An Epidemiological Profile of Malaria in Ethiopia

National Malaria Control Team & Ethiopian Public Health Institute, Federal Ministry of Health

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World Health Organization

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Addis Ababa University

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The INFORM Project

Department of Public Health Research

Kenya Medical Research Institute - Wellcome Trust

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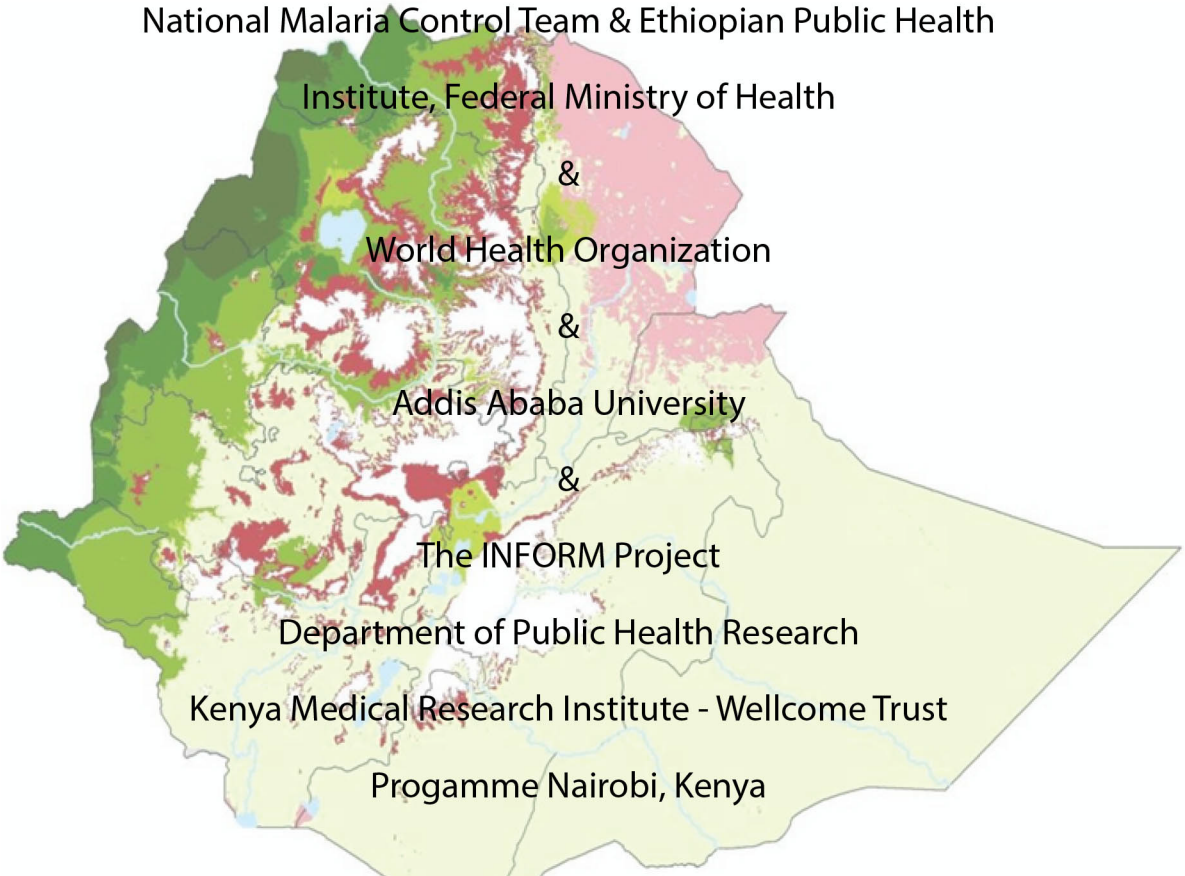

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Federal Democratic Republic of Ethiopia
Ministry of Health

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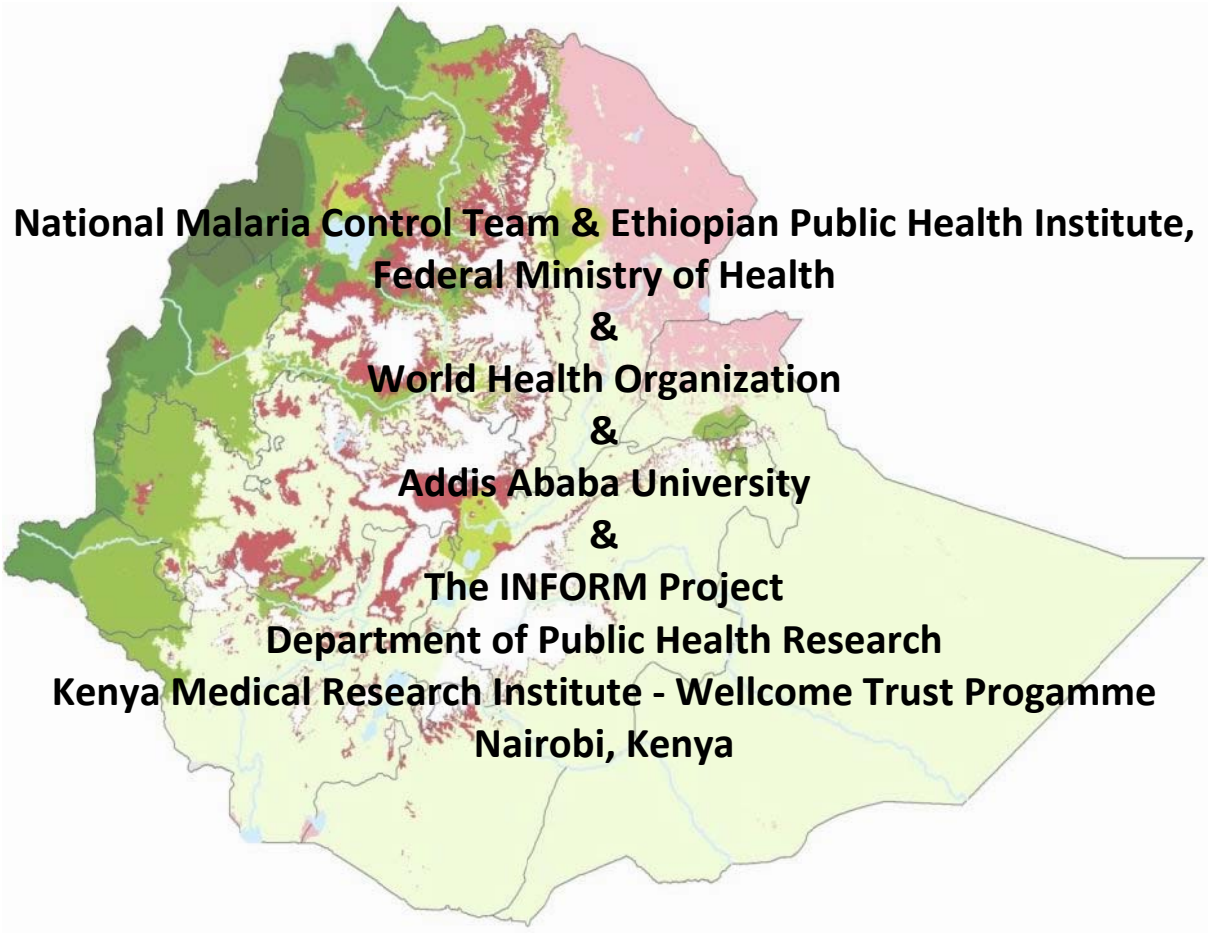

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Abbreviations

ABER	Annual Blood Examination
ACD	Active Case Detection
AJOL	African Journals Online
AL	Artemether-Lumefantrine
ANVR	African Network for Vector Resistance
AOI	Africa Orientale Italiana
API	Annual Parasite Incidence
APRD	Arthropod Pesticide Resistance Database
BIC	Bayesian Inference Criteria
CGIAR	Consultative Group for International Agricultural Research
CPC	Climate Prediction Centre
CQ	Chloroquine
CRDT	Constrained Refined Delaunay Triangulation
CSA	Central Statistical Agency
DCW	Digital Chart of the World's Populated Places
DHS	Demographic and Health Surveys
DDT	Dichloro Diphenyltrichloroethane
DRC	Democratic Republic of Congo
EPHI	Ethiopian Public Health Institute
EMRO	Eastern Mediterranean Regional Office
EVI	Enhanced Vegetation Index
FAO	Food and Agriculture Organization
FEM	Fine Element Method
FEWS-NET	Famine Early Systems Network
FIND	Foundation for Innovative New Diagnostics
FMoH	Federal Ministry of Health
G6PD	Glucose 6-Phosphate Dehydrogenase
GAUL	Global Administrative Unit Layers
GIS	Geographic Information Systems
GF	Gaussian Field
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GLWD	Global Lakes and Wetlands
GMEP	Global Malaria Eradication Programme
GMP	Global Malaria Programme
GMRF	Gaussian Markov Random Field
GPS	Global Positioning Systems
GRF	Gaussian Random Field
GRUMP	Global Rural Urban Mapping Project
HMIS	Health Management Information System
HIMAL	Highland Malaria Project
HIS	Health Information Systems

HSDP	Health Sector Development Programme
IAMAT	International Association for Medical Assistance to Travelers
ICA	International Co-operation Administration
IDP	Internally Displaced Persons
IDSR	Integrated Disease Surveillance and Response
IGE	Imperial Government of Ethiopia
IGME	Inter-Agency Group for Child Mortality Estimation
INLA	Integrated Nested Laplace Approximations
IPT	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
LLINs	Long Lasting Insecticidal Nets
LSE	Low Stable Endemicity
malERA	Malaria Eradication Research Agenda
MAP	Malaria Atlas Project
MAPE	Mean Absolute Prediction Error
MARA	Mapping Malaria Risk in Africa
mASL	Metres Above Sea Level
MBG	Model Based Geo-Statistics
MCST	Malaria Control Support Team
MDTPs	Malaria Detection and Treatment Posts
MeSH	Medical Subject Headings
METC	Malaria Eradication Training Centre
MIS	Malaria Indicator Survey
MODIS	MODerate-resolution Imaging Spectroradiometer
MoH	Ministry of Health
MPE	Mean Prediction Error
MPR	Malaria Programme Review
NASA	National Aeronautics & Space Administration
NDVI	Normalised Difference Vegetation Index
NMES	National Malaria Eradication Service
NOAA	National Oceanic and Atmospheric Administration
NOCMVD	National Organization for Control of Malaria & other Vector Borne Diseases
OA	Open Access
ODA	Overseas Development Assistance
PCR	Polymerase Chain Reaction
PA*Pf*PR_{2-10}	Population adjusted *Pf*PR_{2-10}
PfPR_{2-10}	Age-corrected *Plasmodium falciparum* parasite rate in children aged 2-10 years
PHC	Primary Health Care
PHEM	Public Health Emergency Management
PMI	President's Malaria Initiative
PQ	Primaquine
RBM	Roll Back Malaria
RDTs	Rapid Diagnostic Tests

SD	Standard Deviation
SMC	Seasonal Malaria Chemoprevention
SMCO	Sector Malaria Control Offices
SP	Sulphadoxine-Pyrimethamine
SNNPR	Southern Nations Nationalities and Peoples Region
SPDE	Stochastic Partial Differential Equations
SRTM-DEM	Shuttle Radar Topography Mission Digital Elevation Model
TPC	Tactical Pilotage Charts
TSI	Temperature Suitability Index
UN	United Nations
UNDP	United Nations Development Programme
UNHCR	United Nations High Commissioner for Refugees
UNICEF	United Nations Children's Fund
UoP	University of Pennsylvania
USAID	United States Agency for International Development
WDP	Water Dispersible Powder
WHO	World Health Organization
WorHO	Woreda Health Office

Executive summary

This epidemiological review of malaria has been developed to assist partners involved in malaria control and elimination in Ethiopia.

We have assembled and geo-coded national data on malaria parasite prevalence, parasite species, dominant vector species, altitude, aridity and the location of areas of special ecological risk. These data have been spatially and temporally modeled to provide a plausible, evidence-based stratification of malaria risk at 1x1 km resolution across Ethiopia. This information has been re-configured with population density to provide risk metrics for most of the 731 *woreda* used to plan malaria control and elimination.

The report provides a contextual narrative on the history of malaria risk mapping and elimination efforts since the 1940s and attempts to draw upon this experience in providing a more informed risk stratification for current control and elimination ambitions.

An. arabiensis and *An. funestus* have been the dominant malaria vectors for decades and have a ubiquitous and sympatric distribution across the country. There is some evidence that following 60 years use of DDT, *An. funestus* contributes less to parasite transmission today compared to the 1960s. *An. pharoensis* and *An. nili* play minor roles in transmission. *An. pharoensis* is widespread, whilst *An. nili* has a much restricted ecological niche.

The ecology of malaria transmission in Ethiopia differs significantly from that of its southern neighbours, dependent in space and time on dramatic variations in elevation, cycles of drought and excessive rainfall and changes in human settlement. This unique malaria ecology has important implications for its control.

Plasmodium vivax transmission is high, among a population with receptive red cell polymorphisms that support *P. vivax* infection. However, far less is known about the epidemiological distribution or clinical consequences of this parasite compared to *P. falciparum*. *P. malariae* and *P. ovale* are remarkably rare. We have focused on mapping the risks of *P. falciparum* but there is an urgent need to improve the epidemiological stratification of *P. vivax* in Ethiopia.

Using model based geo-statistical techniques to interpolate *P. falciparum* prevalence data from 1380 locations, we predict that only 16% of Ethiopia's population live in areas where malaria transmission is stable and represented by a parasite rate in children aged 2-10 years (*Pf*PR_{2-10}) above 1% in 2010; and only 0.5% of the population experience transmission intensity above a predicted *Pf*PR_{2-10} of 10%. Areas of stable transmission require increased coverage of insecticide-treated nets, with attempts at reaching universal coverage, so that these areas may undergo a rapid epidemiological transition over the next five years.

There are large areas of Ethiopia that have, since 2000, supported very low *P. falciparum* parasite transmission intensity (*Pf*PR_{2-10} <1%), covering 653,000 km^2 and inhabited by an estimated 32.2 million people in 2010 (39% of the total population). Combined with areas of extreme aridity (inhabited by 0.84 million people), these "near zero transmission" areas are the dominant feature across the country and represent operational challenges for malaria control. It is unlikely that universal treated net coverage or household insecticide spraying would be a cost-efficient approach to control and attempts to reduce sites of focal transmission combined with household contact follow-up is probably a more viable means of disease control.

Given the topography and human settlement patterns of Ethiopia, 27% of the 2010 projected population live in areas where low average ambient temperatures affect the parasite's development in the mosquito such that transmission cannot occur. Bordering this malaria free zone, 17% of Ethiopia's population lives in highland fringe areas above 2000 mSAL. These communities have a poorly developed immune response to the consequences of malaria infection and are at high risk of epidemics following small aberrations in climatic conditions or when they travel to higher risk areas.

Ethiopia has been plagued by cycles of epidemics and better prediction, preparedness and response systems are necessary to mitigate their effects in affected areas.

Finally, we have made some provisional maps of where additional special risk areas might need additional strategic approaches to mitigating risks including the suitability of urban malaria control, refugee populations and the rapidly changing landscape of dams and water management for agriculture. These areas can be better defined through collaboration across government sectors and should be considered in future epidemiological stratification mapping.

We have focused on using widely available spatial data on parasite prevalence. Modeling these data has demonstrated the very constrained regions of "intense," stable transmission in the northwestern areas of the country, bordering Sudan. Parasite prevalence, however, is a far less valuable metric of malaria risk when transmission intensity is low, a characteristic of the majority of Ethiopia's land mass. There is an urgent need to improve, reconcile and model malaria case incidence. This will support metrics for pre-elimination, monitoring the progress of elimination and importantly serve as an entry point for more reactive, focal control approaches.

Different approaches to risk profiling should be compared: a) ecological and parasite prevalence (as provided in this report); b) more empirical climate driven time-series vulnerability mapping approaches; and c) the use of IDSR and HMIS facility-level data. This is work in progress and will provide layers of information to improve targets for future predicted risks, control options and areas targeted for elimination.

We have attempted to resolve malaria transmission risk strata at *woreda* level. There is presently an incomplete *woreda* map and the very focal, short-distance changes in malaria risk also means that 11% of *woreda* fall between several risk strata highlighting the need for very local level risk mapping.

The epidemiological profile is intended as a living, dynamic process of evidence generation, cyclic generation of updated models and new layers of information, research and enquiry necessary for effective control planning. New information on parasites, vectors, drug and insecticide resistance, health facility mapping (not attempted here), case-incidence, human settlement and administrative boundaries used for planning must continue to be assembled.

Dwindling resources, mounting insecticide resistance, recurrent epidemics, and underdeveloped health systems and surveillance capacity call for an improved use of epidemiological evidence for planning control. Such evidence is crucial to the development of a much stronger business case for continued funding to support the achievement of the ambitious goals of the national strategy by 2020.

1. Introduction

Little was known about the epidemiology of malaria in Ethiopia before the late 1930s. The earliest surveys of malaria were conducted between 1936 and 1941 during the Italian occupation, by malariologists from the Instituto di Malariologia, Rome. These investigations provided important geographic reconnaissance of dominant vectors, infection prevalence and the general health status of communities from the coast in Somalia to the northern Eritrean territories under the *Africa Orientale Italiana* (AOI). These studies laid the foundation for understanding the basic malaria epidemiology across the country related to altitude, seasonality, factors related to agriculture and vectors (Section 3).

In 1952, the Imperial Government of Ethiopia (IGE) invited the malariologist, Sir Gordon Covell, to assess the malaria situation in the southern region of Lake Tana. On a second visit in 1955, Covell collected baseline malariometric data at several sites in order to describe the epidemiology of malaria at different sites across the country (Section 3). He concluded from his reconnaissance survey that "*the future of malaria control depends on the creation of a permanent antimalarial organization within the framework of the Public Health Service*" and "*the first essential is the provision of trained Ethiopian staff*" [Covell, 1957].

The IGE's first organized malaria control efforts were structured as eradication projects from the mid 1950s and supported by the USA International Co-operation Administration (ICA)[1], WHO and UNICEF. Four pilot sites were established in present day Ethiopia: the Upper Awash Valley, the Kobo-Chercher Plain and the Dembia Plain to establish the technical feasibility of eradication at high altitudes (>1,000 mASL) and an additional site in the lowland area of Gambella on the Sudanese border [Fontaine & Najjar, 1959a; 1959b; Zaphiropoulos, 1959][2]. Control focused on indoor residual spraying (IRS) with dichloro diphenyltrichloroethane (DDT) and building up a cadre of local staff trained in vector control methods.

A major epidemic in between July and December of 1958 affected three quarters of the densely populated areas of the central highland provinces of Shewa, Gojjam, Begemeder and Wollo (1600 - 2150 mASL; *circa* 100,000 Km^2) causing over 3.5 million cases of malaria and an estimated 150,000 deaths [Fontaine et al., 1961].

Despite a mixed set of results from the pilot projects, the IGE maintained a strong commitment to national eradication, galvanized by the devastating epidemic in 1958/1959 and followed an elimination pathway at a time when there was a growing consensus in the Africa region that elimination was not feasible.[3] In June 1959, the national Malaria Eradication Training Centre (METC) was opened at Nazareth, near the Awash Valley project that became the base for the National Malaria Eradication Service (NMES). In March 1966, concerted eradication efforts began, with the ambition being to eradicate malaria from

[1] The USA ICA became the United States Agency for International Development (USAID) in 1966

[2] A fifth project site was located in Massawa and Kulu in Eritrea, then part of Ethiopia

[3] Ethiopia was then part of the Eastern Mediterranean Regional Office (EMRO) and many EMRO countries were still aggressively following elimination strategies, notably those in North Africa

Ethiopia by 1980 [Chand, 1965; Gish, 1992]. Over the subsequent years, large amounts of detailed epidemiological data were assembled and mapped, millions of people were protected with DDT and millions of dollars invested in elimination by the IGE and overseas donors.

Despite scaled coverage of DDT spraying, an independent review team in 1970 concluded that "*the anti-malaria activities carried out have thus provided considerable benefit for the population protected, and for these reasons the energy, man-power and substantial funds expended may be justified. On the other hand, in spite of four years of spraying, interruption of transmission - which is the sine qua non for achieving eradication within a specified time limit - has not been demonstrated in any sizeable portion of Area A, not even in a situation with a comparatively favourable operational and epidemiological favourable conditions such as those prevailing in the Debre Zeit Sector*" [Anon, 1970].

The revolution of 1974 changed the country's political landscape dramatically, including views related to how health care and malaria prevention might be integrated into broader rural health sector development strategies [Gish, 1992]. Furthermore, the revolutionary government was justifiably concerned by a long-term dependence on overseas aid. In April 1977, a third international review team comprised of a technical team from WHO and USAID, staff of the NMES and the Ethiopian Government, visited Ethiopia. The review team concluded that "*eradication of malaria from Ethiopia is not feasible under present circumstances even in the foreseeable future*" [Anon, 1977], but recommended that eradication should be maintained as a long-term goal while selective control, rather than blanket spraying, should be applied based on the epidemiology of malaria and that malaria control should be integrated within basic health services [Anon, 1977]. Ethiopia subtly moved from an eradication ambition and embraced malaria "control" with the objectives to reduce morbidity, mortality and inability to work.

The National Organization for the Control of Malaria and other Vector Borne Diseases (NOCMVD) evolved from the NMES and continued to pursue the longer term objective to eradicate malaria with effectively planned and selected control measures through the primary health care (PHC) system [Anon, 1970]. During the 1980s, DDT and surveillance were still maintained as activities of Sector Malaria Control Offices (SMCOs). The SMCOs were supported by more than 1,400 malaria detection and treatment posts (MDTPs) that conducted regular active case detection among 800,000 people, costing over US$ 500,000 per year [Gish, 1992; Teklehaimanot, 1986a].

Following decades of neglect, the 1990s witnessed a renewed interest in malaria as a major global public health threat [WHO, 1993]. Ethiopia was emerging from civil war that ended in May 1991, and was suffering from a collapsed health infrastructure including a much depleted malaria control service. Epidemics increased in frequency and burden [Teklehaimanot, 1991; Tulu, 1996; Cohen et al., 2012]. The alarming malaria mortality statistics led to a new Plan of Action for Malaria Control [FMoH, 1993]. In 2000, the Government signed the Abuja declaration in support of the Roll Back Malaria (RBM) commitments to halve malaria morality by 2010 [WHO, 2000]. A Malaria Control Support Team (MCST) comprising representatives from the FMoH, donors, and NGOs was set up to provide technical assistance to the government. In 2002, the Global Fund to fight AIDS,

Tuberculosis and Malaria (GFATM) was established and was to award Ethiopia over US$ 400 million during Rounds 2, 5 and 8 between 2003 and 2014. From 2008 the US President's Malaria Initiative (PMI) provided over US$ 197 million and the Federal Government continues to support national malaria control efforts. Other significant funders have included UNICEF, the World Bank and WHO. These funds have supported three national malaria strategic plans since 2000, promoting effective case-management with efficacious drugs, targeting (IRS) and insecticide treated net distribution (ITN) and selecting other forms of integrated vector management strategies [FMoH, 2001; 2006; 2009].

In 2010, the national malaria strategy was launched covering the period to 2015 with a renewed emphasis on elimination [FMoH, 2010]. Its ambition was to achieve malaria elimination within specific geographical areas with historically low malaria transmission by 2015, near zero malaria transmission in the remaining malarious areas of the country by 2015 and to eliminate malaria from Ethiopia by 2020 [FMoH, 2010]. The US$ 264.5 million Global fund application in 2010 (Round 10) was specifically designed to resource pre-elimination ambitions [GFATM, 2013].

The Ethiopian government remains committed to an elimination agenda as part of its pending national strategic plan to be launched in 2014. The ability to design an effective elimination strategy, and more importantly, measure its progress, will depend on an intimate knowledge of the spatial patterns of risk across the country [Feachem et al., 2010; Moonen et al., 2010; Cohen et al., 2010].

At the launch of the RBM initiative, the call for universal coverage of all available interventions was probably an appropriate response to the epidemic that affected most of sub-Saharan Africa during the mid-late 1990s [WHO, 2000; Snow et al., 2012]. At a time when the international donor community is constrained by the global financial crisis, accessing overseas development assistance (ODA) and using limited national domestic funding for malaria control will require a much stronger evidence based business-case. This future business-case must be grounded in the best available epidemiological evidence to predict the likely impact of future interventions, assess the impact of current investment and, equally important, demonstrate what might happen should funding and intervention coverage decline.

The use of survey data, maps and epidemiological intelligence was a routine feature of control planning across many African countries during the Global Malaria Eradication Programme (GMEP) era from the mid-1950s. The IGE's first efforts at malaria elimination during the 1960s and 1970s championed detailed epidemiological reconnaissance. Data included epidemiological descriptions of transmission, vectors, topography and climate. There was recognition, over 50 years ago, that one important source of planning data was infection prevalence among children aged 2-10 years ($Pf\mathrm{PR}_{2\text{-}10}$). This was used to define categories of endemicity risk, designed to guide and monitor progress towards malaria elimination targets [Metselaar & van Thiel, 1959; Macdonald & Göeckel, 1964; Lysenko & Semashko, 1968].

The art and skills necessary to design malaria control and elimination based on an understanding of the spatial epidemiology was lost during the 1980s when the agenda for

malaria control fell under a less specialized, integrated primary care mandate focused on managing fevers. In 1996, there was a renewed plea for better malaria cartography to guide malaria control in Africa [Snow et al., 1996a] and over the last decade there has been a growth in spatial data on malaria, climate and populations not available to malariologists or programme control managers 60 years ago. The growth in data has been accompanied by the development of statistical approaches to model and map risk and intervention access in space and in time using Model Based Geo-Statistics (MBG) [Diggle & Ribeiro, 2007].

Here we attempt to assemble the epidemiological evidence base for a plan of action targeted at malaria elimination in Ethiopia. This work aims to draw together historical and contemporary data on the spatial patterns and constraints to parasite transmission, distributions of dominant vector species and resistance data for drugs targeting parasites and insecticides targeting vectors. Plausible stratifications of risk are provided that are cognizant of the history of malaria strata in Ethiopia and might provide an evidence platform for sub-national district planning of targeted control to promote the long-term ambition of elimination.

2. Context: geography, population and administration

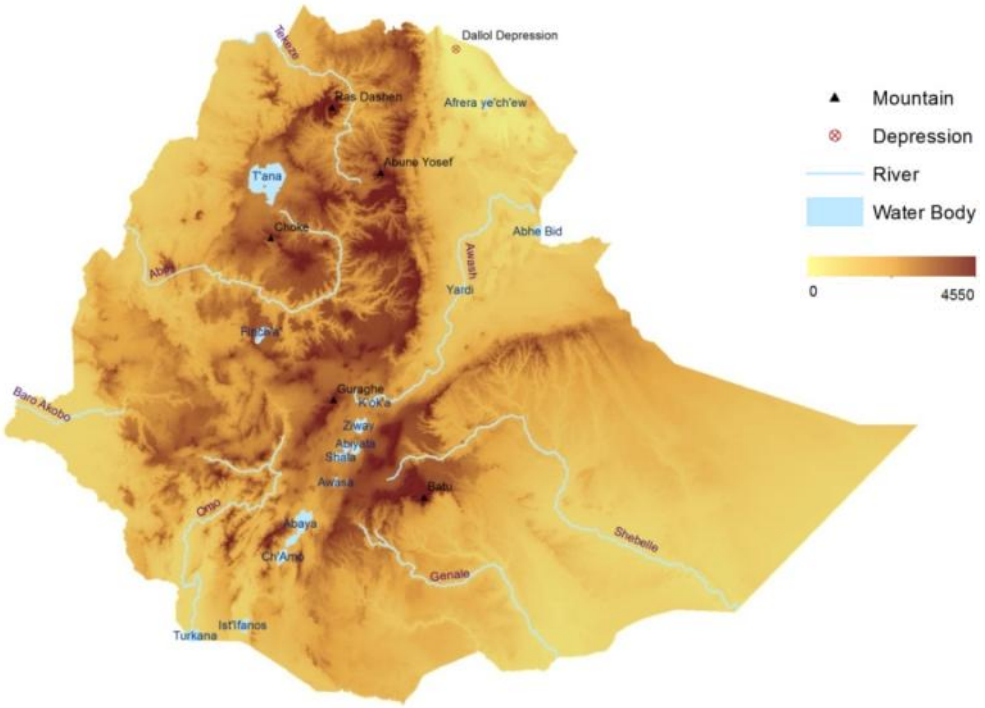
2.1 Location and geographical features

The Federal Democratic Republic of Ethiopia is located in the Horn of Africa, lying between latitudes 3-18°N and longitudes 33-48°E. It is a landlocked country[4], bordered by Eritrea in the east and northeast, Djibouti and Somalia in the east and southeast, the Republic of the Sudan to the west and Kenya in the southwest. Ethiopia has a general elevation ranging from below sea level to 3,000 metres above sea level (mASL) with mountain ranges, cratered cones and active volcanoes.

