Multi-Scale Modeling and Assessment of Malaria Risk in Northern South America

Temitope O. Alimi
University of Miami, temitope.alimi@cantab.net

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MULTI-SCALE MODELING AND ASSESSMENT OF MALARIA RISK IN NORTHERN SOUTH AMERICA

Temitope O. Alimi

Approved:

Douglas Fuller, Ph.D.  John Beier, Sc.D.
Professor of Geography and Regional Studies  Professor of Public Health Sciences

Kenneth Broad, Ph.D.  Justin Stoler, Ph.D.
Professor of Marine Ecosystems and Society  Assistant Professor of Geography and Regional Studies

Kristopher Arheart, Ph.D.  Guillermo Prado, PhD
Professor of Biostatistics  Dean of the Graduate School
With malaria control in Latin America firmly established in most countries and a growing number of these countries in the pre-elimination phase, malaria elimination appears feasible. A review of the literature indicates that malaria elimination in this region will be difficult without locally tailored strategies for vector control, which depend on more research on vector ecology, genetics and behavioral responses to environmental changes, such as those caused by land cover alterations, and human population movements. An essential way to bridge the knowledge gap and improve vector control is through risk mapping. Malaria risk maps based on statistical and knowledge-based modelling can elucidate the links between environmental factors and malaria vectors, explain interactions between environmental changes and vector dynamics, and provide a heuristic to demonstrate how the environment shapes malaria transmission. Changes in land use and land cover (LULC) as well as climate are likely to affect the geographic distribution of malaria vectors and parasites in the coming decades. At present, malaria transmission is concentrated mainly in the Amazon basin where extensive agriculture, mining, and logging activities have resulted in changes to local and regional hydrology, massive loss of forest cover, and increased contact between malaria vectors and hosts. Thus, employing presence-only records, bioclimatic, topographic, hydrologic, LULC and
human population data, I modeled the distribution of malaria and two of its dominant vectors, *Anopheles darlingi*, and *Anopheles nuneztovari s.l.* in northern South America using the species distribution modeling platform Maxent. This was done to address the gap in knowledge about the spatial and temporal distribution of malaria and its vectors in this region. Results from the land change modeling indicate that about 70,000 km² of forest land would be lost by 2050 and 78,000 km² by 2070 compared to 2010. The Maxent model predicted zones of relatively high habitat suitability for malaria and the vectors mainly within the Amazon and along coastlines. While areas with malaria are expected to decrease in line with current downward trends, both vectors are predicted to experience range expansions in the future. Elevation, annual precipitation and temperature were influential in all models both current and future. Human population mostly affected *An. darlingi* distribution while LULC changes influenced *An. nuneztovari s.l.* distribution. Secondly, I set out to assess the risk of malaria transmission and vector exposure in northern South America using multi-criteria decision analysis, as well as examine experts’ perceptions of strategies needed for malaria elimination. The risk of malaria transmission and vector exposure in northern South America was assessed using multi-criteria decision analysis, in which expert opinions were taken on the key environmental and population risk factors. Results from the risk maps indicated areas of moderate-to-high risk along rivers in the Amazon basin, along the coasts of the Guianas, the Pacific coast of Colombia and northern Colombia, in parts of Peru and Bolivia and within the Brazilian Amazon. When validated with occurrence records for malaria, *An. darlingi*, *An. albimanus* and *An. nuneztovari s.l.*, *t*-test results indicated that risk scores at occurrence locations were significantly higher (*p*<0.0001) than a control group of
geographically random points. Public education, better environmental management and effective anti-malaria drug administration were the experts’ most highly ranked strategies for malaria control. Finally, armed conflicts are considered important obstacles to achieving malaria control and elimination; however, such association is seldom documented. Here, I test the hypothesis that armed conflicts have reduced effectiveness of efforts for elimination of malaria and other infectious diseases in Colombia. I utilized diverse spatio-temporal data aggregated to the municipal level in the Pacific Coastal region of Colombia to analyze how socio-political and environmental variables may explain trends in malaria cases over a 15-year period from 2000 to 2014. The spatial trends revealed subtle differences and patterns in the distribution of malaria cases at the municipality level, which were not evident when aggregated at the state level. The results show that when environmental and conflict-related variables are combined in a single parsimonious linear regression, temperature, conflict-related homicides, precipitation, and elevation produced a highly robust model (adjusted $R^2 = 75.7\%$). A model that included only socio-political variables such as internally displaced persons, coca cultivation, and population density explained much less of the variance (adjusted $R^2 = 43.0\%$) relative to a model that included only environmental variables (adjusted $R^2 = 69.1\%$). The results establish a novel quantitative link between conflict-related variables, particularly conflict-related homicides per municipality through time, and malaria trend in a war-torn country indicating that political stability may be essential to achieve malaria elimination. Hence, as the region tackles the challenge of malaria elimination, prioritizing areas for interventions by using spatially accurate, high-resolution (1 km or less) risk maps may guide targeted control and help reduce the disease burden in the region. The
findings also provide information to the public health decision maker/ policy makers to give additional attention to the spatial planning of effective vector control measures. Finally, investigations such as this could be useful for planning and management purposes and aid in predicting and addressing potential impediments to elimination.
DEDICATION

“All that I am, or hope to be, I owe to my angel mother”....Abraham Lincoln

I dedicate this dissertation to the memory of my mother, Mrs. Abiodun Aramide Alimi, who passed on November 30, 2002.

I am where I am today because she loved me and nurtured the gift of God in me. She taught me to shine like the star that I am for kings will come to the brightness of my rising.
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My first thanks is to the Almighty God who brought me this far. He picked me from the dunghill and set me among the princes. It was He who began this good work in me, and has today brought it to a successful completion, to Him be all the glory. Amen.

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Contributions and status of Dissertation Chapters

Chapter 1: General introduction and scope of work: Prospects and recommendations for risk mapping to improve strategies for effective malaria vector control interventions in Latin America.

Synthesis and review were conducted by Temitope O. Alimi. Text written by Temitope O. Alimi, Douglas O. Fuller, Martha L. Quinones, Rudy D. Xue, Socrates V. Herrera, Myriam Arevalo-Herrera, Jill N. Ulrich, Whitney A. Qualls, and John C. Beier. Published in *Malaria Journal* in 2015.

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Chapter 3: A multi-criteria decision analysis approach to assessing malaria risk in northern South America and local perceptions of the impact of current malaria control and socio-economic/behavioral factors on malaria elimination strategies.

Fieldwork on expert opinions was conducted by Temitope O. Alimi. Data mining and statistical analysis were performed by Temitope O. Alimi, Douglas O. Fuller, Socrates V. Herrera, Myriam Arevalo-Herrera, Martha L. Quinones, Justin B. Stoler, and John C. Beier. Published in *BMC Public Health* 2016.

Chapter 4: Civil conflict and environment as drivers of malaria trends in Colombia from 2000-2014.

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Chapter 5: Summary and Conclusions

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Chapter 1. General introduction and scope of work: Prospects and recommendations for risk mapping to improve strategies for effective malaria vector control interventions in Latin America

1.1. Background

The public health and economic burden imposed by malaria has made the disease a top priority for control efforts and its elimination is center stage on the global health agenda [1-4]. The Roll Back Malaria (RBM) program has taken giant strides towards malaria control and elimination in the past decade and recorded some successes including a fall in global malaria incidence by about 17% [5], increased number of countries in the pre-elimination and elimination stages [5, 6], decline in morbidity and mortality experienced in the most endemic countries [2, 7], and progress towards the development of new drugs and vaccine [8]. These accomplishments were aided by increased international funding and renewed political commitment by endemic countries [2, 9] as well as increased urbanization [10].

Consistent with global trends, in South America (SA), significant reductions in malaria incidence have been observed in the last decade. Between 2000 and 2009, the number of confirmed cases reported declined by 43% [5] and mortality dropped by 20% from 2000-2006 [9]. Although SA accounted for only about 1% of the global malaria burden in 2007 and the lowest Plasmodium falciparum endemicity and morbidity [11], about half of its population is at risk of malaria transmission [12, 13]. This P. falciparum burden, while low equaled an estimated 3 million clinical cases in 2007 and is consequently of great concern especially to countries in SA with large populations or those close to elimination [11]. Key factors limiting effective implementation of control
strategies include lack of robust health systems to optimize delivery of scaled-up malaria services and interventions in target areas [4, 14-15], health sector reforms which sometimes prevent program continuity [16], and insufficiently equipped local health services for malaria control [17]. More significantly, knowledge and understanding of the geographic distribution of vector species in the region remains incomplete, and delineation of areas at risk of malaria infection both at the national and regional scales is scant or outdated. Furthermore, little is known about local variations in malaria incidence and the factors which may account for the differences.

Like all diseases, malaria is spatially constrained, occurring where and when the epidemiological factors necessary for its propagation (pathogens, vectors, susceptible human hosts and environment) converge [18]. The risk of exposure is also spatially heterogeneous because pathogens, vectors and susceptible human populations are unevenly distributed in space and time [19]. When combined with varying environmental and anthropogenic factors, the result is spatially significant (non-random) differences in disease burden even across similar geographies. Thus, capturing the geographical variation across landscapes is essential to the proper characterization of malaria risk.

Vector control, any method that limits or eradicates vectors of disease pathogens, is one of the main strategies for malaria control. Targeted vector control is a crucial element of malaria management because of its capacity to lower or disrupt pathogen transmission by reducing human-vector contact and vector population density and survival [20, 21]. Therefore, implementing targeted vector control requires knowledge of appropriate mosquito distributions. However, current *Anopheles* distribution maps in the region are for individual countries [22] or single species/sub-group [23]. While
distribution maps for the continent were recently produced by Sinka et al. [24], the implications of changes in land use, population growth and climate change on current and future mosquito distributions have not been fully explored for the region.

Although analysis of malaria infection/transmission at regional or national scales provides much needed information on current distributions and aid interventions at these scales, evidence has shown that disease investigations conducted at smaller geographical scales reveal minute variations and distributions of risk that would not be evident in larger geographical areas [25]. Variations in environmental, socio-economic, political factors or malaria control strategies which would be aggregated at national scales but disaggregated at local scales, such as states or municipalities, may highlight differences in malaria incidence that could aid targeted control. Therefore, an understanding of the dynamics of malaria transmission at local scales such as the municipality may provide insights to guide malaria interventions.

1.2. Ontology of spatial modeling in risk assessment

The overarching goal of any intervention or study in public health is to lessen the burden of disease in a given population. Spatial models are applied to public health problems to produce information that would aid decision making either for the public e.g. preventive actions, or public health agencies e.g. allocation of resources for disease management [26]. Here, spatial models are geographical information system (GIS) based statistical models applied in the estimation of disease/vector distribution. For vector-borne diseases, they help identify the spatio-temporal patterns of both disease and vector, provide a better understanding of environmental influence on the patterns observed and forecast spatial risk pattern given future changes in environmental or socio-economic
Risk mapping may be conducted to test hypotheses or identify knowledge gaps, e.g. factors affecting disease/vector distribution, to interpolate data within a given geographic area or extrapolate outside known boundaries [27]. They may also be employed to aid control efforts or assess an intervention [28].

The type of model employed for risk assessment depends on the intent of enquiry or data availability. When based on intent, spatial models could be descriptive, explanatory/predictive. Descriptive models explore and detail the spatial patterns of risk of a disease or vector based on the spatial dependence/correlation of points in the given data [26]. Explanatory/predictive models on the other hand seek to provide insight on the biological mechanisms leading to disease occurrence and attempt to predict disease occurrence/vector distributions in different geographical locations or in a future time [27]. But for the purpose of this research, I focus on ontology of spatial models based on data availability.

On this basis, there are two classes: data-driven models and knowledge-driven models. The data driven approach to modeling risk is one in which presence and/or absence data on vectors, prevalence/incidence and clinical case data on diseases are available. Often referred to as disease distribution models, they are concerned with modeling the distribution and habitat suitability of disease microorganisms or their vectors [27]. There are several distribution models including traditional methods such as the generalized linear models, generalized additive models and Bayesian estimation methods [29]. A new generation of models requiring absence and/or presence data are now available. One of such is the maximum entropy method, which I employ to examine the distribution of malaria and its vectors both in the current and future time frame. The
knowledge-driven approach is the class of models applicable in data-sparse situations where maps are generated based on theoretical knowledge of interactions between disease vectors and environmental data. This method, in the form of multi-criteria decision analysis (MCDA) is employed both at a broad and small scale to examine risk of malaria transmission in one of my studies.

The utility and efficacy of these modeling approaches are examined in detail in the subsequent chapters. However, in the rest of this chapter, I present a summary of risk mapping as a useful tool for mapping malaria risk and directing evidenced-based malaria interventions in Latin America. By describing the progress of malaria vector control, and highlighting factors limiting its advancement in the region, I identify how current vector control strategies can be improved using novel methods in risk mapping to enhance malaria elimination programs.

1.3. Progress of malaria control in Latin America

Malaria transmission in Latin America, including Central America, the Caribbean, and South America is a persistent problem. With highly focal malaria, about 120 million people in Latin America are at risk, out of which an estimated 25 million people are at high risk of malaria transmission [30, 31]. Malaria risk has no standard definition, with risk being defined according to the subject of interest. However, generally in public health, risk is defined as ‘the probability of disease developing in an individual in a specified time interval’ [32]. Malaria risk is estimated by the World Health Organization (WHO) based on annual parasite index (API), the number of positive parasite slides per thousand population. On this basis, most of the at-risk population in Latin America live in low transmission settings where cases are ≤1 per 1,000 (see Table 1.1), the rest live in
high transmission areas with >1 case per 1,000 [33]. The spatial distribution of infections is heterogeneous with the majority caused by infections by *P. vivax*, which accounts for about three-quarters of all cases in the region; whereas, *P. falciparum* is exclusively responsible for the infections in parts of the Caribbean (Haiti and Dominican Republic), most of the infections in the Guyana Shield (French Guiana, Guyana and Suriname) and along the Pacific coast of Colombia [17, 30-31]. The burden of malaria is also widely disparate. Approximately 90% of the malaria burden of the region is borne by countries in the Amazon Rainforest [33]; three countries accounted for 72% of cases in 2013: Brazil (42%), Colombia (12%), and Venezuela (18%) [31].

Nevertheless, malaria control has vastly improved in the past decade. Confirmed malaria cases fell from 1.2 million to 427,000 cases from 2000 to 2013, while deaths from malaria declined from 390 to 82 deaths [31]. Although Guyana and Venezuela recorded increased incidence in cases in 2012 [30, 31], two countries in South America (Chile and Uruguay), and all Caribbean countries except Haiti and Dominican Republic, are malaria free. Thirteen countries recorded 75% or greater decline in malaria incidence between 2000 and 2013[31]. Progress toward elimination is also ongoing in many of the low-transmission settings in the region. Seven countries (Argentina, Belize, Costa Rica, Ecuador, El Salvador, Mexico, and Paraguay) are currently in the pre-elimination phase [31], a stage in which malaria control is firmly established and access to preventive measures, diagnostic testing and treatment is available to the population at risk [34].

The observed progress is facilitated by improvements in malaria surveillance and monitoring, more efficient use of control measures, prompt and efficient malaria treatment/drugs, and better integrated vector management (IVM) implementation [35].
IVM is a rational decision-making approach for optimizing the use of resources for vector control by involving the adaptation of strategies and interventions based on local vector ecology and epidemiology [20]. Confirmation of malaria cases is expedited through routine malaria surveillance, and countries such as Mexico, Ecuador, Costa Rica and Paraguay implemented intense case surveillance [5, 36]. The range of diagnostic testing and reporting also expanded, a development that may account for the increased reported malaria cases in Venezuela and Haiti, rather than an actual increase in malaria incidence [5, 31]. Long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) or both are now applied for at-risk populations in all countries with ongoing malaria transmission [31]. Six countries (Bolivia, Mexico, Guatemala, Nicaragua, Ecuador and Costa Rica) have more than 50% of populations at high risk covered with LLINs and IRS [5, 30-31]. Antimalarial drugs are also sufficiently available for all patients who seek treatment in public health centers in most of the endemic countries [31]. These marked improvements in malaria control have been made possible mainly by international (e.g. Global Fund, President’s Malaria Initiative and World Bank) and domestic funding, which increased from US $153 million in 2005 to US $214 million in 2011, but dropped to US $140 million in 2013 [31]. Regional collaborations (e.g. Malaria Control Program in Andean-country Border Regions, the Amazon Malaria Initiative and the Amazon Network for the Surveillance of Antimalarial Drug Resistance) have also been instrumental in developing drug efficacy protocols and monitoring drug resistance [5, 35]. These achievements indicate that malaria elimination in Latin America is feasible if current efforts are strengthened and new interventions are developed and implemented.
The strategies needed to achieve malaria elimination are thus multi-pronged and require different approaches. There is a need to explore how using novel methods incorporated in risk mapping/modelling, can enhance the progress already accomplished. Risk mapping is a methodology that provides spatial detail on the expected distribution of vectors or risk of exposure to malaria that may help identify underlying factors, which contribute to risk and burden [18].

1.4. Constraints of malaria vector control in Latin America

Despite appreciable progress, the final steps toward malaria elimination in the region are challenging, yet surmountable. Differences in epidemiology coupled with the geography of each country determine the kind of malaria intervention required in a particular region and its efficacy [30, 31]. The unique Latin American landscape for the most part favorably predisposes the region to malaria elimination compared with other regions where malaria is endemic e.g. Africa and South-east Asia, if efforts are effectively tailored. For instance, the significant areas of Montane and upland environments associated with the Cordilleras of Latin America provide greater altitudinal variability than in Africa or Southeast Asia. Further, the Cordillera that runs from Mexico to Chile serves as a major barrier to transmission and vectors. Location of settlements in Latin America is also determined largely by access through river networks [37], as opposed to that in Africa, where spread and movement of people and parasites is more porous because much of the transportation is land-based [38]. Moreover, vast areas of savanna and semi-arid lands are interconnected in Africa [39] whereas in Latin America, because of the highly focal nature of the disease, geographic isolation of the Amazon and other low-lying zones, the areas where population are at risk are much more easily
delineated and spatially heterogeneous relative to Africa, for example. These geographical advantages can be incorporated and exploited in risk mapping to broaden knowledge of malaria epidemiology and mosquito ecology in Latin America and thus help to strengthen malaria control. However, despite this advantage, several factors discussed in the next section limit malaria elimination in the region.

1.4.1. Limited entomological capacity

Despite the improved entomological capacity evident in Latin America, there still remains a shortage of skilled entomologists and entomological infrastructure e.g., insectaries, laboratories equipped with microscopes, and trained personnel [40, 41]. As a result, there are few transmission studies and investigations of outdoor-resting and early evening biting (behavioral traits of Latin American vectors that could confound current vector control gains) [24, 42-44]. National needs assessments of current capacity are needed and such survey data can also be mapped to indicate where more investment in training and laboratory infrastructure is needed.

