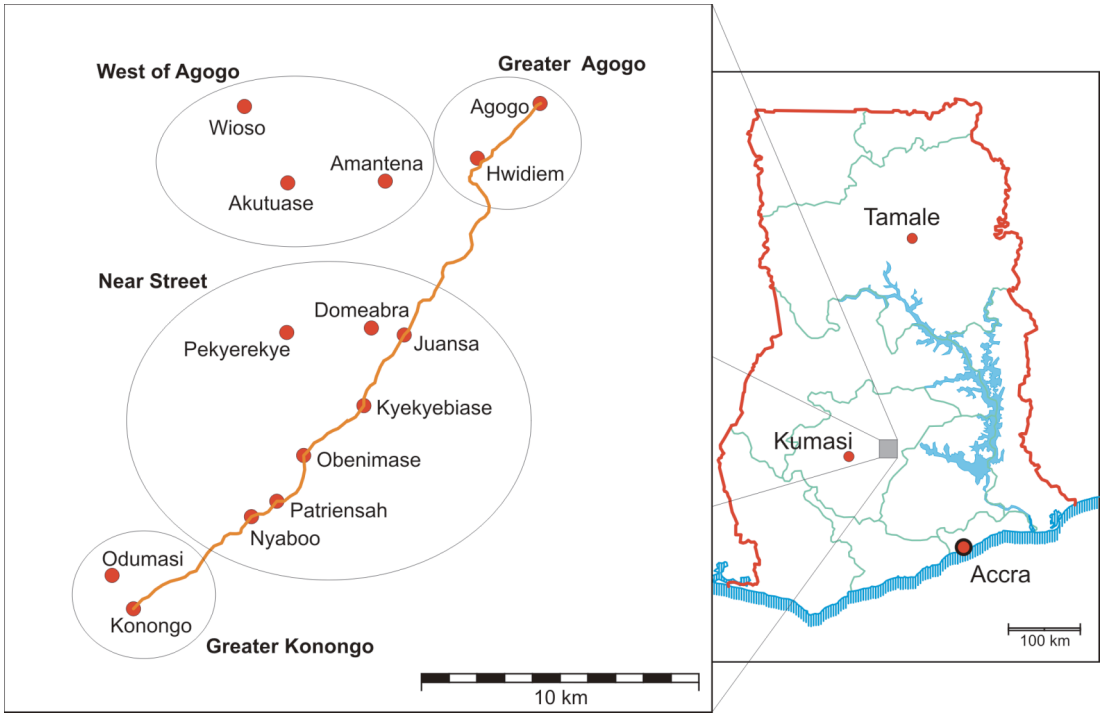

Figure 1: Map of the 14 included villages and village clusters in the Asante Akim North District, Ashanti Region, central Ghana, West Africa. Red dots indicate villages; the solid line indicates the main road.

Data collection

Information on personal or family characteristics with a possible influence on malaria (sex, ethnic group, age, mother's age, use of protective measures [usage of bed net, window net, other or no protection], number of children and place of residence), and information about factors indicating the family's financial situation (living in a brick or wood/mud house, existence of electricity, water supply, mother's education and profession, father's education and profession, indoor toilet and use of freezing as measure of conservation, income management, existence of a relative abroad for possible financial, support and membership in the national Health Insurance Scheme [NHIS]) was collected through interviewing a parent or the guardian who accompanied the child to the hospital using a structured interview with a questionnaire in

English or if necessary in the local language, Twi. The question sheet was composed according to standard questionnaires adjusted to local requirements and appropriateness. Data from questionnaires and forms were double entered after case closed, plausibility checked, and cleaned before the database was locked. All information on participants and their parents was treated confidentially. Only children who were examined for malaria and where information about the sociodemographic and socioeconomic situation was available were included in the analysis (n=1,496).

The study was approved by the Committee on Human Research, Publications, and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Data analysis

Participants were allocated into one of the four village clusters described above (Greater Agogo, Greater Konongo, West of Agogo, and Near Street), according to their place of residence. Additionally, all participants were classified into two ethnic groups according to their tribal background: the Akan and those who are the natives of the area and the Northeners who have a migratory background but are now permanent residents of the area. It was hypothesised that children between the ages of 1 to 5 years are at highest risk of acquiring malaria; hence we stratified for age (≤1 year, >1 to ≤5 years, and >5 years). It was also suggested that the mother's age might be of importance for the child and its risk for malaria; all mothers were stratified and grouped to young mothers (≤30 years) and older mothers (>30 years). High numbers of children living in a household were assumed as an influence factor (two groups: ≤4 children and >4 children). Additionally, it was asked in the interview whether a family used protective measures such as bed nets or window-screens. Individuals with missing values on any of these variables (n=18) were excluded from the analysis (n=1,478).

To classify the family's economic status, the following socioeconomic indicator variables were considered: mother's and father's profession (employed/unemployed) and education (ability to read and write: yes/no), type of house the family is living in (cement/brick house or mud/wood house), water supply (open water source/closed

water source), existence of an indoor kitchen (Yes/No), electricity (Yes/No), indoor toilet (Yes/No), use of freezing as measure of conservation (Yes/No), existence of a relative abroad who might financially support the family (Yes/No), the self-rated ability to manage with the available monthly income (difficult or not difficult) as well as the membership in the health insurance (Yes/No). All socioeconomic and sociodemographic data including information on protective measures based on self-reports of the mothers or guardians and were not confirmed by direct observations during household visits.

For the sake of the multivariable analysis, a principal component analysis (PCA) was applied to those socioeconomic indicator variables, which showed relevant contributions (>10%) to the combined socioeconomic status score factor [12]. The factor of the PCA with the highest eigenvalue was used as the variable, which describes sufficiently the socioeconomic status of a household. The respective factor scores were categorised in terciles and used in the regression analysis. The lowest 33% of households according to the economic status variable were classified as poor, the highest 33% as rich, and the rest as average economic status [13].

For the PCA, missing values of distinct binary variables were replaced by the means of all summarised “0” values (asset not present) and “1” values (asset present) of this variable (n=1,496) [12]. This approach may have reduced variation among households and may have increased the potential for clumping and truncation [12,14]. In the presented study population, the percentage of households with missing values was, however, small (<1%) and such a bias might be negligible.

For each potential risk factor of malaria, the odds ratio (OR) was calculated and the significance level was tested by the chi-square test. Adjusted ORs were estimated by multivariate logistic regression. Confounding was determined as a relative difference of 15% between crude odds ratios and odds ratios adjusted for predefined covariates without signs of effect modification. All covariables in the multivariate regression model were examined for possible effect modification by Wald tests and preference of the model with interaction by log-likelihood tests (both $p<0.05$).

Results

In total, 1,496 children were examined for malaria parasites and participated in the questionnaire survey; 1,478 without missing values were included in the multivariate model. Most participants came from the region Greater Agogo (n=871), fewer came from Greater Konongo (n=333), Near Street (n=229), and West of Agogo (n=63). Most malaria cases were reported from Greater Agogo (n=364), followed by Greater Konongo (n=66), Near Street (n=61), and West of Agogo (n=21) (see additional file 1).

Of those variables with a possible influence on malaria use of individual control measures had a protective effect on malaria (crude OR=0.69, p=0.02). Malaria odds were increased if a child was between >1-<5 or above 5 years of age (OR=3.41, and OR=2.07, both p<0.001). Notably, the area of residence was strongly associated with the frequency of malaria. About twice as many children living in Greater Agogo visited the hospital with malaria than children from Greater Konongo (OR=2.9, p<0.001). The variables “ethnic groups”, “sex”, “mother’s age”, and “number of children in the family” did not show any significant association with malaria (see additional file 1).

Of those factors indicating the family’s socioeconomic status the proportion of literate fathers was very high (>75%) and evenly distributed under children with and without malaria. Likewise, the variables “house type”, “income manage”, “membership in a health insurance”, “existence of an indoor kitchen”, and “mother’s and father’s occupation” did not show any distinct association with malaria (see additional file 1). In the univariate analysis, the variables “existence of electricity”, “indoor toilet”, “use of freezing as food conservation”, “mother’s ability to read and write”, and a “closed water supply” were negatively associated with malaria odds (OR=0.72, OR=0.67, OR=0.63, OR=0.68, OR=0.70, respectively, all p-values <0.01). Additionally, the variable “existence of a relative abroad”, known to be indicative for a substantive contribution to the household income in Africa, had a protective effect on malaria (p=0.05). All variables with relevant contributions (>10%) to the combined socioeconomic score were used to generate a combined socioeconomic indicator by PCA; hence “mother’s occupation” and “father’s occupation” were excluded from the final PCA (weight mother’s occupation and father’s occupation: 5% and 4%,

respectively).

The results of the PCA are presented in Table 1. The eigenvalues demonstrated that one principal factor had a weight greater than two (2.20) and thus was suited to appropriately represent the socioeconomic status in further analyses. This variable (Factor 1 in Table 1), now interpreted as a socioeconomic score, explained 20% of the variance of the 11 original variables. All variables included in the PCA had positive factor scores, and therefore were associated with higher socioeconomic status. Freezing as measure of conservation had, with a weight of 0.65, the highest contribution to the combined socioeconomic status score (Table 1), membership in the NHIS had the lowest impact on the combined indicator with a weight of 0.15. For further analyses, we classified the socioeconomic score in three categories using tertiles: “poor”, “average”, and “rich”. The village clusters Greater Agogo and Near Street had the highest proportion of households considered poor with 38% and 35%, respectively. In Greater Konongo was the highest proportion of households categorised as being rich (47%). Most malaria cases were reported from individuals classified as “poor” (n=202, 39%) followed by those grouped as “average” (n=189, 37%), and “rich” (n=121, 24%).

Additionally, clumping and truncation (if the distribution of scores tend not to follow a normal curve or if they were skewed) was checked by using a histogram to show the distribution of socioeconomic scores. Internal coherence for our study region could be shown, suggesting appropriate and sufficient choice of asset variables.

Table 1: Results from the principal component analysis (PCA)

Factor	Eigenvalue	Variance proportion	Cumulative variance proportion
Factor 1	2.20	0.20	0.20
Factor 2	1.07	0.10	0.30
Factor 3	1.06	0.10	0.40
Factor 4	1.01	0.09	0.49
Factor 5	0.97	0.09	0.57
Factor 6	0.94	0.09	0.66
Factor 7	0.85	0.08	0.74
Factor 8	0.82	0.07	0.81
Factor 9	0.76	0.07	0.88
Factor 10	0.71	0.06	0.94
Factor 11	0.62	0.06	1.00
Observed variable	**Weight for factor 1 (economic status score)**		
Freezing as conservation	0.65		
Education mother	0.58		
Toilet supply	0.56		
Electricity	0.53		
House type	0.47		
Education father	0.43		
Income manage	0.43		
Relative abroad	0.33		
Water supply	0.27		
Cooking	0.22		
NHIS	0.15		

All potential risk factors, together with the newly created variable describing the socioeconomic status, were included in the final logistic regression model to assess their independent effect on malaria risk (Table 2). In the full multivariable model, an independent association was seen for the family's socioeconomic status. In comparison to the poor group, belonging to the group of average socioeconomic status decreased the odds to 0.88 ($p=0.35$), and being rich decreased the odds for malaria further to 0.56 ($p<0.001$). The results remained consistent in the parsimonious stepwise logistic regression. All significant risk factors were checked

for effect modification with place of residence, but none could be detected.

Table 2: Influence of socioeconomic and sociodemographic factors on malaria in a multivariate logistic regression analysis

				Stepwise logistic Regression		
Determinants	**OR[1]**	**CI[1]**	**p-value**	**OR[1]**	**CI[1]**	**p-value**
Reference[*]	1					
Economic status[2]						
'average'	0.88	0.66 - 1.16	0.35	0.88	0.67 - 1.15	0.34
'rich'	0.56	0.41 - 0.76	<0.001	0.56	0.42 - 0.75	<0.001
Use of protection measures[3]	0.71	0.51 - 1.00	0.05	0.72	0.51 - 1.00	0.05
Age >1 - ≤5 years	3.34	2.57 - 4.36	<0.001	3.39	2.61 - 4.40	<0.001
Age >5 years	2.10	1.52 - 2.88	<0.001	2.04	1.51 - 2.75	<0.001
Place of Residence						
West of Agogo	0.77	0.43 - 1.37	0.38	0.78	0.44 - 1.37	0.38
Near street	0.52	0.37 - 0.74	<0.001	0.51	0.36 - 0.72	<0.001
Greater Konongo	0.39	0.28 - 0.53	<0.001	0.39	0.29 - 0.54	<0.001
Ethnic group	0.90	0.63 - 1.29	0.58			
Number of children	1.19	0.87 - 1.64	0.28			
Sex	0.88	0.70 - 1.10	0.26			
Mother´s age	1.02	0.78 - 1.33	0.91			

[*] Reference: Economic status ‚poor', no use of protection measures, age ≤1year, place of residence ‚Greater Agogo', Ethnic group ‚Northeners', >4 children, sex: male, mother age ≤30 years of age

[1] OR = odds ratio mutually adjusted with all other variables in a multivariable logistic regression; CI = confidence interval; p-value = chi-square test

[2] Economic status classified by using factor 1 of PCA (Table 1)

[3] Reported protection measures such as bed net or window fences

Discussion

The analysis showed that, in an area of high endemicity, the proportion of malaria in children presented to a hospital is markedly influenced by the socioeconomic status of the family: children from households classified as poor had a significantly higher chance to get malaria. This is in agreement with previous reports on distinct

socioeconomic risk factors for malaria [6-8,15,16]. One possible explanation of this observation is that the proportion of children using protective bed nets increases with the socioeconomic status as reported before [17,18]. However, after adjustment for the use of bed nets in the multivariate analysis an association of the socioeconomic status with malaria still remained. Other possible explanations for the association between malaria and socioeconomic status are (i) differences in the coverage of health insurance [19] which was, however, not of significant influence in the univariate analysis, (ii) differing access to health facilities, whereas such a selection bias might be low due to the hospital-based study design, (iii) various environmental or housing conditions in the vicinity of households e.g. preferred habitats or breeding sites for vectors what is difficult to exclude [20,21].

Socioeconomic levels might also be associated with diseases beyond malaria and may influence the proportion of malaria cases among all children seen in the hospital. This would have an indirect influence on the calculated odds ratios. However, the two symptom complexes predominant in children without malaria, namely respiratory distress and gastrointestinal symptoms, were not or only weakly associated with socioeconomic levels. The study design, which bases on a single hospital, might limit the generalisation of the results to other regions. On the other hand, the focus on one hospital allowed the thorough collection of data on the clinical condition, infectious disease agents, and exact diagnosis.

One problem of the determination of individual socioeconomic levels in Africa is the fact that unambiguous quantitative measures often do not exist and various proxy measures must be used as an approximation. The use of single variables as risk indicators often leads to false conclusions because they only reflect parts of the general view. In contrast, in PCAs socioeconomic indicator variables were combined to enable a quantification and classification of individual socioeconomic levels and to use the resulting score for risk analyses. The PCA showed that usage of a freezer as conservation method, which was interpreted as ownership of a freezer in a household, had the highest weight for the socioeconomic score. On the other hand, having a health insurance was the smallest compared to the other 10 variables and, hence, was of a minor importance for the socioeconomic score.

An advantage of the PCA is that it reduces measurement problems, such as recall bias, and that it reduces the complexity of correlated data, which can be easily collected as single indicator variables in household surveys [12,22]. On the other hand, the process of generalisation leads to a loss of information, the criteria for the selection of variables for PCA are not well defined, and the number of selected components is arbitrary. Whether a single principal component can sufficiently determine the socioeconomic status is entirely dependent on the data and the correlation matrix of the variables, their validity, and reliability [12].

Apart from the socioeconomic status, sociodemographic factors were associated with malaria. As expected the malaria risk was highest in the age group of children between 1 and 5 years, compared to children below the age of 1 year [23] and lower in children from families, which reported the use of mosquito protection measures [16,24]. There was a decrease of odds for malaria with increasing distance from the study hospital. A simple selection bias is not a sufficient explanation for that observation since all children included had access to the hospital. However, it is conceivable that the willingness to bring a child with malaria symptoms decreases with increasing distance from the study hospital and, in contrast, the readiness to bring a child with other symptoms is more independent from distance. If so, the relative contribution of malaria cases decreases with distance and this would falsely suggest a protective effect of distance against malaria. Nevertheless, data from a recently performed community survey in the same area showed that the health seeking behaviour among differing symptoms did not change with distance. It was not possible to include the village population size as influence factor due to the village-cluster based analysis. Geographical risk factors seem to exist independently from other influences, maybe through environmental and habitat factors favouring the occurrence of vectors. To assess environmental influence factors remotely sensed data with high resolution should be analysed with geographic information systems (GIS) to detect microspatial patterns in relation to malaria risk.

Age of mothers did not influence the occurrence of malaria of their children. However, in the study group only 3% of the mothers were younger than 20 years of age, which does not represent the mother's age distribution in Ghana or other African countries. Although ethnicity was found to influence malaria risk in a study conducted

in an adjacent region in Ghana [6] this could not be confirmed in the presented study possibly due to the predominance of one ethnic group.

Conclusions

In conclusion, the herein presented results show that children from poorer households are of greater risk for malaria. It is under discussion how far poverty influences the occurrence of malaria or malaria influences the occurrence of poverty. In either case, the fight against malaria has to be escorted by the fight against poverty and improvement of living standard. Moreover, the spatial variability of malaria risk might be of importance for the planning of control measures and the conduction of intervention trials.

Competing interests

The authors declare that they have no competing interests.

