Aus dem Fachbereich Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

betreut im
Zentrum der Gesundheitswissenschaften
Institut für Arbeitsmedizin, Sozialmedizin und Umweltmedizin
Direktor : Prof. Dr. Dr. h.c. mult. David A. Groneberg

Determinants of Malaria in Indonesia

Dissertation
zur Erlangung des Doktorgrades der theoretischen Medizin
des Fachbereichs Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

vorgelegt von
Hamzah Hasyim
B.Sc. (PH) Occupational Health and Safety
(MPH) Environmental Health

aus Ujung Pandang, South Sulawesi, Indonesia
Frankfurt am Main, 2019

Dekan/in	:	Prof. Dr. med. Josef Pfeilschifter
Referent/in	:	Prof. Dr. rer. nat. Ruth Müller
Korreferent/in	:	Prof. Dr. Maria Vehreschild
Tag der mündlichen Prüfung	:	09.12.2019

Table of Contents

Zusammenfassung 4
Summary 7
List of abbreviations 9
Comprehensive Summary 11
1.1 An introduction with reference to the overall research question 11
1.2 A presentation of the manuscripts respectively the publications 12
1.3 Discussion of the results obtained and their relevance with regards to the research question. 16
Overview of the manuscripts and publications accepted for release 21
The manuscripts/publications 23
Presentation of the personal contribution regarding manuscripts/publications 24
Publication #1 Spatial modelling of malaria cases associated with environmental factors in South Sumatra, Indonesia 25
Publication #2 Does livestock protect from malaria or facilitate malaria prevalence? A cross-sectional study in endemic rural areas of Indonesia 41
Publication #3 Social Determinants of Malaria in an Endemic Area of Indonesia 53
Bibliography 65
An Annex 71
Additional file 1 71
Additional file 2 74
Additional file 3 77
Additional file 4 83
Acknowledgements 86
Curriculum Vitae 89
Schriftliche Erklärung 92

Zusammenfassung

Malaria ist eine Umweltkrankheit, die nicht nur von den physischen und biologischen Umweltfaktoren, sondern auch von soziokulturellen Faktoren beeinflusst wird. Einige Faktoren, die eine mit der Krankheit verbundene hohe Morbiditätsrate verursachen, umfassen den Klimawandel, die geografische Umgebung, sozioökonomische Umstände, und das menschliche Verhalten. Weitere Risikofaktoren sind das Vorhandensein von Tieren, Wohnbedingungen mit schlechten sanitären Einrichtungen, fehlende Hygienepraktiken und unzureichende Gesundheitsdienste in Endemiegebieten. Die Bemühungen zur Beseitigung von Malaria und zur Beseitigung von Vektoren sind seit Jahrzehnten Gegenstand zahlreicher Tagungen und Initiativen im Bereich der öffentlichen Gesundheit. In Indonesien ist Malaria nach wie vor eine der Hauptursachen für Morbidität und Mortalität. Das Ziel dieser Studie ist es, die multiplen Determinanten von Malaria in den endemischen Gebieten Indonesiens zu analysieren, die mit soziodemografischen als auch physischen Umgebungen korrelieren. Wir teilen diese Forschung in drei Teilstudien auf, um ein Vorstellungsmodell zu entwickeln, das die Determinanten für Malaria in Indonesien umfassend beschreibt.

Diese Dissertation folgt einer Querschnittsdesignstudie. Die Forschungsdaten dieser Dissertation stammen aus vier Quellen: routinemäßige Berichterstattung über Malaria aus der Gesundheits-Provinz in Süd-Sumatra; die nationalen Grundlagenforschungsdaten (IDN-Akronym: Riskesdas); Klimadaten aus der Klimatologie-Agentur Meteorologie, Klimatologie und Geophysik (IDN-Akronym: BMKG); Geodaten von Geospatial Information Agency (IDN-Akronym: BIG). In dieser Studie wurde ein ganzheitlicher Ansatz verfolgt, der die folgenden univariaten, binär-logistische Regressionsanalyse, und multivariate-logistische Regressionsanalyse, um eine Modellierungsdeterminante von Malaria zu etablieren. Darüber hinaus haben wir beide Modelle, die geographisch gewichtete Regression (GWR) und die Methode der kleinsten Quadrate (OLS) verglichen. Wir verwendeten folgende statistische Programme für die Datenverarbeitung, Analyse, Visualisierung und die Entwicklung der Modelle: Statistisches Paket für die Sozialwissenschaften (SPSS), Stata, Aeronautical Reconnaissance Coverage Geographisches Informationssystem (ArcGIS) und Geographisch gewichtete Regression 4 (GWR4).

Die Prävalenz von Malaria variiert in Abhängigkeit von der lokalen Umgebung und diese Varianz wird durch die örtlich unterschiedliche physische Umgebung verursacht. Es zeigte sich in dieser Studie zudem, dass die Determinanten für Malaria in lokalen Regionen unterschiedlich waren. Wir folgern, dass ländliche Gebiete mit einem hohen Prozentsatz von Haushalten mit Nutz- und Haustieren einhöhere Malaria-Prävalenz aufwiesen als der nationale Durchschnitt in Indonesien. Darüber hinaus weist die Studie darauf hin, dass soziodemografische Variablen der Teilnehmer (z.B. Geschlecht, Alter, Bildungsgrad, Kenntnis der Zugänglichkeit und Nutzung von Gesundheitsdiensten, Maßnahmen zum Schutz vor Mückenstichen, und Wohnzustand der Studienteilnehmer) mit der Malariaprävalenz in endemischen Provinzen in Indonesien zusammenhängen.

In Süd-Sumatra, Indonesien sind die unabhängigen Variablen Höhe, Entfernung vom Wald und Niederschlag im globalen OLS Modell signifikant mit Malariafällen assoziiert. Das ergänzende GWR Modell zeigte schlüssig, daß die Ursache der Malariafälle auf der dörflichen Ebene erheblich variiert. Daher ist es für den Entscheidungsträger, d.h. die Regierung, sehr wichtig, ein tiefergehendes Verständnis der regionalen und ökologischen Faktoren zu entwickeln, welche die bestätigten Malariafälle beeinflussen. Auf Grundlage der vorliegenden Ergebnisse empfehlen wir die Entwicklung nachhaltiger regionaler Malariakontrollprogramme, welche Anreize für die Beseitigung von Malaria schaffen, und insbesondere auf Dorfebene. Das Vorhandensein von bestimmten Tieren stellt einen Hauptrisikofaktor für Malaria im ländlichen Indonesien dar und muß in Bekämpfungsstrategien berücksichtigt werden. Hier empfehlen wir insbesondere für das Untersuchungsgebiet einen One Health Approach mit Integriertem Vector Management (IVM), beispielsweise die simultane Umsetzung von insektizidbehandelten Bettnetzen (ITN) und insektizidbehandelten Nutztieren (ITL). Darüber hinaus sind auch soziodemografische Faktoren, zum Beispiel die gesundheitliche Versorgung für die lokale und regionale Malaria-Prävalenz wichtig.
Wir empfehlen den Ausbau von Bildung und öffentlichen Informationsmöglichkeiten und eine verbesserte Zugänglichkeit bzw. Nutzung der Gesundheitsfürsorge, um das Wissen und das Bewusstsein der Dorfbewohner bezüglich der Reduktion von *Anopheles* Stechmücken zu fördern. Wir empfehlen den Ausbau von Bildung und öffentlichen Informationsmöglichkeiten und eine verbesserte Zugänglichkeit bzw. Nutzung der

Gesundheitsfürsorge, um das Wissen und das Bewusstsein der Dorfbewohner bezüglich der Reduktion von Anopheles Stechmücken zu fördern.
Diese Forschungsarbeit zeigt, dass es einen Zusammenhang zwischen soziodemografischen Faktoren gibt, welche die Malaria-Prävalenz beeinflussen. Die unterschiedlichen Beziehungen zwischen Malaria und den soziodemografischen Faktoren, die die Krankheit beeinflussen können schliessen Merkmale der Teilnehmer ein. Diese Forschung stellt Faktoren dar, die verwaltet werden können und die Beseitigung der Malaria begünstigen würden. Dazu gehören eine Reihe von Präventionsverhalten auf individueller Ebene und die Nutzung der Netzwerke von primären Gesundheitszentren auf Gemeindeebene. Diese Studie legt nahe, dass die Verbesserung der Verfügbarkeit einer Vielzahl von Gesundheitseinrichtungen in endemischen Gebieten, insbesondere Informationen zu ihren Diensten und des Zugangs zu diesen wesentlich ist.

Schlüsselwörter: Geographisch gewichtete Regression (GWR), Methode der kleinsten Quadrate (OLS), Akaike Information Criterion (AIC), physikalische Umwelt, lokalKlima, Sumatra, Regenfälle, Elevation, Entfernung zum Wasser, Ländliches Gebiet, Vieh, Zooprophylaxe, Zoopotenzierung, Multivariate-logistische Regressionsanalyse, Malaria-prävalenz, Soziale Gesundheitsdeterminanten, Sozialepidemiologie und Gesundheitsdienste der Gemeinschaft.

Summary

Malaria is an environmental disease, influenced not only by physical and biological environmental factors but also by socio-cultural ones. These factors affect each other, and, in turn, cause the disease in endemic areas. Some factors that cause the high morbidity rate associated with the disease include climate change, physical environment that varies geographically, socio-economic circumstances, and human behaviour in the affected areas. Other risk factors include housing conditions and poor sanitation, lack of hygiene practices, and inadequate health services in endemic areas. Efforts to eliminate malaria have been a topic at various public health meetings for decades. However, in Indonesia, malaria continues to be one of the leading causes of morbidity and mortality. The research aimed to analyse and model the critical variables associated with malaria in endemic areas of Indonesia. So, this included relationships between malaria and both socio-demographic variables and physical environments. The research is in **three parts**, adding value to a model that determines malaria in Indonesia.

This dissertation follows a cross-sectional design survey. The research data in this PhD dissertation is drawn from four sources: routine reporting of malaria from provincial health departments in South Sumatra; the national basic health research data (IDN acronym: Riskesdas); climate data from the Meteorology, Climatology, and Geophysics Climatological Agency (IDN acronym: BMKG); spatial data from Geospatial Information Agency (IDN acronym: BIG). This study takes a holistic approach, integrating the following univariate, bivariate, and multivariable logistic regressions, to establish a modelling determinant of malaria. Additionally, the researchers compared the performance of both Geographically Weighted Regression (GWR) and Ordinary Least Square (OLS). It also used some statistical analysis software tools for data processing, analysis, visualisation, and the development of the model as follows: Statistical Package for the Social Sciences (SPSS), Stata, Aeronautical Reconnaissance Coverage Geographic Information System (ArcGIS) 10.3, and GWR 4.0 version 4.0.90 for Windows.

The prevalence of malaria varied according to the local area, which, in turn, was related to the local physical environment that varied geographically. The determinants for malaria cases varied locally and regionally as well. Rural areas with a high percentage of households keeping livestock/pets showed a higher proportion of malaria prevalence than the national average. Other socio-demographic risk factors included gender, age, occupation, knowledge about healthcare, protection against mosquito bites, and condition of dwellings. This study reveals that the independent variables - "rainfall", "altitude", and "distance from mosquito resting sites in the forest," in global OLS analysis- are significantly associated with malaria cases in South Sumatra, Indonesia.

On the other hand, in the GWR analysis, the determinants of malaria cases at the village level vary geographically. Therefore, it is essential for the decision maker, the government, to acquire a more in-depth understanding of region-specific, ecological factors that influence confirmed malaria cases. The findings lead to the recommendation for developing sustainable regional malaria control programs and incentivising malaria elimination efforts, particularly at the village level. In another setting, the research led to the conclusion that the presence of mid-sized livestock comprised a significant risk factor for contracting malaria in rural Indonesia. The recommendation, especially for the study area, is to employ integrated vector management (IVM), for example, the simultaneous implementation of insecticide-treated bed nets (ITNs) and insecticide-treated livestock (ITL). Other factors such as socio-demographic and use of health care facilities were also crucial as they related to malaria prevalence. Further, the research leads to the recommendation for increased education and increased promotion and utilisation of the health care framework to promote knowledge and awareness of villagers on how to protect themselves from Anopheles bites. Finally, improving information concerning the availability of health care services and access to various health facilities in endemic areas is essential.

Keywords: Geographically weighted regression (GWR), ordinary least squares (OLS), Akaike information criterion (AIC), physical environment, local climate, Sumatra, rainfall, elevation, distance to water, rural area, livestock, zooprophylaxis, zoopotentation, multivariable analysis, malaria prevalence, social health determinants, social epidemiology, and community health services.