Risk mapping methodologies can to a large extent address the limitations in current entomological capacity for malaria control in Latin America. The methodologies provide insights into pathogen transmission dynamics, including knowledge about the transmission and endemicity of parasites. For instance, Patil et al. [45] used Bayesian geo-statistics (BG) to produce candidate maps of *P. falciparum* endemicity in Africa. Bayesian geo-statistics accounts for the spatial variability inherent in a dataset by finding the unknown true map from a large sample of maps that reflect the dataset [45]. The approach was similarly used by Gething et al. [46, 47] to map global *P. falciparum* and *P. vivax* endemicity respectively. Using georeferenced parasite rates and incidence data,
a continuous surface showing transmission intensity for \textit{P. falciparum} was created \cite{46}. For \textit{P. vivax} mapping, georeferenced age standardized \textit{P. vivax} parasite rates were incorporated with climatic factors (temperature and aridity) and medical intelligence data to produce maps of \textit{P. vivax} endemicity \cite{47}. The method is particularly useful in estimating risk in areas with limited data and has the added advantage of accounting for uncertainties in the results. It is however noteworthy that maps generally report single estimates for each location without conveying the variability inherent (temporal or within pixel), even when data are evenly distributed, e.g. in un-sampled locations \cite{45}, an important limitation, which may preclude the widespread use of risk modelling.

While exploring risk of malaria transmission based on outdoor and early-biting mosquitoes is newly developing, risk-modelling methodologies can provide necessary tools for mapping locations, distribution and effects on transmission of exophilic and exophagic mosquitoes and direct vector control efforts geared towards them. For example, using an individual-based simulation model, Griffin \textit{et al.} \cite{48} showed that very high coverage of current vector control interventions (>90\%) or development of new control measures are necessary to reduce \textit{P. falciparum} transmission in high transmission areas of Africa where outdoor biting, \textit{An. arabiensis} prevail, but similar studies utilizing risk modelling have yet to be conducted in Latin America. This is probably due to the limited knowledge about outdoor vectors species in the region, limited coverage and knowledge of the effectiveness of current vector control tools, as well as limitations in human resources.
1.4.2. Increasing insecticide resistance

Growing insecticide resistance among malaria vectors in Latin America has raised concern, yet data on insecticide resistance are sparse [49, 50] and their mapping limited. Resistance to dichlorodiphenyltrichloroethane (DDT), pyrethroids and organophosphates (OP) has been observed in parts of the region. For instance, in Colombia, resistance to DDT occurs in *An. darlingi* around Quibdó and the Atrato River [51, 52] and resistance to pyrethroids exists for both *An. darlingi* and *An. albimanus* in Chocó [53]. Mild cross-resistance to DDT and pyrethroids, and high resistance to pyrethroids and OP occurs in populations of *An. nuneztovari* in parts of Colombia [63]. In Peru, *An. albimanus* is resistant to pyrethroids [55], while relatively lower resistance to OP and pyrethroids and high resistance to DDT occur in the same species in southern Mexico [56]. Laboratory colonies of *An. albimanus* from Guatemala show resistance to DDT and pyrethroids, whereas field species from El Salvador and Belize were susceptible to these two insecticides [57]. Although resistance of mosquitoes to insecticides may be more widespread in this region than has been reported, the limited data available provide opportunities for mapping insecticide resistance and risk associated with it, so efforts to tackle the problem can be better targeted.

Risk mapping and modelling technologies have capabilities for describing the distribution of insecticide resistance in mosquitoes. Coleman *et al.* [58] used a malaria information system equipped with geographic information system (GIS) capability to map locations of insecticide resistance across Africa. Geo-referenced resistance information were obtained from published reports to show a spatial distribution of resistance across the African continent. Additionally, Insecticide Resistance (IR) Mapper,
an online mapping tool, has also been developed to examine spatio-temporal trends in *Anopheles* resistance using geo-referenced data [59]. Incorporating insecticide resistance and susceptibility data from various countries, the developers conclude that the IR mapper would aid visualization and direct vector control through insecticide applications. However, such mapping technologies are data-driven, depending on accurately geo-referenced insecticide resistance information, which may be limited in developing countries. Thus, although the facilities to map and display mosquito resistance to insecticides are now available, more studies documenting insecticide resistance, including accurate locational information in different parts of Latin America are required. It is particularly necessary to have a routine system of insecticide resistance surveillance in Colombia, Honduras, Nicaragua and Brazil, where mass distribution of LLINs is currently promoted and implemented in high risk areas [30, 31].

1.4.3. Inconsistent policy implementation and monitoring of program efficacy

Vector control in Latin America is increasingly implemented based on principles and policies of IVM, but operations are yet to be consistently employed throughout the region. Being evidence-based, the IVM approach advocates that vector control interventions be introduced and implemented based on prior information [20]. However, this does not always happen in practice. In an assessment of malaria control strategies conducted in Ecuador, Peru, Colombia, Bolivia and Guyana, Flores *et al.* [41] observed that information on research, extent and quality of IRS application was incomplete. Likewise LLINs were administered without prior studies to determine target populations, as well as understand vector behavior or their response to insecticides in all the countries except Bolivia and Colombia [41, 60].
Whereas coverage and delivery of vector control tools to populations has greatly improved in the past decade, strict compliance with technical guidelines on the tools are still lacking. For instance, Flores et al. [41] found that WHO guidelines for IRS applications were not strictly followed. Moreover, target populations in remote areas often live in houses that do not conform to technical criteria for IRS spraying. Although LLINs were delivered, delivery was sometimes diverted to areas not targeted for bed nets [41]. Coverage of entire target populations also fell below the 80% coverage criteria for LLINs [41]. Furthermore, other vector control measures such as environmental management and mosquito proofing of houses are not as widely used especially in remote areas. Evaluation of application strategies is also sporadic [61, 62]. For example, assessment of the efficacy of interventions, timeliness and frequency of applications for IRS or insecticide resistance is limited [39, 63].

Parts of the policy implementation issues arising from lack of information can be improved through risk modelling. Risk maps can provide prior knowledge on target (at-risk) populations and their stratifications [64-66], information that can help identify specific locations for prioritization of malaria interventions. For instance, Tatem et al. [64] used spatial models to improve estimates of children under five at highest risk of \textit{P. falciparum} transmission in Tanzania. Noor et al. [66] also mapped population distribution, stratifying by age, in order to estimate malaria risk and quantify coverage of interventions. This is analogous to the application of remote sensing (RS) in precision agriculture to help farmers better target where pesticides, herbicides, fertilizers, water, etc. are needed within their fields [67, 68]. This has allowed farmers save millions of dollars by targeting only those areas that need inputs the most (i.e., pesticides, etc.) rather
than broadcasting chemicals indiscriminately [67, 68]. Maps containing information on housing location and type [69, 70] can also provide knowledge which together with information on target population and vector distribution can guide targeted LLIN and IRS applications [64-66]. In some villages in northern Sri Lanka, Van Der Hoek et al. [69] found proximity of housing to vector breeding sites and poor housing construction major risk factors for malaria in the area. Information on vector behavior and distribution [23-24, 71] and about insecticide resistance [59] is also enhanced through risk mapping. Such information gives an indication of where vectors can be found and targeted. For example, a number of studies such as Sinka et al. [24] and Fuller et al. [23] used species distribution model (SDMs) to map the distribution of dominant anophelines in the Americas and current *An. albimanus* distribution in Mesoamerica respectively. In the latter, the mosquito data was extrapolated to a future period, thus reducing the impact of sampling bias on the data, an implication that may have more of an impact on policy.

Risk mapping methodologies also have capabilities to generate information on monitoring malaria interventions e.g. the effect of continued dissemination of LLINs, IRS, mass drug administration and future vaccine on malaria transmission [48] or keeping track of vector control coverage e.g. IRS application [72]. Malaria surveillance, especially in areas with limited resources, is also enhanced through risk mapping. Combining satellite imagery, mobile phone call records and surveillance data in Namibia, Tatem et al. [73] showed that the maps produced could help track and contain malaria, by limiting exported cases and directing efforts in areas with imported cases. Routine mapping of malaria incidence or prevalence [74, 75] and targeting hotspots of transmission [76-78] are also strengthened through risk mapping. Bousema et al. [77]
elucidated on the spatial patterns of malaria transmission in northeastern Tanzania, identifying hotspots of transmission through clusters of higher malaria incidence created using geo-referenced malaria incidence and mosquito sampling data. de Castro et al. [79] also used spatial modelling to identify clusters of malaria and patterns of transmission in Machadinho, one of the colonization areas in Brazil, highlighting their utility in targeted malaria control.

To monitor progress of malaria control and actualize malaria elimination, risk mapping efforts in Latin America and elsewhere need to focus more on the geo-referencing of implementation of specific intervention strategies as a way to better understand why transmission persists in some places and not in others. This process of ‘efficacy mapping’ involves the mapping of control efforts (either through investments of resources, training, or implementation e.g., distribution of LLINs) relative to outcomes, which are regularly monitored and mappable, e.g. incidence through time. This kind of mapping has the potential to greatly enhance elimination efforts in Latin America and elsewhere. However, the difficulties associated with the implementation and monitoring of policies in the region are not limited to information deficits, but also related to human capacity and infrastructural deficiencies, corruption, as well as political will, all factors that risk mapping may not be readily able to address. Furthermore, if efficacy remains low in the face of sustained investment in control measures, it may signal lack of institutional capacity or will to achieve elimination.

1.4.4. Varying definitions of risk and measurement methods

Risk assessment is an important component of public health, which provides information that may aid decision-making either for the public or public health agencies
Yet, there is currently no standard definition of risk, rather it is described based on the subject of interest. Risk is defined broadly by the Society for Risk Analysis as ‘the potential for realization of unwanted, adverse consequences to human life, health, property or the environment’ [80]. Definition of risk becomes increasingly varied for vector-borne diseases, such as malaria, because of the complexity of the disease [81] and is, therefore associated with variables related to both the disease and its vectors (See Table 1.2). Thus in the context of mapping, ‘malaria risk’ may be considered an array of factors that relate not only to the presence and density of vectors and parasites, but also to the level of investment and implementation of different malaria control measures, which vary greatly in space and time. Maps based on repeatable, reliable measurements (e.g., those based on remote sensing) provide a basis for visualizing changing risk landscapes that are inherent in many parts of Latin America. Malaria risk could also be considered in terms of trends over time, which could be estimated from time series data and displayed in map form as a multi-year trend. Time series analysis of malaria incidence data, which are available for many countries in Latin America, may be disaggregated to the municipal level, and could represent an innovation in malaria risk mapping.

The measurement of risk is also as widely varied as its definition. Risk may be estimated using various modelling methods (biological or statistical), explanatory variables (depending on the etiology of the disease and how well this is established) or mapped at different scales and resolutions [81]. Biological models use variables that represent important biological pathways of the infection in modelling risk e.g. including temperature in malaria modelling [45], or hypnozoites in modelling *P. vivax* [82]. Statistical models on the other hand seek statistical associations between the variable of
interest (e.g. malaria cases) and its predictors based on the epidemiology of the disease [24, 83]. The scale e.g. continental, regional, national or local, and the spatial resolution, i.e. the size of the smallest possible feature that can be seen on an image, at which malaria risk is represented are also important considerations. Available maps of malaria risk in Latin America such as is produced by the Pan American Health Organization (PAHO) are highly generalized, and aggregated at scales which do not allow for meaningful application [85]. They are also of low resolution and often delineated according to political rather than natural boundaries [85]. The variable definitions, conceptualizations, and measurements of risk limit the application of risk maps because there is no risk-mapping standard for malaria.

Considering that they provide consistent measurements of environmental factors associated with vector dynamics, remote sensing provides a viable means of estimating risk and how risk factors change through time. RS technologies are used for malaria vector mapping and malaria case mapping. Vector mapping involves estimation of malaria risk using mosquito location data [24, 83] while risk is estimated in malaria case mapping using actual malaria incidence or prevalence data [75]. Risk is assessed in both cases by combining those data (i.e., malaria incidence or mosquito data) with environmental and socio-economic factors, which favor mosquitoes and malaria [27, 83, 86]. However, the choice of approach is dependent on the availability of geo-referenced data, which is still restricted to small areas or to aggregated state or county level data in many countries of Latin America [83].

Risk modelling tools available in GIS and RS are efficient for the mapping and analysis of disease distribution and variation, and of environmental elements that may
predict or explain these variations [87]. With RS, environmental information, such as vegetation density, location of water bodies and water quality [88], presence of submerged and emergent vegetation in wetlands (aquatic macrophytes or AM) [89, 90], presence and density of settlements [88], including impervious surface area and bare soils [91], which can be correlated with risk of vector-borne diseases are extracted from images. These are potentially important risk factors in different context that sum in different ways to create composite risk or overall risk for any given location, which is represented by a pixel on an image. Such images are captured on earth features and climatic factors, through instruments placed on satellites [92]. These instruments record the interaction of earth surface features with radiant energy in different wavelength bands.

The mapping capabilities provided by high to medium resolution satellite imagery enable improved targeting of areas and populations at risk, so that risk may be reduced [93]; abilities that aid efficient direction of control efforts in both endemic and epidemic situations [94]. The technologies have proven useful in mapping malaria risk in different parts of the world e.g. mapping global *P. falciparum* [46] and *P. vivax* [47] endemicity, mapping dominant *Anopheles* vectors globally [71], in the Americas [24], or in specific countries e.g. Belize [88-90] (See Table 1.2). The issues of scale and resolution are also effectively handled through risk mapping, as high resolution remotely sensed data are increasingly made publicly available. This has led to the generation of high quality and very fine resolution risk maps, which provide more spatial detail that can aid targeted vector control [83]. By combining knowledge of interactions between vectors, environmental factors and malaria epidemiology, maps of malaria risk may also be
generated even if empirical data on malaria distribution are not abundant [83] (See Fig. 1.1). However, the high cost of fine-resolution RS images as well as cloud cover [95] may limit their widespread use in many Latin American countries.

1.4.5. Need to sustain investments and bolster political will to achieve malaria elimination

The political climate influences vector control continuity and progress. Domestic government spending on malaria control in many Latin American countries increased from approximately US $130 million in 2005 to US $160 million in 2011, contributing to the gains earlier mentioned [31]. Yet, unsustained political will and determination of some governments (at least at the local level) and the variable power supply (power grids) sometimes slow down vector control. Government bureaucracies, which are frequently guided by donor priorities and policies, may be responsible for delays in program implementation; while, local corruption may also lead to uneven application of malaria control measures [96]. In many countries, ministries of health (MoH) and malaria control programs are frequently reorganized and their activities decentralized during health sector reforms [16, 97] e.g. the reorganization of the project for control of malaria in the Amazon basin during the Brazilian health sector reform [98, 99].

Brazil has however demonstrated that sustained government commitment to elimination is feasible. In 1993, the country changed the malaria control strategy to focus efforts on high-risk municipalities through early case detection and management [98-101] and more selective use of IRS and environmental management [100], thereby focusing more on individuals than the environment [102]. The MoH increased the number of health posts able to carry out diagnosis and treatment of malaria so that by 2009, there
were approximately 3500 diagnostic laboratories, about 50,000 malaria control agents and \(2.8 \times 10^6\) blood examinations were conducted [103]. Surveillance, monitoring and evaluation activities were also strengthened through the management of Sistema de Informação de Vigilância Epidemiológica (SIVEP-Malaria), the malaria information system for the nation [100]. The result of the concerted efforts was a sustained decrease in malaria cases, disease severity and number of municipalities at risk of malaria in the Amazon [100]. Although Brazil is ahead of its Amazonian neighbors, their systematic approach could/should be used as a model for countries, such as Bolivia, Guyana, Suriname, Venezuela, where malaria control is still in its early stages.

Financial investments in malaria control have started to decline in the region. In 2013, domestic funding decreased to about US $110 million [31]. If this reduction continues, it would become increasingly difficult to maintain the gains in malaria control already achieved. To avert such a situation, investments at the national and local levels must be sustained and governments encouraged to pursue malaria elimination in their territories. Expenditures on malaria control at the subnational level need to be mapped so that political factors can be considered more explicitly and outcomes (e.g., reduced incidence through time) can be matched to investment. To facilitate this, the program on eliminating malaria in Mesoamerica and Hispanola by 2020 (Eliminación de Malaria en Mesoamerica y la Isla Española, (EMMIE)) was initiated by the Global Fund for Aids, Tuberculosis and Malaria (GFATM) and supported by participating countries [104]. The initiative was launched to encourage transition from malaria control to elimination, foster collective action among the countries and bolster sub-regional and political commitment towards elimination [104].
Delivery efficiency [105] for vector control programs can be enhanced through risk mapping techniques. Mapping transportation routes and human population movements [73], or geographical distribution of interventions delivered through community health workers [105] can help improve distribution channels and give an indication of how effective interventions are. Going forward, by investing in research, which advances the use of risk mapping methodologies in their countries, national and regional governments will produce more value for every dollar spent. This is because risk mapping will guide targeted vector control [64-66], and invariably lead to more efficient use of resources for malaria control. Moreover, mapping things such as investment in control measures per capita, distribution of LLINs per capita, density of health clinics per municipality, degree of spatial isolation, etc. (information which are readily available through national census data and can be realized quickly) that require mapping but have not yet been made spatially explicit can accelerate drive to achieve malaria elimination by highlighting areas where risk remains persistent through time in the face of sustained investment in control measures.

1.4.6. Gaps in the understanding of vector ecology

The high incidence of *P. vivax* infections, and the different species of vectors and their behaviors make malaria transmission in Latin America unique. Experience based on past control efforts shows that interventions cannot be applied universally regardless of the local environment. There are currently major gaps in understanding distribution, ecology, behavior, and vector competence of the primary vectors of malaria in Latin America, namely, *An. darlingi*, *An. nuneztovari*, *An. pseudopunctipennis*, *An. albimanus*, and *An. aquasalis* [35, 61, 106]. These gaps in knowledge limit the ability of health
authorities to apply adequate vector control measures [35]. With low rates of transmission, government commitment, and fewer residents at risk, relative to other malaria regions, Latin America would appear to be the most feasible location for malaria elimination [61, 107]. However, final steps toward elimination require decreasing the number of infective bites per person to less than one per year [108]. Unfortunately, current vector control strategies in Latin America do not cover the full range of environmental conditions where mosquito exposure occurs, and the existence of even a small percentage of mosquitoes that rest and bite outdoors may prevent the transition from pre-elimination to elimination [109]. This, coupled with the lack of entomological expertise and laboratories equipped with trained personnel to identify vectors and parasites, remains an impediment to elimination.

IRS and LLINs are currently the principal vector control tools in Latin America. IRS use in Latin America began with the introduction of DDT for malaria control in Venezuela [91]. Earlier studies conducted by Gabaldon [110-111] reported the successful elimination of malaria in most parts of Venezuela using IRS, especially in areas where *An. darlingi* and *An. albimanus* were the main vectors. However, the feeding and resting preferences of most vectors make them poor candidates for control using these tools. IRS targets endophilic mosquitoes while LLINs target anthropophilic, night-biting mosquitoes; characteristics not commonly exhibited by Latin American anophelines. The vectors in Latin America are primarily exophilic, although the degree of exophily varies by region [24, 42]. *Anopheles darlingi* is the main vector, feeding during sleeping hours [43, 44]. *Anopheles albimanus* also exhibits late-night biting and indoor feeding preference [44]. Exophily is however not uncommon with both species as early evening
and outdoor biting has been observed [49, 50, 106], as is the case with other species, such as *An. nuneztovari* and *An. pseudopunctipennis* [110]. Despite evidence that these behaviors allow Latin American vectors to evade insecticide exposure with IRS and LLINs, both measures are still the main tools for malaria vector control [44, 112]. It is unclear whether these measures may promote behavioral changes of the vectors (irritability, exiting, or feeding inhibition) and thus contributes to more sporadic malaria transmission in Latin America [31].