Authors´ contributions

ACK participated in the conception, performed the statistical analysis, was involved in the interpretation of results and participated in drafting the results. NGS participated in the design, assisted in performing the statistical analysis, was involved in the interpretation of the results, and helped to draft the manuscript. WL created Case Report Forms and was responsible for data management and data preparation for analyses. UR was involved in the initial design of the study, assisted in performing the statistical analysis and participated in drafting the manuscript. JM conceived and coordinated the study, was involved in the initial design of the study and writing of the manuscript. NS organized the day-to-day work on the ground, BN and SA carried out the malaria parasite examination and contributed to the writing of the manuscript, and YAS planned, initiated the study, and reviewed manuscript. All authors have read and approved the final manuscript.

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Additional file 1: Characteristics of the study group

The table shows the results of a first univariate analysis including variables which give information on personal or family characteristics with a possible influence on malaria and information about factors indicating the family's financial situation.

Characteristics of the study group

Characteristic	Malaria yes	Malaria no	OR	CI	p-value
	n=512	n=984			
Sex					
Male	278 (35%)	522 (65%)	1		
Female	234 (34%)	462 (66%)	0.95	0.77 – 1.18	0.65
Place of residence					
Greater Agogo	364 (42%)	507 (58%)	1		
West of Agogo	21 (33%)	42 (67%)	0.70	0.41 – 1.20	0.19
Near Street	61 (27%)	168 (73%)	0.51	0.37 – 0.70	<0.001
Greater Konongo	66 (20%)	267 (80%)	0.34	0.25 – 0.47	<0.001
Ethnic group[1]					
Northeners	70 (39%)	108 (61%)	1		
Akan and others	441 (33%)	876 (67%)	0.78	0.56 – 1.07	0.12
Age child					
≤ 1 year of age	147 (22%)	522 (78%)	1		
>1-≤ 5 years of age	244 (49%)	254 (51%)	3.41	2.65 - 4.40	<0.001
> 5 years of age	121 (37%)	208 (63%)	2.07	1.55 – 2.76	<0.001
Age mother					
≤ 30 years of age	265 (33%)	540 (67%)	1		
> 30 years of age	247 (36%)	444 (64%)	1.13	0.92 – 1.40	0.25
Protective measure					
No protection	73 (42%)	101 (58%)	1		
Protection[2]	437 (33%)	878 (67%)	0.69	0.50 – 0.95	0.02
Mother´s occupation					
Unemployed	63 (37%)	107 (63%)	1		
Employed	442 (34%)	867 (66%)	0.87	0.62 – 1.21	0.39
Father´s occupation					
Unemployed	5 (28%)	13 (72%)	1		
Employed	498 (34%)	966 (66%)	1.34	0.47 – 3.78	0.58
Mother´s education[3,5]					
No	340 (37%)	571 (63%)	1		
Yes	165 (29%)	410 (71%)	0.68	0.54 – 0.85	<0.001

(*table continuous*)

Father´s education[3,5]					
No	123 (38%)	200 (62%)	1		
Yes	375 (33%)	774 (67%)	0.79	0.61 – 1.02	0.07
Water supply[4,5]					
Open water	118 (41%)	170 (59%)	1		
Closed water	392 (33%)	812 (67%)	0.70	0.53 – 0.91	0.007
Children, no					
> 4 children	103 (35%)	188 (65%)	1		
≤ than 4 children	403 (34%)	792 (66%)	0.93	0.71 – 1.21	0.59
House type[5]					
Mud/wood	61 (31%)	137 (69%)	1		
Brick/cement	449 (35%)	846 (65%)	1.19	0.86 – 1.65	0.29
Income manage[5]					
Difficult	295 (36%)	526 (64%)	1		
Not difficult	210 (32%)	455 (68%)	0.82	0.66 – 1.02	0.08
Health insurance[5]					
No	126 (32%)	265 (68%)	1		
Yes	365 (35%)	682 (65%)	1.13	0.88 – 1.44	0.35
Cooking[5]					
Outside	143 (33%)	288 (67%)	1		
Inside	367 (35%)	695 (65%)	1.06	0.84 – 1.35	0.61
Electricity[5]					
No	139 (40%)	209 (60%)	1		
Yes	367 (32%)	768 (68%)	0.72	0.56 – 0.92	0.009
Toilet supply[5]					
Outdoor	264 (39%)	409 (61%)	1		
Indoor	248 (30%)	575 (70%)	0.67	0.54 – 0.83	<0.001
Relative abroad[5]					
No	419 (35%)	764 (65%)	1		
Yes	89 (29%)	214 (71%)	0.76	0.58 – 1.00	0.05
Freezer usage[5]					
No	379 (37%)	639 (63%)	1		
Yes	116 (27%)	312 (73%)	0.63	0.49 – 0.80	<0.001
Economic status[6]					
poor	202 (41%)	287 (59%)	1		
average	189 (36%)	332 (64%)	0.81	0.63 – 1.04	0.10
rich	121 (25%)	365 (75%)	0.47	0.36 – 0.62	<0.001

OR = odds ratio, CI = confidence interval, p-value = chi-square test
[1] Ethnic groups „Others“ = Ewe, Ga, Other, not clear
[2] Protection = Bed net, Other, Window net
[3] Education = Ability to read and write
[4] Closed water source = Inside tap or Stand pipe; open water source = River or well
[5] Variables included in the Principal component analysis
[6] Computed by means of Principal component analysis

Chapter 3

Modeling the Relationship between Precipitation and Malaria Incidence in Children from a Holoendemic Area in Ghana

Modeling the relationship between precipitation and malaria incidence in children from a holoendemic area in West Africa

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Abstract

Climatic factors influence the incidence of vector-borne diseases such as malaria. They modify the abundance of mosquito populations, the length of the extrinsic parasite cycle in the mosquito, the malarial dynamics, and the emergence of epidemics in areas of low endemicity. The objective of this study was to investigate temporal associations between weekly malaria incidence in 1,993 children <15 years of age and weekly rainfall. A time series analysis was conducted by using cross-correlation function and autoregressive modeling. The regression model showed that the level of rainfall predicted the malaria incidence after a time lag of nine weeks (mean = 60 days) and after a time lag between one and two weeks. The analyses provide evidence that high-resolution precipitation data can directly predict malaria incidence in a highly endemic area. Such models might enable the development of early warning systems and support intervention measures.

Introduction

Malaria is the most common vector-borne infectious disease in the world, with nearly 250 million estimated clinical cases among 3.3 billion people under risk in 2008 and approximately one million deaths each year [1]. With a vast majority of cases (85%) Sub-Saharan Africa carries most of the burden [1,2]. In malaria-endemic areas children <5 years of age are at highest risk of malaria morbidity and mortality. The number of disability-adjusted life years, a measure of disease burden caused by malaria, was estimated to be 34 millions for 2004 worldwide, with 31 millions in Sub-Saharan Africa [3]. Malaria alone costs Africa's economy more than US$ 12 billion annually [4]. In the Ashanti Region of Ghana, malaria is prevalent during the entire year and one of the major in-patient causes of death [5].

In contrast to a retrogressive trend of malaria morbidity and mortality in some areas, malaria burden has been increasing in many other areas because of factors such as deteriorating health systems, growing drug and insecticide resistance, failure of water management, and climate, socioeconomic, sociodemographic, and land-use factors [1,6,7]. Simple methods that enable accurate forecasting, early warning, and timely case detection in low- and high-transmission areas are needed to enable implementation of more effective control measures [8,9].

Climate and meteorological factors (precipitation, temperature, and relative humidity) have considerable impact on *Anopheles* vector abundance and the extrinsic cycles that the parasites perform inside mosquitoes. Thus, they may affect malaria incidence and constitute driving forces of malaria epidemics [10-12]. Therefore, precipitation, which is probably the most important climatic factor in tropical areas with relatively constant temperature and humidity, was the focus of our models.

Our objective was to investigate the association between weekly malaria incidence in children <15 years of age and rainfall in two village clusters of high endemicity during an 18-months period (end of May 2007 to the end of November 2008) to assess the extent to which precipitation data can be used to predict malaria incidence in a holoendemic area.

Materials and Methods

Study area

This hospital-based survey was conducted at the Child Welfare Clinic and the Pediatric Ward of the Agogo Presbyterian Hospital, Asante Akim North District, Ashanti Region, Ghana (Figure 1). The district lies within the moist semi-deciduous forest belt, although there are some transitional zones caused by farming and logging activities. The climate is tropical and has a mean annual ambient temperature of 26°C and two rainy seasons; the first occurs during May-July and the second occurs during September-November with monthly rainfall up to 400 millimeters. The dry season or the harmattan (a dry and dusty West African trade wind from the arid and dessert areas north of Ghana) occurs during December-April and is associated with drought conditions. The topography of the study district is generally undulating and the altitude variation is approximately 600 meters between the lowest area near the Volta Lake (152 meters) and the Akwapim-Mampong range (≤762 meters). The local economy is mainly agriculture; major staple food crops include maize, cassava, plantain, cocoyam, and yam [13].

The main malaria vectors are mosquitoes of the *Anopheles gambiae* complex and *A. funestus*. Malaria is holoendemic in this area, *Plasmodium falciparum* accounts for most (>90%) human malaria infections [14].

In this study, two village clusters of four villages were included: two (Agogo and Hwidiem) in Greater Agogo and two other adjacent villages (Konongo and Odumasi) in Greater Konongo (Figure 1). The two areas are approximately 20 km apart and are connected by a main road.

The population figures according to the 2004 census were 13,559 and 1,402 for Agogo and Hwidiem, respectively, and 15,383 and 8,502 for Konongo and Odumasi, respectively. Greater Agogo has an area of 16 km^2 and an altitude of 430 meters above sea level. Greater Konongo has an area of 18 km^2 and an altitude of 230 meters above sea level.

Figure 1: Map of the two village clusters Greater Agogo (Agogo and Hwidiem) and Greater Konongo (Konongo and Odumasi), Asante Akim North District, Ashanti Region, central Ghana. Circles indicate the two village clusters, and the solid line indicates the main road. There are additional settlements along the main road.

Data collection and analysis

All hospital visits of children <15 years of age from the two village clusters were included. Criteria were an axillary temperature ≥37.5°C and a positive result for a *P. falciparum* parasitemia (>0 parasites/μL) during the study period of 80 weeks (end of May 2007 to the end of November 2008). Parasite examinations were conducted according to quality-controlled standardised procedures described elsewhere [15]. Children with cases of malaria who visited the hospital within 21 days after the initial malaria diagnosis were considered as relapses and were not included as a new case. The study was reviewed and approved by the Committee on Human Research, Publications, and Ethnics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

For the calculation of cumulative incidences, population size, admission rate, proportion recruited, and proportion of the population seeking health care in the study hospital were considered. We used census data to determine that 42% of the population was <15 years of age [16]. According to a community survey conducted in 2007, 93% of persons from Greater Agogo and 25% of persons from Greater Ko-

nongo were seeking health care at the Agogo Presbyterian Hospital. The denominator/reference population was corrected for these proportions. Likewise, the reference population was corrected for the proportion of children that met the inclusion criteria but were not recruited (30%). Weekly malaria incidences per 1,000 inhabitants <15 years of age were then calculated for each village cluster.

Data on daily rainfall in Agogo and Konongo during March 2007 - November 2008 (90 weeks) were obtained from the Ghana Meteorological Agency (Accra, Ghana). For both areas, weekly precipitation was calculated.

To model the association between rainfall and malaria incidence during March 2007 - November 2008 in the two clusters by linear regression analysis, we used the logarithm of the weekly incidence. If the number of weekly malaria cases equaled zero, we assumed the logarithm of half of the minimum weekly incidence excluding zero. The cross-correlation function between the time series of the weekly precipitation and the log-transformed weekly incidence was analysed to assess time lags with peak correlations between the course of malaria incidence and the course of precipitation. These time lags were used in the linear regression of precipitation on log-transformed malaria incidence. Furthermore, to account for autoregression of the incidence time series, autoregressive terms of white noise had to be included in the regression model. The following general regression model results were used:

$$\log[I_t] = \mu + \sum_{i=1}^{k} \alpha_i \cdot R_{t-l(i)} + e_t + \sum_{i=1}^{m} \beta_i \cdot e_{t-i}$$

where I_t = incidence, R_t = precipitation and e_t = white noise (e~N(0,1)) at time t, μ = geometric mean of weekly incidence, $l(i)$ = ith lag (i = *1,...,k*), and α_i (i = *1,...,k*) and β_i (i = *1,...,m*), respectively, being regression coefficients.

The regression models were applied to estimate expected incidence. Furthermore, using the estimated and observed malaria incidence, we determined that the amount of explained variance (R^2) could provide a measure of overall goodness-of-fit. STATA/SE software version 10 (StataCorp LP, College Station, TX) was used for calculations.

Results

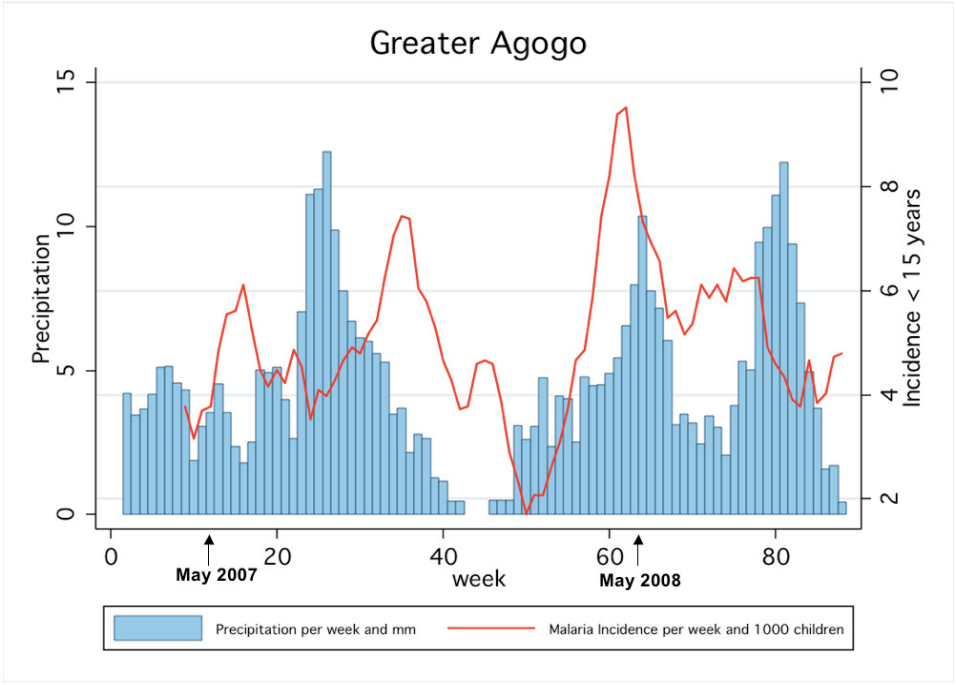
During the study period, a total of 7,313 hospital visits by children <15 years of age were reported: 5,276 cases from Greater Agogo and 2,037 cases from Greater Konongo. A total of 1,993 (27%) fulfilled the case definition for malaria and thus were included in the analysis. The annual incidence was 270.6 and 144.2 per 1,000 per year in Greater Agogo and Greater Konongo, respectively. The weekly incidence per 1,000 inhabitants and weekly precipitation varied over time in both village clusters (Table 1, Figure 2).

Table 1: Population, incidence and precipitation in the two village clusters

	Greater Agogo	Greater Konongo
Total population	14,961	23,885
Children <15 years of age	5,140	2,008
No of malaria cases[1]	1,610	383
Total yearly incidences[2]	270.6	144.2
Minimum weekly incidences[3]	1.0	0
Maximum weekly incidences[3]	12.4	7.3
Minimum weekly precipitation[4]	0	0
Maximum weekly precipitation[4]	20.3	30.2

[1] No of cases over the study interval of 80 weeks (end of May 2007 – end of November 2008)
[2] Incidences per year and 1,000 inhabitants
[3] Incidences per week and 1,000 inhabitants
[4] Mean weekly precipitation in millimeters

The weekly malaria incidence lagged a few weeks behind weekly precipitation (Figure 2). The cross-correlation functions for the two village clusters showed a seasonal pattern of the influence of precipitation on the log-transformed incidence (Figure 3). The cross-correlation function of Greater Agogo clearly indicated a 26-week cycle. Because of low case numbers, the cross-correlation function of Greater Konongo exhibited a large fluctuation with respect to a sinusoidal course. However, the phase difference i.e., the time lag between a peak in precipitation and in malaria incidence was nine weeks for both areas. Additionally, peaks of the cross-correlations functions at lags of one week and two weeks in Greater Konongo and in Greater Agogo, respectively, indicated a relevant influence of preceding rainfall events on malaria incidence.



