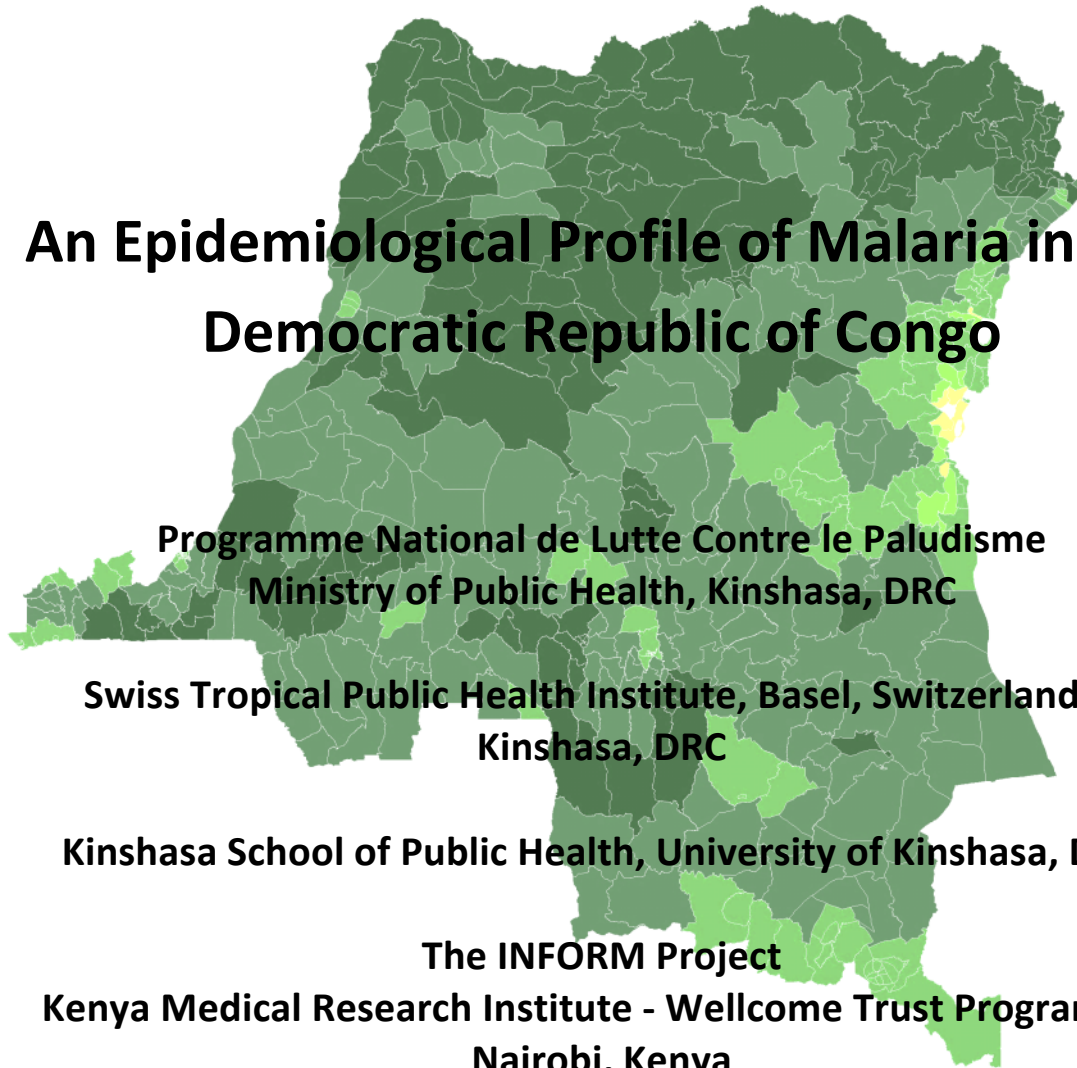**Programme National de Lutte Contre le Paludisme**
Ministère de la Santé Publique
République Démocratique du Congo

An Epidemiological Profile of Malaria in the Democratic Republic of Congo

Programme National de Lutte Contre le Paludisme
Ministry of Public Health, Kinshasa, DRC

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Cover image:

 Map of the population adjusted *P. falciparum* parasite ratio among children aged 2-10 years (PA*Pf*PR$_{2-10}$) in 2007 according to Zones de Santé in the Democratic Republic of Congo.

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Abbreviations

ACT	Artemisinin Combination Therapy
ADB	African Development Bank
ADFL	Alliance of Democratic Forces for the Liberation of Congo
AFPMB	Armed Forces Pest Management Board
AJOL	African Journals Online
AL	Artemether-Lumefantrine
AS	Aires de Santé
AS-AQ	Artesunate-Amodiaquine
BIC	Bayesian Inference Criteria
CBS	Chromosome Banding Sequences
CDC	Centers for Disease Control
CRDT	Constrained Refined Delaunay Triangulation
CSR	Centre Sanitaire de Référence
CQ	Chloroquine
DCW	Digital Chart of the World's Populated Places
DDT	Dichloro Diphenyltrichloroethane
DFID	Department for International Development (UK)
DHS	Demographic and Health Surveys
DRC	Democratic Republic of Congo
DVS	Dominant Vector Species
ESIA	Environmental and Social Impact Assessment
ETM+	Enhanced Thematic Mapper
ETF	Early Treatment Failure
EU	European Union
EUSRP	Emergency Urban and Social Rehabilitation Project
EVI	Enhanced Vegetation Index
DRC	Democratic Republic of the Congo
FAO	Food and Agriculture Organization
FEM	Fine Element Method
FIND	Foundation for Innovative New Diagnostics
FOREAMI	*Fonds Reine Elisabeth pour l'Assistance Médicale aux Indigènes*
GAUL	Global Administrative Unit Layers
GIS	Geographic Information Systems
GDP	Gross Domestic Product
GF	Gaussian Field
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GLWD	Global Lakes and Wetlands Database
GMRF	Gaussian Markov Random Field
GPS	Global Positioning Systems

GRF	Gaussian Random Field
GRUMP	Global Rural Urban Mapping Project
HAT	Human African Trypanosomiasis
HDI	Human Development Indicators
HGR	Hôpital Générale de Référence
HSRSP/PARSS	Health Sector Rehabilitation Support Project/ Project d'Appui à la Réhabilitation du Secteur de Santé
IDP	Internally Displaced Persons
IGC	Institute Geographique du Congo
INFORM	Information for Malaria Project
INLA	Integrated Nested Laplace Approximations
INRB	Institut National de Recherche Biomédicale
IPT	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
KOICA	Korean International Cooperation Agency
KSPH	Kinshasa School of Public Health
LLINs	Long Lasting Insecticidal Nets
MAPE	Mean Absolute Prediction Error
MARA/ARMA	Mapping Malaria Risk in Africa
mASL	Metres Above Sea Level
MBG	Model Based Geo-Statistics
MECNT	Ministère de l'Environnement, Conservation de la Nature et Tourisme
MeSH	Medical Subject Headings
MIBA	Société Minière de Bakwanga
MICS	Malaria Indicator Cluster Survey
MODIS	MODerate-resolution Imaging Spectroradiometer
MONUC	Mission de l'Organisation de Nations Unies en République Démocratique du Congo
MPE	Mean Prediction Error
MPR	Malaria Programme Review
MPSMRM	Mise en œuvré de la Révolution de la Modernité
MSP	Ministère de la Santé Publique
SNAME	Système d'Approvisionnement en Médicaments Essentiels
Swiss TPH	Swiss Tropical Public Health Institute
NMSP	National Malaria Strategic Plan
OA	Open Access
PAPfPR$_{2\text{-}10}$	Population adjusted PfPR$_{2\text{-}10}$
PCA	Pacquet Complémentaire d'Activités
PCR	Polymerase Chain Reaction
PfPR$_{2\text{-}10}$	Age-corrected *Plasmodium falciparum* parasite rate
PMI	Presidents Malaria Initiative

PMURR	Projet Multisectoriel d'Urgence de Réhabilitation et Reconstruction
PNLP	Programme National de Lutte contre le Paludisme
PNLTHA	Programme National de Lutte contre la Trypanosomiase Humaine Africain
PSI	Population Services International
RAP	Resettlement Action Plan
RBM	Roll Back Malaria
RDTs	Rapid Diagnostic Tests
RGC	Referentiel Geographique Commune
SANRU	Santé en Milieu Rural
SD	Standard Deviations
SECLA	Service d'Etude et de Coordination de Lutte Antiplaudique
SP	Sulphadoxine-Pyrimethamine
SPDE	Stochastic Partial Differential Equations
SRTM	Shuttle Radar Topography Mission
SSF	Single Stream of Funding
Swiss TPH	Swiss Tropical and Public Health Institute
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
UNOCHA	United Nations Office for the Coordination of Humanitarian Affairs
USAID	United States Agency for International Development
WHO	World Health Organization
WRBU	Walter Reed Biosystematics Unit
WRI	World Resources Institute

Executive summary

This epidemiological profile of malaria in The Democratic Republic of Congo aims to assist national level partners in malaria control by providing an overview of the historical, current and future context of malaria in the country based on data generated from local investigations.

Malaria control in DRC faces several unique challenges that include a very fragmented health care delivery system and an expanding and highly mobile IDP and refugee population. The majority of financial support to the health sector is derived from multiple development partners and health care delivery is segmented according to the partners across regions and decentralized zones. The result is that national strategies for malaria control have been difficult to implement uniformly, according to epidemiological characteristics, rather than regional development partner priorities. This has resulted in gaps in service delivery (currently 50 Zones de Santé have neither funding nor operational support for malaria control) and significant challenges in monitoring and evaluation of malaria control interventions.

Here we provide a national cartography of risk that is based on malaria prevalence rather than donor locations. Previous maps of malaria risk in the DRC have been imperfect representations of very sparse data or based entirely on climate and none have resolved information to decision making units necessary for health planning, Zones de Santé. We have assembled and spatially located over 1000 survey estimates of *P. falciparum* prevalence from studies undertaken since 1914. We have used modern techniques of model-based geo-statistics to interpolate these data to provide population-adjusted risks in 2007 for each of the 512 Zones de Santé.

In 2007, an estimated 64.3% (62 million) of the population lived in areas with an average *P. falciparum* prevalence above 50% (hyper-endemic to holoendemic transmission), making the DRC one of the most intense transmission areas of Africa. 29% of the 2007 population lived under conditions of mesoendemicity (parasite rates 10-50%) and only 0.2% of the country's population live in areas that would be classified as hypoendemic.

A comparison with a modeled risk map of 1939 shows that overall there has been a long-term reduction in malaria transmission in the DRC, but equally some areas remain in 2007 at levels of endemicity described over 60 years ago. *Plasmodium falciparum* continues to be the dominant malaria parasite, however low levels of *P. vivax*, *P. ovale* and *P. malariae* have been described across the country.

There have been significant efforts to expand the distribution of insecticide-treated nets (ITN) since 2007 and small, localized efforts to use indoor residual house-spraying at mining concessions. These activities may have changed the landscape of malaria transmission. The recent completion of the 2013-2014 national household sample survey provides an opportunity to re-model malaria risks across the country. If data are provided this will be done to provide a malaria risk map for 2014.

The DRC has a diverse vector species ecology, and we have identified over 600 site-specific descriptions of vectors recorded since 1906. There is, however, very few descriptions of vectors, their habitats and broader bionomics since the 1960s. More information exists on current levels of insecticide resistance which now appears widespread to most commonly used insecticides.

This profile highlights several key issues that require future work: a) the contemporary descriptions of malaria transmission and vector ecology requires a considerable investment in new data to provide a

more relevant understanding of the potential and threats to future vector control; b) malaria control in the DRC is a complex problem requiring multiple layers of information to target and tailor resources and partnerships, including refugees, mining concerns and approaches to reaching inaccessible communities in forested areas; c) planning targeted resources requires a clear definition of where people live; the last census in the DRC was over 30 years ago and this restricts any accurate predictions of populations at risk or needs assessments. It is not clear when the next national census will happen; d) data on the numbers of ITN delivered and the use of ITN by communities in 2013-2014 is available and can be modeled to provide a map of "ITN needs" against biological risk. This can be done when the 2013-14 DHS data are made available; and e) one of the greatest needs for malaria sector planning, and more broadly, is an accurate map of clinical service providers.

This epidemiological profile should be 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 parasite prevalence, vectors, drug and insecticide resistance, health facility mapping, intervention distribution, intervention coverage, new census data, location mapping of special target groups (refugees, miners etc.) should all from the basis of future national data assemblies.

With this report we provide geo-coded databases of parasite prevalence, vector species occurrence, district-level estimates of malaria risk and development partner locations. The report serves as the metadata for these databases but require constant updating for a more informed future of evidence-based planning.

1. Introduction

The use of survey data, maps and epidemiological intelligence was a routine feature of control planning across most African countries during the Global Malaria Eradication Programme (GMEP) era from the mid-1950s. Data included epidemiological descriptions of transmission, vectors, topography and climate. There was a recognition over 50 years ago that one important source of planning data was infection prevalence among children aged 2-10 years (PfPR$_{2-10}$), used to define categories of endemic risk designed to guide and monitor progress toward malaria elimination targets [Metselaar & van Thiel, 1959; Macdonald & Göeckel, 1964; Lysenko & Semashko, 1968].

The art and skills necessary to design malaria control based on an understanding of the spatial epidemiology was lost during the 1970s 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., 1996] and over the last decade there has been a growth in spatial data on malaria 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].

At the launch of the Roll Back Malaria (RBM) initiative, calls 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. These future business cases must be grounded in the best possible epidemiological evidence to predict the likely impact of future intervention, assess the impact of current investment and, equally important, demonstrate what might happen should funding and intervention coverage decline.

In 2011, the WHO Office for the Africa Region (AFRO) developed a manual to assist countries in developing their National Malaria Strategic (NMS) plans including, as a prelude, the undertaking of a National Malaria Programme Performance Review (MPR) [WHO-AFRO, 2012]. It is recommended that the MPR should include a detailed review of the malaria epidemiology and stratification including the geographical distribution of malaria burden, parasite prevalence and parasite species.

The MPR, undertaken in the DRC in 2011, states that *"It is necessary to take urgent measures to better define the epidemiology of malaria and distribution of diseases in the country. This would allow a better choice of strategies for a real impact by 2015...... to regularly update the stratification of health zones based on the malaria prevalence and entomological mapping to a better understanding of the distribution of Plasmodium species and vector*s" [PNLP, 2012a]

This epidemiological profile attempts to assemble the epidemiological evidence base for a more targeted approach to malaria control in the DRC. It draws together historical and more current evidence of parasite transmission risk, data on the distribution of dominant vector species also since historical times and available data on antimalarial drug and insecticide resistance. Risk is described in the context of DRCs federalized health system and it is hoped that the report will form the beginnings of the evidence platform for planning of targeted sub-national control towards the achievement of the targets of the country's national malaria strategic plan 2013-2015.

2. Country context

2.1 Location and geographical features

The Democratic Republic of Congo (DRC), formerly the Congo Free State (1885–1908), Belgian Congo (1908-1960), Republic of the Congo (or Congo-Léopoldville) (1960-1964) and Democratic Republic of Congo (1964-1971) and Republic of Zaire (1971-1997), is Africa's second largest country covering an area of approximately 2.345 million km^2 [PNDS, 2010; Putnam, 2012]. It is located in the heart of Africa, with one third of the landmass lying to the north and two thirds to the south of the equator between latitudes 6°N-14°S and longitudes 12°-32°E. The country shares borders with nine countries: Angola, Burundi, Central African Republic, Peoples Republic of the Congo, Rwanda, South Sudan, Tanzania, Uganda and Zambia (Figure 2.1) and has a narrow 37 km Atlantic Ocean coastline. Angola's Cabinda province sits to the north and Zaire Province to the south of DRC's coastline. The port town of Boma lying 100 km upstream on the Congo River is accessible to sea-going vessels and was established originally as a port for the slave trade. Boma was the capital city from 1886 before the establishment of Léopoldville (now Kinshasa) in 1926.

The River Congo is the country's main drainage system providing 15,000 km of navigable inland waterways. The river extends to a length of about 4700 km forming a giant anticlockwise arc flowing north-west and emptying into the Atlantic Ocean. It originates from the highlands and mountains of the East Africa Rift Valley and Lakes Tanganyika and Mweru and is fed by several lakes and tributaries along its course including Lake Mai-Ndombe, Lake Tumba and Rivers Lomami, Aruwimi, Ubangi, and Kwa [Shahin, 2002; Munzimi, 2008] (Figure 2.1).

The river's exceptional network provides a hydroelectric power potential estimated at about 106,000 MW (about 13% of global potential for electricity); 40% of this power is concentrated at the Inga Falls, the largest waterfall, by volume, in the world (Figure 2.1). The Congo River Basin in the central region occupies 60% (3.46 million km^2) of the nation's area and is a vast rolling plain with an average elevation of about 520 metres above sea level (mASL). The lowest point (338 mASL) is at Lake Mai-Ndombe, and the highest (700 mASL) is in the northern Mobayi-Mbongo and Zongo Hills in these plains (Figure 2.1). The country's highland mountainous region lies along the eastern border and is formed by the western arm of the East African Rift Valley system and includes Lakes Albert, Edward, Kivu, Tanganyika, and Mweru

(Figure 2.1). High plateaus almost surround the central basin including the Ubangi-Uele plateau (915-1,220 mASL) in the north and the plateaus of Katanga Province in the south (Figure 2.1).

Figure 2.1: Map of major relief features (browns rising to 4533 mASL) ,[1] rivers and lakes,[2] and major cities.

2.2 Climate

There are a very limited number of meteorological stations for the quantitative description of the climatological characteristics of rainfall and temperature within the greater Congo basin area. Available long-term, interpolated data on rainfall and temperature are therefore associated with a high uncertainty, based on as few as seven reliable meteorological ground stations [Bultot, 1971; Kazadi & Kaoru, 1996; Washington et al., 2013]. In general, the DRC has a tropical climate with two distinct seasons; the June to August "dry season" (18 to 27°C) called the "Congolese Winter" and the September to May "rainy season" (22 to 33°C) with its heavy, monsoon rains. The length of the dry season (contiguous months with < 50 mm precipitation) increases from 0-6 months further south. Areas within 5° of latitude north or south of the equator experience a bimodal peak in rainfall with the lower rainfall peak in March-April and the main peak in October-November. The average rainfall for the entire country is about 1,070 mm but varies north and south of the equator (Figure 2.2a), the drier regions in the south affecting remotely sensed indices of vegetation (Figure 2.2b). Temperatures are hot and humid in the central region, cooler and drier in the southern highlands, and cooler and wetter in the eastern highlands. The monthly duration of low ambient temperatures affects the likelihood of malaria transmission in mountainous areas (Figure 2.2c). Climate and topography have been used to delineate malaria risk strata in the 1960s (Section 4.1).

Figure 2.2: Climate features of DRC a) Long-term annual precipitation; b) Enhanced Vegetation Index (EVI); and c) Temperature Suitability Index (TSI) for sporogony in dominant vectors

2.a.) Precipitation	Rainfall is a major determinant of vector abundance. Monthly rainfall surfaces are produced from global weather station records gathered from a variety of sources for the period 1950-2000 and interpolated using a thin-plate smoothing spline algorithm to produce a continuous global surface [Hijmans et al., 2005] and monthly average rainfall raster surfaces at 1×1 km resolution available from the WorldClim website (http://www.worldclim.org/download.html). Data shown here are mean annual rainfall in mm
650 1880	

Figure 2.2 continued

2.b.) EVI	For vegetation, Fourier–processed EVI, derived from the MODerate-resolution Imaging Spectroradiometer (MODIS) sensor imagery and available at approx. 1×1 km spatial resolution [Scharlemann et al., 2008] was used to develop an annual mean EVI surface. EVI is an index of intensity of photosynthetic activity and ranges from 0 (no vegetation) to 1 (complete vegetation)
2.c.) TSI	As a metric for the effect of temperature on malaria transmission, a temperature suitability index (TSI) has been developed at a spatial resolution of 1×1 km [Gething et al., 2011a]. The TSI model uses a biological framework based on 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 and constructed using monthly temperature time series [Hijmans et al., 2005]. On a scale of increasing transmission suitability, TSI ranges from 0 (unsuitable) to 1 (most suitable). Unsuitable areas represented by a TSI value of 0 are classified as malaria free (Section 4.3)

2.3 Forests

Forests govern the distribution of populations, accessibility to health services and in the case of DRC the ecological niches of important secondary malaria vectors. DRC is Africa's most forested country with over 122 million hectares representing 6% of the world's forests. The main areas of commercial forestry are the Mayombé Forest of western Bas-Congo (240,000 hectares), north of the Congo River in Équateur Province (21 million hectares) and tropical rain hardwood forests in northern Bandundu Region (101 million hectares) [Ernst et al., 2010; Lubamba, 2013;

Library of Congress, 2012]. Deforestation rates in DRC (0.25% per annum) are significantly lower than other tropical forests in Southeast Asia and the Amazon [WRI & MECNT, 2010, 2010][3].