Knowledge about the range and distribution of mosquito vectors that transmit malaria is important to guide vector control strategies and provide information that may help prevent future malaria outbreaks. This information has progressively become available through SDMs, which are important tools in the risk-mapping arsenal. SDMs integrated with GIS mapping techniques has seen wider applications in vector mapping in recent years [84, 113-114] using different modelling applications, e.g. boosted regression trees (BRT) [24, 115], and MaxEnt [91, 116]. Extensive use of these tools in Latin America is essential to fill the gaps in the knowledge of the vector species in the region. Alternative vector control tools that target outdoor-resting mosquitoes, partially zoophilic mosquitoes, and mosquitoes that feed in the early evening are also vital to the success of malaria elimination in Latin America. Risk mapping can aid the deployment of alternative tools such as attractive toxic sugar bait (ATSB) by identifying high-priority areas for placement of bait stations or spraying an attractive sugar solution containing an oral toxin on spots of vegetation in order to kill mosquitoes that feed on it [117-122].
1.4.7. Understanding the influence of human and environmental disruptions

The terrain of Latin America is also a major determinant of applicable vector control interventions. Considering that many countries contain extensive wetlands, and flooding is frequent during the rainy season, vector management through larval control becomes difficult. It is important to note that the rainy season is typically not the time of peak transmission because the larvae and pupae are swept away in currents; whereas at the end of the wet season/beginning of the dry, is when transmission occurs owing to the slower flow rates in rivers, streams, and wetlands [123]. Larval control is often difficult in slums where some of the houses are built on stilts in water because of the cost, and possible harmful effects on non-target organisms, the environment or humans [124]. Locating breeding sites where larval control could be successful is also challenging especially in isolated areas in the Amazon where the logistics of locating and treating individual breeding sites may preclude control directed at the larval stage [123]. Despite these challenges, larval control with microbial larvicides is effective, particularly in small clearly defined larval habitats, like stagnant water bodies, storm drains or inundated forest floors and insect growth regulators or OP larvicides are effective in clearly defined large water bodies as evidenced in studies in Central America [125, 126], Ecuador [36] and Peru [126].

Remote sensing has been extensively used to characterize location and distribution of larval habitats and direct target efforts towards mosquitoes at the larval stage. A number of vector studies have used RS to measure and identify AMs, which are typically found along the shallow margins of water bodies [127-129]. These AMs provide sources of information to identify where within water bodies and wetlands interventions
such as larval control should be targeted. For instance, Rejmankova et al. [88, 128] used Systeme Probatoire d'Observation de la Terre (SPOT) images to identify and examine marshes in Belize which contained AMs which serves as larval habitats for An. albimanus [88], An. vestitipennis and An. punctimacula [128] respectively. Roberts et al. [127] also used multispectral SPOT XS images containing thermal bands essential for mapping vegetation to predict presence of An. pseudopunctipennis in central Belize. Samson et al. [91] used a RapidEye image of the northern provinces of Haiti pre (2010) and post (2013) the earthquake to devise and implement a larval sampling strategy in the area.

Environmental changes, whether by humans or nature plays an important role in vector distribution and malaria control. In many parts of Latin America, increased malaria incidence is associated with land use changes. Land conversion for subsistence agriculture, pasture and livestock production [130], and infrastructural development e.g. dam construction such as the Belo Monte Dam project [131], in the Amazon basin lead to widespread deforestation [132]. The environmental alterations create larval habitats for specific anopheline larvae development [133] e.g. dams create stagnant water which serve as ideal breeding habitats [84] that will likely increase risk of malaria transmission in the near future. In their study, Taddei et al. [134] found An. darlingi in 13 out of 14 altered environments in the Brazilian Amazon whereas none was found in 5 unaltered areas. Vittor et al. [135] also observed that An. darlingi biting rates in deforested areas was 278 times those of forest areas in the Peruvian Amazon. So, as long as regulations on deforestation in the Amazon basin are not fully enforced, illegal activities such as gold mining and cacao cultivation remain unchecked, unplanned urbanization increases and
more land acquisitions for agriculture and infrastructural developments continue, vector ecology will keep changing [130, 132-134, 136].

A huge problem remains in frontier areas along forest boundaries in Brazil where deforestation and extractive activities (mining, agriculture, logging, etc.) occur [137]. These create frontier settlements which favor human clustering close to vector habitats [137, 138], leading to ‘frontier malaria’ which are mapped through risk mapping methodologies [79, 137-139]. The dense tree cover in the Amazon facilitates clandestine extractive activities, which often take place without government sanction. The loggers and miners engaged in extractive activities are a focal point for transmission and dispersal of parasites within and between Amazonian countries. By mapping forest disturbance at small scales, elimination can be advanced because such disturbances are frequently associated with extractive activities where transmission is concentrated. Conflicts are also rife in these frontier zones in Brazil [140] as well as in other parts of the region such as Colombia [141]. These conflicts have destabilized communities, caused disruptions in government services (e.g. health care), and forced people to move from their homes, where they are likely to come into more contact with vectors. Thus, civil conflict is a risk factor that bears mapping. Data on measures that can serve as proxies for civil conflicts such as number of internally displaced persons at lower geographies, e.g. municipalities, can be potentially invaluable source of information to improve assessment of risk and risk maps. Remote sensing from satellites has played an important role in facilitating understanding of how land use land-cover (LULC) changes relate to malaria, particularly in the Amazon [142, 143]. The methodology has been used to associate deforestation [144, 145] and the environment [146] with malaria and its
vectors. In a study conducted in Mancio Lima, Brazil, Olson et al. [144] showed through geographical and statistical analyses that a 4.3% change in deforestation in the county between 1997 and 2000 was associated with 48% rise in malaria incidence. Studies by Conn et al. [147] and Moreno et al. [148] suggests that human interference may foster the presence of An. marajoara while Vittor et al. [135, 145] observed that environmental changes may propagate spread of An. darlingi. Thus, small changes in forest cover can lead to major consequences and these changes can be assessed systematically through time using remote sensing from satellite and aircraft.

1.5. Specific aims and objectives

- **Aim 1:** Characterize and evaluate malaria risk in northern South America given changes in malaria and mosquito distribution using a data-driven method.
  - Hypothesis: Land-use and land cover changes and population expansion are associated with current and future distribution of malaria infection and vectors.

- **Aim 2:** Characterize risk of malaria transmission in northern South America based on environmental and climatic factors and examine local perceptions on the role of socio-economic/behavioral factors and malaria control in malaria elimination.
  - Hypothesis: Expert knowledge on the environment and malaria control strategies play a major role in depicting malaria risk and driving malaria elimination.

- **Aim 3:** Examine trends in malaria cases in parts of Colombia and factors which account for observed trend.
Hypothesis: Armed conflicts, and illicit extractive activities are associated with trends in malaria cases.

1.6. Dissertation outline

This dissertation investigates and presents the problem of risk in different ways and over a variety of time and space scales. In this first chapter, I highlighted the utility of risk mapping in strengthening vector control strategies and identified areas of incomplete knowledge in the literature. In Chapter 2, I address malaria risk from a data-driven modeling approach, and move to a representation of risk through the knowledge-driven modeling at broad scales in Chapter 3. In Chapter 4, I engage in a more specific assessment of trends using time series analysis and other statistical methods at more local scales. The final chapter compares and contrasts the results and produces an overall set of conclusions that reveal the contributions of the dissertation, policy implications, directions for future work as well as some of the limitations.
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Table 1.2. Some definitions of malaria risk and types of risk mapped

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Figure 1.1. Map of relative risk of exposure to malaria vectors derived from multi-criteria decision analysis (MCDA) guided by expert opinion (EO) in Colombia, parts of Ecuador, Venezuela, Peru and Brazil [65]. Areas in red denote high relative risk, areas in green, moderate risk, and the areas in blue low relative risk of malaria vector exposure.
Figure 1.2: Recommendations for locally tailored vector control using risk mapping methodologies
Chapter 2. Predicting potential ranges of primary malaria vectors and malaria in northern South America based on projected changes in climate, land cover and human population

2.1. Background

As more countries in Latin America experience economic growth brought about by increased external trade and natural resource exploitation [159], the continuous demand for land to accommodate growing infrastructural development, agricultural and livestock production, and frontier settlements, especially in the Amazon, is leading to rapid deforestation [144, 160]. Additional factors such as accelerated rate of internal migrations, expected global climate changes and population expansion [161] may influence the transmission of malaria and other vector-borne diseases [144, 145]. However, the direction of this influence is uncertain; vulnerability to malaria may increase if deforestation continues unabated, or the region could reach a tipping point and experience a major climate shift that may not favor vectors. This could occur as feedbacks between land cover and climate change in the Amazon may lead to rapid (decadal scale) changes within the climate of the Amazon basin itself. For example, recent studies point to the increasing effects of drought in the Amazon on species diversity, biomass, and fires, which appear to be linked to deforestation over the past 30 years [162]. Furthermore, future temperature changes and ecosystem alterations may impact malaria transmission by accelerating life cycles of parasites and mosquitoes [106, 163]. At present, our knowledge of both malaria and vector distribution in the region is incomplete [35] although there have been a number of efforts to model the distributions [22-24, 46-47, 150-153, 164]. Filling this knowledge gap would help to mitigate potential
obstacles to malaria elimination by lending new insights into how vectors and the disease are likely to shift given a business-as-usual scenario.

A number of attempts have been made to map malaria and vector distribution in the Americas. Global maps of *P. falciparum* and *P. vivax* endemicity generated by Gething *et al.* [46, 47] indicated that the nine countries in NSA have stable or unstable malaria risk, and the Americas account for 6% of the global at-risk population for *P. vivax* infection on 22% of global land area at risk. Previous efforts to map mosquito distributions in the Americas have involved multiple genera [150], or species [24, 151-153, 164] or have been based on single species [23] and at different geographic scales, ranging from continental or sub-continental [23-24, 150, 153] to national [22, 152]. Foley and colleagues [150] used geo-located museum specimen records to model mosquito species richness and endemicity in the Neotropics. By employing climatic and LULC information, Sinka *et al.* [24] mapped the distributions of dominant *Anopheles* in the region whereas an eco-regional approach for the Neotropics was used by Rubio-Palis and Zimmerman [151]. Fuller *et al.* [23] modeled the distribution of *An. albimanus* in the Mesoamerican and Caribbean basin based on climatic and topographic data. While some previous attempts have been criticized as lacking a sufficient number of occurrence records and simplicity of techniques used [24], more recent attempts have employed techniques modeling the realized niche or habitat suitability of species. Such studies have generally limited their evaluations of mosquito distribution to bioclimatic, topographic variables [24, 23], and LULC [24]. Moreover, with the exception of Fuller *et al.* [23], who modeled future distribution of *An. albimanus* by 2080, most studies that have focused on Neotropical vectors have limited their investigations to current distribution
patterns. However, the increasing availability of downscaled climate projections from General Circulation Models (GCMs) creates new opportunities to drive modeling techniques that can project future distributions as a function of climate as well as land cover.

Numerous approaches to model species distribution are available, including the presence-only maximum entropy method implemented through the modeling platform, Maxent [165, 166]. Although originally designed to model species habitat suitability, the maximum entropy approach to probabilistic modeling has applications well beyond species niche modeling. For example, some studies have used Maxent to project disease distributions such as dengue [167] and Chagas disease [168]. Thus, using models of this type, one may be able to visualize the current distribution of malaria and where it is likely to persist in the future or shift, and prioritize such areas for current eliminations efforts. In addition, by overlaying current and future distributions, one can visualize where malaria may be continuously problematic through time as a function of climate and land cover change. In this study I model the distribution of malaria, *An. darlingi*, and *An. nuneztovari* s.l. in NSA using bioclimatic, topographic, hydrologic, as well as LULC and population data using Maxent. The aims are to: (i) show the current spatial distribution and examine how the above factors may influence species habitat suitability in NSA and (ii) investigate the potential influence of changes in climate, LULC and population on future species range.

2.2. Methods

The study area comprises parts of Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname and Venezuela (Fig. 2.1), and includes all parts of the
Amazon rainforest. As outlined in Chapter 1, the area has the combination of socio-environmental and climatic conditions that favor the proliferation of vectors species and malaria.

### 2.2.1. Vectors and disease occurrence data

I obtained georeferenced point collection data with records of locations where both larvae and adult *An. darlingi* and *An. nuneztovari* s.l. were sampled (Fig. 2.1) through VectorMap [169] and the Global Biodiversity Information Facility [170]. These records were collected by different investigators between 1980 and 2007 and made available through an online spatial database, MosquitoMap [171]. I checked the downloaded data points, excluding those with high estimated spatial uncertainty and multiple entries. Additional sample locations of both species were gathered through field studies conducted in Colombia [172].

The Brazilian Amazon is the core area where the most malaria infections occur in the region [100]. I therefore obtained malaria incidence data comprising of both parasite species (~75% of all infections are caused by *P. vivax*) for Amazonas state in Brazil through SIVEP-Malaria (http://200.214.130.44/sivep_malaria/), the national official malaria database. The incidence data originated from passive case detection of patients who reported symptoms consistent with malaria and were cases confirmed using thick-blood smears as is currently the standard procedure in clinics in Brazil. However, I was unable to account for the treatment seeking rates in the area as a review of literature suggests that these are not well established for the Amazon as a whole.

These incidence data were originally aggregated by municipality and then converted to point data using a point-in-polygon analysis in ArcGIS ® [173] before being
used in the disease distribution modeling (Fig. 2.1). A population weighting was applied
to determine the location of each point representing a municipality, to ensure that the
distribution of points were influenced by population clusters rather than being randomly
situated in the center of the polygon. Bearing in mind that malaria is usually a rural
disease, away from the most densely populated areas, the weighting was carried out such
that the points were situated in the least densely populated areas. This was achieved by
first creating a fuzzy layer from the population density raster on the premise that
populations between 2 and 150 per square kilometer are sufficient for malaria
transmission. This fuzzy layer was then converted to points and a spatial join between the
points and the municipality polygons was subsequently implemented. The location of the
mean center of points was weighted by low population and interpolated from the
surrounding points within each municipality. Such weighting was particularly necessary
to mitigate limitations of the data. For instance, the aggregation of cases by municipality
gave no indication about the exact location of transmission or clustering of cases;
however, by locating the points based on population density, a point distribution was
achieved.

2.2.2. Environmental variables

I employed 23 environmental variables as possible explanatory factors in the
distribution models. Nineteen bioclimatic variables representing various measures of
temperature and precipitation were obtained from WorldClim [174]. This is a set of
interpolated global climate surfaces at ~1km spatial resolution [175]. The layers
representing current conditions (1950-2000) and future projections for 2050 and 2070
were collated. The future climate projection layers were chosen from two models from
the Intergovernmental Panel on Climate Change (IPCC) Fifth Assessment Report of 2014 [176] - the National Aeronautics and Space Agency (NASA) Goddard Institute for Space Studies (GISS-E2-R) models, and the Hadley Center (HadGEM2-AO ) models. The models were chosen because their representation of future predictions of precipitation and temperature in the study area were varied, potentially leading to a range of prediction scenarios. The NASA model generally predicted warmer temperatures compared to the Hadley model in the study area by 2050 and 2070. For precipitation, the Hadley model predicted much drier conditions around the Andes for both periods compared to the NASA models (see Fig. 2.2), and wetter conditions in parts of the Amazon, and the Atlantic coasts from southern Venezuela to southern Brazil. The NASA model on the other hand predicted higher precipitation in many patches in the Amazon. The climate surfaces were generated under four different greenhouse gas concentration trajectories called representative concentration pathways (RCP). For the analyses, I utilized the most conservative climate projections under the first, RCP 2.6, which assumes a peak in global annual greenhouse gas emissions between 2010-2020, after which emissions are expected to decline [177]. The scenario depicts mean global temperature increase of 10° C (range from 0.4 to 1.6) by mid-21st century (i.e. 2046-2065) [178].

To account for the altitudinal gradients in the area, which is an important consideration for mosquito and malaria dispersal, I obtained data on elevation from the Shuttle Radar Topographic Mission (SRTM) [179]. An additional factor, the topographic wetness index (TWI) was derived (equation 1) from this topographic information as a measure of soil moisture content especially in low elevation areas [180], providing an indication of potential vector breeding sites. These two layers were gridded to 1km
resolution to retain environmental heterogeneity and ensure data compatibility with other variables.

$$\ln \frac{a}{\tan b}$$  \hspace{1cm} (1)

where \(a\) is the upstream contributing area in m\(^2\), and \(b\) is the slope of the area.

The availability and distribution of human hosts as potential sources of blood meals for vectors was represented using population density layer for 2010 provided by the LandScan product [179]. Since environmental changes, whether natural or human-induced, play an important role in vector and malaria distribution [133], I included changing land use land cover (LULC) patterns in the analysis. The LULC data was derived from Moderate Resolution Imaging Spectrometer (MODIS) imagery for 2001 and 2010 [182], containing 17 LULC classes generated using the International Geosphere-Biosphere Program (IGBP) classification scheme. The IGBP classes were aggregated into two land cover classes for the land cover projection modeling: forest (containing all forest classes) and non-forested (containing all other classes excluding water bodies).

2.2.3. Predicting LULC and population changes

To adequately predict distributions of the vectors and malaria for 2050 and 2070, future LULC scenarios as well as population changes in the study area for the requisite periods were projected in Idrisi Selva [183]. The land change modeler (LCM) was used to estimate LULC changes. LCM is an application designed to model land conversion by using historical changes from land cover maps to project future land use change scenarios [184]. The process began with the introduction of land cover maps of the two time
periods, 2001 and 2010 to assess changes between them. By incorporating change drivers related to forest access such as distance from roads, water bodies [185], past deforestation [182], and elevation [179], land use transition potentials were produced. Probability of change (transition probabilities) between both time periods was quantified using the Markov transition matrix [116]. I assumed the transition probabilities remain unchanged over time, and used these to project future LULC scenarios for 2050 and 2070. LULC change was estimated using the Area module in Idrisi and each land cover map for 2010, 2050 and 2070 entered as a categorical variable in Maxent for the species distribution modeling for the respective time periods.

Population changes for 2050 and 2070 were predicted by applying an exponential population function (Equation 2) to the base population year, 2010. Using an average annual growth rate of 1.1% across the region [186], the projected population for the two time periods was estimated by the formula:

\[ P = P_0 \ e^{rt} \]  

(2)

where \( P \) = Estimated population, \( P_0 \) = Initial population, \( r \) = rate of natural increase, and \( t \) = number of years between \( P \) and \( P_0 \)

2.2.4. Modeling species and malaria distributions using maximum entropy

Maxent is a machine-learning method that estimates the distribution of a target by finding the distribution with the largest spread [187]. Maxent predicts species habitat suitability by incorporating its documented occurrence points with relevant environmental predictors in a defined geographic space [188, 189], subject to the constraint that the expected value of each predictor under this estimated distribution matches its empirical average [190]. The output is the relative habitat suitability
calculated by converting the exponential values of the raw estimates of suitability to logistic values [190].