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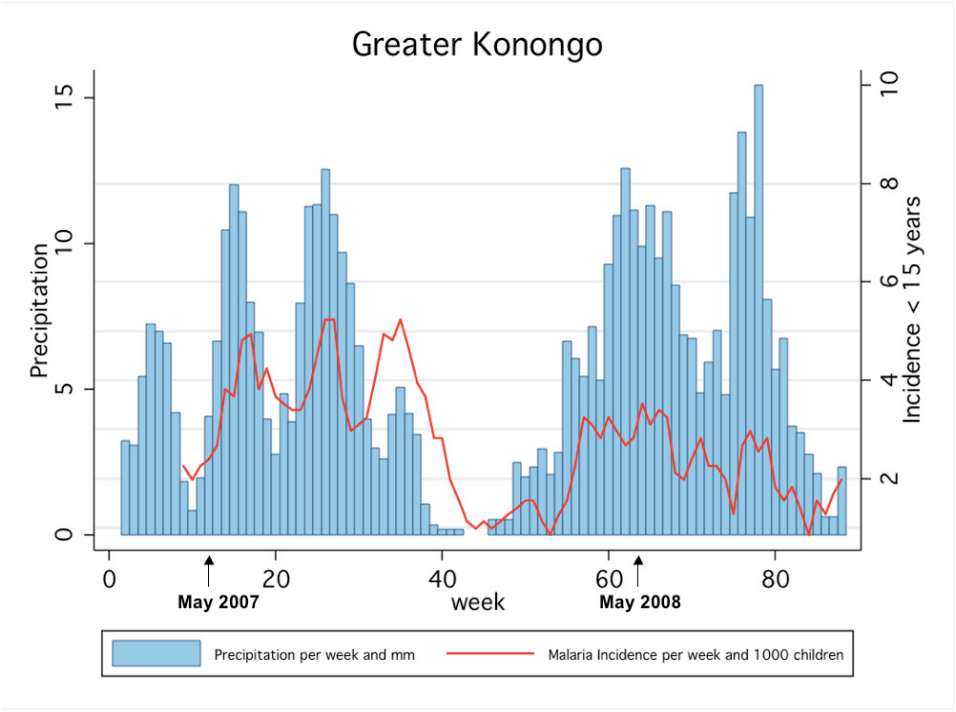

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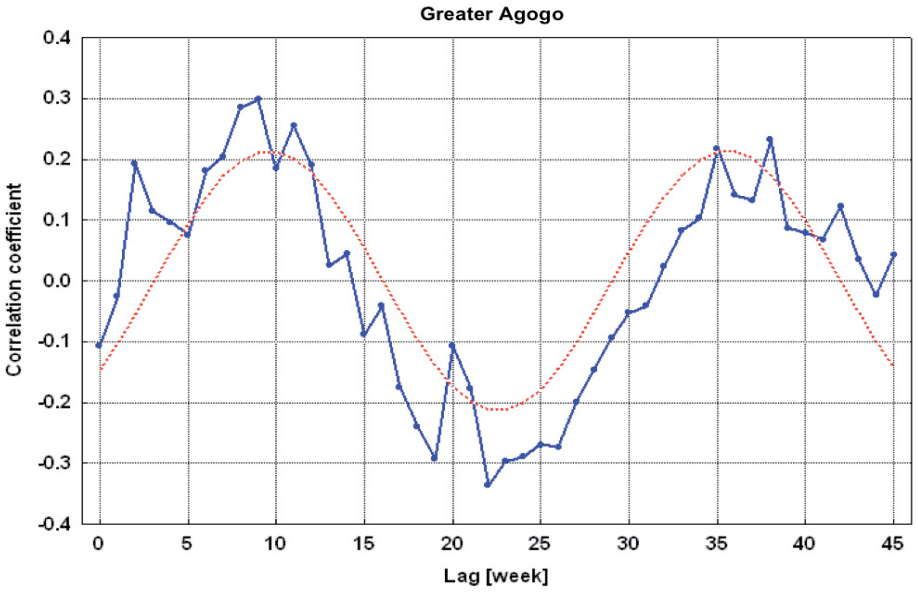
Figure 2: Weekly precipitation and four-weeks average of malaria incidences per week and 1,000 children <15 years of age in the two village clusters, Ghana. (a) Greater Agogo and (b) Greater Konongo.



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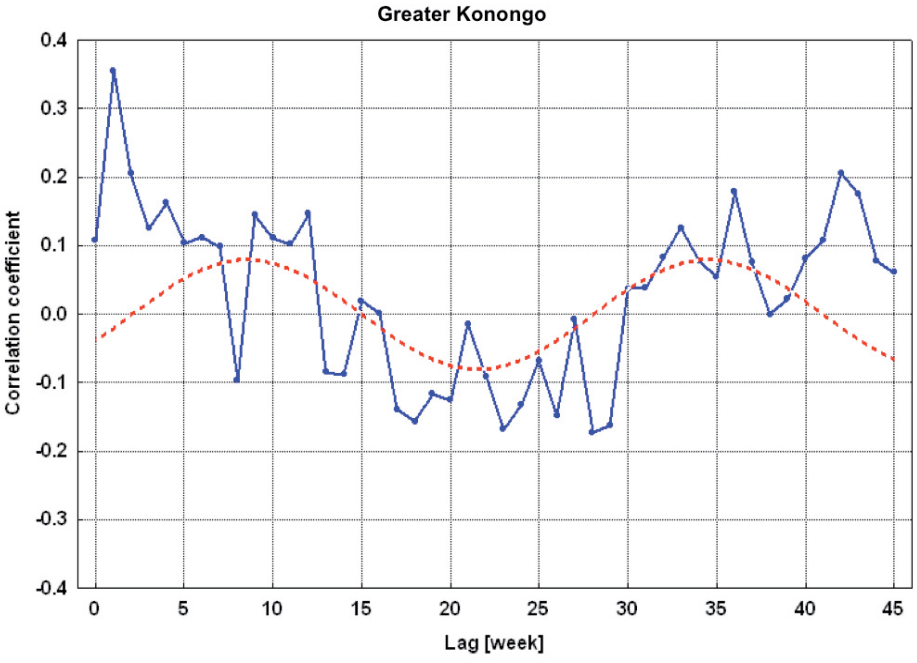


(b)

Figure 3: Cross-correlation between log-transformed malaria incidences of children <15 years of age and precipitation in the two village clusters, Ghana. (a) Greater Agogo and (b) Greater Konongo.
The dashed lines represent approximations of the cross-correlation functions by sinus functions with period length of a half year, i.e., 26 weeks.

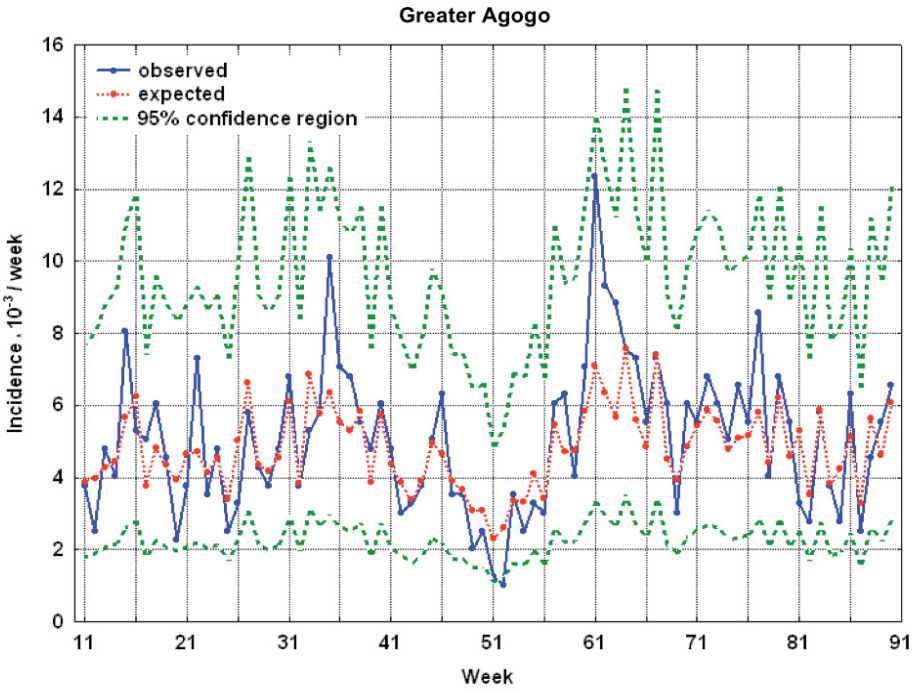
If one considers the results of the cross-correlation between precipitation and incidence, time lags of nine weeks for both village clusters and one and two weeks for Greater Konongo and Greater Agogo, respectively, were applied for regression modeling. A first-order autoregressive term for the white noise was sufficient to model the autocorrelation of the incidence. For the village cluster of Greater Agogo, all coefficients of the regression model were statistically significant, and the model could explain 63% of incidence variation (R^2 = 0.634) (Table 2). Because of low case numbers in Greater Konongo, the regression model could explain only 31% of incidence variation (R^2 = 0.311), but with similar regression coefficient (Table 2).

Table 2: Estimated model parameters

	Greater Agogo			Greater Konongo		
Model parameter [1]	**Coefficient**	**SE** [2]	**p-value** [3]	**Coefficient**	**SE** [2]	**p-value** [3]
Mean log incidence rate [μ] [4]	1.366	0.097	<0.001	0.381	0.158	0.016
lag: 1 week [α_1] [5]	--	--	--	0.042	0.014	0.003
Lag: 2 weeks [α_1] [5]	0.022	0.009	0.017	--	--	--
Lag: 9 weeks [α_2] [5]	0.017	0.009	0.051	0.022	0.014	0.122
White noise [β_1]	0.467	0.103	< 0.001	0.262	0.112	0.019
R^2 [6]	0.634			0.311		

[1] For explanation of model parameters see text (model formula)
[2] Standard error
[3] By t-test
[4] Unit = 10^{-3}/week
[5] Unit = mm/week
[6] Explained variance by regression model

Observed and expected malaria incidences including 95% confidence intervals in children <15 years of age according to regression modeling in the two village clusters are shown in Figure 4. The time series of expected malaria incidences, estimated by the regression models, clearly showed a time pattern that closely followed the time pattern of the observed incidences.



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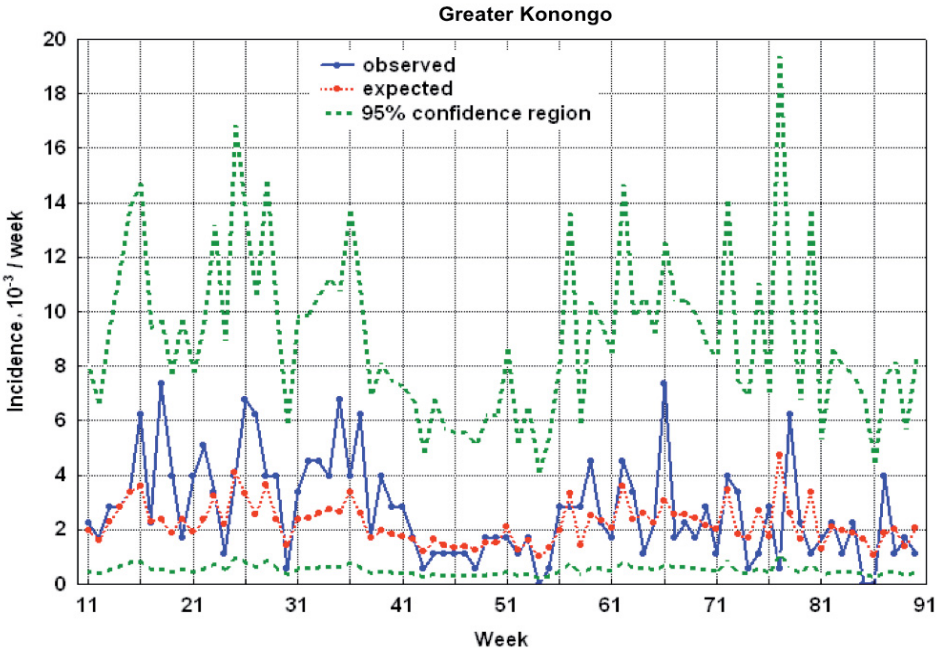

(b)

Figure 4: Weekly malaria incidence per 1,000 of children <15 years of age in the two village clusters, Ghana. (a) Greater Agogo und (b) Greater Konongo. Observed incidence (continuous line) and expected incidence by means of regression modeling with precipitation as predictor (dashed line) with 95% confidence interval (broad dashed lines).

Discussion

The analysis of the malaria epidemiology in two village clusters in Ghana with high endemicity indicated a strong temporal association between rainfall and incidence of malaria. The cross-correlation functions gave the most appropriate congruence of malaria incidence and precipitation with a time lag of nine weeks (mean = 60 days). This period coincides with the theoretical vector-parasite-host cycle of the three organisms involved under optimum conditions, assuming that the first blood meal of *Anopheles* is on an infected human and that the temperature is at mean ≥25°C (Figure 5). This cycle has three components: 1) the growth of the *Anopheles* vector from egg to adults that are able to transmit parasites; 2) the development of the *Plasmodium* parasite in the vector from gametocytes to sporozoites that are able to infect humans; and 3) the incubation period in the human host from infection to the onset of malarial symptoms [17,18]. According to this timeline, an incidence peak can be expected between day 50 and 60 after breeding (Figure 5).

Additionally, the cross-correlation functions showed a strong association between rainfall and the malaria incidence one or two weeks later dependent on the village cluster. This shorter time lag might be caused by higher biting activities of adult mosquitoes at the beginning of rainy season and in due course breeding habitats for the mosquito that soon become available [19,20].

The modulation of the estimated and observed incidences was less coherent in Greater Konongo than in Greater Agogo (demonstrated by a smaller R^2 in Greater Konongo), which may be explained by the lower case numbers and therefore a decreased power. Amplitudes of the expected incidences were lower than those of observed incidences because of the phenomenon of the regression to the mean.

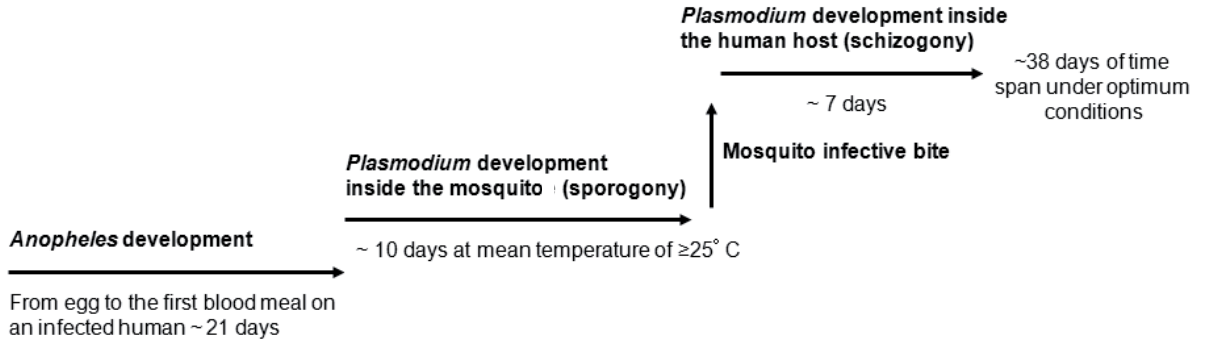

Figure 5: Model of time required from precipitation and deposition of mosquito eggs to onset of malarial symptoms in the human host under optimal conditions. In our study site in Ghana, *Anopheles* development needs approximately 19 days in total. Two days after hatching, the female *Anopheles* mosquitoes need their first blood meal and after uptake of gametocytes, the development in the mosquito (sporogony) takes a minimum of 10 days. After transmission of sporozoites during a bite by an infective mosquito, *Plasmodium* development in the human host (schizogony) takes approximately seven days. Therefore, it takes a minimum of approximately 38 days under optimum conditions from precipitation and deposition of mosquito eggs to the outcome malaria (assuming that the first blood meal of *Anopheles* is on an infected human and that the mean temperature is ≥25°C). During the rainy season more breeding habitats are available. This factor increases the likelihood that more mosquitoes hatch in a certain period of time and that they reach successively higher densities. The life expectancy of *A. funestus* and *A. gambiae* is approximately 30 days at a mean temperature of ≥25°C.[18] After the first two days until a female mosquito needs its first blood meal plus the 10 additional days of sporogony and the seven days of schizogony described in our model, the theoretically remaining life expectancy of a mosquito after the minimum time span of 38 days from precipitation to malaria is 11 more days (30 – 2 – 10 – 7 = 11). Therefore the mosquito stays infective for 11 more days and can transmit the disease. Thus, if one considers our model, the highest *Anopheles* densities can be first expected after approximately 50 days (minimum time span of 38 days + 11 days of remaining life expectancy). The successively higher densities could theoretically then be highest after approximately 60 days, which complies with our results.

The regression model was not able to predict a peak incidence in Greater Agogo in May 2008 over a time period of four weeks (Figure 2a). This observation may be explained by exceptional meteorological conditions. To validate this possibility, temperature and relative humidity from the area was analysed during March 2007 - May 2008. The prevailing temperature in the study area during this period was in the optimum temperature range for *A. gambiae* and *A. funestus* which is approximately ≥25°C up to 30°C. Thus, temperature should not have influenced the abundance of mosquitoes. Relative humidity, which in Ghana is constantly 85 -

90% during the entire year, did also not show any aberrations during this interval. The malaria incidence peak in May 2008 was also found in other villages in our study area, which argues against temporal-spatial change of exposure. A temporal reporting bias is improbable because the number of all hospital admissions or the proportion of children included in the study did not increase during this period.

Although the reason for the short increase of the malaria incidence is unknown, the peak does not contradict the model. First, there are certainly temporal and spatial events that influence the malaria incidence, which are unpredictable in the model, e.g., temporal control measures or impassable roads for a limited time. Second, not all relevant events can be detected, e.g., short but intensive rainfall periods or fluctuations of population and hospital personnel. Third, the amount of rainfall per week might not provide all information necessary to predict the likelihood of mosquito breeding and survival. Thus, the optimal conditions for the development of breeding sites might be determined by the amount of rainfall until a certain threshold. There is a minimum amount of rainfall required to maintain constant water bodies of a critical size and at the other sites, heavy rainfall can have an opposite effect by rinsing out breeding sites [21]. Such a putative threshold might have been achieved at the end of February 2008 when an extraordinary high amount of rainfall was recorded.

Other investigators have also reported a strong temporal link between climatic indices and increasing risk for malaria disease. In China, increasing monthly malaria incidences were positively correlated with monthly mean climatic variables (relative humidity, temperature, and precipitation), with a one-month lagged effect [22]. In Eastern Sudan, rainfall was a significant climatic variable in the transmission of the disease [23]. However, in a study conducted in central India, no relation between rainfall and malaria incidence was observed [24]. Instead, in other malaria-endemic areas, mean or minimum temperatures were the best predictors of clinical malaria [25,26]. However, most such analyses have been carried out at monthly time scale and were not able to provide a time lag on a weekly scale. More precise results with a resolution of weeks such as this study are rarely reported [27].