Recent efforts to remotely map the extent of forest cover in the DRC have used Landsat ETM+ (Enhanced Thematic Mapper) and MODIS (MODerate Resolution Imaging Spectroradiometer) satellite imagery to classify forested and woodland areas using boosted regression tree analysis [Hansen et al., 2008; ftp://congo.iluci.org/FACET/DRC/]. Forest was defined as 30% or greater canopy cover for trees of 5 metres or more in height and standard tree model algorithms identify three major classes (woodlands, primary and secondary humid tropical forests; Figure 2.3)[4]. The Ministry of Environment, Nature Conservation and Tourism (MECNT) and the World Resources Institute (WRI) has developed web-based tools to represent the country's forests, the Interactive Forest Atlas - combines information from 30m resolution remote sensed imagery and other geo-databases [WRI & MECNT, 2010] and correspond to the Landsat-MODIS algorithms shown in Figure 2.3.

Figure 2.3: Forest cover in the DRC modeled from remotely sensed data and forests algorithms: dark green - primary humid tropical forest; light green secondary humid tropical forest; mid-brown woodlands; light yellow - non-forested areas [Hansen et al., 2008; ftp://congo.iluci.org/FACET/DRC/]

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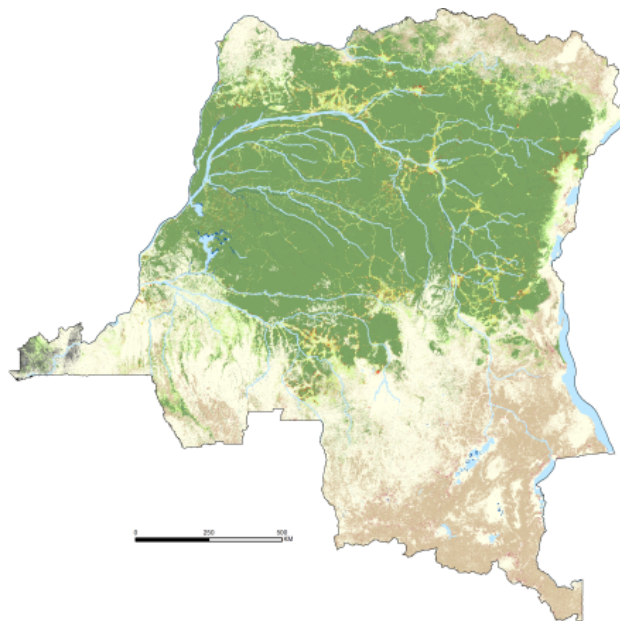
[3] The heaviest logging in the country takes place in Bas-Congo. Logging restrictions in Mayombé Forest have been in place following severe deforestation during the 1960's. Unfavorable farming practices i.e. slash and burn techniques have had negative impacts on forests in Equateur, however Bandundu's forests remain relatively unaffected. In 1990, 11 multinationals ran 90% of DRC's logging operations [Library of Congress, 2012].

[4] Primary forest cover is defined as mature forest with greater than 60% canopy cover. Secondary forest is defined as re-growing immature forest with greater than 60% canopy cover. Woodland is defined as forest cover with greater than 30% and less or equal to 60% canopy cover. Edaphic (Soil acidity defined bio-diverse areas and regularly flooded forests and dense moist forests defined by WRI & MECNT (2010) can be compared at http://www.wri.org/publication/interactive-forest-atlas-democratic-republic-congo-atlas-forestier-interactif-de-la#en

2.4 Economy, the mining sector and poverty

The DRC is potentially one of the richest mining countries in Africa and economic growth is primarily dependent on the performance of the mining and agriculture sectors, together accounting for 50% of the GDP in 2013 [African Economic Outlook, 2014]. Several World Bank and IMF initiatives are assisting the government in developing strategies for economic recovery following the civil strife of the last two decades and some recovery has taken place since power sharing agreements set in 2003 [World Bank, 2013; SADC, 2012]. By 2009, the national GDP of the DRC was 10.82 billion, with an annual growth rate of 2.7% [WRI & MECNT, 2010].

Policies allowing increased mining concessions to multinational companies have contributed to increased economic growth. In 2011, 7,732 mineral mining permits were issued for 112.7 million hectares (48% of the country) covering almost all of Bas-Congo and much of Kasai (Occidental and Oriental) and Kivu (Nord & Sud), Maniema and Orientale Provinces [Javelle & Veit, 2012]. The extent of the potential mining concession areas is shown in Figure 2.4.

Figure 2.4: Mining Areas showing areas where official licenses operated (dark grey) and where mining potential exists, artisanal miner's work or research licenses granted (light grey). Reproduced from [WRI & MECNT 2010]
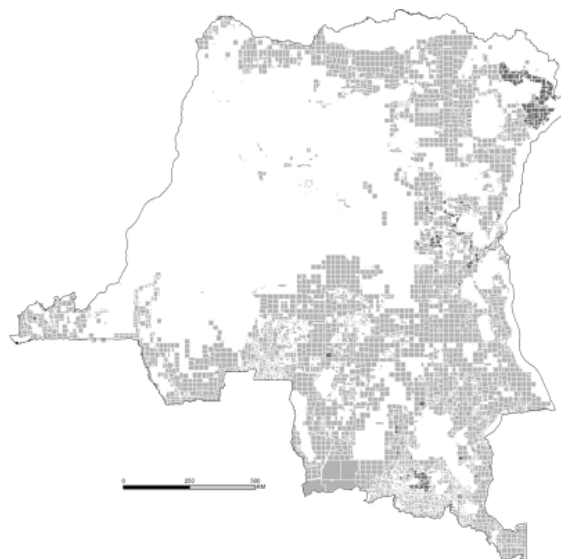
Diamonds are mined in Kasai-Occidental and Kasai-Oriental regions, mostly around the cities of Mbuji-Mayi, Tshikapa, and Lodja [Library of Congress, 1993]. Bakwanga Mining Company (Société Minière de Bakwanga - MIBA) is the largest state-owned mining concession in Kasai-Oriental Region and produces most of DRC's total diamond exports (MIBA exported an estimated 9.6 million carats in 1991 [Library of Congress, 1993]. The expansive MIBA concession is part of DeBeers South Africa mining company and covers a 62,000 km^2 area. Minerals found in Katanga include copper, cobalt, zinc, cassiterite, manganese, coal, silver, cadmium, germanium, gold, palladium, uranium, and platinum. Most of Katanga's copper and cobalt goes to China; 166,000 tons of cobalt in 2012, representing 90% of China's total imports of cobalt (177,000 tons) [Amnesty International, 2013]. The Lake Kivu area is also mineral rich region

containing cassiterite, columbotantalite, wolframite (a source of tungsten), beryl, gold, and monazite as well as reserves of methane, carbonic, and nitrogen natural gases. The Shaba Region, stretching from Kolwezi to Lubumbashi, has the greatest concentration of minerals in the copper-cobalt zone. Most of DRC's coal and manganese deposits also come from Shaba. Limestone deposits are found throughout the country.

Despite the challenging world economic and domestic political situations, DRC's economy grew by 7.2% in 2012 largely due to extractive industries, agriculture, trade and construction as well as improved macroeconomic policies[5]. Growth was predicted to continue to 8.2% in 2013 and 9.4% in 2014, due to increasing global demand for minerals and the major investment in the sector in recent years [African Economic Outlook, 2014].

Today, DRC's mineral wealth is estimated to be US$ 24 trillion, roughly 50% more than the GDP in the United States in 2011 [Javelle & Veit, 2012]. However, decades of war and unrest have meant that most artisanal mining has dominated the sector and most of the country's mineral wealth remains untapped. Despite the country's potential mineral wealth, the DRC has only 300 km of paved roads and almost 71% of the population lived on less US$ 1.25 a day in 2006 [CIA, 2013]. DRC ranks among the lowest Human Development Indicators (HDI)[6] in Africa (186th out of 187) and capita gross national income was only US$ 220 in 2012 [World Bank, 2013]. Reliable, geographically disaggregated data on poverty are scarce and most analyses focused on main urban centres [PNDS, 2010].

2.5 Population distribution

Given the political instability characterised by armed conflicts, the 1984 census is the country's most recent complete population enumeration. The 1984 census recorded 30.7 million inhabitants indicating a near doubling of the population since independence which was estimated at 16.2 million in 1960 [INS, 1984]. It is difficult to estimate the current size and spatial distribution of DRC's population. Current population estimates are based on 1984 figures projected by a fixed growth rate without consideration of changes in fertility, mortality (conflict-related and otherwise) or displacement. For 2012, population estimates are between 68 and 70 million people, even within this range the country is the 3rd most populated nation in Africa [UNICEF/DFID, 2013; Ministère de la Santé Publique, 2008; PNDS, 2010].

For disease mapping purposes, high spatial resolution population distribution maps are required. Recently, spatial modelling techniques for the reallocation of populations within

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[5] The IMF backed macroeconomic policy in 2012 aimed to cut inflation, stabilize the exchange rate and increase foreign currency revenues. Efforts were made to increase tax revenue and limit spending

[6] The HDI is a single statistic that allows comparison of social and economic development across and within countries and combines indicators of life expectancy, educational attainment and income by calculating the geometric mean of these indices. The HDI sets a minimum and a maximum for each dimension based on data for the year of reference and then shows where each country stands in relation to these ranges, expressed as a value between 0 and 1.[http://hdr.undp.org/en/statistics/hdi]

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][7]. The resulting population density map is shown in Figure 2.5, however this map remains imprecise given the course spatial resolution of population data assembled over 30 years ago.

In 1984, the percentage of the population living in urban areas was 28% mainly within 14 cities [INS, 1984]. As a result of economic instability and insecurity many Congolese have been forced to leave rural homes and settle in the major cities. Currently, an estimated 34.3% of the population live in urban centres, the largest being Kinshasa with an estimated annual urbanization rate of 4.19% between 2010 and 2015 [MONUC, 2004]. The most densely populated urban areas include Kinshasa (7.27 million)[8], Lubumbashi (1.28 million), Mbuji-Mayi (1.22 million), Kananga (0.72 million), Kisangani (0.68 million), Bakavu (0.47 million), Kolwezi (0.46 million), Likasi (0.37 million), Tshikapa (0.37 million), Kikwit (0.29 million) and Mbandaka (0.26 million) [MONUC, 2004] (all shown in Figure 2.1).

Figure 2.5: Modelled population density projected to 2010 using methods described in Footnote 7 and represented as increasing density as shown in legend ranging from zero to circa 19,850 per km^2

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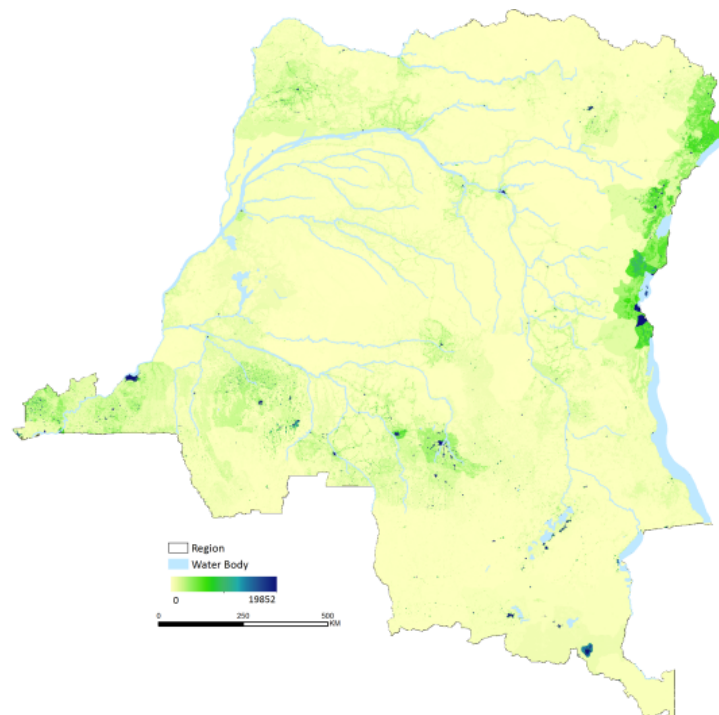
[7] A dasymetric modelling technique [Mennis, 2009] was used to redistribute population counts within 188 enumeration regions used during the 1984 census and adjusted for total populations presented across 11 census regions assisted by land cover data sets and satellite imagery. A different population weight was assigned to each land cover class in order to shift populations away from unlikely populated areas, such as protected areas, forest cover 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 rural and urban growth rates provided by the UN [UN, 2011]

[8] Population estimates of major cities in 2004, derived from UN Mission estimates [MONUC, 2004]

2.6 Conflict and refugee populations

Opponents to Mobutu's government began demanding reform in 1990, with heightened tensions in 1996 as the Rwandan Civil War and genocide entered Zaire. Hutu militias, including the *Interahamwe*, attacked Rwanda using refugee camps in the Kivu region of DRC as a base. Rwandan and Ugandan armed forces invaded DRC to fight the militias and ultimately overthrow Mobutu, in what was termed the First Congo War. The *Mouvement Populaire de la Révolution* splintered into factions and Mobutu fled to Togo and then Morocco majority of displaced populations majority of displaced populations majority of displaced populations in May 1997, and Laurent-Désiré Kabila named himself president. Kabila formed an alliance with the Rwandan and Ugandan forces under the Alliance of Democratic Forces for the Liberation of Congo (AFDL).

A rift between President Kabila and his former Rwandan AFDL allies resulted in a new rebellion in 1997 in which Angola, Namibia and Zimbabwe sided with Kabila against Rwandan rebels supported by Ugandan rebels. The Second Congo War raged for 5-years (1998–2003), during which, Kabila was assassinated in January 2001 and succeeded by his son, Joseph Kabila[9]. Joseph Kabila committed himself to ending the civil war that has resulted in the death of an estimated 3.9 million people between 1998 and 2004 [Coghlan et al., 2006]. Most of Laurent-Désiré Kabila's Southern African allies eventually withdrew but rebel groups remain active in the four Eastern provinces of South Kivu, North Kivu, Ituri and Maniema with an intensification of fighting in 2004[10]. Conciliation efforts are ongoing and 11 African countries have pledged to assist in ending the conflict at a meeting held in Ethiopia in February 2013.

UNHCR estimates for 2014 suggest that due to the ongoing instability in the eastern part of the country, about 450,000 refugees from the DRC remain in neighboring countries, particularly Burundi, Rwanda, Tanzania and Uganda [http://www.unhcr.org]. Over 2.6 million people remain internally displaced as a result of continued conflicts [http://www.unhcr.org]. The *Commission Nationale pour les Réfugiés,* Ministry of Interior, now oversees the refugee crisis and coordinates NGO partners who provide refugee assistance[11].

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[9] A power-sharing agreement on 17th July 2003 created a transitional constitution providing for an interim government of representatives from various rebel groups, the previous government, the political opposition and civil organizations. A new, formal constitution was promulgated in February 2006, significantly devolved power to provincial administrations. The most recent presidential and parliamentary elections were held on November 28th 2011 and Joseph Kabila was elected for his second term as President of DRC.

[10] Rebel groups in Eastern DRC include the March 23 Movement (M23), Ugandan led Islamists (ADF-NALU), Mia Mai groups (APCLS and Sheka), Hutu Rwanda rebels (FDLR), the FRPI in the gold rich Ituri area, the anti FDLR group (Rai Mutombooki) and other armed self-defense militias [Oxfam, 2012]

[11] MSF, Actions et Intervention pour le Développement et l'Encadrement social, African Initiative for Relief and Development, Agir pour le genre, Association pour le Développement social et la Sauvegarde de l'Environnement, Equipe d'Encadrement des Réfugiés urbains de Kinshasa, Femmes en mission pour soutien et action aux vulnérables confondus, German Agro-Action, Groupe d'appui conseils aux réalisations pour le développement endogène, *International Emergency and Development Agency Relief, INTERSOS,* Médecins d'Afrique, Mouvement international des droits de l'enfant, Première urgence - Aide médicale, Search for Common Ground, Women for Women International

Maps of the movements of refugees, IDPs political asylum seekers and Congolese returnees are published by the UNHCR [http://www.unhcr.org/pages/49c3646c4ca.html] and information on refugee settlements, camps, transit centres and locations since 2000. Refugee/IDP sites from various sources have been linked to the country's 512 health zones (Figure 2.6) [UNHCR 2001b; 2005; 2006; 2008b; 2014]. The location of the majority of displaced populations is along DRC's borders and these are highly mobile populations frequently crossing into Rwanda and Uganda in the east and the Republic of Congo in the west. More permanent settlements are located in the south western Bas Congo region (mostly assisted Angolans within Cabinda and Kimpese) [UNHCR, 2001c]; Katanga [UNHCR, 2000; UNOCHA, 2014]; in North Kivu around Goma [UNHCR, 2008a-c] and Aru [UNHCR, 2001a].

Figure 2.6 Health zones (Green) where IDPs and refugees are located across the 11 provinces

2.7 Decentralized planning

DRC is a highly decentralized unitary state which is organized into three administrative tiers that, until recently, included ten provinces and one City Administration (Kinshasa). Currently, each of the 11 administrative provinces is presided over by a governor. The provinces are further divided into 48 administrative districts and 188 administrative territories (the lowest administrative unit) [PNDS, 2010].

In 2006, there was a constitutional provision (Article 226) to further subdivide the provinces into 26; while the current 48 administrative districts were to be subdivided into 150 units by 2009. This would enable more autonomy and decentralization of resources at grassroots level where populations are often dispersed over large areas, and difficult to access. However, this

change is yet to be effected despite multiple meetings on decentralization and substantial pressure from lobby groups [Weiss & Nzongola-Ntalaja, 2013].

Defining the health administrative units used by a country is central to resolving health information for planning and disease burden estimation. Without congruence to accepted health decision making units at national levels the cartographic information of risk has diminished value. DRC's health system is organized according to a separate system of administrative boundaries. Policy decisions are made at central level by the office of the Minister of Health and the General Secretariat of Health. The next tier comprises 26 health directorates, whose boundaries are the same as the proposed 26 administrative provinces, and provincial level directorates perform the functions of technical support and monitoring. These are however no used for decentralized planning at present and the health sector continues to use the 11 provinces.

The peripheral 515 *Zones de Santé*, lie under 65 *Districts Sanitaires* [health districts][12] and do not correspond to the 48 government administrative districts. The *Zone de Santé* is the operational unit for planning and implementation of the national health policy. They operate as autonomous decentralized entities with their own management. Generally, a health zone covers an average population of 100,000 to 150,000 people in rural areas and 200,000 to 250,000 people in urban areas. The Zones de Santé are further subdivided into 8504 *Aires de Santé* (AS) or health areas. Each health area serves between 5000 and 10000 people and consists of several health centers and or a general hospital [Ministère de la Santé, 2008, 2010]. We have reconstructed a map of Zone de Santé used throughout this report that represents 512 contiguous units used for peripheral health planning (Figure 2.7).

Overseas support and technical assistance for development and health remains anchored in a federal approach to segmenting partnerships across regions and decentralized zones. This includes the provision of assistance for malaria control since 2008. The country has been divided up to support the allocation of donor assistance from the Global Fund (since 2009), President's Malaria Initiative/ USAID (since 2009), Projet d'Appui à la Réhabilitation du Secteur de la Santé (PARSS), World Bank (since 2005), the World Bank Booster programme (since 2008) the UK's Department for International Development (DFID, since 2010) and Korean International Cooperation Agency (KOICA, since 2009). During the period 2013-2014 the development assistance partner's map was as shown in Figure 2.8.