The Ethiopian highlands constitute one half of an uplifted dome, the other half being centred in southern Yemen, where the three rift systems of the Great Rift Valley meet. In Ethiopia this dome is divided into the northern and southern massifs by the upper reaches of the Eastern Rift Valley (Valley of Abay, Blue Nile). Of these, the northern massif is the larger and more elevated, with the Simien range, north of Gonder. The highest point, at 4,550 mASL, is Ras Dashen Terara (Figure 2.1). The southern massif (Somali or Eastern Plateau), forms a tilted block sloping gently south eastwards towards the Indian Ocean. Approximately a third of the country (376,000 km^2) lies above 1500 mASL, of which 45% (168,135 km^2) is higher than 2000 mASL. The Great Rift Valley consisting of desert, semi-desert and savannah, divides the country into the northwestern highlands and the southeastern highlands. The lowest point is the Dalol Depression (Figure 2.1) in the Denakil Desert at 125 m below sea level, on the northern border with Eritrea and one of the hottest places on earth.

[4] The entire coastline along the Red Sea was lost with the *de jure* independence of Eritrea on 24th May 1993

Figure 2.1: Major relief (browns rising to 4550 mASL), rivers, lakes and key features in Ethiopia[5]



All of Ethiopia's rivers originate in the highlands. Most notable is the Blue Nile, the country's largest river. The Blue Nile and its tributaries account for two-thirds of the Nile River flow below Khartoum in the Republic of Sudan. As part of the Nile system, the Blue Nile, Tekezé, and Baro rivers (Figure 2.1) account for approximately half of the country's water outflow. The Awash River flows through the northern half of the Great Rift Valley (Figure 2.1) and several dams along this river provide hydroelectric power and irrigation for major commercial plantations. The Awash flows east and disappears into saline lakes near Ethiopia's border with Djibouti. The southeast is drained by the Genale and Shebele Rivers and tributaries while the southwest is drained by the Omo River (Figure 2.1).

Climate is affected by altitudinal limits and altitude is used to describe the climate zones in Ethiopia: *kola* or hot lowlands (<=1500 mASL; mean annual temperature 23-33^{o}C), *weyna dega* (1500-2400 mASL; mean annual temperature 16-29^{o}C) and *dega* or cool highlands (>2400 mASL; mean annual temperature 10-16^{o}C). Rainfall is strongly correlated with altitude and thus varies significantly across the country. The main rainy season, known as *kremt*, is from June to August and rain falls across most regions during this period. March–May is the second wet season and is the main rainy season in the southern and southeastern parts of the country. The southern and southeastern regions also receive moderate rainfall during September–November. The dry spell between the two rainy seasons lasts only a few weeks over some regions and December, January and February are mostly dry. Thus, some areas receive rainfall for several months of the year; others for only

[5] The DEM is at 90m resolution available at http://www.diva-gis.org/gdata; rivers shape file developed by the Ethiopian Ministry of Water Resources and available at https://cod.humanitarianresponse.info/; both accessed on 13th October 2013

a few months and some areas experience two distinct rainfall seasons. The well-known recurrent droughts, famine and epidemics of diseases, notably malaria, that have characterized Ethiopia's history are tied to a combination of the complex topography and long, and short-term rainfall cycles, to the extent that rainfall and altitude are the two major determinants of malaria transmission that have been used in risk mapping over the last two decades (Section 3.1).

2.2 Population distribution

Ethiopia is currently Africa's second most populous nation with a total *de facto* population of 73.75 million according to the 2007 census. The annual population growth rate is 2.6% [CSA, 2010] and the population was estimated to reach 86.5 million in 2012 [UN, 2011]. Over 2.7 million people live in the capital city of Addis Ababa. The crude population density was 34.0 persons per km^2 in 1984, 48.6 persons per km^2 in 1994 and 67.1 persons per km^2 in 2007 [CSA, 2010] but this is highly variable across the country. The majority of people live in the highland areas and over 80% of the population live in the Amhara, Oromiya and SNNP Regions.

For disease mapping purposes, very high spatial resolution population distribution maps are required. Recently, spatial modelling techniques for the reallocation of populations within census units have been developed in an attempt to overcome the difficulties caused by input census data of varying, and often low, spatial resolution [Linard et al., 2012]. In brief, a dasymetric modelling technique [Mennis, 2009] was used to redistribute population counts within the 17,363 urban and 69,462 rural enumeration areas used in the 2007 census and adjusted for total populations presented across 11 regions reported in the 2007 census assisted by land cover data sets and satellite imagery[6]. The resulting population density map is shown in Figure 2.2.

The pace of urbanization since the end of the *Derg* has not been even across the regions [Schmidt & Kedir, 2009] and projections for the country as a whole suggest that only 23% of the population will live in urban areas by 2030 and 35% by 2050, far less than many neighbouring countries [UN, 2011]. With only 16% of the population living in urban areas, the country is one of the least urbanized countries in the world. Addis Ababa constitutes about a quarter of the urban population of the country [CSA, 2012].

The 2007 census defines an urban centre as "*a locality with 2,000 or more inhabitants*" [CSA, 2012]. Defining an urban settlement only by the numbers of residents without a spatially constrained component poses challenges in measuring the impacts urbanization in space and time. Therefore we have used an urbanization classification that combines the spatial extent of urban settlements developed by the Global Rural Urban Mapping Project (GRUMP) and population density developed by the AfriPop project [Linard et al., 2012; Figure 2.3].

[6] A different population weight was assigned to each land cover class in order to shift populations away from unlikely populated areas, such as game reserves or arid deserts and concentrate populations in built-up areas. The net result was a gridded dataset of population distribution (counts) at 0.1 x 0.1 km resolution. The population distribution datasets were the adjusted using national rural and urban growth rates [UN, 2011] and made to match the total national population estimates for 2000 and 2010.

Figure 2.2: Modeled population density projected to 2010 using methods described in the text and represented as increasing density as shown in legend below. Ranging from zero to *c*. 123,000 per km^2

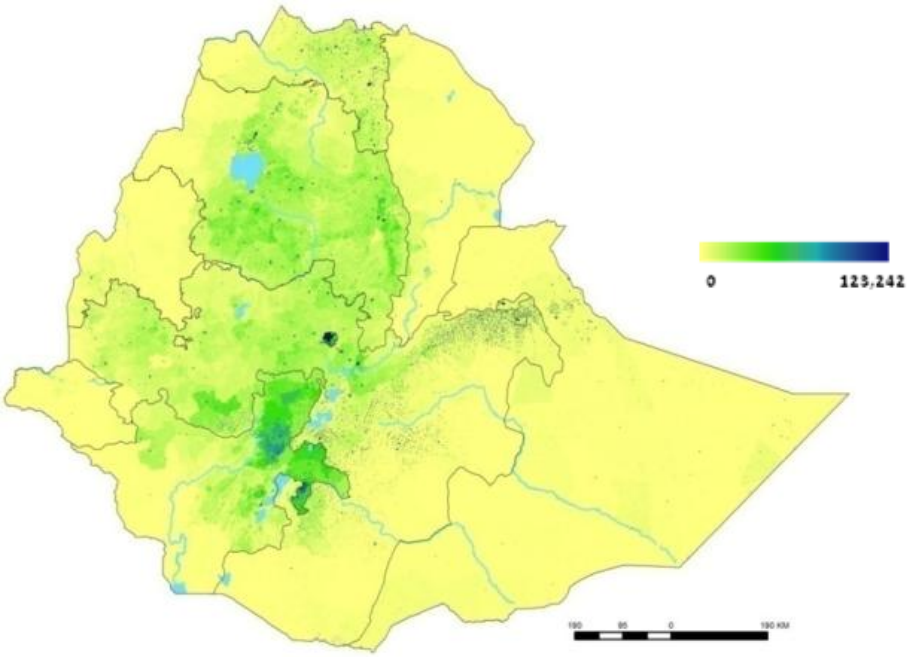
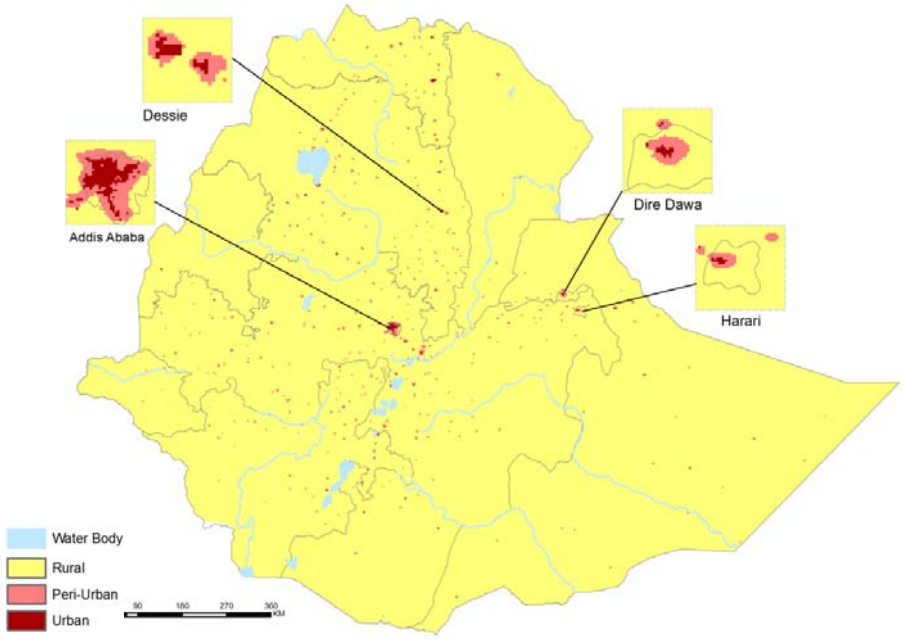


Figure 2.3: Urban and peri-urban settlements in Ethiopia[7]



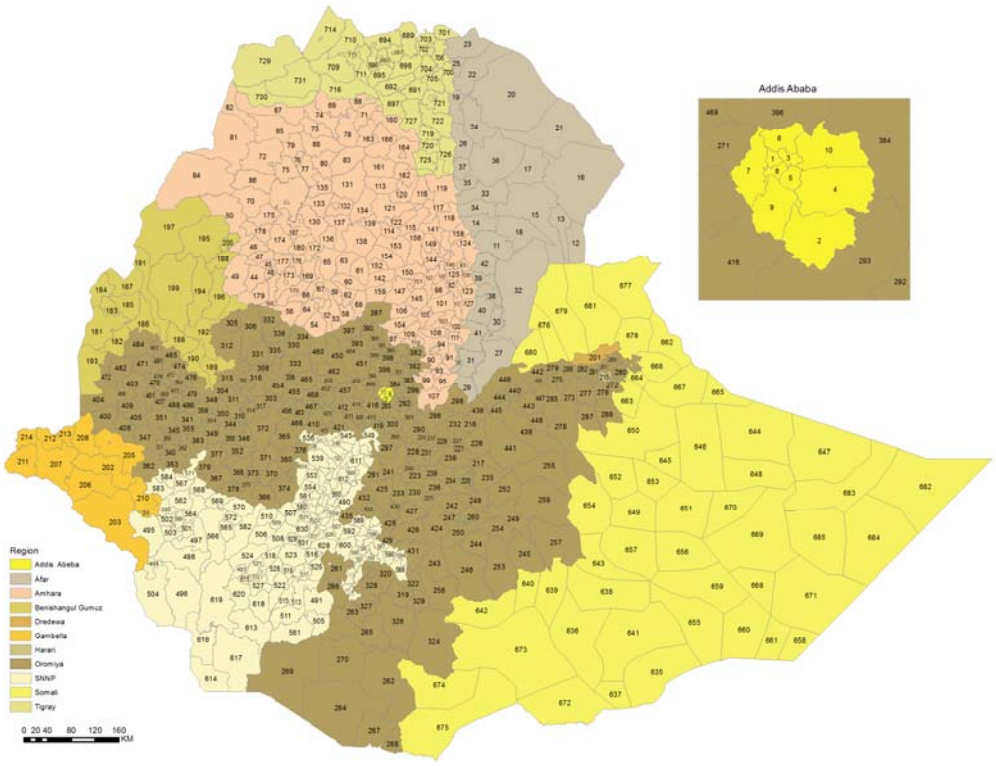
[7] GRUMP urban extent grids distinguish urban and rural areas based on a combination of NOAA's Night-time lights dataset [Elvidge et al., 1997], settlements data and population counts. Population counts used were derived from GRUMP spatial population database based on areal weighted census input data [Balk et al., 2004] while settlements data sources include ESRI's Digital Chart of the World's Populated Places (DCW), Tactical Pilotage Charts (TPC) from Australian Defense Imagery and Geospatial Organization and some LandSAT-derived polygons [Balk et al., 2004; CIESIN, 2013]. To define urban extents, a border was defined around each set of contiguous lighted pixels whose total population count was greater than 5,000 persons. The GRUMP urban extent was further refined to produce a 'peri-urban' classification constrained by population density using the Afripop data [Linard et al., 2012; AfriPop, 2013]. Urban areas were defined as locations with a density of more than 1,000 persons per km^2 with the rest of the GRUMP urban extent defined as peri-urban.

2.3 Decentralized planning

Three tiers of administration have been established: the central government, 11 regional governments (nine states plus two metropolitan areas) and the *woredas* or districts. The management of social services, in particular, health, education, agricultural extension and water supply, is devolved to the *woredas* [Assefa & Gebre-Egziabher, 2007]. They are based on population size, encompassing 100,000 – 120,000 people [Hasen, 2001]. *Woreda* based plans and sector budgets are submitted to Regional Health Bureaus and health development partners to ensure that the plans are in line with budgets. The Woreda Health Office (WorHO) is the administrative body for health planning at sub-national level [FMoH, 2005]. The regional level defines its own constitution regarding the governance function of *woredas*. The smallest unit of government is the *kebele*. These are grassroots units comprising population groups of 5,000 governed by approximately 100 council members and originally intended for population enumeration.

The current exact number of *woredas* is unclear as changes are frequent and there is varied use of terms in describing *woredas* particularly those in urban centres and within the two city administrations. A 2008 World Bank study counted 769 (671 rural and 98 urban) *woredas* across the nine Regions based on the number of *woreda* council electoral seats voted into during local government elections [Yilmaz & Venugopal, 2008], while the most recent Health Sector Development Programme (HSDP-IV) mentions 817 *woredas* and over 16,253 *kebeles* [FMoH, 2010]. For the purposes of this report we have defined 731 *woreda* boundaries, using a shape file provided by the WHO country Office (Figure 2.4).

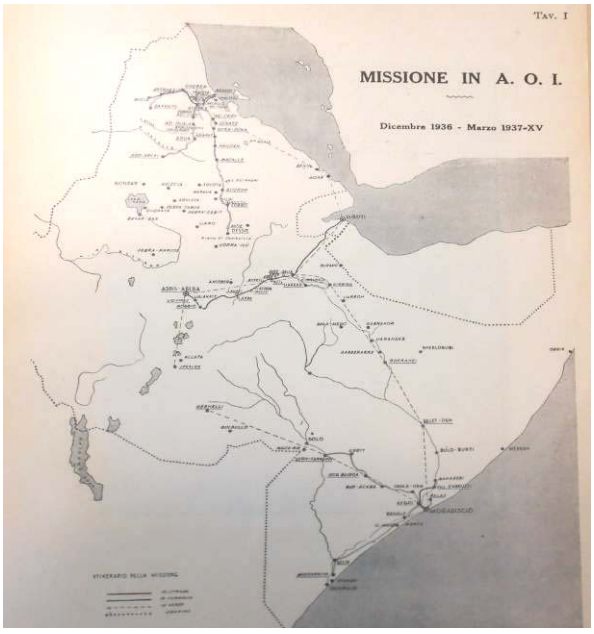
Figure 2.4: Eleven Regions and 731 Woreda used in malaria risk mapping
(Section 5.6; all codes are provided in accompanying Excel file)



3. The early descriptions of the epidemiology of malaria

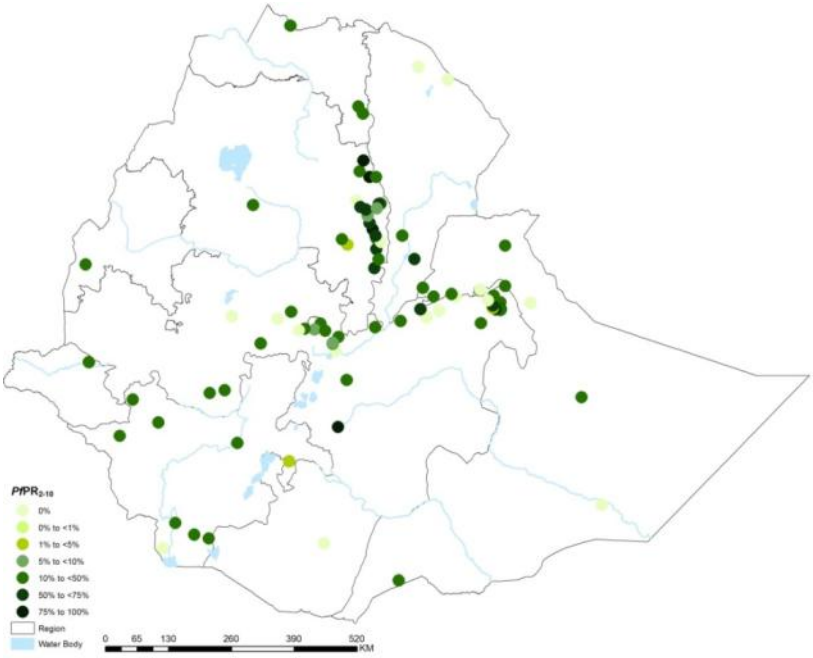
Italian malariologists from the Instituto di Malariologia were the first to provide a detailed description of the varied intensity of malaria and dominant vector species across the territories occupied by Mussolini's Africa Orientale Italiana (AOI). Reconnaissance surveys started in 1936 and were undertaken from the Somali coast to present day Eritrea [Lega, 1937; Figure 3.1]. Lega also provided maps of annual rainfall and temperature to illustrate the diversity of malaria risk across the AOI territories [Lega, 1937]. A series of other surveys were undertaken between 1937 and 1943, investigating spleen rates, species specific parasite prevalence and descriptions of local ecology that affected transmission [Archetti, 1940; Brambilla, 1940; Castellani, 1938a; Castellani, 1938b; Corradetti, 1939a; 1940a; Giaquinto-Miram, 1940; Jannone et al., 1946; Lega et al., 1937; Mara, 1950; Moise, 1951]. In 1937, Professor Augusto Corradetti highlighted the importance of altitude as he surveyed communities from Assab on the Red Sea coast to Combolica (1968 mASL) and Dessie (2470 mASL) [Corradetti, 1939a]. The work of the Italian malariologists has been assembled from the University Archives, Sapienza University of Rome and parasite prevalence survey results summarized in Figure 3.2.

Figure 3.1: Route taken by Lega in 1936 [Lega, 1937]



Manson-Bahr summarised the situation of malaria based on the work by the Italians "*In Abyssinia the incidence of various forms of malaria is exceptionally wide in spite of the mountainous nature of the country. Below 3000 ft.* [940 mASL] *malaria is endemic near permanent collections of water; and during the rainy seasons, from July to October, it appears in epidemic form. In the southeastern desert districts malaria is present also in the dry season in the vicinity of perennial streams, increasing to epidemic proportion during the rains. Between 3000 and 1500 ft. malaria is largely seasonal, and throughout this zone two epidemic seasons occur, from April to June and again from September to November*" [Manson-Bahr, 1941].

Figure 3.2: Summary of *P. falciparum* parasite prevalence based on 106 surveys at 90 unique locations undertaken between 1936 and 1943 in Ethiopia[8]



During the British occupation between April 1941 and March 1942, malariologists working for the British Army, Drs A Melville, DB Wilson, JP Glasgow and KS Hocking, continued the reconnaissance of malaria risks across Ethiopia. They commented that "*As the level of the country falls from the high plateaus of the East and West to the floor of the rift valley, malaria endemicity increases until a zone of moderate hyperendemicity is reached at a varying level between 1500 and 1800 metres. Below this level there may be either hyperendemic malaria of intense degree, in the neighbourhood of streams, rivers or lakes or malaria that is slight owing to low rainfall*."…. "*Malaria is essentially seasonal owing to the rainfall and conditions of the rivers*" [Melville et al., 1945]. The authors highlight that owing to the acute transmission season, that is variable between years, the lack in some years of any acquired functional immunity can lead to epidemics of severe clinical disease in all age groups [Melville et al., 1945].

Sir Gordon Covell made a further nationwide investigation of the distribution of malaria prevalence, spleen rates and dominant vectors in October 1955 at sites shown in Figure 3.3 focusing on Gondar, Jimma, Awash valley and the Kobbo Chercher plain [Covell, 1957]. He noted that malaria was almost non-existent above 1980 mASL and from 1670 to 1980 mASL "*endemicity is usually low, though severe regional epidemics occur from time-to-time. Below this level malaria may be hyperendemic wherever suitable mosquito breeding places exist in the immediate vicinity for a sufficient period of the year*"…. "*the degree of endemicity throughout Ethiopia depends on proximity to streams and riverbeds. Lakes are important as breeding places only when the margins are sufficiently flat to allow flooding during the rains*" [Covell, 1957].

[8] Data presented as an age-corrected *P. falciparum* parasite prevalence based on algorithm described in Annex A.1 [Smith et al., 2007a]

Figure 3.3: sites visited by Covell in 1955 [Covell, 1957]

Before the first eradication pilot experiments began in mid 1950s the epidemiology of malaria across Ethiopia was characterized by all observers according to altitude, patterns of seasonal rainfall, proximity to breeding sites and the susceptibility to epidemics.

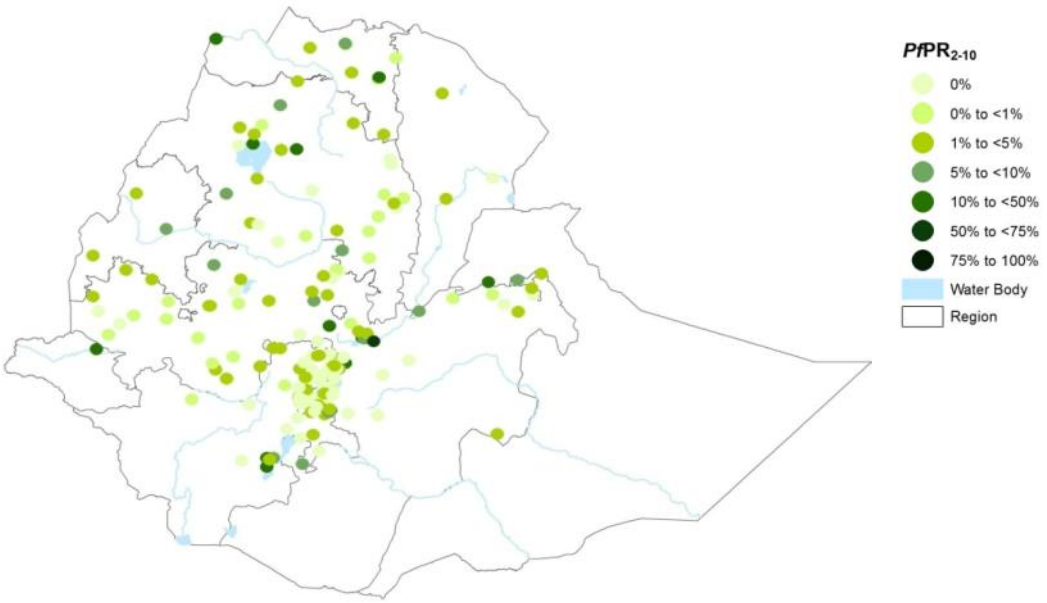
During the preparatory phases of the malaria eradication programme from the mid-1960s, very detailed mapping of populations and zones and segmentation of attack phases was undertaken. These mapped operational guides often demarcated the malaria free areas above 2000 mASL and the location of rivers and lakes (Figure 3.4).

Figure 3.4: Detailed maps used during malaria eradication projects during the 1960s [Left= Teckle et al., 1970; centre=Eshete & Mohtadi, 1970; right=Chand et al., 1964].

The pre-eradication and eradication phases of the Imperial Government's malaria programme included very detailed malaria reconniasance and surveillance. Multiple parasite prevalance surveys were undertaken within the principal control regions and summarized by zone or provided by individual villages as part of quarterly reports between

1962 and 1976. Copies of these reports have been made during a reveiw of the WHO archive in Geneva and the data abstracted and summarized in Figure 3.5. Overall 414 surveys were identified providing information on malaria prevalence among 523,000 people.

Figure 3.5: Age-corrected *P. falciparum* parasite prevalance (*Pf*PR_{2-10}) from 414 surveys undertaken between 1962 and 1976 during the Imperial Government's Malaria Eradication Programme. Where sites surveyed more than once the highest value is shown dominant.



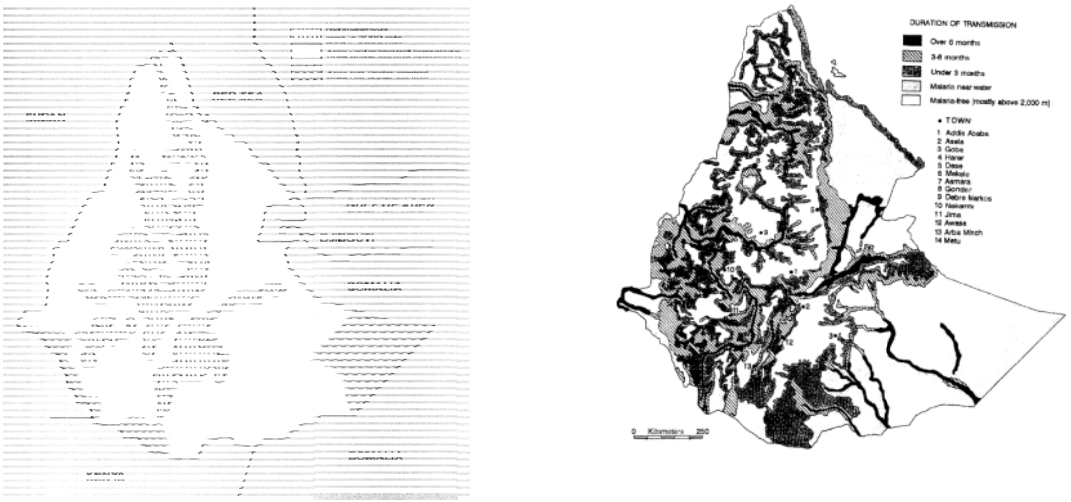
Both altiude and malaria seasons continued to be the primary descriptives of the epidemiology of malaria at the end of the eradication programme [Teklehaimanot, 1986a; Tulu, 1993; Figures 3.6]. An unpublished WHO report on the epidemiological basis for control of malaria, elaborates the malaria risk profiling by identifying three eco-climatic zones that detemine endemicity: a) the cold zone (*dega*) above 2500 mASL and covering 40% of the population; b) the temperate zone (*weya dega*) between 1500 and 2500 mASL, mean annual rainfall between 400 and 2400 mm and home to 44% of the population; and c) the warm zone (*kolla*) below 1500 mASL with between 100 and 400 mm of annual rainfall where only 16% of the population lived but covered 46% of Ethiopia's land mass [Anon, 1991]. The report recognized that the most important malaria zone was the warm zone, where intense, seasonal transmission occurs not charcterized by epidemics except as a result of the introduction of non-immune labourers, soldiers, settlers and refugees. The report acknowledges difficulties in defining suitable strata for control operations in Ethiopia but goes on to suggest seven paradigm classifications 1) highland malaria (1800-2000 mSAL), 2) urban malaria[9], 3) settlement malaria[10], 4) traditional rural agricultural malaria, 5)

[9] Specifically the rapidly growing urban centres at Dire Dawa, Nazareth, Arbaminch, Bahir Dar and Jimma. Recommendations made for larviciding (Abate), environmental management and municipal control.