In addition to climatic factors, the risk for malaria transmission or mosquito abundance may be influenced by other factors such as seasonal fluctuations of mi-

grant workers or the accessibility of the hospital in the rainy season when roads are flooded. However, the study area has a relative stable population, and considerable plantations that would attract seasonal field workers are not present. Additionally, the main road, along which the surveyed villages are located, is a well-constructed tarred road, which is passable in the rainy season. Therefore, seasonal variation in accessibility should not influence temporal changes of malaria incidence. The importance of socioeconomic factors such as ethnic group, parent's education and occupation, use of protective measures, and the family's financial situation on malaria transmission have been described in a number of studies [28-30]. Geographic and environmental factors such as altitude and land cover have also been suggested as variables influencing the transmission of malaria. The abundance of water bodies and favorable temperatures, maize plantings, extensive deforestation, or farmland have been associated with increased larval or mosquito abundance and thus increased risk for malaria transmission in human populations [31-34]. Other studies have used geographic information systems and satellite imagery to investigate environmental factors that potentially drive the dynamics of malaria vector populations [34-36] and other vector-borne and zoonotic diseases such as dengue fever or hantavirus [37-39].

It has been shown that the efficacy of control measures such as intermittent preventive treatment (IPT) can be strongly dependent on the present malaria incidence [40-42], and it can be assumed that direct and contextual effects increase with malaria risk after an intervention. The results of the present study highlight that it is feasible in holoendemic areas to predict fluctuations in the malaria incidence with information that is easy to obtain. This enables optimising the planning of malaria interventions.

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Chapter 4

Spatial analysis of land cover determinants of malaria incidence in the Ashanti Region, Ghana

Spatial analysis of land cover determinants of malaria incidence in the Ashanti Region, Ghana

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Abstract

Malaria belongs to the infectious diseases with the highest morbidity and mortality worldwide. As a vector-borne disease malaria distribution is strongly influenced by environmental factors. The aim of this study was to investigate the association between malaria risk and different land cover classes by using high-resolution multispectral Ikonos images and Poisson regression analyses. The association of malaria incidence with land cover around 12 villages in the Ashanti Region, Ghana, was assessed in 1,988 children <15 years of age.

The median malaria incidence was 85.7 per 1,000 inhabitants and year (range 28.4 - 272.7). Swampy areas and banana/plantain production in the proximity of villages were strong predictors of a high malaria incidence. An increase of 10% of swampy area coverage in the 2 km radius around a village leads to a 43% higher incidence (relative risk [RR]=1.43, $p<0.001$). Each 10% increase of area with banana/plantain production around a village tripled the risk for malaria (RR=3.25, $p<0.001$). An increase in forested area of 10% was associated with a 47% decrease of malaria incidence (RR=0.53, $p=0.029$).

Distinct cultivation in the proximity of homesteads influenced the risk of childhood malaria significantly in a rural area in Ghana. This demonstrates the usefulness of satellite images for the prediction of malaria endemicity. Thus, planning and monitoring of malaria control measures should be assisted by models based on geographic information systems.

Introduction

With 250 million estimated malaria cases in 2008 and more than one million deaths malaria is the most common vector-borne infectious disease with Sub-Saharan Africa carrying most of the burden. In regions of stable transmission children <5 years of age are at highest risk of becoming symptomatic after infection with malaria parasites. The causal protozoon *Plasmodium falciparum* is transmitted from person to person through the bite of adult female *Anopheles* mosquitoes [1,2].

Vector-borne diseases such as malaria are highly influenced by spatial and temporal changes in the environment. Adult vector abundance is positively associated with the availability of aquatic habitats necessary for the deposition of eggs, and the areas with highest malaria risk are often found within just a few hundred meters of such larval habitats [3,4]. It has been suggested that extensive cultivation of maize might influence the larval development of mosquitoes, pupation success, and size of adults in the vicinity [5]. Recent studies from Kenya have shown that highland habitats created by deforestation or cultivation of natural swamps were associated with preferred breeding habitats [6,7].

During the last 20 years geographic information systems (GIS) and remotely sensed (RS) data have been used to describe and predict geographical and temporal patterns in vector-borne disease transmission and prevalence [8,9]. Studies mapping potential mosquito habitats, transmission risk, or disease prevalence have been performed in Africa [10-13], South and Central America [14,15], and Asia [16,17].

In Ghana, where the present study was conducted, malaria is prevalent during the entire year and accounts for about 32-42% of all outpatient admissions and for the major in-patient causes of death [18]. The main malaria vectors are mosquitoes of the *Anopheles gambiae* complex and *A. funestus* [19].

The aim of the study was to investigate the association between malaria incidence and different classes of land cover that potentially influence the malaria vector abundance as well as human population density. High spatial resolution satellite images as well as statistical modeling was used to assess the influence of land cover classes and the human population at risk on the malaria incidence (per year and 1,000 inhabitants) in children <15 years of age in an area of high endemicity. This

information might be of importance to the understanding of environmental determinants of malaria transmission heterogeneity at a micro-geographical scale.

Materials and Methods

Ethics Statement

Aims and principles of the study were explained in detail to participants and informed consent was obtained by signature or thumb print by the caregiver. The study design and the informed consent form were approved by the Committee on Human Research, Publications, and Ethnics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Study area and data collection

The hospital-based survey was accomplished at the Child Welfare Clinic and the Pediatric Ward of the Agogo Presbyterian Hospital (APH), Asante Akim North District, Ashanti Region, Ghana. The study area was restricted to the 12 study villages Agogo, Hwidiem, Akutuase, Amantena, Wioso, Domeabra, Juansa, Kyekyebiase, Nyaboo, Obenimase, Patriensah and Pekyerekye and their 2 km surrounding areas (Figure 1). The total area of our study side covered approximately 170 km^2. For more detailed information about the study area see Krefis *et al.* 2010 [20].

All children <15 years of age visiting the Child Welfare Clinic of the APH and with permanent residency in one of the 12 study villages were examined for malaria (criterion: fever ≥37.5°C and positive for asexual *P. falciparum* parasitaemia with >0 parasites/μL) during the study interval of 18 months (end of May 2007 to November 2008). Parasite examination was done according to quality-controlled standardised procedures described elsewhere [21]. Malaria cases presented within 21 days after the initial malaria diagnosis were considered as a relapse and not counted as a new case.

For the calculation of cumulative incidences the population size, the admission rate, the proportion recruited, and the proportion of the population seeking health care in the study hospital were considered. Population figures were taken from the population census 2004 with the estimate that 42% of the individuals were <15 years of age [22]. The proportion of people from each village attending the APH was

assessed by a community survey on health seeking behaviour that was carried out in 2007 and the denominator/reference population for the calculation of incidence was corrected for these proportions [23]. After comparing the study population with the hospital admission records it was estimated that 70% of all individuals admitted to the hospital were included into the study and therefore the reference population was likewise corrected for this factor. Finally, annual malaria incidences per 1,000 children <15 years of age were computed for each of the villages. The human population density per village was computed by using population census and village area data (Table 1).

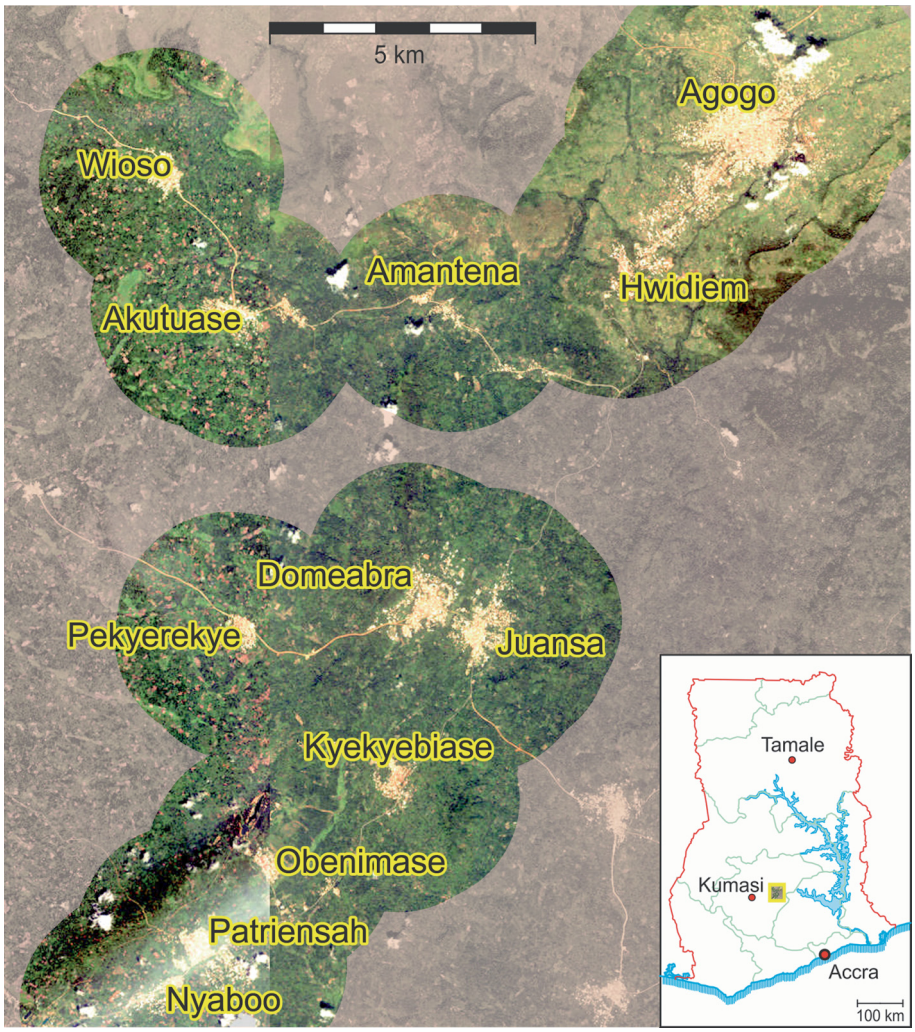

Figure 1: Map of the 12 included study villages. Merger of two satellite images (Ikonos) depicting an area with 12 study villages in the Asante Akim North District, Ashanti Region, central Ghana, West Africa. Areas with a radius of 2 km surrounding the study villages, which were analysed by supervised maximum likelihood classification, are coloured.

Mapping land cover classes using remote sensing

In order to map the land cover classes around each village, we acquired two multispectral Ikonos images with 4-meter spatial resolution and four broad spectral bands (wavelengths: blue, 0.45-0.52 µm; green, 0.52-0.59 µm; red, 0.62-0.68 µm; and near-infrared (NIR), 0.77-0.86 µm), along with one panchromatic band with 1 pixel/m. Images were acquired on May 4, 2009, and on November 26, 2009 (it was not possible to obtain two contemporaneous images of high quality from the area due to weather, cloud condition, and other acquisition difficulties).

All pre-processing steps were carried out using ENVI 4.4 (ITTVIS, 2009). For easier computation the images were divided into subsets, each covering one or two village areas. For each subset a Normalized Difference Vegetation Index (NDVI = [NIR – red] / [NIR + red]) image was calculated, which is a commonly used measure of vegetation productivity [24]. Beside the spectral domain, the spatial domain was also considered by calculating a set of textural measures based on a grey level co-occurrence matrix in order to improve the classification [25,26]. Different textural measures (contrast, homogeneity, angular second moment, variance, mean, dissimilarity, entropy, and correlation) were received by moving several windows of different pixel areas (3x3 to 15x15) over the image, leading to a new textural image for each measure. The optimal window size was determined by using a confusion matrix to assess the accuracy of the solely texture based classification [25]. Afterwards, the textural images were combined with the NDVI image and the four spectral bands for further analysis.

In March 2010, field sampling of different land cover classes was conducted by the direct inspection of 490 points randomly selected in the vicinity of the 12 study villages. We marked the points using a Garmin eTrex®H Global Positioning System (GPS) and took notes and photographs on the dominant vegetation or crop type.

By using the ENVI software, these reference areas were digitised as regions of interest and were used to represent one of the following land cover classes: banana or plantain, cacao, palm trees, oranges, swampy area, water, deforested area and roads, built-up areas (houses), and forest. Classes describing the crops “banana/plantain”, “cacao”, “palm trees” producing palm oil fruits, and “oranges” were mostly mixed fields but dominated by one of these crops, respectively. Either the

presence of a river or stream nearby or near the ground agricultural crops (such as eggplants, maize, tomatoes, pepper), which was mostly cultivated in the vicinity, characterised the combined variable “swampy area”. “Water” was characterised by a river, stream or lake. “Deforested area” was characterised by burned, grassy or bushy underground or open spaces; additionally we assigned roads within this class. “Forest” referred to areas with dense tree cover with a closed canopy.

It was not possible to get images completely free of clouds. Therefore, two additional classes, one for clouds and one for the shadow of a cloud were generated to mask out those particular areas.

All combined bands were classified using a supervised maximum likelihood classifier. Therefore, a random subset of 70% of the pixels for each of the classes was chosen for a basic analysis (“training data”) and 30% were used for assessment of accuracy (“validation data”). In the post classification process, we applied a majority/minority analysis for generalisation of the classification image to minimise “salt and pepper effects”, a term which describes the existence of dark pixels in bright regions and bright pixels in dark regions, usually causing noise in the validation procedure. Validation of the accuracy of the post-processed classification image was based on the overall accuracy computed from the confusion matrix. The maximum likelihood classification is usually considered to be satisfiable when the overall accuracy is higher than 85%. The final image was transferred to ArcGIS version 9.3, developed by Environmental System Research Institute (ESRI, 2008).

Taking into account that adult mosquitoes remain generally up to 2 km of their breeding side [27-29] a radius of 2 km around each village was created and the percentage of various land cover classes in each radius was computed. Due to the particular size of the village Agogo an oval-shaped radius was used (Figure 2). In order to test the validity of the analyses additional radii of 0.5 km, 1 km, and 1.5 km around each village were used.

Analyses and statistical modeling

The quantitative assessment of associations between proportional land cover and the incidence of malaria was done by Poisson regression analyses with adjustment for overdispersion (STATA/SE software, version 10; StataCorp LP, College Station, TX).

By using Spearman rank correlation we calculated the cross correlation between potential determinants for malaria: population density as a measure for human-mosquito-contact, deforested area and roads, swampy area, respectively prone to the formation of puddles and hence breeding sites, water, houses to look for shelter for mosquitoes during daytime, forest, and vegetation of banana/plantain, oranges, cacao, and palm trees as potential resting and breeding sites or food sources. Land cover proportions were analysed as continuous variables and human population density as per 1,000 inhabitants. The approximated interquartile range was used as unit increase for the continuous variables.

Because of the small sample size (12 village clusters), the influence of each potential determinant was assessed separately in a univariate Poisson regression in a first step. For a measure of association between a determinant and malaria incidence, the relative risk (RR) was calculated and complemented by a 95% confidence interval (CI) and p-value. In a second step as sensitivity analysis and to account for confounding, the high correlated determinants with a p-value less than 0.05 were included in a bivariate Poisson regression analysis.

Results

Malaria incidence and human population density

A total of 1,988 malaria cases were reported in the study hospital during the study interval of 18 months (end of May 2007 to November 2008) and were included in the analysis. Annual malaria incidence ranged from 28.1 in Akutuase to 271.9 per 1,000 children <15 years of age and year in Agogo. A crude annual malaria incidence of 194.5 per 1,000 children <15 years age and year with a 95% confidence interval of [144.9, 261.3] could be estimated for the whole study area. The total population of the study villages was 37,461 inhabitants (census data 2004). The human village population density ranged from 1,298 inhabitants/km^2 in Hwidiem to 8,265 inhabitants/km^2 in Patriensah (Table 1).

Table 1: Characteristics of the villages

Village	Village area[1]	Total population[2]	Population density[1]	Proportion with hospital access[3]	Population study group[4]	Malaria cases[5]	Incidence[6]
Agogo	5.12	13,559	2,648	90%	3,588	1,463	271.9
Akutuase	0.61	1,692	2,774	43%	214	9	28.1
Amantena	0.27	890	3,296	55%	144	21	97.3
Domeabra	1.33	3,509	2,638	42%	433	73	112.3
Hwidiem	1.08	1,402	1,298	95%	392	147	250.3
Juansa	1.27	3,992	3,143	40%	469	52	73.8
Kyekyebiase	0.54	1,801	3,335	46%	244	28	76.6
Nyaboo	1.02	1,582	1,551	46%	214	28	87.2
Obenimase	0.51	1,096	2,149	37%	119	15	83.9
Patriensah	0.54	4,463	8,265	38%	499	92	123.0
Pekyerekye	0.37	1,692	4,573	45%	224	27	80.4
Wioso	0.34	1,783	5,244	52%	273	33	80.7

[1] per km^2
[2] Population according to the national census 2004 [21]
[3] Proportion of people in each village who reported to visit the Agogo hospital, data from Community Survey
[4] Population of children <15 years of age estimated as a proportion of 42% of the population counted at national census 2004 [21] and an additional proportion of 70% due to inclusion into the study at hospital admittance and by taking into account hospital access
[5] Study period from May 2007 to November 2008 (18 months)
[6] Incidence in children <15 years (per year and 1,000 children <15 years)
Formula: incidence = 1,000*cases/(total_population*0.42*0.70*hospital_access*1.5)

Classification and correlation of land cover determinants

All four broad spectral bands (blue, green, red, and near-infrared) from the acquired multispectral Ikonos image along with the NDVI image were considered in our study. A window size of 9x9 pixels (equivalent to 9x9 meters) had the highest accuracy of the texture-based classification and respective textural measures were chosen for the analyses accordingly (data not shown).