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[12] The 65 health district boundaries appear not to be used in any decentralized planning process and therefore are not used here to define malaria risks

Figure 2.7: Eleven administrative provinces and 512 health zones used in malaria risk mapping (Section 4.3; all codes are provided in accompanying Excel file)[13]
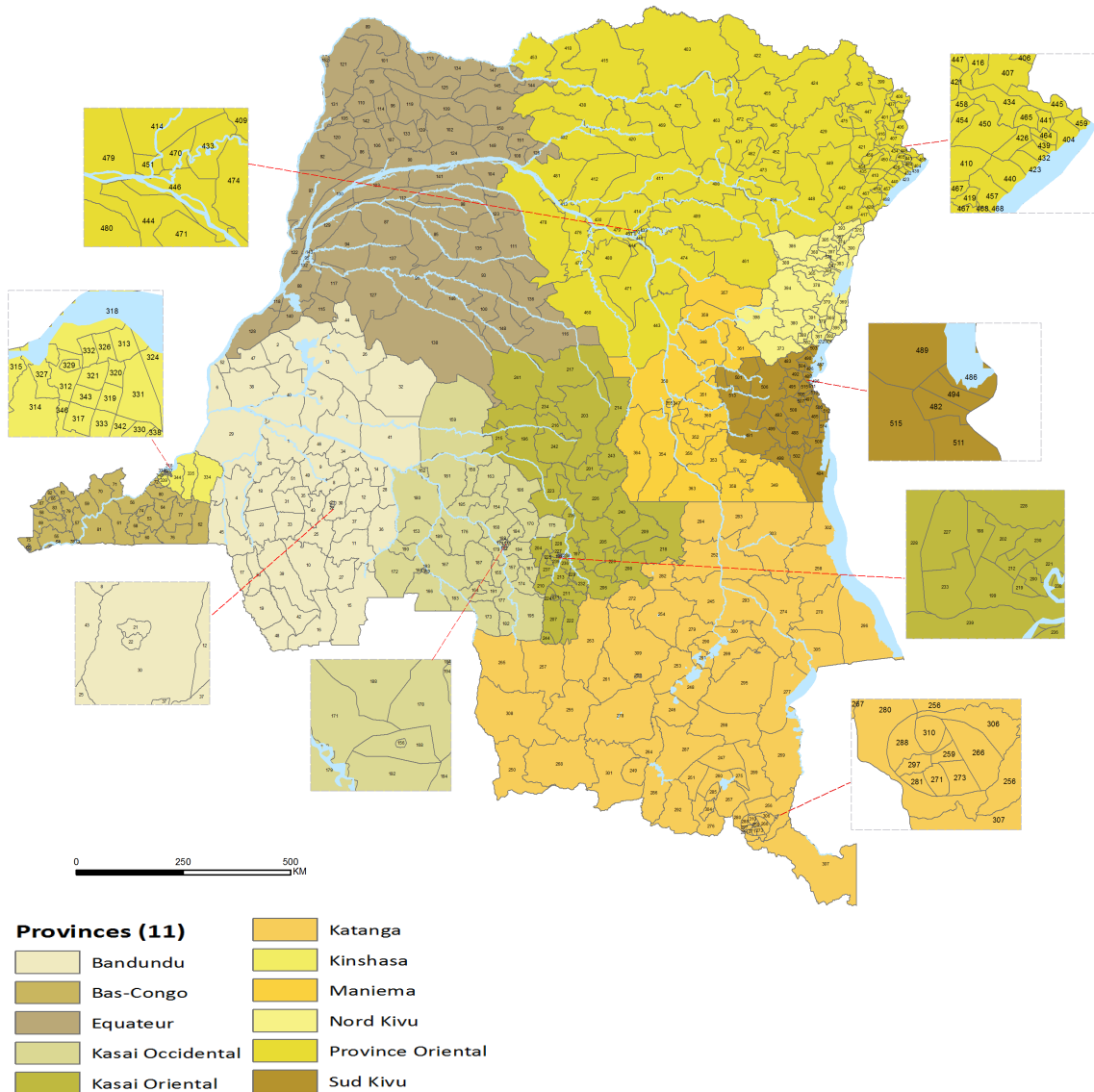
[13] The health zone (Zones de Santé) shapefile containing 515 polygons was provided by Henry Ntuku ((Ecole de Santé Publique), Swiss Tropical and Public Health Institute (Swiss TPH) PNLP collaboration, Kinshasa, on 27th February, 2014 which originated from DRC Ministry of Health (Department of Health Monitoring Information Systems). The shapefile had topological errors, and we therefore corrected common errors such as over-shoots (26,055 errors), unclosed polygons, and overlapping lines forming sliver polygons with intersections not properly snapped. We corrected for overlapping polygons (n=26055), gaps/slivers (n=25344) and matched zones to country boundary using the GAUL admin 0 shapefile. Three health zones (Kowe, Vanga, and Police, representing police administrative headquarters) have surface areas of less than 1 km², These we merged to Lubumbashi and Lingwala zones thus reducing the overall number to 512 health zones.

Figure 2.8: Malaria partners map. Note information on partners and activities supported provided in accompanying Zone de Santé Excel spreadsheet.
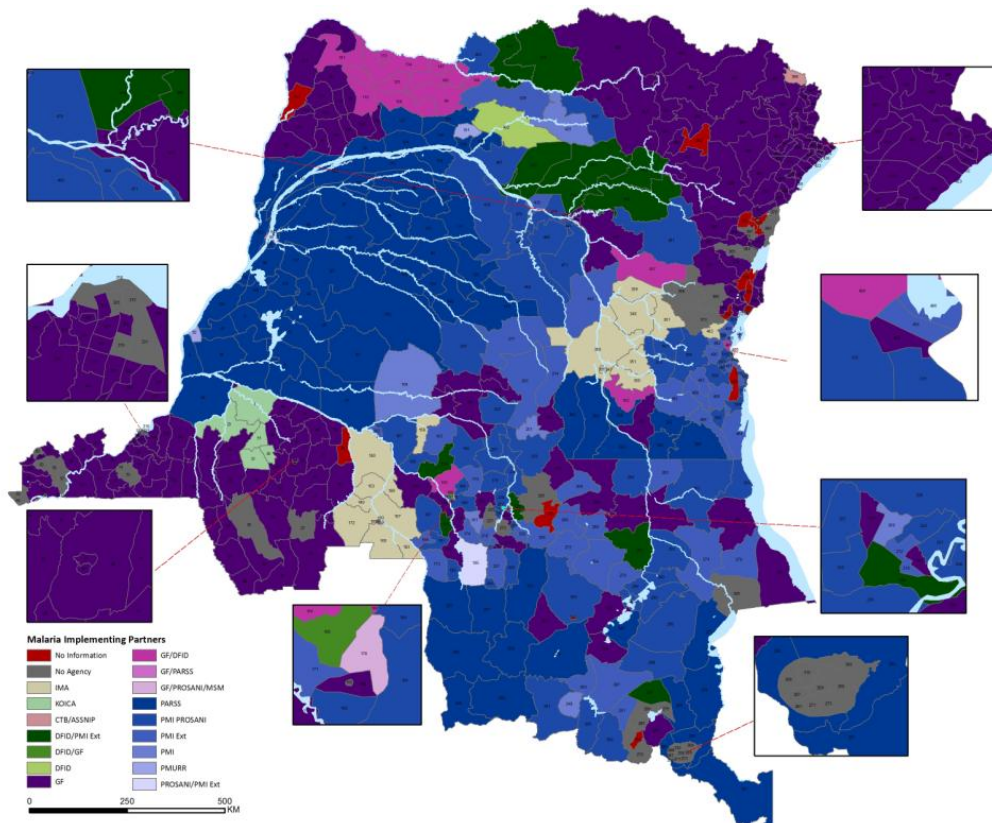
2.8 Health service mapping

The location of clinical service providers is critical for planning the future health sector requirements. The last available health service provider map for the DRC was developed in 1953 (Figure 2.9a; Anon, WHO Archive, Geneva); while sub-national health service mapping was an important planning resource during the *Fonds Reine Elisabeth pour l'Assistance Médicale aux Indigènes* (FOREAMI) project, a pioneer in rural public health in Africa, that provided medical assistance to populations in the lower Congo from 1930 and moving later into Kwango by the 1950s [Andre, 1953; 1957].

Figure 2.9: a) Map of important health service providers in DRC in 1953; b) map of health service providers and access routes in FOREAMI project area in 1953

a)

b)
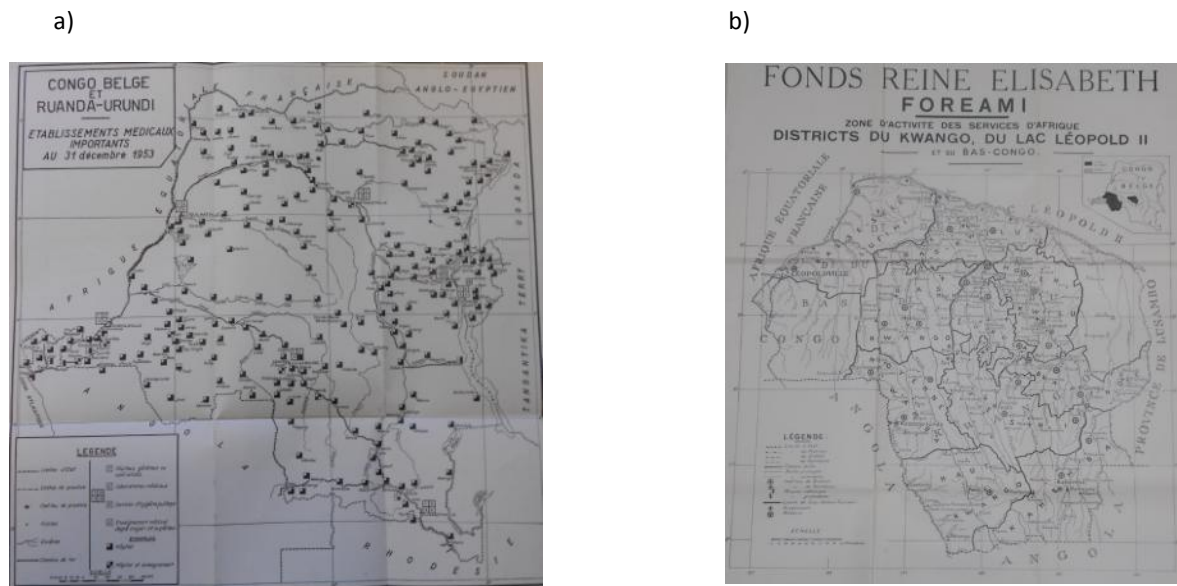
The present public health service is organized around a pyramid of service levels. Rural health centres or health posts serve as the first point of healthcare contact for majority of Congolese with the health system. They are usually constructed from semi-durable housing materials and in most cases are understaffed and underequipped (some do not have beds while others have up to 5 beds). Generally, they provide basic outpatient and curative services, while complicated cases are referred to referral health centres. Health centres cover a population of 5,000 in rural areas and 10,000 in urban areas within a maximum radius of 8 km. There are between 15 to 20 health centres serving a Zone de Santé (ZS), an offshoot of the local community [Ministère de la Santé, 2002; 2006]. In urban settings, health centres employ circa 11 medical personnel including six trained nurses to provide curative care (nutritional rehabilitation, minor surgeries, ectopic deliveries, diagnostics and treatment of chronic diseases such as tuberculosis, leprosy, hypertension), preventive care (maternal, antenatal, postnatal and expanded programme on immunization), and promotional services as defined under the minimum package activities (PMA) [Ministère de la Santé, 2006].

General referral hospitals (HGR) or referral health centres (CSR) cover catchment populations of 100,000 - 150,000 in rural areas and 200,000-250,000 in urban areas. Each of the 515 Zone de Santé should have a general referral hospital, currently there are only 393 referral general hospitals at the peripheral level [Ministère de la Santé, 2002; 2011]. General hospitals employ circa 120 medical personnel, of whom six should be doctors. HGRs provide basic medical services such as Pediatrics, Gynecology obstetrics, internal medicine and minor surgery as defined under the complimentary package activities (PCA).

At the intermediate level, there are eleven public provincial hospitals that provide services not possible at the general referral hospital level and support training of medical professionals, operational research, and quality control [Ministère de la Santé Publique, 2010]. Finally, tertiary level facilities (National hospitals) are at the apex of the health system offering specialized care, training, and research [Ministère de la Santé Publique, 2010].

Since independence there has been a rapid growth in public, commercial employer-based, private, non-governmental and faith-based services across the country, however, there is no contemporary inventory of service providers.

The current health service distribution has been mapped in some areas of the DRC by different agencies with varying health interests. The most detailed map although limited only to Human African Trypanosomiasis (HAT) endemic health districts has been developed by DRC's National Sleeping Sickness Control Programme in collaboration with the Foundation for Innovative New Diagnostics (FIND). Additional contemporary information is available for Zones de Santé located in North Kivu, South Kivu and Lualaba Provinces developed by the UN OCHA programme, with geo-coordinates. A much older set of geo-coded hospital facilities is available from the WHO's 1998 Health Mapper project.

The absence of a master health facility list covering the multiple service providers across the DRC, combined with the lack of a recent national population census are major rate limiting steps in designing broad health sector initiatives (including malaria), providing a logistics and management platform for the adequate delivery of clinical commodities and the informed use of health information. We return to the possibilities of up-grading the national health facility database in Section 6.5.

Figure 2.10: Location of health facilities by PNLTHA (blue)[14], UNOCHA (magenta)[15] and WHO health mapper (district/regional hospitals in red crosses)[16]

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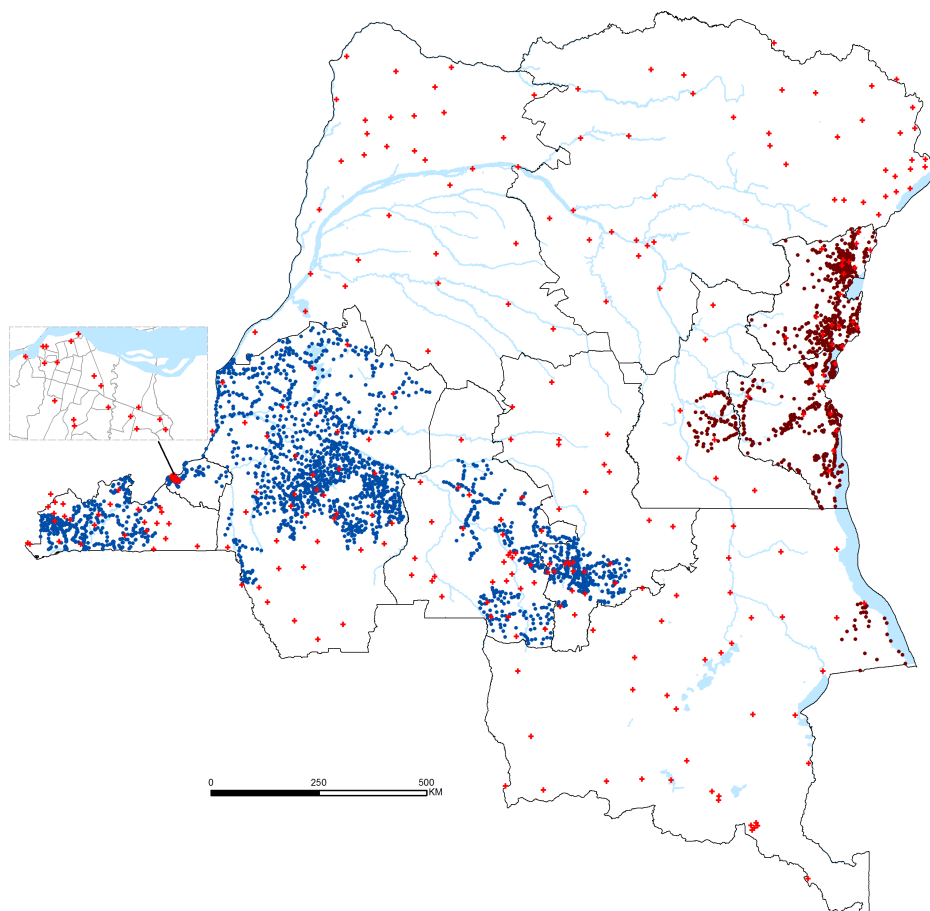
[14] PNLTHA: A list of 3845 facilities was provided by Dr. Crispin Lumbala, Director of the National Human Trypanosomiasis programme (PNLTHA). The facilities were part of a PNLTHA-FIND project to map the location and capacities of health facilities in sleeping sickness areas, these are shown in Figure 2.10 as blue dots. The project began in 2010 and has currently covered 93 health zones in 5 provinces [FIND, 2014]. Plans are underway to complete the remaining HAT endemic health zones. It is however not clear when this will be completed; : http://www.finddiagnostics.org/programs/hat-ond/hat/health_facilities.html.

[15] UNOCHA: A list of 1760 facilities were obtained from United Nations Office for the Coordination of Humanitarian Affairs website [UNOCHA, 2010]. The data was archived/hosted at Le Référentiel Géographique Commune (RGC). RGC is an online spatial data portal for DRC maintained by OSFAC, World Resource Institute (WRI), and Institute Géographique du Congo (IGC). The facilities are mainly concentrated in the eastern areas where OCHA is monitoring refugee camps. We eliminated 377 facilities that overlapped with PNLTHA facilities and thus Figure 2.1 shows distribution of 1383 OCHA facilities on the eastern areas of DRC; https://cod.humanitarianresponse.info/search/field_country_region/109?search_api_views_fulltext=&page=1.

[16] WHO: Separate lists were provided by Louis Ilunga from WHO country office on 22 May, 2014. The first list of 17,864 facilities contained information on facility code, type and name. None of the facilities had coordinates and it would take considerable time to geo-locate them and these are not included in the map. The second list was provided as part of HealthMapper software. The HealthMapper is a surveillance and mapping application, developed by WHO to address surveillance on infectious disease programmes at national and global levels [Hossaina, 2010]. We extracted 301 general reference hospitals that were distributed across the country, these are shown in Figure 2.10 as red crosses. We left out 191 health centers, and 16 health posts, as they overlapped with data from PNLTHA.

3. 100 years of malaria control

In this section we provide an overview of the evolution of malaria control in the DRC from the period before independence, through the era of the Global Malaria Eradication Programme (GMEP), from the abandonment of elimination to the present Roll Back Malaria (RBM) control period. This chapter is motivated by a need to: a) capture a historical perspective of control to be applied to today's control ambitions; and b) maintain an institutional memory of the last few decades of malaria control in the DRC - who was involved, what was done, what worked and more importantly what did not work. The work is laid out as a timeline highlighting the major events, data and locations of activities and resistance emergence.

1894-1899

Henri De Marbaix founded the Boma laboratory in 1894 (named after and located in the then capital of the Congo)[17] [Bosman & Janssens, 1997]. The Belgian Society of Colonial Studies took over the project and in 1899 created the Léopoldville laboratory (Kinshasa) and appointed Dr. Jean Emile Van Campenhout as its head [Dubois & Duren, 1947].

At the turn of the last century malarial fevers and blackwater fever were the most devastating of all diseases affecting the European community in Congo [Van Campenhout & Dryepondt, 1901].

1903

Drs Dutton and Todd from the Liverpool School of Tropical Medicine visited the then Independent State of Congo from 1903 to 1906 to report on the state of malaria, specifically in the towns of Boma, Matadi, Léopoldville, Coquilhatville and Lusambo. Their recommendations reflected international opinions on malaria control at the time: mosquito breeding site management, individual protection with nets, window/door screening, quinine prophylaxis and racial segregation [Dutton & Todd, 1906].

1908

Congo Free State was transferred to the Belgian Parliament.

Malaria attracted great interest from the colonial authorities and the urgent need to develop a solid health policy led to the establishment of the Colonial Medical Service in 1909 [Dubois & Duren, 1947; Porter, 1994].

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[17] De Marbaix was repatriated after two years of service in January 1896 and died a year later, halting progress at the laboratory

1922

Colonial Hygiene Service was established marking a new direction in public health in the Congo and independent of the Colonial Medical Service.[18]

1930

Fondation Reine Elisabeth pour l 'Assistance Médicale aux Indigènes (FOREAMI)[19] established in Lower Congo, Kwango and Lake Leopold II, later expanding to Katanga [Schwetz et al., 1939; Hunt, 1999].