List of abbreviations

An.	:	Anopheles
ANC	:	Antenatal care
ANOVA	:	Analysis of variance
AOR	:	Adjusted odds ratio
API	:	Annual parasite incidence (number of slides positive for parasite × 1000/total population)
ArcGIS	:	Aeronautical Reconnaissance Coverage Geographic Information System
Balitbangkes	:	Badan Penelitian dan Pengembangan Kesehatan (National Institute for Health Research and Development)
BIG	:	The Geospatial Information Agency (IDN acronym: BIG)
BMKG	:	Meteorology, Climatology, and Geophysics Climatological Agency
BPS	:	Central Agency on Statistics (IDN acronym: BPS)
CI	:	Confidence interval
CV	:	Cross validation
DEM	:	Digital elevation model
DOF	:	Degrees of Freedom
GRDP	:	Gross regional domestic product
GWR	:	Geographically weighted regression
HDI	:	Health Development Index
IDN	:	Indonesia
IRS	:	Indoor residual spraying reduction
ITL	:	Insecticide-treated livestock
ITNs	:	Insecticide-treated bed nets
IVM	:	Integrated Vector management
LLINs	:	Long-lasting insecticidal net
MDGs	:	Millennium development goals
MoH	:	Ministry of Health
MP	:	Malaria prevalence
NAD	:	Nanggroe Aceh Darussalam
NIHRD	:	The national institute for health research and development

NMCP	:	National malaria control programme
NMTDP	:	National Medium-Term Development Plan (IDN acronym:RPJMN)
NTB	:	West Nusa Tenggara
NTT	:	East Nusa Tenggara
OLS	:	Least squares regression
OR	:	Odds ratio / unadjusted odds ratio
P	:	*Plasmodium*
PHCs	:	Primary health centres
Polindes	:	Pos bersalin desa (village maternity clinic)
Poskesdes	:	Pos kesehatan desa (village health post)
Posyandu	:	Pos pelayanan terpadu (integrated health post)
Puskesmas	:	Pusat kesehatan masyarakat (primary health care centre)
Pv	:	P-values
RDTs	:	Rapid diagnostic tests
Riskesdas	:	Riset kesehatan dasar (Basic Health Research)
Ristekdikti	:	Ministry of Research, Technology and Higher Education (IDN acronym:Ristekdikti)
SPSS	:	Statistical Package for the Social Sciences
Susenas	:	the National Socioeconomic Survey (Indonesia acronym: Susenas)
Svy	:	Survey
UNICEF	:	United nations children's fund
VBDs	:	Vector-borne diseases
VIF	:	Variance inflation factor
WGS84	:	the World Geodetic System 1984
WHO	:	World Health Organization

Comprehensive Summary

1.1 An introduction with reference to the overall research question

Malaria, as a vector-borne disease is still a public health problem in the world, including in Indonesia.[1]. More than 80% of the deaths related to the *Plasmodium vivax* pathogen are in Ethiopia, India, Indonesia, and Pakistan. Although *Plasmodium vivax* infection is generally related to severe disease and death, the specific risks are uncertain[2]. Malaria is endemic in nine of the 11 countries of South-East Asia Region, accounting for approximately 70% of the burden outside the WHO African Region[3]. Almost 63% of the cases are due to *P. falciparum*. Indonesia accounted for 16% of the reported cases, and 30% of malaria deaths in 2016. Instead, 85% of estimated vivax malaria cases occurred in just five countries, including in Indonesia [3]. There are more than 3.3 million people at potential risk of malaria, who live in regions of high malaria transmission when the world changes the paradigm of the Millennium Development Goals (MDGs) to the Sustainable Development Goals (SDGs), it is crucial that the fight against malaria keep on [4]. Malaria elimination policy included in the MDGs target in 2015, and also contained in the Decree of the Minister of Health of the Republic of Indonesia, as well as in the national medium-term development plan (NMTDP) 2010-2014 with the target of reaching the annual parasite incidence (API) of 2015 is 1 ‰. National Strategic of Ministry of Health 2015 – 2019: number of districts with API < 1 per 1,000 (under MoH monitoring). The emphasis on health development is done through preventive and curative approaches by improving public health to reduce malaria morbidity[5]. Currently, as in medium-term development plan of 2015-2019 has a target enhanced control of communicable and non-communicable diseases. Numbers of districts/cities that are succeeded in eliminating malaria from initial status is 212 of districts/cities in 2013 to achieve target 300 of districts/cities in 2019 [6]. The Indonesian government has set a national goal for Indonesia to be malaria-free by 2030 [1,7,8]. However, malaria is still one of the leading causes of morbidity and mortality in Indonesia [9]. The National Malaria Eradication Program of 1959-1968; which we called of KOPEM (Komando Operasi Pembasmian Malaria, the Malaria Eradication Operation Command) was set up in 1962 by the first Presiden Indonesia, who initiated malaria control efforts, and Indonesia has set the year 2030 as a deadline for the elimination of malaria in the archipelago [10,11]. However, malaria remains a public health problem in Indonesia despite various attempts being made for its elimination, including its discovery and management, infection prevention, surveillance performance, availability of logistics and follow-up plans. There, 15 provinces with malaria prevalence higher than the national average. Each region has different geographical conditions, causing differences between the areas of malaria cases. The national prevalence of malaria (based on the diagnosis of health professional and respondent complaints) was 2.85% in 2007 and malaria prevalence in 2013 was 6.0 % [12,13]. Besides, malaria is a serious disease and a threat to life in South Sumatra Province, Indonesia. Some studies show the complexity of causes for malaria prevalence [14, 15, 16, 17]. Its target coincides with the level of malaria endemicity and the strength of the health infrastructure [18]. The country shows nationwide a continuously decreasing incidence of malaria, but at the district level, the situation is more complex[16]. For example, the regional deadline for malaria elimination for the island of Java was the end of 2015[7]. Some areas have shown efforts to eliminate malaria [7],[19]. Furthermore, the Purworejo Region, a malaria-endemic zone in Java with an API of 0.05 per 1,000 resident in 2009, wants to introduce this elimination phase[7]. To achieving malaria elimination, good evidence is needed concerning the relationship between malaria and environmental risk factors.

1.2 A presentation of the manuscripts respectively the publications

This present study explores some risk factors that influence malaria in Indonesia. Furthermore, this dissertation **divided into three studies** to get comprehensive information regarding determinants malaria in an endemic area in Indonesia, which evidence-based. An increased understanding of the dynamics of transmission of *falciparum* and *vivax* malaria could suggest improvements for malaria control efforts [20]. As an example, China has experienced noticeable changes in climate over the past 100 years, and modelling shows that the potential impact of climate change on the transmission of mosquito-borne infectious diseases poses a risk to Chinese populations[21]. Henceforth, malaria transmission is also affected by changes in meteorological conditions which influence the biology of the parasite and its vector [22]. There are a large number of factors that affect potential susceptibility to malaria that involves social, demographic and geographic dimensions[23]. The principal factors associated with malaria prevalence include environmental, socio-demographic and behavioural ones[24]. Infection with malaria parasites is directly dependent on mosquitoes and human characteristics. Environmental variables such as "altitude", and "land cover" are predicted to affect malaria[25]. Besides, the "rainfall", and "temperature" can predict the risk of malaria transmission and modify the breeding site of Anopheles. The regions with having a significant "precipitation" and higher "temperatures" are expected to possess a higher prevalence of malaria because this condition supports the breeding of many Anopheline species and reproduction of parasites in mosquitoes[26]. The analysis of the spatial malaria epidemiology can describe a geographical distribution of the prevalence of the disease. To analyse the elements of geographical influence (a risk factor for spatial epidemiology of malaria), so, a modelling approach can be used to uncover the relationship with malaria prevalence [27,28]. At its simplest, maps can identify the location of cases of malaria. There are issues to be overcome with the production of charts and analysis of data [29]. First, modelling can be used to map disease distribution and attempt to uncover underlying patterns. Second, is to analyse the spatial relationships between the variables: disease and critical factors). It is usually done at a regional level by aggregating local level data. Finally, general clustering is done to identify areas of unusual incidence [29]. Also, the presence of livestock in a rural area, and socio-demographic factors (gender, age, education, and job), the behaviour of participants (using insecticide-treated mosquito nets) influence malaria prevalence [30]. In Indonesia, the presence of livestock in households is common with 39.4% of households raise poultry, 11.6% raise medium-sized, 9.0% raise large-sized animals and 12.5% raise animals such as dogs, cats, or rabbits. Of the families who raise livestock, around 10-20% raise them in house[12]. Since malaria had been early acknowledged as being transmitted by zoophilic vectors, zooprophylaxis is used to prevent disease, but also zoopotentation has been observed. While the existence of livestock as a variable of interest for malaria risk has been widely accepted, the other outcomes of small-to-medium-sized studies are still highly debated. For example, Franco *et al.* (2014) stated that there was controversy over research on the presence of livestock, although based this was based on studies investigating. The presence of animals as a protection against malaria in countries such as New Guinea, Papua and Sri Lanka.

On the contrary, cattle have been proven to be a risk factor for malaria in several countries, such as Pakistan, Philippines and Ethiopia [31]. Habtewold *et al.* (2001) analysed the habits of *An. arabiensis and An. quadriannulatus* are known as a low proportion of human blood meal occurrence [32]. In this study, based on the Riskesdas questionnaire, the animal domestic categorised are livestock, pets, and poultry. The term livestock includes here large-sized animals (cattle, horses, buffaloes), medium-sized animals (goats, sheep, pigs). Additionally, poultry, such as chicken and ducks, and pets, such as dogs, cats and rabbits, are included in the term of *pets* [12]. The proportion of households who raise livestock indoors is lower in urban areas than in the countryside [12]. The present study investigates if the prevalence of malaria is higher amongst participants who raise cattle in rural malaria endemic areas. Indeed, malaria is a global health challenge and is an increasing concern, especially in the endemic provinces in Indonesia. Further explanatory variables are the accessibility to and utilisation of health services, environmental sanitation as well as the quality of drinking water, primary water source, distance to drinking water, wastewater disposal associated with malaria prevalence. However, the extent to which the explanatory variables influence malaria prevalence remains poorly understood. A range of environmental risks, socio-demographic, behaviour, and structural factors have been implicated affect malaria prevalence. This study used data from the large-scale survey Riskesdas to explore the accessibility and utilised of healthcare facilities such as a public hospital or government hospitals; private hospitals; primary health care (PHC) and investigated their connection with malaria prevalence. In addition, healthcare facilities others are clinics or doctor practices, midwife practices or maternity hospital; and integrated health posts (Posyandu). The participants were also asked for utilised and access healthcare of rural health posts (Poskesdes) and rural clinics (Polindes). Next to these potential explanatory variables for malaria prevalence, environmental sanitation like and preventative behaviour against mosquito bites by using mosquito repellent, or insecticide sprays, anti-malaria drugs, and housing conditions were investigated.

The present study aimed to analyses multiple potential determinants of malaria in Indonesia. Data collection described the local physical environment, presence of livestock in a rural area and socioeconomic data not only from regular health reporting in the endemic area but also from large-scale surveys in Indonesia 2007 and 2013, respectively. The data were integrated and analysed utilising an epidemiological modelling approach.

The specific objective of this research was divided into three studies. Firstly, the particular goal of this dissertation is to examine the relationship between confirmed malaria cases and local environmental risk factors in high malaria endemic areas with spatial analysis. (**Study #1**). Secondly, the objective of this paper is to determine the effect of the presence of livestock on malaria prevalence in malaria-endemic rural areas in Indonesia, in a large endemic setting. (**Study #2**). Thirdly, the last part explored the relationship between the prevalence of malaria and social and demographic factors (**Study #3**). The research data in this dissertation was drawn from four primary sources: routine reporting malaria from health provinces in South Sumatra; the national basic health Research data (Indonesia

(IDN) acronym: Riskesdas); climate data from Meteorology, Climatology, and Geophysics Climatological Agency (IDN acronym: BMKG); and spatial data from Geospatial Information Agency (IDN acronym: BIG) [30,33,34]. In general, these sources provided data for the years 2007 and 2013 [12,13]. The research generated descriptive data for all variables, and the data were analysed using bivariate, and multivariable logistic regression analyses to predict malaria prevalence at a significance level of P value < 0.05. For s**tudy #1**, The malaria cases were distributed over 436 out of 1,613 villages. This study performs both Ordinary least square (OLS) and geographically weighted regression (GWR) analyses to demonstrate connection confirmed malaria cases and potential ecological predictors [33]. The research explored the global pattern and spatial variability relationships among of six potential environmental predictors: were the altitude, aspect, distance from the river, distance from lakes and pond, distance from the forest, and rainfall and confirmed malaria cases in the study area [33]. Local variations in environmental variables potentially predicted confirmed cases of malaria. Therefore, the local spatial epidemiology and the distribution of risks of malaria cases were investigated and associated environmental risks identified using spatial discrimination. This study analysed environmental risk factors for malaria that performs at the global OLS and local GWR modelling at the regional level in South Sumatra.

Further, **study #2** using Riskesdas 2007, the subset included 259,885 study participants who resided in the rural area at 176 regencies of 15 provinces with malaria prevalence higher than the national average. The research used multivariable logistic regressions to investigate the role of several variables in the prevalence or status of malaria. These included "the existence of livestock" and other independent demographic, social and behavioural variables [30]. The participants had been diagnosed positive for malaria by a health professional (i.e., with malaria during the past month). Generally, rapid diagnostic tests (RDTs) and microscopy by health services confirmed the diagnosis. Independent questionnaire data at the individual and household level added further information. This included characteristics of participants (gender, age, education, principal occupation), mosquito bite avoidance behaviour (e.g., sleeping under a mosquito net, using net insecticide, defecating habits), and access to and use of health services (health services access by travelling), environmental sanitation (type of container/media, sewage canal, sewage canal conditions), and, for medium and large livestock, the location of cages. The binary categories of the independent variables were "yes" and "no" and led to an analysis of a potential relationship with the response variable malaria.

Furthermore, s**tudy #3** used Riskesdas 2013 data[13]. The current study **(# 3**) included 130,585 participants (the population of five provinces in 83 districts endemic to malaria). The third study investigated the relationship between socio-demographic determinants and malaria prevalence using multivariable logistic regression analysis [34].