By using reference areas for all nine land cover classes a maximum likelihood classification was conducted of the combined NDVI image, the spectral, and the textural bands. Overall accuracy of the classification ranged from 87% in Wioso and Akutuase to 95% in Obenimase (data not shown).

The proportion of areas with banana/plantain vegetation within a village radius of 2 km varied from 4.8% in Pekyerekye to 19.7% in Agogo. The highest proportion of swampy area was found around the village Agogo (37.0%), the lowest proportions (4.7% and 4.9%) around the two villages Akutuase and Juansa, respectively. The proportion of forest coverage varied from 6.3% around Domeabra to 28.7% around Wioso (Table 2, Figure 2).

Spearman rank tests resulted in high positive correlations between the land cover proportions of forest and deforested area/roads ($r=0.79$, $p=0.002$), banana/plantain and built-up areas ($r=0.86$, $p<0.001$), and palm trees and cacao ($r=0.91$, $p<0.001$) (Table 3). Highest negative correlations were observed between the land cover proportions of cacao and banana/plantain ($r=-0.73$, $p=0.007$) and swampy area and oranges ($r=-0.78$, $p=0.003$).

As expected, the proportions of land cover in the vicinity of villages in the 0.5 km, 1 km, and 1.5 km radii differed from what was found in the 2 km village radius. The proportions of built-up areas (houses), deforested areas and roads, and banana/plantain vegetation decreased with distance to the village whereas the proportion of areas with forest, palm trees, orange trees, and cacao trees increased (Supplementary Material 1).

Table 2: Proportion (in %) of land cover around a 2 km village centre radius

Village radius[1]	Banana/ Plantain	Cacao	Palm trees	Oranges	Deforested area and roads	Built-up areas (Houses)	Swampy area[2]	Water	Forest
Agogo	19.7	9.5	4.5	6.9	9.2	4.1	37.0	0.1	6.4
Akutuase	11.5	10.9	4.1	28.7	9.4	1.4	4.7	1.4	27.9
Amantena	12.1	22.2	23.3	20.4	2.6	0.7	7.5	0.1	10.1
Domeabra	9.8	26.2	23.9	22.7	3.9	2.1	5.0	0.0	6.3
Hwidiem	18.7	13.3	12.6	13.2	5.6	2.6	23.9	0.1	9.9
Juansa	9.2	25.9	24.5	24.0	3.8	2.2	4.9	0.0	5.5
Kyekyebiase	7.3	28.9	24.3	26.6	1.6	0.6	5.2	0.1	5.4
Nyaboo	17.4	15.5	13.9	2.2	19.6	3.9	8.9	0.1	15.1
Obenimase	14.0	19.2	19.5	3.0	17.6	2.5	6.9	0.3	15.0
Patriensah	16.2	15.1	16.5	2.3	18.4	3.4	8.9	0.0	16.0
Pekyerekye	4.8	26.4	22.1	13.5	9.1	0.6	8.4	4.3	10.8
Wioso	9.3	14.4	5.0	22.5	10.2	0.7	7.8	1.2	28.7

[1] Size of each radius 2 km^2
[2] Swampy area: either the presence of a river or stream nearby or near the ground agricultural crops (such as eggplants, maize, tomatoes, pepper)

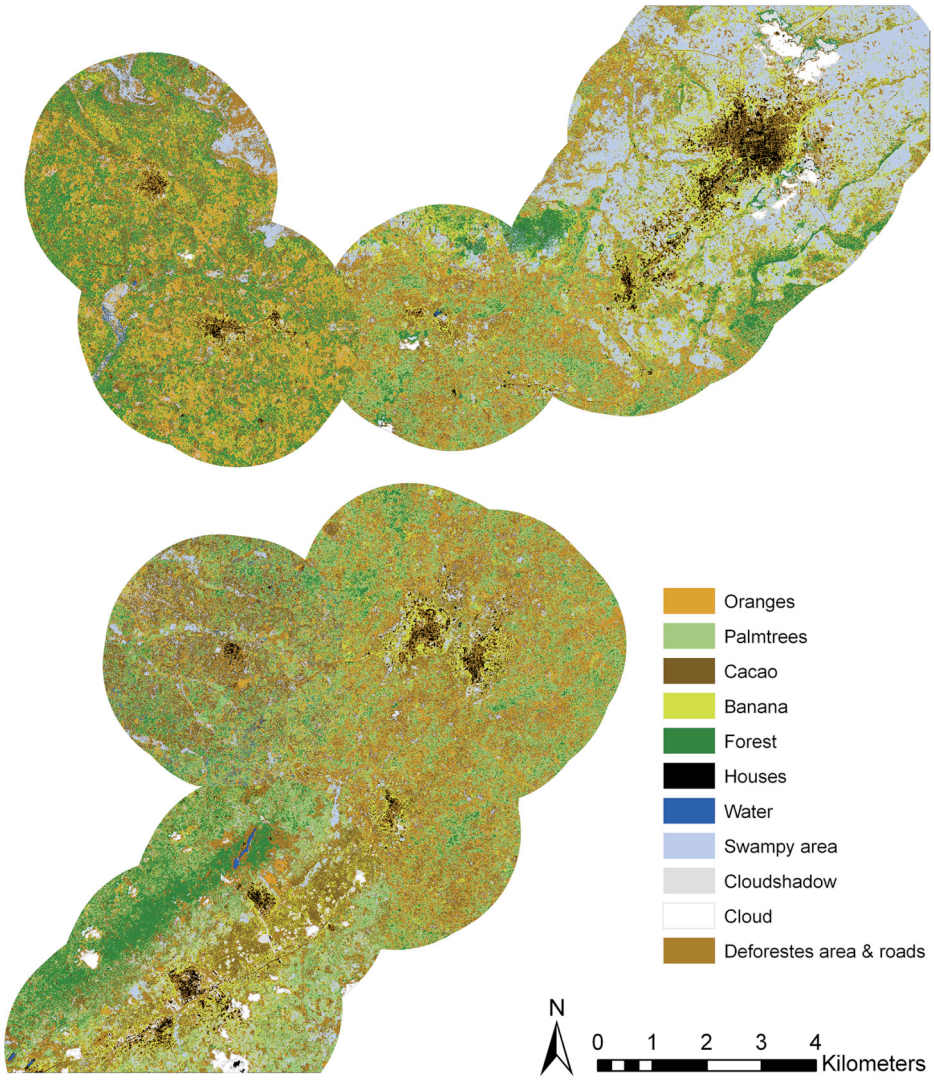

Figure 2: Supervised maximum likelihood classification map (combined NDVI image, the texture bands, and the four spectral bands). Classification of land cover within a village radius of 2 km with 11 colours indicating different land cover classes.
All classes describing the crops banana/plantain, cacao, palm trees producing palm oil fruits, and oranges were mainly mixed fields but dominated by one of these crops. Swampy areas were characterised by either the presence of a river or stream nearby or an agricultural crop cultivated in the vicinity. Water was characterised by a river, stream or lake. Deforested areas were characterised by roads as well as burned, grassy or bushy underground or open spaces. Forest referred to areas with dense tree cover, mostly with a closed canopy.

Table 3: Correlation coefficients of the cross correlation function between land cover variables using Spearman rank correlation

	Population density	Built-up areas (Houses)	Deforested area and roads	Forest	Swampy area	Water	Banana/ Plantain	Oranges	Cacao	Palm trees
Population density		-0.51	-0.08	0.22	-0.11	0.07	-0.55	-0.24	0.24	0.17
Built-up areas (Houses)	0.09		0.55	0.08	0.52	-0.38	0.86	-0.66	-0.62	-0.41
Deforested area and roads	0.80	0.06		0.79	0.37	0.23	0.46	-0.66	-0.52	-0.62
Forest	0.50	0.81	0.002		0.14	0.42	0.18	-0.30	-0.51	-0.67
Swampy area	0.75	0.08	0.23	0.66		-0.03	0.64	-0.78	-0.42	-0.43
Water	0.84	0.22	0.48	0.17	0.92		-0.24	0.13	-0.14	-0.46
Banana/Plantain	0.06	<0.001	0.13	0.57	0.02	0.46		-0.67	-0.73	-0.57
Oranges	0.46	0.02	0.02	0.34	0.003	0.70	0.02		0.27	0.26
Cacao	0.44	0.03	0.08	0.09	0.17	0.66	0.007	0.39		0.91
Palm trees	0.60	0.19	0.03	0.02	0.16	0.13	0.05	0.42	<0.001	

Note: Above the diagonal are the correlation coefficients r, below all p-values

Regression modeling

In the univariate Poisson regression analysis, all determinants with the exception of population density, water, and deforested area and road coverage showed a significant influence on malaria incidence, which was adverse for banana/plantain cultivation (RR=3.25), swampy areas (RR=1.43), and built-up areas (RR=2.24), but protective for forest (RR=0.53), oranges (RR=0.63), cacao (RR=0.48), and palm trees (RR=0.59) plantation (Table 4). However, in the sensitivity analysis by means of bivariate Poisson regression analysis, the univariate results for built-up areas and oranges, cacao, and palm trees plantations turned out to be confounded because of high correlation between several determinants (Table 3) and not to be of statistical significance (data not shown).

The association of land cover with malaria incidence in the other 3 radii were similar to those of the 2 km radius (Supplementary Material 2) and the sensitivity analysis showed similar results (data not shown).

Table 4: Influence of determinants on malaria incidence[1]

Determinant	RR[2]	95% confidence interval	p-value
Population density[3]	0.87	0.70 – 1.07	0.176
Built-up areas (Houses)[4]	2.24	1.54 – 3.24	<0.001
Deforested area and roads[5]	1.00	0.70 – 1.44	0.988
Forest[6]	0.53	0.28 – 0.99	0.029
Swampy area[6]	1.43	1.33 – 1.55	<0.001
Water[7]	0.70	0.37 – 1.32	0.270
Banana/Plantain[6]	3.25	2.23 – 4.76	<0.001
Oranges[6]	0.63	0.44 – 0.91	0.012
Cacao[6]	0.48	0.33 – 0.70	<0.001
Palm trees[6]	0.59	0.43 – 0.81	<0.001

[1] Poisson regression analysis
[2] RR = relative risk
[3] Unit: 1,000/km^2
[4] Unit = 2%.
[5] Unit = 5%.
[6] Unit = 10%.
[7] Unit = 1%.

Discussion

The risk for malaria is dependent on a number of individual and environmental factors whereas their impact is dependent on the endemicity in a certain area [5,6,20]. Recently, it has been shown that the spatial variance of malaria incidence might be pronounced not only in areas with low and seasonal endemicity but also in holoendemic areas [20,30]. It can be assumed that mosquito occurrence, the existence of breeding sites, and human population density are the most important spatial determinants, all significantly linked to land cover and land use [3,4,13,30]. Accordingly, land cover has been associated with entomological measures mainly accumulated as entomological inoculation rates (EIR, infectious mosquito bites per person per year) [8,10]. Studies using high-resolution satellite images in association with vector-borne diseases have already been conducted in other areas [8-17]. However, analyses of the direct relationship between environmental factors and human malaria, especially using high-resolution images and/or subclassification of land cover in such detail are scarce, most probably due to the absence of precise data on malaria incidence and exact description of the land cover in large areas.

The presented analyses have used malaria incidence data over 18 months from a hospital-based survey and high-resolution satellite images of a holoendemic coverage area in the Ashanti Region, Ghana. The analyses demonstrate that an accurate stratification of land cover by satellite images is possible in areas of small-scale cultivation and changing agriculture. Land cover of banana/plantain vegetation and swampy areas significantly increased the malaria risk. In contrast, an increased proportion of forest around villages was associated with decreased malaria risk. These trends remained when conducting the analysis using smaller radii. However, the RRs for banana/plantain cultivation and forest vegetation decreased with each diminished radius. This trend may be explained by the increasing proportions of banana vegetation and decreasing proportions of forest near homesteads and hence the reducing divergence among all villages (Supplementary Material 1).

The increase of malaria risk in the vicinity of swampy areas, which are preferred mosquito breeding sites, has already been documented and can be considered as an internal control of the validity of the analyses [3,4,6,31]. In the

presented model each 10% increase of the proportion of swampy areas around villages increased the malaria risk by 43%.

An increase of the proportion of all cultivated areas around villages was associated with a slightly increased risk of malaria (data not shown). The main plantations in the study area are with banana/plantain, oranges, cacao, and palm trees [32]. After stratification for the distinct cultivations, a plantation with banana/plantain was found of particular impact and a 10% increase was associated with about 300% higher malaria risk whereas plantations of oranges, cacao, and palm trees showed a negative association. A number of studies that were conducted at a microhabitat scale demonstrated an association between ovipositions of various mosquito species in rainwater retained in tree-holes and the leaf axils of a variety of numerous wild and cultivated plants such as banana or plantain [33-36]. However, none of these studies has directly linked the existence of breeding sites with malaria incidence.

Likewise, deforested areas and dirt roads have been suspected as environmental factors associated with malaria risk in the surrounding areas since both create conditions favourable for the formation of small puddles that are preferred breeding sites for *Anopheles spp.* [6,7,29,37,38]. However, a significant influence of deforested areas and roads on malaria incidence could not be observed in the presented study. Similarly, population density as a measure for human-mosquito contact did not show an effect on the outcome.

A high proportion of forest coverage was associated with lower malaria incidence with statistical significance. Indeed, the forest floor with a closed canopy tends to be heavily shaded and littered with a thick layer of organic matter that absorbs water and renders it more acidic. Therefore, the proximity of forest could decrease mosquito abundance and hence decrease malaria risk as the preferred habitat of *A. gambiae* larvae are sunlit pools with turbid water and little or no emergent vegetation and that of *A. funestus* are clear water with vertical, emergent vegetation without organic material [31,37].

There was a tendency of an association between an increased proportion of build-up areas and malaria incidence. However, this effect disappeared after adjustment for the highly correlated variable “banana/plantain” what indicates confounding which is, however, difficult to formally test due to the ecological study design. The

observation that vicinity to banana/plantain cultivations seems to be a risk factor for malaria may be because of the frequent closeness of this vegetation with homesteads.

A limitation of our study is that the proportion of children <15 years of age in each village was estimated and not directly measured when computing malaria incidences. Moreover, the underlying values for the total population were three years old (census data from 2004) and hence might be subject to biases. However, it was the best data available for our study population and census data not more than five years old represent a quite good estimate. Additionally, the villages should be comparable in the proportions of children since they have similar social and ethnic structures, are of similar size, and are all situated in a rural area and closely together. Therefore, it is unlikely that a differential bias has been created.

Climate conditions are suspected to be of importance for the malaria risk and higher precipitation could be directly linked, with a time lag, to an abundance of vectors and an increase of disease frequency [39]. The satellite images, which were analysed here, were taken during or immediately after a rainy season (May and November). Therefore, most of the open lakes, rivers or streams should have been detected and included in our analysis. Nevertheless, an association of the proportion of open water bodies and risk of malaria could not be demonstrated in the presented study. A limitation of the analysis is that the proportion of water in the surrounding of the villages was very low and streams and little rivers were mostly located close to forests and, therefore, difficult to detect on our satellite images.

Another limitation of the analyses was that some areas were covered with clouds and their shadows in both images. However, the proportion of cloudy areas was very low (<5% in total) and randomly distributed hence should not significantly affect our results.

In Ghana, the major farming practice is a shifting cultivation, often accompanied by deforestation, and crops mostly change twice to three times a year [32]. Due to the fact that a time span of nine and four months occurred between the acquisition of images (May and November 2009) and the conducted field sampling (March 2010), respectively, the assigned land cover might be biased. By interviewing the

local population about previous crops and land cover we attempted to minimise this potential misclassification.

Maximum likelihood procedures were used for supervised classification of land cover data, which gave more accurate results than other classification methods such as Decision Tree-, Minimum Distance- or K-Means Classification [40-42]. Even though the overall accuracy of the correlation matrix of the NDVI image, the spectral and the spatial classification in the subsets ranged from 87% to 95%, land cover still might be misclassified to some extent. In the study area as in most areas of Ghana mixed cultivation is widespread [32] which makes it very difficult to unambiguously allocate land covers.

Our study was limited by the inability to sub-classify swampy areas, which are mostly used for near-ground cultivation, into different crops such as maize, eggplants or pepper for the analysis of various influences on malaria risk. In Ethiopia a strong association between maize cultivation in the vicinity of water bodies, used as breeding habitats, and the larvae development was demonstrated [5]. However, because of a high number of classes in relation to 12 village clusters and weak accuracy of data in this classification analyses, this sub-classification was not possible.

Other geo-ecological influence factors for the malaria risk are altitude, slope, geology, and soil types [29,43-46]. However, the intra-radius variation in these measures did not differ significantly.

The consequent next step would be to map individual data in order to link individual spatial patterns and malaria risk. Indeed, in an adjacent study area a continuous and linear reduction of the malaria rate was demonstrated with an increasing distance between children's households and forest fringe [30]. Other individual factors such as socioeconomic conditions and the access to health facilities could then be included in the model [20,47,48].

The performed analysis demonstrates that satellite images together with appropriate analytical tools are able to predict the risk of malaria in an area of high malarial transmission. Even though only 12 village sides were included in the study a significant association of different land cover classes with the occurrence of malaria incidence could be demonstrated. Human cultivation in the vicinity of homesteads, in particular with banana/plantain, may increase the risk for malaria. On the contrary,

forest preservation may decrease malaria risk. In the future, mapping of GPS positions of each household would enable to include individual risk data and to confirm and to improve the validity of the model. Malaria persists to be an important public health problem and policy makers should involve geographic information systems for planning and monitoring malaria control strategies.

Competing interests

The authors declare that they have no competing interests.