1935-1941

At Kisangani (then Stanleyville), methodical larviciding with fuel oil within a radius of several kilometres reduced anopheles populations but there were no documented effects on parasite transmission. Larviciding also conducted by the 'Union Minière' at Likasi (then Jadotville), again with little effect [Vincke, 1950].

1947-1959

Indoor Residual Spraying (IRS) project with Dichloro Diphenyltrichloroethane (DDT) supported by WHO and coordinated by Dr IH Vincke, Director of the Malaria Control Research & Investigation Section, Elisabethville [Vinke, 1950]. The initial phase concentrated in the urban areas of Elisabethville, Manono, Albertville, Kasenga, Bukama, Kongolo and Kamina in Katanga Province.

DDT spraying in Jadotville by the Union Minière du Haut Katanga (UMHK) expanded to all its mining centres by 1948; sites at Kwango within the FOREAMI project area subject to DDT IRS between 1947 and 1948 [Himpe, 1949]; and IRS using Gammexane at Yaligimba [Davidson, 1949].

Several attempts at vector control made using aerial DDT spraying from helicopters in 1950s [Lebrun & Ruzette, 1956].

In 1951, a committee of the Colonial Health Council, chaired by J. Rodhain studied the issue of malaria and highlighted the importance of malaria mortality in the Belgian Congo, emphasizing the need for chemical prophylaxis against malaria and insecticides in the fight against vectors.

In 1955, a 5-year project (1955-1960) on the use of mass chemoprophylaxis with pyrimethamine in over 5,500 children is initiated in Yangambi,[20] in the Isangi territory of Tshopo District. Parasite prevalence (plasmodial index) reduced from 30-50% in 1954 to 4.5% in 1959 [Lahon et al., 1960].

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[18] The Colonial Hygiene Service was responsible for campaigns against insect vectors. Laboratories were opened in the provincial capitals, Léopoldville, Elisabethville and Bukavu as well as the ports of Banana, Boma, Matadi, Jadotville and Albertville [Porter, 1994]

[19] Established with a combination of funding from Belgian and Congo governments, the Queen of Belgium and a permanent endowment fund it aimed to launch an intensive, methodological, systematic, exhaustive and simultaneous campaign against all the diseases of a specified area (over a period of 4-5 years) after which the team would move on to a new area leaving the 'cleansed' area to regular medical care. Several studies of prophylactic use of quinine, atebrin, paludrine, chloroquine were undertaken during this project [Mouchet, 1951; Hunt, 1999]

In 1957, following the 1951 commission recommendations a central body was established, Service d'Etude et Coordination de la Lutte Antipaludique au Congo (SECLA), to coordinate malaria control activities under the Directorate of Medical Services.

1960-1970

Belgian Congo gains independence from Belgium on June 30th 1960 and Republic of the Congo (or Congo-Léopoldville) is established.

Experimental primary health system: at Bwamanda (Equateur), Kisantu (Bas-Congo), Kasongo (Maniema) and Vanga (Bandundu) leading to national expansion by 1970 and origins of decentralized health planning [MoH, 2006].

1976

The *Programme de Lutte Antipaludique* was launched by an agreement between the United States Agency for International Development (USAID) and the Government with an aim to implement and evaluate malaria vector control measures in Kinshasa. The primary anopheline mosquito control measure was intra-domiciliary spraying with DDT [Kazadi et al., 2004; PNLP, 2007].

1982-1983

The antimalaria programme, Lutte Anti Paludique (LAP), was integrated into the Expanded Programme on Immunization and the Fight against Childhood Diseases (EPI/MITA) [PNLP, 2007].

First case of chloroquine (CQ) resistance[21] was detected through an *in vivo* study in Katana (paediatric patients recruited at Fomulac Hospital) on the western shore of Lake Kivu, eastern DRC [Delacollette et al, 1983]; CQ fully sensitive in Kinshasa and Mbuji-Mayi[22] during the same year [Nguyen-Dinh et al., 1985].

1985

The country is divided into 306 health zones that are separate from the boundaries of administrative areas [Molisho et al., 2002].

CQ resistance established around Kinshasa (5% day 28 Early Treatment Failure (ETF)) [Ngimbi et al., 1985], Kinshasa (66% day 7 ETF) and Bwamanda (8% day 7 ETF) and further studies at Kindu (Kivu),

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[20] During the colonial era, Yangambi was home to the *Institut National pour les Études Agronomiques du Congo Belge* (INEAC).

[21] 46 children aged 0.5-6 years recruited between June-December 1982; 91.3% parasitaemia and fever cleared by day 4. RI resistance was observed in 2 children, 3 children showed RII and 1 child RII resistance.

[22] Both *in vivo* and *in vitro* tests were conducted during April-June, 1983. 92 parasitaemic school children in the southern outskirts of Kinshasa and 17 symptomatic individuals (non-confirmed) in Mbuji Mayi; all 109 subjects showed no signs of recrudescence during 1 week of observation

Bwamanda (Equateur), Kimpese (Bas-Congo) and Kinshasa were conducted to inform the national treatment strategy [Paluku et al., 1988]. All subjects from Bwamanda cleared parasitaemia after treatment with 25 mg/kg CQ. Treatment Failure was observed in Kimpese (44%), Kindu (26%) and Kinshasa (56%) [Paluku et al., 1988].

1986

In vitro pyrimethamine resistance detected in Kinshasa [Nguyen-Dinh et al., 1987].

1994

Rwandan genocide enters DRC, leading to over a decade of sustained civil conflict in Eastern DRC.

1995

Sulphadoxine-Pyrimethamine (SP) recommended for first line treatment for malaria in the Eastern Provinces [Likwela, 2012].

1998

In July 1998 the Programme National de Lutte contre le Paludisme (PNLP) was established by Ministerial Order[23] under the leadership of Dr Charles Paluku Kalenga.

1999

Dr Makina Aganda is appointed Director of the PNLP (1999-2001).

2000

Seven *in vivo* studies conducted by the Ministry of Health (MOH) of the therapeutic efficacy of CQ and SP at Kinshasa, Mikalayi, Kapolowe, Vanga, Kimpese, Kisangani and Bukavu, and from May 2000 to November 2001 show TFR between 29.4% - 80% in the CQ group and 0 -19.2% in the SP group. The highest TFRs were observed in Eastern DRC, both in the CQ group (Bukavu: 80%) and the SP group (Kisangani: 19.2%) [Kazadi et al, 2003].

Studies showed SP therapeutic failure rates ranging from 2-61% [Odio, 2005; PNLP, 2007].

Re-establishment of USAID support for malaria control in DRC [PMI, 2011].

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[23] The programme's mission was to develop appropriate methods and strategies for malaria control; to provide technical and logistical support to different areas of the health sector in relation to the prevention and treatment of malaria; and to develop and implement strategies to ensure the people of the DRC, particularly children under 5 years of age and pregnant women, live a life with a lower risk of contracting or dying from malaria and thus contribute to reducing the socio-economic burden of endemic malaria.

2001

Dr. Celestin Nsibu Ndosimao is appointed Director of the PNLP (2001-2004).

Malaria Indicator Cluster Survey (MICS) undertaken [INS/UNICEF/USAID, 2002]: 12% of children under 5 years slept under a mosquito net and 0.7% under an ITN on the night before the survey; Of reported fevers in children during last two weeks, 52% were treated with at least one conventional antimalarial (45% with chloroquine, 10% with quinine and 1% with SP).

SP replaces CQ as the national first line drug [PNLP, 2007].

2002

National System for Procurement of Essential Medicines (SNAME)[24] established under the MOH to centralize procurement of essential drugs [Ministère de la Santé, 2010a].

National Malaria Strategic Plan (NMSP) 2002-2006 launched [PNLP, 2002]; focused on mobilizing human, and material resources and financial structuring and organization of malaria services at provincial level.

NMSP 2002-2006 goals were to ensure that at least 80% of people with suspected uncomplicated malaria fevers and severe malaria should have access to appropriate treatment within 24 hours; at least 60% of those at risk, especially children under 5 years of age and pregnant women should sleep under ITNs; at least 60 % of pregnant women should receive intermittent malaria treatment in accordance with national policy [PNLP, 2002].

2003

33 Zones de Santé were identified as potential sentinel surveillance sites for malaria indicators, notably drug and insecticide sensitivity testing, facility-based malaria morbidity and mortality data, use of ITNs and other preventative measures [PNLP *personal communication*].

2004

Dr. Benjamin Atua Amatindii is appointed Director of the PNLP (2004-2013).

MOH adopts policy of IPT use to prevent malaria in pregnancy [WHO, 2013].

Global Fund Round 3 funding awarded (US$ 53.94 million) to DRC covering five years support to scaled ITN coverage among pregnant women and children under 5 years, improved malaria case management (with ACTs) at tertiary level health facilities, improved fever management at the community level,

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[24] The SNAME is based on a centralized purchasing system through two procurement agencies, the Office for the Coordination of Purchasing (CFAB) in Kinshasa and the Regional Association for Supply Essential Drugs (ASRAMES) in Goma. At the provincial level supply is cascaded through a network of 15 Central Regional distribution (CDR) centres [Ministère de la Santé, 2010].

application of intermittent presumptive treatment for pregnant women and strengthening management capacity of the NMCP and the intermediate level of the health system[25] [GFATM, 2003].

2005

Parliament adopts a new consensus constitution [GoDRC, 2006].

Number of Zones de Santé of the DRC increased from 306 to 515 (Section 2.7).

WHO support for Malaria Control in the Conflict-Affected Eastern Region of the DRC (US$ 4.14 million) targeting 3.3 million children in Maniema, Ituri, North and South Kivu and Orientale in 2006 by improving malaria case management through implementation of treatment guidelines, training and provision of ACTs [WHO, 2005].

World Bank Malaria Booster Programme (US$ 193 million) provided four year support for a) The Health Sector Rehabilitation Support Project (HSRSP/PARSS)[26] and b) The Emergency Urban and Social Rehabilitation Project (EUSRB/PMURR)[27] which included a goal of delivering at least three ITN per household [World Bank, 2007].

Therapeutic efficacy studies of combinations of AS-AQ and AL performed at five sentinel sites (Bolenge, Kisangani, Kingasani, Kimpese and Rutshuru) [Odio, 2005]. Early Treatment Failure (ETF) rates recorded on day 28 for Amodiaquine-Artesunate (AS-AQ) versus Artemether-Lumefantrine (AL) were as follows: Bolenge (1.4/1.6%); Kisangani (3.7/9.2%); Rutshuru (5.5/2.7%); Kimpese (6.8/6.7%); Kingasani (6.9/0.0%).

First-line therapeutic policy changed from SP to an artemisinin-based combination therapy with Artesunate-Amodiaquine (AS-AQ) for uncomplicated malaria.[28] AS-AQ is recommended for both the public and private sectors while Artemether- lumefantrine (AL) may be used in the private sector or in the public sector if AS-AQ is contraindicated [PNLP, 2010; 2012].

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[25] The funds supported 119 health zones to ensure that at least 50% of households would have at least one ITN and 50% of children under 5 and pregnant women would sleep under ITNs; other ambitions included a 70% target for the proper management of severe malaria, 80% of children under 5 years with uncomplicated malaria treated properly in health facilities; 80% of General Reference Hospitals (Hôpital Général du Référénce-HGR) in selected health zones would be able to provide parasite diagnosis and 50% of pregnant women attending health facilities for ANC should receive IPT during pregnancy.

[26] The Health Sector Rehabilitation Support Project (HSRSP/PARSS) is a US$ 150 million project with a booster component of US$ 30 million over four years. The project covers a population of 10 million people with interventions including 3.2 million LLINs to Zones de Santé supported by the PARSS and health zones supported by the Emergency Multisector Rehabilitation and Reconstruction Project/Projet Multisectoriel d'Urgence de Réhabilitation et Reconstruction (PMURR). It also provides IPT for pregnant women and ACTs. IRS is being tested within pilot projects and will be scaled up if successful. Funding is provided to firms, NGOs, institutions or specialized agencies to oversee the supply and distribution of interventions.

[27] The Emergency Urban and Social Rehabilitation Project (EUSRB/PMURR) covers a further 10 million people with support of approximately US$ 180 million that includes US$ 13 million for the procurement of 2 million LLINs for households in Kinshasa.

[28] Parental quinine was recommended treatment for all severe malaria cases and oral quinine for patients who fail to respond to AS–AQ. Rectal artesunate was recommended as a pre-referral drug at health facility level. Severe cases are managed at the hospital level with parenteral quinine.

2006

MOH adopts policy of distribution of ITNs/Long-lasting Insecticide Treated Nets (LLINs) free of charge to major risk groups (children under 5 and pregnant mothers). The policy was extended to all age groups in 2008 and a policy of free access to ACTs in the public sector.

2007

Dr Jean Angbalu becomes the interim Director of the PNLP until the return of Dr Benjamin Atua.

NMSP 2007-2011 launched [PNLP, 2007].

NMSP 2007-2011's goals were to reduce malaria specific morbidity and mortality by 50% by 2011. The plan was revisited in 2008 and replaced by a modified Strategic Plan 2009-2013 that was more in line with RBM targets for malaria control introduced in 2008 [PNLP, 2009].

Of the original 33 possible sentinel sites, 11 were selected including four for vector and parasite resistance studies.[29]

MOH introduces community case management guidelines that include community-level deployment of ACTs.[30]

Confirmation of malaria infection with Rapid Diagnostic Tests (RDT) introduced by the MOH [GFATM, 2013].

A national Demographic and Health Survey (DHS) undertaken: 5.8% of children under-five and 7.1% of pregnant women had slept under an ITN the night before the survey; 5.1% of women received IPTp and 17.3% of children with fever received an antimalarial within 48 hours of fever onset [Ministère du Plan, Macro International INC, 2008].

Oral artemisinin monotherapies discontinued but the ban was enforced only in 2009.

European Union (EU) pledged €1.8 million (approx. US$ 2 million) over three years from the European Development Fund to support the distribution of nets by UNICEF in the DRC[31] [EU, 2012].

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[29] Bolenge (Equateur), Kabondo (Province Orientale), Kalima (Maniema), Katana (Sud-Kivu), Kapolowe (Katanga), Kimpese (Bas-Congo, Kingasani (Kinshasa), Mikalayi (Kasai Occidental), Mwene Ditu (Kasai Oriental), Rutshuru (Nord-Kivu) and Vanga (Bandundu) [PNLP, *personal communication*].

[30] Community distribution of ACTs by CHWs was initiated in late 2008, though treatment has been largely presumptive as RDTs were only permitted at the community level in 2010 [PMI, 2011].

[31] During the first three years of the project nets were distributed to households with children under three (Bas-Congo in 2008) and under five (Sud-Kivu and Équateur, in 2009 and 2011. At least 14.5 million nets were distributed between 2006 and 2011. Campaigns took place in 2009 and 2010 in Oriental and Maniema, in 2011 in Kasai Oriental, Kasai Occidental, Bas Congo and parts of Bandundu and in 2012, campaigns aiming at universal coverage took place in Nord-Kivu, Sud-Kivu, Katanga, and to finish covering Banduna. Net replacement distributions were conducted in Équateur, Kinshasa, Maniema and Province Orientale in 2013.

2008

Tenke-Fungurume Mining Company's Malaria Reduction Programme initiated in October 2008 to reduce malaria incidence within the 50,000 households in Lubudi and Fungurume health zones within the mining concession area [Tenke-Fungurume, 2009; 2012].[32]

2009

NMSP 2009-2013 launched [PNLP, 2009] with a vision to contribute to improving the health status of the population of the DRC by reducing the human and socio-economic burden due to malaria.

The goal was to reduce the malaria specific morbidity and mortality by 50% by 2013 to be achieved through expanding LLIN coverage, parasitological diagnosis, effective ACT treatment, community case management, and monitoring and surveillance through routine health information systems and special surveys.[33]

Institut National de Recherches Biomédicales (INRB) begins studies on vector susceptibility to insecticides at one sentinel site in each of 4 provinces: Bas-Congo, Kinshasa, Equateur, and South Kivu. Widespread pyrethroid (deltamethrin, permethrin, lambda-cyhalothrin), organochlorine (DDT) and organophosphate (malathion) resistance detected in *An. gambiae*[34] [Basilua Kanza et al., 2013].

2010

Global Fund Round 8 funding awarded to the DRC approved (US$ 383 million) for five years to "*contribute to universal access of DRC populations to effective interventions to fight malaria*" [GFATM, 2008]; i.e. across all 515 Zones de Santé and continue Round 3 activities in the initial 119 Zones de Santé.[35]

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[32] An integrated malaria control program was commenced in 2009 to decrease malaria infection through vector control, including annual rounds of indoor residual spraying (IRS) using Gammaxene and the distribution of LLIN, education and awareness, and training to provide improved diagnosis and treatment. The 1st spray round in May 2009, covered over 19,967 houses and 39,963 ITNs were distributed to 23,420 children under five and 2,871 pregnant women [Tenke-Fungurume, 2009]. In 2010 over 36,000 households were covered with IRS and more than 43,000 ITNs were distributed [Nilsson et al., 2011]. Universal coverage with LLINs has achieved 60% reduction in incidence of malaria in the workforce and a 56% reduction of malaria prevalence in school age children in the HZ [Tenke-Fungurume, 2012].

[33] Since 2002 there has been no emphasis on indoor residual spraying (IRS) in any of the national strategic plans and the only IRS is undertaken by Tenke-Fungurme mining company [PNLP, 2009].

[34] Evidence for phenotypic resistance in *A. gambiae* was found for DDT at all sites, whilst pyrethroid resistance was detected at all sites except Kisangani (see Section 5.4).

[35] The specific goals to be attained through this proposal were to: 1) reach a rate of at least 80% of the general population sleeping under LLINs nationwide; and b) in the original 119 Zones de Santé reach a rate of at least 80% of children < 1 and pregnant women sleeping under LLINs, at least 80% of pregnant women receive IPT and treatment rate of at least 80% in accordance with national guidelines. LLIN scale-up activities were conducted mostly via large-scale mass distribution campaigns in Katanga, Kasai Occidental, Kasai Oriental and Nord-Kivu (2010); Bas Congo and Sud-Kivu (2011); Kinshasa and Equateur (2012); Bandundu, Maniema and Province Orientale (2013).

African Development Bank (ADB) initiates support towards malaria case management to procure 1 million doses of ACT, support for IPT delivery and 78,000 LLINS in 24 Health Zones of Orientale Province [GFATM, 2010].

MICS4 national household survey undertaken: 38.1% of children less than five years of age and 42.6% of pregnant women had slept under a bed net the night before the survey; only 21% of women received at least two doses of SP during their pregnancy; and <2% of febrile children received AS-AQ within 48 hours of fever onset [INS/UNICEF, 2011].

ACTwatch undertook a sub-national household survey in 185 census enumeration areas in four geographic regions[36] representing all areas of the country to document anti-malarial treatments used by children under five. 45% of urban and 37% of rural children with fever took anti-malarial medicines within two weeks prior to the survey; however only 3.1% of all children took AS-AQ within 48 hours of fever onset [ACTwatch Group, 2011; 2012; Littrell et al., 2011].

2011

NMSP 2011-2015 launched [PNLP, 2013] revising the NMSP of 2009 to align strategy with broader health sector strategic plan [Ministère de la Santé Publique, 2010b].

DFID bi-lateral support of US$ 67 million (£39.5 million) for malaria programme initiated that aims to deliver 9.5 million LLIN to at least 15 million adults and children by 2015 [DFID, 2011].

DRC becomes the 16th USAID/PMI country with a budget of US$37 million in financial year 2011 [USAID/PMI, 2011].

Korean International Cooperation Agency (KOICA) supported malaria control in five Zones de Santé of Bandundu Province; Bagata, Kikongo, Masi Manimba, Mosango and Yanga Bosa [PNLP, *personal communication*], however there is very little published information on activities completed.

2012

Malaria Programme Review (MPR) undertaken between March and November [PNLP, 2012a]. Key recommendations included: national mass LLIN distributions should be conducted every two years to maintain universal coverage (including scale-up of ITN coverage in South Kivu eastern Katanga); monitoring systems for vector insecticide susceptibility should be strengthened; Rapid Diagnostic Tests (RDTs) and microscopy should be scaled up to include improving access to ACTs; and IPTp should be provide free in all provinces.[37]

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[36] Geographic areas used in the ACTwatch household studies were defined according to the following 4 domains: Centre-south domain representing provinces of Katanga, Kasai Oriental, and Kasai Occidental; North-east domain representing Oriental, Nord Kivu, Sud Kivu, and Maniema; North-west domain representing the provinces of Bas-Congo, Bandundu, and Equateur; and Kinshasa. An equal allocation of households was sampled from each domain

[37] Despite a high rate of utilization of ANC services (87% DRC MICS- 2010 and 85%, EDS 2007), coverage of IPT was low (21% DRC MICS-2010 and 7% DHS 2007). LLIN coverage among pregnant women was also below targets. Stock outs were also common in the supply of SP and the MPR recommendations emphasized the need to improve prevention of MIP.