[10] Large re-settlements occurred after droughts in 1984, 221 new settlements created in 1985 in Western and southern lowland fertile areas and over 300,000 people relocated

development related malaria[11], 6) coastal malaria (no longer appropriate) and 7) desert fringe malaria. These were later used in the National Plan of Action for Malaria Control covering the period 1993-1998 [FMoH, 1993].

Figure 3.6: Maps of malaria risk used post-eradication era in Ethiopia: a) Teklehaimanot (1986a); b) Tulu (1991)



The 1993-1998 national malaria plan uses the following description of the epidemiology of malaria to set the scene for control: "*The epidemiology of malaria in the country is mainly characterized by its unstable nature which is governed by topographical and climatic features as well as socio-economic patterns of the population. Six major ecological prototypes of malaria have been noted in the country. This include malaria of savanna grass land, desert and highland fringe malaria, urban malaria, malaria associated with development projects and settled agricultural communities. In southwestern low lands of savanna grassland, the nature of malaria is mainly stable. Desert and highland fringe areas are usually prone to malaria epidemics and these areas are found mainly in southeastern and eastern semi-desert areas and the southern and northern escarpments of the rift valley as well as northern Ethiopian plateaus. Development projects which are at present totalling about twenty are concentrated to the rift valley and created favourable conditions for all year round transmission of the disease. At present there are about 44 towns in the country where transmission of malaria is going on. Thus, different control strategies have been devised and implemented on the particular epidemiological features of each of the major ecological prototypes*" [FMoH, 1993]. This important narrative signals the importance of tailoring interventions to suit local malaria epidemiology. However, it is hard to define what strategies were adopted under which strata during the 1990s.

4. The contemporary use of malaria maps for control: the RBM era

The first strategic plan after the launch of the RBM initiative covered the period 2001-2005 [FMoH, 2001]. No map was provided but the epidemiology was described as follows: "*In Ethiopia, altitude and climate (rainfall and temperature) are the most important determinants of malaria transmission. Transmission is seasonal and largely unstable in*

[11] Including large agro industrial project concerns at the Tana Beles, Omo Valley, Baro-Akobo, Wabi-Shabelle and Anger Didessa

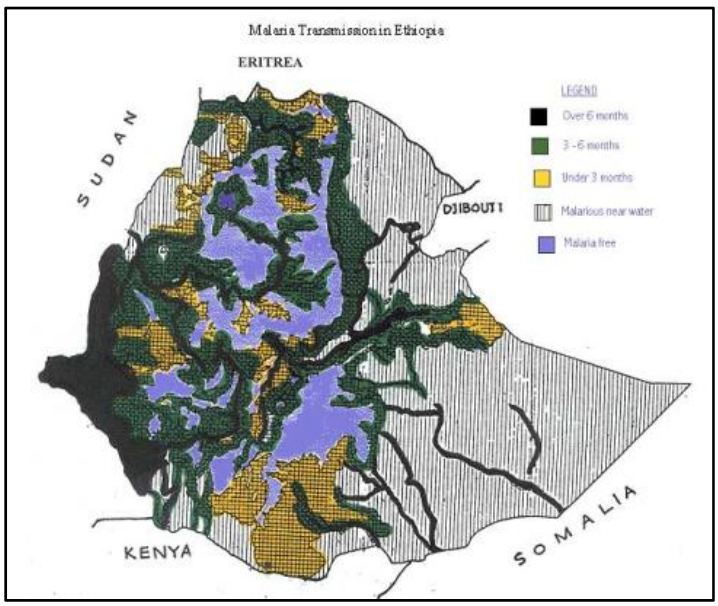
character. The major transmission of malaria follows the June – September rains and occurs between September - December while the minor transmission season occurs between April – May following the February – March rains. Areas with bimodal pattern of transmission are limited and restricted to a few areas that receive the small/Belg rains. The major transmission season occurs in almost every part of the country" [FMoH, 2001]. It describes four major epidemiological strata a) Malaria free highland areas above 2,500 meter altitude, b) Highland fringe areas between 1,500 – 2,500 meter affected by frequent epidemics; c) Lowland areas below 1,500 meters with seasonal patterns of transmission; and d) Stable malaria areas characterized by all year round transmission [FMoH, 2001].

The second National Malaria Strategy (2006-2010) used a map to describe the seasonal nature of malaria in Ethiopia and delineated malaria free areas as those above 2500 mASL (FMoH, 2006; Figure 4.7). The narrative that accompanied the map repeated the four eco-epidemiological strata defined in the 2001-2005 national strategy although it added that the stable, perennial transmission areas are "*limited to the western lowlands and river basins*" [FMoH, 2006]. The strategy states that 25% of the lowland areas below 1500 mASL are characterized as hyper- and holoendemic transmission, confined to the western and north western lowlands. The strategy identified these areas as most suitable for deployment of "*lower intensity interventions such as ITNs that may reduce disease and mortality, but do not significantly impact immunity*" [FMoH, 2006]. Apart from the statement on selective distribution of ITNs, and unlike strategic plans of the 1990s, there were no obvious definitions of tailored control options based on the descriptions of the varied malaria ecology. It is also notable that at this stage the characterisation of altitudinal limits of transmission had increased from a previously widely used definition of 2000 mASL to 2500 mASL.

The map shown in Figure 4.1 was used by the Ministry of Health during its first submission to the Global Fund in 2001 and highlighted that ITN would not be distributed above 2500 mASL. No map or detailed description of the epidemiology of malaria was provided in the Global Fund Round 5 submission [FMoH, 2005]. However, an altitude map was provided during the Global Fund Round 8 submission which emphasised that the proposal only targeted populations living below 2000 mASL [FMoH, 2008].

Other maps had been developed for Ethiopia between 2002 and 2010 based on climate suitability (Figure 4.2a; Mapping Malaria Risk in Africa (MARA); Craig et al., 1999) and a model based prediction of malaria prevalence in children aged 2-10 years (Figure 4.2b; Malaria Atlas Project (MAP)). Neither of these empirical data-derived maps have been used in Ethiopia, largely because they have not been developed as part of a direct collaboration with the Ministry of Health and also because their resolution and representation of risk does not reflect the needs and ambitions of the control programme.

Figure 4.1: Malaria risk map used to define varied transmission patterns in the 2006-2010 national malaria strategy based on seasonality and altitude [FMoH, 2006][12].



By 2009, the Ethiopian Ministry of Health developed a much more elaborate description of malaria risks in support of the national malaria strategy for prevention, control and elimination 2010-2015 [FMoH, 2009]. This map followed a long-standing tradition of using combinations of malaria seasons and altitude but extended classifications to seven strata [FMoH, 2009; Figure 4.3]. The narrative that accompanies the map states that "*Malaria transmission exhibits a seasonal and unstable pattern in Ethiopia, with transmission varying with altitude and rainfall. The major malaria transmission season in the country is from September to December, following the main rainy season from June/July to September. There is a shorter transmission season from April to May following the shorter rainy season in some parts of the country. Currently, areas <2,000 meters of altitude are considered malarious*". The strategy adds that "*In general terms, 75% of the landmass of Ethiopia is considered at risk of malaria, which corresponds to areas below 2000m altitude. However, this estimate has not recently been revised to account for possible changes such as urbanization or land use (irrigation or dams)*" [FMoH, 2009].

[12] This map was also used for the Global Fund Round 1 application [FMoH, 2001] and the analysis of the malaria epidemiological stratification during the malaria programme review (MPR) undertaken in 2011 [FMoH, 2012a]

Figure 4.2: Other maps of malaria risk in Ethiopia: a) climate fuzzy suitability for stable malaria risk developed by MARA[13]; and b) predicted risks of malaria prevalence from 678 survey data points showing prevalence below 5%, 5-39% and 40% or greater by MAP[14]

a) b)

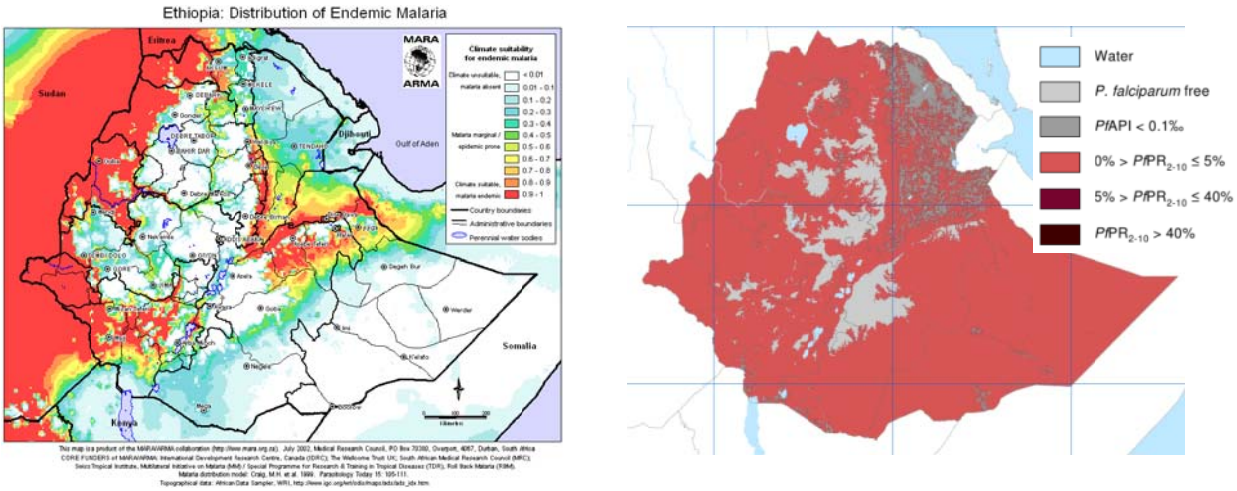
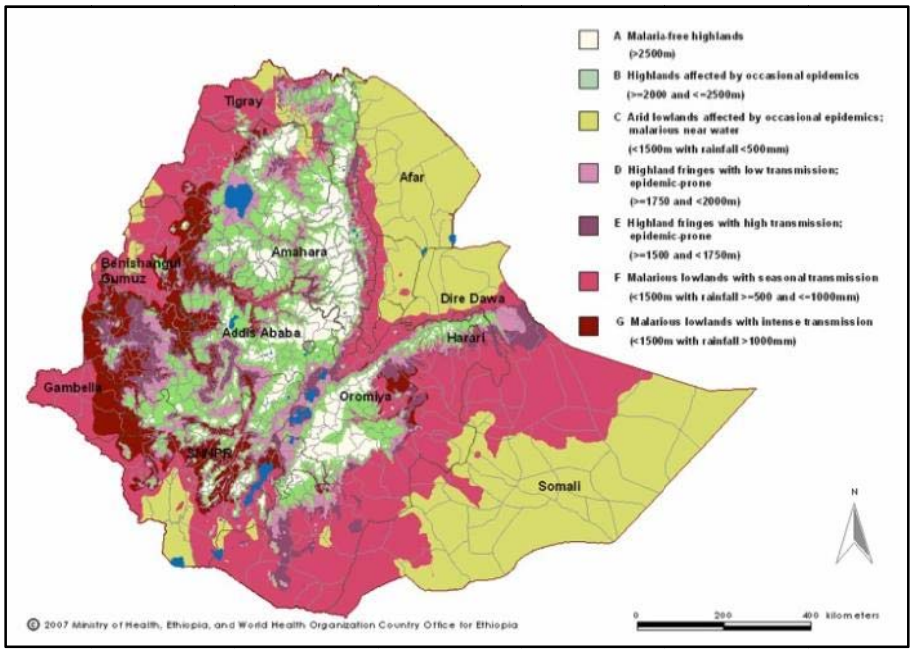


Figure 4.3: Map of seven strata of malaria risk used in the 2010-2015 national malaria strategy [FMoH, 2009] and used by President's Malaria Initiative (PMI) in their strategic funding plans [PMI, 2011]



[13] The climate suitability maps are based on the likelihood of stable transmission using a rules-based, fuzzy logic approach based on long-term rainfall and temperature data [Hutchinson et al., 1995] that affect transmission [Craig et al., 1999]. These theoretical maps are not trained on empirical data. The fuzzy logic model of suitability uses monthly temperature ranges between 22-32^{o}C for optimized parasite sporogny within the mosquito and consecutive months of rainfall above 80 mm to support adequate vector abundance. The models assigns fuzzy values between 0 (unsuitable) and 1 (suitable)

[14] Based on parasite prevalence data from 678 time-space locations surveyed between 1987 and 2008 using Bayesian methods with the inclusion of 14 covariates (urban, peri-urban, a temperature suitability index, land surface temperature (six variants), precipitation (six variants) and normalized difference vegetation index (NDVI, two variants) [Gething et al., 2011a; www.map.ox.ac.uk]. The model depended heavily on over-fitted covariates.

The national strategy 2010-2015 did not make any specific recommendations on which intervention mixes should be deployed within each of the seven risk strata, other than the obvious no intervention in areas of no risk. The strategy did, however, recognize that "*long-standing 'expert knowledge', based on classifying whether Kebeles are malarious or not, is used to decide on the targeting of intervention strategies, including bednets, indoor residual spraying (IRS) and drugs. This micro-planning varies from region to region, and takes into account factors such as altitude, usual rainfall, expectation of malaria cases, proximity to breeding sites, and historical occurrence of outbreaks*" [FMoH, 2009].

5. Re-defining the cartography of malaria risk for elimination and control post-2015

5.1 Background

The MPR undertaken in 2011 made a number of observations and recommendations related to improving the risk mapping of malaria in Ethiopia, it noted that a) existing maps developed and used for operational purposes have remained largely unchanged for over 50 years and may not be fit-for-purpose for the next phase of malaria control and elimination; and b) existing malaria risk maps are mainly based on altitude and do not reflect changes in climate, population dynamics, and development policies. The MPR suggested two action points: a) the use of appropriate technology to map existing current risk of malaria; and b) use these to adapt the malaria strategies according to the malaria epidemiological strata [FMoH, 2012a].

In this section we use combinations of remotely sensed data, long-term climate data, digital elevation, empirical survey observations on malaria prevalence within model-based geostatistical (MBG) frameworks, population density models based on the 2007 national census and cartographic intelligence to derive a more empirical mapped extent of malaria risk in Ethiopia to plan for pre-elimination ambitions as articulated in the 2010-2015 strategy and beyond.

The review of previous map use and descriptions of the epidemiology of malaria in Ethiopia is important as it would be inappropriate to derive entirely new metrics of risk which would require a completely new paradigm shift in the national understanding of risk for control. We have combined, therefore, the dominant features of altitude and seasonality while recognizing the constant historical and contemporary reference to urban, dam/irrigation, agro-industry and settlement/refugee risks within the stratifications and mapping. These, however, have been developed using a more empirical data-driven approach to provide high resolution risk mapping based on biological correlates and targets for control.

5.2 Malaria free

Definitions of malaria free areas of Ethiopia have been used over the years, all entirely based on altitudinal limits. These have varied between reports and between national strategic plans. However, altitude is largely a proxy for temperature and its extreme effects when interrupting malaria transmission [MacDonald, 1957; Lunde et al., 2013a; Beck-Johnson et al., 2013]. Laboratory experiments have shown that at temperatures $<16^{o}C$ larvae are unable to produce viable adults [Bayoh & Lindsay 2003; 2004] and temperatures

of between 25°C and 30°C are considered optimum for *P. falciparum* sporogony [Molineaux, 1988; Lindsay & Martens, 1998]. Recently a *Temperature Suitability Index* (TSI) has been developed as a quantitative value of optimal *P. falciparum* and *P. vivax* sporozoite development [Gething et al., 2011b]. The TSI model uses a biological framework based on the survival of vectors and the fluctuating monthly ambient temperature effects on the duration of sporogony that must be completed within the lifetime of a single generation of Anophelines. The TSI is constructed using long-term monthly temperature time series [Hijmans et al., 2005] and represented on a scale of increasing transmission suitability, from 0 (unsuitable) to 1 (most suitable). Figure 5.2 shows those areas unsuitable for parasite development in local vectors and thus classified biologically as malaria free.

International travel advisories specify that Addis Ababa is malaria free [IAMAT, 2013]. However, malaria cases are diagnosed within the city limits as a result of infections acquired outside the city or within its growing periphery [Woyessa & Ali, 2003; Woyessa et al. 2004]. The area of Akaki, now a connected suburb of the greater Addis area, defined transmission during the 1950s [Ovassa & Neri, 1959] and transmission was identified at hot springs located at Fihoha near the railway during the 1940s [Martin, 1942]. For the purposes of risk mapping we have elected to zero risks within densely populated the inner city limits, but allowed the periphery and peri-urban areas the possibility of focal, unstable transmission where altitude or temperature limits support this.

Malaria free areas of Ethiopia occupy 103,642 km^2 and are inhabited by an estimated 22.6 million people in 2010.

5.3 Epidemic prone highlands

Altitude has long been recognised as an important determinant of malaria endemicity [Gill, 1923; Schwetz, 1942; Garnham, 1948]. However, factors that determine "highland" malaria are complex and not always directly related to a single altitude limit across regions or within countries[15] [Cox et al., 1999; Abeku et al., 2004a; www.himal.uk.net]. The most important factor is environmental temperature which affects the development and survival of the vector and the duration of plasmodium development within the vector (Section 5.2). Defining highland malaria is important in relation to the stability and hence epidemic potential of malaria transmission. Epidemics are "*acute exacerbation[s] of disease out of proportion to the normal to which the community is subject*" [MacDonald, 1957] and can be caused by anything facilitating transmission above the normal level, disturbing a previously existing equilibrium of the ecological system [Nàjera et al., 1998].

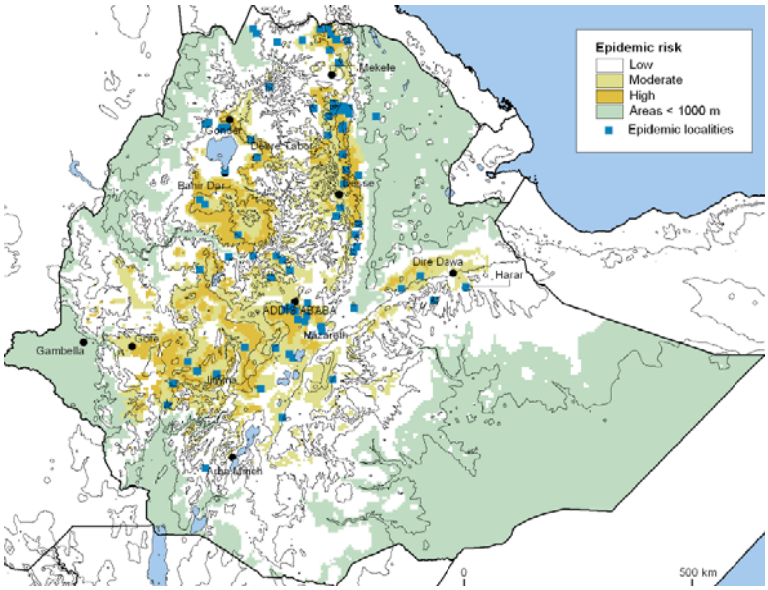
In Ethiopia, epidemics reflect irregular, temporary disturbances to an equilibrium of low, stable transmission caused by exceptional meteorological conditions [Fontaine et al., 1961; Mouchet et al., 1998; Abeku et al., 2002; 2003; 2004a; 2004b; Negash et al., 2005; Checchi

[15] The relationship between altitude and temperature may vary substantially over time and space. Solar radiation received at the earth's surface is greatest in the tropics and declines towards the poles. Latitude also influences the relative importance of seasonal and diurnal variations in climate, with the latter tending to predominate in tropical highlands.

et al., 2006; Guthmann et al., 2007][16]. A detailed analysis was undertaken by the Highland Malaria Project (HIMAL) of combinations of parasite survey data assembly by MARA, the location and timing of historical epidemics and altitude across Ethiopia [Cox et al., 1999]. The authors found no suggestion of transmission above 2000 mASL but a wide variation in infection prevalence (0-15%) within altitudes of 1750–2000 mASL [Cox et al., 1999]. Analysis of reported epidemic locations versus altitude indicated that the average altitude at which epidemics have occurred is 1977 mASL within a range of 1172–2777 mASL and a probability quotient was used to map likely epidemic susceptibility [Figure 5.1; Cox et al., 1999]. The highland fringe definitions used by the Ministry of Health in the current national malaria strategic plan of 2000 mASL [FMoH, 2014], seems therefore a good approximation based on this evidence and therefore retained here as the margins of epidemic prone malaria [Figure 5.2]. The area occupies 77,600 km^2 and is inhabited by an estimated 13.8 million people in 2010.

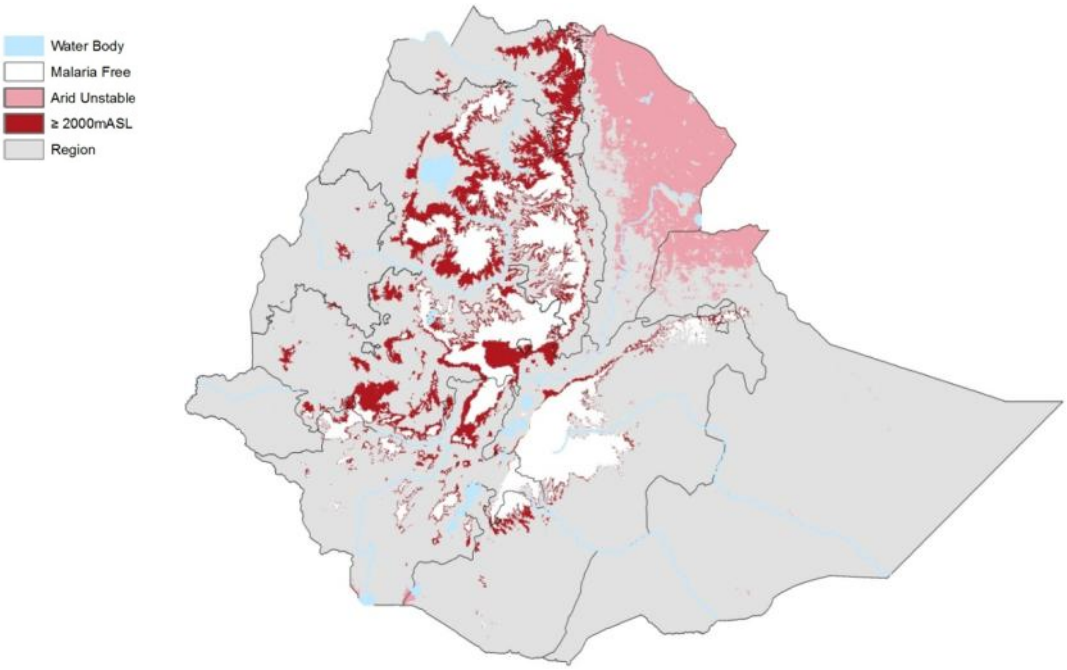
There is a large variability in epidemic susceptibility within this range within a given year and work based on climate and malaria case data from 49 *woreda* in Amhara region suggests that very localised spatial patterns of risk occur over distances as short as 300 km [Wimberly et al., 2012].

Figure 5.1: Probability of epidemic occurrence based on models developed by HIMAL [Cox et al., 1999]



[16] Considerable work has also been undertaken on defining epidemic alert thresholds in Ethiopia [Abeku et al., 2002; 2003; 2004b; Teklehaimanot et al., 2004a; 2004b; 2004c; Zhou et al., 2004; Loha & Lindtjørn, 2010; Midekisa et al., 2012]; this is not part of this current malaria epidemiological description, that aims to delineate broad areas likely to experience epidemics.

Figure 5.2: Areas of no malaria risk based on TSI and densely urban centre of Addis Ababa (White); marginal, highland epidemic transmission areas above 2000 mASL[17] (dark pink) and arid constrained areas based on EVI (light pink)[18]



5.4 Aridity (malarious near water)

In several mapped extents and narratives of malaria transmission in Ethiopia reference is made to the dry, arid lowland areas in the Somali Region and the borders with northern Kenya and the Danakil depression of Eritrea. Here malaria is often described as "*malarious near water*" (e.g. Figures 3.6b and 4.1). Arid conditions affect anopheline development and survival [Shililu et al., 2004]. Limited surface water reduces the availability of sites suitable for oviposition and reduces the survival of vectors at all stages of their development through desiccation [Gray & Bradley, 2005]. It is possible to define extreme aridity using the Enhanced Vegetation Index (EVI) derived from Moderate Resolution Imaging Spectrometer (MODIS) satellite imagery [Scharlemann et al., 2008]. Here we have used monthly EVI datasets archived over 11 years and averaged to a synoptic year to classify areas likely to support transmission, defined by an EVI of greater than 0.1 for any two consecutive months and areas without two or more consecutive months of an EVI > 0.1 as unable to support stable transmission [Guerra et al., 2008]. This aridity "mask" identifies small foci of risk across borders of Eritrea near the Danakil desert and Djibouti that are likely to support stable transmission only when proximal to seasonal rivers, while retaining a plausible mask

[17] The Shuttle Radar Topography Mission Digital Elevation Model (SRTM-DEM) was developed by the National Aeronautics and Space Administration (NASA) and post processed by the Consultative Group for International Agricultural Research (CGIAR) at 90 meters resolution for the entire globe. Before post-processing, the original SRTM data was in 1 degree tiles and contained areas of no-data especially in water bodies, mountainous areas, and desertic areas. After post-processing, no-data cells were filled by using different interpolation techniques [http://srtm.csi.cgiar.org/SRTMdataProcessingMethodology.asp]/ [http://www.diva-gis.org/gdata].

[18] The arid areas bordering the Lake Chew Bahir Basin, in the south on the border with Kenya are a continuous sediment core

of almost zero transmission across these arid, barren regions (Figure 5.2). This mask we have used conservatively as representing unstable transmission, rather than malaria free, as transmission might be possible in the presence of man-made water bodies such as dams or underground water storage. These areas, however, are prone to acutely seasonal exacerbations in average annual rainfall that can lead to severe epidemics, albeit rarely as defined in the guidelines for epidemic control developed by the Ministry of Health in 2004 [FMoH, 2004a]. The area occupies 81,000 km^2 and was inhabited by an estimated 0.84 million people in 2010.

5.5 Defining malaria endemicity based on parasite prevalence

The terms hyperendemic and holoendemic were used by British malariologists in the 1940s to describe malaria risk in Ethiopia [Melville et al., 1945; Covell, 1957]; and again in the 2005-2010 national malaria strategy [FMoH, 2006]. However, the mapped extent of malaria endemicity based on parasite ratios has never featured in the cartography of malaria in Ethiopia.

The clinical epidemiology [Snow & Marsh, 2002], the impact of vector control [Killeen et al., 2007; Smith et al., 2009; Griffin et al., 2010], cost-effectiveness of treatment and prevention interventions [Okell et al., 2012a] and timelines to malaria elimination [Cohen et al., 2010] all depend on pre-control, parasite transmission intensity. There was a recognition over 50 years ago, across Africa, that one important source of planning data was infection prevalence among children aged 2-10 years ($Pf\text{PR}_{2\text{-}10}$), used to define categories of endemic risk designed to guide and monitor progress towards malaria elimination targets [Metselaar & van Thiel, 1959; Macdonald & Göeckel, 1964; Lysenko & Semashko, 1968].