1.3 Discussion of the results obtained and their relevance with regards to the research question.

Detecting the spatiotemporal distribution and mapping of high-risk areas are useful to strengthen malaria control efforts and ultimately achieve elimination[35].Therefore, understanding the spatial epidemiology of malaria is essential for developing strategies for disease control and elimination[36]. This study provides an exciting opportunity to advance our knowledge of the role of physical environment locally, the presence of livestock in the rural area, and sociodemographic influences on malaria prevalence. Based on the research questions, this study shows that in **study #1** reveals that the most significant correlations with malaria were with the independent variable altitude, distance from forest, and rainfall (global OLS) [33]. However, as noted by the GWR model and in line with recent reviews, the relation between malaria and environmental influences in South Sumatra was found to vary spatially greatly between different regions. The global OLS model reveals that rainfall had a significant positive coefficient, whereas altitude and distance to the forest had substantial negative coefficients. These indicated a meaningful relationship with confirmed malaria cases. Regions with high rainfall, lowland, and areas adjacent to the forest had high malaria cases globally. Whereas there was no meaningful relationship between malaria, and. Environmental factors such as aspect or direction towards the slope, distance from the river, and the distance from lakes and pond globally. On the other hand, in the GWR analysis indicate the determinants of malaria cases at the village level vary geographically. For example, the variable "altitude" and "distance from lakes and ponds" shows a positive correlation and "aspect" presents a negative association with confirmed malaria cases in the North study area (Musi Banyuasin) locally. Also, "Rainfall" and "distance from the river" parameter denotes a positive connection with malaria cases in the eastern part of Musi Rawas and Lahat. Besides, variable "aspects", "distance from lakes and ponds" and "distance from forests" were positively associated with confirmed malaria cases which reported in most study areas. In line with previous studies, climatic factors that influence the prevalence of malaria include precipitation (rainfall), temperature and humidity[37]. Variations and changes in local weather and meteorological conditions are well known to affect malaria transmission. The effect of climate on the *Anopheles* populations is well established [38]. Rainfall, temperature and humidity are associated with malaria transmission and are important determinants of the dynamics, and the spread of the malaria vector population [38, 39, 40,41, 42.] Altitude significantly influences the type of malaria vectors [25,43]. Moreover, the density of the vector and the frequency of bites on humans [25]. Also, both altitude and direction toward the slopes contribute to the transmission of malaria in the highlands [44]. However, some studies have shown that the drivers of malaria seasonality are not always clear [14]. The understanding concerning the complexity of malaria transmission from climate aspects is still found a significant gap. So, it needs there have been motivated efforts to develop more comprehensive models [15]. At best case, climate variability can provide information for an early warning system for epidemic malaria, and this has been investigated in previous studies [45]. It is crucial that we have a better knowledge of the spatial and temporal patterns of determinants of malaria risk for the prevention and control of the malaria program [46]. Furthermore, GIS presentation of environmental health data could provide an efficient means of translating this knowledge to lay audiences[9]. Further, in **study #2** was in rural malaria endemic areas of 15 highly malaria-endemic provinces in Indonesia and indicated that certain livestock facilitated malaria prevalence and was not suitable as a prophylactic tool. The research found that the participants who raised medium livestock (1.16%, OR = 1.80) had a significantly increased risk of malaria ($P < 0.001$). After adjusting for gender, age, education, job, use of insecticide-treated mosquito nets, and keeping of pets, participants who raised goats, sheep and pigs had an increased likelihood of having malaria (adjusted for other variables; AOR = 2.809; 95% CI 2.207–3.575; $P < 0.001$) [30]. These proceeds lead to the conclusion that the existence of medium-sized livestock (e.g., goats, sheep, and pigs), is a significant risk factor for malaria in the study area. Other principal factors affecting the prevalence of malaria are demographic factors: for gender, age, education, job, use of insecticide-treated mosquito nets, and keeping of pets. The existence of livestock as an essential variable for malaria risk has already been assessed in small to medium scale surveys in both developed and developing countries and has been controversially discussed. One notable finding is the planned control of using livestock to divert the vector bites, called "zooprophylaxis", or as a switch to draw vectors to insecticide sources, called "insecticide-treated livestock (ITL)." These strategies have been used since malaria was acknowledged to be transmitted by zoophilic vectors [31]. Zooprophylaxis is defined by WHO as "The value of wild or domestic animals, which are not the source hosts of a given condition, to alter the blood-seeking mosquito vectors from the human hosts of that disease"[47]. Active zooprophylaxis consists of strategically placing animals between mosquito breeding sites *and* people's houses. Meanwhile, passive zooprophylaxis is the protective effect of the constant presence of animals within a community [48]. Researcher, Escalar G (1933), Saul A (2003) Kawaguchi (2004), Killeen (2007), et al. in the study stated that since the early 1900s, zooprophylaxis has been recognised as an essential tool to decrease malaria transmission to people in some locations of the world and this approach has been evaluated for another vector-borne disease [48]. Livestock has been considered the most appropriate host for this strategy. The term used to refer to livestock includes cattle and small and large ruminants and other domestic animals, such as buffalo, sheep, goats, donkeys, horses, and pigs [31]. Studies have revealed that ownership of livestock investigated at the household level has a substantial impact on the behaviour of the malaria vector. However, there is no clear risk of malaria exposure to livestock presence [49]. The profusion of *An. gambiae* and *An. arabiensis* in housing is related to the spread of domestic animals and humans[50]. Additionally, livestock is thought to be mostly accountable for generating high mosquito densities. With further analyses, the researchers Bouma and Rowland revealed a strong, positive correlation between the cattle-to-man ratio and malaria incidence [51]. Furthermore, in **study #3** revealed, using multivariable analysis, that independent socio-demographic risk variables were related to malaria prevalence. These were: gender, age, occupation, knowledge about healthcare services, preventative measures against mosquito bites, and housing conditions. Participants who did not know about the available health facilities were 4.2 times more likely to have malaria than those who did know adjusted odds ratio (AOR) = 4.18; 95% CI 1.52 - 11.45; P = 0.005, adjusted by other covariates [34]. Healthcare facilities included in the data were government hospitals, private hospitals, primary healthcare (puskesmas), clinics, midwife practices, integrated health posts (posyandu), village health posts (poskesdes), and village maternity clinics (polindes). The study concluded that health services, as well as their networks, are essential for malaria elimination. To guide the development of effective strategies for malaria elimination needs an understanding of the connections between malaria and other factors. In Indonesia, little is known about the determinants of malaria prevalence among sociodemographic factors. The potency of the PHC system in achieving those most at risk and reducing the disease burden and that inadequate approach is a significant risk factor particularly for the poor households [52]. Currently, a major component of malaria control strategies to reduce malaria-related mortality and severe morbidity is early diagnosis and prompt treatment at peripheral health services such as village health posts and dispensaries[53]. The study demonstrates that the incidence of hospitalised malaria more than doubled as travel time to the nearest primary care resource built from ten minutes up to two hours. Good access to PHC facilities may reduce the burden of disease by 66%[54]. Recently illustrated from a Tanzanian demographic surveillance site (DSS) section suggests that the most impoverished infants and kids under five years old had higher risks of death than those in the least-poor socio-economic quintiles [23]. Primary education on the prevention of malaria should be built up by the National Malaria Control Programme (NMCP) in all the countries to reduce malaria prevalence, particularly among under-five children[55]. Also, ITN use and the age of the child were found to be significantly related to fever incidence[23]. To focus on the shortcomings in local education about malaria, health personnel worker serving in malaria-endemic regions should be skilled in providing more proper counselling for changing certain deeply ingrained traditional behaviours such as settling time outdoors in the evening, inappropriate use of bed nets and occasional use of insecticides during sleep [56]. This research concludes as follows: **firstly,** regarding the analysis using GWR that the importance of different environmental and geographic parameters for malaria disease was shown at global and village levels in South Sumatra, Indonesia. It has been conclusively shown that the independent variables altitude, distance from forest, and rainfall in global OLS were significantly associated with malaria cases. However, as shown by the GWR model and in line with recent reviews, the relationship between malaria and environmental factors in South Sumatra strongly varied spatially in different regions (**Study #1**). **Secondly,** it has been noted that the presence of only certain livestock is the major risk factor for contracting malaria in rural Indonesia. Raising medium-sized animals in the house was a significant predictor of malaria prevalence (OR = 2.980; 95% CI 2.348–3.782, $P < 0.001$) when compared to keeping such animals outside of the house (OR = 1.713; 95% CI 1.515–1.937, $P < 0.001$). After adjusting for gender, age, access to the community health facility, sewage canal condition, use of mosquito nets and insecticide-treated bed nets, the participants who raised medium-sized animals inside their homes were 2.8 times more likely to contract malaria than respondents who did not. (**Study #2**). **Thirdly,** this study indicates that there is a relationship between socio-demographic factors and their influence on malaria prevalence. This study reported that the different relationships between malaria and those variables, the socio-demographic factors can affect malaria included characteristics of participants. The analysis of baseline socio-demographic data revealed the following independent risk variables related to malaria prevalence: gender, age, occupation, knowledge of the availability of healthcare services, measures taken to protect from mosquito bites, and housing condition of study participants. Multivariable analysis showed that participants who were unaware of the availability of health facilities were 4.2 times more likely to have malaria than those who were aware of the health facilities. Factors that can be managed and would favour malaria elimination include a range of prevention behaviours at the individual level and using the networks at the community level of primary healthcare centres (**Study #3**). In addition, this research recommends a multi-disciplinary approach to be able to understand transmission. The four components, i.e. human, vector, parasite, and environment, all play an essential role in the system. Therefore, the vector component of the system, the parasite component of the system, those that address environmental and the last two each address the human element. The findings reported here suggest that attention needs to be given to vulnerable populations. Also, improving the accessibility and utilisation of health services to protect the community from malaria effectively. Improving proper environmental sanitation, promoting prevent techniques from mosquito bites, and improving housing conditions. Ensuring appropriate systems, services, and support for reducing malaria prevalence should be a priority for vulnerable groups. Besides, this study recommends having interventions for all components systems that are being scaled up in malaria-endemic areas. The strategies are not enough to focus on in the parasite side, that is treatment, and they address the vector component. So, one of the reasons is that those interventions have prominent implementation protocols that have been designed. The findings of this study have some significant implications for future practice. Taken together, these findings support strong recommendations to campaign for the reduction and elimination of malaria in an endemic area. Finally, providing resources to implement recommendations is essential.

Overview of the manuscripts and publications accepted for release

Malaria is a public health hassle inside the international included in Indonesia. The causes of malaria prevalence are quite complex. Understanding the link among the environmental risk factors, the presence of livestock, and socio-demographic factors will help the decision maker to create a strategy for elimination and eradication of the disease in Indonesia and beyond. Factors which potentially influence malaria prevalence, and which were investigated in the present studies included not only the presence of livestock in a rural area that may affect vector abundance, density, or activity but also physical environmental factors, socio-demographic and behavioural factors. The research also described the direct cause of malaria: plasmodium parasites and vector specificity in Indonesia. The research described spatial epidemiology, climate and the physical environment, livestock issues, and socio-demographics as one determinant of malaria. The general purpose of this doctoral dissertation was to analyse the determinants of malaria in malaria-endemic areas of Indonesia. Relevant analytical methods included univariate, bivariate, and multivariable logistic regression analysis (including Geographically Weighted Regression (GWR)) to explore the relationships between malaria incidence and other epidemiological, local weather, geographic, and socio-demographic data. The overview of the publications accepted for release is below.

Publication #1 summarises the main findings of this PhD dissertation that malaria prevalence was related to different local environments, which varied geographically. This chapter analysed temporal and spatial variations of malaria prevalence and described territories and periods with a higher risk of malaria on a local geographic scale within the endemic malaria country, Indonesia. The research identified local environmental risk factors by comparing GWR and OLS analysis to understand the influence of the local environment on malaria cases. This study hypothesised that the global OLS and local GWR modelling could be performed to analyse the environmental risk factors for malaria case in South Sumatra province, Indonesia, that varied geographically at the regional level. This result of this research expected that would be useful for malaria elimination in a defined geographic area. **Publications #2 - #3**, showed that the presence of livestock and socio-demographic determinants affect malaria prevalence based on the analysis of secondary data from Indonesian regular reporting on malaria and large-scale survey Riskesdas. **Publication #2** used data from the large-scale survey Riskesdas 2007 and hypothesised that there was a relationship between malaria and livestock presence in rural endemic areas in Indonesia. This part of this paper showed that the presence of livestock was associated with malaria prevalence in eastern Indonesia. Similarly, another study revealed associations between malaria risk and environmental, socio-demographic, and behavioural variables in western Kenya of East Africa [24]. **Publication #2** assessed the significance of the presence of livestock for malaria prevalence in rural areas that had a higher proportion of malaria disease than the national average in Indonesia. **Publication # 3** hypothesised that malaria prevalence (dependent variable) in endemic areas in Indonesia was influenced by the socio-demographic characteristics of the population (independent variable). The research explored socio-demographic variables related to malaria prevalence, characteristics of participants, including gender, age, education, and employment and behaviour (e.g., use of bednets). The large-scale cross-sectional survey of the national basic health research (Riskesdas 2013) provided the socio-demographic data for this study. The design of the overall Riskesdas investigation was mainly to describe the health problems of all the people of Indonesia. It focused on many Indonesian health problems, including malaria and its potential drivers and data specific for this dissertation were derived from this. **Publication #3** analysed the socio-demographic factors noted above and behavioural factors, including accessibility and utilisation of health services and environmental health factors related to malaria prevalence. The socio-demography epidemiological models resulting from the present study are expected to produce comprehensive information both for spatial and non-spatial issues and to provide information for decision-makers to develop effective strategies to reduce and eradicate malaria in Indonesia. The doctoral dissertation may also strengthen national capacities for epidemic preparedness and response in support to the national implementation of the malaria prevention and elimination program in malaria-endemic areas. The success of roadmaps of national malaria elimination programs depends on using a sophisticated One Health approach and local interventions, namely interconnecting biological, social, physical, ecological, vector, local environment topography and weather, and technological processes. The government, academic institutions and some related agencies and the multidisciplinary professional team should support these efforts. At the same time, community awareness must be established to support the country's malaria elimination goals through knowledge sharing, capacity building, operational research, and advocacy.

The manuscripts/publications

This doctoral dissertation is based on the following publications as listed in the following:

Hasyim H, Nursafingi A, Haque U, Montag D, Groneberg DA, Dhimal M, et al.: **Spatial modelling of malaria cases associated with environmental factors in South Sumatra, Indonesia.** *Malar J* 2018, **17:**87., that available in https://malariajournal.biomedcentral.com/articles/10.1186/s12936-018-2230-8

Hasyim H, Dhimal M, Bauer J, Montag D, Groneberg DA, Kuch U, et al.: **Does livestock protect from malaria or facilitate malaria prevalence? A cross-sectional study in endemic rural areas of Indonesia.** *Malar J* 2018, **17:**302., that available in https://malariajournal.biomedcentral.com/articles/10.1186/s12936-018-2447-6

Hasyim H, Dale P, Groneberg DA, Kuch U, Müller R. **Social determinants of malaria in an endemic area of Indonesia**. *Malar J.* 2019;18(1):134. that available in https://malariajournal.biomedcentral.com/articles/10.1186/s12936-019-2760-8

Parts of the doctoral dissertation were also presented at prestigious scientific meetings. An oral presentation was given in the workshop " One Past Health” at Max Planck Institut für Evolutionsbiologie, Plön, Germany from 15-17th February 2017.

Also, a poster was presented at the European Conference on Biodiversity and Health in the Face of Climate Change in Bonn, Germany from 27-29 June 2017.