A forum of experts recommend the inclusion of AL as an alternative first line in both the public and private sectors for patients intolerant to AS–AQ and cases of therapeutic failure [PNLP, 2012c].

World Malaria Day campaign distributed 13.7 million mosquito nets in the provinces of Bandundu, Katanga, North Kivu and South Kivu. The campaign led by UNICEF in partnership with the Government of DRC, and funding from the World Bank and PMI-USAID, reached 24.6 million people [UNICEF, 2012].

Global Fund Round 10 (US$ 185.12 million) awarded to DRC to continue to "*contribute to a 50% reduction in the morbidity and mortality rates linked to malaria in the DRC by 2016*"[38]; the Principal Recipients of R10 funding were US$ 130 million to Santé Rurale (SANRU), US$ 65 million to Population Services International (PSI) and US$ 17 million to the MoH's Support Management Unit.

2013

Prof. Dr. Joris Losimba Likwela is appointed Director of the PNLP (2013 –present).

Global Fund Board approved US$ 85 million interim funding through the new funding model [GFATM, 2013] to expand the strategies currently being implemented through the active Single Stream of Funding (SSF) malaria grants to allow greater impact, and to replace bed nets through mass distribution campaigns in three provinces, to extend community-based approaches, improve access to RDTs and ACTs in remote areas through community agents and 720 community care sites.[39]

Mass distribution campaigns distributed 4.1 million LLINs in Kinshasa.

DfID assistance to PNLP and PSI announced (*circa* US$ 6.65 million through to 2018) to protect six million people with LLIN, improved ACT access and PNLP institutional and information systems development[40] [DFID, 2013].

2014

Mass distribution campaigns distributed 5.5 million LLINs in Province Orientale.

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[38] Target populations of the Global Fund R10 proposal were those living in 103 health zones located in nine provinces. Funds included the provision of free LLINs to children under the age of one year who complete the immunization schedule and pregnant women during their CPN1 in the 103 Health Zones.

[39] Additional interventions include the introduction of artesunate injection for treatment of severe malaria and blood transfusion activities and artesunate suppositories for pre-referral treatment; reinforcement of sentinel sites, supervision of community agents by senior nurses, coordination capacity, monitoring and evaluation activities, and functioning costs; investigations of malaria epidemics; and expansion of existing activities into health zones not currently covered by the Global Fund or another donor, using savings already identified in the CCM request.

[40] DfID (Malaria Control Grant No. GB-1-203458: May 2013 –March 2018) aims to support distribution of between 3.5 and 4.0 million LLIN through mass free distribution alone or a combination of mass distribution and social marketing, across one or more provinces to be identified. The expected impact in targeted areas include: The prevalence of malaria infection will fall by about 13%; number of cases of uncomplicated malaria will fall by about 50%, resulting in about 2.5 million fewer episodes of malaria amongst children under five per year; The lives of approximately 4,500 children under five will be saved per year. Additional benefits will be achieved through support to PNLP objectives to improve the availability and use of information for malaria control, and to enhance the availability and accessibility of ACTs in the private sector.

November 2013-February 2014 national household sample survey showed that 56% of children aged below five years slept under an ITN the night prior to the survey; 60% of women aged 15-49 slept under an ITN; only 14% of women received recommended SP IPTp during their last pregnancy; among children who had had a fever in the last two weeks, 29% had taken an antimalarial but only 5% had received an ACT; ACT access much lower within 48 hours of symptom onset and in rural areas compared to urban areas [MPSMRM & MSP, 2014].

4. Mapping the epidemiology of malaria transmission

4.1 The early years

Malaria reconnaissance formed an important part of the Belgian colonial medical department's activities through to the mid-1950s [Colonie du Congo Belge, 1929; 1931; 1936; 1955]. Detailed descriptions of malaria infection rates in infants, parasite prevalence rates in local communities and vector species ecology were provided in the annual reports. Malaria surveillance focused largely on the European inhabited areas of Leopoldville (Kinshasa) [Van den Branden & Van Hoof, 1923; Van Hoof, 1925], Stanleyville (Kisangani) [Schwetz & Baumann, 1929], Costermansville (Bukavu) [Schwetz et al., 1948], Coquihatville (Mbandaka), Albertville (Kalemie), Jadotville (Likasi) [Van Nitsen, 1925] and Elizabethville (Lubumbashi) [Walravens, 1923; Bourguignon, 1940], however there were regular malaria surveys across the country among rural communities connecting major settlement areas, mining camps and river courses [Schwetz 1940a; 1940b; 1941; Schwetz & Baumann, 1929; 1941; Schwetz et al. 1933a; 1933b; 1934a; 1934b; 1941a, 1941b; 1942a; 1942b; 1948a; 1948b][41].

In 1937, Albert Duren[42] published an essay on the malaria situation in the Belgian Congo, in which he prefixed the detailed epidemiological descriptions of malaria infection rates from different parts of the country with the presumed association between the distribution of malaria risk, rainfall patterns and altitude [Figure 4.1; Duren, 1937].

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[41] Jacques Schwetz (1876-1954) graduated in medicine at Lausanne in 1902 before moving to the Belgian Congo in 1909. He published over 300 papers during his career including many seminal works on malaria and the most prolific of all malariologists working in the Congo before independence. During his colonial service became the Director of the laboratory in Stanleyville in 1927 and served on the WHO's Expert Committee on Malaria after the Second World War

[42] Albert Nicolas Duren (1891-1971) qualified in medicine on the eve of the First World War. After military service in Europe he joined Dr Jerome Rodhain as part of the medical team supporting colonial troops in the Congo. He served as a central figure of the medical and research communities in Congo and most notable was his attempts to enumerate the precise contribution of malaria to infant and childhood mortality [Duren, 1951]; one the earliest efforts to define the mortality burden in Africa
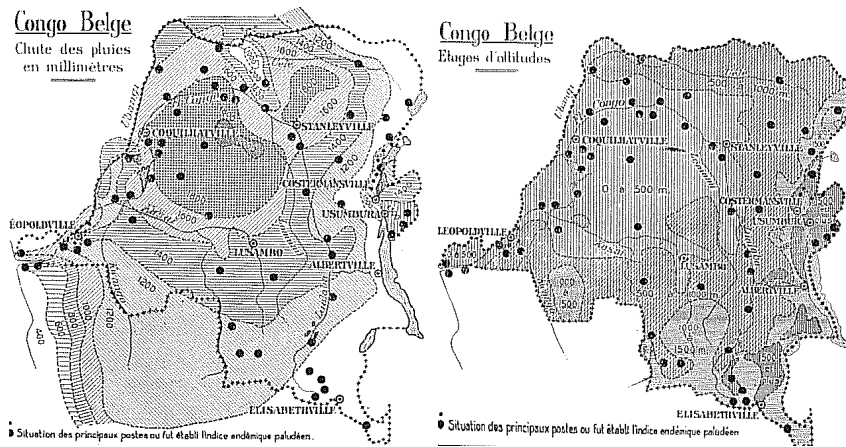
It was not until 1961 that D'Haenens and colleagues, from the Service d'Etude et de Coordination de Lutte Antiplaudique (SECLA) in Stanleyville, published a detailed map of malaria in the DRC [Figure 4.2; D'Haenens et al., 1961]. This map divided the country into ecological zones and sub-zones thought relevant for malaria stratification, although no direct reference was made to how this zonation defined control ambitions other than their relationship to dominant vectors and human population density.

Figure 4.2: Digitised malaria stratification map 1961 [D'Haenens et al., 1961]
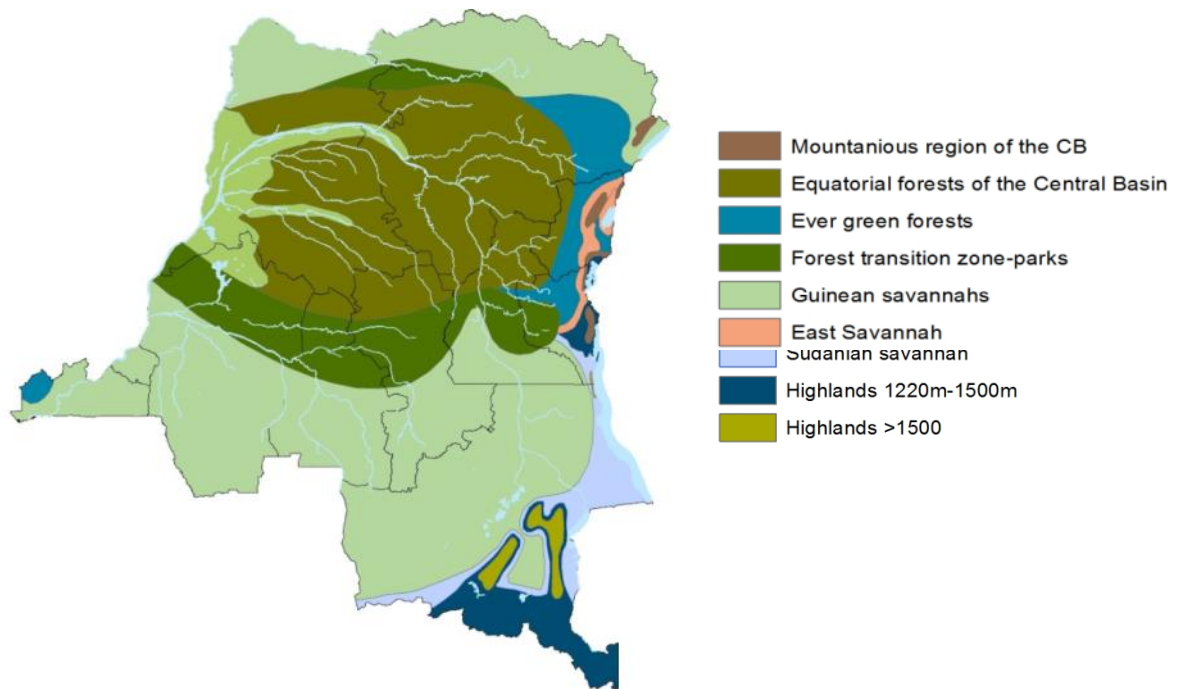
The 1961 complex zonation covered:

1) **Coastal** areas covering the narrow margin of mangrove, especially at the mouth of river Congo, supporting *An. melas.*

2) **Equatorial forest** with an "equatorial climate" (except Mayumbe forest), with no dry season and an annual rainfall of 1600 mm; subdivided into a) *flooded and marshy forest zone* (an exclusive enclave of *An. moucheti*); b) *Central Basin equatorial forest zone* with an extremely sparse population, scattered in the forest and where *An. moucheti* breed along the large water courses and sympatric with *An. funestus* and *An. gambiae* s.l; c) *suborophiles forest zone* including the Ituri and Mayumbe forests and the Rutshuru region where *An. funestus* and An. *gambiae* are the main vectors; and d) *forest parks transition zone* that covers a mixture of equatorial and savanna, where the later dominates further from the equator and *An. funestus, An. moucheti* and *An. gambiae* s.l. predominate.

3) **Savannah** that encompasses three sub-zones dependent upon rainfall and seasons away from the equator: a) *savannah North zones* that occupy the whole of Northern DRC where the dry season ranges from 1-3 months and rainfall between 1400 and 1800 mm per year supporting *An. funestus, An. gambiae* s.l. and *An. moucheti;* b) *savannah oriental zone* that lies along the Rwanda-Burundi eastern border below 1500 mASL and occupies also two small areas north and south of Lake Edward; here *An. funestus* and *An. gambiae* s.l. predominate and it was reported that a high proportion of patients harbor *Plasmodium malariae;* and c) *savannah south zone* supporting *An. funestus* and *An. gambiae* s.l.

4) **Highland areas and eastern mountains** that were divided into a) a) Submontane transition zones (1000-1200 mASL) including the western foothills of the eastern mountains and Haut-Katanga highlands with valleys with forests that were used to further sub-divide this sub-zone into i) submontane equatorial transition zones from Ugoma Mountains in Ruwenzori (*An. funestus* and *An. gambiae);* ii) submontane transition zone of Rwanda-Burundi central plateau (not part of DRC); and iii) submontane Sudanese transition zone borders Lakes Tanganyika and Moero and borders South-West Katanga (*An. gambiae* s.l*., An. funestus. An. nili* Theobald and *An. pharoensis);* b) *Katangais highlands zone* (more than 1200 mASL), subdivided into areas that are altitude lower than 1500 mASL (with a reported parasite rate up to 90% and where *An. funestus, An. gambiae* s.l. and *An. nili* are found; altitudes higher than 1500 mASL where *An. funestus* and *An. gambiae* dominate transmission; and the Eastern mountains zone (more than 1750 mASL) where malaria is epidemic and influenced by humans pursuing agriculture (*An. gambiae garhhami* Edwards and *An. christyi* reported in this sub-zone).

5) **Large rivers shores and extended swamps zone** distributed in small stretches all over the DRC among several large malaria zones and limited to waters courses along rivers and their extended marshes, which harbor, in some regions *An. moucheti.*

4.2 Malaria risk stratification 2002-2013

The following 40 years saw no renewed attempts to provide a stratification of malaria in the DRC, nor was there any evidence that the 1960s cartography of malaria was ever used to guide disease control. The first national strategic plan for malaria control, launched after the start of the Roll Back Malaria (RBM) initiative, covered the period 2002-2006 [PNLP, 2002] and included the aim to develop a description of malaria zones based on eco-faciae widely used across Francophone Africa [Mouchet et al., 1993]. These covered three principal strata:

1) **Equatorial facies** (central African forests and post forest savannas) where transmission is intense and perennial, reaching up to 1000 infected bites per person and per year which results in an early acquisition of clinical immunity before the fifth birthday; the most common vectors in this zone are *An. gambiae, An. funestus, An. nili* and *An. moucheti*.

2) **Tropical facies** (African humid savanna) where transmission predominates during the long rains lasting for between 5-8 months and where people might receive between 60-400 infected bites per person and per year but still results in a clinical immunity in childhood; the most common vectors in this zone are *An. gambiae, An. arabiensis, An. funestus* and *An. nili* (very localised)

3) **The mountain facies** between an altitude of 1000 and 1500 mASAL where the period of transmission is very short, there may even be years without transmission and clinical immunity is acquired much later in life or may not be complete resulting in severe malaria in all age groups; *An. arabiensis* (uplands and mountains), *An. funestus* (often in poorly drained depressions)

This stratification has been used to describe the epidemiology of malaria in DRC since 2002 and was included in the strategic plans of 2007-2011 [PNLP, 2007], the revised strategy 2009-2013 [PNLP, 2009] and the most recent strategy 2013-2015 [PNLP, 2013]. The national strategic plans since 2002 have highlighted that 97% of all Congolese are within the first two strata. The maps shown in the strategic plans represent all of Africa but the area covered by DRC is depicted in Figure 4.3.

The 2009-2013 revised strategic plan [PNLP, 2009] also included a map of malaria seasons developed by the MARA/ARMA collaboration in 1999 [Craig et al., 1999; Tanser et al., 2003]. This map highlighted the ubiquity of perennial transmission (transmission lasting for more than seven months a year) except along the eastern mountainous and the south eastern areas of the country (Figure 4.4)[43]

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[43] The MARA models of seasonality are defined using the combination of temperature and rainfall thresholds and a catalyst month. Areas where mean annual temperatures were <5°C were considered not to have a malaria transmission season. A pixel was considered "seasonal" if the temperature range varied considerably or if annual rainfall was <720 mm. Seasonal zones classified according to the numbers of average months in which temperature was > 22^{0}C and rainfall > 60 mm within a 3-month moving window and at least one month of highly suitable conditions (> 22^{0}C, > 80 mm) occurred as a catalyst month. For areas considered "stable" the equivalent values were 19.5^{0}C and 80 mm with no requirement for a catalyst month.

Figure 4.3: Malaria ecological strata representing two dominant ecological zones: Equatorial (green) and Tropical (Orange) used in national strategic plans since 2002; note mountainous zone not shown in map provided by PNLP

Figure 4.4: MARA climate malaria seasons map [http://www.mara.org.za/]
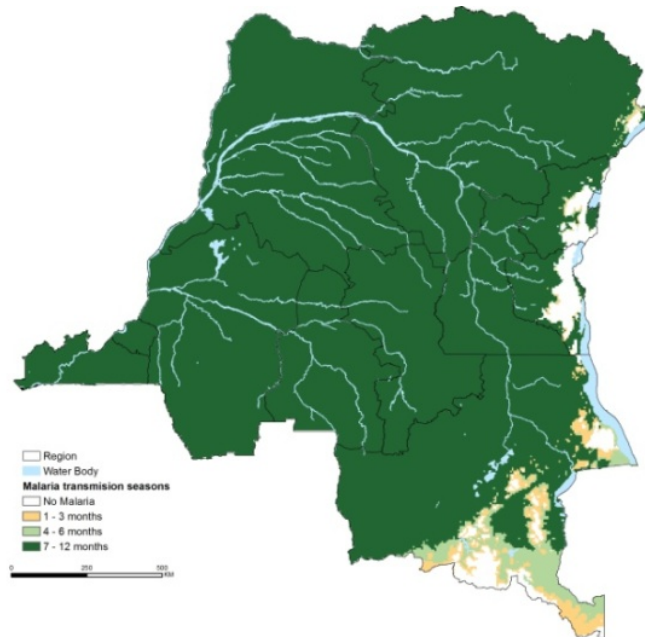
A recently completed map of malaria transmission intensity was included in the report of the Malaria Programme Review (MPR) in 2012 (Figure 4.5). The map was based on the results of the malaria module of the Demographic and Health Survey (DHS) undertaken in 2007 that included malaria infection status [PNLP, 2012a; Messina et al., 2011; Taylor et al., 2011]. This

was the first attempt to use, for programmatic purposes, a malaria risk map based on the intensity of transmission as measured by parasite prevalence. The data included were results of Polymerase Chain Reaction (PCR) analysis of plasmodial infections from filter paper samples from 8,838 individuals living in 300 clusters across the country. This survey significantly changed the amount of information of malaria infection prevalence in the DRC where, prior to the survey, there were only limited parasite prevalence mapping in the country[44]. The model of malaria prevalence used very simple geo-statistical techniques to interpolate between clusters using a non-Bayesian, Indirect Distance Weighting techniques[45] and did not include important environmental determinants likely to provide a more robust prediction across un-sampled locations.

Figure 4.5: Smoothed, interpolated *P. falciparum* prevalence (%) in adults in 2007 [Taylor et al., 2011; PNLP, 2012a]
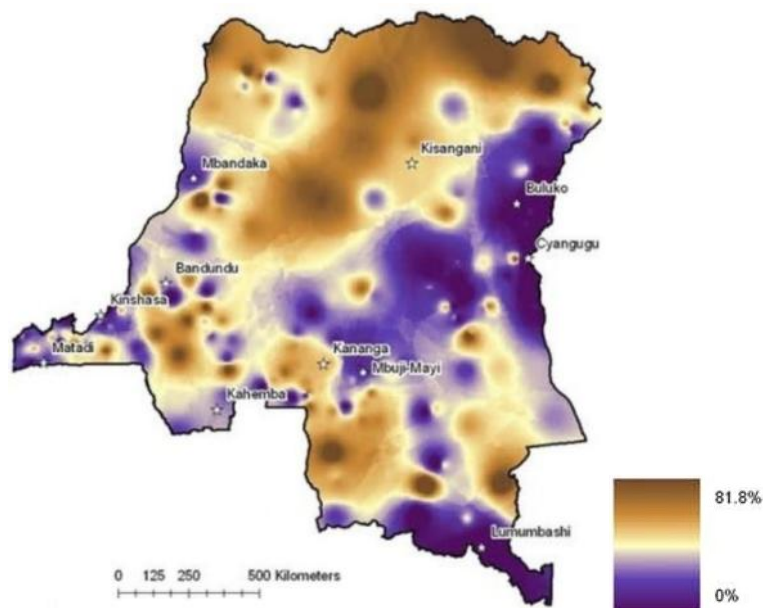
The MPR in 2012 concluded; "*It is necessary to take urgent measures to better define the epidemiology of malaria and distribution of diseases in the country. This would allow a better choice of strategies for a real impact by 2015...... to regularly update the stratification of health zones based on the malaria prevalence and entomological mapping to a better understanding of the distribution of Plasmodium species and vectors*" [PNLP, 2012a].