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Authors´ contributions

ACK participated in the conception, performed the classification and the statistical analysis, was involved in the field sampling, in the interpretation of results, and participated in drafting the results and the manuscript. NGS participated in the design, assisted in performing the statistical analysis, was involved in the field sampling and in the interpretation of the results, and helped to draft the manuscript. WL created Case Report Forms and was responsible for data management and data preparation for analyses. JO performed the classification, was involved in the field sampling and reviewed the manuscript. UR was involved in the initial design of the study, assisted in performing the statistical analysis and participated in drafting the manuscript. JM conceived and coordinated the study, was involved in the initial design of the study

and writing of the manuscript. NS organized the day-to-day work on the ground, BN and SA carried out the malaria parasite examination and contributed to the writing of the manuscript, and YAS planned, initiated the study, and reviewed manuscript. All authors have read and approved the final manuscript.

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Supplementary Material 1

Table 1: Proportion (in %) of land cover around a 1.5 km village centre radius

Village radius[1]	Banana/ Plantain	Cacao	Palm trees	Oranges	Deforested area and roads	Built-up areas (Houses)	Swampy area[2]	Water	Forest
Agogo	20.8	7.8	3.1	5.2	11.2	5.2	38.4	0.1	4.8
Akutuase	12.0	10.3	3.9	28.6	13.2	2.6	4.4	1.0	24.0
Amantena	11.1	24.2	24.7	21.8	2.8	0.8	5.3	0.1	8.5
Domeabra	14.3	23.8	16.8	18.2	9.3	5.5	7.0	0.0	4.8
Hwidiem	22.9	11.7	9.1	12.7	8.5	3.9	25.9	0.0	5.2
Juansa	13.3	25.1	16.2	19.3	9.7	5.8	7.2	0.0	3.2
Kyekyebiase	8.2	28.7	20.8	26.9	2.9	1.2	6.4	0.0	4.8
Nyaboo	22.6	14.4	10.2	2.3	25.8	7.1	11.0	0.0	3.3
Obenimase	17.6	26.0	12.1	3.7	19.5	2.2	6.2	0.6	10.1
Patriensah	23.8	17.1	10.2	1.9	23.7	5.7	11.3	0.0	1.6
Pekyerekye	3.9	30.8	19.8	13.1	11.6	1.3	8.5	3.7	7.2
Wioso	11.6	14.6	4.6	25.9	9.1	1.2	0.1	1.1	28.7

[1] Size of each radius 1.5 km^2

[2] Swampy area: either the presence of a river or stream nearby or near the ground agricultural crops (such as eggplants, maize, tomatoes, pepper)

Table 2: Correlation coefficients of the cross correlation function between land cover variables using Spearman rank correlation[1]

	Population density	Built-up areas (Houses)	Deforested area and roads	Forest	Swampy area	Water	Banana/ Plantain	Oranges	Cacao	Palm trees
Population density		-0.38	-0.12	-0.02	-0.29	0.19	-0.47	0.28	0.36	0.19
Built-up areas (Houses)	0.23		0.61	-0.69	0.61	-0.72	0.72	-0.58	-0.35	-0.32
Deforested area and roads	0.71	0.04		-0.24	0.27	-0.20	0.48	-0.62	-0.17	-0.38
Forest	0.95	0.01	0.46		-0.69	0.89	-0.44	0.48	-0.06	-0.15
Swampy area	0.37	0.04	0.39	0.01		-0.50	0.62	-0.71	-0.26	-0.22
Water	0.56	0.008	0.54	<0.001	0.09		-0.59	0.43	0.10	-0.09
Banana/Plantain	0.12	0.008	0.12	0.15	0.03	0.04		-0.76	-0.57	-0.54
Oranges	0.38	0.05	0.03	0.12	0.009	0.16	0.005		0.11	0.17
Cacao	0.25	0.26	0.60	0.85	0.42	0.76	0.05	0.73		0.85
Palm trees	0.56	0.31	0.23	0.65	0.50	0.77	0.07	0.59	<0.001	

[1] Size of each radius 1.5 km^2

Note: Above the diagonal are the correlation coefficients r, below all p-values

Table 3: Proportion (in %) of land cover around a 1 km village centre radius

Village radius[1]	Banana/ Plantain	Cacao	Palm trees	Oranges	Deforested area and roads	Built-up areas (Houses)	Swampy area[2]	Water	Forest
Agogo	21.7	6.5	2.0	3.7	23.3	7.0	36.5	0.1	3.6
Akutuase	12.7	9.1	3.4	23.8	18.2	4.9	4.5	1.0	22.3
Amantena	12.2	25.4	22.1	20.1	4.5	1.2	5.6	0.2	7.2
Domeabra	19.0	22.3	11.0	14.6	13.7	7.8	8.6	0.0	2.7
Hwidiem	24.8	12.4	7.0	12.8	11.9	6.2	20.6	0.0	4.2
Juansa	18.0	22.2	12.0	14.9	13.2	8.4	8.8	0.0	2.2
Kyekyebiase	11.7	28.5	15.6	26.1	5.9	2.6	6.1	0.0	3.3
Nyaboo	25.6	15.9	9.1	1.9	25.8	7.2	12.7	0.0	0.9
Obenimase	21.0	28.3	7.7	4.7	22.2	3.4	6.0	0.2	4.0
Patriensah	26.1	14.2	4.9	0.9	31.6	8.5	8.7	0.0	0.9
Pekyerekye	3.4	31.6	17.0	13.2	15.3	2.3	8.5	3.7	4.8
Wioso	11.2	4.3	4.3	25.3	12.1	2.3	2.8	0.7	26.3

[1] Size of each radius 1 km^2
[2] Swampy area: either the presence of a river or stream nearby or near the ground agricultural crops (such as eggplants, maize, tomatoes, pepper)

Table 4: Correlation coefficients of the cross correlation function between land cover variables using Spearman rank correlation[1]

	Population density	Built-up areas (Houses)	Deforested areas and roads	Forest	Swampy area	Water	Banana/ Plantain	Oranges	Cacao	Palm trees
Population density		-0.24	-0.10	0.20	-0.45	0.29	-0.50	0.32	0.07	0.13
Built-up areas (Houses)	0.46		0.58	-0.80	0.67	-0.60	0.75	-0.58	-0.23	-0.29
Deforested area and roads	0.76	0.05		-0.47	0.35	-0.10	0.61	-0.78	-0.23	-0.51
Forest	0.54	0.002	0.12		-0.66	0.77	-0.65	0.57	-0.02	-0.13
Swampy area	0.13	0.02	0.27	0.02		-0.62	0.68	-0.68	-0.13	-0.13
Water	0.36	0.04	0.77	0.003	0.03		-0.68	0.37	0.02	-0.01
Banana/Plantain	0.10	0.005	0.04	0.02	0.02	0.01		-0.82	-0.33	-0.42
Oranges	0.31	0.05	0.003	0.05	0.02	0.24	0.001		0.10	0.27
Cacao	0.83	0.47	0.47	0.57	0.68	0.96	0.30	0.76		0.86
Palm trees	0.68	0.37	0.09	0.70	0.70	0.97	0.17	0.40	<0.001	

[1] Size of each radius 1 km^2
Note: Above the diagonal are the correlation coefficients r, below all p-values

Table 5: Proportion (in %) of land cover around a 0.5 km village centre radius

Village radius[1]	Banana/ Plantain	Cacao	Palm trees	Oranges	Deforested area and roads	Built-up areas (Houses)	Swampy area[2]	Water	Forest
Agogo	22.4	4.5	1.0	2.1	18.2	10.0	31.8	0.1	2.9
Akutuase	14.4	7.1	1.7	17.8	28.1	11.4	6.5	0.6	12.4
Amantena	19.0	25.5	12.6	14.4	9.2	3.4	7.5	0.8	6.0
Domeabra	25.5	12.4	0.5	5.0	28.7	17.2	10.1	0.0	0.1
Hwidiem	29.5	12.8	0.4	7.7	19.4	16.0	7.7	0.0	3.9
Juansa	27.2	9.8	3.2	2.8	30.2	19.4	9.1	0.0	0.1
Kyekyebiase	19.6	24.5	1.0	16.1	17.2	7.9	7.0	0.0	1.8
Nyaboo	25.7	14.9	5.5	1.0	29.3	12.3	9.5	0.0	0.3
Obenimase	30.0	21.5	6.4	3.4	28.6	10.4	5.5	0.0	0.2
Patriensah	27.3	6.4	0.9	0.5	41.0	14.5	5.7	0.0	0.3
Pekyerekye	2.3	26.4	12.0	10.5	25.3	7.5	9.5	4.1	2.2
Wioso	12.6	11.3	2.0	19.2	26.9	8.1	3.7	0.4	15.7

[1] Size of each radius 0.5 km^2
[2] Swampy area: either the presence of a river or stream nearby or near the ground agricultural crops (such as eggplants, maize, tomatoes, pepper)

Table 6: Correlation coefficients of the cross correlation function between land cover variables using Spearman rank correlation[1]

	Population density	Built-up areas (Houses)	Deforested areas and roads	Forest	Swampy area	Water	Banana/ Plantain	Oranges	Cacao	Palm trees
Population density		-0.43	-0.02	0.19	-0.36	0.41	-0.53	0.27	-0.04	0.20
Built-up areas (Houses)	0.17		0.73	-0.57	0.17	-0.70	0.66	-0.51	-0.53	-0.57
Deforested area and roads	0.95	0.007		-0.64	-0.10	-0.50	0.45	-0.57	-0.42	-0.48
Forest	0.56	0.05	0.03		-0.30	0.67	-0.59	0.67	0.00	0.49
Swampy area	0.25	0.60	0.76	0.34		0.03	-0.07	-0.37	0.01	0.00
Water	0.19	0.01	0.10	0.02	0.92		-0.83	0.55	0.19	0.47
Banana/Plantain	0.08	0.02	0.14	0.04	0.83	<0.001		-0.68	-0.20	-0.48
Oranges	0.40	0.09	0.05	0.02	0.24	0.07	0.02		0.34	0.38
Cacao	0.91	0.08	0.17	1.00	0.98	0.54	0.53	0.29		0.64
Palm trees	0.53	0.05	0.11	0.10	1.00	0.13	0.11	0.23	0.03	

[1] Size of each radius 0.5 km^2

Note: Above the diagonal are the correlation coefficients r, below all p-values

Supplementary Material 2

Table 1: Influence of determinants on malaria incidence[1]

Radius	2 km			1.5 km			1 km			0.5 km		
Determinant	**RR[2]**	**95% CI[2]**	**p-value**	**RR[2]**	**95% CI[2]**	**p-value**	**RR[2]**	**95% CI[2]**	**p-value**	**RR[2]**	**95% CI[2]**	**p-value**
Population density[3]	0.87	0.70 – 1.07	0.176	0.87	0.70 – 1.07	0.176	0.87	0.70 – 1.07	0.176	0.87	0.70 – 1.07	0.176
Built-up areas (Houses)[4]	2.24	1.54 – 3.24	<0.001	1.32	0.89 – 1.97	0.171	1.22	0.87 – 1.76	0.238	0.92	0.78 – 1.08	0.309
Deforested area and roads[5]	1.00	0.70 – 1.44	0.988	0.93	0.68 – 1.26	0.619	1.19	0.96 – 1.48	0.110	0.77	0.63 – 0.92	0.005
Forest[6]	0.53	0.28 – 0.99	0.029	0.65	0.33 – 1.27	0.208	0.67	0.33 – 1.35	0.264	0.83	0.33 – 2.08	0.695
Swampy area[6]	1.43	1.33 – 1.55	<0.001	1.42	1.32 – 1.53	<0.001	1.44	1.32 – 1.58	<0.001	1.46	1.24 – 1.71	<0.001
Water[7]	0.70	0.37 – 1.32	0.270	0.69	0.35 – 1.34	0.274	0.71	0.36 – 1.40	0.323	0.79	0.44 - 1.40	0.418
Banana/Plantain[6]	3.25	2.23 – 4.76	<0.001	2.34	1.36 – 4.02	0.002	1.93	1.04 – 3.58	0.038	1.22	0.67 – 2.22	0.508
Oranges[6]	0.63	0.44 – 0.91	0.012	0.60	0.43 – 0.84	0.003	0.58	0.41 – 0.84	0.004	0.50	0.27 – 0.94	0.032
Cacao[6]	0.48	0.33 – 0.70	<0.001	0.51	0.39 – 0.66	<0.001	0.57	0.42 – 0.77	<0.001	0.50	0.31 – 0.80	0.004
Palm trees[6]	0.59	0.43 – 0.81	<0.001	0.49	0.34 – 0.71	<0.001	0.40	0.24 – 0.67	<0.001	0.37	0.09 – 1.47	0.160

[1] Poisson regression analysis
[2] RR = relative risk; CI = confidence interval
[3] Unit: 1,000/km^2
[4] Unit = 2%.
[5] Unit = 5%.
[6] Unit = 10%.
[7] Unit = 1%.

Chapter 5

Results and Discussion

5.1 Main findings

The main findings of this thesis were that even in an area of high endemicity, the proportion of malaria in children presented to a hospital (n=1,478) is markedly influenced by the socioeconomic status of the family where the proportion of children with malaria decreased with increasing socioeconomic status. Malaria risk was highest in the age group of children between 1 and 5 years, compared to children between 6 and 15 years. Children <1 year of age had the lowest malaria risk. Additionally, the proportion of malaria was lower in children from families, which reported the use of mosquito protection measures. Another independent factor for malaria risk was the place of residence.

The analysis of the malaria incidence in the two Ghanaian village clusters Greater Agogo and Greater Konongo (n=1,993) indicated a strong temporal association between precipitation and incidence of malaria. The regression model showed that the level of rainfall predicted the malaria incidence after a time lag of nine weeks (mean 60 days). Additionally, lags of one week and two weeks in Greater Konongo and in Greater Agogo, respectively, indicated a significant influence of preceding rainfall events on malaria incidence.

The spatial analysis of remotely sensed data demonstrated that increased banana/plantain vegetation and swampy areas in the proximity of villages (2 km radius) were strong and weak, respectively, predictors of a high malaria incidence (n=1,988). In contrast, an increased proportion of forest around villages was associated with a decrease of malaria incidence.

5.2 Methodological considerations and limitations

Some methodological aspects and limitations of our study have to be considered: The hospital-based study design, which bases on a single hospital, might limit the generalisation of the results to other regions. On the other hand, the focus on one hospital allowed the thorough collection of data on the clinical condition, infectious disease agents, and exact diagnosis.

However, data from self-medication for malaria and treatment from private health facilities were not considered in our study. Therefore, our data only capture a fraction of the estimated cases and are subjected to an underestimation bias in their collection.

It should be noticed that all the data describing the socioeconomic influence on malaria in children are based on self-report of the caretakers and are not validated by direct observations, as is frequently the case in cross-sectional household survey designs, which might result in a response or recall bias.

Another bias, which has to be considered in our study, is a selection bias. There was a decrease of odds for malaria with increasing distance from the study hospital, suggesting differing health seeking behaviour among differing symptoms, which is discussed in Paper I. However, this potential selection bias was avoided when computing malaria incidence in our second and third paper. By using information from a community survey we estimated the proportion of people from all villages seeking health care at the APH.

A limitation of our study is that the proportion of children <15 years of age in each village was estimated and not directly measured when computing malaria incidences. Additionally, the underlying values for the total population were three years old (census data from 2004) and hence might be subject to biases. However, it was the best data available for our study population and census data not more than five years old represents a quite good estimate. Moreover, the villages should be comparable in the proportions of children since they have similar social and ethnic structures, are of similar size, and are all situated in a rural area and closely together. Therefore, it is unlikely that a differential bias has been created.

Confounding is a problem which has to be addressed in nearly all studies. A confounder is a variable in a statistical model that correlates with both, the dependent and the independent variable [42]. Relevant potential risk factors for malaria such as age of a child and use of protection measures (Paper I) or banana/plantain and built-up areas (houses) (Paper III) were either included in the questionnaire or in the spatial analysis. To control for these potential confounders they were either stratified and/or included in a bivariate or multivariate regression model.

Effect modification or interaction occurs, when the measure depends on the level of another factor [43]. In Paper I all covariables in the multivariate regression model were examined for possible effect modification by Wald tests and preference of the model with interaction by log-likelihood tests (both $p<0.05$).

Beside the already discussed limitations in Paper I-III, there are other factors that were not considered in our study, which might influence the risk of a child acquiring infectious diseases such as malaria as well as its severity for example gestational (e.g. malnutrition or underlying disease of the mother), genetic (e.g. sickle cell traits which influence the risk for malaria), or perinatal factors (e.g. perinatal hypoxaemia and respiratory complications) [44-48]. Additionally, previous morbidity and nutritional status of the child can be of importance for the risk of mortality [49-53].

5.3 Conclusions and recommendations

Malaria remains as an important public health problem and persists at the top of the agenda at World Health Organization (WHO) and Roll Back Malaria (RBM) Partnership, launched in 1998 by WHO, United Nations International Children's Emergency Fund (UNICEF), United Nations Development Programme (UNDP), and the World Bank [54,55]. Three preventive approaches for malaria control tools are endorsed: fight against the anopheline larvae (better sanitation systems to reduce potential breeding habitats, utilisation of larvicide, biological control tools), fight against adult mosquitoes (indoor residual spraying (IRS), usage of insecticide-treated net (ITN) or long-lasting insecticidal nets (LLIN), window screens or insect-repellents) or prophylactic treatment (e.g. Malarone®, Lariam® for travellers or intermittent preventive treatment (IPT) which is recommended for pregnant women and infants in areas of high transmission) [1,7,13,54,55].

Laboratory-based diagnosis for all suspected cases of malaria (e.g. confirmation by microscopy or with a rapid diagnostic test (RDT)) and effective treatment for all confirmed cases with an artemisinin-based combination therapy (ACT) is recommended [1,7,13].

Even though interventions to roll back malaria are already implemented in many parts of the world, there is still a need to further scale up the malaria control tools that are already available.