Presentation of the personal contribution regarding manuscripts/publications

My contribution to the publications in the following:

In the first publication, I was responsible for managing this research, design, and data collection, including malaria case data collected from the Provincial Health Department, Ministry of Health, Indonesia. Further, topography map and climate data (rainfall maps). Primary spatial data is obtained from Indonesia's topographic map known as the Indonesian Topographic Map (RBI), and rainfall maps (annual average) are collected by entering the average annual rainfall data from the BMKG Class I Climatology Station in Palembang, South Sumatra, Indonesia. I analysed data using GWR 4.0 version 4.0.90 and Arc GIS 10.3 used for data processing, analysis, and visualisation. I was responsible for data acquisition, pre-processing, and processing supported by a co-author. I also contribute to the interpretation and display of results and compile papers under supervising my supervisor.

In the second publication, I obtained the Riskesdas sub-dataset as of a large dataset based on a cross-sectional survey of the Indonesia Basic Health Research (Indonesia acronym: Riskesdas), which is organised by National Institute for Health Research and Development with a sample framework conducted by the Central Bureau of Statistics. Besides, the study was conceived and designed by me together with my supervisor. Further, I analysed and interpreted the dataset. Finally, my supervisor and I drafted the manuscript with subsequent contributions and revisions.

In the third publication, I designed and performed the collection and analysis of the Riskesdas sub-dataset and managed the study. I contributed to the interpretation and visualisation of the results using Stata software supervised by my advisor. I also drafted the paper under the supervision and guidance of my supervisor independently.

All authors read and approved all the final manuscripts before publication.

Publication #1 Spatial modelling of malaria cases associated with environmental factors in South Sumatra, Indonesia

Hasyim H, Nursafingi A, Haque U, Montag D, Groneberg DA, Dhimal M, Müller R: Spatial modelling of malaria cases associated with environmental factors in South Sumatra, Indonesia. Malaria Journal 2018, **17:**87.

https://doi.org/10.1186/s12936-018-2230-8

Malaria Journal

RESEARCH

Open Access

Spatial modelling of malaria cases associated with environmental factors in South Sumatra, Indonesia

Hamzah Hasyim[1,2*], Afi Nursafingi[3], Ubydul Haque[4], Doreen Montag[5], David A. Groneberg[1], Meghnath Dhimal[1,6], Ulrich Kuch[1] and Ruth Müller[1]

Abstract

Background: Malaria, a parasitic infection, is a life-threatening disease in South Sumatra Province, Indonesia. This study aimed to investigate the spatial association between malaria occurrence and environmental risk factors.

Methods: The number of confirmed malaria cases was analysed for the year 2013 from the routine reporting of the Provincial Health Office of South Sumatra. The cases were spread over 436 out of 1613 villages. Six potential ecological predictors of malaria cases were analysed in the different regions using ordinary least square (OLS) and geographically weighted regression (GWR). The global pattern and spatial variability of associations between malaria cases and the selected potential ecological predictors was explored.

Results: The importance of different environmental and geographic parameters for malaria was shown at global and village-level in South Sumatra, Indonesia. The independent variables altitude, distance from forest, and rainfall in global OLS were significantly associated with malaria cases. However, as shown by GWR model and in line with recent reviews, the relationship between malaria and environmental factors in South Sumatra strongly varied spatially in different regions.

Conclusions: A more in-depth understanding of local ecological factors influencing malaria disease as shown in present study may not only be useful for developing sustainable regional malaria control programmes, but can also benefit malaria elimination efforts at village level.

Keywords: Geographically weighted regression (GWR), Ordinary least squares (OLS), Akaike information criterion (AIC), Physical environment, Local climate, Sumatra, Rainfall, Elevation, Distance to water

Background

Malaria is a significant public health concern worldwide, including Indonesia [1]. The Indonesian government has set a national goal to be malaria-free by 2030. Currently, 24 out of 576 districts in Indonesia classified as being malaria endemic, and an estimated 45% of Indonesia's total population are living at risk of contracting malaria [2]. In South Sumatra Province, the malaria incidence was 0.46 per 1000 people in 2013. In this province, the proportion of children under 5 years of age who applied mosquito nets was 32.7%, and the percentage of children under five who treated for fever with antimalarial medication was 89.8% in 2013 [2]. Malaria elimination has been a priority in the millennium development goals (MDGs) [3], and since then has continued to be central to the sustainable development goals (SDGs), supporting Indonesia's malaria elimination commitments [4]. It is now essential to generate the knowledge that is necessary to develop lasting policies for the national malaria elimination programme.

Several meteorological and environmental variables are risk factors for malaria [5]. Since specific meteorological,

*Correspondence: hamzah.hasyim@stud.uni-frankfurt.de; hamzah@fkm.unsri.ac.id
[1] Institute for Occupational Medicine, Social Medicine and Environmental Medicine, Faculty of Medicine, Goethe University, Frankfurt am Main, Germany
Full list of author information is available at the end of the article

environmental factors are at interplay and different factors can affect malaria transmission within a given province [3, 6, 7], it is important to differentiate between factors that influence the vector, the parasite and the host-vector relationship [8]. Atieli et al. have demonstrated that the topographic variables elevation, slope, and aspect are influencing the development of *Anopheles* mosquitoes [9]. In north-eastern Venezuela, there is a significant association of malaria transmission with local spatial variations like population density, lowland location, and proximity to aquatic environments [10]. Elsewhere (e.g., Ethiopia and Senegal) spatial relationships between climatic variability like rainfall and malaria occurrence have been demonstrated [11]. Rainfall indirectly benefits *Anopheles* mosquitoes by increasing relative humidity which prolongs adult longevity [12], and the number of breeding places which in turn favours population growth [13]. Temperature and the extent of water availability for larval breeding are crucial factors in the vector life-cycle, affecting transmission [3]. Vectors and parasites are both highly sensitive to any temperature changes, for example, the parasite proliferation depends on temperatures [14]. Temperatures above 28 °C have been shown to reduce malaria incidence in Africa [15]. In Indonesia, the optimum temperature for malaria mosquitoes ranges between 25 and 27 °C [3]. For the vector-host relationship, factors such as the distance of people's houses from a river, lakes, pond, distance to the regional urban centre [16–18] distance to forest [19, 20] were shown to be significant predictors.

Spatial nonstationary is a condition in which a simple "global" model cannot define the relationship amongst several sets of variables [21]. Thus, global OLS and local GWR modelling was performed to analyse the environmental risk factors for malaria in South Sumatra that vary geographically at the regional level. The locally different ecological factors studied to potentially predict the response variable 'confirmed malaria case' (Y) are altitude (X1), aspect (X2), distance from the river (X3), distance from lakes to pond (X4), distance from the forest (X5), and rainfall (X6).

Methods

Study area

The study area is located between 1°46′ and 4°55′ of southern latitude and between 102°4′ and 104°41′ of eastern longitude and has a total surface area of 46,377.40 km^2 (Fig. 1). It covers eight endemic malaria districts of South Sumatra, Indonesia, namely Lahat, Muara Enim, Musi Banyuasin, Musi Rawas, North Musi Rawas, Ogan Komering Ulu, South Ogan Komering Ulu, and Lubuk Linggau. The topography of the area varies from lowland to mountainous landscapes. The elevation in the study area varies between 0 and 3150 metres above sea level. The climate is tropical and wet [22]. In 2013 in South Sumatra, the lowest rainfall was 31 mm (August) in Lahat district, and the highest rainfall was 613 mm (March) in Palembang City. Monthly average temperatures ranged from 26.6 to 28.3 °C and relative humidity from 81 to 88% in 2013 [23].

Indonesia's South Sumatra Province is home to 7828,700 inhabitants. In 2013, the gross regional domestic product (GRDP) with oil and gas was IDR 231.68 trillion (17.32 billion USD) [22], based on IDR to USD exchange rates at the time of writing. South Sumatra is an ethnically highly diverse province and home to different local languages and diverse cultural and socioeconomic practices [2]. Local people engage in coffee, rubber and palm oil plantation activities or work in the industrial mining area, which shapes not only people's lives but also the environment [24]. Indonesia contributes significantly to deforestation in Southeast Asia. Recent developments of deforestation have led to unsustainable practices which have resulted in a high frequency of deforestation in some regions and are an important factor influencing malaria incidence [25]. Deforestation has been shown to be connected with malaria incidence in the county (Município) of Mâncio Lima, Acre State, Brazil. There, a cross-sectional study shows 48% increase in malaria incidence are associated with cumulative deforestation within respective health districts in 2006 [26].

Study population and data collection

36,372 patients seeked treatment due to suspected malaria fever in 140 primary health centres (PHC) in the study region South Sumatra during January to December 2013. Among them, 3578 were laboratory positive for malaria. The cases spread over 436 out of 1613 villages that were used for unit analysis. The detailed number of malaria cases in different provinces are presented in Fig. 2. The spatial distribution of participants who had confirmed cases of malaria is shown in Fig. 3.

The patients are categorised into "clinical diagnosis", "suspected malaria" and "confirmed malaria cases". Categories "clinical diagnosis" or "suspected malaria" are based on the patient's symptoms and physical findings at examination. A "confirmed malaria case" is a case of malaria diagnosed microscopically (examination of blood specimen/preparation) or rapid diagnosis test (RDT) with positive results for *Plasmodium*. Either RDT or microscopic assessment or both were used to confirm the diagnosis of malaria. The malaria diagnostic data were obtained from the regular health information reporting system of the Provincial Health Office of South Sumatra. The data had been collected during 12 months (January to December 2013) at the village level from patients

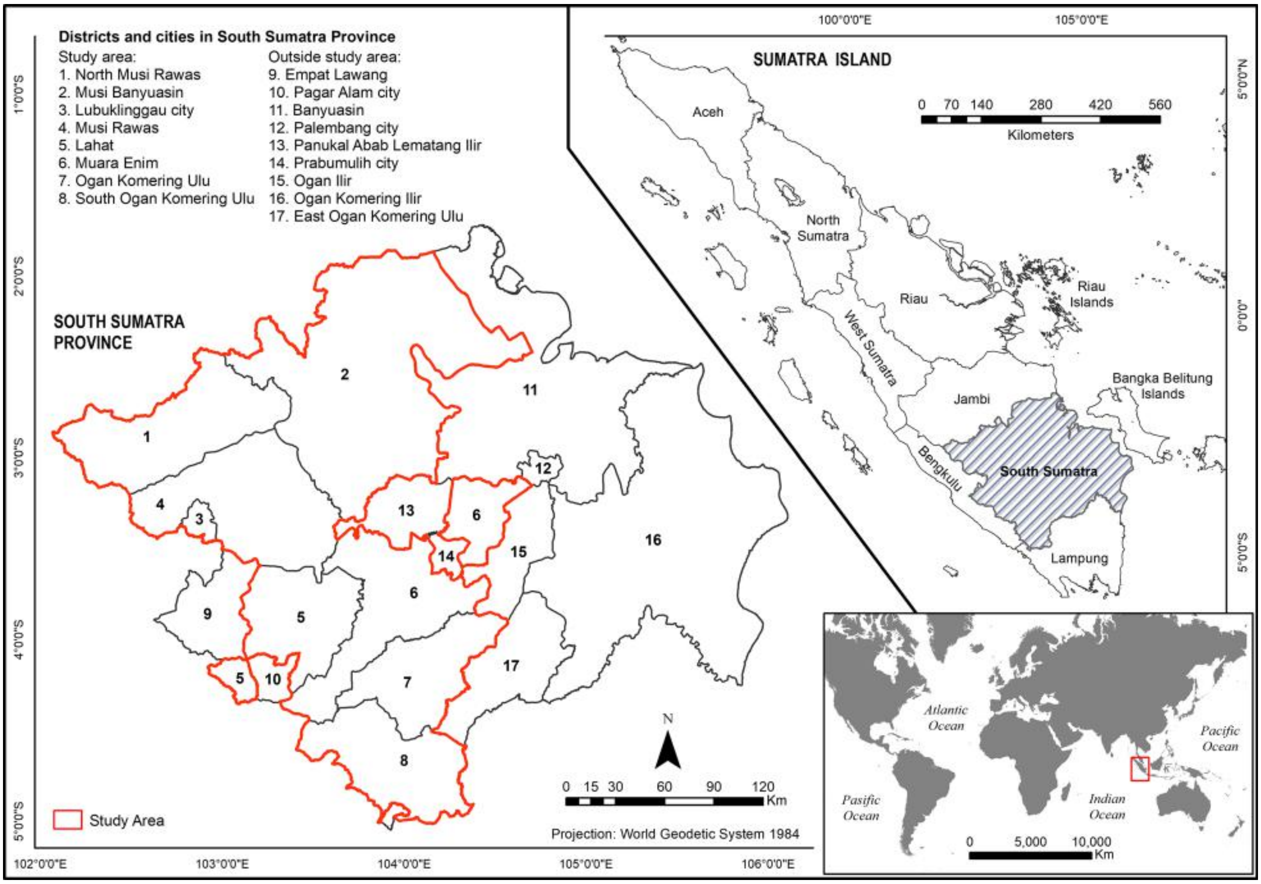

Fig. 1 Map of the study area covering one city and seven districts of South Sumatra Province, Indonesia

seeking treatment in PHC, locally called Pusat Kesehatan Masyarakat ("puskesmas"), and that were reported monthly to the Provincial Health Office via the malaria programmes in the District Health Offices.

Geographic information

The study area map (Fig. 1) uses the World Geodetic System (WGS84) as its reference coordinate system. As shown in Fig. 4, three stages of working with geographic information were distinguished: data acquisition and processing, data analysis and data presentation [27]. GWR 4.0 version 4.0.90 and Arc GIS 10.3 were used for data processing, analysis, and visualization. Malaria case data were collected from the Provincial Health Department, Ministry of Health (see previous paragraph) as well as topographic (toponymy map, hypsographic map, hydrographic maps, land cover map) and climate data (rainfall map). The primary spatial data were obtained from a topographical map of Indonesia (cartographic material) which has a scale of 1:50,000 and consists of several layers of plots grouped. The malaria input data is aggregated village level data with the village centroid used as the spatial unit. This map consisted of a collection of geographic data presented as thematic layers for land cover, hydrographic data and a sheet of hypsography. Indonesian topographic map known as Peta Rupabumi Indonesia (RBI) was updated in 2014. In 2013, topographic data visualisation has been changed into geodatabase cartography to reduce the steps of creating cartography visualisation in topographic mapping activity [28]. These maps were obtained from the Geospatial Information Agency (BIG) of Indonesia. Authorization for the use of the topographical map of Indonesia was provided by the Indonesian Geospatial Information Agency. However, restrictions were put to use the availability of these data and therefore are not publicly available. Data were collected by creating a research protocol which is used under license for the current study. The data that backs the findings of the research are served in the main paper.