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[44] The Malaria Atlas project produced a map of malaria in the DRC for the year 2010 based only on only 46 empirical surveys of infection prevalence and over-fitted with 14 environmental covariates, resulting in a highly uncertain predicted map [Gething et al. 2011b]

[45] IDW is one of a suite of global linear interpolation approaches useful for exploring data but does not empirically accommodate spatial dependence

4.3 Revised malaria risk maps

4.3.1 Background

There was a recognition over 50 years ago that one important source of planning data was infection prevalence among children aged 2-10 years (PfPR$_{2\text{-}10}$), used to define categories of endemic risk designed to guide and monitor progress toward malaria elimination targets [Metselaar & van Thiel, 1959; Macdonald & Göeckel, 1964; Lysenko & Semashko, 1968]. There is a growing body of evidence that 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., 2012] and timelines to malaria elimination [Cohen et al., 2010] are all dependent on pre-control, parasite transmission intensity.

A wealth of parasite survey data was collected under the Belgian colonial administration, but never presented in a cartographic form. More recent attempts to map the risks of malaria in the DRC have defaulted to broad delineations of ecological zonation based on climate, altitude and vegetation. More contemporary maps of malaria risk in the DRC, based on parasite prevalence, have used very limited data (46 survey locations) [Gething et al., 2011a] or sub-optimal spatial modeling techniques [Taylor et al., 2011]. Here we have developed a more comprehensive inventory of geo-coded parasite prevalence data and have applied more rigorous Bayesian, model-based geo-statistical methods to interpolate estimates of PfPR$_{2\text{-}10}$ across the DRC in 1939 and 2007 and quantities of population-adjusted risk per Zone de Santé.

4.3.2 Assembling empirical data on malaria infection prevalence

We have identified and assembled parasite prevalence survey reports through combinations of on-line published journal searches, investigations of archive material in Antwerp, Geneva and Brazzaville and contacts with national academics and research groups for unpublished data (details provided in Annex A.1). We located 1152 estimates of malaria infection prevalence over a 100-year interval 1914 to 2013. Five surveys that sampled less than 10 individuals and seven surveys where the survey locations could not be geo-located, were excluded. The temporal distribution of the remaining 1140 surveys is shown in Figure 4.6. Sixty-eight (6%) of all data were from surveys undertaken before 1930, 479 (42%) from surveys undertaken between 1930 and 1969, and only 72 surveys were undertaken over the thirty year period between 1970 and 1999. 501 communities have been sampled for malaria infection since 2000, the majority during the national household sample survey of 2007. A full database is provided with this report.

Figure 4.6: Number of *P. falciparum* infection prevalence surveys (Y-axis) by year 1914-2013 (X-Axis)
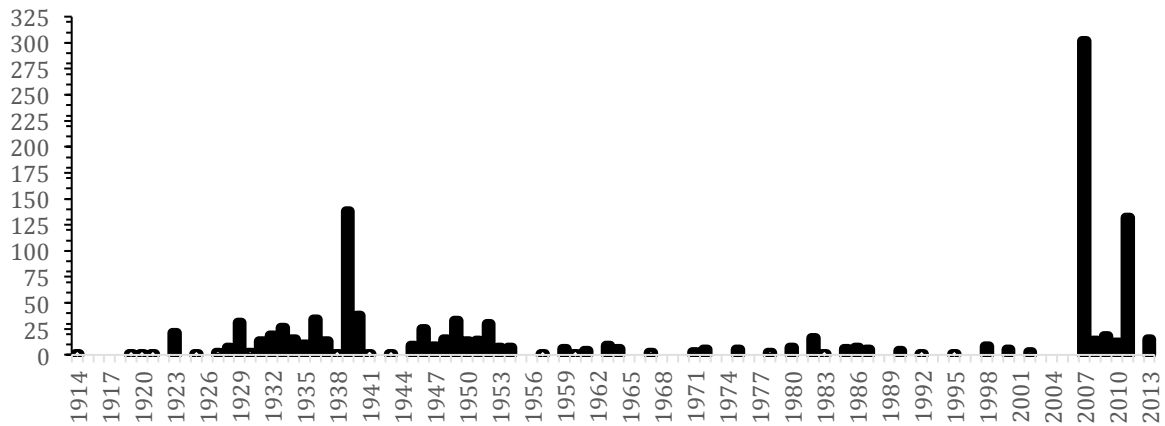
The surveys sampled varying age-groups at each sampled site, including young children to adults aged over 15 years. To make any meaningful comparisons in time and space we have adapted catalytic conversion models to standardize all survey data to one age group, children aged 2-10 years, $PfPR_{2-10}$ [Smith et al., 2007]. The mean overall trends in averaged $PfPR_{2-10}$ suggest that risks of *P. falciparum* infection are lower over the last decade (*circa* 40%) compared to prevalences reported before 1950 (*circa* 60%) (Figure 4.7). However, caution is required in interpreting these data, as survey sites will not have been the same within each decadal period. We approach this using modeled data within different time-periods to highlight long-term change more precisely in Section 4.3.3.

Figure 4.7: Box and Whisker plot of *P. falciparum* infection prevalence surveys by decade (The thick middle line in the box is the median, the upper and lower bounds of the box show the 75th and 25th percentiles, the upper and lower bounds of the whiskers show the maximum and minimum values excluding the outliers)

40
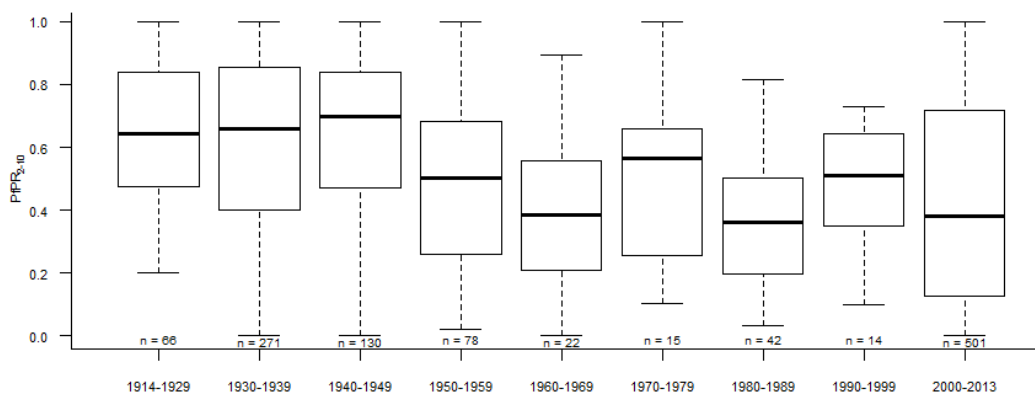
4.3.3 Modeling PfPR$_{2-10}$ in space and in time

The empirical prevalence survey data were non-randomly over-dispersed in time and in space. The spatial and temporal dependencies of the data within the country, however, allow for the application of model-based geo-statistical (MBG) methods[46] that interpolate from data at known locations and time to provide predictions of quantities and estimates of their uncertainty at locations and times where data do not exist [Diggle & Ribero, 2007].

We have used information from the available age-corrected survey data (sample size and numbers positive) at known locations (longitude and latitude) and times (year) with a minimal set of conservative, long-term covariates traditionally used in vector-borne disease mapping. In statistical modelling, a set of independent covariates (precipitation, TSI and EVI; Figures 2.2 a-c), of the main outcome measure is often used to improve the model fit and increase the precision of predicted estimates.

A Bayesian hierarchical space-time model was implemented through Stochastic Partial Differential Equations (SPDE) using Integrated Nested Laplace Approximations (INLA) for inference. We partitioned the data into the two time-periods where data are maximal (Figure 4.6): 1929-1949 (n = 477 data points) to predict to 1939 and 2007-2013 (n = 421 data points) to predict to 2007. Two models were run for each time period to provide continuous predictions of mean *Pf*PR$_{2-10}$ at each 1 x 1 km grid in 1939 and 2007. See Annex A.2 for full model details, model outputs and model precision metrics.

The modeled and projected population density grid (Figure 2.5), projected to 2007, was then used to extract populations at risk by Zone de Santé at each 1 × 1 km *Pf*PR$_{2-10}$ grid location classified by predicted *Pf*PR$_{2-10}$ estimate using the *Zonal Statistics* function in ArcGIS 10.1. Matching population density to malaria risk allows for the calculation of Population-Adjusted risks (PA*Pf*PR$_{2-10}$) within each of the 512 Zone de Santé for the year 2007 using the 2007 predicted *Pf*PR$_{2-10}$ risks (Figure 4.8). For Zone de Santé risk data see accompanying excel. Overall approximately 6% of the 2007 population (3.73 million people) lived in areas where malaria transmission was not possible given sustained long-term low ambient temperatures preventing sporogony in the mosquito (Figure 2.2c). A very small fraction of the population (<0.01%) lived in areas that supported a *Pf*PR$_{2-10}$ of less than 5%; and a small proportion of the population (0.2%) lived in areas supporting *Pf*PR$_{2-10}$ of between 5% and <10%. As such the traditional hypoendemic malaria risk classification is almost absent in the DRC. 28.6% (17.4 million) of the 2007 population lived in areas that were predicted to be between 10% and <50% *Pf*PR$_{2-10}$ (meso-endemic transmission), 37.3% (22.6 million) of the population lived in areas predicted to support a *Pf*PR$_{2-10}$ of between 50% and <75% (hyperendemic transmission) and 27% (16.8 million) of the population lived in areas that were classified as traditionally holoendemic (≥75% *Pf*PR$_{2-10}$) (Figure 4.9).

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[46] MBG methods 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]

Figure 4.8 Zone de Santé (n=512) map of population adjusted $PfPR_{2-10}$ ($PAPfPR_{2-10}$) in 2007
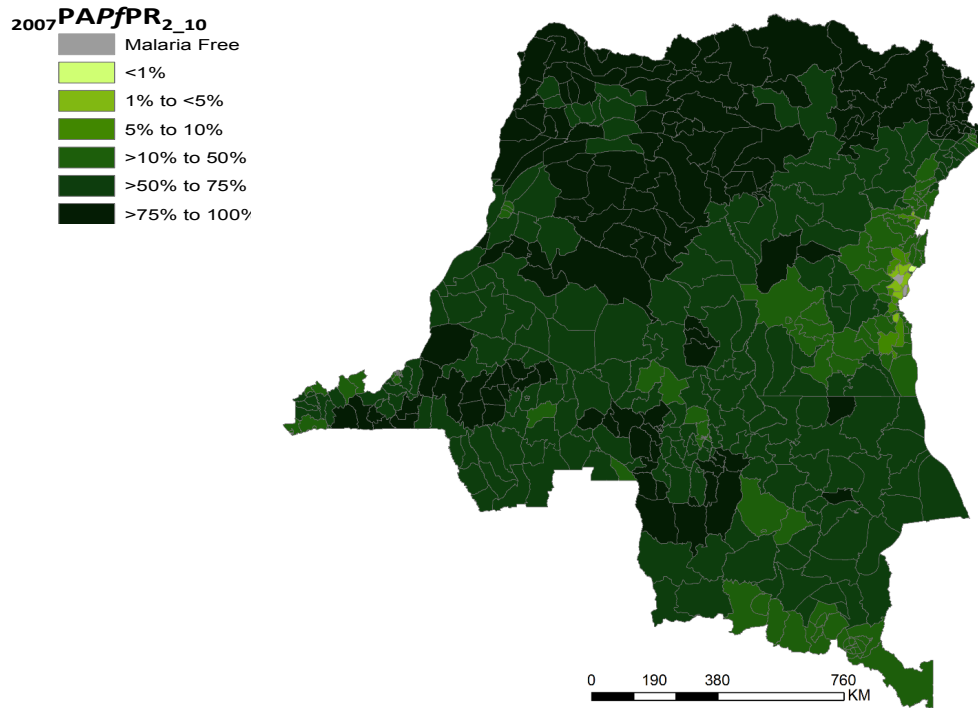
Figure 4.9: proportion of 2007 DRC population living in various predicted malaria endemicity classes (legend greens etc to match those shown in Figure 4.8)
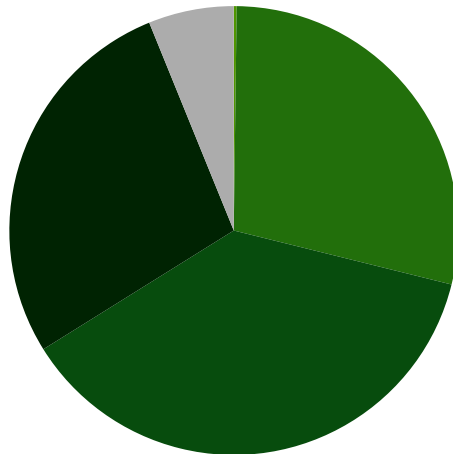
For comparison we have also computed a further 2007 $PAPfPR_{2-10}$ based on what zonal risks would look like if malaria risks of 1939 prevailed in 2007 (Figure 4.10). As might be expected, and suggested in Figure 4.7, here has been a long-term cycle of change in malaria risk in the DRC, as shown by the predominantly holoendemic state across the country with lower risks on the Eastern borders in 1939.

Figure 4.10 Zone de Santé (n=512) of population adjusted 1939 PfPR$_{2-10}$ (PAPfPR$_{2-10}$) in 2007: 2007 map assuming predicted 1939 risks affected the 2007 population
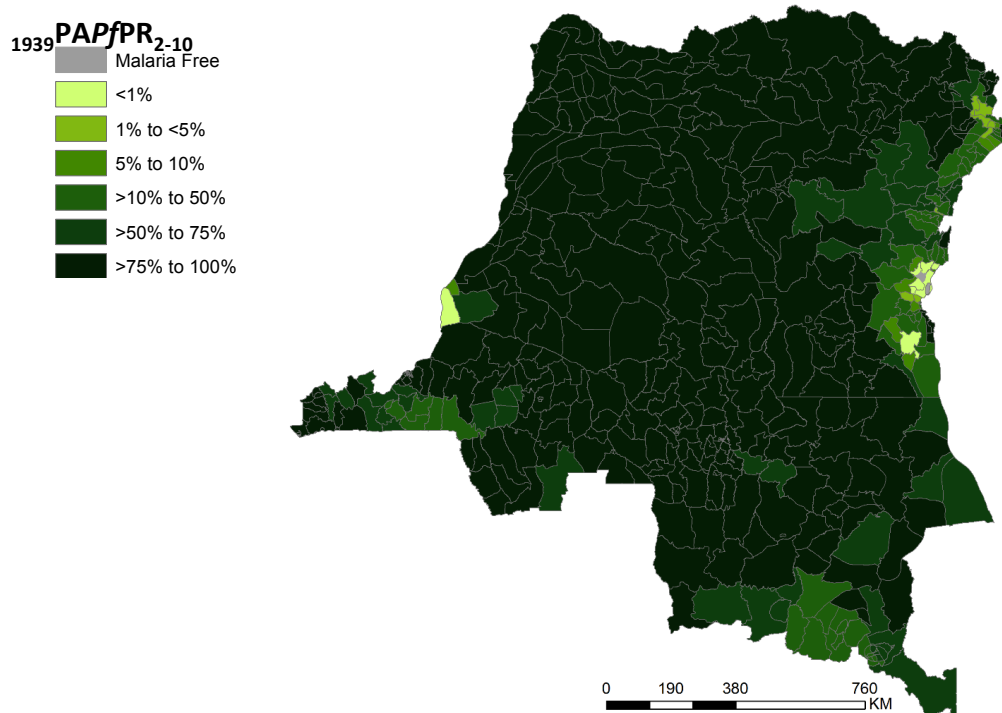
2007 endemic conditions are best described for the majority of the country as hyper-holoendemic ≥ 50% PAPfPR$_{2-10}$), these conditions prevailed to affect over 39.5 million people in the DRC in 2007, or 64% of the Congolese population. Despite a long-term change in endemicity since 1939, some areas remain holodendemic after nearly 80 years, notably Zones de Santé located in the north and within the forested belts in northwest DRC.

The 2007 malaria risk map shown in Figure 4.8 serves as a valuable baseline risk map pre-scaled and accelerated coverage of LLIN nationwide (Section 3); in 2007 less than 6% of children slept under an ITN.

Some data are available after 2007 to allow for a prediction to 2013 but these data are restricted to only a few areas of the country. Between November 2013 and February 2014 a household survey was completed that included biomarkers (RDTs and PCR)[47] for malaria infection status among 8,037 children aged 6 months to the fifth birthday living in 530 clusters nationwide. RDT test positivity overall was 30.8%, ranging from 2.9% and 12% in North and South Kivu provinces respectively, to 17.1% in Kinshasa and five provinces (Bas-Congo, Orientale, Maniema, Katanga, Kasaï-Oriental and Kasaï-Occidental) all above 40% infection prevalence [MPSMRM & MSP, 2014].

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[47] The University of North Carolina have been mandated to undertake the PCR analysis on all samples; it seems unlikely that these data will be made available in the public domain for immediate analysis.

The provisional report has now been released and making the parasitological data available for further time-space modelling will allow the PNLP to make a comparison between Zone de Santé risks in 2007 with those in 2014, and therefore examining any progress made as a result of scaled vector control activities nationwide.

4.4 Other malaria parasites

4.4.1 Plasmodium vivax

Between 1920 and 1961, 248 survey sites reported details of all malaria parasite species among sampled populations. These surveys collectively examined 23,337 people, of whom 356 (1.5%) were reported to harbor *P. vivax* infections compared to 12,280 (52.6%) *P. falciparum* infections. The only contemporary study of multiple malaria infections that has described *P. vivax* was undertaken in 1980 in Kinshasa; among 1595 children aged 0-15 years, 714 (45%) harboured *P. falciparum*, 63 (4%) were reported to be infected with *P. vivax*, 42 (3%) with *P. malariae* and six (0.3%) with *P. ovale* [Ngimbi et al., 1982].

While relatively a small fraction of all plasmodial infections these records of *P. vivax* infection are significant. It is difficult however to interpret these data as *P. vivax* can often be mistaken for *P. ovale* during microscopy [Rosenberg, 2007][48] and endemic *P. vivax* transmission is thought to be absent from much of sub-Saharan Africa owing to the refractory nature of Duffy-negative red blood cells that lack a necessary receptor (Fy(a-b-)) for *P. vivax* 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], People's Republic of Congo [Culleton et al., 2009], 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].

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, 2013]. Further investigations on the epidemiology of vivax infection in the DRC should be undertaken.

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[48] *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 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]

4.4.2 *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]. Both parasites 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.

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]. *P. ovale* is a very rare parasite in the DRC: among the 23,337 people investigated for all parasite species between 1920 and 1961 only 109 (0.5%) were identified as harbouring this parasite. In 1980 in Kinshasa prevalence of *P. ovale* was 0.3% [Ngimbi et al., 1982] and in the same areas in 2000 was 0% among 503 children aged 5-9 years [Kazadi et al., 2004]. The relative absence of reports of this parasite elsewhere is intriguing.

Plasmodium malariae is far more common and easier to detect on microscopy. Between 1920 and 1961, 2789 (12%) infections were detected. Among 5757 people investigated for *P. malariae* between 1975 and 2013, 425 (7.4%) were reported to be infected with *P. malariae*. This decline is consistent with an overall trend toward lower transmission intensity described for *P. falciparum* (Section 4.3).

5. Dominant vectors and bionomics

5.1 Background

All national malaria strategies across sub-Saharan 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 insecticides remains largely unknown or under-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 [Ferguson et al., 2010; Gatton et al., 2013; Pates & Curtis, 2005; Ranson et al., 2011]. A lack of reliable entomological monitoring systems 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].