Ethiopia has a very diverse pattern of malaria risk and many of the traditional endemicity classes are no longer prevalent. On the whole, since the 1960s Ethiopia is best characterized as a predominantly low, stable hypo-endemicity ($Pf\text{PR}_{2\text{-}10}$ <10%), with pockets of higher meso-endemic transmission ($Pf\text{PR}_{2\text{-}10}$ 10-49%) and large areas of unstable transmission prone to epidemics. The challenge therefore is to adequately characterize the hypo-mesoendemic areas within the stable transmission margins that do not fall into the classifications of malaria free, highland epidemic or arid constrained transmission described above.

One important distinction from traditional endemicity classes has been the recent sub-division of hypo-endemicity to include a risk class characterized by $Pf\text{PR}_{2\text{-}10}$ less than 1% that supports exceptionally low disease burdens during an average year [Cohen et al., 2010]. This classification has been introduced to identify geographical areas, and countries, that might consider either an elimination pathway or elect to sustain low-stable endemic conditions and very low disease burdens [Cohen et al., 2010; Feachem et al., 2010].

However, it is also important to recognize that some areas will be "transitional" areas which are now characterized by a $Pf\text{PR}_{2\text{-}10}$ <1% as a result of sustained intervention but were historically, higher endemicity areas before intervention. As such defining "receptive" endemicity is equally valuable for selecting intervention priorities and setting targets [Noor et al., 2012; 2013]. For example, discontinuing sustained universal vector control in an area

that is today *Pf*PR_{2-10} < 1% would have disastrous, rebound effects; conversely areas which have always been *Pf*PR_{2-10} <1% might not benefit from universal vector control and more targeted approaches to infection risk prevention and disease management are more appropriate.

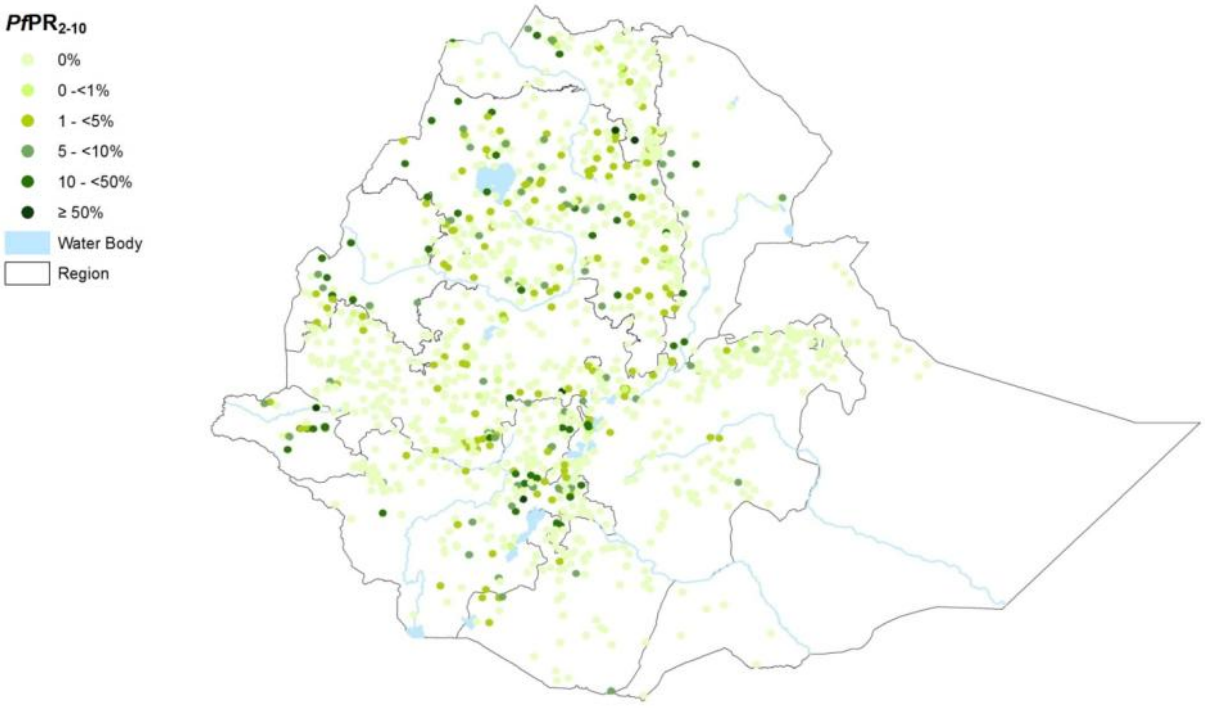
New opportunities exist to map the intensity of stable transmission based on parasite prevalence using model-based geostatistics (MBG) and the growth in survey data that describe prevalence in the community. Survey data are, however, often non-randomly over-dispersed in time and in space. MBG methods accommodate these properties of nationally assembled malaria data and use the basic principles that the values of more proximal information (either in time or space) are more similar than more distal points in space or in time [Tobler, 1970]. MBG methods interpolate from observed measures of interest of known locations in space and time to provide predictions of quantities and the empirical estimates of their uncertainty at locations and times where data do not exist [Diggle & Ribeiro, 2007].

Here we have used 1380 empirical parasite survey estimates collected by the FMoH, scientists and supporting partners between 1980 and 2013 and assembled as described in Annex A.1 and these survey data are shown in Figure 5.3. Data were corrected to a single age group, 2-10 years, based on a catalytic conversion algorithm [Smith et al., 2007a] described in more detail in Annex A.1.

We used the data from the infection prevalence surveys (sample size, adjusted numbers positive) at known locations (longitude and latitude), times (month and year) and selected environmental covariates within the Bayesian hierarchical space-time model, implemented through Stochastic Partial Differential Equations (SPDE) using Integrated Nested Laplace Approximations (INLA) for inference using a super-computing facility established in Kilifi, Kenya for proteomic analysis (Annex A.2). The model took approximately 19 days to run and was repeated to provide precision metrics. The continuous predictions of mean *Pf*PR_{2-10} at each 1 x 1 km grid for 2000 and 2010 are shown in Annex Figures A.2a and A.2b respectively.

Using both prediction surfaces for 2000 and 2010 we have identified areas of Ethiopia that supported transmission intensity described by a *Pf*PR_{2-10} of <1% in both years, representing areas of that on average are traditional low, stable endemicity (Figure 5.4). This area occupies a vast 653,000 km^2 and is inhabited by an estimated 32.2 million people in 2010. These areas reflect a situation where infection and disease risks are low, but will be very over-distributed in time and space [Smith et al., 2007b] and where very focal and targeted disease prevention and surveillance is more appropriate, and cost-effective, compared to blanket, universal prevention measures [Cohen et al., 2010; Moonen et al., 2010].

Figure 5.3: 1380 estimates of *P. falciparum* infection prevalence age-corrected to 2-10 years of age from community-based surveys undertaken between 1980 and 2012; used in models to provide predicted quantities of malaria in 2000 and 2010



Outside of the low stable endemic areas of the country we have used the posterior mean predictions of *Pf*PR_{2-10} in 2010 to represent revised classifications of hypoendemic transmission: *Pf*PR_{2-10} <1%, 1-4.9% and 5-9.9% and mesoendemic transmission as described by a *Pf*PR_{2-10} >10%[19] in 2010. While there has been a reduction in infection prevalence intensity in some areas, notably in the western regions, since 2000, the predictions in 2010 allow a more contemporary description of risk for the design of future elimination targets as specified in the national strategic plan of 2010 to 2015 [FMoH, 2009]. The most intractable areas of highest transmission intensity (*Pf*PR_{2-10} >= 10%) are located in small areas along the western borders with Sudan in Tigray, Amhara and Benishangul Gumuz regions (Figure 5.4) affecting approximately 401,062 people in 2010 located in 26,400 km^2. There were 2.43 million people living in areas that supported *Pf*PR_{2-10} <1% in 2010, 9 million people living in areas that supported *Pf*PR_{2-10} 1-4.9% in 2010 and 1.913 million people living in areas that supported *Pf*PR_{2-10} 5-9.9% in 2010 (Figures 5.5 and 5.6).

[19] No areas were predicted to support parasite prevalence above 32%.

Figure 5.4: Areas shown in light green representing predicted *Pf*PR_{2-10} in both 2000 and 2010 outside of malaria free, unstable highland risks and aridity constrained transmission.

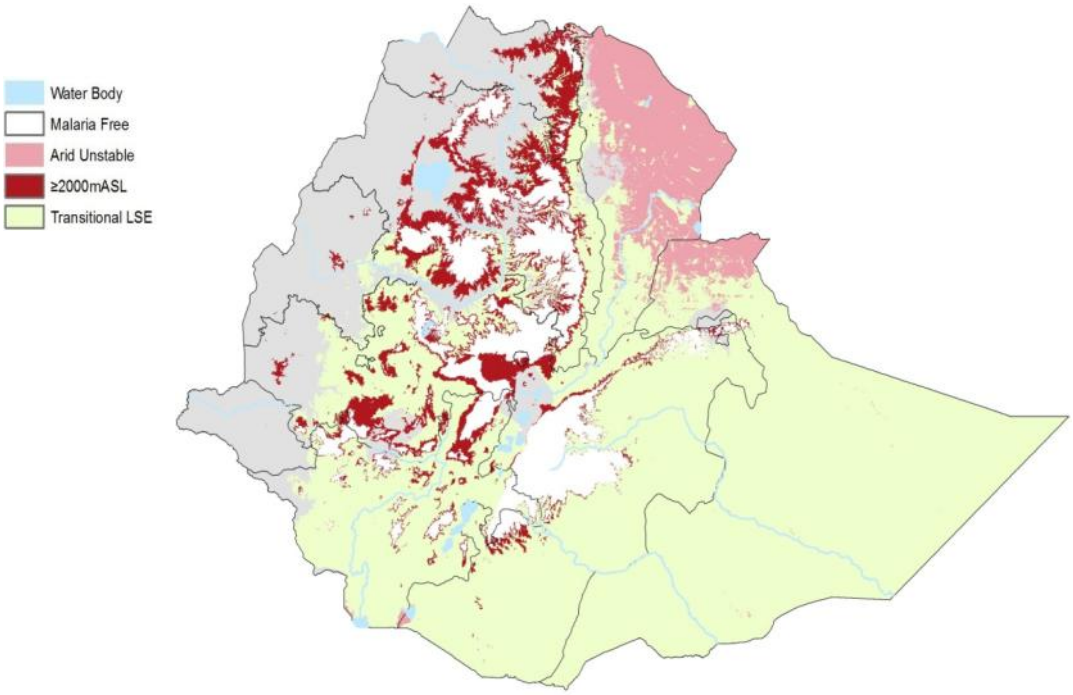


Figure 5.5: Areas represented by stable transmission intensity in 2010 of *Pf*PR_{2-10} >= 10% (dark green), 5-9% (mid-dark green) and 1-4% (mid-light green); areas of low-stable endemic transmission, *Pf*PR_{2-10} <1%, in 2000 and 2010 (light green), unstable aridity defined transmission (pink), highland fringe areas (> 2000 mASL) and no malaria risk based on TSI = zero and urban centre of Addis Ababa. Populations at risk of each stratum shown in Figure 5.6

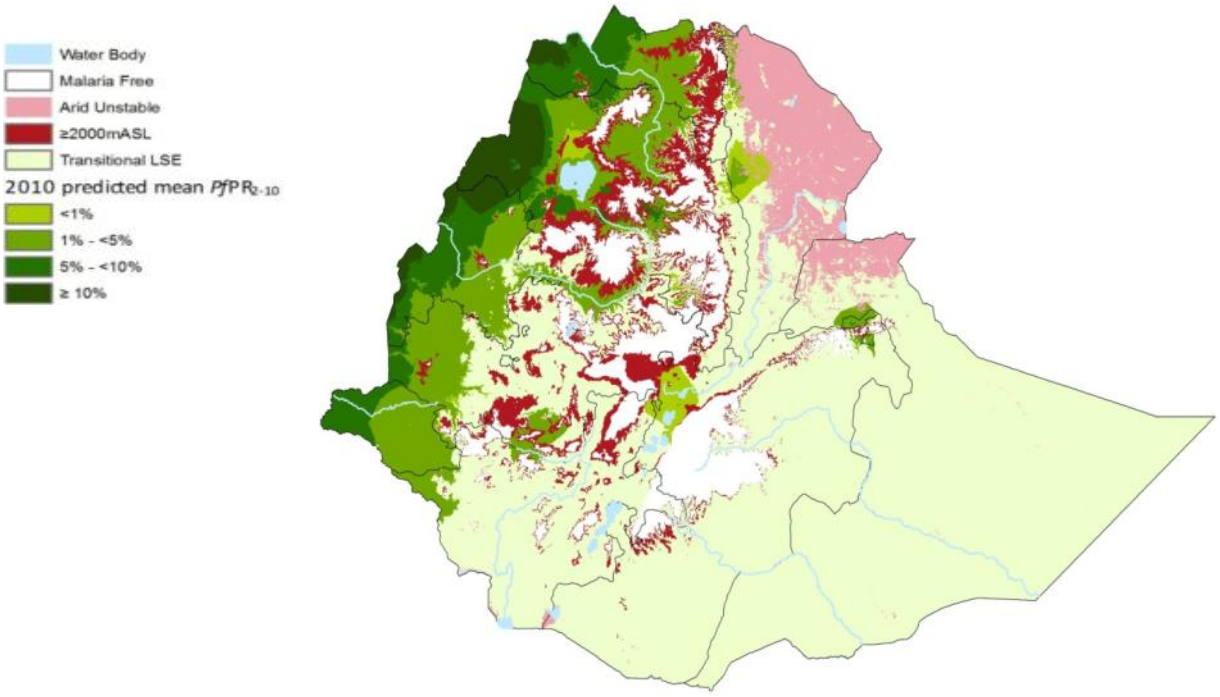
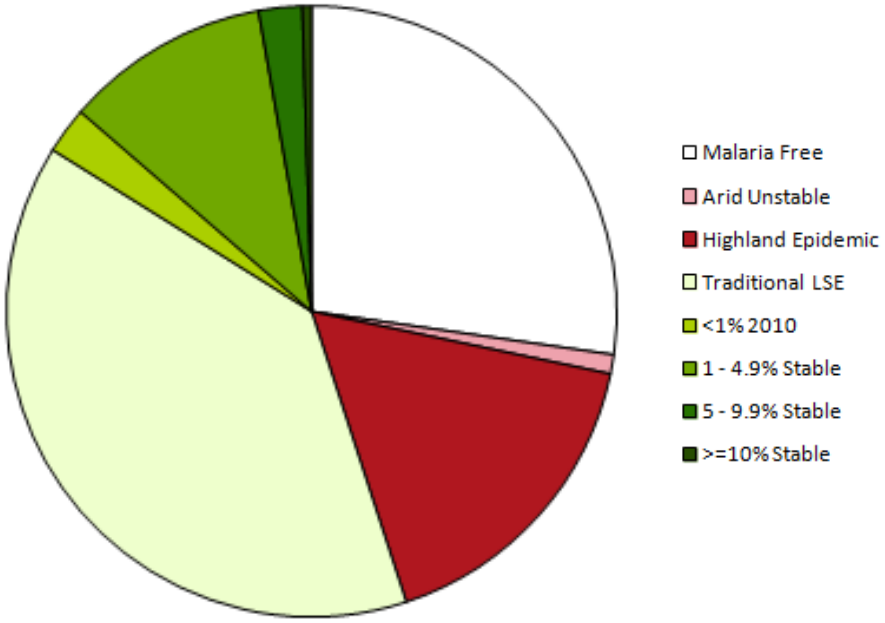


Figure 5.6: Pie chart of populations in 2010 at risk by endemicity strata



The areas of stable malaria transmission in 2010 are shown in Figure 5.7, these areas are likely to be most suited to sustained, increased coverage of LLIN to reduce transmission further along Ethiopia's western border. Since 2000, transmission intensity in this area has declined, probably as a result of interventions, and the number of people living in the highest endemicity class (*Pf*PR_{2-10} >= 10%) has declined from 630,000 people in 2000 to 381,000 people in 2010 (Figure 5.8).

Figure 5.7: Areas of stable *P. falciparum* transmission in 2010 covering 13.4 million people (see legend in Fig 5.5 for classes)

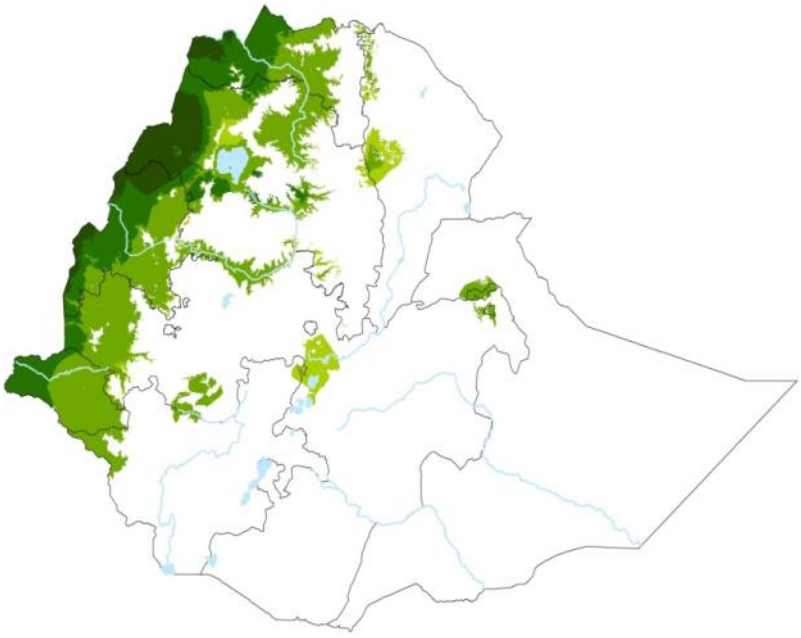
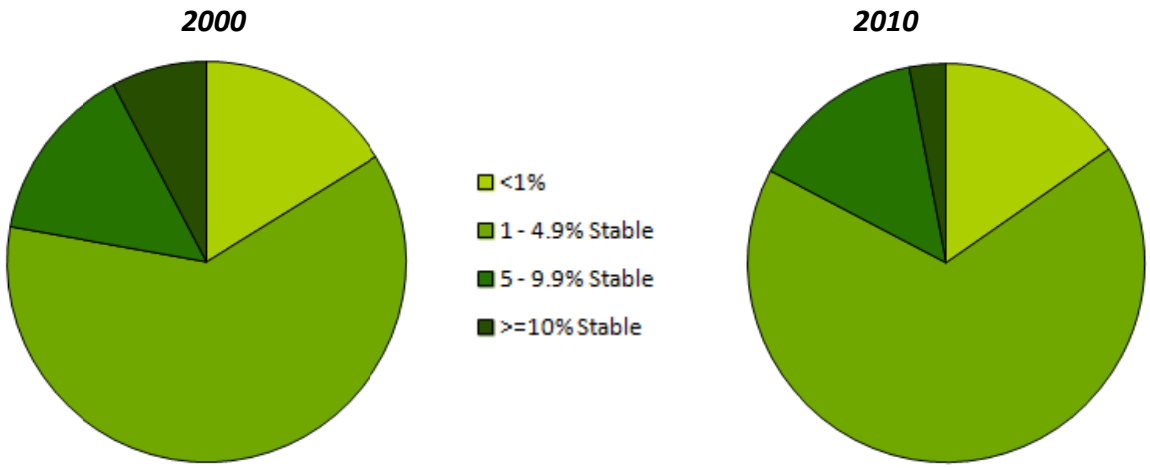


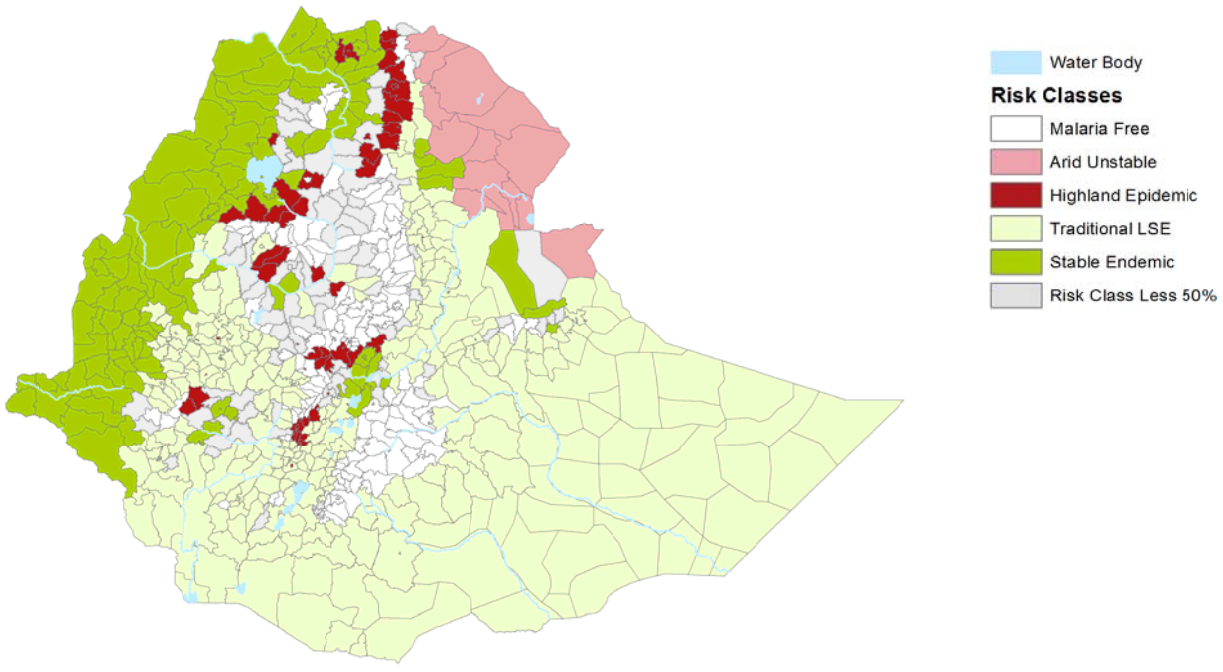
Figure 5.8: Proportion of population 2000 & 2010 living in areas shown in Fig 5.7 by stable endemicity class



5.6 Risk classification for woreda planning

Given the importance of providing estimates of risk at decision-making units used within health sector planning, we have computed the percentage of the *woreda* population exposed to stable transmission, traditions LSE, arid unstable risks, highland fringe risks and malaria free. These are shown in accompanying Excel spreadsheet. To present this information visually we have determined for each *woreda,* which main class of risk 50% or more of the population are exposed to (Figure 5.9). Using this criterion it was not possible to uniquely attribute a single risk class to 83 (11%) of the 731 *woreda* shown in Figure 5.9.

Figure 5.9: Dominant malaria risk class for 648 *woreda* where 50% or more of the resident population live in one single risk class. 83 *woreda* could not be classified in this way and are shown in grey



6. Other special malaria risk areas

6.1 Areas suitable for seasonal malaria chemoprevention

Ethiopia's malaria stratification has traditionally been described through a combination of altitude and the seasonal nature of transmission. Relationships between climate, seasonal parasite transmission and disease outcomes are however complex and have been poorly defined for many years [Gill, 1938]. There is a suggestion that areas with acute seasonal transmission represent settings that are more adapted to synchronized infections leading to higher host parasite densities [Mckenzie et al., 2001]. Acutely seasonal malaria exposure areas may lead to poorly "designed" immunization for new-born children, resulting in different disease-severity profiles compared with settings with equivalent annual parasite exposure more evenly distributed throughout a year (spaced immunization) [Carniero et al., 2010; Greenwood et al., 1991].

In practical terms an understanding of the timing and frequency of malaria seasons is a necessary planning tool for indoor residual house-spraying operations, and more recently the possible targeting of Seasonal Malaria Chemoprevention (SMC) [Meremikumu et al. 2012; WHO, 2012a]. SMC is currently recommended in areas where malaria transmission is stable (with *Pf*PR_{2-10} at least >=5%) but clinical disease is concentrated within a few months of the year. Drug combinations for pulsed drug administration include combinations of amodiaquine and the long half-life antifolate, sulphadoxine-pyrimethamine (SP). Therefore a second requirement is that SP resistance is low. SP resistance is high in Ethiopia and overall transmission intensity is low so there is no policy on intermittent presumptive treatment and nor has there been a history of mass drug administration[20]. However, in a broader control sense the knowledge that the length of the transmission season is extremely short remains a valuable planning tool for single, targeted IRS campaigns and awareness raising activities. Areas of less than three months transmission have been defined in previous epidemiological maps of Ethiopia based on expert opinion (Figures 3.6b & 4.1). As such we have created a seasonality layer that highlights areas with acute seasonal transmission.

We have used a biological target definition of 60% of annual rainfall occurring within three consecutive months [Cairns et al., 2012][21]. We have used daily rainfall estimates from the African Rainfall Estimates version 2 (RFE 2.0) dataset,[22] based on monthly data at 10 x 10 km resolution between 2002 and 2009, to identify areas of Ethiopia with a precipitation concentration index of 60% within three consecutive months and where mean predicted

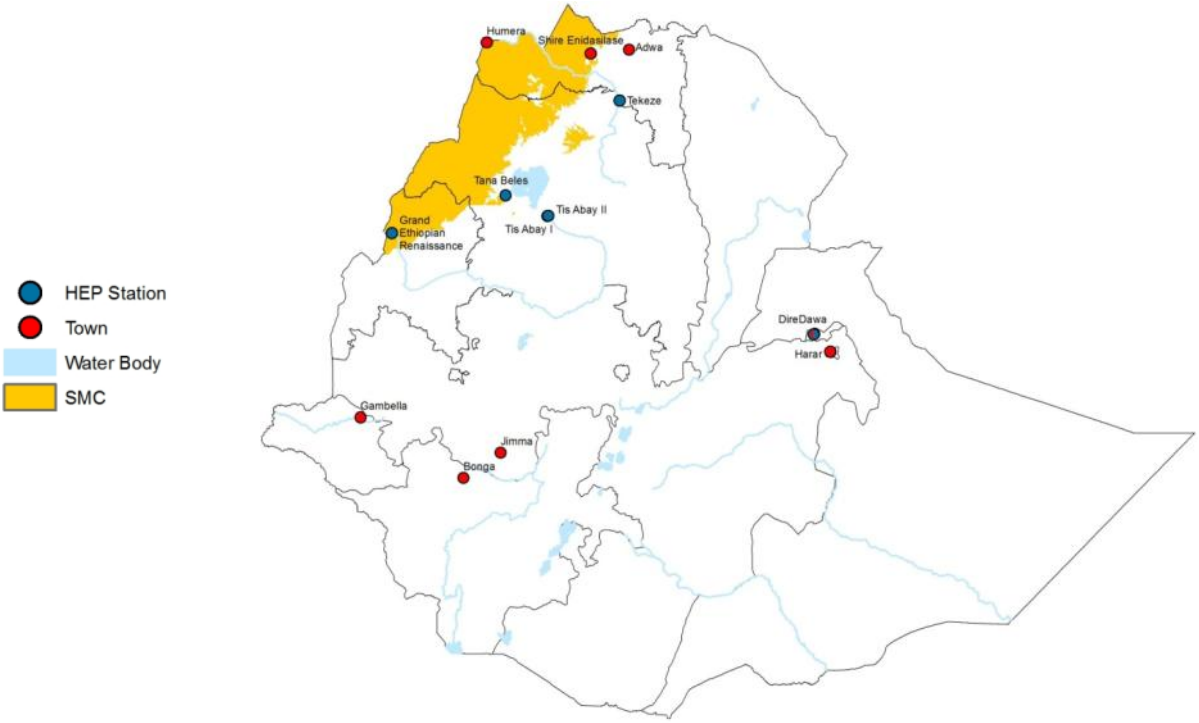
[20] One study of seasonal chemoprophylaxis was undertaken in the Awash Valley in 1988 using chloroquine to children aged 1-14 years and no difference in clinical attacks when compared to placebo [Wolde et al., 1994]

[21] This definition best fitted the seasonal clinical profiles of >60% of cumulative cases occurring in 4 consecutive months and malaria incidence patterns suitable for SMC were identified, with a sensitivity of 95.0% and a specificity of 73.5% [Cairns et al., 2012].