The forest cover maps were extracted from the land cover map in 2013 on the scale of 1:250.000. The map was sourced from Ministry of Environment and Forestry, Indonesia. The precipitation map (annual average) was obtained by inserting the data of average yearly rainfall

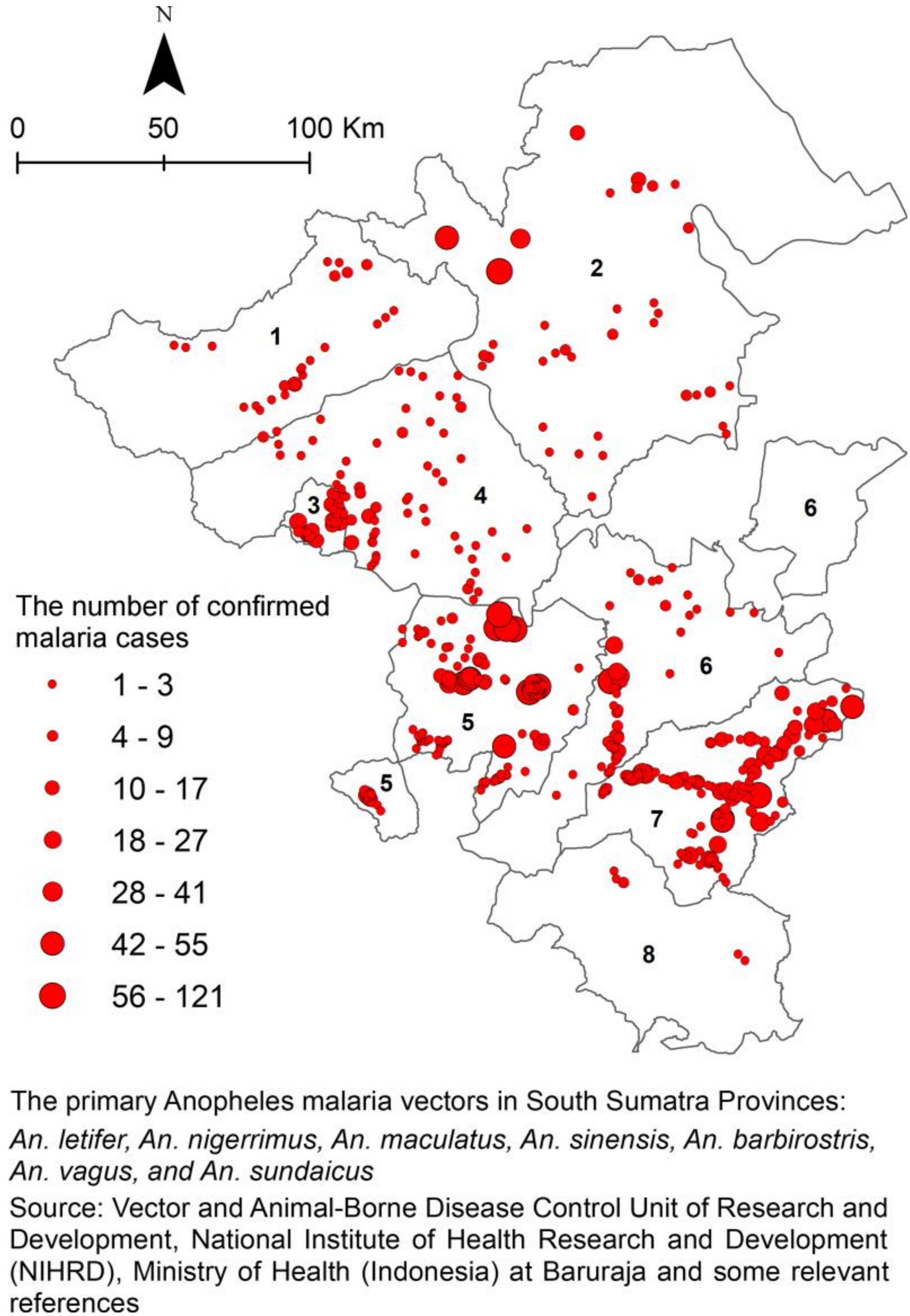

Fig. 2 Malaria cases and their geographical locations in the study area

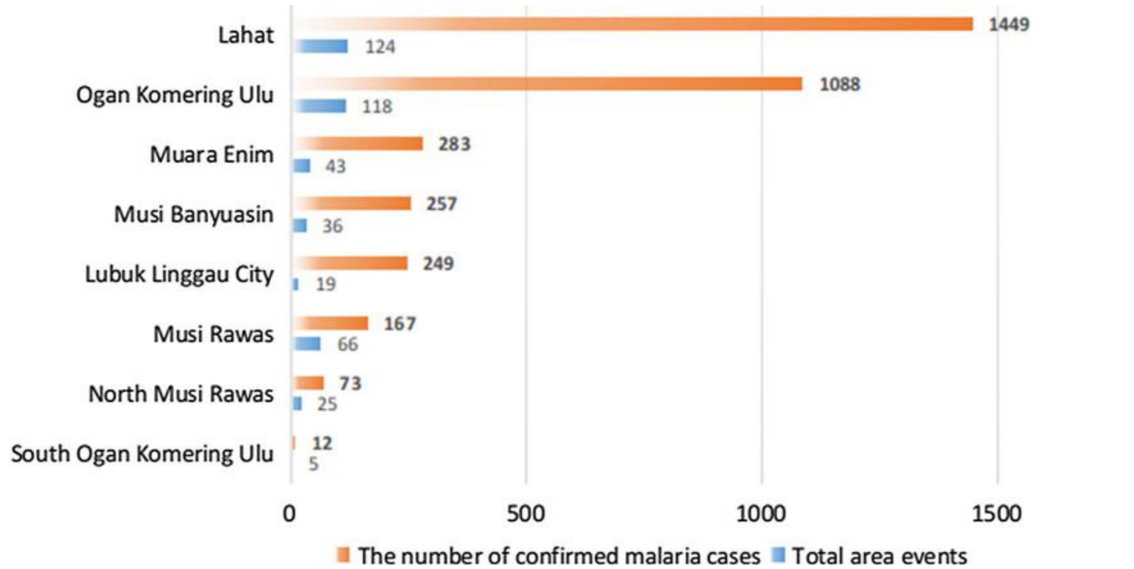

Fig. 3 Malaria cases at village level

from BMKG Climatological Station Class I in Palembang, South Sumatra, Indonesia. The distance between weather observation stations was 50–100 km in flat topography and 10 km in hilly terrain.

Data pre-processing

The malaria distribution map (Fig. 2) was created and six selected explanatory variables plotted (Fig. 5). The altitude map was obtained by interpolation and contouring of the map into a digital elevation model (DEM). Subsequently, the DEM data was converted into a map containing the direction of the slope (aspect). The parameter distance from the river, and distance from lake and pond processed from river, lakes, and ponds maps which were derived from the topographic map whereas distance from the forest processed from forest cover map. These variables were analysed using Euclidean distances. Rainfall parameter was calculated based on annual average rainfall over 5 years, and it was interpolated from several weather observation stations in study area. The rainfall map (isohyets map) was obtained from the scanned maps which are the result of interpolation and classified into several classes. The map needed to be rectified and digitised to get a digital rainfall map.

Data processing and modelling

The response variable "malaria case" and explanatory variables "altitude/aspect", "distance from river", "distance from lake and pond", "distance from forest" and "rainfall" were tested for multicollinearity. Therefore, the values of all explanatory variables were extracted for each case location. An index based on predictive modelling variance, the variance inflation factor (VIF) was used [29]. Multicollinearity could occur when one independent variable was a linear function of another independent variable and previously observed in GWR modelling [30]. The pattern of connection between confirmed malaria cases and environmental factors was expressed by the OLS method. Here, OLS model is called global regression model because the existence of local variation had not taken into account in regression so that the estimate of the regression remained constant. Thus, the regression parameters had the same value for each point within the study area. If spatial heterogeneity occurred in regression parameters, then the information that could not be processed by the global regression model was seen as an error. In such cases, the global regression model was less able to explain the actual data phenomenon [31]. A global regression coefficient value close to zero indicated that the explanatory variables had a small effect on the response variable.

As alternative, the GWR model was used to investigate the relationships between response and explanatory variables since the study area was characterized by spatial heterogeneity [32]. A semiparametric GWR4.09 for Windows (provided by Nakaya et al. [32]) was carried out which is a new release of the windows application software tool for modelling spatially varying relationships among variables by calibrating GWR.

The estimated parameter of the GWR model uses the least squares given the location coordinates as a

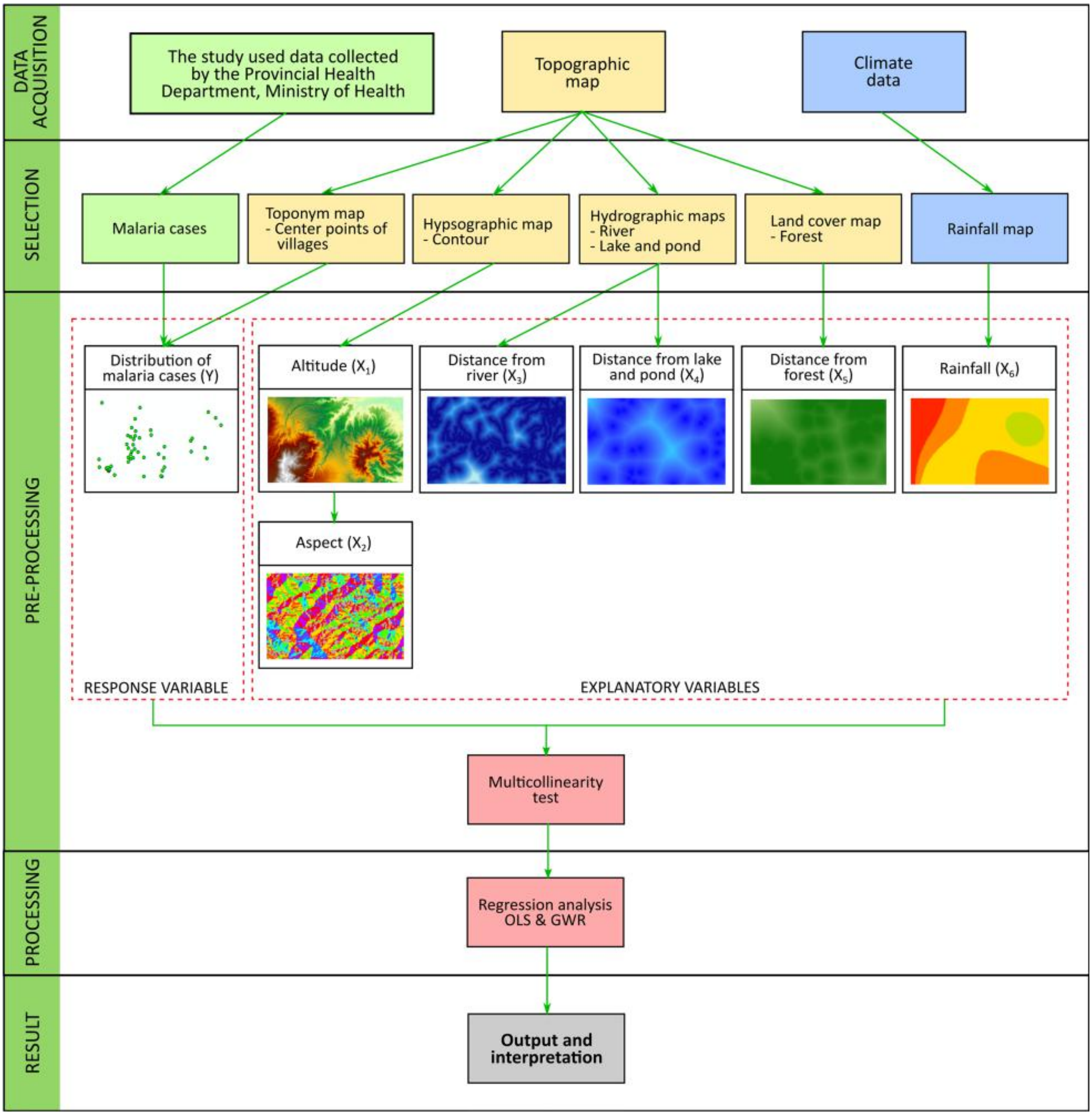

Fig. 4 Flow chart of the research strategy

weighting factor. The influence of the points in this neighbourhood varies according to the distance to the central point [33]. The optimum distance threshold (also known as the bandwidth) or the optimum number of neighbours determined in two ways: by minimising the square of the residuals cross-validation (CV) or by minimising the Akaike Information Criterion (AIC) [34]. At this stage, the type of weighing (kernel type) and optimum bandwidth selection method based were selected on AIC selection criteria. Classic AIC chooses smaller bandwidths in geographically varying coefficients are possible to be under smoothed [32]. In a GWR context, the measurement of utility is the AIC to know whether a global regression model or GWR is most useful [33].