All cleaned presence data for *An. darlingi* (n=271), *An. nuneztovari* s.l. (n=175) and Malaria (n=62) (Fig. 2.1) were used in the distribution models. Twenty-five percent of each of the datasets were randomly selected to independently assess the accuracy of each model while the rest were used for model training. The collection data used were suited for the analyses at ~1km resolution because the distance between the data points were relatively greater than 1km. The resolution was selected to be consistent with the highest resolution available for the environmental layers as has been used by other studies e.g., Drake and Beier, 2014 [191].

Due to a lack of absence data, a set of pseudo-absence (background) points were created for each species as Maxent determines habitat suitability by relating the values of predictors at presence points with those of randomly generated pseudo-absence points within the same area [192, 193]. Knowing that the number of pseudo-absences affects the models [24], I created multiple background points in ratios 1:1, 2:1, 5:1, and 10:1 to presence points for the vectors and evaluated the model results both visually (mapped distribution) and statistically (how well the area under the curve (AUC) improved). Based on the evaluation, the optimal ratio of background to presence points was 1:1 for the vectors while the default 10,000 background points in Maxent was optimal for malaria. To account for the inherent sampling bias in the presence data [189], bias files encompassing the area of study were created for each species to ensure that both the occurrence and pseudo-absence points had the same geographical bias [194]. I tested for multi-collinearity among pairs of predictors through a correlation matrix and excluded
one predictor in each pair that showed high correlation (Table 2.1) in the vector models. However all 23 predictors were used in the malaria model as AUC value improved when this was done.

Modeling was carried out by identifying the current niche suitability drivers from the current models and based on the assumption that all factors remained constant except a changing landscape, I applied these to the future scenarios. I used auto features for model generation, an option which allowed the set of features used to be determined by the number of presence points, using general empirically-derived rules. All modeling was performed using the subsample replicated run in Maxent v3.3.3k, the most current version of the software [195].

2.2.5. Assessing model performance

Various measures of model performance were used in the accuracy assessment. The model’s ability to discriminate between species presence and absence sites was measured using AUC [196]. Generally, models with AUC ≤ 0.5 are deemed to behave no better than random, while an AUC of 1 indicates a perfect fit between observed and predicted surfaces [197]. In practice, models with AUC above 0.75 are considered useful and results applicable [190]. Further assessment of model performance requires setting a threshold at which species habitat suitability can be converted to binary predictions of species presence or absence [198, 199]. While many threshold approaches are available, I chose the sensitivity-specificity equality approach that has been identified as one of the best performing thresholds [198]. The equal sensitivity-specificity threshold (ETSS) maximizes the absolute value of the difference between sensitivity and specificity [198, 200]. A good model is expected to accurately predict a high proportion of test sites by
having a low omission rate or high sensitivity [201]. However, because it possible for a model to have high sensitivity (low omission rate) just by predicting species presence in large parts of the area of interest, I evaluated the statistical significance of the omission rate obtained using the exact one-tailed binomial test (because of the small size of the test data) [202, 203]. The acceptability of the omission rate is determined by comparing the observed rate to theoretical expectations [204]. For instance, ideally in a model where the threshold is the 10th percentile presence, approximately 10 percent omission is theoretically expected. Omission rates higher than this value therefore indicate overfitting [204]. In this study, I used the ETSS as a threshold, therefore omission rates less than the ETSS value for each model are acceptable. Finally, because the AUC has been criticized as assessing the degree to which predictors can restrict species range rather than model performance [203, 205], I employed the true skill statistic (TSS) as a further test of model performance. The true skill statistic is the mean of net prediction success rate for presence and absence [91, 203]. Although TSS takes into account omission and commission errors, it avoids reliance on prevalence or size of validation set, and is thus a good measure of predictive accuracy of presence-only models [205]. TSS values also range from 0 to 1, with values >0.6 considered good, >0.7 very good [206].

2.3. Results

2.3.1. LULC changes

The LCM outputs for LULC changes in 2050 and 2070 are presented in Fig. 2.3. The maps indicate that at current rates of deforestation, large parts of the Amazon forest, particularly in the interior and the South would be lost by the mid-century, assuming a business-as-usual scenario in which deforestation progresses at approximately the same
rate as over the past decade. Most of the loss is expected along transportation routes (roads and rivers) as the interior opens up to urbanization and infrastructural developments. Forest loss would also increase in the South, particularly in Beni and Santa Cruz (Bolivia), Mato Grosso, Rondônia, Pará, Maranhão and Tocantins (in Brazil, particularly due to soy plantations), along the coasts of Guyana, French Guiana and Suriname. Non-forest areas, such as the savanna between Roraima (Brazil) and Bolívar (Venezuela) are also expected to expand by 2050 and 2070. While the results are similar to those previously published [207], I advise caution in the interpretation as the change pattern in the interior closely follows the drivers of LULC change I employed.

Altogether, the forecast indicates an estimated 780,000 km² of forests (12% of 2010 forest extent) would be lost area by 2070 (Table 2.2), a development that may have an impact on vector and malaria distribution in the region.

2.3.2. Habitat suitability modeled using current conditions

Predictive maps of habitat suitability using current conditions are presented in Fig. 2.4. For malaria, areas of relatively high habitat suitability (high = 0.5- 0.75; very high $0.75-1$) are predicted within the interior of the Amazon in Brazil, along the coasts of the Guianas, along the Pacific coast of Colombia and in western Venezuela, covering a total land area of about 672,000km². Zones of moderate habitat suitability (0.25-0.5) are predicted in the Amazonian regions of Peru, Bolivia and Colombia while the rest of the study area, including the Andes and the Brazilian highlands have low habitat suitability (< 0.25). Elevation was the biggest contributor to the model (45.6%), followed by precipitation of the driest quarter (16.3%), mean temperature of the coldest month (12.9%) and precipitation of the driest month (9%). Population (0.1%) and LULC (0.2%)
did not contribute to the model (Fig 2.5 for response curves and jackknife of variable importance). The model had excellent discriminatory power as indicated by the test AUC (0.90) (Table 2.1). The mean values of the test points and ETSS were relatively moderate, as was the omission rate showing that a reasonable proportion of the test sites were correctly predicted. The reported TSS value of 0.57 also indicated fair model performance.

Model results for *An. nuneztovari* s.l. show areas of relatively high habitat suitability along the coast of Ecuador, the Pacific coast and the Llanos of Colombia, western Venezuela, the coasts in the Guiana Shield, and the states of Pará, Mato Grosso and Amazonas in Brazil, occupying about 460,000 km² of land area. Relatively moderate to low (<0.5) suitability are shown in other parts of Colombia, Peru, Bolivia, Venezuela and the rest of Brazil. As expected, the presence of this vector is not predicted in the Andes where high altitudes are associated with freezing temperatures that kill eggs juvenile forms, and adults. Elevation was the most important predictor for this species (33.4%), followed closely by temperature seasonality (30%) and annual precipitation (13.9%). Population (8.7%) and LULC (4.4%) also contributed marginally to the model (Response curves in Fig. 2.6). The surface depicting *An. nuneztovari* s.l. habitat suitability (Fig. 2.4) clearly distinguished between presence and absence sites (AUC=0.79), had a good TSS value (0.68) and a moderate omission rate (0.30) (Table 2.1).

The model indicated relatively high suitability for *An. darlingi* in areas such as the interior of Ecuador, the Pacific and Caribbean coasts of Colombia, the Llanos, western and coastal Venezuela, the coasts of the Guianas, the Amazonian states in Brazil and
Loreto in Peru, an area of approximately 920,000 km². Moderate suitability was predicted in the other parts of the study area except the Andean mountains, the Brazilian Highlands and a few patches within the Amazon where probabilities are low. Elevation alone accounted for 53.3% of the model while annual precipitation (18.4%) and population (11%) were the next biggest contributors. Precipitation seasonality (7.9%) was a marginal contributor whereas LULC did not influence the model (Fig. 2.7). This suggests a limitation of the Maxent model rather than lack of influence from land cover and land use, as Fuller et al. [116] found that Maxent sometimes produced unrealistic results when categorical land cover maps were used as covariates. This model had fair discriminatory power (AUC=0.75), a fair TSS value (0.58) and moderate omission rate.

2.3.3. Habitat suitability modeled using predicted future conditions

2.3.3.1. Malaria

Figure 2.8 reveals the projected distributions for malaria in the years 2050 and 2070 using the NASA and Hadley center climate models. As shown, the foci of malaria are expected to remain in the interior of the Amazon, along the coasts in the Guiana Shield, in northern Colombia and along the southern border of Colombia and Venezuela. Moderate habitat suitability (0.25-0.5) was predicted mostly around North-western Brazil, eastern Peru and South-western Colombia in the NASA model while the Hadley model prediction included more regions in the Amazon and Bolivia. However, total land area of suitability is expected to decrease compared with current distributions, except with the 2050 Hadley model. By 2050, the NASA model predicts a 28% reduction in suitable area whereas a 3% increase is estimated from the Hadley center model.
By 2070 however, the area occupied by the disease is expected to have decreased by 6% and 17% according to the Hadley and NASA models, respectively, compared with the current distribution. The NASA model is less conservative, predicting lesser areas of malaria presence by 2050 and 2070, but bigger changes. When the gains and losses in each habitat suitability category were analyzed for the future predictions (see Fig. 2.9), only areas of low suitability reduced in area (~129,000km²) between 2050 and 2070 whereas the other categories gained in the NASA model. With the Hadley model, areas of low and very high suitability increased in area (~33,000km² and 27,000km² respectively) while medium and high suitability had losses. The full cross-tabulation of current and future distributions of malaria is presented in (Fig. 2.10). Maxent predicted a range contraction within the Amazon, along the coast of Guyana, Antioquia and Chocó in Colombia, and around the northern border between Colombia and Venezuela. Range expansion was predicted around the border regions of Brazil, Colombia and Peru and in south-east Colombia in the northwest Amazon.

2.3.3.2. *Anopheles nuneztovari* s.l.

Areas of relatively high habitat suitability for *An. nuneztovari* s.l. are predicted along rivers in the Amazon, the coasts in the eastern part of the study area, and in patches in Venezuela and Colombia from both models for 2050 (Fig. 2.11). Most of the Amazon, eastern Brazil and middle belt of Colombia and Venezuela have moderate probabilities of vector presence. Both the Hadley and NASA models forecast a 5% and 20% increase in range respectively by 2050. It is noteworthy that though the species was mostly absent around the Andes with current conditions, its presence in this area is predicted by 2050. The range is expected to increase by 14% in 2070 according to the Hadley model.
whereas a 10% increase is projected by NASA model. During this period, the Llanos, southern Colombia, eastern Peru, Pacific and Caribbean coasts of Colombia and large parts of the Amazon have medium predicted probabilities as estimated by the Hadley model whereas most of the Llanos are excluded in the NASA model.

As with the malaria model, only areas of low suitability in the NASA model decreased in size (~232,100km$^2$) when gains and losses were analyzed between the 2050 and 2070 models. On the other hand, moderate and high suitability areas gained, while low and very high suitability areas lost in the Hadley model for the same period (Fig. 2.9). An. nuneztovari s.l. range is shown to expand in the Amazon interior possibly along transportation routes, and along the coast in the Guianas according to NASA model (see Fig. 2.12). A similar pattern is observed along the coast in the Hadley model with additional areas in parts of Brazil and at the border of Venezuela and Colombia. Range contraction is mostly expected around Pará in Brazil, along the Pacific coast of Ecuador and Colombia, and in northern Colombia by both periods.

2.3.3.3. Anopheles darlingi

Most parts of the study area are expected to remain favorable to An. darlingi presence by 2050 and 2070 according to model predictions (Fig. 2.13). Areas of relatively high suitability are mostly found along the coasts in Ecuador, Colombia, the Guianas and Brazil. Other patches are in the Amazonian regions of Colombia, Peru and Brazil whereas moderate suitability was estimated mainly in the Amazon, Venezuela and the Guianas. While the Hadley model predicts a slight reduction in land area by 2050 and 2070, the NASA model estimates no decline in range by 2050 but a 3% increase by 2070.
Again, areas of moderate, high and very high suitability gained in area between 2050 and 2070 in the NASA model whereas only low suitability areas (~107,000km²) gained in the Hadley model for same period (see Fig. 2.9). Range contraction is predicted for *An. darlingi* in patches around Rondônia, the Amazon states in Brazil, Colombia and Peru, and Apure and Bolívar in Venezuela (Fig. 2.14). Expansion is expected in a few areas around Bolivia, Brazil, Colombia and the Guianas.

### 2.4. Discussion

This study is unique in that it investigates the influence of climate, LULC and population changes on potential distributions of the malaria parasites, *An. darlingi*, and *An. nuneztovari* s.l. in NSA. I applied the presence-only Maxent model to project the current and future spatial distribution of malaria parasites and mosquito vector species, highlighting the potential environmental drivers of changes in their ranges. The relatively moderate-to-high AUC values for *An. darlingi*, malaria and *An. nuneztovari* s.l. respectively not only reveal the model’s ability to distinguish presence and absence sites [196], but also the higher chance of occurrence points being given relatively higher probabilities of presence compared to pseudo-absence points [193]. The TSS values reported also indicate that the models were fairly accurate in predicting the presence and absence of the species by keeping false positives and negatives to a minimum [203]. When the ability of the models to predict test sites was evaluated, they were relatively sensitive with significantly moderate omission rates, indicating that many of the test points fall into areas predicted present by the models [201, 202], even as the mean probabilities of the test points were moderate as well.
The maps produced based on current conditions for both vectors and malaria parasites to a large extent agree with other studies. The modeled potential distribution of *An. darlingi* and *An. nuneztovari* s.l. are consistent with previously published work by Sinka *et al.* [24], except for areas of slight divergence around the Brazilian Highlands, and parts of the Andes and the Pacific coast in Ecuador and Colombia for *An. darlingi* and *An. nuneztovari* s.l. The malaria map differs from earlier published extent of endemicity by Gething *et al.* [46, 47] mostly because the malaria occurrence points are from one state within the Amazon and combine both parasites. However, the model accurately predicts core areas of high malaria incidence within the sub-region where control efforts should be focused. Moreover, current malaria interventions such as vector control were not considered in the model development. Thus, taking into account the possibility of anophelism without malaria (i.e. the occurrence of *Anopheles* vectors in an area/region without malaria [81, 208] as was discovered in Europe for the species complex, *An. maculipennis* [209] and may be the case with *An. nuneztovari* species complex in the Brazilian Amazon [210]), it is highly plausible that the actual extent of malaria is limited to areas of known incidence in the region, rather than where vectors may be found. Moreover, a map depicting probability of vector presence does not necessarily imply risk of the parasites it transmits [81].

When projected on future climatic and human-induced changes, model simulations generally showed a decrease in malaria extent by 2050 and 2070. The areas of range contraction for malaria (in Brazil, Guyana and Colombia) in particular bolster optimism as these are currently the localities with some of the highest malaria incidence in the region [106, 211-212]. These results are especially informative when considering
the renewed drive towards malaria elimination in the region [104]. Although the areal extent for the vectors are projected to increase, the decrease in malaria extent despite this implies that the interplay of climatic, population and local land use patterns brought about by urban development can naturally force a decline in malaria incidence [191]. For example, development may lead to lower malaria as more infrastructure and better living conditions become available, while climate change and deforestation produce range expansion of vectors. The spatial extent of malaria may decrease even further as principles of integrated vector management (IVM) become more entrenched in vector control programs [20], surveillance and monitoring are sustained, more efficient and effective drugs and vector control measures become available, and malaria treatment become more accessible [35]. Elimination in this region by 2050 may be feasible as strategies outlined by Feacham [213], such as development of new drugs, vaccines, and insecticides and strengthening national and regional collaborations are executed. Unsurprisingly, measures of precipitation and temperature as well as elevation were the highest predictors of malaria in the region as found in several previous studies [214-216]. The impacts are especially important as other studies have shown that climate change may lead to warmer and drier conditions, which may aid mosquito and parasite development provided the climate does not become so arid that breeding locations disappear, and thus potentially increase malaria risk, even in highland areas [134].