Since 1996, there has been a renaissance in the assembly of spatially defined databases of vector species occurrence, following the launch of the Mapping Malaria Risk in Africa collaboration [Snow et al., 1996; Coetzee et al., 2000]. There are six on-line databases that now provide useful information on the location of the major dominant vector species in Africa[49]. However, these databases do not capture all published observations, exclude much unpublished work and do not cover the entire species diversity within each country. For example, in the MARA and MAP databases there are only four and 20 site locations respectively for DRC reporting only the dominant vector species (DVS) of the *An. gambiae* and *An. funestus* complexes. In 2007, the WHO regional office supported an entomological review in the DRC [Anon, 2007]. This exercise identified 32 publications, theses and reports that provided vector species information at 78 locations between 1927 and 2006 and highlighted the sympatric distributions of dominant (*An. gambiae* s.l. and *An. funestus*) and secondary (*An. nili* s.l., *An. moucheti, An. paludis and An. hancocki*)[50].

Here we attempt to update the anopheline inventory for DRC from the earliest documented surveys undertaken by Belgian malariologists during the first decades of the last century through to the present day.

5.2 Data assembly

We first ran on-line searches of medical literature databases including PubMed, Google Scholar and Web of Science using search terms "Anopheles AND Congo" and "Anopheles AND Zaire" for all study publications after January 1966 and post the last searches undertaken by MAP [Sinka et al. 2010]. We searched all on-line publications on malaria in the DRC from the historical archive maintained by the library services of the Institute of Tropical Medicine, Antwerp [http://lib.itg.be/], the Wellcome Trust Library in London [https://catalogue.wellcomelibrary.org/] and the Institute Pasteur, Paris [http://www.pasteur.fr]. The Antwerp library service proved to be an invaluable resource allowing remote access to all volumes of the *Annales de la Société Belge de Médecine Tropicale* since 1920. In addition, we made manual searches of unpublished archive material held at the Tropical Institute in Antwerp, Institute Pasteur in Paris and all unpublished archive material held WHO libraries in Geneva and Brazzaville. Finally, we contacted local entomologists working in university faculties, supporting PMI vector control or providing technical assistance to the mining sector to provide any additional data from unpublished sources, post-graduate student theses and routine monitoring reports.

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

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

[50] The original database for this work could not be located. AFRO have been contacted as this exercise was repeated in seven African countries and represents an important resource.

complex or species levels, whether adults or larvae were collected, 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 (morphological keys, Polymerase Chain Reaction (PCR), Chromosome Banding Sequences (CBS), DNA probes or enzyme electrophoresis) and the full citation source. All species and sibling species names were recorded whether implicated in transmission or not. Care was taken to ensure that sites that were reported several times by the same or different authors in different reports were collapsed to single site records with multiple citations. Records at the same site were included multiple times only when separated by at least three years. A complete database is provided with this report.

5.3 Distribution of Anopheles

The final database contained 670 site/time specific reports of anopheline malaria vector occurrence between 1906 and 2013. 123 (18.4%) sites were investigated before 1940 and 531 (79%) of locations were investigated before 1960. 115 (17%) locations were sampled after 1980 including only 71 (10.6%) since 2000, mostly in Kinshasa. Under Belgian colonial rule there were extensive surveys of anopheline populations and habitats across the country. Many surveys were unpublished but assembled during reviews undertaken first by Dr Duren [Duren, 1938] and later by Lips and others [Lips, 1960; Rahm & Vermylem, 1966]. Notable published works included the extensive surveys by Dr J Schwetz between 1921 and 1946 [Schwetz, 1930; 1933; 1938; 1939; 1941a; 1941b; Schwetz et al., 1947a; 1947b]. Of all the surveys in the database, we were unable to geo-locate 22 (3.3%) of the survey sites.

Over the last 100 years a diverse range of anopheles has been described in DRC[51], in part because of the country's rich bio-diversity. Many species were first identified in the DRC and some are almost uniquely found in DRC, including *An. symesi*, *An. faini*, *An. concolor*, *An. vinckei*, *An. kingi* and *An. dureni* [Gilles & Demeillion, 1968]. The data search identified over 45 species or sibling species of anopheles reported since 1905, listed below:

An. ardensis Theobold, 1905
An. argenteolobatus Gough, 1910
An. brunnipes Theobold, 1910
An. christyi Newstead & Carter, 1911
An. concolor Edwards, 1938
An. coustani coustani Laveran, 1900
An. coustani tenebrosus Donitz, 1900
An. coustani ziemanni Grünberg, 1902
An. cydippis De Meillion, 1931
An. demeilloni Evans, 1933
An. distinctus (Newstead & Carter), 1911

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[51] Sampling sites across DRC were extensive and comprehensive with the exception of the forested areas of the Congo Basin, noted as an area requiring further investigation during the 1960s [Rahm & Vermylem, 1966].

An. dureni dureni Edwards, 1938
An. dureni millecamps Lips, 1960
An. faini Leleup, 1952
An. funestus Giles, 1902
An. *gambiae* Giles, 1902
An. hancocki Edwards, 1929
An. hargreavesi Evans, 1927
An. implexus Theobald, 1903
An. kingi Christophers, 1923
An. *leesoni* Evans, 1931
An. longipalpis Theobald, 1903
An. maculipalpis Giles, 1902
An. marshalli Theobald, 1903
An. mortiauxi Edwards, 1938
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. quadriannulatus Theobold, 1911
An. rhodesiensis Theobald, 1901
An. rivulorum Leeson, 1935
An. rufipes Gough, 1910
An. rodhaini Leleup & Lips, 1950
An. schwetzi Evans, 1931
An. seydeli Edwards, 1929
An. squamosus Theobald, 1901
An. symesi Edwards, 1928
An. tenebrosus DÖnitz, 1902
An. theileri Edwards, 1912
An. vanhoofi Wanson & Lebied, 1945
An. walravensi Edwards, 1930
An. wellcomei Theobald, 1904
An. ziemanni Grunberg, 1902

The important, confirmed dominant vectors of malaria include *An. gambiae* s.l. and *An. funestus* s.l. with more minor roles played by *An. moucheti* [Wanson et al., 1949; Antonio-Nkondjio et al., 2002; 2007; 2008; 2009], *An. coustani* s.l. [Lambrecht, 1954,] *An. nili* s.l. [Lejeune, 1958] and *An. pharoensis*. The distribution of these vectors, as reported in the surveys identified during our literature search, is shown in Figure 5.1. *An. marshalli* [Vinke et al., 1957; Bafort, 1985], *An. paludis* [Karch & Mouchet, 1992] and *An. rufipes* are either very focal in nature or do not contribute significantly to transmission.

Figure 5.1: Spatial distribution of reported observations of adult or larval stages of a) *An gambiae* s.l.; b) *An funestus* s.l., c) *An moucheti* s.l., d) *An nili* s.l., e) *An coustani*, f) *An pharoensis.*
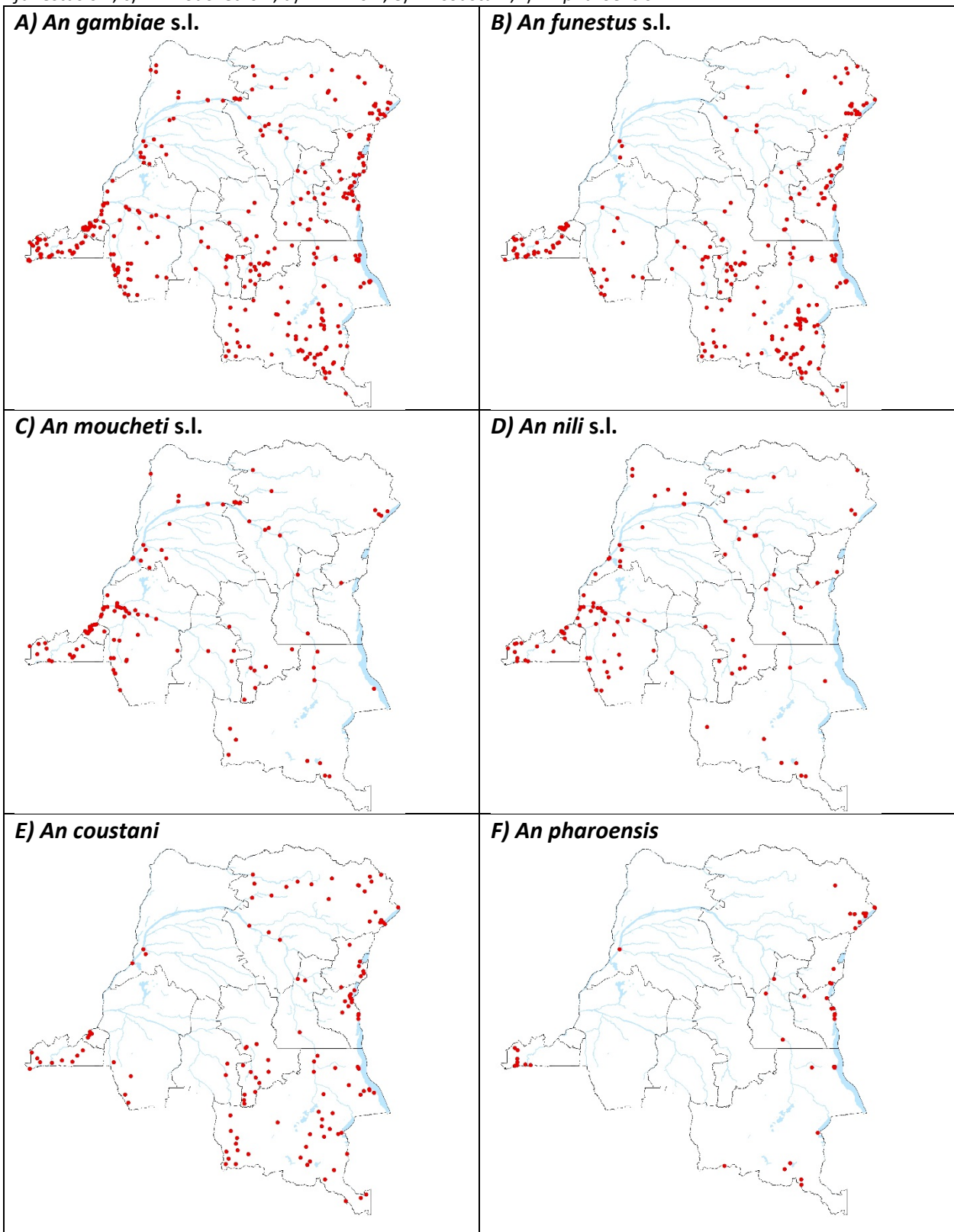
***Anopheles gambiae* s.l.** (Figure 5.1.a; 448 site-time identifications): For older survey data it is recognized that there is a degree of taxonomic ambiguity. The *Anopheles gambiae* complex was only fully categorised in 1998 following the genetic distinction of *An. quadriannulatus* species B and designated a separate species after this date [Hunt et al., 1998; Harbach, 2004]; recently named *An. amharicus* [Coetzee et al., 2013]. The *Anopheles gambiae* complex comprises eight members of which *An. gambiae*, *An. coluzzii* and *An. arabiensis* are major malaria vectors, *An. merus*, *An. melas* and *An. bwambae* are minor/localised vectors, and *An. quadriannulatus* and *An. amharicus* are not known to transmit malaria. *An. merus*, *An. amharicus* and *An. bwambe* have not been described in the DRC. There is one report of *An. melas* at Banana, a coastal town in the Bas-Flevre region [Rahm & Vermylem, 1966]. Given that the majority of the data pre-date effective taxonomy between the sibling species of the complex the relative contributions of *An. gambiae* s.s. and *An. arabiensis* cannot be established. However, recent molecular studies of *An. gambiae* s.l suggest that *An. gambiae* s.s. predominates and while M and S forms have been detected the S form is dominant in Kinshasa and Kisangani [Watsenga et al., 2003; 2004; 2005].

Anopheles gambiae s.s. larvae typically inhabit sunlit, shallow, temporary bodies of fresh water such as round depressions, puddles, pools and hoof prints. This aspect of their bionomics may allow members of the *An. gambiae* complex to avoid most predators, and the larvae are able to develop very quickly (*circa* 6 days from egg to adult under optimal conditions). *An. gambiae* s.s has been reported from habitats containing floating and submerged algae, emergent grass, rice, or 'short plants' in roadside ditches and from sites devoid of any vegetation. It is considered to be highly anthropophilic, with many studies finding a marked preference for human hosts. This vector typically feeds late at night and is often described as an endophagic and endophilic species, *i.e.* biting and resting mostly indoors. The species is considered to be one of the most efficient vectors of malaria in the world.

Anopheles 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, although very little is known about its current distribution in the DRC. 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. *An. 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 are reported to begin between the early evening (19:00) and early morning (03:00). This species usually has a greater tendency than *An. gambiae* s.s. to bite animals and to rest outdoors.

***Anopheles funestus* s.l.** (Figure 5.1.b: 283 site-time identifications): The exact composition of the *An. funestus* complex (*An. funestus* s.s., *An. parensis*, *An. vaneedeni* and *An. rivulorum*) remains unclear without molecular identification techniques. Only *An. funestus* s.s. is implicated

in transmission, while other sibling species have either no role or only limited roles in transmission. We have assumed that reports of *An. funestus* were all *sensu stricto*. 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 and endophagic feeding behaviours are 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, endophagic 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.

Anopheles moucheti (Figure 5.1.c: 128 site-time identifications): *An. moucheti* is a species with two morphological forms: *An. moucheti moucheti*, and *An. moucheti nigeriensis* which are distinguishable by morphological features of the adult and larval stages [Gillies & De Meillon, 1968]. *An. moucheti nigeriensis* seems to be restricted to a few areas of Southern Nigeria and Gabon [Holstein, 1951]. *An. moucheti bervoetsi*, previously considered a third morphological form, has recently been raised to full species status, *An. bervoetsi*, and has only been described at Tsakalakuku in the DRC [Antonio-Nkondjio et al., 2008]. *An. moucheti* is a poorly studied species, however it appears to be entirely restricted to forested areas [Antonio-Nkondjio et al., 2007], specifically where the canopy is broken allowing sunlight to penetrate to the ground and often is found where large rivers flow through the forest [Gillies & De Meillon 1968]. Deforestation may decrease the density of *An. moucheti* and lead to replacement by *An. gambiae* s.l. [Antonio-Nkondjio et al., 2009; Manga et al., 1995]. *An. moucheti* larvae are found at the edges of large, slow flowing rivers, often with turbid waters. Antonio-Nkondjio et al. (2009) studied the larval habitats along the river networks of southern Cameroon and found the greatest numbers of *An. moucheti* larvae along the margins of rivers within deep, evergreen forest, substantially fewer in the degraded forest and none in the savannah areas. This vector is highly anthropophilic and depicts endophilic behaviour [Mouchet & Gariou, 1966] which might be derived from the fact that there are few domestic animals within forested environments [Gilles & De Meillion, 1968]. Only two studies have examined the biting cycle of *An. moucheti*, with both reporting biting gradually increasing towards the second half of the night to dawn [Antonio-Nkondjio et al., 2002; Mattingly, 1949]; Mattingly (1949) reports peak biting activity in the early morning between 03:15 and 06:15. Sporozoite rates vary significantly between sampled sites but average 2% [Vincke & Parent, 1944; Manga et al., 1995].

Anopheles nili (Figure 5.1.d: 112 site-time identifications): The *An. nili* complex includes *An. carnevalei, An. nili* s.s., *An. ovengensis* and *An. somalicus. An. nili* s.s. is among the most important malaria vectors in sub-Saharan Africa. It has a wide geographic distribution range spreading across most of West, Central and East Africa mainly populating humid savannas and degraded rainforest areas but the complex in the DRC appears to have a distinctive genetic

structure [Ndo et al., 2010]. It is considered to be strongly anthropophilic [Gillies & de Meillon, 1968; Costantini & Diallo, 2001; Awono-Ambene et al., 2004; Dia et al., 2003; Antonio-Nkondjio et al., 2002; 2006], and will readily feed both indoors and outdoors [Carnevale & Zoulani, 1975; Krafsur, 1970; Coene, 1993; Brunhes et al., 1999]. It is sometimes found biting outdoors in the early evening when people are socialising and then continues to bite indoors once people move inside, with peak feeding occurring before midnight. Forest populations are usually highly anthropophilic and feed regularly indoors whereas savanna populations are more exophilic and exophagic [Awono-Ambene et al., 2004; Dia et al., 2003; Antonio-Nkondjio et al., 2002; 2006]. Despite feeding preferentially on humans, this mosquito can be at times highly zoophilic [Carnevale et al., 1975; Krafsur 1970]. *An. nili* is usually responsible for transmission in villages close to rivers, but its abundance rapidly decreases within a few kilometres from the breeding sites [Brunhes et al., 1999]. It is also present at the periphery of urban areas. Larvae thrive at the sunny edge of fast running streams and rivers, where floating vegetation and debris provide suitable shelters. The prevalence of *Plasmodium* infections in wild females typically ranges between 1% and 3% and transmission rate reaching 200 infective bites/human/year have been reported in the literature for *An. nili* [Carnevale & Zoulani, 1975; Antonio-Nkondjio et al., 2006; Awono-Ambene et al., 2009].

Anopheles coustani (Figure 5.1.e: 132 site-time identifications): *An. coustani* is widespread across much of Africa although not described in Mauritania or Niger. In west and central Africa, the *ziemanni* form is exclusively found along the coast and coexists with the typical form [Hamon, 1951]. Larvae are found in extremely varied locations: swamps, ponds, edges of lakes and rivers, rice fields, grassy pools temporary, hollow rock, *etc.* and can also proliferate in manmade habitats. They can tolerate a slight salinity *(An. coustani ziemanni)* and develop in those habitats where the water temperature drops until 4°C overnight (*An. coustani typicus*) [Gilles & De Meillion, 1968]. Adults are exophilic over most of its range and it is known to enter lighted tents probably for the purpose of resting [Haddow, 1945]. *An. coustani ziemanni* is thought to be an aggressive outdoor biting vector, especially during the early hours of the evening at the edges of rivers [Fornadel et al., 2011]. Vincke (1946) captured large numbers on human bait in a marsh near Lubumbashi and reports one gland and one stomach infection in 1,407 dissections. *An. coustani* s.l. has been shown to display both exophagic tendencies, along with early evening foraging behavior in Zambia [Fornadel et al., 2011], Nigeria [Hanney, 1960], Mozambique [Mendis et al., 2000] and Ethiopia [Taye et al., 2006]. *An. coustani* displays peak biting outdoors before 21:00, being most active from 20:00 to 21:00 with its biting activity steadily declining throughout the night. The combination of outdoor and early evening foraging behavior for this species could increase its potential as a secondary vector in areas where indoor control measures such as indoor residual spraying or ITNs are employed. The *An. coustani* complex in Macha, Southern Zambia, has demonstrated unexpectedly high anthropophily, whereas it has been found harboring sporozoites in Katanga in the DRC [Vincke, 1946], Tanzania [Gillies, 1964] and Kenya [Mwangangi et al., 2013].

Anopheles pharoensis (Figure 5.1.f: 53 site-time identifications): *An. pharoensis* is primarily a species of large vegetated swamps; also found along lakeshores and among floating plants, reservoirs, rice fields, streams, ditches and overgrown wells. Largely a swamp breeder

throughout its range; Schwetz (1941c) found it in very large numbers associated with the aquatic weed *Ceratophyllum demersumIt*. It is a variable species both in morphology and bionomics, adults have varying behaviors depending on the region in which they are found; sometimes anthropophilic, sometimes zoophilic, sometimes endophilic or exophilic [Zahar, 1975; 1989; Mouchet et al., 2008]. *An. pharoensis* bites humans and animals indoors or outdoors, and rests outdoors after feeding [Mouchet et al., 2008]. It feeds from dusk to dawn with a peak at about 01:00h. A peculiarity of *An. pharoensis* is that it may occur in very large numbers for several nights and then disappear for long periods from a particular area. It is the major vector of malaria in Egypt, but its role as a malaria vector is minor elsewhere. There is evidence from Egypt that it may be blown for comparatively long distances on a prevailing breeze; a phenomenon which is presumed to have caused a malaria epidemic in Israel in 1959 [Garret-Jones, 1962]. *Plasmodium falciparum* infection rates in *An. pharoensis* ranges from 0.5% in Senegal [Carrara et al., 1990] to 1.3% in Kenya [Mukiama & Mwangi, 1989].