The local GWR model as earlier described is as follows:

$$y_i = \beta_0(u_i, v_i) + \sum_k \beta_k(u_i, v_i)x_{ik} + \varepsilon_i \quad (1)$$

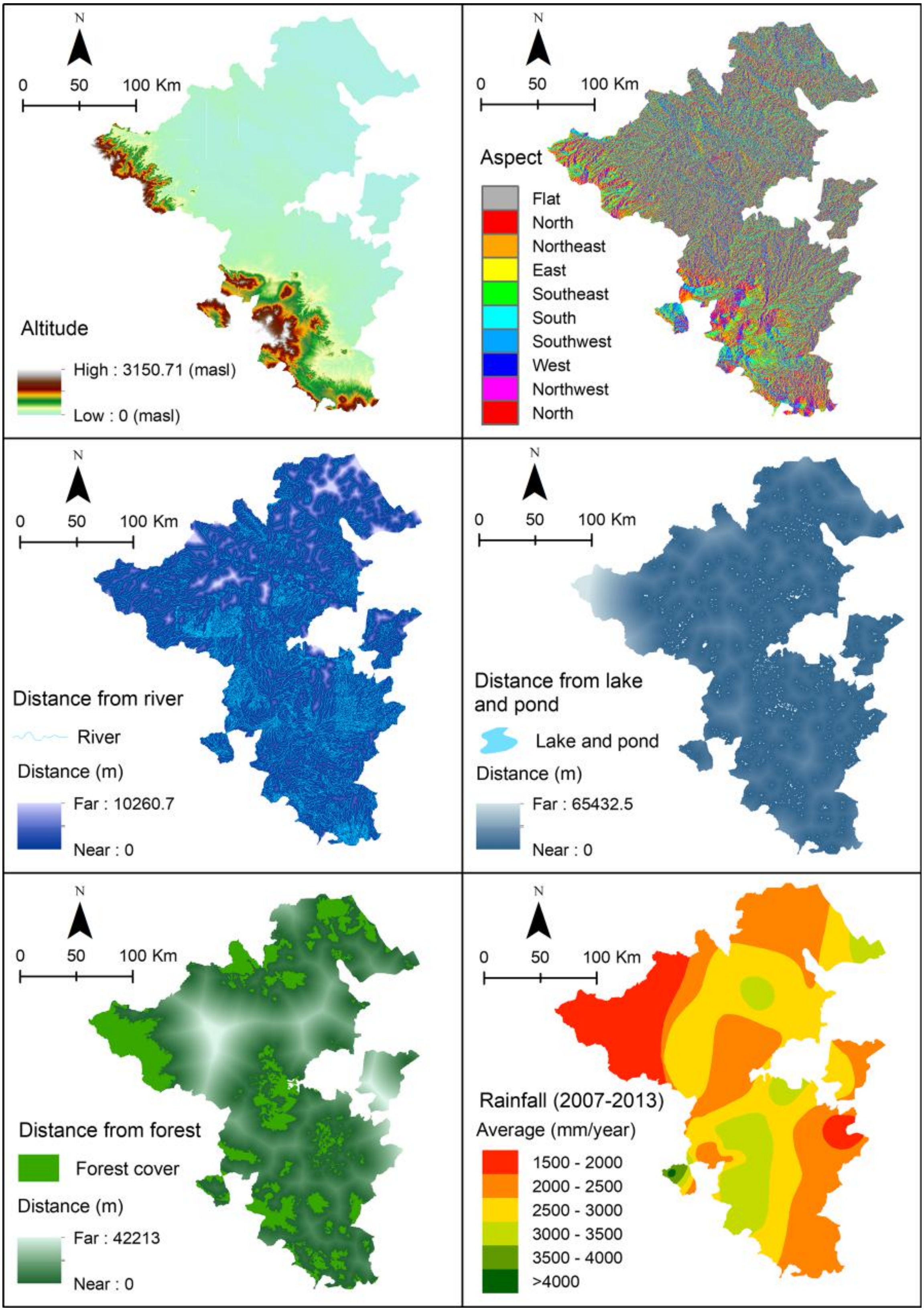

Fig. 5 Each explanatory variable mapped in the study area

Based on the model, y_i, x_{ik}, (u_i, v_i), $\beta_k(u_i, v_i)$, and ε_i were sequentially the response and explanatory variables k to location i, location coordinates to i, realization of the continuous function $\beta_k(u_i, v_i)$ at point i, and Gaussian error to location i. It is noteworthy that the kernel Fixed Gaussian function was used which highlights the optimal bandwidth found by using the Golden section search with the AIC selection criteria. Also, the Gaussian kernel supported the constant weight, and the value became less from the centre of the kernel but never touched zero. The kernel was suitable for fixed kernel because it could prevent the risk of the absence of data in the kernel. The Fixed Gaussian kernel earlier described [33] is as follows:

$$w_{ij} = \exp\left[-\left(d_{ij}/b\right)^2\right] \quad (2)$$

Also, w_{ij} was the weight value observed at the location j to approximate the calculation of the coefficients on area i, d_{ij} was the Euclidean distance between i and j, and b was the size of fixed bandwidth given by the size of metric. The Golden section automatically searched the optimal frequency range value by comparing indicators of the model with the bandwidth size. A positive R^2 indicates a positive correlation. A positive coefficient means X and Y changed in the same direction and if the environmental risk factor increased, then number of confirmed malaria cases increased. Conversely, a negative coefficient means X (explanatory variable) and Y (the response variable) changed in opposite directions. Student's t distribution that had values outside the range of − 1.97 and 1.97 formed a critical region with a 0.05 (95% CI) level of significance, whereas values outside the range of − 2.59 and 2.59 formed critical regions with a 0.01 (99% CI) level of significance. Step-wise computation performed with these data is shown in Fig. 4.

The locally weighed R^2 between the observed and fitted values has been calculated to measure how well the model replicates the local malaria incident values around each observation. A variable is correctly clarified for each location by the model if $R^2 = 1$ with values ranging from 0 to 1.

To compare the performance between global OLS and local GWR, GWR4 software was also used. We performed an ANOVA testing the null hypothesis that the GWR model represents no improvement over a global model. For local GWR, the sufficient number of degrees of freedom was a function of the bandwidth.

Results

Data pre-processing

Multicollinearity does not occur, because the VIF value is less than 10 and the tolerance value is higher than 0.1.

Environmental factors influencing confirmed malaria cases at global level: OLS model

The global OLS model reveals that altitude and distance to the forest (negative coefficients) and rainfall (positive coefficient) significantly influence the number of malaria cases. Confirmed malaria cases are more common in regions with high rainfall, lowland and areas adjacent to forest. On the other hand, environmental factors such as aspect or direction towards the slope, distance from the river, and the distance from lakes to pond do not have any significant association with malaria cases. Based on OLS model each factor has a different predictor of malaria case preferences in GWR model stage.

Environmental factors influencing confirmed malaria cases at local level: GWR model

The results of GWR using Fixed Gaussian are shown in Table 1. The best bandwidth generates 9184 neighbours and a significant spatial relationship with a specific region has been found. The GWR model provides evidence for a locally different influence of environmental factors on malaria cases as shown by varying parameter estimate value (Fig. 6). "Altitude" and "distance from lake and pond" show a positive association and "aspect" a negative association with malaria incidence in the Northern study area (Musi Banyuasin). "Rainfall" and "distance from river" show a positive association with malaria cases in the Eastern part of Musi Rawas and Lahat. The variables "aspect", distance from lake and pond" and "distance from forest" are positively associated with confirmed malaria cases in large parts of the study area. The significance thresholds of explanatory variables according to Student's *t* test in the GWR model are shown in Fig. 7. The local coefficient of determination (local R^2) for confirmed malaria cases at the local level ranges between 0.18 and 1 (Fig. 8).

Table 1 GWR result based on fixed Gaussian (distance) kernel function for geographical weighting

Bandwidth and geographic ranges	Value
Bandwidth size	9184.47
Diagnostic information	
Residual sum of squares	33,549.28
Classic AIC	3482.17
BIC/MDL	4198.30
CV	178.92
R^2	0.69
Adjusted R^2	0.41

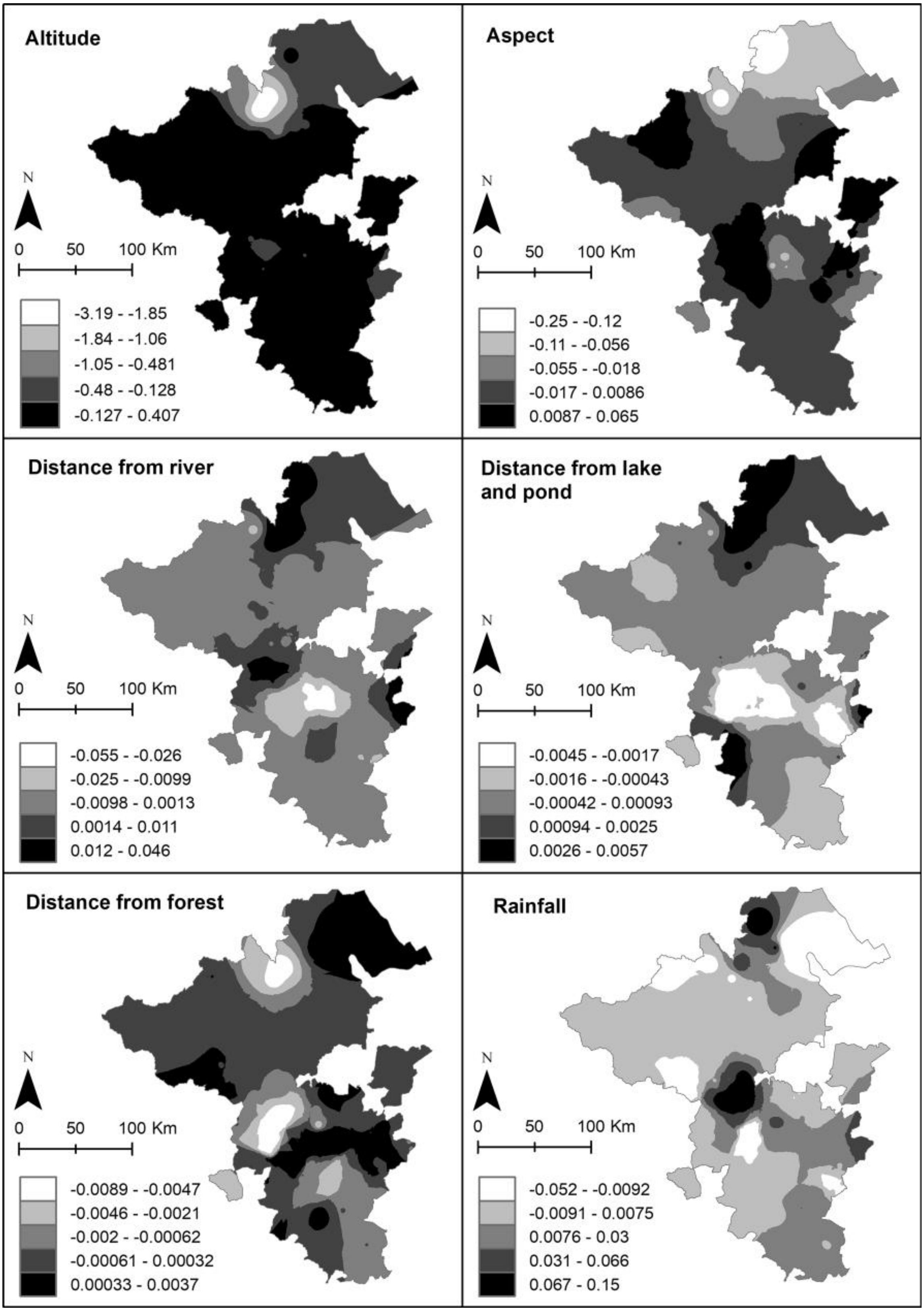

Fig. 6 Predicted value from GWR for parameter estimates of explanatory variables of malaria cases in the study area

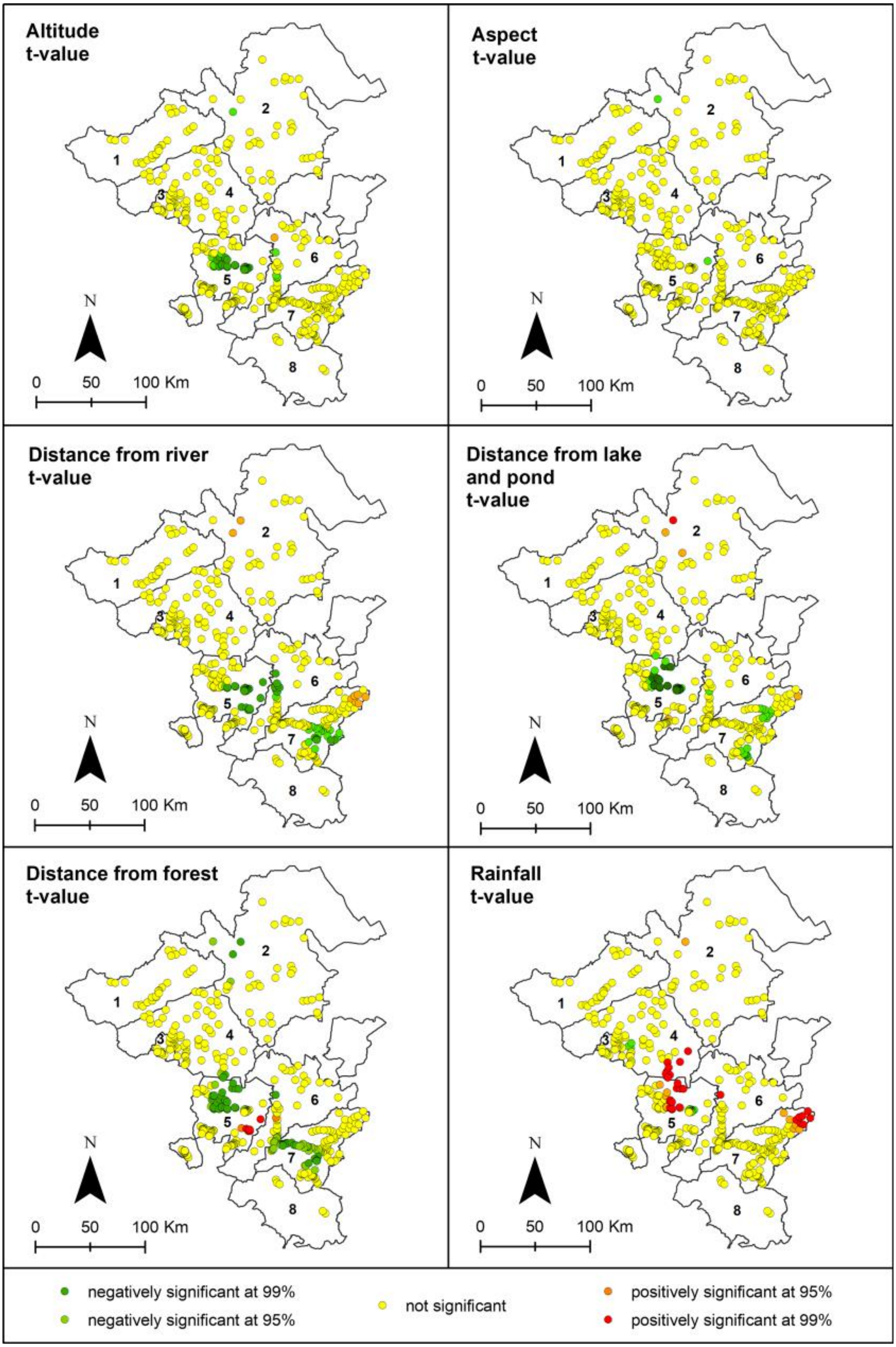

Fig. 7 Student's test significance (95 and 99% confidence interval) for each explanatory variable and village location