Future projections reveal a modest increase for An. darlingi and a slightly larger range expansion for An. nuneztovari s.l. by 2050 and 2070. The areas of range expansion and contraction for both species are likely to be influenced by human activities as more parts of the Amazon become urbanized, infrastructural projects increase [106] and gold
mining continues [217]. This is especially important as change in LULC was a predictor for An. nuneztovari s.l., consistent with earlier reports of the species colonizing altered environments and being associated with deforestation [212, 218-221]. Surprisingly, LULC was not a predictor for An. darlingi in the models despite numerous studies indicating a correlation between the species and land cover or deforestation [106, 134-135, 212, 218-221]. Population density was shown as an important predictor for An. darlingi and a marginal predictor for An. nuneztovari s.l., consistent with their known behavior [135, 145] and that of other species such as Culex pipiens [193]. Elevation was the most important predictor of both species and malaria for all models. Such a result was expected considering that recent studies have reported some other mosquito species at higher altitudes than regularly found, for example in Ecuador [222] and projected for parts of Mesoamerica in 2080 [23]. Moreover, malaria has been reported in highland areas of Bolivia [223] and some East-African countries [214, 224-225], so vectors must be present for transmission. Finally, the results are in agreement with the current understanding of climate interaction with mosquitoes; i.e. temperature and precipitation were major contributors to the projected vector distributions for all climate scenarios. This is supported by other studies that have established associations between temperature, precipitation and both An. darlingi and An. nuneztovari s.l. [24, 107, 212]. These variables have also been linked to other Anopheles species [214, 226-228], and to An. albimanus [23] and An. arabiensis [116, 206] in future periods.
**Table 2.1** MaxEnt models validation parameters evaluated using test points

<table>
<thead>
<tr>
<th>Species</th>
<th>Time/ Model</th>
<th>Parameters in model</th>
<th>Training AUC</th>
<th>Test AUC</th>
<th>Mean [sd]</th>
<th>ETSS</th>
<th>Omission rate*</th>
<th>TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Current</td>
<td>23</td>
<td>0.93</td>
<td>0.9</td>
<td>0.53 {0.23}</td>
<td>0.271</td>
<td>0.25</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>2050 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.49 {0.16}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2050 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.46 {0.18}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.46 {0.17}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.45 {0.19}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>An. darlingi</em></td>
<td>Current</td>
<td>13</td>
<td>0.77</td>
<td>0.75</td>
<td>0.51 {0.12}</td>
<td>0.463</td>
<td>0.34</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>2050 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.51 {0.14}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2050 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.50 {0.13}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.50 {0.13}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.50 {0.13}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>An. nuneztovari</em> s.l.*</td>
<td>Current</td>
<td>0.8</td>
<td>0.79</td>
<td></td>
<td>0.53 {0.14}</td>
<td>0.492</td>
<td>0.3</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>2050 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.53 {0.12}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2050 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.55 {0.10}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (Hadley)</td>
<td></td>
<td></td>
<td></td>
<td>0.54 {0.11}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2070 (NASA)</td>
<td></td>
<td></td>
<td></td>
<td>0.53 {0.13}</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Significant at p<0.001

1 Excluded parameters with high correlation to avoid over-fitting

2 Estimated using 12, 65 and 44 test and background points each for Malaria, *An. darlingi* and *An. nuneztovari* respectively
Table 2.2 Summary statistics of projected changes in LULC

<table>
<thead>
<tr>
<th>Year</th>
<th>Category (Km²)</th>
<th>Period</th>
<th>Change (Km²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Forested</td>
<td>Deforested</td>
</tr>
<tr>
<td>2010</td>
<td>6432680</td>
<td>5903650</td>
<td>2010-2050</td>
</tr>
<tr>
<td>2050</td>
<td>5733205</td>
<td>6603125</td>
<td>2010-2070</td>
</tr>
<tr>
<td>2070</td>
<td>5655415</td>
<td>6680915</td>
<td>2050-2070</td>
</tr>
</tbody>
</table>
Figure 2.1. *An. darlingi*, *An. nuneztovari* s.l. and malaria sample locations. Malaria cases by municipality in Amazonas state of Brazil were converted to population-weighted points representing each municipality.
Figure 2.2. Differences in annual precipitation between current and future conditions. NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right)
Figure 2.3. Projected LULC changes obtained using LCM: 2010 (top panel), 2050 (middle panel), and 2070 (bottom panel)
Figure 2.4. Habitat suitability for Malaria (top left), An. nuneztovari s.l. (top right), and An. darlingi (bottom panel) modeled using current bioclimatic conditions, population, LULC, elevation and TWI.
Figure 2.5. Response curves of Malaria model to: (A) Elevation (srtm); (B) Precipitation of the driest quarter (bio 17); (C) Mean temperature of the coldest month (bio 6); (D) Precipitation of the driest month (bio 14); and (E) Jacknife of variable importance (Red bar shows the gain when all variables are used. The light blue bar shows the gain when a specific variable is excluded from analysis, a lower gain indicating that the specific variable has more information not contained in other variables. The dark blue bar indicates gain when the specific variable is used in isolation)
Figure 2.6. Response curves of *An. nuneztovari* model to: (A) Elevation (srtm); (B) Temperature seasonality (bio 4); (C) Annual precipitation (bio 12); (D) Population; (E) LULC; and (F) Jacknife of variable importance (Red bar shows the gain when all variables are used. The light blue bar shows the gain when a specific variable is excluded from analysis, a lower gain indicating that the specific variable has more information not contained in other variables. The dark blue bar indicates gain when the specific variable is used in isolation)
**Figure 2.7.** Response curves of *An. darlingi* model to: (A) Elevation (srtm); (B) Annual precipitation (bio 12); (C) Population; (D) Precipitation seasonality (bio 15); and (E) Jacknife of variable importance (Red bar shows the gain when all variables are used. The light blue bar shows the gain when a specific variable is excluded from analysis, a lower gain indicating that the specific variable has more information not contained in other variables. The dark blue bar indicates gain when the specific variable is used in isolation).
Figure 2.8. Habitat suitability for malaria modeled using future climate, population and LULC: NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right)
Figure 2.9. Analysis of gains and losses in area between 2050 and 2070 models. From left to right: Malaria (NASA (top), Hadley (bottom)), *An. darlingi* (NASA (top), Hadley (bottom)), *An. nuneztovari* (NASA (top), Hadley (bottom))
Figure 2.10. Cross-tabulation of present and future distribution to show likely shifts in Malaria habitat suitability: NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right)
Figure 2.11. Habitat suitability for *An. nuneztovari* s.l. modeled using future climate, population and LULC: NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right).
Figure 2.12. Cross-tabulation of present and future distribution to show likely shifts in *An. nuneztovari s.l.* habitat suitability: NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right)
Figure 2.13. Habitat suitability for *An. darlingi* modeled using future climate, population and LULC: NASA 2050 (top left), 2070 (bottom left) and Hadley 2050 (top right), 2070 (bottom right)
Figure 2.14. Cross-tabulation of present and future distribution to show likely shifts in *An. darlingi* habitat suitability: NASA 2050 (top left), 2070 (bottom left) and Hadley2050 (top right), 2070 (bottom right)
Chapter 3. A multi-criteria decision analysis approach to assessing malaria risk in northern South America and local perceptions of the impact of current malaria control and socio-economic/behavioral factors on malaria elimination strategies

3.1. Background

Global efforts to eliminate malaria such as the Roll Back Malaria program aim to “shrink the malaria map by progressively eliminating malaria from endemic margins inward” [17]. Achieving malaria elimination in the NSA, as in other region, will involve the systematic and synergistic use of multiple strategies including targeting areas for malaria interventions based on a stratification of risk as well as incorporating expert local knowledge of the efficacy of control strategies. Such knowledge may provide an understanding of experts’ opinions and perceptions regarding current risk and elimination strategies for malaria in the region and aid decision-making. Moreover, spatially accurate, high-resolution risk maps delimiting areas of likely human-vector contact would not only help prioritize areas for malaria intervention, but also aid monitoring and evaluation of such interventions [83].

The stratification of risk depends on how risk is defined, yet there is currently no standard definition. Risk definitions have been dependent on the subject matter or purpose of the investigation [81]. Malaria risk is broadly considered as an array of factors that relate to the presence and density of vectors and parasites, all of which vary in space and time. The direct estimation of malaria risk often involves malaria diagnosis and its relationship to populations at risk [229], but periodic, field-based survey data are typically limited in space and time in developing countries. Alternatively, in areas with
limited data, malaria risk may be estimated indirectly through environmental covariates, which often show strong associations with malaria and mosquito distributions. The combination of these environmental surrogates in GIS decision-support algorithms can reveal unexpected spatial patterns of malaria risk at unprecedented spatial resolutions [83]. Many types of spatial data derived from remotely sensed observations such as digital elevation models from the Shuttle Radar Topography Mission (SRTM) are now publicly available for most parts of the world, thus facilitating the potential estimation of malaria risk across large areas across multiple political units [83].

One method of mapping disease risk with limited field-based epidemiological or vector data is multi-criteria decision analysis (MCDA). This approach is preferred for its participatory framework, which employs statistical methods and human intuition, allows expert interaction, and accommodates non-linear relationships common between disease organisms and the environment [18, 27]. MCDA allows the combination of multiple environmental factors in estimating disease risk by employing decision rules derived from existing knowledge or hypothesized understanding of the causal relationships leading to disease occurrence [27, 83]. The output is a composite map that indicates lower or higher potential of disease occurrence in a location relative to surrounding areas on the same map [230]. MCDA has been useful in assessing risk of vector-borne diseases such as predicting suitable areas for rift valley fever in Africa [231], prioritizing areas of tsetse fly control in Zambia [232], malaria vector control in Madagascar [233] and risk of malaria vector exposure in parts of South America [83]. I set out in this study to (i) evaluate malaria risk in the NSA based on environmental factors to produce risk maps that could guide targeted malaria interventions and potentially accelerate the drive
towards malaria elimination; and (ii) examine experts’ perceptions of strategies needed for malaria elimination in the region.

3.2. Methods

3.2.1. Data sources

3.2.1.1. Mosquito data

Sample locations for both parasite species were obtained through the Malaria Atlas Project (MAP) website. The data comprises surveys conducted by researchers and organizations between 1985 and 2009 in the various countries. Downloaded data also contained geo-referenced location of cases, the diagnostic method used for detection, age, the number of individuals examined, and number of individuals with parasites in the blood. Similar georeferenced data (Fig. 2.1) for the 3 vector species were obtained through the Walter Reed Biosystematic Unit [234] and the Global Biodiversity Information Facility [170]. These records included locations where both larvae and adult *An. darlingi*, *An. albimanus* and *An. nuneztovari s.l* had been sampled by different investigators between 1980 and 2007.

3.2.1.2. Variable selections

Nine parameters associated with the environment, including climate were chosen based on their association with malaria and its vectors (Table 3.1). These included factors related to availability of vector breeding sites (wetlands, precipitation and topographic wetness index -TWI, which was derived from the digital elevation model), thermal and altitudinal limits for parasites and vectors (elevation and temperature), and access to blood meals (population density, roads, urban areas and deforestation).
3.2.2. Procedure

3.2.2.1. Risk map generation

Two data layers (elevation and TWI) were resampled to 1km spatial resolution to maintain consistency with the other layers originally provided at 1km. Resampling was carried out using the nearest neighbor algorithm, which preserves original data values. A binary discrete raster was created from the elevation layer to serve as a constraint, excluding areas with elevation >1800m where risk of transmission was assumed to be negligible [83]. Because the influence of categorical variables on risk of malaria and vector exposure was based on access (Table 3.2), I created distance layers measuring proximity to the features before further analyses.

The data layers contained variably scaled information; hence, fuzzy functions were employed to standardize all the layers to a common data range needed to facilitate factor integration. Fuzzy functions measure the degree of membership of data cells in a layer through control points that are set based on the relationship between the layer and disease/vectors. These relationships determine the shape (linear, sigmoidal or J-shaped) and direction (increasing, decreasing or symmetric) of the fuzzy function (See Table 3.1), which were represented on an 8-bit (0-255) scale in the analysis. For instance, I used a linear decreasing function to scale risk associated with access to blood meals such as deforestation by assuming highest risk when close and no risk when more than 5 km away from the feature.

Prior to use in the MCDA, each fuzzy layer was assigned a weight indicating its importance in the risk assessment. To facilitate the process of weighting, the nine factors were combined into two logical groups: (i) access-related factors relying on distance/
proximity to features; and (ii) environment/climate related factors (Table 3.2). Weights were subsequently assigned in four ways: (i) by weighing all factors equally; (ii) assigning higher weights to access-related variables; (iii) scaling environment/climate related factors higher (approximately three-quarters of total weights assigned to group of factors with higher weighting in each case); and (iv) assigning weights based on interaction between factors and disease/vectors using the analytical hierarchical process (AHP). The AHP assigns weights to each factor by assessing the relative importance of factor pairs in a pairwise matrix [237]. Pair comparisons were conducted by evaluating the importance of each factor relative to the other in a pair and assigning values ranging from 1 (extremely less important) to 9 (extremely more important). Evaluation for 6 of the factors were carried out by a group of malaria experts in a risk mapping workshop in Cali, Colombia (details of procedure published elsewhere [83]). The ranking of the other 3 factors was based on literature searches by which I determined that temperature, precipitation, and deforestation be ranked in descending order [236]. The principal eigenvector was subsequently used to determine the final weight of each factor. The consistency of the pairwise matrix was evaluated using a threshold of 0.1, a ratio above which the pairwise matrix should be revised while values below indicate acceptable consistency [237]. Table 3.2 shows all factor weights assigned using the AHP and the other methods.

Finally, the multi-criteria evaluation (MCE) module was used to integrate all data layers to create composite risk maps for the study area. A number of user-specified options exist in the MCE module for this purpose but for the analysis, I chose the weighted linear combination (WLC). The WLC is a linear function which combines
fuzzy layers according to their weight of importance (all factor weights add up to 1) [83, 238, 239], producing final composite maps of risk based on the four weighting methods. All analyses were conducted using the raster-based GIS software, Idrisi (Selva edition) [239].

3.2.2.2. Assessment of risk maps from sample points

Resulting risk maps were evaluated by comparing differences in mean risk scores between randomly generated points (n=1502) and the risk scores at the sample locations of *An. darlingi* (n=168), *An. albimanus* (n=38), *An. nuneztovari* s.l. (n=114) and malaria cases (n=218) respectively. Assuming normal distribution, differences between the mean risk scores for each vector and malaria occurrence points and random control points were assessed using unpaired *t*-test. A one-way analysis of variance (ANOVA) was used to compare the means of the four groups of sample points. Both statistical analyses were performed in SPSS v. 21 software [240]. Spatial autocorrelation of the sample points was tested using the Moran’s *I* statistic in ArcGIS 10.2 software [173]. Moran’s *I* tests the null hypothesis that the attribute of the feature of interest is randomly distributed where a statistically significant Z-score indicates spatial autocorrelation. To correct autocorrelation found in sample points, I systematically excluded points until arriving at a distribution that was spatially independent.

3.2.2.3. Eliciting expert opinions

Forty-four malaria scientists and health practitioners from nine countries participated in a three-day malaria risk mapping workshop (see Table 3.3). The GIS workshop was part of the 3rd Symposium on “Perspectives on Malaria Elimination in Latin America”, held in Cali, Colombia, in August 2014. The workshop was designed
primarily to teach participants how to employ GIS mapping capabilities in modelling malaria risk. It was also a forum to elicit expert opinions on the relative importance of various malaria control strategies and socio-economic factors and how they influence the drive towards malaria elimination in the region. A workshop participatory method was chosen because it is an ideal forum for convening experts, but more so because past studies have shown that data elicited help identify the breadth and range of public values which could be used in a planning process [241].

The variables presented to the experts comprised of current WHO approved interventions for malaria control and management including vector control tools, diagnostic tests anti-malaria drug administration (Fig. 3.1). Also included were socio-economic, political and behavioral factors known to be associated with malaria [232]. Expert opinion was sought so as to incorporate local knowledge of the role of socio-economic and behavioral factors and the efficacy of current malaria control strategies based on on-going field investigations in the analysis [62, 83]. Following Saaty’s AHP approach [237], factor pairs were presented to the participants, who were asked to evaluate the importance of each factor for effective malaria control relative to the other in a pair. The AHP approach reduces complex decisions to a series of pairwise comparisons, helping decision makers in setting priorities and making the best decisions from a set of objective and subjective variables [18, 237]. This approach was utilized because it is easily understood by both decision-makers and modelers and easily implemented [18]. The experts assigned values ranging from 1 to 9 as previously described (see section 3.2.2.1.) in a pairwise matrix within the AHP, and the principal eigenvector was subsequently used to determine the final weight of each factor. Thus, by employing this
procedure, we arrived at a scale of preference among the available set of alternatives based on the experts’ opinions [18].

3.3. Results

3.3.1. Malaria risk distribution

The composite maps of risk produced using the four weighting methods are presented in Figure 3.2A-D. In Fig. 3.2A, the risk map was produced by assigning an equal weight of 0.11 to each of the twelve factors. The composite layer in Fig. 3.2B included all the factors weighted through AHP. All five access-related factors in Fig. 3.2C were assigned equal weights, which summed up to 0.7, thus giving access-related factors a higher weighting than environment-related factors which had a total of 0.3. For Fig. 3.2D these weightings were reversed; the four environment-related factors were given a cumulative value of 0.7 while access-related factors were assigned a total of 0.3.

The various maps reveal noticeable differences in the level and distribution of risk. For instance, the distribution of risk in Fig. 3.2C is more heterogeneous compared to the other maps. In this composite layer, the Amazonian areas of Brazil, Venezuela, Colombia, the Guianas, and Peru, as well as southern Brazil and areas on the fringes of the Andes display low risk scores relative to areas outside the Amazon basin. The relatively higher weight given to access-related factors may account for this distribution particularly in the Amazon, as the area is associated with low population density and limited access via roads and rivers, hence the lower imputed risk. Areas of relatively moderate to high risk on this map were found mostly along stretches of rivers in the Amazon basin, along the coasts of the Guianas, in the seasonally flooded wetlands
around the Llanos, in patches around south-western Brazil, in areas west of the Andes in Peru and Bolivia, along the coasts of Ecuador and Colombia, and in northern Colombia.

The areas delineated as moderate to high risk locations in Fig. 3.2C are common to all the maps; however, additional areas of high risk are highlighted in the other maps. Contrary to what was shown in Fig. 3.2C, the Amazon forest had elevated risk of transmission, particularly in the AHP guided map (Fig. 3.2B), which displays moderate risk relative to the other maps. In the equally weighted map (Fig. 3.2A), moderate to low risk can be seen especially throughout the Amazon basin, Southern Venezuela, and central Brazil. Although the AHP and the environment-related maps (Fig. 3.2B and 3.3D respectively) appear similar because the total weight assigned to environmental factors in both maps was similar (0.6221 and 0.7 respectively), differences in the maps are evident. High risk areas in Fig. 3.2B are displayed along the rivers in the Amazon basin, the wetlands, and along the coasts in the study area whereas risk is depicted in a spatially homogeneous fashion in Fig. 3.2D. Overall, similar areas of low risk are displayed in central Brazil, southern Venezuela and the Andean fringe while the high risk areas identified in all the maps are consistent with current understanding of malaria risk in the region [27, 35].

3.3.2. Validation of risk maps from sample points

The test for spatial autocorrelation showed that vector occurrence points for An. darlingi (Moran’s $I = 0.036$, $z= 0.07$, $p = 0.94$) and An. albimanus (Moran’s $I = 0.458$, $z= 0.68$, $p = 0.39$) were spatially random within the study area. Autocorrelation was detected in An. nuneztovari s.l (Moran’s $I = 0.758$, $z= 2.902$, $p = 0.03$) and malaria (Moran’s $I = 747$, $z= 8.632$, $p = 0.00$) occurrence points. The $z$-scores however remained significant
after systematically reducing the number of sample points (n= 90 and 172 for An. nuneztovari s.l and malaria respectively), thus suggesting that spatial dependence did not significantly influence results. Figure 3.3 shows the means from the MCE risk maps for the validation points. The $t$-test results indicated that mean cell-level risk scores at the occurrence locations were significantly different and higher ($p<0.0001$) than risk scores of the random points (Table 3.4). Output from the one-way ANOVA test performed on 467 observations (Table 3.4: between and within group df) showed no significant difference in mean risk scores among occurrence points, suggesting that the occurrence points may be pooled into a single sample. Further analysis with $t$-test indicated that the pooled vector points were significantly different and higher ($p<0.0001$) than randomly distributed points (Table 3.4).

3.3.3. Ranking of strategies based on experts’ perceptions

Analysis of the relative importance of factors (related to mosquitoes and people) in accelerating the steps towards malaria elimination in the region showed that socio-economic/behavioral factors were highly ranked. Public education, propagated through community engagement was ranked the most important strategy (Table 3.5). Involvement in outdoor occupations such as agriculture, mining, fishery and forestry, as well as occupational risk (i.e. ratio of male-to-female inhabitants in the municipalities) were also ranked as important factors influencing malaria control. This is because these activities involve continuous outdoor exposure, increasing the chances of being bitten by mosquitoes, without recourse to vector control tools such as bed nets. Others include reducing mosquito breeding sites through environmental management, the population density, level of education, internal displacement. Surprisingly, income, housing quality
and corruption in the government were not highly ranked among the variables. On the other hand, of the current malaria control strategies used in the region, artemisinin combination therapies (ACTs), rapid diagnostic tests (RDT) and distribution of bed nets were ranked as highly effective. This is probably because antimalarial drugs are more available and promptly administered to patients, the range of diagnostic testing and reporting in the past decade has expanded, and relatively more at-risk populations have access to bed nets [5, 30, 31].