[22] This rainfall database was developed as a collaborative programme between NOAA's Climate Prediction centre (CPC), USAID/Famine Early Systems Network (FEWS). The RFE 2 gridded dataset combines gauge and satellite information on a near-real time basis to provide daily rainfall estimates over the African continent and is archived from January 2000 at 10 km spatial resolution [Novella & Thiaw, 2012].

*Pf*PR$_{2-10}$ was >= 5% in the baseline, receptive period of 2000 (Figure 6.1). This area occupies 61,759 km^2 and was home to 2 million people in 2010, with the majority in Amhara and Tigray Regions and far fewer in Benishangul Gumuz Region.

Figure 6.1: Areas of acutely seasonal transmission as defined by 60% of annual rainfall within three consectutive months in areas where stable transmission occurs above *Pf*PR$_{2-10}$ 5% in 2000 (Orange). Also showing major densley populated towns (Red) and dams (Blue) in stable endemic areas (2010)



6.2 Urban municipal malaria control

The availability of optimum environments for the development of malaria transmitting anopheline populations is limited in urban areas resulting in reduced vector density, biting rates and transmission intensity. Overall malaria infection rates are lower in urban compared to neighbouring rural areas of Africa [Robert et al., 2003; Hay et al., 2005]. Despite Ethiopia being one of the least "urbanized" countries in sub-Saharan Africa (Section 2.2), there is a growth in small to medium-sized towns that might drive the changing malaria ecology[23] or offer unique opportunities for alternative control strategies. Many of the most densely populated cities and towns of Ethiopia are located in unstable, or areas with low receptive risk. Of the top 20 most populous towns, those that have reported a significant clinical burden or are located in a stable endemic area include Humera [Seboxa & Snow, 1997], Gambella [Krafsur & Armstrong, 1978], Gondar [Mengistu et al., 1979], Dire Dawa and Jimma [Alemu et al., 2011a; 2011b] (Figure 6.1). These towns might benefit from specialized municipal vector control strategies and surveillance.

[23] For example proximity of households to standing water proved to be a significant risk factor for increased malaria infection in Nazareth town [Yohannes & Petros, 1996], Jimma town [Alemu et al., 2011a] and Adama town [Peterson et al., 2009]. Evidence of established water management practices was reported in Gondar in 2004 [Tilaye & Deressa, 2007]

6.3 Dams and irrigation schemes

Dams and irrigation schemes, developed to improve access to water for agriculture or the provision of electricity, have long been recognized as potential changers of risks posed by vector of human pathogens [Coosemans & Mouchet, 1990; Hunter et al., 1993]. The importance of agricultural development and possible changing malaria risks were first raised during the 1970 WHO review of the eradication campaign [Anon, 1970]. There has been a wealth of important research in Ethiopia demonstrating the increased risks of malaria exposure and disease incidence with proximity to dams including the Gilgel-Gibe Dam [Yewhalaw et al. 2009; 2013], the Koka Dam [Lautze et al. 2007; Kibret et al. 2012] and several microdams in the Tigray region [Alemayehu et al., 1998; Ghebreyesus et al., 1999; Yohannes et al., 2005; Dejenie et al., 2011] and irrigation schemes for sugar plantations in East Wollega Zone, western Ethiopia [Jaleta et al., 2013] and other subsistence and commercial agriculture in the central Rift Valley area [Kenea et al., 2011; Kibret et al., 2010; Stryker & Bomblies, 2012].

Ethiopia has recently constructed a large number of dams to increase electricity production and irrigate agricultural lands for commercial farming and as a means to support rural, subsistence farming as part of poverty reduction strategies. Using a variety of sources[24] we have identified 18 hydroelectric power projects located in different intrinsic malaria risk settings. Clearly, the most significant for sustained, stable malaria risks are the Dire Dawa and Tekeze dams located in hypoendemic areas and the potential to sustain very high risks around the Grand Ethiopian Renaissance Dam currently under construction on the Sudan border (Figure 6.1). Communities located close to the hydrodams in the highland epidemic and traditionally low, stable endemicity (*Pf*PR_{2-10}) areas require careful surveillance that feeds into hot-spot, epidemic foci intelligence for targeted control. The irrigated areas of the Rift Valley, SNNP and Somali regions are too many to map in a meaningful way and most are located in semi-arid malaria free areas or historically low stable endemic areas. There is little impact analysis of the reservoirs and irrigation schemes in SNNP and Somali regions and this would merit further investigation. The natural flood plains of the Baro Akobo in the Gambella Region are of particular note as they are associated with high disease burdens during flooding and are located in a stable endemic area [Wakuma et al., 2009].

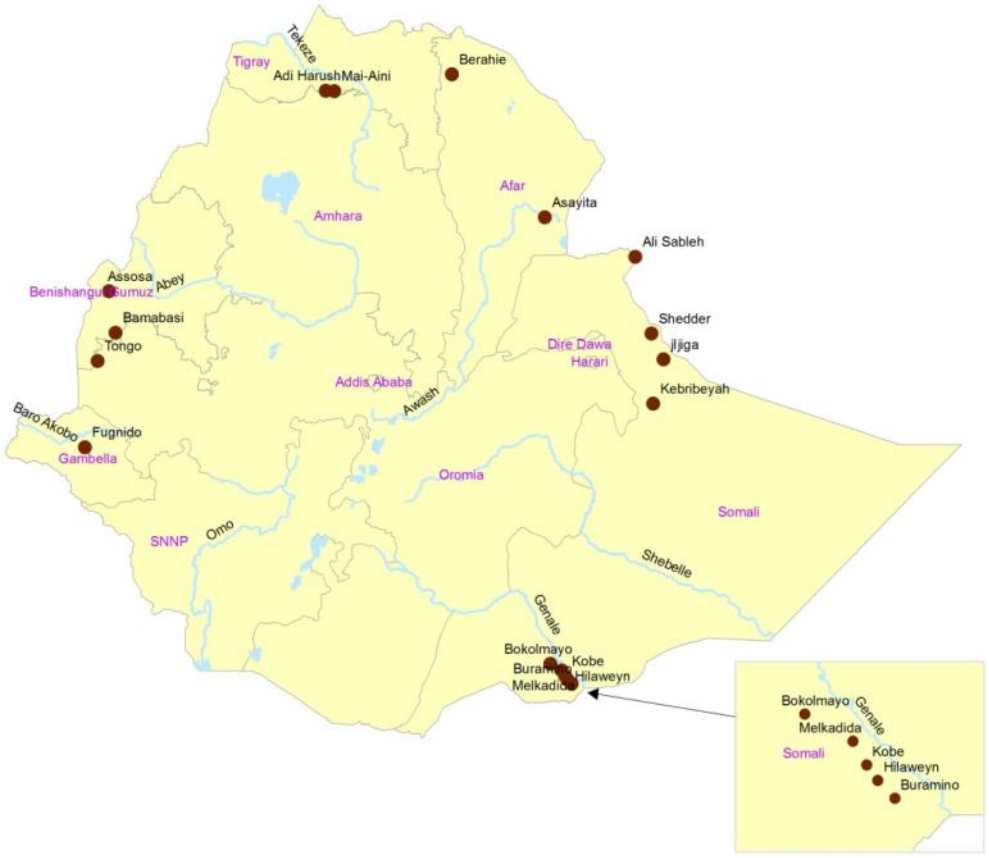
6.4 Refugees

Continuing internal and cross border conflicts have resulted in the influx of large populations of refugees and internally displaced persons (IDP). In 2011, border disputes along Sudan's Blue Nile and South Kordofan states pushed many refugees into camps in western Ethiopia. During 2011-2012, the refugee population in Ethiopia nearly doubled

[24] Global Energy Observatory: http://globalenergyobservatory.org
Wikipedia: https://en.wikipedia.org/wiki/List_of_power_stations_in_Ethiopia
Enipedia : http://enipedia.tudelft.nl/wiki/Ethiopian_Electric_Power_Corp
Ministry of Water and Irrigation Website at http://www.mowr.gov.et/index.php?pagenum=4.2
Awulachew *et al,* Water Resources and Irrigation Development in Ethiopia, Working Paper 123 from Columbia University, http://www.ldeo.columbia.edu/users/menke/data/ethiopia/WP123.pdf

following the entry of over 100,000 Somalis into the Dollo Ado region, Sudanese entering around Assosa and a significant number of Eritreans entering the Afar and Tigray regions. There are currently five refugee camps located in Dollo Ado, Fungido, Assosa, Tongo and Bamabasi and the estimated refugee population in 2013 was 243,643 from Somalia (56%); 96,460 Sudanese (23%) and 62,996 Eritreans (17%). Most IDPs are in Tigray and Gambela Regions and the majority of Somali refugees (>206,000 at mid-2013) are in eastern and south-eastern Ethiopia (Figure 6.2) [UNHCR, 2013]. In addition, there are a number of displaced people from Moyale in Kenya (approximately 2,800 Borena who arrived in Ethiopia from Kenya in 2005-2006), and urban refugees from other countries, including Eritrea, Burundi, the Democratic Republic of the Congo (DRC), Djibouti, Rwanda, Uganda and Yemen. There were nearly 3,900 registered urban refugees in June 2012 [UNHCR, 2013].

Figure 6.2: location of refugee settlements 2013 data from UNHCR (2013)



7. *Plasmodium vivax*

The current focus of control in Africa is justifiably on *P. falciparum*, by far the most pathogenic of the five human malarias, contributing to over 95% of the world's mortality from malaria. For *P. vivax* there are two dogmas not necessarily supported by adequate empirical data within sub-Saharan Africa. First, endemic *P. vivax* transmission is thought to be absent from much of the continent due a restricted distribution in Africa owing to the refractory nature of Duffy-negative red blood cells that lack a necessary receptor (Fy(a-b-)) for invasion [Miller et al., 1975; 1976; Livingstone, 1984]. There is, however, growing epidemiological and molecular evidence that a parasite with characteristics of *P. vivax* is

being transmitted among Duffy blood group–negative inhabitants in Kenya [Ryan et al., 2007], Congo [Culleton et al., 2009], Madagascar [Menard et al., 2010], Mauritania [Wurtz et al., 2011], Uganda [Dhorda et al., 2011] and among travellers to central and west Africa [Gautret et al., 2001]. It would appear that vivax transmission is possible and can persist in predominantly Duffy-negative populations which may not be 100% refractive [Culleton et al., 2008; Rosenberg, 2007]. Second, the dominant opinion has for many years been that *P. vivax* is clinically benign. There is a growing body of epidemiological and clinical evidence that suggests that *P. vivax* is far from benign and directly causes, and not simply associated with, severe life-threatening disease, mortality and indirect consequences on pregnant women [Baird, 2007; 2013; Mendis et al., 2001; Price et al., 2007; 2009]. The clinical burden of *P. vivax* mono-infections was described recently in southwest and southern Ethiopia among children aged less than 10 years with over 40% presenting with anaemia; severe complications including hypoglycaemia, respiratory distress, hyper-pyrexia and persistent vomiting [Ketema & Bacha, 2013].

Since the very first epidemiological descriptions of malaria in Ethiopia, during the 1930s, *P. vivax* was recognized as an important parasite and felt to be sustained in this part of Africa because of its ability to survive colder, more temperate climates [Archetti, 1940; Brambilla, 1940; Castellani, 1938a; Castellani, 1938b; Corradetti, 1938; 1940b; Giaquinto-Mira, 1940; Jannone et al., 1946; Lega et al., 1937]. Since the late 1960s, when active and passive case detection was introduced, approximately 40% of all clinical infections in Ethiopia have been associated with *P. vivax* [Anon, 1970; Delfini & Shidrawi, 1976]. Between 1976 and 1991 this ratio of *P. falciparum* to *P. vivax* fluctuated between years but remained overall at around 60:40% [FMoH, 1993]. There is some suggestion that in some areas of Ethiopia the ratio of falciparum to vivax is changing. At the Gambo General Rural Hospital in Shashemane, the percentage of cases involving *P. vivax* had declined from 55% in 1998 to 22% in 2003 [Manuel Ramos et al., 2005].

Differences in susceptibility to vivax infections between ethnic groups were first described by Armstrong (1978) during studies of infection prevalence among Nilotic, Anuaks (*P. vivax* infection rates 0.7%) and Hamitic-Semitic Tigreans, Galla and Amhara (*P. vivax* infection rates 4.6%) in the Gambella Region between 1966 and 1977. These observations suggested a genetic refractory feature of Nilotics in this part of Ethiopia, later confirmed through the examination of Duffy-positive antigens in the Nilotic and Hamitic-Semitic populations of Gambella and communities in Addis: Duffy-positivity rates 8%, 70% and 98% respectively [Mathews & Armstrong, 1981]. The data presented by Mathews and Armstrong did however suggest that Duffy-negative individuals were not completely refractory to *P. vivax* or that *P. ovale* might have been misclassified as *P. vivax*. More recently, homozygote Duffy negative populations in Harar have been found to harbour *P. vivax* infections [Woldearegai et al., 2013] consistent with a growing body of evidence from across Africa that Duffy-negative red cells are not completely refractory to vivax.

The biological features of *P. vivax* infection present distinct challenges to the modelling of endemicity comparable to methods used to define *P. falciparum* endemicity. Unlike *P. falciparum* infections, *P. vivax* includes a dormant hypnozoite liver stage not detectable during routine cross-sectional surveys and may persist for months and years that lead to clinical relapse episodes indistinguishable from the primary infection [White, 2011; Battle et

al., 2011]. A large reservoir of infection is therefore missed during routine surveys. The *P. vivax* parasite rates observed in population surveys detect both new and relapsing infections, although the two are almost never distinguishable which significantly limits attempts to model relationships between observed infection prevalence and measures of transmission intensity such as force of infection or the entomological inoculation rate.

Two features of infections with *P. vivax* lead to under-estimates of true blood stage prevalence: *P. vivax* typically occurs at much lower densities compared to those of falciparum malaria and routinely occurs as a co-infection with *P. falciparum*. Routine microscopy therefore traditionally routine clinical microscopy misses vivax, or where co-infections occur, only *P. falciparum* is reported [Rosenberg, 2007]. Currently available RDTs are less sensitive in the detection of *P. vivax* mono-infections compared with pure *P. falciparum* or mixed infections [WHO-FIND, 2012]. Recent studies in Ethiopia of three RDTs CareStart® (pf-HRP2/pan-pLDH), ParaScreen® (pf-HRP2/pan-pLDH) and ICT Combo® (pf-HRP2/pan-aldolase) showed sensitivities in the range of 70% to 90% [Sharew et al., 2009; Ashton et al., 2010; Mekonnen et al., 2010; Chanie et al., 2011; Moges et al., 2012; Woyessa et al., 2013].

Attempts have been made to use MBG to describe the prevalence of *P. vivax* infections at the global scale but these have used Duffy-negativity to constrain risk and have been based on limited data [Gething et al., 2012]. There is an urgent need to revisit the biological and diagnostic constraints to modelling the distribution of *P. vivax* intensity for Ethiopia. This work is beyond the scope of the present report but should draw upon the wealth of historical data and be integrated into MBG models that accommodate clinical infection risks from health facility data. We return to this in Section 12. Meanwhile here we summarize the community-defined infection prevalence data in three time intervals 1937-1949; 1951-1979; and 1980-2011, by province (Table 7.1). Only surveys where both parasites were recorded and where microscopy was used as the method of parasite detection have been included. No adjustment has been made for age of each surveyed community.

During the early period (1937-1949) the overall prevalence of *P. vivax* at 105 sampled locations was high reported at 13% and accounting for 39% of combined *P. vivax* and *P. falciparum* infections. This is consistent with much higher levels of transmission intensity recorded during this period (Figure 3.2). During the period that included an expansion of IRS as part of the first elimination campaigns (1951-1979), *P. vivax* prevalence declined to less than 1% across 418 locations nationwide and accounted for approximately 26% of combined *P. vivax* and *P. falciparum* infections. More recent data from 1376 locations sampled between 1980 and 2011, suggest that the overall prevalence of *P. vivax* remains low, circa 1%, but accounts for 34% of combined *P. vivax* and *P. falciparum* infections. There are, however, important differences between regions. Between 1980 and 2011 almost half of infections were due to *P. vivax* in SNNP region, compared to circa 13% in Gambella and Benishangul Gumuz (Table 7.1).

Table 7.1: Prevalence of *P. vivax* and ratio to *P. falciparum* infections by 11 Provinces 1937-49; 1951-79; 1980-2011

Province	1937-1949 Number of surveys/Individuals examined Pf & Pv positives/PV positives Pv positives (%); Pv positives of Pf+Pv [%]	1951-1979 Number of surveys/Individuals examined Pf & Pv positives/PV positives Pv positives (%); Pv positives of Pf+Pv [%]	1980-2011 Number of surveys/Individuals examined Pf & Pv positives/PV positives Pv positives (%); Pv positives of Pf+Pv [%]
Addis Abba	3/300 90/18 6.0%/20.1%	N/A	5/2272 79/54 2.4%/68.4%
Afar	4/333 60/2 0.6%/3.3%	17/19706 1189/266 1.4%/22.4%	33/2648 865/181 6.8%/20.9%
Amhara	23/4595 2253/1040.6 22.7%/46.2%	81/69352 3109/982 1.4%/31.6%	315/18566 594/283 1.5%/47.6%
Benishangul Gumuz	1/100 31/1 1.0%/3.2%	7/27331 1039/132 0.5%/12.7%	36/1094 53/7 0.6%/13.3%
Dire Dawa	5/1085 197/131 12.1%/66.5%	7/4103 262/69 1.7%/26.6%	3/60 0/0 0%/0%
Gambella	1/100 30/1 1.0%/3.3%	5/1009 271/38 3.7%/14.0%	37/2,437 45/42 1.7%/12.5%
Harari	10/1000 296/32.5 3.3%/10.9%	5/9441 28/6 0.1%/22.2%	3/266 45/28 10.5%/62.2%

Province	1937-1949 Number of surveys/Individuals examined Pf & Pv positives/Pv PV positives (%)/Pv positives of Pf+Pv (%)	1951-1979 Number of surveys/Individuals examined Pf & Pv positives/Pv PV positives (%)/Pv positives of Pf+Pv (%)	1980-2011 Number of surveys/Individuals examined Pf & Pv positives/Pv PV positives (%)/Pv positives of Pf+Pv (%)
Oromia	32/2699 625/180 6.7%/28.8%	199/265664 5741/1524 0.6%/26.5%	550/122812 2954/1052 0.9%/35.6%
SNNP	10/807 129/32 3.98%/24.8%	54/19573 894/231 1.2%/25.8%	180/29981 334/165 0.6%/49.4%
Somali	13/968 308/134 13.9%/43.5%	4/104 28/6 5.8%/21.4%	22/474 0/0 0%/0%
Tigray	3/250 61/15 6.0%/24.6%	39/1007112 2697/670 0.7%/24.9%	192/20789 802/239 1.2%/29.8%
Totals	105/12237 4082/1588 13.0%/38.9%	418/516994 15257/3923 0.8%/25.7%	1376/201399 6062/2051 1.0%/33.8%

8. *Plasmodium ovale* and *P. malariae*

Plasmodium ovale and *P. malariae* have been reported in most regions of the world, however, both parasites seem to be largely confined to sub-Saharan Africa and a few islands in the Western Pacific [Lysenko & Beljaev, 1969; Collins & Jeffery, 2005; 2007; Mueller et al., 2007]. There appears to be no Duffy blood group restrictions to infection for either of these parasites [Collins & Jeffery, 2005; 2007].

Plasmodium ovale was first reported in 1966 at Arba Minch and in 1968 in Gambella and Humera [Armstrong, 1969]. Recent genetic studies of parasite populations in Africa suggest that there may be more than one genetically distinct form of *P. ovale, Plasmodium ovale* curtisi (classic type) and *Plasmodium ovale* wallikeri (variant type) [Sutherland et al., 2010]. Both variants detected by PCR at low frequencies in North Gondar [Alemu et al., 2013a]. *P. ovale* has been rarely reported during surveys since the 1960s; explicit reports of the presence or absence of *P. ovale* have only been documented at 28 sites and found present at only six sites at very low prevalence, principally in North Gondar [Collins et al., 1971]. The relative absence of reports of this parasite elsewhere is intriguing and might be a result of confusion with *P. vivax* during microscopy.

Plasmodium malariae was first described in 1938 in South Omo District, SNNP Province [Archetti, 1940]. Between 1937 and 2008, the presence of *P. malariae* was investigated at 440 time-space locations across Ethiopia among 462,921 individuals, and found to be present at 146 (33%) locations in 933 (0.2%) individuals.

The non-falciparum human malarias are often susceptible to most antimalarial drugs including those that currently fail to treat *P. falciparum* [White, 2008], however most evade drug action as they are more often benign and/or relapse.

9. Parasite resistance to anti-malaria drugs

Chloroquine (CQ) was the first line drug for the treatment of uncomplicated malaria in Ethiopia for over two decades from the 1950s. Early investigations indicate that it remained effective, with parasitological failure rates less than 4% until the early 1970s [Armstrong et al., 1976; Palmer et al., 1976]. The first report of CQ resistant falciparum malaria in Ethiopia was detected at Woyto and Bare areas close to Ethiopia's borders with Kenya and Somalia in 1985 [Teklehaimanot, 1986b]. Studies undertaken across various regions between 1989 and 1991 showed that 7-day *P. falciparum* parasitological CQ failure rates were below 5% [Alene & Bennett, 1996]. A further nationwide study was conducted at 18 sites across Ethiopia from 1996 to 1998 and found 14-day *P. falciparum* parasitological failure rates to CQ in excess of 40% [FMoH, 2001]. Only one site in the Benishangul-Gumuz Region had a CQ treatment failure rate lower than 40%. Amodiaquine was also assessed at six sites as a possible alternative for *P. falciparum* therapy but also demonstrated high (36%) clinical failure rates [FMoH, 2001]. In contrast, despite the wide use of sulphadoxine-pyrimethamine (SP) during the 1990s, resistance to SP was low (5-10%) [Wezam, 1993; Tulu et al., 1996]. The studies during the late 1990s were used to inform the national guidelines for malaria treatment at a multi-partner workshop on the national antimalarial drug policy convened in July 1998. This meeting recommended a change from CQ to SP/Fansidar as the

first line therapy for uncomplicated *P. falciparum* [FMoH, 2004b]. The SP treatment failure rate at this time was only about 7% [FMoH, 2001].

From 2001, the monitoring of drug efficacy was made a priority and 15 sentinel sites were established and used day 28 clinical protocols [WHO, 2003] in all age groups and included testing of anti-malarials used in the treatment of *P. vivax*. Very soon after the change from CQ to SP, evidence of *P. falciparum* SP failure began to emerge at Amhara [Kassa et al., 2005], Tigray [Degefa, 2004], and SNNPR [Abebe, 2006]. A national survey at ten of the sentinel sites in 2003 showed high 28-day *P. falciparum* clinical and parasitological SP failure rates across the country ranging from 21-53% [Jima et al., 2005a]. These findings were supported by evidence from molecular studies of emerging *dhfr* and *dhps* folate resistance markers [Schunk et al., 2006; Gebru-Woldearegai et al., 2005; Mula et al., 2011]. A national workshop on anti-malarial treatment policy was held in May 2004 in Addis Ababa that recommended a change from SP to artemether-lumefantrine (AL) as the 1st line therapy [FMoH, 2004b] which had proven high clinical and parasitological efficacy against *P. falciparum* in Ethiopia [Jima et al., 2005b] and continues to be efficacious [Kefyalew et al., 2009; Assefa et al., 2010; Kinfu et al., 2012]. In 2013, recommendations emerged, in line with elimination ambitions to include the use of 0.25 mg/kg single dose Primaquine (PQ)[25] as a means to target gametocytes for *P. falciparum* transmission reduction, notably in epidemic prone areas [FMoH, 2014]. It has also been suggested that Dihydroartemisnin/Piperaquine (DHA/PPQ) might be used in areas of high population movement in the treatment of *P. falciparum* malaria, given its slightly longer half-life than AL and its simpler dosing regimen [FMoH, 2014].

It would appear the *P. vivax* resistance to CQ established itself later than for *P. falciparum* [Tulu et al., 1996; Schunk et al., 2006; Ketema et al., 2009; 2011; Yeshiwondim et al., 2010]. Between 2009 and 2010 at the Bishoftu Malaria Clinic and Bulbula Health Centre, in Oromia Region, CQ continued to provide 91% 28-day *P. vivax* cure rates, higher than AL vivax cure rates (76%) [Hwang et al., 2013]. The national malaria treatment guidelines recommend chloroquine for the treatment of *P. vivax* and PQ 0.5mg/kg is recommended for radical cure [Yeshiwondim et al., 2010; FMoH, 2012a]. Currently Artemether-Lumefantrine (AL) is recommended for mixed *P. falciparum* and *P. vivax* infections.

10. Dominant vectors and bionomics

10.1 Background

All national malaria strategies across Africa implement interventions aimed at reducing human exposure to infectious malaria vectors. These include insecticide treated nets, applications of residual insecticides on household walls, or the targeting of larval stages of vectors to reduce vector abundance, survival and/or human-feeding frequency. However, the distribution of vector compositions linked to their intrinsic behavioural bionomics and their resistance to currently available insecticides remains largely unknown or under-

[25] PQ is associated with haemolysis in patients with specific variant types of Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency. There is very limited information on the distribution of variant forms of G6PD deficiency in Ethiopia [Perine & Michael, 1974]. Rapid tests exist for G6PD and could be used in patient management or during national surveys to establish regional frequencies

emphasized when planning vector control at national scales. Vector resistance to insecticides and behavioural adaptive changes accompanied by changing vector biodiversity pose real challenges to the future effectiveness of current vector control strategies [Ferguson et al., 2010; Gatton et al., 2013; Pates & Curtis, 2005; Ranson et al., 2011]. Furthermore, a lack of reliable entomological monitoring systems to capture all relevant phenotypes and their effect on vector population dynamics, on national scales, limit the capacity of malaria control programs to manage on-going vector control efforts by adapting to changes in vector behaviour and insecticide susceptibility [Govella et al., 2013].

10.2 Historical descriptions of malaria vectors

The Italian malariologists during the 1930s undertook vector surveillance and determined that *An. gambiae* was the dominant and most prolific vector across Ethiopia [Lega et al., 1937; Coradetti, 1938; Castellani, 1938a]. Several *An. pharoensis* breeding sites were found on the shoreline of Eritrea and parts of Ethiopia [Coradetti, 1939b, 1940b]. *An. funestus* was identified in Oromia, SNNP and Benishangul Gumuz [Giaquinto-Mira, 1948; Brambilla, 1941] and later confirmed as an important vector in lowland areas primarily with permanent water [Anon, 1972; Anon 1977, NMES, 1972]. *An. d'thali* was thought to be an important secondary vector in Ethiopia [Lega et al., 1937, Mara, 1940]. Very few *An. mauritianus* and *An. paludis* were also sampled. Other less important vectors - such as *An. chrisstyi, An. pritoriensis* and *An. garnhami* were not considered to be malaria transmitting mosquitoes.

During vector surveillance undertaken during the malaria eradication programme of the 1960s *An. gambiae, An. funestus* and *An. pharoensis* were confirmed as the dominant vectors; *An. nili* was detected as a secondary vector in several locations; *An. demeilioni* and *An. marashali* were also indentified in large numbers but their precise role in transmission was never ascertained [Krafsur, 1970; Anon 1972; NMES, 1972; Delfini & Shidrawi, 1976, Anon, 1977].