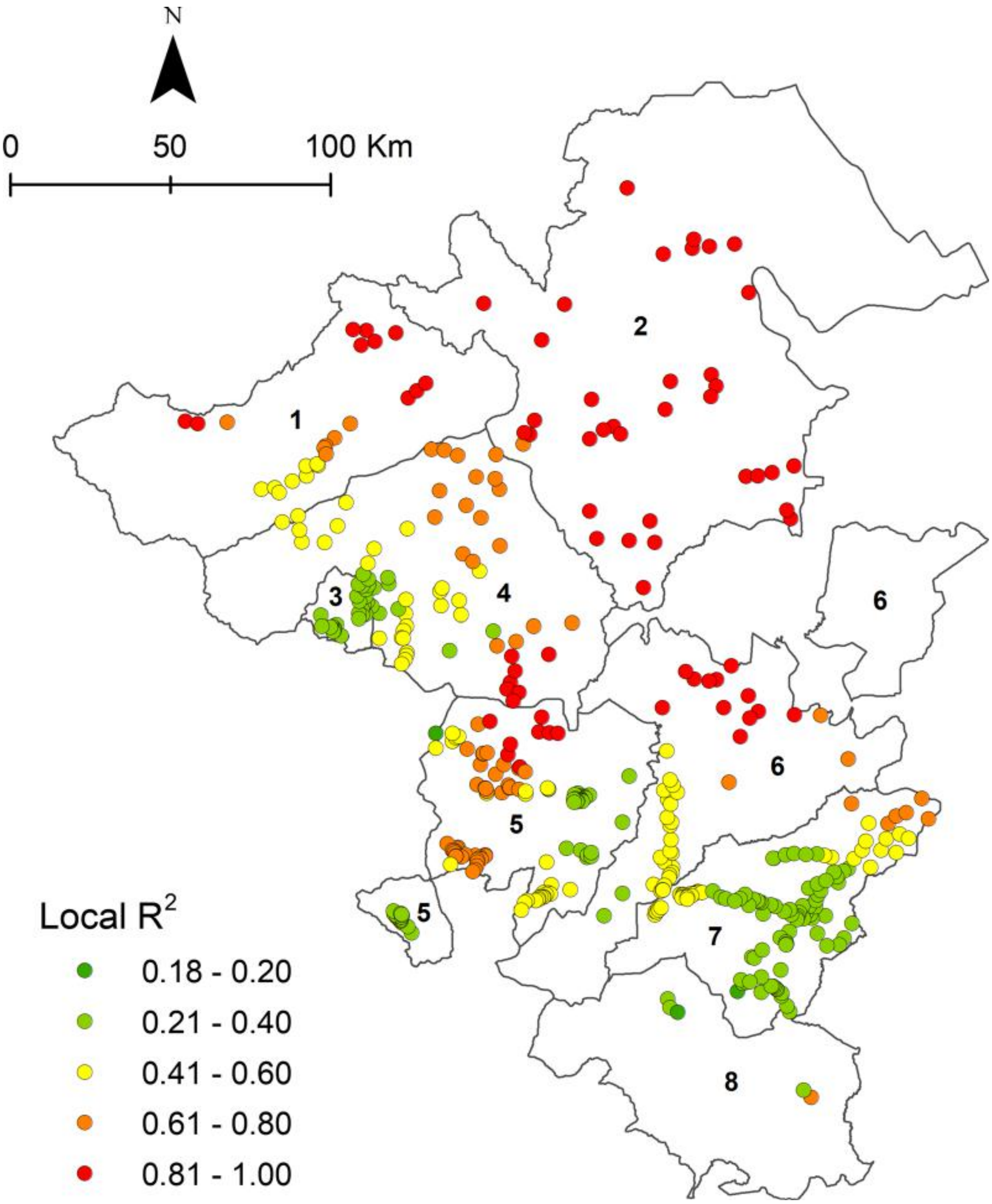

Fig. 8 Goodness-of-fit of GWR model (local coefficient of determination R^2) for malaria cases associated with environmental factors in South Sumatra, Indonesia

Comparison between the two methods OLS and GWR

Like OLS, GWR is a statistical model that provides insights into the relationship between the dependent variable confirmed malaria cases and six independent explanatory variables. GWR is selected as best model based on the residual sum of square, and classic AIC, and the R^2 as stated in Table 2.

The global regression model indicates that the variables have some influence on the study area (Table 3). The

Table 2 Comparison between global OLS and local GWR models

Value	OLS	GWR
Residual sum of square	100,625.26	33,549.28
Classic AIC	3625.82	3482.17
R^2	0.06	0.69
Adjusted R^2	0.05	0.41

global OLS model explains 6.2% variation of malaria incidences by environmental factors ($R^2 = 0.06$). This implies that 93.8% of the malaria incidence is caused by unknown environmental factors related to local variation which are not taken into account in the OLS model [33]. The local GWR explained 68.7% variation in malaria incidences (Y) by environmental factors ($R^2 = 0.69$). The DIFF criterion indicates that the spatial distribution of malaria incidence is associated with the independent variables "altitude", "distance from lakes and pond", "distance from forest", and "rainfall" with local spatial heterogeneity (Table 3). Though the testing of local coefficients for "aspect" and "distance from river" suggests no spatial variability (Table 3).

The GWR model explains the relationship between the response variable "confirmed malaria case" and six explanatory variables significantly better than the global regression model OLS ($F = 2.12$, $P < 0.05$) (Table 4). The best model weights are automatically determined for each location and are mapped in Fig. 7.

Discussion

Climate data are frequently used to predict for the spatial, seasonal and interannual variation for malaria transmission, for example the dynamic malaria model forecasting malaria prevalence with seasonal climate published by Hoshen and Morse [35]. The global OLS model revealed here that altitude, distance to forest, and rainfall significantly influence malaria incidence in South Sumatra. Similarly, land use, humidity, altitude and rainfall have been identified by GWR to determine the regional vulnerability to malaria in Purworejo, Indonesia [36]. However, the GWR model considering spatial heterogeneity explains better the association of malaria case with environmental factors in South Sumatra. Likewise in Venezuela, GWR analysis revealed that ecological interactions that act on different scales play a role in malaria transmission and that modelling enhances the understanding of relevant spatiotemporal variability [10]. The environmental factors shown to be significantly associated with malaria cases vary strongly at the village level. This finding is consistent with those obtained in studies in Ethiopia (Addis Ababa), the Amazon region of Brazil (Rondôia), and Cambodia [11, 37, 38]. A validated OLS can lead to a global policy and a validated relationship with GWR is more appropriate to drive to the local system. A geostatistical model based on analysis of residuals and using climatic, population and topographic variables has also been shown to be an important tool for local malaria prediction in Mali [39]. In the highlands of western Kenya, topographic parameters could be used to identify the risk of malaria and thereby helped to improve malaria monitoring or targeted malaria control activities [9].

The relationship of altitude and malaria cases has been shown in present study as well and may relate to the biology of malaria vectors. Globally, *Anopheline* species diversity and density decline from the lowlands to highlands [40]. Accordingly, poor villagers living in forested lowland areas in Papua, Indonesia, were found to be at higher risk of malaria infection than those in the highlands [41]. In contrast, a positive correlation between altitude and the abundance of *Anopheles* mosquitoes has observed in the highlands of Ethiopia, Colombia and Ecuador, particularly in warmer years [42–44]. This observation may be related to the direction towards the slopes as the distribution and density of mosquito populations may be affected by wind direction [45]. In an Ethiopian study, minimum temperatures were significantly associated with malaria cases in cold areas, while precipitation was associated with transmission in hot areas [46]. In accordance to many studies, malaria case was significantly associated with rainfall in villages of South Sumatra. Rainfall showed correlation with the incidence of clinical malaria cases in Tubu village, Botswana [47]. Variations in monthly rainfall in rural Tanzania were

Table 3 The result of global regression model and geographical variability test of local coefficients for six environmental factors

Variables	Global regression model output				Geographical variability test			
	Estimate	SE	T value	P value	F	DOF for F test		DIFF of criterion
Intercept	7.98	4.63	1.72	0.04	33.20	10.48	261.38	− 347.99
"Altitude (X1)"	− 0.02	0.00	− 4.03	0.00	0.24	12.02	261.38	19.19
"Aspect (X2)"	− 0.01	0.01	− 1.60	0.05	0.55	22.68	261.38	24.91
"Distance from the river (X3)"	0.00	0.00	− 0.84	0.24	1.84	18.15	261.38	− 16.03
"Distance from lakes and pond (X4)"	0.00	0.00	0.39	0.71	0.90	15.04	261.38	7.99
"Distance from forest (X5)"	0.00	0.00	− 3.69	0.00	2.99	14.61	261.38	− 38.12
"Rainfall (X6)"	0.00	0.00	2.38	0.02	13.07	10.17	261.38	− 158.91

largely associated with malaria [48]. Rainfall creates oviposition sites for female mosquitoes, whereas humidity is a key parameter for adult mosquito daily survival [49]. *Anopheline* mosquitoes require stagnant water to complete their larval and pupal development. Thus, rainfall affects the transmission of malaria by providing water to create aquatic habitats. The number of malaria cases was significantly positively connected with higher winter rainfall, but also with a higher average maximum temperature and significantly negatively associated with increasing distance from water bodies in South Africa [50]. Southern Africa Development Community estimates the positive correlation between increasing rainfall and the number of cases in Botswana during 2013 and 2014 [51].

Next to climatic and environmental factors, distance of houses to a forest are interrelated through anthropogenic activities influencing the local and regional climate [52, 53]. These observations can be confirmed for the relationship of malaria case with distance to lake, pond and forest for South Sumatra. A cross-sectional view in Brazil revealed for example that malaria incidence across health districts is positively correlated with the percentage of aggregated deforestation [26]. Indonesia contributes indeed significantly to deforestation in Southeast Asia. *Anopheles* was reported from eight sources at 47 independent sites. The first record of *Anopheles parangensis* from Sumatra was reported by O'Connor and Sopa (1981), but with no details on location [54]. *Anopheles (Cellia) leucosphyrus* is considered to be of epidemiological importance for malaria transmission in forested areas of Sumatra [54]. In current research, the main *Anopheles* vector diversity in each study area was however not investigated.

Present study has identified Lahat as the South Sumatran district in which environmental factors were of greatest relevance for malaria incidence. Lahat District has both lowland and mountain regions and is home to diverse ethnic groups, such as the Gumai who live along the rivers of the highland areas [55].

One of the key activities for malaria elimination should be the establishment of systems and tools to reduce disease burden where local transmission is high. By comparing the local GWR model with the global OLS model (Table 4), it became apparent that GWR yielded new information about the spatial variation of malaria incidence and thereby better explains local phenomena. The variability of malaria cases in our study was due to environmental and geographical local differences [8]. GWR should be used as a diagnostic model discovering spatially varying relationships between confirmed malaria cases and environmental factors. The use of GWR allows the uncovering of significant environmental variation for malaria incidence, which has previously been unobservable in a specific location [56].

Table 4 ANOVA testing the null hypothesis that the GWR model represents no improvement over a global model

Source	SS	DF	MS	F Count	F Table
Global residuals	100,625.26	429.00			
GWR improvement	67,075.98	197.74	339.22		
GWR residuals	33,549.28	231.26	145.07	2.34	2.12

Limitations of research

Due to practical constraints, this study was unable to encompass the entirety of environmental factors, particularly climate parameters, temperature and humidity, for which only limited data were available and hence not-representative data could not be included. Also the factor land use was eliminated. Malaria location information was plotted using a village centre approach which ignored all other locations where actual infections may have occurred (e.g., forests, plantations). The number of positive malaria per village, did not include the specific coordinates of each positive malaria case and thus, each positive case was placed in the centre of the settlement. Therefore, if land use variables would be involved, there will very likely be a strong bias. However, these eliminated or uninvestigated variables may be correlated with existing variables, for example, the temperature connected with altitude and with aspect or direction of the slope. In the same way, land use may be associated with the distance from the river and the distance from lakes and ponds. Thus, although these parameters (temperature, humidity, land use) were excluded from analysis, these environmental factors were represented by our chosen set of variables. In the future, additional explanatory variables should be addressed to provide a comprehensive review of malaria in the study area. It should comprise, for example, the behavior of mosquito vectors and that of community members, the access to and the delivery of health services, and other eco-bio-social factors that affect the incidence of malaria. Despite these limitations, our study sheds light on relevant information, not only in regional but also local realities regarding environmental variation which might interplay with vector-host relationships and sociocultural practice and provide a suitable environment for malaria mosquitoes.

Conclusion

In the present study, the importance of different environmental and geographic parameters for malaria disease was shown at global and village-level in South Sumatra, Indonesia. The independent variables altitude, distance from forest, and rainfall in global OLS were significantly associated with malaria cases. As shown by GWR model and in line with recent reviews, the relationship between malaria and environmental factors in South Sumatra was found to vary spatially in different regions. A more in-depth understanding of local ecological factors influencing confirmed malaria case cannot only be used for developing sustainable regional malaria control programs but can also benefit malaria elimination efforts at village level.

Authors' contributions
HH was responsible for the management of this study, design and collection of data. Under the supervision of HH, NA performed the data analysis and was responsible for data acquisition, pre-processing, and processing. HH, UH, DM, MD, DAG, UK and RM contributed to the interpretation and visualisation of the results. HH, UH, DM, MD, NA, UK and RM wrote the paper. All authors read and approved the final manuscript.