3.4. Discussion

3.4.1. Spatial distribution of vector exposure and malaria risk

Using publicly available environmental, vector, and case data, this study elucidates the spatial distribution of malaria and potential vector exposure risk and provides important spatial information that may guide targeted malaria interventions in the region. Although the environmental parameters typically change very little or gradually over time [83], the inclusion of a deforestation measure reflects a highly dynamic landscape variable that is strongly associated with malaria risk. This is exemplified in the four composite maps, which show most areas in the Amazon and southern Brazil where deforestation has been most pronounced in the past decade [242] as having moderate-to-high risk of malaria.

Although there are common areas with moderate to high risk on all four maps, there are also areas of model over-estimation. While the risk surface in Fig. 3.2B aligns relatively well with known malaria risk [35, 85], the result of the access-related grouping is similar to that produced by Fuller et al. [83] for parts of the study area. Overall, based on Figs 3.2 and 3.3, A and C provide a more realistic depiction of risk; however, it should
be noted that malaria transmission does not occur along the Atlantic Coast of Brazil south of the Amazon basin; therefore, what the maps depict is more likely a better representation of risk of vector exposure than actually malaria transmission. Risk was however over-estimated in all four maps in areas around central and along the Atlantic Coast of Brazil south of the Amazon Basin where urbanization, transportation infrastructure, and environmental factors have favored vector control.

The consistently higher mean risk scores for *An. darlingi* and *An. albimanus* may also reflect their importance in malaria transmission in the region [106, 125, 135]. While *An. darlingi* is the predominant vector in the study area [106], *An. albimanus* is more widespread particularly in Colombia and the northern-most portions of the study region [125].

3.4.2. Comparison with previous studies

Further, whereas many previous risk-mapping exercises focus on individual political units, these maps show how risk is represented across political boundaries, whether national or local [35, 85]. While previous malaria risk maps show current risk based on actual malaria cases aggregated by municipalities [35, 85], the composite maps indicate the effects of environmental and climatic conditions and their perceived degree of association with vectors and malaria transmission [83, 163]. The approach avoids limitations of aggregating cases by municipality (e.g. giving no indication of the location of transmission or clustering of cases) by producing a continuous risk surface with high spatial detail and clearly defined risk gradients.

Unlike the weak relationship reported between malaria cases represented by municipalities and mean risk scores in Fuller *et al.* [83], mean risk scores for malaria
points used in this study were consistently higher than at random locations. This may be
the result of employing geo-referenced malaria point locations as this is more easily
relatable to pixel-level risk scores than political units represented as polygons.

3.4.3. Implication of expert rankings

According to the expert opinions, preventive measures remain the key to malaria
elimination in the region as indicated by the top three highly ranked measures.
Community education and participation (through information sessions, hands-on
involvement in environmental management and vector control etc.) has been identified as
an essential tool for prevention of malaria transmission as it induces social and behavioral
changes that may lead to reduction in pathogen transmission [21, 243-244]. Its role in
implementation and sustainability of malaria control measures has also been widely
established [243-244]. Public education has been shown to engender ownership and a
feeling of responsibility on the communities’ part for their health outcomes. My findings
are consistent with previous studies by Rojas et al. [244] and Kroeger et al. [244], who
demonstrated that involving communities in malaria prevention and control leads to a
reduction in malaria deaths, incidence and length of sick-leave [244], as well as improve
people’s knowledge about aetiology and medications for malaria.

Expectedly, engagement in outdoor occupations, as well as source reduction were
important factors identified by expert opinion, consistent with previous studies. The
involvement of many inhabitants of the indigenous communities in agriculture, fishing,
mining and wood extraction increases their risk of contracting malaria as they have been
shown to be focal points for transmission and dispersal of parasites within and between
the Amazonian countries [137-139, 247]. While these outdoor activities form the basis of
many local economies, community education provide the people with information on protective measures. Source reduction has also been long established as one of the most effective and economical malaria control measures because it permanently eliminates mosquito breeding sites. Such environmental management measures are used when the species targeted are concentrated in a small number of discrete habitats, and are used in conjunction with larvicides and lavivorous fish [17]. For instance, Ghosh et al. [245] observed in their study that people’s knowledge of reducing malaria breeding sites and introducing lavivorous fish resulted in significantly reduced malaria cases in rural India.

Coverage of population at risk by bed nets and anti-malarial drug administration as identified by the experts have a long history of effectiveness [44]. Bed nets alone can reportedly reduce child mortality by almost 25% [248], malaria incidence by 50% in high transmission areas, and by 62% in areas of low transmission [249] and is more protective compared to IRS in unstable areas [250]. ACTs are the first line treatment against \textit{P. falciparum} infections [17] because they are composed of artemisinin derivatives and chemical classes of longer acting drugs which are effective against the pathogenic blood stages of \textit{Plasmodium} [251]. The drugs in this group are widely used and highly efficacious [252].

The implications of these rankings in relation to the risk maps is also informative. While the risk maps identify the level of risk each area may be exposed to, the expert rankings give an indication of what malaria control measures may be effective in preventing or reducing transmission. Generally, community education provides people with necessary information to reduce mosquito proliferation and prevent bites, thus limiting their susceptibility to malaria infection. Moreover, some of the areas at higher
risk of exposure are along the coasts where fishing and farming are the primary occupations; thus engagement in outdoor occupations play an important role in malaria control in those areas.

Interestingly, the actual monetary allocation for malaria control in the nine countries do not align with the experts’ rankings. According to the World malaria report for 2015 [253], only 4 of the 9 countries provided information on their spending. Colombia, Ecuador and Guyana spent approximately 85%, 100% and 55% of their malaria funding respectively on management and other costs, and human resources and technical assistance. Except for Guyana and Peru which spent about 30% and 27% of funding respectively on anti-malarial drugs, allocation to ITNs, diagnostic testing, and monitoring and evaluation were low for 3 of countries; only Peru spent an estimated 70% on monitoring and evaluation. While investments in human capacity and technical support, as well as management are necessary, they should not be at the expense of vector control and malaria treatment for at-risk populations. As such, allocating financial resources based on expert rankings may lead to a more efficient and equitable distribution, and may improve the gains already achieved.

In this chapter, I employed a knowledge-driven approach, the MCDA, which allows the integration of expert interactions, to delineate the risk of malaria transmission in the region. To a large extent, the risk maps produced based solely on environmental covariates, aligned well with areas where malaria is known to be problematic. Further analysis of local expert opinions also indicated that role of preventive measures as well as prompt diagnosis and treatment of malaria patients cannot be over-emphasized if elimination is to be achieved in the region.
Table 3.1. Risk factors and fuzzy membership functions used to create risk maps.

<table>
<thead>
<tr>
<th>Data</th>
<th>Source</th>
<th>Factor</th>
<th>Control points</th>
<th>Fuzzy function</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deforestation</td>
<td>Global Forest change [235]</td>
<td>Distance (km)</td>
<td>0, 5</td>
<td>Linear ↓</td>
<td>Vectors are found within 5 km of deforested areas</td>
</tr>
<tr>
<td>Elevation</td>
<td>SRTM 90 m</td>
<td>Elevation (m)</td>
<td>500, 1800</td>
<td>J-shaped ↓</td>
<td>Exposure to vectors decrease above 500 m and is non-existent above 1800 m</td>
</tr>
<tr>
<td>Population</td>
<td>LandScan</td>
<td>Population density</td>
<td>2, 50</td>
<td>Sigmoidal ↑↓</td>
<td>Populations between 2 and 150/km² are sufficient for malaria transmission</td>
</tr>
<tr>
<td>Precipitation</td>
<td>WorldClim</td>
<td>Precipitation (mm)</td>
<td>0, 80</td>
<td>Linear ↑</td>
<td>Precipitation of 80mm is suitable for vectors for stable transmission to occur [236]</td>
</tr>
<tr>
<td>Roads</td>
<td>DCW</td>
<td>Distance (km)</td>
<td>0, 5</td>
<td>Linear ↓</td>
<td>Transmission occurs within 5 km of roads where blood meals are available</td>
</tr>
<tr>
<td>Temperature</td>
<td>WorldClim</td>
<td>Temperature °C</td>
<td>18, 22, 32, 40</td>
<td>Sigmoidal ↑↓</td>
<td>Sporogony starts at 18°C and is completed at 22°C, vector survival decreases above 32°C and death occurs at 40°C [236]</td>
</tr>
<tr>
<td>TWI</td>
<td>SRTM 90 m</td>
<td>Soil Saturation (%)</td>
<td>0, 5%</td>
<td>Linear ↑</td>
<td>An area requires about 5% water saturation to serve as breeding site</td>
</tr>
<tr>
<td>Urban areas</td>
<td>DeLorme, Inc.</td>
<td>Distance (km)</td>
<td>1, 10, 20, 30</td>
<td>Sigmoidal ↑↓</td>
<td>Vectors are absent in urban areas but found in the urban periphery</td>
</tr>
<tr>
<td>Wetlands</td>
<td>WWF</td>
<td>Distance (km)</td>
<td>0, 3</td>
<td>Linear ↓</td>
<td>Vectors are found within 3 km of wetlands</td>
</tr>
</tbody>
</table>

Abbreviations and Symbols: SRTM= Shuttle Radar Topography Mission, DCW= Digital Chart of the World, WWF= World Wildlife Fund. The ↑ arrows indicates an increasing function, ↓ a decreasing function and ↑↓ a symmetric function.
Table 3.2. Factor groupings and weights used for risk maps.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Factor groupings</th>
<th>AHP(^1)</th>
<th>Equal(^2)</th>
<th>Access related(^3)</th>
<th>Environment/ Climate related(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance from deforested patches</td>
<td>Access</td>
<td>0.0996</td>
<td>~0.11</td>
<td>0.14</td>
<td>0.06</td>
</tr>
<tr>
<td>Population density</td>
<td></td>
<td>0.0593</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance from roads</td>
<td></td>
<td>0.0379</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance from urban areas</td>
<td></td>
<td>0.0420</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance from wetlands</td>
<td></td>
<td>0.1391</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevation</td>
<td>Environmental/ Climatic</td>
<td>0.1680</td>
<td></td>
<td><strong>0.075</strong></td>
<td><strong>0.175</strong></td>
</tr>
<tr>
<td>Precipitation</td>
<td></td>
<td>0.1784</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td>0.2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWI</td>
<td></td>
<td>0.0751</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Factors weighed based on ecological relationship with mosquitoes and malaria

\(^2\)No difference in weighting

\(^3\)Access more important (group weight sum up to 0.70)

\(^4\)Environment/Climate related factors more important (group weight sum up to 0.70)

TWI= Topographic Wetness Index
Table 3.3. Cross section of malaria experts

<table>
<thead>
<tr>
<th>Country</th>
<th>Sex</th>
<th>Number of Participant/Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Belize</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Colombia</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>El Salvador</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Guatemala</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Honduras</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Panama</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peru</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30</td>
<td>14</td>
</tr>
</tbody>
</table>
**Table 3.4.** Validation of risk maps using t-test and one-way ANOVA

<table>
<thead>
<tr>
<th>Models</th>
<th>Validation points</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( t ) statistic</td>
<td>Between groups (df)</td>
</tr>
<tr>
<td></td>
<td>An. albimanus*</td>
<td>An. darlingi*</td>
</tr>
<tr>
<td>AHP</td>
<td>6.12</td>
<td>15.44</td>
</tr>
<tr>
<td>Equal</td>
<td>8.61</td>
<td>17.70</td>
</tr>
<tr>
<td>Access</td>
<td>9.77</td>
<td>18.57</td>
</tr>
<tr>
<td>Environment/</td>
<td>5.05</td>
<td>12.77</td>
</tr>
<tr>
<td>Climatic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically different from random at \( p < 0.0001 \)

** Comparison of means for *An. albimanus*, *An. darlingi*, *An. nuneztovari* and Malaria cases
**Table 3.5.** Expert Opinions on relative importance of malaria control strategies

<table>
<thead>
<tr>
<th>Strategy/Socio-economic factor</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public education</td>
<td>0.222</td>
</tr>
<tr>
<td>Outdoor Occupation</td>
<td>0.153</td>
</tr>
<tr>
<td>Source reduction</td>
<td>0.104</td>
</tr>
<tr>
<td>Population Density</td>
<td>0.067</td>
</tr>
<tr>
<td>Artemisinin Combination Therapy (ACTs)</td>
<td>0.061</td>
</tr>
<tr>
<td>Education</td>
<td>0.055</td>
</tr>
<tr>
<td>Internal displacement</td>
<td>0.051</td>
</tr>
<tr>
<td>Occupational risk (Male-to-female ratio)</td>
<td>0.051</td>
</tr>
<tr>
<td>Rapid Diagnostic Testing (RDT)</td>
<td>0.035</td>
</tr>
<tr>
<td>Bed nets</td>
<td>0.035</td>
</tr>
<tr>
<td>Income</td>
<td>0.032</td>
</tr>
<tr>
<td>Housing quality</td>
<td>0.029</td>
</tr>
<tr>
<td>Indoor Residual Spraying</td>
<td>0.028</td>
</tr>
<tr>
<td>Coca cultivation</td>
<td>0.024</td>
</tr>
<tr>
<td>Larviciding</td>
<td>0.023</td>
</tr>
<tr>
<td>Corruption</td>
<td>0.021</td>
</tr>
<tr>
<td>Primaquine and Chloroquine administration</td>
<td>0.010</td>
</tr>
</tbody>
</table>
Figure 3.1. Schematic of malaria control and socio-economic factors that influence malaria incidence.
Figure 3.2. Risk maps derived from weighted linear combination of 9 factors. Higher values indicate relatively higher risk scaled from 0 to 255. (a) Each factor assigned an equal weight of 0.11; (b) Factors weighed according to ecological relationship with mosquitoes and malaria through AHP; (c) Access was assigned more weight (0.7 out of 1); (d) Environmental/Climatic factors was given more weight (0.7 out of 1)
Figure 3.3. **Mean risk scores for MCE models validated with vectors and malaria data points.** (a) Equal weights for all 9 factors; (b) Factors weighed according to ecological relationship with mosquitoes and malaria using AHP; (c) Access factors have higher weighting; (d) Environmental/Climatic factors have higher weighting. Mean scores for all vectors and malaria points are statistically different from random at $p < 0.0001$.
Chapter 4. Civil conflict and environment as drivers of malaria trends in Colombia from 2000-2014

4.1. Background

Recent efforts to broker a peace accord between Colombia’s main rebel group, the Fuerzas Armadas Revolucionarias de Colombia (FARC), and the Colombian government may signal an end to the 50-plus year armed conflict that has resulted in more than 6 million displaced persons and over 220,000 deaths [254, 255]. The consequences of this prolonged armed conflict in Colombia include not only direct loss of life from acts of war but also poor health of displaced and marginalized rural and urban populations. In particular, armed conflict in Colombia’s rural areas has also seriously undermined the government’s ability to deliver health-care and implement strategies that reduce risk of exposure to vectors and other disease agents, particularly those related to malaria, which is the most common vector-borne disease in rural parts of the country. Although malaria cases in Colombia have declined in recent years [35], the disease remains a threat particularly in Pacific coastal areas where various resource-extractive industries such as mining, logging, and coca-cultivation have become more prevalent [256, 257].

Colombia has in the past decade scaled up its malaria control efforts by bolstering its surveillance and monitoring system through active and passive case detection [75, 258], improving diagnostic testing [75, 259], ensuring coverage of at-risk populations with insecticide treated nets and indoor residual spraying [31], as well as, by promoting prompt treatment of patients with antimalarial drugs [31, 258]. These measures have
resulted in significant reductions in hospital admissions and deaths due to malaria [31]. There are, however, areas in the country where malaria remains problematic, particularly the Urabá-Sinu/Bajo Cauca and Pacific coast regions (UBPC), where approximately 70-80% of cases are reported [260, 261]. I therefore focused the analysis on the 303 municipalities in this region and utilized a regression approach with multiple environmental and political covariates to explain variance in long-term malaria trends from 2000 to 2014.

Although armed conflicts and malaria outbreaks have been well documented in many parts of the world [262-267], many such investigations have been conducted at national or regional scales, missing subtle patterns only evident at smaller geographical scales such as the municipality. Moreover, there has been no empirical evidence of such a relationship in Colombia, despite the protracted duration of the war. The Colombian insurgency has been financed largely by proceeds from cocaine trafficking [268], and more recently by small-scale mining operations. Approximately 31.6% of malaria cases were from gold mining districts of Antioquia, Córdoba, Chocó and Valle del Cauca, all coastal departments (S. Herrera personal communication). These activities, along with logging and small-holder and large-scale agriculture, produce forest clearing as well as in-migration of settlers to facilitate extractive activities. While some studies have alluded to a possible association between armed conflict, drug cultivation and malaria [75, 260], this association has yet to be quantified. I set out in this study to examine the influence of socio-political and environmental factors on malaria incidence in UBPC. The findings provide new insights on how these factors may shape malaria trends and the underlying mechanisms needed to achieve malaria elimination in a war-torn country.
4.2. Methods

4.2.1. Data sources

4.2.1.1. Malaria and hospital location data

Colombia has the second highest incidence of malaria in the continent after Brazil [215], with infections attributable to two main parasite species, *P. vivax* and *P. falciparum* [31]. Although transmission is unstable and focal, it remains at endemic/epidemic levels [260, 269], putting about a quarter of the population at risk, particularly in rural communities [75, 270]. The study area is the Urabá-Sinu/Bajo Cauca and Pacific coast regions, which comprises of five departments: Antioquia, Chocó, Cauca, Nariño and Valle de Cauca (see Fig. 4.1). I obtained malaria incidence data for both parasite species between 2000 and 2014 for these regions, as well as georeferenced locations of health centers in each municipality through SIVIGILA, the country’s official malaria database (http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Paginas/sivigila.aspx). The incidence data were collected through passive case detection of patients reporting symptoms consistent with malaria and confirmed using thick-blood smears. The georeferenced health center records, which comprised of hospitals, clinics and health outposts locations, were used to measure access to health care in the departments. Only 287 of the 303 municipalities in UBPC were available as polygons in a shape-file after multiple polygon entries had been deleted.

4.2.1.2. Climate data

Temperature and precipitation play important roles in *Anopheles* entomological and *Plasmodium* parasite development and malaria transmission [236]. Annual temperature and precipitation layers interpolated from average monthly data from
weather stations across the country at ~1km resolution were obtained from Worldclim
http://www.worldclim.org/ [175].

4.2.1.3. Environmental data

Environmental variables including elevation, wetlands and deforestation influence
malaria transmission and mosquito densities. Elevation in Colombia varies, with the
Andes serving as a major barrier to transmission and vector dispersal while most of
UBPC is composed of lowlands. I included digital elevation data obtained through
http://glcf.umd.edu/data/srtm/ to account for these altitudinal gradients. Because
wetlands serve as important sources of sugar and shade, as well as breeding sites for
vectors, the area covered by wetlands in each municipalities was also included as an
explanatory variable (Fig 4.4B). This data was downloaded through ArcGIS online from
the World Wildlife Fund [271]. Deforestation has been linked to increased malaria
incidence in many parts of South America [134, 135] as the environmental alterations
create habitats suitable for anopheline larvae development. Data on forest loss in
Colombia was obtained from a global dataset on forest extent and change from 2000-
2013 available through http://earthenginepartners.appspot.com/science-2013-global-
forest [235].