A detailed assembly of information on the location of reported vector species was undertaken by Charles O'Connor covering survey reports from the National Malaria Eradication Service, field reports from the WHO and USAID and occasional research surveys conducted between the 1950s and December 1965 [O'Connor, 1967]. The following species and sub-species made up the anopheline fauna in the 1960s:

An. adenensis Christophers 1924
An. *ardensis* Theobald 1905
An. christyi Newstead and Carter, 1911
An. cinereus Theobald, 1901
An. coustani coustani Laveran, 1900
An. coustani tenebrosus Donitz, 1900
An. coustani ziemanni Grunberg, 1902
An. dancalicus corradetti, 1939
An. demeilloni Evans, 1933
An. d'thali Patton, 1905
An. funestus Giles, 1902
An. *gambiae* Giles, 1902
An. garnhami Edwards, 1930
An. harperi Evans, 1936
An. implexus Theobald, 1903

An. kingi Christophers, 1923
An. *leesoni* Evans, 1931
An. longipalpis Theobald, 1903
An. macmahoni Evans, 1936
An. maculipalpis Giles, 1902
An. marshalli Theobald, 1903
An. natalensis Hill and Hayden, 1907
An. nili Theobald, 1904
An. obscurus Grunberg, 1905
An. paludis Theobald, 1900
An. pharoensis Theobald, 1901
An. pretoriensis Theobald, 1903
An. rhodesiensis Theobald, 1901
An. rivulorum Leeson, 1935
An. rufipes Gough, 1910
An. rupicolus Lewis, 1937
An. seydeli Edwards, 1929
An. squamosus Theobald, 1901
An. theileri Edwards, 1912
An. turkhudi Liston, 1901
An. wellcomei Theobald, 1904

An. culicifacies adenensis Giles and *An. erythraeus* Corradetti are only found in present day Eritrea. Since this early comprehensive description of the Anopheles family, others have identified further species bringing the total number to between 42 and 44 [Mekuria, 1983; Gebre-Mariam, 1988].

10.3 Updating the malaria vectors inventory for Ethiopia

Across Africa, detailed inventories of species distribution began during elimination campaigns launched in the 1950s. The notion of mapping vector species was resurrected during the mid 1990s as part of the Mapping Malaria Risk in Africa (MARA/ARMA) project [Coetzee et al., 2000]. There have been several recent attempts to model the distributions of DVS in Africa using sparse data and climatic determinants notably, temperature, soil moisture and other environmental drivers of vector species presence and abundance [Lindsay et al., 1998; Moffett et al., 2007; Sinka et al., 2010; Lunde et al., 2013a; 2013b]. These model predictions have used different statistical approaches and different data sets and are hard to systematically compare.

The coincidental growth of geo-located databases of vector species has, however, provided some unique resources for countries to access, augment and adapt to local planning needs; notably the following

AnoBase [http://skonops.imbb.forth.gr/]
VectorBase [https://www.vectorbase.org]
MARA/ARMA collaboration [https://www.mara.org.za]
Walter Reed Biosystematics Unit (WRBU) Mosquito Catalog [http://www.mosquitocatalog.org]
Malaria Atlas Project (MAP) [http://www.map.ox.ac.uk]
Disease Vectors database [https://www.diseasevectors.org]

The database on insecticide resistance, the Arthropod Pesticide Resistance Database (APRD) [http://www.pesticideresistance.org/], covers a large variety of arthropods, but only reports

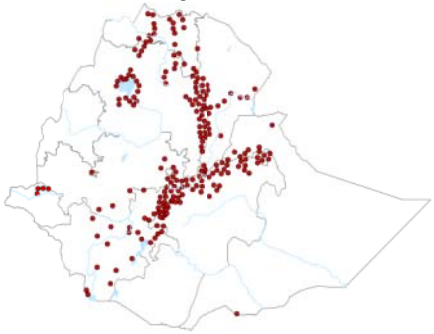
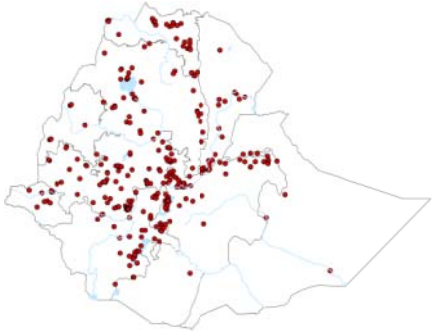
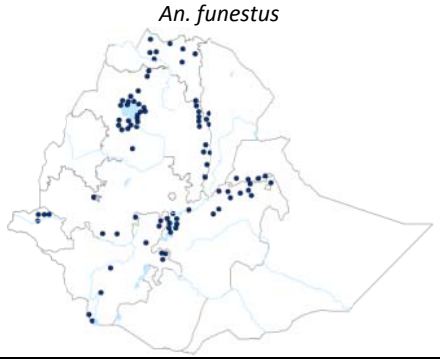
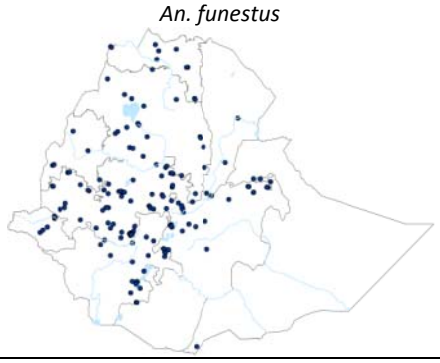
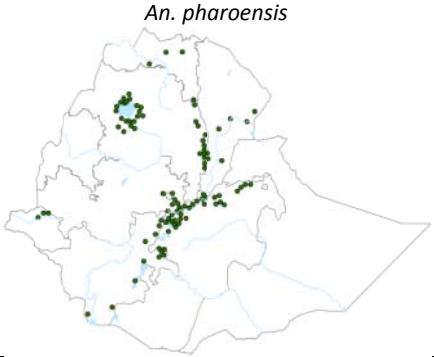
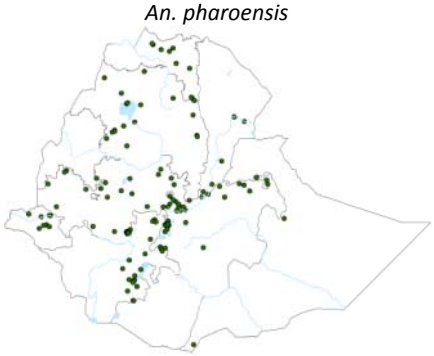
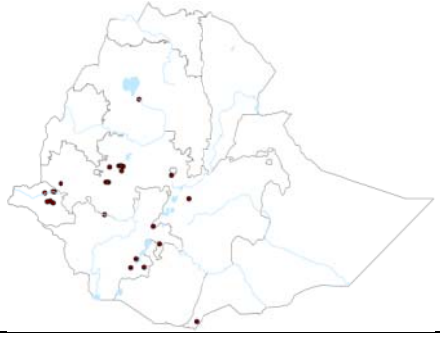
instances of occurrence of resistance, without any precision on geographic location nor actual data. The African Network for Vector Resistance (ANVR) was established in 2000, and amongst its objectives was the important goal of improving dissemination of resistance data [ANVR, 2005]. Over the last 10 years, a database has been developed to store the results of resistance monitoring activities by ANVR members. This database has now been integrated for open access with the launch of IRBase [Dialynas et al., 2009].

The most comprehensive available, geo-coded species-specific data are currently held on the MAP database [Sinka et al., 2010]. We re-ran on-line searches of medical literature databases including PubMed, Google Scholar and Web of Science using search terms "Anopheles AND Ethiopia" for all study publications after January 1966 and post the last searches undertaken by MAP. In addition, we contacted local entomologists working in university faculties to provide any additional data from unpublished sources, post-graduate student theses and routine monitoring reports. Finally, we reviewed all the malaria eradication literature from unpublished sources identified at the WHO archive in Geneva. Each study site was geo-coded using methods described in Annex A.1.3. Data abstracted from each report included the start and end of the entomological survey, species identified at complex or species member levels, methods of sampling (animal bait catches, bed net traps, CDC light traps, human landing catches, indoor resting searches, pyrethrum spray catches, exit traps, larval searches), methods of species detection (Polymerase chain reaction (PCR), Chromosome Banding Sequences, Morphology, DNA probes) and the full citation source.

For older survey data it is recognized that there is a degree of taxonomic ambiguity. For example the *Anopheles gambiae* complex was only fully categorised in 1998 following the genetic distinction of *An. quadriannulatus* species B at Jimma and designated a separate species after this date [Hunt et al., 1998; Harbach, 2004; Pates et al., 2006]. Recently, this species was named as *An. amharicus* [Coetzee et al., 2013]. The exact composition of the *An. funestus* complex remains unclear.

The final database contained 329 site/time specific reports of DVS occurrence between 1966 and 2013. We were unable to geo-locate 15 (4.6%) sites. At the 314 geo-located sites, 99 (32%) were sampled after 2000. Here we display the locations of the DVS *An. gambiae* s.l (almost universally *An. arabiensis*), *An. funestus*, *An. pharoensis*, and *An. nili* sampled between 1966 and 2013 and compared to the reported distributions before 1966 [O'Connor, 1967] (Figure 10.1).

Figure 10.1: Distributions of DVS in Ethiopia pre- [O'Connor, 1967] and post 1966 (present search)[26]

Pre-1966	1966 - 2013
An. gambiae s.l 	*An. gambiae* s.l 
An. funestus 	*An. funestus* 
An. pharoensis 	*An. pharoensis* 
An. nili 	*An. nili* 

[26] Note: location points are where surveys undertaken and species identified not a random sample. The vast majority of *An. gambiae* s.l. will be *An. arabiensis*.

10.3.1 Anopheles arabiensis: An. arabiensis is now thought to be the only malaria vector from the *An. gambaie* complex involved in malaria transmission in Ethiopia [FMoH, 2002]. *An. arabiensis* is considered a species of dry, savannah environments or sparse woodland. Evidence is growing of a more ubiquitous range of *An. arabiensis* across Africa. Its larval habitats are generally small, temporary, sunlit, clear and shallow fresh water pools, although *An. arabiensis* is able to utilize a variety of habitats including slow flowing, partially shaded streams, large and small natural and man-made habitats, turbid waters and there are reports of larval identification in brackish habitats. *Anopheles arabiensis* is described as a zoophilic, exophagic and exophilic species but has a wide range of feeding and resting patterns, depending on geographical location. This behavioural plasticity allows *An. arabiensis* to adapt quickly to counter indoor residual spraying control showing behavioural avoidance of sprayed surfaces depending on the type of insecticide used. Blood feeding times also vary in frequency; peak evening biting times can begin in the early evening (19:00) or early morning (03:00). This species usually has a greater tendency than *An. gambiae s.s.* to bite animals and rest outdoors. The density of *An. arabiensis* is seasonal across Ethiopia, increasing during the wet months June - September and March - April. Older mosquitoes continue to survive in September, October and May. During the dry months the species survives by breeding in small pools formed on beds of streams, small collection of water on fields and river edges.

10.3.2. Anopheles funestus: A typical *An. funestus* larval habitat is a large, permanent or semi-permanent body of fresh water with emergent vegetation, such as swamps, large ponds and lake edges. *An. funestus* is a highly adaptable species, allowing it to occupy and maintain its wide distribution and utilise and conform to the many habitats and climatic conditions. *An. funestus* is considered to be highly anthropophilic with a late-night biting pattern (after 22.00 hours). Endophilic resting behaviour is also commonly reported, and these characteristics are responsible for rapid disappearance of this vector following expanded indoor residual spraying and insecticide-treated nets. Compared to other dominant vector species in Africa, *An. funestus* shows fairly consistent behaviour (generally anthropophilic and endophilic) throughout its range. In the absence of insecticide use, the endophilic resting behaviour of *An. funestus* combined with a relatively high longevity, makes it as good a vector, or better in some areas, as *An. gambiae s.s*. *An. funestus* is thought to occur frequently in localities along the swamps of Baro and Awash rivers and shores of lakes Tana in the North and the Rift Valley, however, it appears to have a more ubiquitous range (Figure 10.1).

10.3.3. Anopheles pharoensis is a widely distributed anopheline across the country, sympatric with *An. arabiensis* and *An. funestus* (Figure 10.1), but is considered to play a secondary role in malaria transmission along with *An. funestus* and *An. nili. An. pharoensis* is mostly found in the lake and reservoir areas and its density increases after September when the density of *Anopheles arabiensis* start to fall. Primarily a species of large vegetated swamps; also found along lakeshores and among floating plants, reservoirs, rice fields, streams, ditches and overgrown wells. It is considered as zoophilic but seen to bite humans on occasions. It feed from dusk to dawn with a peak at about 01:00.

10.3.4. Anopheles nili was first described in Ethiopia in the Gambella region [Krafsur, 1970]. The *An nili* complex includes *An. carnevalei*, *An. nili*, *An. ovengensis* and *An. somalicus*. It is considered to be strongly anthropophilic, and will readily feed both indoors and outdoors. It sometime found biting outdoors in the early evening when people are socialising and then continuing to bite indoors once people move inside, with peak feeding occurring after midnight. In a lowland region of western Ethiopia, *An. nili* was rarely found resting indoors despite the high densities found biting indoors, indicating its exophilic behaviour [Krafsur, 1970]. Conversely, *An. ovengensis* is rarely found resting indoors and has exophilic habits. Larvae of all members of the *An. nili* complex are found in vegetation at the edges of fast flowing streams and is more abundant along rivers in degraded forest and savannah (Figure 10.1).

11. Insecticide use and resistance

11.1 Insecticide use

Dichlorodiphenyltrichloroethane (DDT)[27] has been used for more than 40 years as the primary agent for indoor residual house spraying. DDT was first used as part of pilot eradiation projects in The Dembia Plain, near Lake Tana (1957-1959) [Najjar & Fontaine, 1959]; Kobo-Chercher project area, Wollo Province (1956-1959) [Fontaine & Najjar, 1959a]; Gambella (1959) [Fontaine & Najjar, 1959b]; and the Awash Valley Pilot Project, Shewa Province (1957-1961), where Dieldrin was also used but discontinued in favour of DDT [Zaphiropoulos, 1959]. Resistance was detected to Dieldrin in 1968. [Delfini & Shidrawi, 1976].

In March 1966, concerted eradication efforts began under the Imperial Government's National Malaria Eradication Service (NMES) with an ambition to eradicate malaria from Ethiopia by 1980 [Chand, 1965; Gish, 1992]. The eradication plan was prepared around four operational geographic areas A, B, C, and D (Table 11.1) [Anon., 1970]. The strategy protected four million people with two rounds of DDT (2 gms per m^2) spraying in Area A, a geographically defined operational area, in 1966 [Pull, 1967].

Table 11.1: Proposed NMES operational areas [Pull, 1967]

Area A	Eritrea, Tigre (currently Tigray), Begemider & Simen (currently Gondar), Eastern Wollo, Northern Harar, Eastern Shewa, Northern Arsi (circa 4.2 million people); Attack Phase to start 1966, Maintenance Phase from 1975
Area B	Gojjam, Western Wollo, Western Shewa, North-eastern Wellega, Northern Kaffa, Eastern Illubabor (circa 2.2 million people); Attack Phase to start 1968, Maintenance Phase from 1978
Area C	South-western Wellega, Western Illubabor, Southern Kaffa, GamoGofa, Western Sidamo (circa 2 million people); Attack Phase to start 1970, Maintenance Phase from 1979
Area D	Southern Harar, Southern Arsi, Bale and Sidamo (circa 1.6 million people); Attack Phase to start 1971, Maintenance Phase from 1980

The coverage of spray operations began to decline from 1973 in Area A, by 1976 only 1.4 million people were protected with DDT and complete expansion into Area B and anywhere in areas C and D was not pursued [Delfini & Shidrawi, 1976; Gish, 1992]. Despite a reduction

[27] DDT was formulated in Ethiopia at the Adami Tulu pesticide processing plant in Oromia for health related use only; this plant also formulates Malathion and Fenitrothion since 2001.

in IRS activities from the late 1970s, DDT use never completely stopped. In 1986, over one million household units were sprayed with DDT in 5,360 localities protecting 3.5 million people [Teklehaimanot, 1986]. During the 1993-1998 national malaria strategic plan the use of DDT for IRS was restricted to areas prone to epidemics, of high economic importance or settlements of non-immune individuals [FMoH, 1993]. IRS was targeted to protect an average of 3.2 million people living in approximately 900,000 households per year, requiring 1,520 tons of DDT (75% Water Dispersible Powder (WDP)), 730 tons of Malathion (50% WDP) and 100,000 litres of permethrin solution [FMoH, 1993].

The national strategies of 2000-2005 and 2005-2010, established under the Malaria Control Support Team (MCST), continued to support IRS using DDT [FMoH, 2000; 2001] and began to be scaled-up: in 2005 when 700 tons of DDT were used to protect 1.75 million households and increased to 1700 tons of DDT to protect 4.25 million households and 11.9 million people by 2008. In 2009, DDT was replaced with deltamethrin given the establishment of wide spread resistance [Yewhalaw et al., 2011]. Malathion (an organophosphate) has been used on a limited extent as an alternative to DDT over the last 10 years; an average of 31,600 kg per year of Malathion was used for IRS between 2003 and 2005 [FMoH, 2014].

The implementation of an insecticide treated net (ITN) programme began with a plan to protect resettled communities in the north-western area of Tigray in 1997, distributing 45,000 permethrin treated nets at subsidized prices [FMoH, 2004c]. Partial cost-retrieval based ITN distribution began during the early 2000s targeting 220 *woreda* classified as malarious[28] [FMoH, 2004c]. Between 2000 and mid-2005, approximately 1.8 million nets were distributed with the support of UNICEF and WHO [FMoH, 2004c; Jima et al., 2005c; PMI, 2008]. Global Fund finances were used from Round 2 Phase I and Phase II and Round 5 to procure and distribute approximately 10.5 million Long-Lasting Insecticide treated Nets (LLIN) by mid-2007 [PMI, 2008]. Additional nets were procured and distributed by the Carter Centre under a dedicated Malaria Programme launched in 2007 in the regional states of Amhara, Oromia, SNNPR, and Benishangul Gumuz: 3 million LLINs distributed in 2007 and a further three million LLINs in 2010 [Carter Center, 2008; 2013]. Combined with other partners it is estimated that between 2005 and 2012 approximately 56 million LLIN have been distributed in Ethiopia [FMoH, 2014]. Despite these efforts the percentage of households with at least one mosquito net in malaria-endemic areas was reported lower during the national household survey between October and December 2011 (55.2%) [FMoH, 2012b] than during the national household survey between October and December 2007 (68.9%) [Jima et al., 2010; FMoH, 2008]. By 2011, LLIN use the night before the survey by children under the age of five years varied between regions from 26.5% in Oromiya to 60.5% in the combined regions of Benishangul-Gumuz & Gambella. It is notable that in the very low risk areas of Somalia and Afar LLIN use was over 41% [FMoH, 2012b].

11.2 Insecticide resistance

Between 1958 and 1968 populations of *An. gambiae* s.l. were fully susceptible to DDT and Dieldrin [Rishikesh, 1968; Delfini & Shidrawi, 1976; NMES, 1972; Eshete, 1973]. Signs of

[28] Defined as experiencing a transmission period of >= 6 months in a year

reduced mortalities during one-hour exposure bioassays to DDT were observed during the early 1970s [Eshete, 1975]. From the late 1980s DDT (4% discriminating dose) showed 1-hour exposure mortalities of *An. gambiae* s.l (presumed *An. arabiensis*) of between 70% and 84% [Abose, 1998]. Between 2005 and 2011, there have been a number of bioassay efficacy tests undertaken across Ethiopia showing alarming rates of reduced sensitivity to most classes of insecticide [Abate & Hadis, 2011; Balkew et al., 2010; 2012; PMI, 2012; Yewhalaw et al., 2010; 2011; Massebo et al., 2013]. At 37 site-time locations, tests of the sensitivity of *An. arabiensis* to DDT showed that only two sites in 2007-08 had vectors sensitive to this organochlorine; at 21 sites Malathion was tested against *An. arabiensis* with 10 sites reporting sensitive vectors; at 52 site-time locations where pyrethroids (permethrin, deltamethrin, alpha cypermethrin, cyfluthrin and lambda cyhalothrin) were tested, only 15 site tests reported sensitive vectors; among the carbamate class Propoxur was regarded as fully sensitive at Gilgel-Gibe in 2009 [Yewhalaw et al., 2011] and in a further 12 localities [Balkew et al., 2012]. Bendiocarb resistance was confirmed at Guraghe, SNNP in 2011 [PMI, 2012] and confirmed elsewhere [Balkew et al., 2012]. Primiphos-methyl, tested at four sites also remains fully susceptible [Balkew et al., 2012]. The West African kdr allele was found in 280 specimens out of 284 with a frequency ranged from 95% to 100% at Gilgel-Gibe in south western Ethiopia [Yewhalaw et al., 2011].

Assays performed on *An. pharoensis* only at Gorgora in 2005, showed this species was sensitive to Malathion but resistant to DDT, permethrin and deltamethrin [Balkew et al., 2006]. There have been no recent studies of the sensitivity of insecticide classes on *An. funestus* and very few detailed studies of changing bionomics or behavioural adaptation in any species [Yohannes & Boelee, 2012]. At present there are no sentinel sites for monitoring vector bionomics, entomological inoculation rate and insecticide susceptibility.

12. Conclusions and future recommendations

12.1 Defining the spatial extents of P. falciparum risk

We have used combinations of empirical data to provide a stratification of *P. falciparum* malaria that could be used in planning the future control and elimination ambitions of the national malaria strategy 2014-2020.

Ethiopia remains a country with a very different malaria ecology compared to its southern regional neighbours. The country's populations are exposed to either traditionally low stable endemic risks represented by a predicted mean parasite prevalence of less than 1% (39%), live in areas of unstable, epidemic transmission in the highlands (17%) or in areas that do not support transmission of either *P. falciparum* or *P. vivax* because of low temperatures (27%) (Figure 5.6).

The largest geographic area and population-at-risk is related to the low stable, endemic regions. Here we have defined these areas as represented by a mean predicted *Pf*PR_{2-10} of less than 1% in 2000 and remained in this state in 2010 (Section 5.5; Figure 5.4), in accordance with new definitions of Low Stable Endemicity (LSE) [Cohen et al., 2010].

Conditions of stable, endemic *P. falciparum* transmission affect only 16% of the population, largely located in the northwest of the country, bordering Sudan (Figures 5.5 & 5.7). Along this belt of stable transmission, only 0.5% of Ethiopia's population experience transmission intensity above a predicted *Pf*PR_{2-10} of 10% and therefore the majority of stable transmission areas are classically hypoendemic.

It is important to reflect on this pattern of malaria for the effective targeting of specific intervention packages. Universal ITN coverage was promoted across Africa based on trial evidence from meso- to holoendemic settings of their impact on child survival, malaria morbidity and cost-effectiveness [Lengeler, 2004]. Very few trials were undertaken in areas of hypo-endemicity, where the fraction of all-cause childhood mortality due to malaria will be considerably less and where the cost-effectiveness of universal ITN coverage on more rare infection frequencies and malaria mortality will be much reduced. ITN distribution in Ethiopia has been targeted to areas regarded as "malarious" since 2005, however those most likely to benefit from universal ITN coverage remain few even within this strata. There are no recommendations for intermittent Presumptive Treatment (IPT) of malaria in pregnancy or childhood in Ethiopia, an entirely legitimate position given the infrequent nature of parasite exposure across the country. However, similar decisions need to be made for other vector-based control options. A dialogue needs to start on the definition of universal coverage of LLIN and IRS and, while difficult, a cost-effectiveness analysis of the risks of not mounting vector control to over 84% of the population (**Recommendation 1**).

The 16% of the population exposed to stable hypo-mesoendemic *P. falciparum* transmission are concentrated in a very defined area along the western borders. These communities would benefit from an immediate increased access to universal LLIN coverage or other integrated vector control options.

This stable risk area represents a significant spatial margin for infections into the rest of the country. Travel as a risk factor for malaria infection has been identified among patients at Adami Tulu Woreda, Oromia Region [Yukich et al., 2013]. Significant human population movement and re-settlement has been a dominant demographic feature of Ethiopia with inherent risks associated with changing malaria exposures [Kloos, 1990; Dessera et al., 2006]. More work should be done on human migration patterns from this area to other parts of Ethiopia as part of elimination planning as recently undertaken in neighbouring Kenya [Wesolowski et al., 2012] (**Recommendation 2**).

This stable transmission margin is a border region, where refugees and economic migrants cross frequently every day [FMoH, 2012a], posing threats to sustaining malaria transmission reductions and elimination ambitions. To sustain effective control in this area will require significant cross-border collaborations with neighbours, for which strong political ties might not currently exist such as the Republic of Sudan and Eritrea.

12.2 Decision making units for control and elimination planning

Planning of malaria control requires information at both federal and *woreda* levels. One major limitation for the present work has been the inability to uniquely identify all the *circa*

840 *woreda* presently used for decentralized health planning. All future work must be able to resolve risk profiles to an accepted *woreda* map (**Recommendation 3**).

Promoting national standards, policy and allocating federal resources requires a national map of priority *woreda*. We have attempted to classify *woreda* according to their dominant risk class (Section 5.6; *Woreda* Excel). It was not possible to uniquely classify 83/731 (11%) of the mapped *woreda* because the risk profiles within a *woreda* were so diverse that it was not possible to attribute 50% or more of the population to one dominant risk class (Figure 5.9). This highlights the important variance in risks over short distances based on either altitude (used to define highland fringe) and temperature (to define malaria free) and aridity suitability. These *woreda*, and those that can be defined by a simple criterion of dominant risk class, require higher spatial resolution planning data. This becomes increasingly important as one moves towards elimination planning [Cohen et al., 2010; Moonen et al., 2010; Bousema et al., 2012]. Malaria risks will become increasingly focalized under low stable transmission conditions and an intrinsic feature of unstable transmission [Bouesma et al., 2012; Alemu et al., 2013b].

12.3 Migrating from parasite prevalence to clinical incidence

Community-based parasite prevalence becomes an increasingly less useful metric of risk when the force of transmission/basic reproduction rate of infection is low [Hay et al., 2008]. We have used community-based *Pf*$PR_{2\text{-}10}$ here to provide the margins of stable endemic risk. These are important spatial criteria for national, federal planning but are unlikely to change with time (Annex A; Figures A2 & A3).

Measuring prevalence with precision becomes increasingly difficult as infection becomes less frequent. National prevalence surveys are expensive and there comes a point where measuring prevalence is not advisable. This was defined operationally during the GMEP: "*As soon, however, as the general volume of malaria has been reduced to any considerable extent, the indices furnished by malariometric surveys are no longer sensitive enough to measure further progress ... Analysis of evaluation data from eradication programmes as well as closer observations in the field have shown that the point at which malariometric surveys cease to be sufficiently sensitive is reached when parasite rates have dropped to a level of between 1% and 3%*" [Yekutiel, 1960] although others argued for greater flexibility [WHO, 1971].

We would therefore recommend that future national parasitological surveys be restricted to only those areas where stable transmission occurs (Figure 5.7) in an attempt to monitor the transitional states to less than 1% infection prevalence as a result of scaled vector control (Figure 5.8) and where standard deviations from current mean predictions are highest (Annex A.4) (**Recommendation 4**).

Across the rest of the country, there is an urgent need to move to being able to measure, model and map clinical incidence.

The measurement of malaria incidence requires every suspected malaria case to be diagnosed through a comprehensive surveillance system comprising passive case detection

(PCD, examination of those suspected, usually febrile cases presenting routinely to any point of the health service), supplemented by active case detection (ACD, examination of fever cases sought through domiciliary visits at regular intervals[29]) [Yekutiel, 1960; Pampana, 1969; Pull, 1972; Molineaux et al., 1988]. The results are usually expressed as an Annual Parasite Incidence (API) per 1000 of the entire population of the administrative areas for which it is representative. During the GMEP the API was only deemed valid if the annual blood examination rate (ABER), the proportion of the target population examined, exceeded 10% [Black, 1968; Pampana, 1969]. The other metric often presented is the slide positivity rate (SPR). These surveillance indices are related as follows: API = (ABER * SPR) / 10[30] [Ray & Beljaev, 1984].

Current WHO recommendations are that pre-elimination is defined by an epidemiological metric based on fractions of fevers that are positive for malaria (<5%) or case-incidence < 5 per 1000 population within a specified area [WHO, 2012b; 2012c]. API now forms the tentative basis for developing strata for control versus pre-elimination in Ethiopia [FMoH, 2014; Annex B]. The problems currently faced with defining strata API in are discussed broadly below and specifically for Ethiopia in Section 12.4.

The ability of a country to measure and know definitively its incidence rate is in itself an indication of the country's readiness to enter pre-elimination [malERA, 2011]. Case-detection data demand systems able to reliably diagnose and report clinical malaria, unfortunately properties notoriously weak [Cibulskis et al., 2007], fevers or other malaria-like syndromes are also often treated outside of the public health sector [Foster, 1995], not all fevers presenting to health facilities are parasitologically confirmed and not all records of cases are compiled for every month at every facility.