Author details
[1] Institute for Occupational Medicine, Social Medicine and Environmental Medicine, Faculty of Medicine, Goethe University, Frankfurt am Main, Germany. [2] Faculty of Public Health, Sriwijaya University, Indralaya, South Sumatra, Indonesia. [3] Remote Sensing Program, Faculty of Geography, Gadjah Mada University, Yogyakarta, Indonesia. [4] Department of Public Health, Baldwin Wallace University, Berea, OH, USA. [5] Barts and the London School of Medicine, Centre for Primary Care and Public Health, Queen Mary University of London, London, UK. [6] Nepal Health Research Council (NHRC), Ramshah Path, Kathmandu, Nepal.

Acknowledgements
We express our gratitude to the Ministry of Research, Technology and Higher Education of the Republic of Indonesia for supporting the first author (HH) with a Ph. D. scholarship in the context of the cooperation between Sriwijaya University and Goethe University. The authors wish to thank the Head of the Geospatial Information Agency (BIG) Indonesia for access to the digitised map, and the Head of the Indonesian Agency for Meteorological, Climatological and Geophysics (BMKG) climatology station Class I, in Kenten Palembang, for providing interpolated data of annual rainfall averages. We are also grateful to the Head and staff of the Health Office of South Sumatra Province who kindly permitted us to do further analyses on the malaria data from the study area.

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
Not applicable.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 11 September 2017 Accepted: 13 February 2018
Published online: 20 February 2018

References
1. Ministry of Health Republic of Indonesia. Decree of the Minister of Health Republic of Indonesia Number 293/MENKES/SK/IV/2009 on Elimination of Malaria in Indonesia, Jakarta. Ministry of Health (MoH) of Indonesia, 2009. Retrieved from http://perpustakaan.depkes.go.id/.
2. Ministry of Health Republic of Indonesia. South Sumatera Province Health Profile 2013. Palembang: South Sumatra Provincial Health Office (Indonesia), 2014. Retrieved from http://www.depkes.go.id/.
3. Ministry of Health Republic of Indonesia. Malaria management: guideline. Jakarta: Directorate of vector borne disease and zoonosis control, directorate general of disease prevention and control, ministry of health (MoH) of Indonesia, 2014. Retrieved from http://eliminasimalaria.blogspot.de/p/download.html.
4. WHO and UNICEF. Achieving the malaria MDG target: reversing the incidence of malaria 2000–2015. Geneva: World Health Organization, 2015. Retrieved from http://www.who.int/malaria/. ISBN: 978 92 4 150944 2.
5. WHO. Regional action framework for malaria control and elimination in the Western Pacific: 2016–2020. Manila, Philippines WHO Regional Office for the Western Pacific, 2017. Retrieved from http://iris.wpro.who.int/handle/10665.1/13578. ISBN: 9789290618157.
6. Elyazar IR, Hay SI, Baird JK. Malaria distribution, prevalence, drug resistance and control in Indonesia. Adv Parasitol. 2011;74:41–175.
7. WHO Country Office for Indonesia and Ministry of Health Indonesia. National malaria control programme review: Republic of Indonesia. Jakarta: WHO Country Office for Indonesia and Ministry of Health, Indonesia, 2013. Retrieved from http://www.who.int/iris/handle/10665/253960. ISBN: 978 979 19477 4 9.
8. Loha E, Lindtjorn B. Model variations in predicting incidence of *Plasmodium falciparum* malaria using 1998–2007 morbidity and meteorological data from south Ethiopia. Malar J. 2010;9:166.
9. Atieli HE, Zhou G, Lee M-C, Kweka EJ, Afrane Y, Mwanzo I, et al. Topography as a modifier of breeding habitats and concurrent vulnerability to malaria risk in the western Kenya highlands. Parasit Vectors. 2011;4:241.
10. Grillet ME, Barrera R, Martinez JE, Berti J, Fortin MJ. Disentangling the effect of local and global spatial variation on a mosquito-borne infection in a neotropical heterogeneous environment. Am J Trop Med Hyg. 2010;82:194–201.
11. Alemu A, Abebe G, Tsegaye W, Golassa L. Climatic variables and malaria transmission dynamics in Jimma town, South West Ethiopia. Parasit Vectors. 2011;4:30.
12. Yamana TK, Eltahir EA. Incorporating the effects of humidity in a mechanistic model of Anopheles gambiae mosquito population dynamics in the Sahel region of Africa. Parasit Vectors. 2013;6:235.
13. Abiodun GJ, Maharaj R, Witbooi P, Okosun KO. Modelling the influence of temperature and rainfall on the population dynamics of *Anopheles arabiensis*. Malar J. 2016;15:364.
14. Weaver HJ. Climate change and human parasitic disease. In: Climate change and global health. CABI Nosworthy Way Wallingford UK: ©CAB International; 2014:95. Retrieved from https://www.cabi.org/cabebooks/ebook/20143328432.
15. Mordecai EA, Paaijmans KP, Johnson LR, Balzer C, Ben-Horin T, Moor E, et al. Optimal temperature for malaria transmission is dramatically lower than previously predicted. Ecol Lett. 2013;16:22–30.
16. Villarreal-Treviño C, Penilla-Navarro RP, Vázquez-Martínez MG, Moo-Llanes DA, Ríos-Delgado JC, Fernández-Salas I, et al. Larval habitat characterization of *Anopheles darlingi* from its northernmost geographical distribution in Chiapas, Mexico. Malar J. 2015;14:517.
17. Ernst KC, Lindblade KA, Koech D, Sumba PO, Kuwuor DO, John CC, et al. Environmental, socio-demographic and behavioural determinants of malaria risk in the western Kenyan highlands: a case–control study. Trop Med Int Health. 2009;14:1258–65.
18. Haque U, Scott LM, Hashizume M, Fisher E, Haque R, Yamamoto T, et al. Modelling malaria treatment practices in Bangladesh using spatial statistics. Malar J. 2012;11:63.
19. Dhimal M, O'Hara RB, Karki R, Thakur GD, Kuch U, Ahrens B. Spatio-temporal distribution of malaria and its association with climatic factors and vector-control interventions in two high-risk districts of Nepal. Malar J. 2014;13:457.
20. Haque U, Glass GE, Bomblies A, Hashizume M, Mitra D, Noman N, et al. Risk factors associated with clinical malaria episodes in Bangladesh: a longitudinal study. Am J Trop Med Hyg. 2013;88:727–32.
21. Brunsdon C, Fotheringham A, Charlton M. Geographically weighted regression: a method for exploring spatial nonstationarity. Geogr Anal. 1996;28:281–98.
22. Badan Pusat Statistik. Sumatera Selatan dalam angka (Sumatera Selatan in figures) 2013. Sumatera Selatan: BPS-Statistics Sumatera Selatan, 2014. Retrieved from http://sumsel.bps.go.id.
23. BMKG. Annual average rainfall 2007–2013 Indonesian Agency for Meteorological, Climatological and Geophysics (BMKG) Climatology Station Class I Kenten Palembang, 2013. Retrieved from http://www.bmkg.go.id.

24. Lee JSH, Abood S, Ghazoul J, Barus B, Obidzinski K, Koh LP. Environmental impacts of large-scale oil palm enterprises exceed that of smallholdings in Indonesia. Conserv Lett. 2014;7:25–33.
25. Abood SA, Lee JSH, Burivalova Z, Garcia-Ulloa J, Koh LP. Relative contributions of the logging, fiber, oil palm, and mining industries to forest loss in Indonesia. Conserv Lett. 2015;8:58–67.
26. Olson SH, Gangnon R, Silveira GA, Patz JA. Deforestation and malaria in Mâncio Lima County, Brazil. Emerg Infect Dis. 2010;16:1108–15.
27. Huisman O, De By R. Principles of geographic information systems. The Netherlands: The International Institute for Geo-Information Science and Earth Observation, 2009. Retrieved from http://www.gdmc.nl/oosterom/PoGISHyperlinked. ISBN: 978–90–6164–269–5.
28. Perdana AP, Juniati E, Hidayat J. Transformation of topographic data visualization from freehand drawing to cartographic representation. Jurnal Ilmiah Geomatika. 2013;19:2. Retrieved from http://jurnal.big.go.id/.
29. Halimi M, Farajzadeh M, Delavari M, Takhtardeshir A, Moradi A. Modelling spatial relationship between climatic conditions and annual parasite incidence of malaria in southern part of Sistan & Balouchistan Province of Iran using spatial statistic models. Asia Pac J Public Health. 2014;4:S167–72.
30. Wheeler D, Tiefelsdorf M. Multicollinearity and correlation among local regression coefficients in geographically weighted regression. J Geogr Syst. 2005;7:161–87.
31. Yasin H. Pemilihan variabel pada model geographically weighted regression. Media Statistika. 2011;4:63–72.
32. Nakaya T. GWR4 windows application for geographically weighted regression modelling. Kyoto: Ritsumeikan University, Department of Geography. 24 March 2016. Retrieved from https://raw.githubusercontent.com/gwrtools/gwr4/master/GWR4manual_409.pdf,.
33. Fotheringham A, Brunsdon C, Charlton M. Geographically weighted regression: the analysis of spatially varying relationships. University of Newcastle, UK: Wiley, 2002. Retrieved from https://www.wiley.com/. ISBN: 0-471-49616-2.
34. Rodrigues M, de la Riva J, Fotheringham S. Modeling the spatial variation of the explanatory factors of human-caused wildfires in Spain using geographically weighted logistic regression. Applied Geogr. 2014;48:52–63.
35. Hoshen MB, Morse AP. A weather-driven model of malaria transmission. Malar J. 2004;3:32.
36. Widayani P, Danoedoro P, Mardihusodo SJ. Pemodelan spasial kerentanan wilayah terhadap penyakit menular terkait lingkungan berbasis penginderaan jauh (kasus malaria, leptospirosis dan tuberkulosis di sebagian wilayah Provinsi Jawa Tengah dan DIY). Universitas Gadjah Mada, Fakultas Geografi; 2016. Retrieved from http://etd.repository.ugm.ac.id/.
37. de Castro MC, Monte-Mór RL, Sawyer DO, Singer BH. Malaria risk on the Amazon frontier. Proc Natl Acad Sci USA. 2006;103:2452–7.
38. Dysoley L, Kaneko A, Eto H, Mita T, Socheat D, Börkman A, et al. Changing patterns of forest malaria among the mobile adult male population in Chumkiri District, Cambodia. Acta Trop. 2008;106:207–12.
39. Kleinschmidt I, Bagayoko M, Clarke G, Craig M, Le Sueur D. A spatial statistical approach to malaria mapping. Int J Epidemiol. 2000;29:355–61.
40. Ovadje L, Nriagu J. Malaria as an environmental disease. In: encyclopedia of environmental health. Burlington: Elsevier; 2011:558–67 Retrieved from https://www.researchgate.net/publication/268515612_Ovadje_L_Nriagu_J_2011_Malaria_as_an_Environmental_Disease_In_Nriagu_JO_ed_Encyclopedia_of_Environmental_Health_volume_3_pp_558-567_Burlington_Elsevier.
41. Hanandita W, Tampubolon G. Geography and social distribution of malaria in Indonesian Papua: a cross-sectional study. Int J Health Geogr. 2016;15:13.
42. Siraj AS, Santos-Vega M, Bouma MJ, Yadeta D, Ruiz Carrascal D, Pascual M. Altitudinal changes in malaria incidence in highlands of Ethiopia and Colombia. Science. 2014;343:1154–8.
43. Pinault LL, Hunter FF. New highland distribution records of multiple Anopheles species in the Ecuadorian Andes. Malar J. 2011;10:236.
44. Alimi TO, Fuller DO, Qualls WA, Herrera SV, Arevalo-Herrera M, Quinones ML, et al. Predicting potential ranges of primary malaria vectors and malaria in northern South America based on projected changes in climate, land cover and human population. Parasit Vectors. 2015;8:431.
45. Messina JP, Taylor SM, Meshnick SR, Linke AM, Tshefu AK, Atua B, et al. Population, behavioural and environmental drivers of malaria prevalence in the Democratic Republic of Congo. Malar J. 2011;10:161.
46. Midekisa A, Beyene B, Mihretie A, Bayabil E, Wimberly MC. Seasonal associations of climatic drivers and malaria in the highlands of Ethiopia. Parasit Vectors. 2015;8:339.
47. Chirebvu E, Chimbari MJ, Ngwenya BN, Sartorius B. Clinical malaria transmission trends and its association with climatic variables in Tubu Village, Botswana: a retrospective analysis. PLoS ONE. 2016;11:e0139843.
48. Thomson MC, Ukawuba I, Hershey CL, Bennett A, Ceccato P, Lyon B, et al. Using rainfall and temperature data in the evaluation of national malaria control programs in Africa. Am J Trop Med Hyg. 2017;97:32–45.
49. Day JF. Mosquito oviposition behavior and vector control. Insects. 2016;7:65.
50. Kleinschmidt I, Sharp BL, Clarke GPY, Curtis B, Fraser C. Use of generalized linear mixed models in the spatial analysis of small-area malaria incidence rates in KwaZulu Natal, South Africa. Am J Epidemiol. 2001;153:1213–21.
51. Chihanga S, Haque U, Chanda E, Mosweunyane T, Moakofhi K, Jibril HB, et al. Malaria elimination in Botswana, 2012–2014: achievements and challenges. Parasit Vectors. 2016;9:99.
52. Steffen W, Persson Å, Deutsch L, Zalasiewicz J, Williams M, Richardson K, et al. The anthropocene: from global change to planetary stewardship. Ambio. 2011;40:739–61.
53. Malhi Y, Roberts JT, Betts RA, Killeen TJ, Li W, Nobre CA. Climate change, deforestation, and the fate of the Amazon. Science. 2008;319:169–72.
54. Elyazar IR, Sinka ME, Gething PW, Tarmidzi SN, Surya A, Kusriastuti R, et al. The distribution and bionomics of Anopheles malaria vector mosquitoes in Indonesia. Adv Parasitol. 2013;83:173–266.
55. Sakai M. Remembering origins ancestors and places in the Gumai society of South Sumatra. In: The Poetic Power of Place comparative perspectives on Austronesian ideas of locality Australia: ANU Press; 2006:42–55. Retrieved from http://www.jstor.org/stable/j.ctt2jbjrm.2.
56. Barati M, Keshavarz-Valian H, Habibi-Nokhandan M, Raeisi A, Faraji L, Salahi-Moghaddam A. Spatial outline of malaria transmission in Iran. Asian Pac J Trop Med. 2012;5:789–95.