4.2.1.4. Population density data

Of the approximately 50 million people in Colombia, about 30% reside in UBPC
on ~195,000 km² of land. The changing economic and political climate in the country has
led to decreasing emigration and more investment in its sustainable growth and
development. Because of its importance in determining how much blood meals are
available to vectors, as well as onward transmission of malaria, I obtained data on
population density from LandScan [181] as a predictor of malaria trend.

4.2.1.5. Data on extent of civil conflict

The decades-long conflict in Colombia has displaced millions of people as well as contributed to the propagation of diseases, including malaria. Data representing various measures of armed conflicts in the nation were obtained as probable predictors of malaria trend in UBPC. These included data on IDP expulsions from 2000-2010, casualties from acts of war from 2000-2010, and direct homicides from armed conflicts between 2005 and 2012 [272]. Additional data on areas used for coca cultivation from 2001-2013 [273, 274] was included as a measure of illicit activities fostered by the armed conflicts.

4.2.1.6. Access data

For many localities in UBPC, water is the primary means of transportation because roads are scarce. I represented the transportation network in the area with data on road and river networks from a global dataset on ArcGIS online (http://hydrosheds.cr.usgs.gov; http://www.worldwildlife.org/hydrosheds; Digital Charts of the World).

4.2.2. Data processing

The area deforested for each year, area occupied by wetlands, as well as values for precipitation, temperature, elevation and population density were estimated by interpolating values from surrounding areas in each municipality using the zonal statistics tool. Proximity between neighboring municipalities (a probable explanation for similar trend) was measured by calculating the number of borders shared, the length of each border, as well as the total length of all borders shared by each municipality using the
proximity tool. Access was estimated by calculating the total length of transportation networks (i.e. sum of roads and rivers). The density of health centers in each municipality, a proxy measure of availability of health care facilities, was estimated using the point density tool. API, the total number of positive slides for parasite in a year per thousand population was calculated for each municipality from malaria incidence data. These, as well as the malaria incidence and armed conflicts data were linked to the polygons. All data pre-processing was carried out using ArcMap 10.2 (ESRI Inc., Redlands, CA).

To examine malaria trends, I utilized the Earth Trends Modeler in Idrisi Selva raster package (Clark Labs, Worcester, MA). Maps of spatial trend were created for each variable from the time series outputs using the contextual Mann-Kendall (CMK) [275] module. The CMK approach uses local spatial variation within small neighborhood of pixels which often results in higher confidence in observed trends as the approach is more robust to outliers than ordinary least squares [275, 276]. The map results included Thiel-Sen (TS) slope [277, 278] and its significance. The TS slope is the median of slopes for observations $X_j$ and $X_i$ at pairwise time steps $t_j$ and $t_i$ given by:

$$\text{TS Slope} = \text{Median} \left( \frac{X_j - X_i}{t_j - t_i} \right)$$

whereas slope significance ($Z$ and $p$) are given by:

$$Z = \begin{cases} \frac{s-1}{\sqrt{\text{Var}(S)}} & \text{for } S > 0 \\ 0 & \text{for } S = 0 \\ \frac{s+1}{\sqrt{\text{Var}(S)}} & \text{for } S < 0 \end{cases}$$

and
\[ p = 2[1 - \Phi(|Z|)] \]

where \( \Phi() \) is the cumulative distribution function of a standard normal variable estimated by

\[
\Phi(|Z|) = \frac{2}{\sqrt{\pi}} \int_{0}^{\frac{|Z|}{\sqrt{\pi}}} e^{-t^2} dt
\]

### 4.2.3. Linear modeling

All statistical analyses were performed using SPSS 22 (IBM Corp, Armonk, NY). First level of analysis involved all 287 municipalities, which did not yield any significant results. Subsequent analysis was performed on a subset of municipalities with significant positive and negative malaria trends (n=39) shown in Fig. 4.4A. This was done after testing for spatial autocorrelation in the municipalities using Moran’s \( I \) statistic. Moran’s \( I \) tests the null hypothesis that the attribute of the feature of interest is randomly distributed where a statistically significant \( Z \)-score indicates spatial autocorrelation.

Thus, using log-transformed average malaria incidence as the dependent variable, which produced a normal distribution as determined by a Kolmogorov-Smirnov test \( (p>0.05) \), all explanatory variables were considered in the model where Automatic Linear Modeling (ALM) guided model selection. ALM selects the most influential predictors and yields the most parsimonious model based on the Akaike’s Information Criterion (AIC). Three sets of linear regression models based on a combination of variables: environmental, socio-political and a combination of both were generated from the influential predictors. Variance inflation factors (VIF) were used to assess multicollinearity, all of which were \(<2\) for each variable, while a Durbin-Watson statistic
value close to 2 was reported for each of the three regression models, indicating no autocorrelation in the residuals.

4.3. Results

4.3.1. Malaria burden and availability of health care facilities in UBPC

I estimated the annual parasite index (API) in municipalities for the most recent year (2014) as an approximation of the disease burden in the population [279] (Fig. 4.2A and Materials and Methods). While 131 municipalities reported no malaria cases, 89 municipalities had APIs <1, which is considered negligible. Twenty-eight municipalities, however, had disease burden ranging from 1-10 while the APIs in the remaining 39 municipalities were above the national average of 10.5 [75]. Three municipalities in Chocó in particular (Tadó, Nóvita and Quibdó) had APIs in excess of 200.

To measure accessibility to health care facilities in the area, I estimated the density of health centers and the number of people served in each municipalities (Fig. 4.2B). Higher clinical accessibility was estimated in densely populated areas around the major cities of Medellin, Quibdó, Cali, Popayán and Pasto. Of the 287 municipalities analyzed, ~8% (7 in Antioquia, 2 each in Cauca and Chocó, 8 in Nariño and 3 in Valle de Cauca), with a combined 2014 population of nearly 190,000, had no health centers, while 5 had 1-4 health centers serving about 100,000 people. These 27 municipalities are in rural areas where the easiest means of access is through rivers. While 13 of those without health centers reported no malaria cases, six of them had APIs between 0.1-10, while the remaining had much higher disease burdens. Thirty-one percent of the municipalities had between 11-200 health centers while the remaining municipalities had access to more than 200 health centers in each.
4.3.2. Spatio-temporal trend in malaria incidence from 2000 to 2014

Non-parametric trend using the Thiel-Sen slope in malaria incidence was estimated as a proxy for malaria status, the effectiveness (or lack thereof) of current malaria control strategies, as well as the variability in malaria incidence in each municipality. The analysis of spatial trend showed a north-south dichotomy: municipalities in the northern departments (the equivalent of states) mostly had positive trends while most of those in the south showed negative trends (Fig. 4.3A). In Antioquia, malaria incidence increased in about 51% of the municipalities over the period, although the increase was significant in only four municipalities (Nechí, El Bagre, Segovia (which are spatial neighbors) and Belmira) (see Fig. 4.4A). However, there was a decreasing trend in 57 municipalities, which was significant in seven (Necoclí, Carepa, Yondó, Bello, Concordia, Montebello and Támesis) while the remaining four municipalities had no changes. Time-series analysis showed that Antioquia had the highest malaria incidence for the period compared to the other departments. However, this trend fluctuated over the years with highest incidence occurring in 2008 and 2010, while the lowest cases were in 2006 and 2012 (Fig. 4.5A). Malaria incidence increased significantly in four (Riosucio, Quibdó, and in Istmina and Nóvita, which share borders) of the 12 municipalities in Chocó with positive trends whereas only Acandí had a significant decrease during the period. Temporally however, incidence remained steady at about 10,000 cases per year until 2010 when the cases almost doubled (Fig. 4.5A). Nine (including Buenaventura, Dagua, Alcalá) out of the 32 municipalities in Valle de Cauca with negative trends (Fig. 4.3A) showed a significant decrease in malaria while the remaining municipalities had positive trends, which were not significant (Fig. 4.4A).
Compared to the other departments, transmission in Valle de Cauca was mostly stable over the period except for an increase in 2010. In Cauca, only Santa Rosa had a significant decrease in trend whereas Guapi, Argelia and Balboa, all neighboring municipalities experienced significant increases. This department also had the lowest incidence over time relative to the other departments as seen in Fig. 4.5A. Finally, 8 municipalities in the southern department of Nariño had significant decreases whereas Santa Barbara and Cumbitara had significant positive trends. The highest malaria incidence was recorded in 2001 and has since been on the decline. Together with Cauca, only these two departments did not report increases in malaria transmission in the 2010 epidemic year.

4.3.3. Spatio-temporal trend in measures of civil conflicts and environmental disturbances from 2000 to 2014

4.3.3.1. Acts of war

This refers to combats (bilateral attacks between armed actors), unilateral attacks, terrorist attacks and ambushes in the country. Generally, the number of casualties from acts of war mostly decreased in all the departments over time. However, spatial differences were evident at municipality level. Casualties in Antioquia decreased significantly in 17% of the municipalities between 2000 and 2014 whereas only two neighboring municipalities (Caucasia and Nechí) had significant increases (see Fig. 4.3B). This department also had the least number of casualties relative to others over the period (Fig. 4.5B). El Carmen, Riofrío, as well as Santa Rosa and La Vega had significant negative trends in Chocó, Valle de Cauca and Cauca respectively over the period, whereas Istmina in Chocó and Timbiquí in Cauca experienced significant positive
trends. In Nariño, three municipalities (Policarpa, San Pablo and neighboring La Cruz) had significantly decreasing numbers while six (Tumaco and neighboring Barbacoas, Providencia and its neighbors Santa Cruz, and Samaniego, and Ipiales) were significantly positive. Over time however, both Valle de Cauca and Nariño had the highest number of casualties over the years compared to others with peaks in the years 2002 and 2007.

4.3.3.2. Coca cultivation

I included the area used for coca cultivation as a proxy for ongoing illicit activities. The analysis showed that these activities continued to rise in all five departments over the period. Three municipalities in Antioquia (Apartadó, Urrao and San Carlos), 12 in Chocó, two in Valle de Cauca (Bolívar and Buenaventura), seven in Cauca and five in Nariño experienced significant increases in the area used for coca cultivation. On the other hand, the number of municipalities with significant reductions fell from four in Antioquia to two in Nariño and one in Cauca (Fig. 4.3C). Temporal analysis indicated that Valle de Cauca and Nariño had the largest cultivated areas by department and 2007 was the year with highest cultivated area in all departments (Fig. 4.5C).

4.3.3.3. Deforestation

Analysis of yearly deforestation showed an increasing trend in many of the municipalities. The number of municipalities with significant positive trends decreased from 10 in Antioquia to five in Chocó and one each in Valle de Cauca and Cauca. Deforested area however significantly declined in seven municipalities in Antioquia, three in Nariño and one in Valle de Cauca (Fig. 4.3D). Overall, Antioquia had the largest deforested area among all the departments (Fig. 4.5D), although the yearly pattern was similar in all departments with peaks in 2004 and 2012.
4.3.3.4. Homicides

Number of direct homicides in the area generally declined during the period of analysis (2005-2012) which coincides with the demobilization of the right wing paramilitaries and a general de-escalation of the armed conflict [280, 281]. About half of the municipalities in Antioquia had significant decreases while 11 municipalities in Cauca, 18 in Nariño and 3 in Chocó experienced the same. Only Corinto in Cauca had a significant increase (Fig. 4.3E). Valle de Cauca, however, had the highest number of casualties for any year (Fig. 4.5E).

4.3.3.5. Internally displaced persons (IDP)

Except for some municipalities with significant positive trends e.g. Valdivia and Yarumal (Antioquia), Litoral del San Juan (Chocó) and Túquerres (Nariño), the number of internally displaced people declined significantly in all the departments, especially Antioquia (Fig. 4.3F). The largest displacement occurred in 2001 and continued to decline until 2007 when there was a slight increase. Valle de Cauca and Nariño had the biggest numbers of internally displaced persons throughout the entire period (Fig. 4.5F).

4.3.4. Impact of environmental and social/civil conflicts on malaria incidence

I included 39 municipalities with significant malaria trend for the period 2000 to 2014 in the regression analyses. The test for spatial autocorrelation showed that there was no spatial dependence in the municipalities (Moran’s $I = 0.126$, Z score = 1.095, $p=0.273$). ALM indicated the most influential explanatory covariates in predicting malaria incidence (Table 4.1).

Results from the first model on environmental variables showed that temperature and precipitation were predictive of malaria (adjusted $R^2 = 69.1\%$) (Table 4.1). Thus,
every 1°C increase in temperature and 1 mm increase in precipitation resulted in an increased malaria risk of 25% and 0.1% ($p=0.002$) respectively. In the second model, for which the amount of variance explained was more modest (adjusted $R^2= 43.0\%$), I included only measures of civil conflicts and population density. This model showed that malaria risk increased by 0.3% for every increase in coca cultivation hectares. However, for every additional internally displaced person in the area, malaria risk decreased by 1.7% ($p=0.003$) and by 0.2% ($p=0.045$) for every additional person per km$^2$ (Table 4.1).

In the final model, which included both environmental and socio-political variables, the percent variance explained increased to 75.7. This model included acts of war, although this covariate was not a predictor of malaria risk at ($p>0.05$), while betas for homicides and elevation, temperature and precipitation were significant ($p<0.05$). The impact of homicides and elevation on malaria risk decreased by 9.2% ($p=0.032$) and 0.1% ($p=0.017$) respectively for each additional increase in both variables. On the other hand, the effect of temperature on malaria risk rose slightly to 29.7% for every temperature increase. Generally, the environmental variables explained most of the variance (represented by $R^2$ values) in the analyses, while the social/conflict variables accounted for a smaller proportion.

4.4. Discussion

I set out to examine the influence of civil unrest and environmental/climatic factors on malaria transmission in the most malarious region of Colombia. The findings indicate that expulsions of internally displaced people and conflict homicides caused mostly by the ongoing armed conflicts, are associated with malaria. To my knowledge, this is the first empirical evidence of such a relationship in Colombia and in Latin
America for that matter, although similar evidence has been documented in other parts of the world [269, 282-284]. While a number of studies have alluded to such relationships in Colombia [75, 285], the associations have been mostly anecdotal without empirical evidence, probably due to limited data availability. Although the spatial analysis shows a generally decreasing trend in number of IDPs and conflict homicides in all but a few of the municipalities (until 2012, Colombia ranked first in the global list of IDP per country [286], it was an influential predictor in the regression analysis. The negative association between internally displaced persons and malaria indicates that the more people were expelled through displacement, the fewer malaria cases occurred in the area. This may occur as people are displaced from areas of high malaria endemicity to low endemicity, exposing host populations to malaria risk particularly if there are competent vectors and suitable environmental conditions [282]. Conversely, non-immune persons may be displaced to areas of high malaria endemicity where they live in unsanitary conditions with limited access to health care, and are thus at high risk of being infected. In the case of Colombia, it appears that the former occurred as most of the internally displaced migrated to major cities, which are generally free of malaria and where the health and public services are better.

The analysis also indicated that the area dedicated to coca cultivation in the region has increased [287], and is associated with malaria risk. This is also the first documented evidence of such a relationship in the area. This is probably because the workers are mostly peasants who often have to migrate from areas of high/low endemicity as the case may be, to frontier areas along forest boundaries where the clandestine cultivation are carried out. These farmers are a focal point for transmission and dispersal of parasites
within and between regions [138], as they create frontier settlements that favor clustered
habitations close to vector habitats [79, 137-139]. The transition of coca cultivation from
the Putumayo region to the Pacific coast, especially in Nariño exemplifies this. The
negative relationship between population density and malaria risk reported is consistent
given that malaria is usually found in rural areas or urban peripheries, far from densely
populated areas [288, 289].

Temperature and precipitation, as well as elevation were also associated with
malaria trends. This is consistent with current understanding of the interactions between
malaria and climatic factors. The role of temperature and precipitation in malaria
transmission is well known [163, 214, 216, 288] in agreement with the findings. Changes
in temperature are shown to be associated with large increases in malaria incidence, and
may be a cause for concern in the study area as climate change is expected to produce
warmer and drier conditions later this century [163, 214]. Precipitation on the other hand
resulted in small increases in malaria risk probably due to time lag and rainfall intensity,
which make large waterbodies and wetlands too deep for breeding or flush out mosquito
eggs during months of heavy rainfall [215]. The negative relationship found between
elevation and malaria in the study area is consistent with known interactions between
temperature, elevation, and transmission. While most parts of the study area were
comprised of lowlands, highland malaria has recently been reported in nearby Bolivia
[290].

The spatial trends revealed subtle differences and patterns in the distribution of
malaria cases at the municipality level, which were not evident when aggregated at the
state (departments) level [25]. Some of the municipalities with significant trends e.g.
Nechí, El Bagre, Segovia share borders and have experienced massacres perpetrated by right wing paramilitaries. Although I observed a generally declining trend in malaria incidence throughout the period, my analysis identified specific municipalities with significant upward trends where malaria control should be intensified. I also observed malaria cases of epidemic proportions in 2010 in all departments, consistent with findings by Chaparro et al. [75] in which the cyclical pattern was attributed to the paraquinquenal transmission peak period associated with El Niño [291]. According to the World Health Organization (WHO) [31], vector control administered through insecticide treated nets and indoor residual spraying, covers <20% of Colombian population. Hence, there is a need for increased coverage, which together with prompt diagnosis and treatment as well as active case surveillance already in place should reduce malaria incidence. Other measures such as proactive surveillance of cases at community level, testing for Glucose-6-phosphate dehydrogenase (G6PD) deficiency before primaquine treatment (to avoid complications in the treatment of *P. vivax*) should also be considered [31].