Our results emphasised the decrease of malaria when protection measures are used. Whereas the gratis delivering of ITNs and LLINs is already implemented in some high–burden countries in Africa [1,13,55] there is still a need of programmes for routine distribution as well as routine monitoring of the durability of ITNs. Additionally, people, specifically parents, should be accurately informed about the correct usage of ITNs to better protect their children from acquiring malaria.

In this thesis it has been shown that the proportion of malaria in children presented to hospital decreases with increasing socioeconomic status. It is under discussion how far poverty influences the occurrence of malaria or malaria influences the occurrence of poverty. In either case, the fight against malaria has to be escorted by the fight against poverty and improvement of living standard. In this context, the accessibility of good primary health care or programmes for home-treatment should be supported [56,57]. Even though funds committed to malaria control from international sources have increased substantially, the current level of financing does not meet the estimated requirements for successful control and monitoring of malaria and for reaching the Millennium Development Goals (MDG) of more than US$ 5 billion per year [1,54,58,59].

A temporal influence of precipitation on malaria incidence could be demonstrated. Due to emerging breeding habitats in the rainy season the fight against the anopheline larvae should be further promoted by better sanitation systems or chemical or biological control [1,60-63]. Additionally, it has been shown that control measures like IPT have a strong seasonal or temporal effect and that efficacy can be strongly dependent on the present malaria incidence [64-66]. In endemic areas such as Ashanti region IPT is recommended by WHO [1,13], hence, efficacy could be increased by an optimised application schedule when the rainy season starts.

Early warning systems are often discussed [67-69] and should be promoted by using climate and disease data. However, in reality a shortage of good quality disease and climate data is often hindering the modeling.

Inadequate case monitoring systems or national surveillance represent a missed opportunity for making epidemic control efforts more effective. It is a major challenge to introduce new specialised, upgraded and especially affordable monitoring systems. One approach to improve the quality of disease data is the usage of handheld computers or mobile phones to rapidly send and receive data on cases. Evaluating these pioneering efforts will be important to determine best practice and identify common issues around implementation [69-72].

The spatial analysis on malaria incidence in our region indicated associations of the increasing percentage of the land cover variable swampy area with high malaria incidence. Swampy areas prone to the formation of puddles are known to be a preferred mosquito breeding sites [73-76]. The fact, that swampy areas are mostly used for cultivation of an agricultural crop suggests, that new agricultural practices that maintain or increase agricultural productivity while reducing puddles and hence malaria vector survival should be promoted as one strategy to reduce malaria.

Additionally, malaria risk increased with increasing coverage of banana or plantain in the vicinity of the villages. In other studies associations were demonstrated between ovipositions of various mosquito species in rainwater retained in tree-holes and the leaf axils of a variety of specific wild and cultivated plants such as banana or plantain [77-80]. Therefore, the planting or cultivating of banana and plantain in the vicinity of houses should be reduced to decrease mosquito-breeding possibilities in the axils of these plants when filled with rainwater and hence malaria risk.

A significant protective effect of high proportion of forest coverage around a village on malaria incidence could be demonstrated, suggesting that forest decreases mosquitoe abundance and hence decrease malaria risk. In contrast, deforestation and not asphalted roads have been suggested as important factors that increase the risks of malaria transmission since both create conditions favourable for the formation of small puddles [23,24,40,75,81]. Hence, forest preservation and reduction of deforestation should be promoted.

As shown in this thesis, malaria variability depends on factors such as precipitation but also land cover changes e.g. caused by deforestation might influence the occurence of the vector and hence the disease [82]. In future, continuous satellite

images to investigate land cover changes and its association with malaria risk would be desirable.

To regard the above-mentioned limitations of our study considering potential gestational, genetic or perinatal risk factors on malaria, a longitudal study design including a birth cohort should be promoted. Such a birth cohort study just started in our study region.

Another limitation of our study are missing exact GPS positions on each included household. Mapping of precice GPS positions of each household would enable to assess malaria risk on an individual level and to confirm and improve our findings.

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Chapter 6

Summary

Worldwide, malaria is with 250 Million estimated cases in 2008 and more than one million deaths each year the most common vector-borne infectious disease. With a vast majority of cases (85%) Sub-Saharan Africa carries most of the burden. Mosquitoes of the *Anopheles gambiae* complex and *A. funestus* serve as the main malaria vectors. In the Ashanti Region of Ghana where our studies were conducted, malaria is prevalent during the entire year and one of the major in-patient causes of death.

In the thesis socioeconomic and spatio-temporal patterns of malaria were analysed in children <15 years of age from a holoendemic area during a 26 months period (May 2007 to August 2009). The primary outcome was the malaria incidence at village level (14 villages) or village cluster level (four village clusters). Potential malaria risk factors considered were attributes associated with the family's socioeconomic and sociodemographic background by using principal component analyses (PCA) and multivariate regression models (Paper I). In Paper II the temporal influence of weekly precipitation on weekly malaria incidence was investigated by conducting a time-series-model using cross-correlation function and autoregressive modeling. The association between malaria risk and nine different land cover classes was investigated by using high-resolution remote sensing data which were edited with the ENVI software and a geographic information system and by using Poisson regression analyses (Paper III).

In the first publication the results of the multivariate model (n=1,478) showed that the proportion of children with malaria decreased with highest socioeconomic status as classified by PCA (odds ratio [OR]=0.56, p<0.001). Another independent factor for malaria risk was the use of malaria protection measures (OR=0.71, p=0.05). Malaria odds increased if a child was between >1 and <5 or above 5 years of age (OR=3.34 and OR=2.10, respectively [both p<0.001]), compared to children <1 year of age. Furthermore, the OR for having malaria was three times higher if a child was from Greater Agogo compared to Greater Konongo (OR=3.1, p<0.001).

Due to the fact that precipitation data was available only from the two villages Agogo and Konongo the second publication was restricted to the two village clusters Greater Agogo and Greater Konongo (n=1,993). The results indicated a strong seasonal association between precipitation and incidence of malaria. The regression

model showed that the level of rainfall predicted the malaria incidence after a time lag of nine weeks (mean = 60 days). Additionally, one week and two weeks of preceding rainfall events in Greater Konongo and in Greater Agogo, respectively, had a significant influence ($p<0.05$) on malaria incidence.

The third paper included the 12 villages where remotely sensed data were available (n=1,988). Malaria incidence increased by 43% with an increase of 10% in coverage of swampy area in a village area of 2 km around each village (relative risk [RR]=1.43, $p<0.001$). Each 10% increase in banana and plantain coverage increased the incidence by approximately 300% (RR=3.25, $p<0.001$). An increase in forested area of 10% in a village surrounding of 2 km was associated with a 47% decrease of malaria incidence (RR 0.53, $p=0.029$).

The results presented herein indicate that even in holoendemic rural areas where economic differences are not much pronounced, the socioeconomic situation is significantly associated with malaria. It could be demonstrated that a PCA is a uselfool technique to reduce the complexity of socioeconomic indicator variables. Valid classification of the socioeconomic level is crucial to be considered as confounder in intervention trials and in the planning of malaria control measures.

Additionally, the time-series-analyses presented in Paper II provide evidence that high-resolution precipitation data can directly predict fluctuations in the malaria incidence in a highly endemic area. Such models might enable the development of early warning systems and support intervention measures.

The significant influence of specific land cover on malaria incidence demonstrates the usefulness of satellite images for the prediction of malaria risk. In future, planning and monitoring of malaria control measures should be assisted by models based on geographic information systems.

Finally, a birth cohort study aimed at elucidate potential gestational, genetic or perinatal risk factors on malaria as well as precice positions on each included household to combine and analyse the socioeconomic and –demographic risk factors together with the temporal and spatial deteminants to improve our findings are important prerequisites to developing strategies to reduce the incidence of malaria in high-burden countries.

Chapter 7

Zusammenfassung

Weltweit ist Malaria mit 250 geschätzen Fällen im Jahr 2008 und mehr als einer Milionen Todesfällen die häufigste Vektor-Erkrankung. Mit 85% aller Erkrankungen haben die subsaharischen Regionen Afrikas die größte Krankheitslast. Moskitos der Gattung *Anopheles gambiae* und *A. funestus* stellen die häufigsten Vektoren dar. In der Ashanti Region Ghanas, das Gebiet in welchem unsere Studie durchgeführt wurde, tritt Malaria ganzjährig auf und ist eine der häufigsten Todesursachen bei stationär aufgenommenen Patienten.

In dieser Studie wurden in einem endemischen Gebiet über einen Zeitraum von 26 Monaten (Mai 2007 bis August 2009) sozioökonomische -sowie räumlich-zeitliche Muster der Malaria in Kindern unter 15 Jahren analysiert. Malaria wurde teils auf Dorfebene (14 Dörfer) teils auf Dorfgruppenebene (4 Dorfgruppen) untersucht. Als potentielle Risikofaktoren der Malaria wurden mittels einer Faktorenanalyse sowie eines multivariaten Regressionsmodells Variabeln berücksichtigt, welche den familiären sozioökonomischen und soziodemograpischen Hintergrund beschreiben (Publikation I). In der zweiten Publikation wurde eine Zeitreihenanalyse angewendet: der temporäre Einfluss von wöchentlichem Niederschlag auf wöchentliche Malariainzidenz wurde untersucht, indem eine Kreuzkorrelation sowie ein autoregressives Modell angewendet wurden. Assoziationen des Malariarisikos mit neun unterschiedlichen Landnutzungen wurden mittels hochauflösenden Fernerkundungsdaten analysiert. Die Fernerkundungsdaten wurden mit der ENVI Software und einem Geographischen Informationssystem aufbereitet; um Assoziationen zu quantifizieren, wurde eine Poisson Regression angewendet (Publikation III).

Die Resultate des multivariaten Modells der ersten Publikation (n=1.478) zeigten im Vergleich zu allen anderen Erkrankungen signifikant geringere Odds an Malaria zu erkranken, wenn ein Haushalt laut Faktorenanalyse der reichsten Gruppe zugeordnet werden konnte (odds ratio [OR]=0,56, $p<0,001$). Ein weiterer unabhängiger Faktor war das Nutzen von gegen Malaria schützende Maßnahmen (OR=0,71, $p=0,05$). Ebenfalls war das Risiko der Malaria bei Kindern erhöht, die zum Vergleich von Kindern unter einem Jahr, ein Alter zwischen >1 und <5 oder >5 Jahren aufwiesen (OR=3,34 und OR=2,10, [beide $p<0,001$]) oder die in Greater Agogo wohnhaft waren (OR Greater Agogo verglichen mit Greater Konongo=3,1, $p<0,001$).

Die zweite Publikation musste aufgrund der Tatsache, dass nur Niederschlagsdaten aus den Dörfern Agogo und Kononго erhältlich waren auf die beiden Dorfgruppen Greater Agogo sowie Greater Kononго beschränkt werden (n=1.993). Die Ergebnisse zeigten eine starke saisonale Assoziation zwischen den beiden Variabeln Niederschlag und Malariainzidenz. Das Regressionsmodell verdeutlichte, dass nach einer Zeitspanne von neun Wochen (durchschnittlich 60 Tage) die Niederschlagsmenge die Malariainzidenz prognostiziert. Des Weiteren hatte Niederschlag, welcher eine (Greater Kononго) bzw. zwei (Greater Agogo) Wochen vorausging, einen signifikanten Einfluss ($p<0,05$) auf die Malariainzidenz.

In der dritten Publikation wurden jene 12 Dörfer berücksichtigt für die Satellitendaten erhältlich waren (n=1.988). Die Malariainzidenz erhöhte sich bei einem Anstieg von 10% an sumpfiger Fläche innerhalb eines Dorfradius von 2 km signifikant um 43% (relative risk [RR]=1,43, $p<0,001$). Bei einem Flächenzuwachs von 10% an Bananen oder Kochbananen stieg das Malariarisiko signifikant um circa 300% (RR=3,25, $p<0,001$). Eine Erhöhung um 10% an Waldfläche innerhalb eines Radius von 2 km um das Dorf, reduzierte das Risiko an Malaria zu erkranken um 47% (RR=0,53, $p=0,029$).

Die hier vorgestellten Resultate verdeutlichen, dass selbst in endemischen Gebieten in welchen ökonomische Unterschiede nicht stark ausgeprägt sind, der familiäre ökonomische Hintergrund signifikant mit Malaria assoziiert ist. Es konnte gezeigt werden, dass eine Faktorenanalyse eine nützliche Methode ist, um die Komplexität ökonomischer Indikatorvariabeln zu reduzieren. Valide klassifizierte ökonomische Daten sind wichtig, um als mögliche Störgrößen in Interventionsstudien berücksichtigt zu werden, und um Malaria-Kontrollmaßnahmen besser planen und umsetzen zu können.

Die Zeitreihenanalysen der zweiten Publikation zeigen, dass detaillierte Niederschlagsdaten direkt zeitliche Schwankungen der Malaria in einem endemischen Gebiet vorhersagen können. Diese Modelle könnten bei der Entwicklung von Frühwarnsystemen helfen sowie Interventionsmaßnahmen unterstützen.

Der signifikante Einfluss spezifischer Landnutzungen auf Malariainzidenzen verdeutlicht den großen Nutzen von Satellitenbildern zur Vorhersage des Malariarisikos. Daher sollten in Zukunft bei der Planung und Überwachung von Malariakon-

trollmaßnahmen Modelle, die auf Geographischen Informationssystemen basieren, miteinbezogen werden.

Des Weiteren wäre eine Geburtenkohortenstudie, welche potentielle intrauterine, genetische sowie perinatale Risikofaktoren verdeutlicht und aufdeckt, empfehlenswert.

Analysen, welche exakte Positionen aller untersuchten Haushalte miteinbeziehen, könnten unsere Ergebnisse verbessern, indem die hier analysierten sozioökonomischen und –demographischen Faktoren zusammen mit den temporären und räumlichen Determinanten berücksichtigt würden.

Diese Ansätze sind wichtige Vorraussetzungen, um Strategien zur Reduzierung der Malariainzidenz in hoch endemischen Ländern zu fördern und weitere Interventionen zu erarbeiten.

Appendix 1

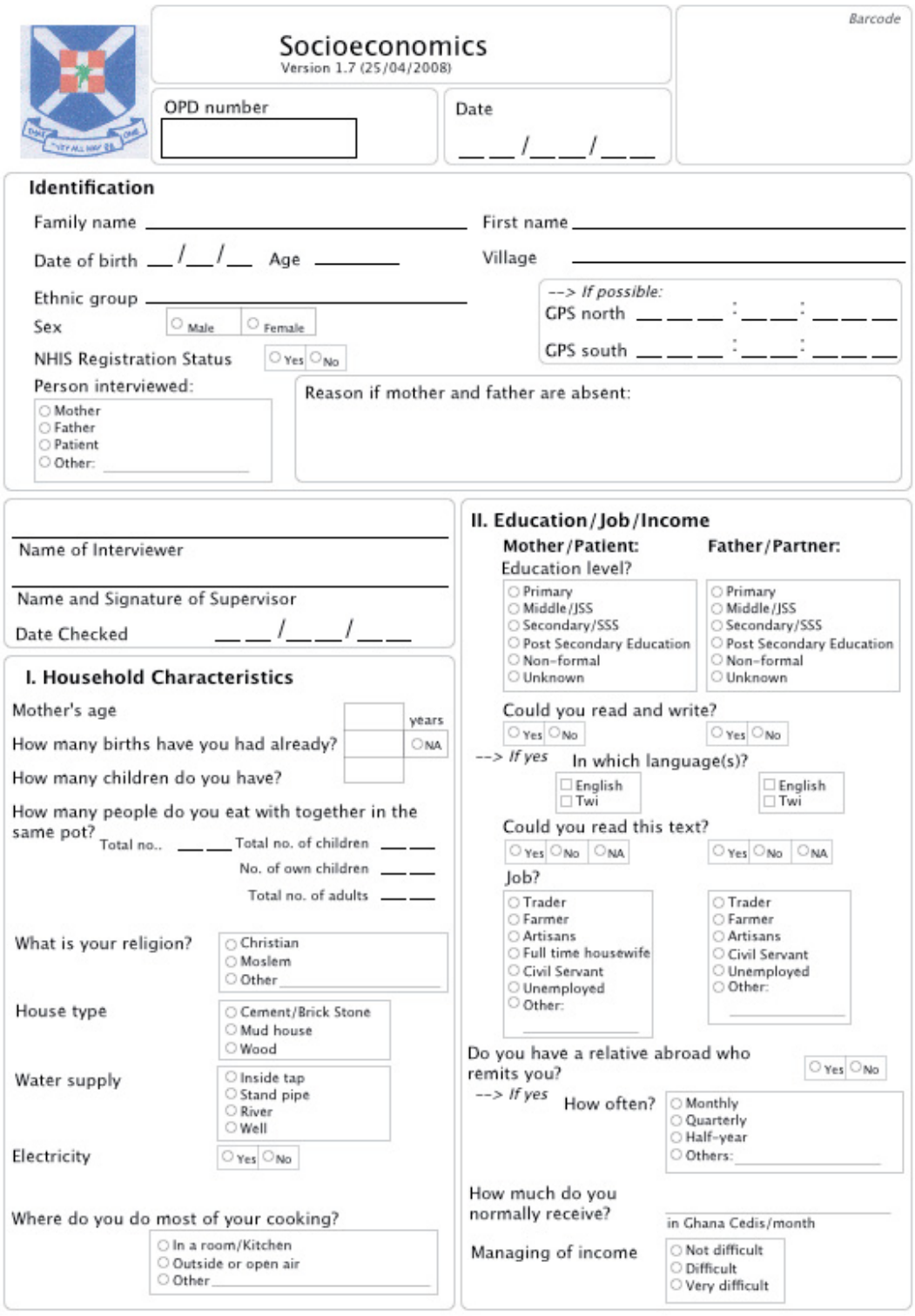
Table 1: Characteristics of the villages