12.4 The national capacity for malaria case surveillance

Ethiopia initiated an Integrated Disease Surveillance (IDSR) system in the late 1990s. Data are entered from paper-based systems using EpiInfo in Addis Ababa and more recently, under the direction of the Public Health Emergency Management (PHEM) centre at the Ethiopian Public Health Institute (EPHI). In 2004, 87 original IDSR units existed nationwide reporting on "zonal" level statistics. These increased to 108 by 2008–2009 through the splitting of zones and the addition of referral hospitals and towns. This system is separate from the national health management information system (HMIS) [FMoH, 2012c].

The coverage of malaria reporting was analysed over the period 2004-2009 where it was shown that of all possible site-reporting months, 82% of reports were captured as part of the IDSR; however in 2009 it was only 56% [Jima et al., 2012]. The authors showed that

[29] The advantage of clinical data is that the likelihood of detecting infections among symptomatic individuals is significantly higher than would be observed in traditional community-based surveys of predominantly asymptomatic individuals [Okiro & Snow, 2010]. The dominant characteristics of risk in very low transmission areas of pronounced seasonal and between year fluctuations are better captured by continuous case detection data as opposed to community-based studies on point-estimate infection risk that represent only a single snapshot in time.

[30] The division by ten is necessary because API is expressed per 1000 and the other terms per 100.

overall *P. falciparum* case-incidence was less than 2.8 per 1000 population p.a., less than 1.8 per 1000 population p.a. for *P. vivax* and that for both infections incidence had not changed during the interval of observation[31] [Jima et al., 2012].

However, the IDSR focused largely on collating data from hospitals and health centres and did not include data from lower level facilities or health extension workers. Nor did the authors examine diagnostic accuracy. In a recent study, up to 19% of *P. falciparum* infections were detected by PCR but missed by routine microscopy or RDTs [Golassa et al., 2013] and the quality and capacity for parasitological diagnosis in 69 facilities in Oromia Region in 2009 was sub-optimal [Hailegiorgis et al., 2010].

During the national Malaria Indicator Survey (MIS) undertaken in 2011, over 40% of fevers treated within 24/48 hours with an anti-malarial, were treated outside the formal public health reporting system [FMoH, 2012b]. Self-medication of fevers at home is common [Deressa et al., 2003a; 2003b; Kebede et al., 2010]. These features of malaria treatment pose challenges to case-management but equally to the reliability of ACD completeness.

In the PMI annual report on Ethiopia in 2011, it states in response to official quotes on the malaria burden that "*The accuracy of these malaria estimates has been in doubt. In a country with a weak health information system, the few data that are available are often unreliable and likely to overstate malaria burden as only a small percentage of those with fever will have malaria*" [PMI, 2011].

Perhaps most significantly, there is no census of the total numbers of possible reporting facilities by Zone. Without the universe of possible clinical centres that provide malaria diagnosis and treatment, the reliability of IDSR or HMIS, to support ambitions to record API remain unclear. Reporting per Zone is a low-resolution indicator that does not provide enough information for *woreda* planning. Using only the total population by Zone does not adjust for the large variance in human settlement and health service access necessary to compute incidence.

Central to a fully operational IDSR or HMIS is a basic inventory of all functioning health facilities and the services that they provide. Such an inventory requires a spatial dimension, allowing facilities to be linked to the catchment populations that they serve by level of care and other proximate determinants of health such as environment, climate, as well as proxies of malaria risk, poverty etc. This spatial linkage can be provided by Geographic Information Systems (GIS). The use of GIS for health service planning is widespread in developed countries but there are few examples of their development in resource poor settings.

Recent work in Namibia has demonstrated the value of combining information of fever treatment behaviours, linked to population access to diagnostic and reporting centres and incomplete HMIS malaria data using MBG to define malaria incidence at high spatial resolutions [Alegana et al., 2012; 2013]. These modelled approaches to interpolating data in

[31] In-patient malaria deaths appeared, however, to decline from 2006 [Jima et al., 2012]

time and space require layers of GIS and HMIS linked data to provide higher resolution information for planning and monitoring pre-elimination.

The FMoH is committed to strengthening its IDSR and HMIS [FMoH, 2012c; Nsubuga et al., 2010][32]. The first step should be to invest significantly in the spatial layers of the health system - geo-coding all hospitals, health centres, health posts and out-reach fixed locations for health extension workers, using unique IDSR and HMIS reporting identifiers. These must be linked to the most up-to-date *woreda* shapefile in a GIS platform (**Recommendation 5**)[33].

With time it should be possible to map malaria cases in very sophisticated ways to guide *woreda* level planning, risk analysis and hot-spot identification. Examples have already been demonstrated in Ethiopia to provide valuable information at high spatial resolutions through applications of GIS using health facility data, residence, topography and remotely sensed data at 543 *kebeles* in East Shoa [Yeshiwondim et al., 2009] and for hot-spot risk analysis in Chano Mille *Kebele* in Southern Ethiopia [Loha et al., 2012]. Further, operational developments include the use of Short Message Service (SMS) in Oromia region to improve existing reporting systems to monitor malaria diagnostic, treatment and control activities[34].

12.5 Non-falciparum parasites: improving the epidemiology & clinical descriptions for elimination

The prevalence of *P. ovale* and *P. malariae* is extremely low. Conversely, *P. vivax* is common and often neglected as a public health threat [Baird, 2013]. Almost one third of combined *P. vivax* and *P. falciparum* infections recorded during cross-sectional, community-based surveys since 1980 were *P. vivax*. There is remarkably little clinical or epidemiological work on *P. vivax* in Ethiopia (Section 7). The true public health burden posed by this parasite and

[32] Significant investments are being made in improving malaria and broader HMIS reporting with support from PMI and as part of the US's expanded Global Health Initiative [PMI, 2013]

[33] There are three potential sources of health service listings that should be reconciled: a) a list of health services developed by the UNDP Emergencies Unit that contains the regional listings of 2056 facilities used for the Expanded Programme of Immunization by UNICEF and the WHO in 2002 [UoP, 2013]. None of the facilities are geo-coded and the list is a mixture of public and private facilities.; b) information from the IDEAS project of the London School of Hygiene and Tropical Medicine, that provides information on maternal and child health projects in Oromia, Amhara, SNNP and Tigray Regions and contains a listing of 2818 health centres [IDEAs, 2013]; and c) a recently completed facility-based survey of over 2600 health centres to support malaria information assembly undertaken in 2012/2013 in all regions except those in the south east. No geo-coordinates were collected during the survey. It should be possible over the next 12 months to begin to reconcile at least all the sentinel health centres into a single health facility master list and use alternative sources of information to geo-code this data base

[34] The project is a collaborative effort led by the Ethiopian Federal Ministry of Health, the Oromia Regional Health Bureau, Tulane University School of Public Health and Tropical Medicine, USAID/President's Malaria Initiative (USAID/PMI), the Addis Continental Institute of Public Health, and MEASURE Evaluation, which began in late 2009 and ended in October 2013. No details are currently available on how it improves coverage an reliability of malaria data.
http://www.cpc.unc.edu/measure/our-work/malaria/monitoring-malaria-trends-using-sms-and-site-visits-in-oromia-region-ethiopia

how best to manage acute and relapsing clinical vivax malaria infections requires more investigation (**Recommendation 6**).

For elimination strategies, *P. vivax* will always be the "*last parasite standing*" [Baird, 2010]. The biology of the parasite, with dormant liver stages, poses challenges for elimination ambitions. There is a need to improve the spatial and temporal epidemiology of *P. vivax*. As with *P. falciparum* spatial modelling, the force of transmission in Ethiopia for *P. vivax* is low and combined methods of model-based geo-statistics encompassing clinical data, community survey data and new models of parasite longevity and survival will be required to map this parasite more effectively (**Recommendation 7**).

The current focus of the Ethiopian pre-elimination ambition is on *P. falciparum*, however a greater degree of understanding of *P. vivax* is required now if elimination is to involve all parasites.

12.6 Vector surveillance

Section 10 provides a catalogue of our historical and contemporary understanding of dominant vector species distributions across Ethiopia. The most recent data come from an opportunistic assembly of published and student thesis data. There has not been a systematic nationwide vector mapping exercise since the 1960s. *An. arabiensis*, *An. funestus* and *An. pharoensis* share sympatric geographic niches across the country; *An. nili* has a more restricted range (Figure 10.1). There are few vector behavioural studies which are necessary to better understand vector species adaptations to insecticide use and land use changes. Building a systematic, longitudinal bionomics profile from sentinel sites, linked to biological resistance monitoring, is an important aspect to monitoring the threats to malaria elimination (**Recommendation 8**).

Resistance has established itself to previously, and widely used, organochlorines and there is emerging evidence of resistance to pyrethroids and organophosphates (Section 11.2). Few sensitivity studies have been conducted on *An. funestus* and *An. pharoensis* and this remains a significant knowledge gap. Given the dependence on insecticides for control phases of the national malaria strategy, longitudinal resistance surveillance should be established as a priority (**Recommendation 9**).

12.7 Special risk areas

As malaria control and elimination becomes more sophisticated there is a growing need to understand and plan control around special risk settings. These include the unique features of malaria transmission in urban settings, agro industry, challenges posed by refugee populations and careful environmental risk assessments of water management and hydro-electric power.

We have made some provisional maps of the most significant areas demanding special attention in Section 6. This is by no means comprehensive but used here to demonstrate the need for layers of information necessary to plan control and elimination beyond malaria risk. Improved special area mapping requires between sector cooperation and coordination.

Developing policy guidelines for special risk groups requires more national, and international, dialogue to move the agenda beyond simply Ministries of Health to other public and private sectors [RBM, 2011] and improve the evidence base for intervention. We would recommend that approaches to building layers of medical intelligence form part of increased GIS planning activities within the FMoH and as a formal collaboration between sectors including ministries of agriculture, planning and water (**Recommendation 10**).

12.8 Profiling climate vulnerability indices

Climate, and aberrations in climate, plays a significant role in the landscape of malaria in Ethiopia. Changes in rainfall and temperature can have a devastating effect on the transmission of malaria among increasingly immunologically naive swathes of Ethiopia's population.

Profiling the long-term climate vulnerabilities for each *woreda* within the full range of endemicity classifications will provide important planning data, signalling those areas most likely to succumb to changes in either temperature or rainfall. This should be linked to revised malaria epidemic warning systems and climate forecasting. Engaging climatologists who understand malaria epidemiology would be a useful addition to layers of planning data for control and elimination strategies (**Recommendation 11**).

12.9 Renewing the 60 year commitment malaria elimination

Ethiopia has been committed to a malaria elimination agenda since the 1950s. It has never waivered from this ambition since the early pilot projects during the late 1950s and the scaled attempts at elimination through to the late 1970s. At no point, however, has the country witnessed an interruption of transmission. Resurgences of malaria have been common, driven by failing health systems, failing efficacy of clinical treatments and climate anomalies.

In recent years, substantial financial resources have been devoted to controlling infection risks across "malarious" areas. These investments have not been targeted at maximal risk areas. Government support has been important in maintaining a focus on malaria control, including the launch of the 'Millennium[35] Malaria Control Campaign' by the then Minister for Health in 2005 and the inclusion of a malaria metric of development within the Growth and Transformation Policy 2010-2015 [MoFED, 2010][36].

The national malaria strategy covering the period 2010-2014 had a specific goal of achieving elimination within specific geographical areas with historically low malaria transmission and near zero transmission in the remaining areas by 2015 [FMoH, 2009]. As this report has demonstrated, "near zero transmission" is a dominant characteristic of the majority of the

[35] Ethiopian Gregorian millennium.

[36] To reduce the prevalence of malaria to below 0.7%; although it is notable that this has been achieved, or sustained, across much of the country already.

country and has probably been so for many years. The provisional, draft strategy for 2014-202 begins to lay the foundations for pre-elimination with a vision to achieve national elimination by 2020 [FMoH, 2014]. This ambitious target will require considerable resources to be able to locate cases, define foci and maintain a malaria reconnaissance and surveillance to be able to define whether ambitions are being met.

New tools and new surveillance methods need to be developed that complement ACD, these might include serological surveys [Drakeley et al., 2005], measurements of recent parasite exposure in infants [MacDonald, 1950; Pull & Grab, 1974; Brabin, 1990; Snow et al., 1996b][37], PCR and parasite genotyping [Okell et al., 2012b] and the screening of migrants [Yekutiel, 1960; Kaiser, 1966]. Defining zero transmission is not easy but a dialogue and investments are needed now to establish systems to define this difficult benchmark of elimination (**Recommendation 12**).

[37] During the Ethiopian eradication programme of the 1960s and 1970s infant infection rates were used to define whether local transmission had occurred in sprayed areas

Annexes

Annex A

A.1: Parasite prevalence data assembly

The following sections provide a detailed description of how empirical parasite prevalence data were assembled, geo-positioned and pre-processed. This description should serve as a meta-data for the final database of contemporary parasite prevalence data in Ethiopia; and therefore a reference source to the final curated database. The focus throughout is on *Plasmodium falciparum*, *P. vivax* distributions are tackled separately in Section 7.

A.1.1 Parasite prevalence data search strategy

Electronic data searches: Online electronic databases were used as one means for identifying peer-reviewed, published data on malaria infection prevalence. Due to its wide coverage of the biomedical literature, PubMed [http://www.ncbi.nlm.nih.gov/sites/entrez] was used as the basis for all the initial online searches of published sources. In addition, we used the Armed Forces Pest Management Board – Literature Retrieval System [http://www.afpmb.org/publications.htm]; The World Health Organization Library Database [http://www.who.int/library]; the Institute de Recherché pour le Development on-line digital library service [http://www.ird.fr]; and African Journals Online (AJOL) [http://www.ajol.info]. In all digital electronic database searches for published work the free text keywords "*malaria*" and "*Ethiopia*" were used. We avoided using specialised Medical Subject Headings (MeSH) terms in digital archive searches to ensure as wide as possible search inclusion. The last complete digital library search was undertaken in November 2013.

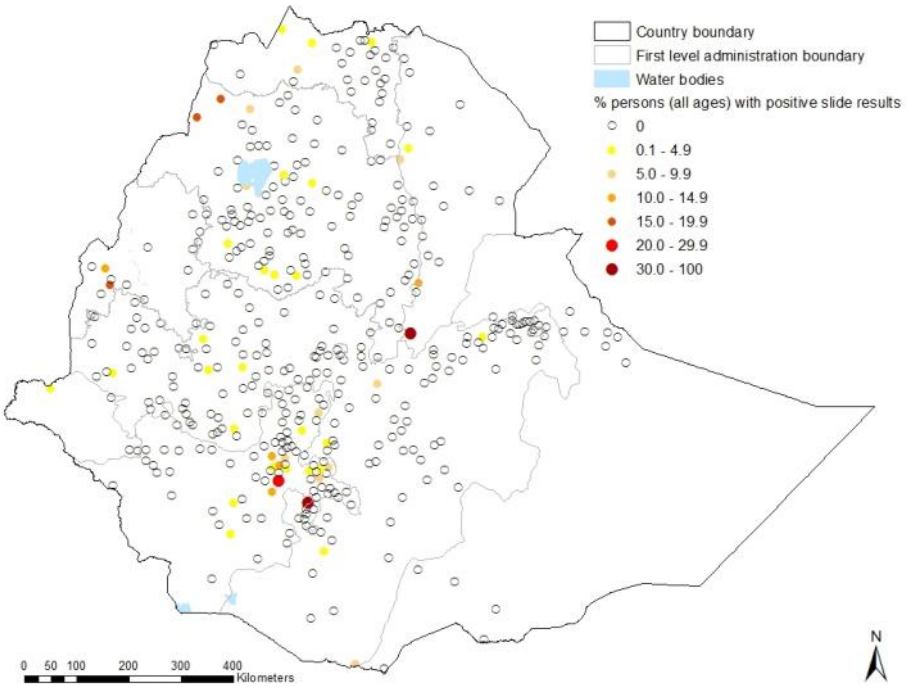
Titles and abstracts from digital searches were used to identify possible parasite cross-sectional survey data undertaken since January 1980 in a variety of forms: either as community surveys, school surveys, other parasite screening methods or intervention trials. We also investigated studies of the prevalence of conditions associated with malaria when presented as part of investigations of anaemia, haemoglobinopathies, blood transfusion or nutritional status to identify coincidental reporting of malaria prevalence. In addition, it was common practice during early antimalarial drug sensitivity protocols to screen community members or school attendees to recruit infected individuals into post-treatment follow-up surveys, often data from the survey sites present the numbers screened and positive. Surveys of febrile populations or those attending clinics were excluded.

Publications with titles or abstracts suggestive of possible parasite data were either downloaded from journal archives where these have been made Open Access (OA) or sourced from HINARI [http://www.who.int/hinari]. If publications were not available OA from HINARI we visited UK library archives at the London School of Hygiene and Tropical Medicine, the Liverpool School of Tropical Medicine and the Bodleian library at the University of Oxford. References not found following these searches were requested using world catalogue searches through the Oxford libraries at a per-page cost. All publications from which data were extracted were cross-referenced using the bibliographies for additional sources that may have been missed or that may correspond to unpublished or 'grey' literature (i.e. not controlled by commercial publishers). In addition, tropical medicine and malaria meeting abstract books were identified from as many sources as possible

produced as part of national and international conferences and congresses. These were used to signal possible data that were followed up through correspondence with abstract authors.

Unpublished archived survey reports: We undertook manual searches of archives at the World Health Organization (WHO) libraries in Geneva, Cairo and Brazzaville at separate archive locations as Project, Country and Parasitology Department files. As part of the RBM monitoring and evaluation initiative national, household surveys were resurrected as a means to monitor country-level progress [Corsi et al., 2012]. These surveys were initially embedded in the DHS as a malaria module and were largely focussed on intervention coverage measures until 2005 when it was agreed to include malaria infection prevalence into survey protocols or as standalone surveys when undertaken as Malaria Indicator Surveys (MIS). In Ethiopia national MIS surveys have been undertaken in October 2007 [FMoH, 2008] and 2011 [EHNRI, 2012]. For both surveys data has not been made open access however it has been possible to extract values and estimated sample sizes per total examined per region from images provided in the report using ARCGIS v.10 and coded keys within the report (see Figure A.1 for example of 2011 survey).

Figure A.1: Digitized national household survey data for 2011 [EHNRI, 2012]



In addition, regional survey data have been provided by partners who have worked with the MoH in Tigray in 2005/6 [WHO GMP, 2009], Amhara region 2006/7 [Emerson et al., 2008], Oromia and SNNP regions in 2007 [Shargie et al., 2008] and school surveys in Oromia in 2009 [Ashton et al., 2010]. We also contacted malaria scientists based in Ethiopia, many of whom generously provided unpublished, raw data from study sites, districts and regions for investigations of malaria they were involved with (all acknowledged at the beginning of this report).

A.1.2 Data abstraction

The minimum required data fields for each record were: description of the study area (name, administrative divisions), the start and end dates of the survey (month and year) and information about blood examination (number of individuals tested, number positive for *Plasmodium* infections by species), the methods used to detect infection (microscopy, Rapid Diagnostic Tests (RDTs), Polymerase Chain Reaction (PCR) or combinations) and the lowest and highest age in the surveyed population. Given its ubiquity as a means for malaria diagnosis, the preferred parasite detection method was microscopy. No differentiation was made between light and fluorescent microscopy.

Data derived from randomized controlled intervention trials were only selected when described for baseline/ pre-intervention and subsequent follow-up cross-sectional surveys among control populations. When cohorts of individuals were surveyed repeatedly in time we endeavoured to include only the first survey and subsequent surveys if these were separated by at least five months from the initial survey to avoid a dependence between observations based on treatment of preceding infected individuals. If it was not possible to disaggregate repeat surveys these were finally excluded from the analysis. Where age was not specified in the report for each survey but stated that the entire village or primary school children were examined we assumed age ranges to be 0-99 years or 5-14 years respectively. Occasionally, reports presented the total numbers of people examined across a number of villages and only the percentage positive per village; here we assumed the denominator per village to be equivalent to the total examined divided by the total number of villages. Where additional information to provide unique time, village specific data was necessary we contacted authors to provide any missing information.

A.1.3 Data geo-coding

Data geo-coding, defining a decimal longitude and latitude for each survey location, was a particularly demanding task. According to their spatial representation, data were classified as individual villages, communities or schools or a collection of communities within a definable area, corresponding to an area within 5 km grid or approximately 0.05 decimal degrees at the equator. Where possible we aimed to retain disaggregated village, "point" level data rather than data across a "wide-area". More recent use of Global Positioning Systems (GPS) during survey work does enable a re-aggregation of household survey data with greater precision and useful in maintaining 5 km grid criteria while combining clusters of small sample sizes in space. To position each survey location where GPS coordinates were not available in space we used a variety of digital resources, amongst which the most useful were Microsoft Encarta Encyclopedia (Microsoft, 2004) and Google Earth (Google, 2009). Other sources of digital place name archives routinely used included GEOnet Names Server of the National Geospatial-Intelligence Agency, USA [http://www.earth-info.nga.mil/gns/html/cntry_files.html]; Falling Rain Genomics' Global Gazetteer [http://www.fallingrain.com]; and Alexandria Digital Library prepared by University of California, USA [http://www.alexandria.ucsb.edu].

Although standard nomenclatures and unique naming strategies are attempted in digital gazetteers [Hill, 2000], these are difficult to achieve at national levels where spellings

change between authors, overtime and where the same names are replicated across different places in the country. As such, during the data extraction, each data point was recorded with as much geographic information from the source as possible and this was used during the geo-positioning, for example checking the geo-coding placed the survey location in the administrative units described in the report or corresponded to other details in the report on distance to rivers or towns when displayed on Google Earth. While in theory GPS coordinates should represent an unambiguous spatial location, these required careful re-checking to ensure that the survey location matched the GPS coordinates. As routine we therefore rechecked all GPS data from all sources using place names and/or Google Earth to ensure coordinates were located on communities.

All coordinates were subject to a final check using second level administrative boundary Global Administrative Units Layers (GAUL) spatial database developed and revised in 2008 by Food and Agriculture Organization (FAO) of the United Nations [FAO, 2008]. The Global lakes and Wetlands (GLWD) database developed by the World Wildlife Fund [Lehner & Doll, 2004] was used to ensure inland points were within defined land area. Here we aimed to identify survey coordinates that fell slightly on the lakes or in incorrect administrative units, every anomaly was re-checked and re-positioned using small shifts in combination with Google Earth.

A.1.4 Database fidelity checks, pre-processing and summaries

The entire database was first checked with a series of simple range-check constraint queries to identify potential errors that could have occurred during data entry. These queries assessed all data fields relevant to modelling for missing or inconsistent information. The final objective was to check for any duplicates introduced during the iterative data assembly process. Pairs of survey sites found within 1 km or within five months at the same location were identified. These may have been entered erroneously into the data assembly where multiple reviewed reports describing similar data. These were listed, checked and duplicates removed.

The search strategy identified 1380 survey estimates at 1285 unique locations where malaria infection prevalence had been recorded between May 1980 and March 2012. We were able to geo-locate every survey location, there were no survey locations exceeding 5 km^2 nor any repeat surveys in the same location within 6 months. Every survey sample had a sample size in excess of 15 people examined, important for survey estimate precision [Gregory & Blackburn, 1991; Jovani & Tella, 2006] and when testing plausible associations between say rainfall and prevalence during covariate selection

There was a large diversity among studies in the age ranges of sampled populations. To make any meaningful comparisons in time and space, a single standardized age range is required. Correction to a standard age for *P. falciparum* is possible based on the observation and theory of infectious diseases where partial immunity is acquired following repeated exposure from birth. We have retained the classical age range of 2-10 years as this best describes the exposure to infection among semi-immune hosts at any given location and conforms to classifications established in the 1950s [Metselaar & Van Thiel, 1959]. We have adapted catalytic conversion Muench models, first used in malaria by Pull & Grab (1974),

into static equations in R-script that uses the lower and upper range of the sample and the overall prevalence to transform into a predicted estimate in children aged 2-10 years, *Pf*PR_{2-10} [Smith et al*.,* 2007a].

Of the 1380 unique time-space *P. falciparum* survey locations identified through the data search strategy described above, 619 (45%) derived from the national sample surveys of 2007 and 2011, 606 (44%) were obtained from other reports or journals with the provision of unpublished raw data, 98 (7%) were abstracted directly from journal publications, 35 (2.5%) from master's and doctoral theses and two from conference abstracts. Survey data were located for time-space survey data points using GPS (497, 36%), on-screen digitization (619, 45%), Encarta (27, 2%), Google Earth (31, 2.2%), GeoNames (2), other digital place names sources, e.g. schools and village databases (304, 22%). Of the time-space survey data, infection was recorded using microscopy in almost all surveys (1374, 99.5%) and RDT (CareStart) was used in only six surveys. No survey data were collected using PCR or combinations of diagnostic methods.

A.2 Model development

A.2.1 Selection of covariates

In statistical modelling, a set of independent covariates of the main outcome measure is often used to improve the model fit and increase the precision of predicted estimates. The inclusion of these covariates increase model complexity and, if not carefully selected, risk over-fitting (using up too many degrees of freedom), which occurs when more terms or covariates than is necessary are used in the model fitting process [Babyak, 2004; Murtaugh, 2009]. Over-fitting can lead to poor quality predictions because coefficients fitted to these covariates add random variations to subsequent predictions and make replication of findings difficult [Babyak, 2004]. Where too many covariates are used, the model tends to produce highly fluctuating regression coefficients increasing the chances of large covariate coefficients and an overly optimistic fit, especially with small sample sizes of empirical. This problem can be particularly pronounced when data assembled are from observational studies based on different study designs, sampling considerations and sample sizes which are then combined to describe a random process [Craig et al., 2007].

The choice of covariates should be underpinned by the principle of parsimony (few strong and easily interpretable covariates) and plausibility (a clearly understood mechanism by which the covariate influences the outcome). In disease mapping there must a pre-determined aetiological explanation of the relationship of the disease and the covariate under consideration. The important determinants of uncontrolled malaria transmission are climate (rainfall and temperature) and ecological (potential breeding sites and urbanisation) [Molineaux, 1988; Snow & Gilles, 2002]. These factors affect the development and survival of the *P. falciparum* parasite and the malaria-transmitting *Anopheles* vector thereby reducing the risks of infection.

We tested five covariates against the empirical age-corrected parasite survey data: 1) *The annual mean temperature* surface developed from monthly average temperature raster surfaces at 1×1 km resolution which were downloaded from the WorldClim website

[http://www.worldclim.org][38]; 2) *Temperature Suitability Index* (TSI) as a continuous variable ranging from 0 to 1 and described in Section 4.3.1. [Gething et al., 2011b]; 3) Synoptic mean monthly precipitation raster surfaces at 1 × 1 km resolution, downloaded from the WorldClim website [http://www.worldclim.org/]; 4) Fourier processed mean annual enhanced vegetation index (EVI), derived from the MODerate-resolution Imaging Spectroradiometer (MODIS) sensor imagery and available at approximately 1×1 km spatial resolution [Scharlemann et al., 2008][39]; and 5) Urbanisation developed from information from the Global Rural Urban Mapping Project (GRUMP) [Balk et al*.,* 2006] and the Afripop project [www.AfriPop.org; Linard et al., 2012]. Urban areas were defined as locations with a density of more than 1000 persons per km^2 with the rest of the GRUMP urban extent defined as peri-urban and in the final test models both were combined.

To begin the covariate selection process the values of the assembled covariates were extracted to each *Pf*$PR_{2\text{-}10}$ survey location using ArcGIS 10 *Spatial Analyst* (ESRI Inc. NY, USA) tool. A correlation test was then undertaken to examine variable that were highly correlated (>0.85). Where two covariates had correlation >0.85, the aim was to select the one with the highest Bayesian Inference Criteria (BIC) for inclusion in the bootstrap and total set analysis using the results of a bivariate regression analysis. Using total-set analysis, the *bestglm* algorithm selected the covariates resulting best-fit model and displayed these together with their coefficients, 95% CI and P-values.