Although the disease burden in all but a few of the municipalities was low, some with higher APIs included relatively large cities, e.g. Quibdó and Tumaco, with access to health centers. I therefore advise caution in interpretation as detected cases in these areas may be from within as well as from neighboring areas without health care access, hence the high API. The burden in the 39 municipalities in Antioquia, Chocó and Nariño with APIs higher than the national average, consistent with previous studies [75] may be cause for concern, especially considering the near linear relationship between malaria incidence and entomological inoculation rate (EIR) [108, 292-293]. Because API measures confirmed/reported cases in the population, asymptomatic individuals who may be
parasite reservoirs are excluded [294]. This limits the quantification of transmission, better captured by EIR, the number of infective bites per person per year, a measure which does not consider clinical outcomes. Despite its advantages, EIRs are not routinely measured by National Malaria Control Programs (NMCPs) in many locations in Latin America because transmission is considered too low for the investment [62, 108]. This is further compounded in areas of armed conflicts in Colombia where NMCPs face difficulties mounting malaria control operations [295]. Notwithstanding these limitations, the results clearly establish a novel quantitative link between conflict-related variables and malaria trend, with the most robust model including a combination of environmental and conflict-related covariates. This suggests that malaria elimination may be especially difficult to achieve without prolonged cessation of armed conflict in Colombia as well as illegal gold mining.
### Table 4.1. Effect of environmental and socio-political variables on malaria incidence in UBPC

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>$\beta$</th>
<th>$p$-value</th>
<th>$R^2$/ Adjusted $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Environmental</td>
<td>Temperature</td>
<td>0.250</td>
<td>0.000</td>
<td>0.723/0.691</td>
</tr>
<tr>
<td></td>
<td>Precipitation</td>
<td>0.001</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevation</td>
<td>0.000</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transportation (roads and rivers)</td>
<td>0.000</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>2 (Social/conflict</td>
<td>Coca cultivation</td>
<td>0.003</td>
<td>0.000</td>
<td>0.475/0.430</td>
</tr>
<tr>
<td></td>
<td>Internally displaced persons</td>
<td>-0.017</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Population density</td>
<td>-0.002</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>3 (All variables)</td>
<td>Temperature</td>
<td>0.297</td>
<td>0.000</td>
<td>0.789/0.757</td>
</tr>
<tr>
<td></td>
<td>Acts of war</td>
<td>0.018</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homicides</td>
<td>-0.092</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Precipitation</td>
<td>0.000</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevation</td>
<td>-0.001</td>
<td>0.017</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4.1. Location of the departments and municipalities in the Urabá-Sinu/Bajo Cauca and Pacific coast (UBPC) regions. Municipalities mentioned in the narrative are highlighted in orange.
Figure 4.2. Estimation of disease burden and access to healthcare in UBPC. (A) Annual Parasite Index (API) for malaria in the municipalities in 2014. (B) Density map showing the degree of accessibility to health care facilities in the area.
Figure 4.3. Spatial trend in malaria and conflict-related/ environmental covariates in UBPC represented by normalized $Z$ scores from the CMK calculations. (A) Malaria incidence, (B) casualties from acts of war, (C) area used for coca cultivation, (D) deforested areas, (E) direct homicides from civil conflicts, and (F) number of IDPs. Areas in red indicate positive trends, those areas in light yellow show no change, and blue indicate negative trends.
Figure 4.4. Significance of malaria trend and wetland distribution in UBPC. (A) Municipalities with significant positive and negative trends in malaria incidence from 2000-2014. Polygons with blue diagonal lines indicate areas where malaria significantly decreased while those with red diagonal lines indicate areas where malaria significantly increased. The degree of significance is indicated by the red to cream color gradient at $p<0.05$. (B) Percentage of wetland area. Municipalities without wetlands are in gray, and municipalities with wetlands are in shades of blue.
Figure 4.5: Temporal trend in malaria and conflict-related/ environmental covariates in UBPC. (A) malaria incidence, (B) casualties from acts of war, (C) area used for coca cultivation, (D) area deforested, (E) direct homicides from civil conflicts, and (F) number of IDP in all 5 departments (X-axis represents years, and values on each Y-axis are in thousands).
Chapter 5. Summary and Conclusions

5.1. Study overview

This dissertation approaches the problem of malaria in NSA using a wide variety of techniques and scales of analysis. Both data-driven and knowledge-driven approaches were used and they both provided new insights into the spatial distribution of malaria risk as expressed by the current and future distribution of vectors and the disease itself. The study area provides enormous spatial heterogeneity and thus affords an excellent opportunity to elucidate heretofore unknown spatial and temporal patterns in vectors and the parasites that cause the disease. To my knowledge, this is the first study that has comprehensively applied both data and knowledge-driven approaches to the study of malaria risk in this region. While a few studies have previously examined global distributions of *P. falciparum* and *P. vivax* endemicity [46, 47], as well as national and regional distributions of some of the dominant malaria vectors [22-24, 150-153, 164], hardly any has investigated the possible distribution of the disease and its vectors in NSA in the future. Moreover, other than a study in Madagascar where the knowledge-driven MCDA method was used to prioritize areas for malarial vector control [233], the approach has not been used for malaria research, nor has malaria risk in the region been delineated without boundaries and at such high resolution. Furthermore, this is the first empirical evidence of the association between armed conflicts, coca cultivation and malaria in Colombia and in Latin America, although similar evidence of war and malaria have been documented for other parts of the world [269, 282-284].

The current focus in the Americas is to establish scientific frameworks that would support the development of new intervention strategies for malaria elimination in areas
with seasonal malaria. But progress can only be made by first understanding factors that limit current strategies and how risk mapping/modelling can be used to overcome them and enhance present accomplishments. This was the object of the review presented in Chapter 1 of this dissertation: *Prospects and recommendations for risk mapping to improve strategies for effective malaria vector control interventions in Latin America*.

As highlighted in the review, even though malaria elimination in Latin America appears more feasible today than a decade ago, continuing with the current state of knowledge and operational system in vector control may delay implementation.

Strengthening aspects of the IVM programs and policies where some NMCPs are still struggling through risk mapping could be a step in the right direction. Aspects where risk mapping methodologies can be helpful are summarized below:

- Evidence-based vector control is a fundamental tenet of the IVM, which cannot be carried out without strong entomological capacity. This entomological capacity can be strengthened through risk mapping methodologies that provides insights into disease transmission dynamics, can help monitor and target insecticide resistance and provide much needed spatial information on outdoor and early-biting mosquitoes. For example, the risk maps produced in Chapter 3 may potentially shed light on malaria transmission and guide interventions in the area. As such, investments in risk mapping technologies for entomological research can produce maps that depict where further investment in capacity is needed.

- The need to implement and monitor IVM policies consistently across board can be met through applying risk-mapping technologies. Integrated information systems and modelling strategies can track malaria interventions and identify areas in need of
improvements. Information on human populations, vector behavior and distribution, malaria transmission foci and updates on malaria surveillance and monitoring can be readily available through risk mapping. When fully integrated in vector control programs, these technologies can accelerate the drive towards elimination.

- The definition and estimation of malaria risk need to be standardized so that risk maps can be comparable across countries and different studies. The maps also need to possess the appropriate scale and resolution for planners to target areas in greatest need of control measures. Since elimination has to occur locally, large scale (1:5,000 or greater) and high-resolution (30 m or less) risk maps are needed to guide IVM implementation and elimination efforts on the ground. Risk mapping should also become an integral part of the information system so that targeted vector control can be conducted. Once integrated, risk-mapping methodologies will aid decision-making, disease risk management and allow more effective allocation of resources for malaria control.

- Brazil’s policies and sustained investment in early detection and treatment in isolated areas demonstrate that government commitment to elimination is feasible and that declines in incidence can be achieved even in geographically isolated parts of the Amazon. However, linking these efforts (i.e., matching investment maps to actual outcomes) to risk mapping (through efficacy mapping) can provide national policy-makers a better understanding of why elimination efforts are succeeding in some areas and not in others. This “risk mapping” frontier could greatly enhance elimination efforts in Latin America and elsewhere. Hence, governments need to take ownership by increasing domestic funding for malaria control and investing in research that advances the use of risk-mapping methodologies in vector control programs.
In order to bridge knowledge gaps in distribution and behavior of Latin American vectors, extensive applications of risk-mapping techniques, particularly SDMs should be encouraged, as SDMs such as MaxEnt are freely available and relatively easy to use to map probability of vector or disease presence as was demonstrated in chapter 2 above. The methodologies can also help improve and facilitate the development of alternative vector control strategies.

Knowledge and understanding of the geographic distribution of vector species and the influence of changing environmental and anthropogenic conditions in the region has been incomplete. In Chapter 2: *Predicting potential ranges of primary malaria vectors and malaria in northern South America based on projected changes in climate, land cover and human population*, I attempted to fill this knowledge gap. I presented models of the current and future spatial distribution of malaria, *An. darlingi*, and *An. nuneztovari* s.l. in NSA using bioclimatic, topographic, hydrologic, LULC and population data.

My analyses revealed that while climatic factors, temperature and precipitation, play important roles in current and future distribution of malaria parasites, *An. darlingi*, and *An. nuneztovari* s.l. in the region, aspects of human influence measured by LULC and population changes will also affect the distribution of *An. nuneztovari* s.l. and *An. darlingi* respectively. Results from the land change modeling indicate that about 70,000 km² of forest land would be lost by 2050 and 78,000 km² by 2070 compared to 2010. The Maxent model also predicted zones of relatively high habitat suitability for malaria and the vectors mainly within the Amazon and along coastlines.

As such, stricter regulations need to be enforced and sustained to reduce further deforestation in the Amazon. Although the models project increased range for the
vectors, sustained vector control as well as deployment of novel strategies in the near future could prevent this expansion. Based on the factors analyzed, malaria extent is expected to naturally decrease in the future. Thus, with increased implementation of IVM strategies and more effective anti-malaria drugs, trajectories of climate change and deforestation may complement efforts underway to achieve the goal of malaria elimination in NSA in the coming decades.

Addressing the problem of delineation of areas at risk of malaria infection and incorporating local expert knowledge in strategies for malaria elimination was the focus of Chapter 3: *A multi-criteria decision analysis approach to assessing malaria risk in northern South America and local perceptions of the impact of current malaria control and socio-economic/behavioral factors on malaria elimination strategies*. Here, I analyzed expert opinions of the most important strategies to achieve malaria elimination. Public education, better environmental management and effective anti-malaria drug administration were the experts’ most highly ranked strategies for malaria control. I also evaluated the exposure of the NSA to malaria risk given current access-related and environmental/climatic conditions using MCDA.

I produced high-resolution composite maps showing gradients of risk which were validated with geo-coded occurrence points for malaria and three dominant vector species. Results from the risk maps indicated areas of moderate-to-high risk along rivers in the Amazon basin, along the coasts of the Guianas, the Pacific coast of Colombia and northern Colombia, in parts of Peru and Bolivia and within the Brazilian Amazon. When validated with occurrence records for malaria, *An. darlingi*, *An. albimanus* and *An.
t-test results indicated that risk scores at occurrence locations were significantly higher ($p<0.0001$) than a control group of geographically random points.

These new map products represent an improvement upon previously published map of malaria risk in the region, which was highly generalized and partly constrained by political boundaries [207, 296]. The incorporation of a deforestation layer representing land-use change, provided additional detail to the risk maps relative to past studies that have employed MCDA for malaria vector exposure risk [83]. This also revealed that the depiction of risk produced was related to malaria occurrence points. Despite limitations of the knowledge-based approach to risk mapping, my 1 km maps provide information to the public health decision makers/policy makers to give additional attention to the spatial planning of effective vector control measures. This may increase the potential for malaria elimination in the region in the near future. Moreover, incorporating a participatory workshop approach to elicit expert opinions was complementary because this led to asking the right kind of questions, and obtaining the right datasets leading to the analyses in Chapters 3 and 4. Thus, the information generated and represented through the risk maps could aid planning to mitigate future malaria outbreaks and prevent reintroduction in areas where elimination has already been achieved.

In Chapter 4: *Armed conflict and environment as drivers of malaria trends in Colombia from 2000-2014*, I examined local factors associated with variations in malaria incidence in an endemic part of Colombia. The spatial trends revealed subtle differences and patterns in the distribution of malaria cases at the municipality level, which were not evident when aggregated at the state level. The results show that temperature, conflict-related homicides, precipitation, and elevation are related to malaria risk (adjusted $R^2 =$
0.757). The results thus establish a novel quantitative link between conflict-related variables and malaria risk in Colombia. Using advanced time series techniques and spatial analysis, this research is the first to establish statistically the relationship between armed conflict and how malaria varies through time.

5.2. Policy implications

The maps in Chapter 3 show risk of malaria transmission and exposure to mosquitoes irrespective of political boundaries, whether local or national. From a government standpoint, this suggests that malaria/vector control efforts both within each country and regionally should be collaborative. There is need for interactions among municipal governments to carry out appropriate interventions in their constituencies. Regional collaborations between the countries (e.g. Malaria Control Program in Andean-country Border Regions, the Amazon Malaria Initiative and the Amazon Network for the Surveillance of Antimalarial Drug Resistance) also need to be strengthened so that malaria may be eliminated, especially in border towns, thus preventing importation of cases. Although the experts’ rankings of strategies differed from the actual monetary allocation for malaria control in the countries, their perceptions align well with my analyses. The generated maps give indication of risk of transmission as well as distribution of malaria and its vectors, while the experts’ prioritization of efforts highlight preventive measures and prompt treatment as very necessary elements of malaria control and eventual elimination.

Maps are known to be powerful visual tools for identifying areas where targeted strategies and resources are most likely to have the greatest impact [297]. The maps produced in this dissertation have the potential to help improve current malaria control in
the region having highlighted areas where vectors may be abundant and the degree of risk in each area. For example, along the coasts of Guyana and Colombia where higher risk of transmission is predicted, these maps may be used by NMCPs and MoH to identify specific areas to be targeted as well as help make informed decisions on allocation of limited resources. This is needed considering that less than 15% of current spending on malaria control in these countries is used for vector control and malaria treatment. This work also provides much needed information on vector ecology and behavior, insights that could help Peru and Guyana to better administer LLINs and IRS [41]. The maps could also be used to conduct anthropological studies, which examine the use of maps at the state or municipal levels to help shape priorities.

The Amazonian countries could also learn from some of their African counterparts using risk maps to bolster their malaria control and to secure funding. For example, Omumbo et al. [297] observed that about 43 of the 47 malaria endemic African countries included in their systematic review defined malaria risk using at least one risk map. Although the risk maps varied, they found that maps created using national data through in-country research partnerships had greater utility. However, only Zambia, Zimbabwe, Somalia and Kenya have used risk maps to tailor intervention plans or resource allocation, with noticeable improvements in their malaria control efforts.

The regression results presented in Chapter 4 also have implications on malaria control and policy decisions in Colombia. For instance, the negative relationship reported for homicides may be tied to increasing urbanization in the area, leading to better health care services, lower crime rates and by implication lesser malaria cases. With internal displacement, malaria risk may be lower in the areas where people move out from but
higher in their new locations. Infected individuals expelled to other areas create a reservoir of potential infection in their new locations given the presence of competent vectors and the degree of immunity of the population. Although temperature had the strongest association with malaria risk in the model, very little policy changes can be made to alter temperature, especially in view of climate change. However, changes in LULC influence temperature and policy decisions may be applied to reduce climate change impacts. For example, laws that aim to limit deforestation may be enforced as is done in Brazil by increasing protected areas, as well as investments in satellite monitoring systems [298] while urban development may also be planned in ways that limit the creation of urban heat islands.

5.3. Limitations of study

The main limitation of the study was the availability of vector and malaria data. In contrast, environmental data sets have become more plentiful over the past few years and thus these provide an important source from modeling the disease. For instance, in Chapter 2, modeling *P. falciparum* and *P. vivax* distributions separately may have been more informative, with the possibility of directing interventions specific to each parasite species [299], but my data access was limited to pooled malaria data in which the infections were not distinctly identified. However, of the two parasites, modeling *P. vivax* distribution may have been more arduous given its latent hypnozoite stage [299], which may be difficult to account for in the models, especially for the future scenarios. In Chapter 3, I acknowledge the possibility of temporal and geographical bias in the sampling of occurrence points as a result of multiple collectors and the variable time of collection. Moreover, the dearth of up-to-date secondary and tertiary road network data
for the study area may also have limited the estimation of risk based on access to roads, particularly in the northern parts of the NSA. Notwithstanding these data limitations, environmental data can only explain a limited amount of the variance and many other factors need to be considered (e.g., human movement, political will to implement elimination efforts, etc.).

Another major limitation is related to the methods and how the models were used. With the Maxent models, I assumed a constant rate of deforestation in the LULC model and that deforestation and climate change are independent, which may be unrealistic given the number of studies that have linked deforestation with global and regional climate change [300, 301]. I also had no information on detection probability, i.e. the probability of a species being detected given that it occupies a location (occurrence probability) and that sampling was conducted in that location [302]. This probability often varies with the same covariates that determine occurrence probability [303], and when not separated from occurrence probability, may under- or over-estimate model results [303]. Thus, I ask readers to exercise caution in interpreting model results. The subjective nature of the MCDA approach in assigning fuzzy functions and weights also undoubtedly produces some biased outcomes as well as probable inflation of risk scores when correlated variables are used [27, 83]. Nevertheless, the risk maps in this dissertation provide a novel set of heuristics to spark further research and inquiry that can lead to more comprehensive understanding of dynamic malaria risk at present and in the coming decades.
5.4. New research frontiers

Although there has been substantial advancement in the quantification of malaria risk from traditional deterministic modelling approaches to environmental modelling such as the ones employed in this dissertation, new frontiers for malaria risk mapping lie ahead. For example, incorporating the impact of human mobility (within and between locations, from national to local scales), as well as malaria control and interventions, in the spatial distribution of malaria risk in my study area would have been ideal, but accessing such data and assessing their impacts remain challenging. However, a new suite of geostatistical modeling approaches able to accommodate these measures are now being developed [46], which other researchers can take advantage of. Including human mobility and connectivity in the delineation of malaria risk could help to determine areas of likely importation of cases [304] or regions acting as sources and sinks of imported cases [305-306] especially for countries nearing elimination. But beyond understanding general human movements, other researchers could focus on specific group behaviors, such as those of indigenous communities able to contract and disseminate malaria, as such studies could aid governments in efficient deployment of limited resources [306].

Moreover, large volumes of data on disease surveillance and control are increasingly available from a variety of big data sources from the web [307, 308]. Taking advantage of the improvements in computational capabilities and these data, other researchers could produce in the near future predictive maps of malaria risk, which could be updated in real-time, thus facilitating their rapid translation in public health policy [306, 307].
Furthermore, other research could focus on developing new methods of quantifying spatial and temporal heterogeneity in malaria risk at the population level in countries still at the control stage and at individual levels in countries nearing elimination, to ensure more efficient allocation of scarce resources [309]. Developing risk maps based on location of houses [310] or at individual levels are necessary to determine whether local malaria infections are autonomous or imported [309]. To do this, the vulnerability of the population (i.e., the rate of malaria importation) and their receptivity (i.e. the potential for local transmission) should be quantified to determine the maliogenic potential of the country (i.e., expected number of local cases arising from malaria importation) [309, 311]. Such calculations help to estimate the reproductive number, R₀ (the number of secondary cases that could arise from a single malaria infection), which helps to guide strategic planning and evaluation of malaria interventions [309, 312].

Finally, taking a more interdisciplinary approach in understanding and tackling malaria questions is necessary. The vast majority of research on malaria, particularly in South America, are focused on medical and environmental approaches, overshadowing studies on social dimensions. Employing quantitative and qualitative approaches from the social sciences in studying individual, communities and experts’ perceptions of risk, researchers can advance our understanding of malaria and the necessary elements for its elimination from those unique social science perspectives.
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VITA

Temitope O. Alimi was born in Lagos, Nigeria, on August 28, 1979. She received her elementary education at Anglican Girls Primary School and her secondary education at Lagos Anglican Girls Grammar School. In December 2000 she entered the Geography Department of University of Lagos from which she was graduated with the B.Sc. degree in December 2005. After completing a one-year National Youth Service in 2007, she was admitted to Cambridge University, UK where she graduated with the M.Phil in Geographic Information Systems and Remote Sensing in 2008. She was employed as an Assistant Professor in the University of Lagos until 2011. In August 2011 she was admitted to the Graduate School of the University of Miami, where she was granted a Ph.D. degree in May 2016.