Village[1]	Village area[2]	Total population[3]	Population density[2]	Proportion with hospital access[4]	Population study group[5]	Malaria cases[6]	Incidence[7]
Agogo	5.12	13,559	2,648	90%	3,588	1,463	271.9
Akutuase	0.61	1,692	2,774	43%	214	9	28.1
Amantena	0.27	890	3,296	55%	144	21	97.3
Domeabra	1.33	3,509	2,638	42%	433	73	112.3
Hwidiem	1.08	1,402	1,298	95%	392	147	250.3
Juansa	1.27	3,992	3,143	40%	469	52	73.8
Kyekyebiase	0.54	1,801	3,335	46%	244	28	76.6
Nyaboo	1.02	1,582	1,551	46%	214	28	87.2
Obenimase	0.51	1,096	2,149	37%	119	15	83.9
Patriensah	0.54	4,463	8,265	38%	499	92	123.0
Pekyerekye	0.37	1,692	4,573	45%	224	27	80.4
Wioso	0.34	1,783	5,244	52%	273	33	80.7
Konongo[8]	-	15,383	-	27%	1221	269	147.7
Odumasi[8]	-	8,502	-	22%	786	114	136.6
Total	~13	61,346	-	-	8820	2,371	139.2

[1] village-cluster = “Greater Agogo” (Agogo and Hwidiem), “Greater Konongo” (Konongo and Odumasi), “West of Agogo” (Akutuase, Amantena and Wioso) and “Near Street” (Domeabra, Juansa, Kyekyebiase, Nyaboo, Obenimase, Patriensah and Pekyerekye)
[2] per km^2
[3] Population according to the national census 2004 [29]
[4] Proportion of people in each village who reported to visit the Agogo hospital, data from Community Survey
[5] Population of children <15 years of age estimated as a proportion of 42% of the population counted at national census 2004 [21] and an additional proportion of 70% due to inclusion into the study at hospital admittance and by taking into account hospital access
[6] Study period from May 2007 to November 2008 (18 months)
[7] Incidence in children <15 years (per year and 1,000 children <15 year). Formula: incidence = 1,000*cases/(total_population*0.42*0.70*hospital_access*1.5)
[8] no village area and inhabitants per km^2 available

Appendix 2

Socioeconomic Questionnaire



Socioeconomics
Version 1.7 (25/04/2008)

Barcode

OPD number

Date ___/___/___

Identification

Family name _____ First name _____

Date of birth ___/___/___ Age _____ Village _____

Ethnic group _____

Sex ○ Male ○ Female

NHIS Registration Status ○ Yes ○ No

--> *If possible:*
GPS north ___ ___ ___ : ___ ___ : ___ ___ ___
GPS south ___ ___ ___ : ___ ___ : ___ ___ ___

Person interviewed:
○ Mother
○ Father
○ Patient
○ Other: _____

Reason if mother and father are absent:

_____
Name of Interviewer

_____
Name and Signature of Supervisor

Date Checked ___ ___/___ ___/___ ___

I. Household Characteristics

Mother's age ____ years

How many births have you had already? ____ ○ NA

How many children do you have? ____

How many people do you eat with together in the same pot? Total no.. ___ ___
Total no. of children ___ ___
No. of own children ___ ___
Total no. of adults ___ ___

What is your religion?
○ Christian
○ Moslem
○ Other _____

House type
○ Cement/Brick Stone
○ Mud house
○ Wood

Water supply
○ Inside tap
○ Stand pipe
○ River
○ Well

Electricity ○ Yes ○ No

Where do you do most of your cooking?
○ In a room/Kitchen
○ Outside or open air
○ Other _____

II. Education/Job/Income

	Mother/Patient:	**Father/Partner:**
Education level?	○ Primary ○ Middle/JSS ○ Secondary/SSS ○ Post Secondary Education ○ Non-formal ○ Unknown	○ Primary ○ Middle/JSS ○ Secondary/SSS ○ Post Secondary Education ○ Non-formal ○ Unknown
Could you read and write?	○ Yes ○ No	○ Yes ○ No
--> *If yes* In which language(s)?	☐ English ☐ Twi	☐ English ☐ Twi
Could you read this text?	○ Yes ○ No ○ NA	○ Yes ○ No ○ NA
Job?	○ Trader ○ Farmer ○ Artisans ○ Full time housewife ○ Civil Servant ○ Unemployed ○ Other:	○ Trader ○ Farmer ○ Artisans ○ Civil Servant ○ Unemployed ○ Other:

Do you have a relative abroad who remits you? ○ Yes ○ No

--> *If yes* How often?
○ Monthly
○ Quarterly
○ Half-year
○ Others: _____

How much do you normally receive? _____ in Ghana Cedis/month

Managing of income
○ Not difficult
○ Difficult
○ Very difficult

(Questionnaire continuous)

III. Migration

How long have you stayed in this village? ____ ○ years ○ months ○ weeks ○ days

Has a member of your household been away from the household for up to 1 month? ○ Yes ○ No

Do you have a visiting member in the household? ○ Yes ○ No

--> If yes

For how long has he/she been with you? ____ ○ years ○ months ○ weeks ○ days

IV. Hygiene and Sanitation

Do you have a toilet within the house? ○ Yes ○ No

--> If yes

How many people use it? ○ 1-10 ○ 11-20 ○ 21+

What type of toilet is it? ○ WC ○ KVIP ○ Other _____

--> If no

Where do you go to toilet? ○ Public toilet ○ Next house ○ Free range

Do you share the same toilet facilities with the children? ○ Yes ○ No ○ NA

How do you clean yourself after visiting the toilet?

○ Wash hands with soap
○ Wash hands with water
○ Don't clean myself

What is the main method of garbage disposal?

○ Garbage dumb
○ In the river
○ Abandoned house
○ Burning
○ Other: _____

V. Accessibility to health facilities

Do you have a functional health facility in this community? ○ Yes ○ No

How long does it take by trotro to get to the closest health facility? ____ minutes

VI. Food Handling

How do you prepare yourself before handling food?

○ Wash hands with soap
○ Wash hands with water
○ Don't clean myself

How do you store fresh food such as meat/fish for use in the next day?

○ In a covered dish
○ Freezing
○ Other means of preservation: _____

How do you serve food?

○ Covered dishes
○ Uncovered dishes

How do you clean yourself before eating?

○ Wash hands with soap
○ Wash hands with water
○ Wash only when my hands are dirty
○ Others: _____

VII. Management of sick child/Medical knowledge

Do you have any medication at home? ○ Yes ○ No

Have you ever been or taken your child to a traditional healer? ○ Yes ○ No

What is the cause of malaria?

○ Mosquito bite
○ Infection
○ Other answer
○ Unknown

Do you have any mosquito protection?

○ Bednet
○ Window net
○ Other
○ No protection

Was your child born in Agogo Hospital? ○ Yes ○ No

Average time elapsed from onset of the first symptom to visit at the hospital ____ days

What health facility do you usually visit when you are or your child is sick? _____

Why do you visit that facility?

○ It is closer to me
○ Inexpensive
○ Good quality of care
○ Other reasons: _____

Who decides on the facility you visit when you are or your child is sick?

○ Myself only
○ Myself and my partner together
○ My partner only
○ Others: _____

1st data entry: Initials:_____ Date: __ __/__ __/__ __

2nd data entry: Initials:_____ Date: __ __/__ __/__ __

Appendix 3

Table 2: Weekly malaria incidence and precipitation for the village groups “Greater Agogo” and “Greater Konongo”

Week	Greater Agogo		Greater Konongo	
	Incidence[1]	*Pecipitation*[2]	*Incidence*[1]	*Precipitation*[2]
1 (12.-18.3.2007)	-	3.4	-	3.6
2 (19.-25.3.2007)	-	1.8	-	0.0
3 (26.3.-1.4.2007)	-	1.1	-	4.4
4 (2.8.4.2007)	-	10.5	-	5.0
5 (9.-4.15.4.2007)	-	0.4	-	2.9
6 (16.-22.4.2007)	-	2.6	-	9.5
7 (23.-29.4.2007)	-	3.2	-	11.5
8 (30.4.-6.5.2007)	-	14.2	-	4.0
9 (7.-13.5.2007)	-	0.5	-	1.3
10 (14.-20.5.2007)	-	0.3	-	0.0
11 (21.-27.5.2007)	3.8	2.3	2.3	2.1
12 (28.5-3.6.2007)	2.5	4.4	1.7	0.0
13 (4.-19.6.2007)	4.8	5.2	2.8	5.7
14 (11.-17.6.2007)	4.0	2.3	2.8	8.5
15 (18.24.6.2007)	8.1	6.2	3.4	12.4
16 (25.6.-1.7.2007)	5.3	0.5	6.2	15.2
17 (2.-8.7.2007)	5.0	0.4	2.3	11.9
18 (9.-15.7.2007)	6.1	0.0	7.3	4.8
19 (16.-22.7.2007)	4.5	9.2	4.0	0.0
20 (23.-29.7.2007)	2.3	10.5	1.7	11.1
21 (30.7.-5.8.2007)	3.8	0.0	4.0	0.0
22 (6.-12.8.2007)	7.3	0.7	5.1	0.0
23 (13.-19.8.2007)	3.5	4.8	3.4	8.3
24 (20.-26.8.2007)	4.8	5.0	1.1	7.2
25 (27.8.-2.9.2007)	2.5	17.7	4.0	16.3
26 (3.-9.9.2007)	3.3	16.9	6.8	13.3
27 (10.-16.9.2007)	5.8	5.6	6.2	8.5
28 (17.-23.9.2007)	4.3	10.2	4.0	12.0
29 (24.-30.9.2007)	3.8	6.8	4.0	10.1
30 (1.-7.10.2007)	4.8	8.4	0.6	8.1
31 (8.-14.10.2007)	6.8	1.4	3.4	4.3
32 (15.-21.10.2007)	3.8	7.9	4.5	3.5
33 (22.-28.10.2007)	5.3	6.3	4.5	0.0
34 (29.10.-4.11.2007)	5.8	6.7	4.0	4.1
35 (5.-11.11.2007)	10.1	0.3	6.8	2.9
36 (12.-18.11.2007)	7.1	0.6	4.0	9.5
37 (19.-25.11.2007)	6.8	7.2	6.2	3.7
38 (26.11.-2.12.2007)	5.5	0.5	1.7	0.6
39 (3.-9.12.2007)	4.8	2.8	4.0	0.0
40 10.-16.12.2007)	6.1	0.0	2.8	0.0
41 (17.-23.12.2007)	4.8	1.8	2.8	0.8
42 (24.-30.12.2007)	3.0	0.0	1.7	0.0
43(31.12.2007-6.1.2008)	3.3	0.0	0.6	0.0
44 (7.1.-13.1.2008)	3.8	0.0	1.1	0.0
45 (14.-20.1.2008)	5.0	0.0	1.1	0.0
46 (21.-27.1.2008)	6.3	0.0	1.1	0.0
47 (28.1.-3.2.2008)	3.5	0.0	1.1	0.0
48 (4.-10.2.2008)	3.5	2.0	0.6	2.2

				table continuous
49 (11.-17.2.2008)	2.0	0.0	1.7	0.0
50 (18.-24.2.2008)	2.5	0.0	1.7	0.0
51 (25.2.-2.3.2008)	1.3	10.4	1.7	7.8
52 (3.-9.3.2008)	1.0	0	1.1	0.2
53 (10.-16.3.2008)	3.5	1.8	1.7	1.4
54 (17.-23.3.2008)	2.5	6.8	0.0	2.4
55 (24.-30.3.2008)	3.3	0.8	0.6	4.3
56 (31.3.-6.4.2008)	3.0	7.0	2.8	3.2
57 (7.-13.4.2008)	6.1	1.5	2.8	16.7
58 (14.-20.4.2008)	6.3	0.7	2.8	0.0
59 (21.-27.4.2008)	4.0	9.9	4.5	1.9
60 (28.4.-4.5.2008)	7.1	5.8	2.3	10.0
61 (5.-11.5.2008)	12.4	1.6	1.7	9.4
62 (12.-18.5.2008)	9.3	2.3	4.5	15.8
63 (19.-25.5.2008)	8.8	12.1	3.4	8.6
64 (26.5.-1.6.2008)	7.6	10.2	1.1	16.5
65 (2.-8.6.2008)	7.3	7.3	2.3	3.7
66 (9.-15.6.2008)	5.5	11.8	7.3	10.8
67 (16.-22.6.2008)	7.3	1.8	1.7	14.2
68 (23.-29.6.2008)	6.1	7.7	2.3	9.3
69 (30.6.-6.7.2008)	3.0	2.9	1.7	10.0
70 (7.-13.7.2008)	6.1	0.1	2.8	0.8
71 (14.-20.7.2008)	5.5	3.2	1.1	7.3
72 (21.-27.7.2008)	6.8	6.5	4.0	8.8
73 (28.7.-3.8.2008)	6.0	0.0	3.4	2.6
74 (4.-10.8.2008)	5.0	4.0	0.6	5.0
75 (11.-17.8.2008)	6.6	1.6	1.1	11.7
76 (18.-24.8.2008)	5.5	2.6	2.8	0.0
77 (25.-31.8.2008)	8.6	6.9	0.6	30.2
78 (1.-7.9.2008)	4.0	10.2	6.2	13.4
79 (8.-14.9.2008)	6.8	0.4	2.3	0.0
80 (15.-21.9.2008)	5.5	20.3	1.1	18.1
81 (22.-28.9.2008)	3.3	9.0	1.7	0.8
82 (29.9.-5.10.2008)	2.8	14.6	2.3	3.9
83 (6.-12.10.2008)	5.8	5.0	1.1	4.2
84 (13.-19.10.2008)	3.8	9.0	2.3	6.0
85 (20.-26.10.2008)	2.8	0.7	0.0	0.0
86 (27.10.-2.11.2008)	6.3	5.1	0.0	0.9
87 (3.-9.11.2008)	2.5	0.0	4.0	1.6
88 (10.-16.11.2008)	4.5	0.5	1.1	0.0
89 (17.-23.11.2008)	5.5	1.2	1.7	0.0
90 (24.-30.11.2008)	6.6	0.0	1.1	7.8

[1] Mean weekly incidence per 1,000 children <15 years
[2] Mean weekly precipitation in millimeters

Eidesstattliche Erklärung

Hiermit erkläre ich ehrenwörtlich, dass ich die der medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf zur Promotionsprüfung eingereichte Arbeit mit dem Titel
„Spatial, temporal, and socioeconomic risk factors of malaria in children from the Ashanti Region, Ghana“
im Leibniz-Institut für umweltmedizinische Forschung an der Heinrich-Heine-Universität Düsseldorf unter Betreuung von

Herrn Professor Dr. Ulrich Ranft

selbständig angefertigt und bei der Abfassung der Arbeit keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe. Ich habe bisher weder an einer in- und/oder ausländischen Universität ein Gesuch um Zulassung zur Promotion im Bereich „Public Health“ eingereicht.

Danksagung

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Abstract

Räumliche, zeitliche und sozioökonomische Risikofaktoren der Malaria bei Kindern aus der Ashanti Reion, Ghana

Spatial, temporal, and socioeconomic risk factors on malaria in children from the Ashanti Region, Ghana

Anne Caroline Krefis

Die räumliche und zeitliche Variabilität der Malaria, speziell in endemischen Gebieten, stellt ein wichtiges Forschungsgebiet im Rahmen von Public Health dar. Über einen Zeitraum von 26 Monaten (Mai 2007 bis August 2009) wurde jene Variabilität in 14 Dörfern der Ashanti Region Ghanas in Kindern unter 15 Jahren untersucht.

Ziel der Dissertation war zum einen, den Zusammenhang zwischen sozioökonomischen und soziodemographischen Faktoren der Familie und der Erkrankung an Malaria zu quantifizieren. Des Weiteren wurde der temporäre Einfluss von wöchentlichem Niederschlag auf wöchentliche Malariainzidenz untersucht. Als dritte Zielsetzung wurden auf Dorfebene mit Hilfe von Fernerkundungsdaten Assoziationen bestimmter Landnutzungen mit Malariainzidenz analysiert. Die vorgenannten drei Zielsetzungen wurden jeweils in wissenschaftlichen Zeitschriften publiziert.

Die Resultate der ersten Publikation zeigen, dass der Anteil der an Malaria erkrankten Kinder mit höherem Sozialstatus abnimmt. Weitere unabhängige Faktoren des Malariarisikos waren die Anwendung von protektiven Maßnahmen, das Alter des Kindes sowie dessen Wohnort.

Die Ergebnisse der zweiten Publikation zeigen eine starke zeitliche Assoziation zwischen Niederschlag und Malaria. Einer Zunahme der Niederschlagsmenge folgte mit einer Verzögerung von neun Wochen ein Anstieg der Malariainzidenz. Niederschlag, der eine bzw. zwei Wochen vorausging, hatte ebenfalls einen signifikanten Einfluss auf die Malariainzidenz.

Die dritte Publikation zeigte eine Erhöhung des Malariarisikos im Zusammenhang mit erhöhten Anteilen sumpfiger Gebiete sowie einer Bananenvegetation innerhalb der näheren Umgebung des Wohnorts auf. Sinkendes Malariarisiko konnte bei ansteigenden Flächenanteilen von bewaldeten Gebieten beobachtet werden.

Malaria, insbesondere bei Kindern unter 5 Jahren, stellt ein bedeutendes Public Health Problem in den betroffenen Ländern dar. Die hier durchgeführten Analysen und hieraus folgenden Resultate bringen wichtige Erkenntnisse, um bestehende Strategien zur Reduzierung der Malariainzidenz in endemischen Ländern zu verbessern und weitere Interventionen zu erarbeiten.

Düsseldorf, 10.01.2011 Prof. Dr. Ulrich Ranft