The relationship of *Pf*$PR_{2\text{-}10}$ with temperature, TSI, EVI, precipitation and urbanisation were all tested and analysis showed that only TSI contributed significantly to the variation in *Pf*$PR_{2\text{-}10}$ and comprised the best fit model (coefficient 0.059 (95% CI: 0.035, 0.083, P<0.001). Given the predominance of very low or zero infection estimates across Ethiopia the selection of only TSI (which is highly correlated with altitude) is both parsimonious and plausible.

A.2.2 $PfPR_{2\text{-}10}$ Model specification

A Bayesian hierarchical spatial-temporal model was implemented through SPDE approach using R-INLA library [R-INLA, 2013] to produce continuous maps of $PfPR_{2\text{-}10}$ at 1 × 1 km spatial resolution using data ranging from 1960-2011. The continuous indexed GF with covariance function was represented as a discretely indexed random process, that is, as a Gaussian Markov Random Field (GMRF) [Rue & Held, 2005; Lindgren et al., 2011; Cameletti et al., 2012]. This is where an explicit link between Gaussian Field (GF) and GMRF formulated as a basis function is provided through (SPDE) approach [Lindgren et al., 2011; Bolin & Lindgren, 2011; Simpson et al., 2012a; 2012b]. The solution for SPDE can be expressed as

[38] These surfaces were produced from global weather station temperature records gathered from a variety of sources for the period 1950-2000 and interpolated using a thin-plate smoothing spline algorithm, with altitude as a covariate, to produce a continuous global surface [Hijmans et al., 2005]

[39] EVI is an index of intensity of photosynthetic activity and ranges from 0 (no vegetation) to 1 (complete vegetation) (Figure A2d). EVI, compared to the more commonly used Normalised Difference Vegetation Index (NDVI), is developed from satellite imagery of higher spatial and spectral resolution and corrects for some distortions in the reflected light caused by the particles in the air as well as the ground cover below the vegetation [NASA].

$$(k^2-\Delta)^{\alpha/2}(\tau x(u)=W(u),\quad u\in\mathbb{R}^d,\quad \alpha=v+d/2,\quad \sigma^2-\Gamma(\mathrm{v})(\Gamma(\alpha)(4\pi)^{d/2}k^{2v}\tau^2)^{-1}$$
$$k>0,\ v>0, \qquad \text{(Equation A.1.1)}$$

This SPDE is a Gaussian random field with Matérn covariance function where W, is the spatial Gaussian white noise, Δ is the Laplacian, α controls the smoothness of the realization and τ controls the variance. The link between Matérn smoothness v and variance σ^2 is $\alpha=v+d/2$ and $\sigma^2-\Gamma(\mathrm{v})(\Gamma(\alpha)(4\pi)^{d/2}k^{2v}\tau^2)^{-1}$, where d is the spatial dimension [Lindgren & Rue, 2013]. An approximation of this SPDE can be solved using a finite element method (FEM), which is a numerical technique for solving partial differential equations [Lindgren et al., 2011]. In this case, the spatio-temporal covariance function and dense covariance matrix of the GF are replaced by a neighbourhood structure and a sparse precision matrix respectively and together define a GMRF. A GMRF can be described as a spatial process that models spatial dependence of data observed at a spatial unit like grid or geographical region and it can be expressed as $u=(u_1\ldots\ldots,u_n)'$ with $u\sim(\mu,Q^{-1})$. This is an n-dimensional GMRF with mean μ and a symmetrical positive definite precision matrix Q computed as the inverse of the covariance matrix [Cameletti et al., 2012]. Thus the density of u is given by

$$\pi(\mathrm{u})=(2\pi)^{-n/2}\left|Q\right|^{1/2}\exp(-\frac{1}{2}(\mathrm{u}-\mu)'\,\mathrm{Q}(\mathrm{u}-\mu)) \qquad \text{(Equation A.1.2)}$$

The sparse precision matrix Q offers computational advantage when making inference with GMRF. This is because the linear algebra operations can be performed using numerical methods for the sparse matrices which results in a considerable computational gain and this is further enhanced by using INLA algorithm for Bayesian inference [Rue & Held, 2005; Rue et al., 2009; Cameletti et al., 2012]. The infinite-dimensional Gaussian Random Field (GRF) is replaced with a finite-dimensional basis function representation

$$x(u)=\sum_{i=1}^{n}\psi_i(u)w_i \quad , \qquad \text{(Equation A.1.3)}$$

where w_i represents the weights and Ψ_i are piece-wise linear basis functions defined on a triangulation of the domain with n nodes which are defined as mesh in the code [Lindgren et al., 2011]. The basic functions are deterministic and are defined by each node in the triangulation while the stochastic property of the process is determined by the weights. The model used in this paper assumed non-stationary GRFs because environmental phenomena which are known to influence *PfPR*$_{2\text{-}10}$ are non-stationary in nature and therefore the distribution of *PfPR*$_{2\text{-}10}$ is non-stationary [Daly et al., 1994]. This non-stationary model was made possible by the flexible nature of SPDE models which allows modification of the SPDE rather than the covariance function to obtain the GRFs with other dependence structures other than the stationary Matérn covariance. The stationary isotropic Matérn covariance function, between locations u and v in $\mathbb{R}^d$ is expressed as

$$C(u,v) = \frac{\sigma^2}{2^{v-1}\Gamma(v)}(k\|v-u\|)^v K_v(k\|v-u\|) \ , \qquad \text{(Equation A.1.4)}$$

Where K_V is the modified Bessel function of the second kind, $\|\cdot\|$ denotes the Euclidean distance and order $v > 0$. $k > 0$ is a scaling parameter and σ^2 is the marginal variance. For the stationary model, k and v are constant in space. The parameter k is linked to the range p by the empirically derived relationship $p = \sqrt{8}/k$. k, here can be described as the range parameter presiding over the spatial dependence structure of the GRF [Lindgren et al 2011]. For the non-stationary, τ and k space-dependent covariance parameters are introduced as functions of the spatial location u, $u \in D$, where D is the spatial domain. Therefore the modified SPDE becomes

$$(k(u)^2 - D)(t(u)x(u)) = W(u) \ , \ u \in \square^2 \ , \qquad \text{(Equation A.1.5)}$$

where x is a non-stationary GRF because τ and k vary by location and as the consequence the variance and correlation range vary by location. The non-stationary described above is defined on the mesh because it controls the local distance metric in the manifold. $\log\tau(u)$ and $\log k(u)$ can be defined as the sum of the basis function, where the basis functions $\left\{B_i^{(\cdot)}(\cdot)\right\}$ are smooth over the domain of interest.

$$\log(k^2(u)) = \sum b_i^{(k^2)} B_i^{(k^2)}(u) \ \text{ and } \ \log(\tau(u)) = \sum \beta_i^{(\tau)} B_i^{(\tau)}(u), \qquad \text{(Equation A.1.6)}$$

Using this SPDE approach, the overall hierarchical space-time binomial and zero-inflated binomial models of the prevalence to malaria parasite were used denoted by

$$y(s,t) = z(s,t)\beta + \xi(s,t) + \varepsilon(s,t), \qquad \text{(Equation A.1.7)}$$

This model is characterised by a GF ***y(s, t)*** built from covariate information ***z(s, t)***, measurement error ***ε(s, t)***, and a second order autoregressive dynamic model for the latent process ***ξ(s, t)*** with spatially correlated innovations ***ω(s, t)***. The *Pf*PR$_{2\text{-}10}$ survey data were modelled as realizations of this spatial process (random field) changing in time. These realizations were used to make inference about the process and predict it at desired locations and at a specified time. This is where $y(s_i,t)$ was the realization of a spatial-temporal process representing the *Pf*PR$_{2\text{-}10}$ at the community location s_i, where $i = 1 \ldots n$, and year t_j where $j = 1 \ldots m$, $z(s_i,t_j) = (z_1(s_i,t_j) \ldots z_p(s_t,t_j))$ represents fixed effect from the covariates for cluster s_i at time t_j, $\beta = (\beta_1 \ldots, \beta_p)'$ is the coefficient vector, $\varepsilon(s_i,t) \square N(0,\sigma_\varepsilon^2)$ is the measurement error defined by the Gaussian white noise process, and $y(s_i,t_j)$ is the predicted posterior mean prevalence of the plasmodium parasite in cluster i at time j. In the model formulation the large scale component that depends on the covariates is defined as $Z(s_i,t_j)\beta$ while the measurement error variance or the nugget effect is σ_e^2. The realization of state process or the unobserved level of *Pf*PR$_{2\text{-}10}$ in this case

is defined by $\xi(s_i, t_j)$ as a spatial-temporal GRF that changes in time as a second-order autoregressive function.

The prior for the SPDE model by default are Gaussian. In the latest version of SPDE function, the default priors are chosen heuristically to match the spatial scale of the MeSH domain. The user can override the defaults by supplying a "hyper" parameter [Lindgren, 2013]. This is normally suitable when the dataset lacks enough information for the likelihood to fully identify the parameters for the prior distribution. In this paper the SPDE default priors were sufficient for the model.

A.2.3 Constructing a suitable MESH

A finite element representation is used to outline the GRF as a linear combination of basic functions defined on a triangulation of the domain, say D. This is achieved by subdividing D into non-intersecting triangles meeting in at most common edge or corner, thus a *mesh*. The GRF in the triangulation is given by Equation (SI 3.3), where n is the total number of vertices, $\{\psi,(s)\}$ are the basis functions and $\{\omega_l\}$ are normally distributed weights [Lindgren et al., 2011; Cameletti et al., 2012].

The mesh function (*inla.mesh.create.helper*) in INLA is used to create a Constrained Refined Delaunay Triangulation (CRDT). The overall effect of the triangulation construction is that, if desired, one can have smaller triangles, and hence higher accuracy of the field representation. However, this will have an effect on the computation of the model. There is therefore a need to balance the number of triangles and the computation time required. If the data points (cluster coordinates) are used to construct the mesh, a cut-off value (specified in the function represents the maximum distance in which data points are represented by a single vertex. If the boundary of the area domain is used to construct the mesh, (i.e. using the function points.domain=border), then the mesh is constructed to cover the border of the domain using restrictions provided in other arguments. But if both data points and area domain (boundary) are used the restrictions are combined. In this model, the mesh was constructed using the boundary of the area domain. This method produces a mesh with regular size of triangles. A cut-off value was specified to avoid building many small triangles around *Pf*$PR_{2\text{-}10}$ input locations. A reasonable offset value was used to specify the size of the inner and outer extensions around the data locations. The maximum edge value was used to specify the maximum allowed triangle edge lengths in the inner domain and in the outer extension. The inner maximum edge value was made small enough to allow the triangulation to support representing functions with small enough features, and typically smaller than the spatial correlation range of the model. Therefore this value was adjusted to fit the range of the area domain in the model.

A matrix was then constructed to link the *PfPR*$_{2\text{-}10}$ input locations to the triangles on the mesh defined by ŋ* as $\eta* = A(x + 1\beta_0)$ and in the inla code in the following *inla.spde.make. A* function. This makes each row in the matrix to have three non-zero elements since every data point is inside a triangle and the corresponding columns are expected to have non-zero elements. In order to obtain a square matrix for the model, the response was linked to the index of the random field, where the length of the index vector was the same as the length of the projection matrix. In order to estimate the intercept, the

stack function introduces a vector of ones in the matrix and this is removed in the formula by putting [-1] [Lindgren, 2013].

A.2.4 Model predictions

Final continuous 1 x 1 km model predictions of *Pf*PR_{2-10} are shown in Figures A.2 and reclassified according to endemicity classes in Figures A.3 for the prediction years 2000 and 2010. The gridded population surfaces for 2000 and 2010 were used to compute population at risk by endemicity class for both years. Within the stable limits of transmission, population adjusted *Pf*PR_{2-10} (PA*Pf*PR_{2-10}) by *Woreda* for 2000 and 2010 was also computed. This was done by first multiplying the *Pf*PR_{2-10} at each 1 × 1 km with the corresponding population at the same spatial resolution to compute the number of people who are likely to be positive for *P. falciparum* by pixel by year. This surface was then used to extract the aggregate number of people positive for *P. falciparum* and the total population in 2000 and 2010 per Woreda to compute the mean PA*Pf*PR_{2-10} for each year.

A.2.5 Prediction accuracy

A series of model uncertainty and validation statistics were generated to assess model performance. For each prediction year, the standard deviations of *Pf*PR_{2-10} were first computed for each 1 × 1 km grid location. The probability of belonging to an endemicity class was also computed from the posterior marginal distributions at similar spatial resolutions. Conventional model accuracy was estimated by computing the linear correlation, the mean prediction error (MPE) and mean absolute prediction error (MAPE) of the observations and predictions of a 10% hold-out dataset. The hold-out set was selected using a spatially and temporally declustered algorithm [Isaacs & Svritsava, 1989] which defined Thiessen polygons around each survey location. Each data point had a probability of selection proportional to the area of its Thiessen polygon so that data located in densely surveyed regions had a lower probability of selection than those in sparsely surveyed regions setting a high threshold for model performance. Sampling and testing hold out sets was done for each regional and time-segmented tile. The Bayesian SPDE using INLA was then implemented in full using the remaining 90% of data and predictions were made to the 10% hold-out within each regional tile. The MPE, MAPE and the correlation coefficient of the observed and predicted *Pf*PR_{2-10} for the full space time *Pf*PR_{2-10} model for Ethiopia were 0.01%, 0.01% and 0.94 respectively indicating very good model accuracy.

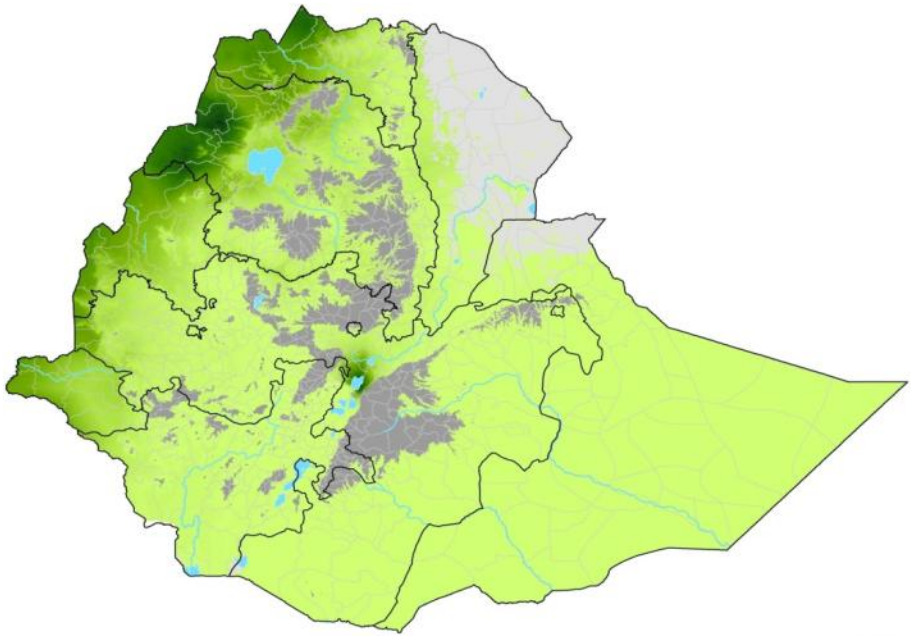
The standard deviation is a measure of the variability or dispersion of an expected value of a variable from its mean. High/low standard deviations indicate that data points are far/close to the mean. In scientific measurements it can be used as a measure of uncertainty. Of particular importance is the distance of the standard deviation (SD) from the mean. This is because the absolute value of the standard deviation could be both because of uncertainty but also a function of generally high base (mean) values of the measure under consideration. In this study, the distance (number) of the standard deviations of the mean *Pf*PR_{2-10} were computed for the years 2000 and 2010. For both 2000 and 2010 the highest uncertainty is along the Western borders, likely to be a combination of sparse input data highly variable survey estimates of infection risk (Figure A.4). For 2000, model predictions were uncertain around the Ziway dam given some survey data reporting high prevalence

against a wide surrounding set of data that were largely negative (Figure A.4). Mean predictions of $PfPR_{2\text{-}10}$ were accurate for large parts of the country outside these areas (Figure A.4).

Figure A.2: Posterior mean *Pf*PR$_{2-10}$ predictions across the entire country at 1x1 km resolution for a) 2000 and b) 2010: Dark grey areas are those represented by a malaria free mask based on TSI (Section 5.2) and the light grey areas are those represented by unstable, virtually no malaria based on aridity (Section 5.4)

a) 2000

.



b) 2010

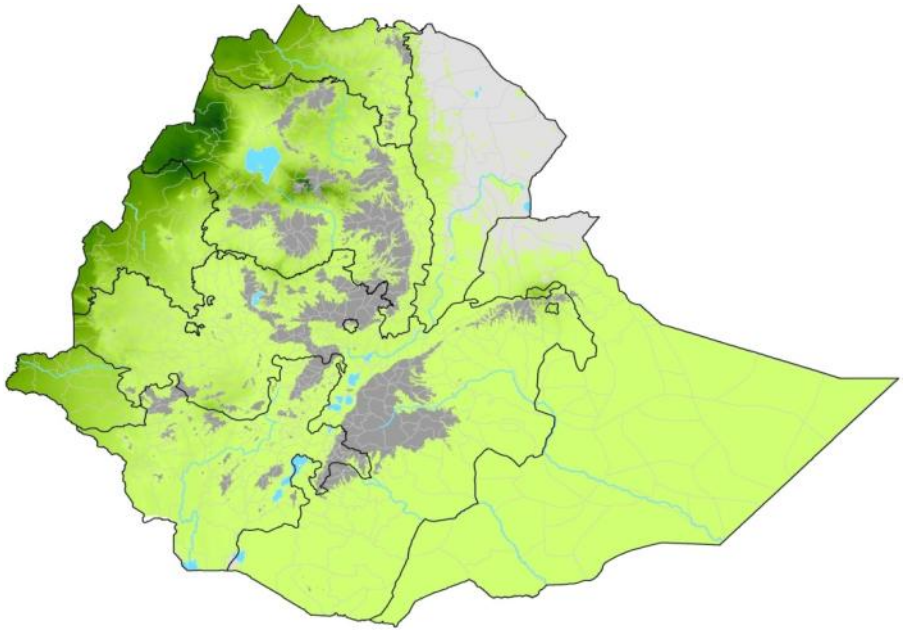
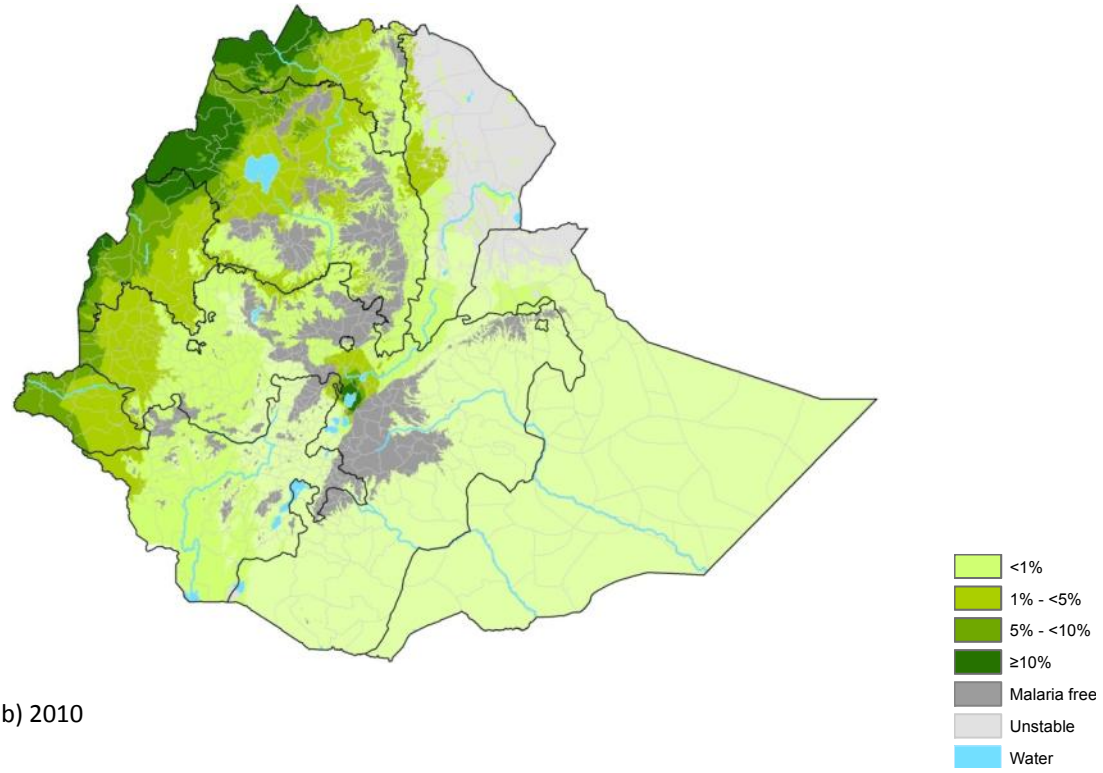


Figure A.3: Categories of hypo- and mesoendemic risks binned from the posterior mean *Pf*PR_{2-10} predictions across the entire country at 1x1 km resolution for a) 2000 and b) 2010: Dark grey areas are those represented by a malaria free mask based on TSI (Section 5.2) and the light grey areas are those represented by unstable, virtually no malaria based on aridity (Section 5.4)

a) 2000



b) 2010

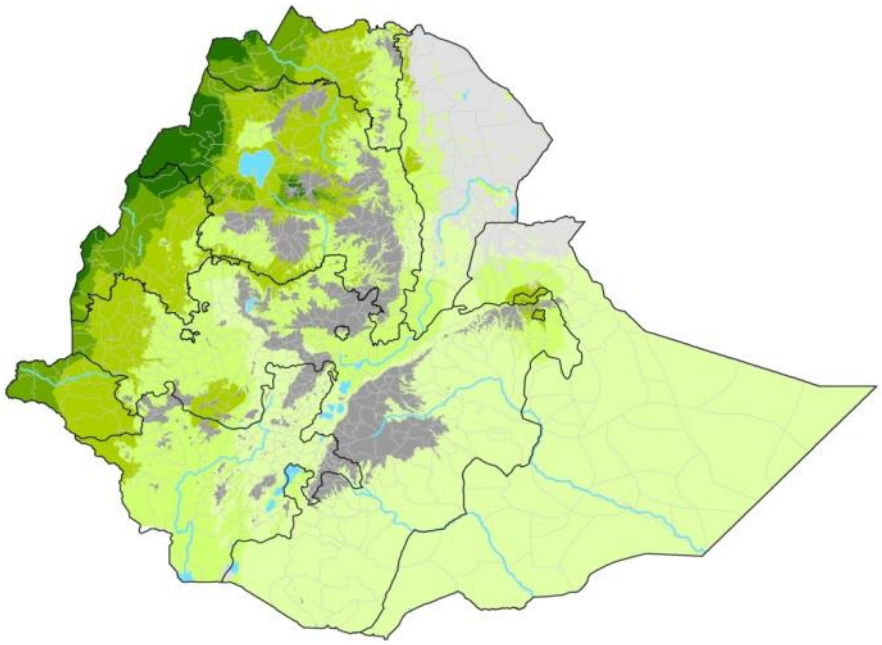
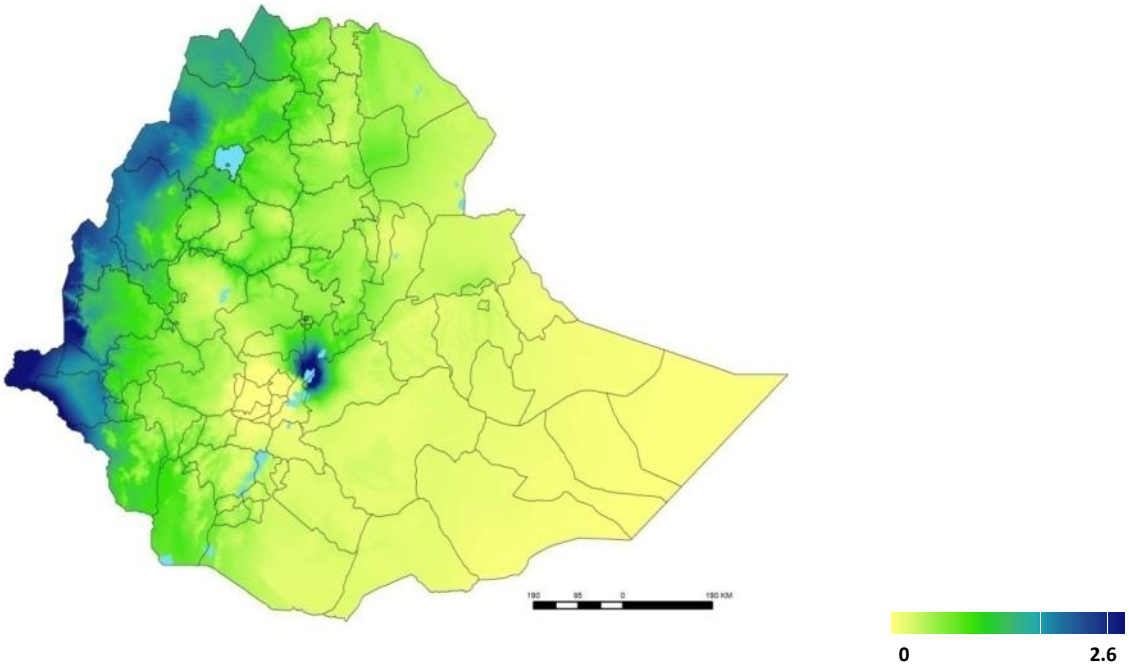
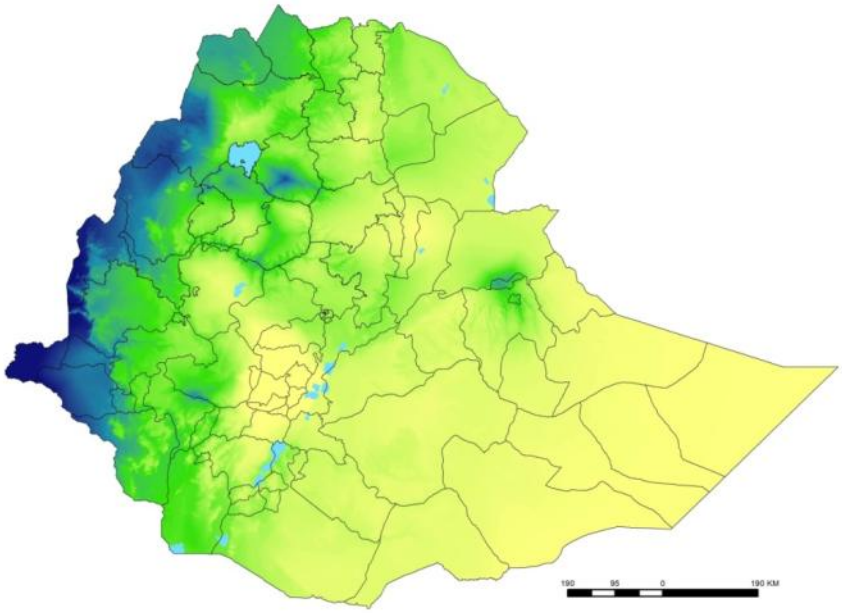


Figure A.4: Standard deviations of posterior distributions of predicted mean *Pf*PR_{2-10} a) 2000 and b) 2010

a) 2000



b) 2010



Annex B:

Provisional stratification or control and elimination based on API 2014 to 2020 [FMoH, 2014]

Strata		Targets 2014-2010	API	mASL	% pop	Pop (millions)	*Woredas*
1	High transmission	Control	>100	<2000	14.3	12.3	190
2	Moderate transmission	Control	25 - 100		26.7	22.96	366
3	Low transmission	Control	10 - 25		8.7	7.48	127
4	Highland fringe areas with unpredictable pattern of malaria transmission: (Elimination targeted areas)	Elimination	<10	2000-2200	15.5	13.33	75
5	Malaria Free areas:		0	>2200	34.8	29.93	85

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