5.4. Insecticide resistance

In 2009, four sites[52] were selected for bio-assay and molecular testing of pyrethroids (deltamethrin, permethrin, lambdacyhalothrin), organochlorines (DDT) and organophosphates (malathion) using wild caught *An. gambiae* s.s. [Kanza et al., 2013]. Reduced kill rates were shown at all sites to DDT and at three sites for all the pyrethroids tested, except Kisangani where *An. gambiae* s.s. was susceptible to all three pyrethoids tested. The L1014F *kdr* gene, that confers resistance to pyrethroids and organochlorines, was confirmed at each site. Malathion proved effective across three sites, with phenotypic evidence of reduced sensitivity at Katana. The molecular marker for organophosphate and carbamate resistance, ace-1^R resistance alleles, were not found at any site [Kanza et al., 2013].

Permethrin, deltamethrin, bendiocarb, propoxur and DDT were all tested against *An. gambiae* s.s. at Kindele and Kimbangu, Kinshasa in 2010. Resistance was noted for both DDT and permethrin, mortality rates of 27.3 and 75.8%, respectively, and investigators identified *kdr* mutations (L1014F) [Bobanga et al., 2013]. Studies undertaken between October 2010 to January 2011 at nine sites in four provinces[53] showed variable sensitivities of *An. gambiae* s.l to Deltamethrin, Permethrin, Bendiocarb and Propoxur. At 7/9 sites DDT resistance was described and at 5/7 sites permethrin resistance was reported. At all sites sites, Deltamethrin, Bendiocarb and Propoxur showed high 24-hour mortality rates against tested vectors [Bobanga, unpublished data].

The National Institute of Biomedical Research (INRB), with support from PMI, established four sentinel sites[54] to monitor vector behaviors and insecticide resistance at [PMI, 2014]. Bioassay

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[52] Kimpese and Kisangani (Bas Congo), Bolenge (Equateur) and Katana (Sud Kivu)

[53] North Kivu (Goma & Butembo), Katanga (Lubumbashi & Kapolowe), Bandundu (BandunduVille & Kikwit) and Equateur (Bolenge, Wendji Secli & Bongonde Cité)

[54] Lodja (Kasai Oriental), Kabondo (Haut Congo), Tshikaji (Western Kasai) and Kapolowe (Katanga)

results from these sites in 2013 using *An. gambiae* s.l suggested that deltamethrin and permethrin showed signs of resistance at all sites, resistance to DDT was evident at the one site it was tested at in Kabondo. Local *An. gambiae* s.l. were sensitive to fenitrothion and bendiocarb at all sites [PMI, 2014]. Conversely, at two Zones de Santé (Kailo and Kibombo) in Maniema Province, deltamethrin, permethrin and lambda-cyhalothrin all showed 100% mortality rates against *An. gambiae* s.l. in 2013 [Watsenga & Manzambi, 2014].

6. Conclusions and future recommendations

6.1 Defining the spatial extents of P. falciparum risk

Empirical data have been used to stratify the spatial extent of malaria transmission intensity across DRC for 2007 and highlight information gaps that could be addressed with improved data.

DRC experiences a predominantly hyper-endemic to holoendemic malaria epidemiology across the country with over $2/3^{rds}$ of the population living in areas where the PAPfPR$_{2-10}$ is >=50% (Figure 4.8). 6% of the population live in areas free from malaria owing to very low ambient temperatures that limit sporogyny in vector populations at high altitudes. Hypoendemic transmission is virtually absent with roughly 0.2% of the population in regions where PAPfPR$_{2-10}$ is <10%. Areas of lowest transmission are located in the higher altitude eastern provinces bordering Rwanda and Burundi (Figure 4.8). Comparison of data of PAPfPR$_{2-10}$ between 1939 (Figure 4.10) and 2007 shows that there has been a reduction in risk across most of the country over the last 80 years, however transmission has remained consistently high (PAPfPR$_{2-10}$ >=75%) in the northernmost regions of the country.

Although over 400 unique PfPR$_{2-10}$ estimates have been used to define spatial risk of malaria in 2007, there is a paucity data representing difficult to access, predominantly forested areas. PAPfPR$_{2-10}$ data from special risk groups, notably displaced populations, are also sparse.

We have only been able to model risks to the year 2007, where most recent data predominate (Figure 4.6), this should be seen as a "baseline" risk map as most ITN activity and distribution has occurred after this date.

In 2013-2014 a national household sample survey included malaria infection prevalence. Accessing these data, to provide a new modelled prediction, for the year 2014 is critical and should be combined with any additional survey data from sentinel sites surveyed for infection prevalence since 2007. This would provide a basis of changing risk since 2007. The INFORM team will re-model these data if made available by September 2014 (**Action Point 1**).

Population data used in defining the Population Adjusted Prevalence (PAPfPR) are projected from the 1984 census (Section 2.5). These are likely to be inaccurate given the huge amounts of population displacement over the last two decades. Finer, more recent resolution population

data are urgently needed for all areas of development planning, however, it is not clear when the next national census will be undertaken.

Given DRC's political, economic and social status, additional data layers are necessary to effectively plan a malaria control service. Notable among these are an estimated 2.6 million internally displaced and over 450,000 refugees (Section 2.6). The communities who inhabit the country's densely forested areas (Section 2.3) are not easily accessible to services and deforestation may lead to a changing malaria ecology. The mining sector (Section 2.4) not only alters the local malaria landscape but also provides unique opportunities to engage private sector corporations in the control of malaria, for which the DRC has a long history (Section 3). These special groups need better, more reliable mapping and enumeration for sub-national disease control planning (**Action Point 2**).

There has been a tradition of urban malaria control from the time of Belgian colonial occupation through to the USAID funded projects in Kinshasa during the 1990s (Section 3). There is thought to be a rapid urban growth in the DRC, in part a result of insecurity in the rural areas. Without more recent census information this urban expansion has been hard to map. Given that an estimated 34% of the population currently live in urban areas it would be appropriate to develop a programme of work that examines urban malaria risks and opportunities for control (**Action Point 3**).

6.2 Decision making units for planning malaria control

Efforts have been made here to accurately define decision-making units and to apply stratifications of malaria transmission to these units (n = 512) (Section 2.7). It is hoped that these empirical stratifications of malaria will aid peripheral level planning of malaria control.

Support to the health sector is highly dependent on ODA and its delivery, rooted in a highly federal system, is segmented according to the priorities of the multiple partners across regions and decentralized zones. There are currently five overseas funding partners and their operational partners that oversee the delivery of health care and malaria interventions across the country. Still, 50 Zones de Santé have neither funding nor operational support for malaria control. Malaria control activities can be improved across the different partners based on epidemiological and intervention needs assessments derived at the Zones de Santé levels.

We have not tackled intervention coverage in this report. This requires an assembly of ITN distribution data and the most recent household coverage data. This can be done when the later become available for analysis and will be attempted by September 2014 (**Action Point 4**)

6.3 National capacity for epidemiological surveillance

Sentinel surveillance was initiated by the PNLP in 2003 to: a) provide readily accessible data on the trends of defined malaria indicators that are not collected by the routine health information systems, b) to monitor the percentage of malaria cases confirmed by microscopy, and c) to

monitor of antimalarial drug resistance particularly those related to sporadic outbreaks of malaria. An estimated 33 surveillance sites were selected in 2003 but to date only 11 sites have been operationalized and only four of these are monitoring vectors and insecticide susceptibility. Treatment seeking and coverage of interventions are monitored through national household sample surveys of which here have only been two DHS and one MICS surveys.

There are plans to include more detailed information on the basic epidemiology of malaria within revised plans of sentinel site surveillance. Given the paucity of nationally representative data on malaria prevalence and vector species distributions this should be actively encouraged and properly funded. However, given the country's size and diversity other more rapid surveillance techniques might also be included in future monitoring and evaluation strategies, including school based surveillance of infection and rapid vector surveillance methodologies (**Action Point 5**).

6.4 Health service mapping needs

The last comprehensive national map of health facilities was produced in 1953. More recent health facility mapping efforts in DRC are limited and fragmented (Section 2.8). A few health delivery partners have mapped facilities within their areas of interest but these efforts are not uniform and do not cover the whole country.

The absence of a geo-coded national level master health facility list, covering the multiple service providers across the country, is a major rate limiting step in designing health sector initiatives (including malaria control), providing a logistics and management platform for the adequate delivery of clinical commodities and the informed use of health information[55].

We have attempted to combine some facility data derived from the WHO and the National Programme for the Control of Human African Trypanosomiasis (Section 2.8) but the coverage of these is clearly inadequate. It will be essential to combined various existing health facility lists and provide geo-coordinates for each of the estimated 71,000 health service providers in the country and initial work has begun and will be provisionally available in September 2014 (**Action Point 6**).

The health system is characterised by multiple NGO providers of health care without central control of the care delivered. In many cases it is not clear what populations or how many people they are reaching and it has been difficult to monitor the extent to which they are following national guidelines for the delivery of care. Mapping the private sector's health care will be as important as mapping public sector providers. This is beyond the current scope of

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[55] 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 time and space require layers of GIS and HMIS linked data to provide higher resolution information for planning and monitoring malaria control.

work but should form part of future Ministry of Health and partner activities, especially in urban areas (**Action Point 7**).

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 the DRC; and therefore a reference source to the final curated database.

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 library services of the Institute of Tropical Medicine, Antwerp [http://lib.itg.be/], 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 "*Congo*" and "*malaria*" and "*Zaire*" 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 April 2014.

Titles and abstracts from digital searches were used to identify possible parasite cross-sectional survey data undertaken since 1900 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, the Bodleian library at the University of Oxford and the library and archive the Wellcome Trust, UK and the Tropical Medicine Institute in Antwerp. 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 Tropical Medicine library in Antwerp and the World Health Organization (WHO) libraries in Geneva and Brazzaville at separate archive locations as Project, Country and Parasitology Department files. Data from the parasite surveys undertaken during the DHS in 2007 were provided by Dr Steve Meshnick. Malariologists who work in the DRC were also contacted individually to provide unpublished data from survey work in Kinshasa, Haut-Katanga, Kolwezi, Haut-Uele, Maniema and Ituri (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]. Old Belgian names for towns and villages were checked s they conformed to today's naming using the following blog space http://www.kosubaawate.blogspot.com/

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 1152 survey estimates unique locations where malaria infection prevalence had been recorded between June 1914 and September 2013. We were unable to geo-locate seven survey locations, there were no survey locations exceeding 5 km^2 nor any repeat surveys in the same location within 6 months. Five surveys sampled less than 10 people, important for survey estimate precision [Gregory & Blackburn, 1991; Jovani & Tella, 2006] and were excluded.

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., 2007].

Of the 1140 unique time-space *P. falciparum* survey locations identified through the data search strategy described above, 564 (50%) were abstracted directly from journal publications, 298 (26%) derived from the national sample surveys of 2007, 194 (17%) were obtained through the provision of unpublished raw data, 182 (7%) were obtained from other reports or those developed by the MoH, 6 (0.5%) were obtained from a master's thesis and one from conference abstracts. Survey data were located for time-space survey data points using GPS (168, 15%), on-screen digitization using maps in reports (550, 48%), Encarta (325, 29%), Google Earth (66, 6%), GeoNames (22, 2%), other digital place names sources, e.g. schools and village databases (14, 1%).

All surveys undertaken before 2000 used microscopy for parasite detection. Since 2000, 163 surveys have used only Rapid Diagnostic Tests, without slide confirmation in Kinshasa (SD

Bioline) and Haut-Katanga (Paracheck). 18S-ribosomal based real-time PCR was used during the 2007 national survey of adult infections at 298 locations included in the analysis[56]

The distributions of the data are shown in section 3 of the report and highlight the high margin of survey data between 1929 and 1949, peaking in 1939 and between 2007 and 2013 peaking in 2007. For these reasons were have elected to restrict our modelling work to predictions using the town partitioned data sets, shown in Figures A.1.a and A.1.b for 1929-49 and 2007-13.

Figures A.1 (a) location of data 1929-1949 (n = 477) used to make predictions of risk in 1939 and (b) locations of data 2007-2013 (n = 421) used to make predictions to the year 2007 (darker green higher $PfPR_{2-10}$)

a)

b)
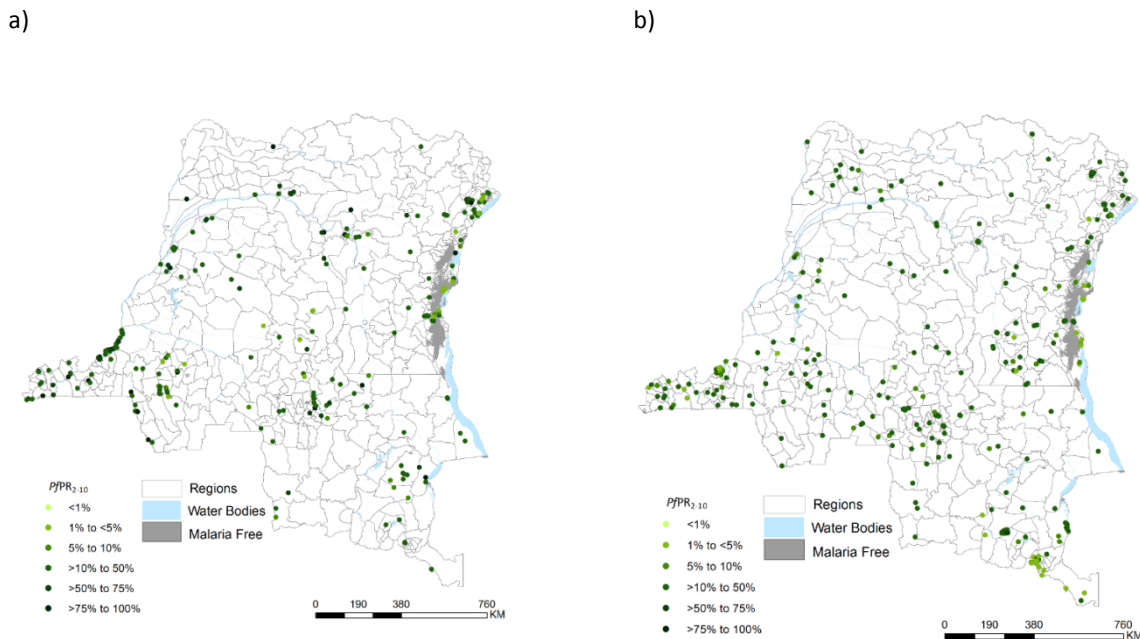
A.2 Model development

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].

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[56] Recent evidence from Burkina Faso's 2010-2011 DHS suggests that RDT's might have low specificity and over-estimate malaria prevalence during community surveys [Samadoulougou et al., 2014]. PCR is a highly sensitive technique to detect sub-microscopic infections [Okell et al., 2009], conversely the quality of microscopy between surveys and laboratory technicians is also very variable [O'Meara et al., 2006]. There is no obvious solution to accommodating the precision of malaria parasite detection techniques between surveys in space or over time from different survey sources

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][57]; 2) *Temperature Suitability Index* (TSI) as a continuous variable ranging from 0 to 1 (Figure 2.2c); 3) Synoptic mean monthly precipitation raster surfaces at 1 × 1 km resolution, downloaded from the WorldClim website [http://www.worldclim.org/] (Figure 2.2a); 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 [Figure 2.2b; Scharlemann et al., 2008]; and 5) Urbanisation developed from information from the Global Rural Urban Mapping Project (GRUMP) [Balk et al*.,* 2006] and the Afripop project [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$_{2-10}$ 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.

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[57] 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]

The relationship of *Pf*PR$_{2-10}$ with temperature, TSI, EVI, precipitation and urbanisation were all tested against the *Pf*PR$_{2-10}$ data 1929-1949 and 2007-2013 separately. Analysis showed for the 1929-1949 TSI provided the best fit model: coefficient 0.563 (95% CI: 0.434, 0.693, P<0.001). For the 2007-2013 data series precipitation and EVI provided the best fit model: coefficient 0.002 (95% CI: 0.0009, 0.004, P<0.001) and coefficient 1.30 (95% CI: 1.02, 1.58, P<0.001)). To allow for direct comparisons of the mapped outputs we used all the three covariates TSI, EVI and precipitation) in the both time series.

A.2.2 PfPR$_{2-10}$ 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 *Pf*PR$_{2-10}$ at 1 × 1 km spatial resolution for year 1939 and 2007 using data from 1929 to 1949 and 2007 to 2013 respectively. 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

$$(k^2 - \Delta)^{\alpha/2}(\tau x(u) = W(u), \quad u \in \circ^{d}, \quad \alpha = v + d/2, \quad \sigma^2 - \Gamma(v)(\Gamma(\alpha)(4\pi)^{d/2}k^{2v}\tau^2)^{-1}$$
$$k > 0, \ v > 0,$$

(Equation A.2.1)

This SPDE is a Gaussian random field with Matérn covariance function where W, is the spatial Gaussian white noise process, Δ is the Laplacian, α controls the smoothness of the realizations and τ controls the variance. The link between Matérn smoothness v and variance σ^2 is $\alpha = v + d/2$ and $\sigma^2 = \Gamma(v)(\Gamma(\alpha)(4\pi)^{d/2}k^{2v}\tau^2)^{-1}$, 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 $u = (u_1 \mathrm{K} \ \mathrm{K}, u_n)'$ 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

$$\pi(\mathrm{u}) = (2\pi)^{-n/2}|Q|^{1/2}\exp(-\frac{1}{2}(\mathrm{u}-\mu)'Q(\mathrm{u}-\mu))$$

(Equation A.2.2)

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

$$x(u) = \sum_{i=1}^{n} \psi_i(u) w_i \quad , \qquad \text{(Equation A.2.3)}$$

where w_i represents the Gaussian distribution 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 phenomenas 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]. The non-stationarity assumption l 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 $\circ^{d}$ is expressed as

$$C(u,v) = \frac{\sigma^2}{2^{v-1}\Gamma(v)} (k\|v-u\|)^{v} K_v(k\|v-u\|) \ , \qquad \text{(Equation A.2.4)}$$

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

$$(k(u)^2 - D)(t(u)x(u)) = W(u) \ , \ u \in \circ^{2} \ , \qquad \text{(Equation A.2.5)}$$

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.

$$\log(k^2(u)) = \sum b_i^{(k^2)} \mathrm{B}_i^{(k^2)}(u) \text{ and } \log(\tau(u)) = \sum \beta_i^{(\tau)} \mathrm{B}_i^{(\tau)}(u),$$ (Equation A.2.6)

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

$$y(s,t) = z(s,t)\beta + \xi(s,t) + \varepsilon(s,t),$$ (Equation A.2.7)

This model is characterised by a GF *y(s, t)* built from covariate information *z(s,t)*, measurement error $\varepsilon(s, t)$, and a second order autoregressive dynamic model for the latent process $\xi(s, t)$ with spatially correlated innovations $\omega(s, t)$. 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 $j = 1 \ldots m$, $z(s_i,t_j) = (z_1(s_i,t_j) \mathrm{K} \; z_p(s_t,t_j))$ represents fixed effect from the covariates for cluster s_i at time t_j, $\beta = (\beta_1 \mathrm{K}, \beta_p)'$ is the coefficient vector, $\varepsilon(s_i,t) \sim N(0,\sigma_\varepsilon^2)$ 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 (A.2.3), 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 PfPR$_{2-10}$ 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$_{2-10}$ input locations to the triangles on the mesh defined by $\eta^* = A(x + 1\beta_0)$ 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 PfPR$_{2-10}$ maps are shown in Figures A.2. a for 1939 and A.2. b for 2007.

A series of model uncertainty and validation statistics were generated to assess model performance. For each prediction year, the standard deviations of PfPR$_{2-10}$ 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[58].

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[58] 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

The MPE, MAPE and the correlation coefficient of the observed and predicted PfPR$_{2-10}$ for the space time PfPR$_{2-10}$ 1939 model was 1.2%, 15.3 % and 0.79 respectively indicating satisfactory model accuracy; corresponding figures for the 2007 map were 1.1%,18.6 % and 0.70.

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. Of particular importance is the distance of the standard deviation (SD) from the mean, 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 PfPR$_{2-10}$ were computed for the years 1939 (Figure A.3a) and 2007 (A.3b). For 1939 predictions areas most uncertain are in the North West, Bas Congo and South East. The 2007 prediction is least certain in south central areas.

Figure A.2 Continuous 1 x 1 predicted mean PfPR$_{2-10}$ for the year a) 1939; b) 2007

a)   b)
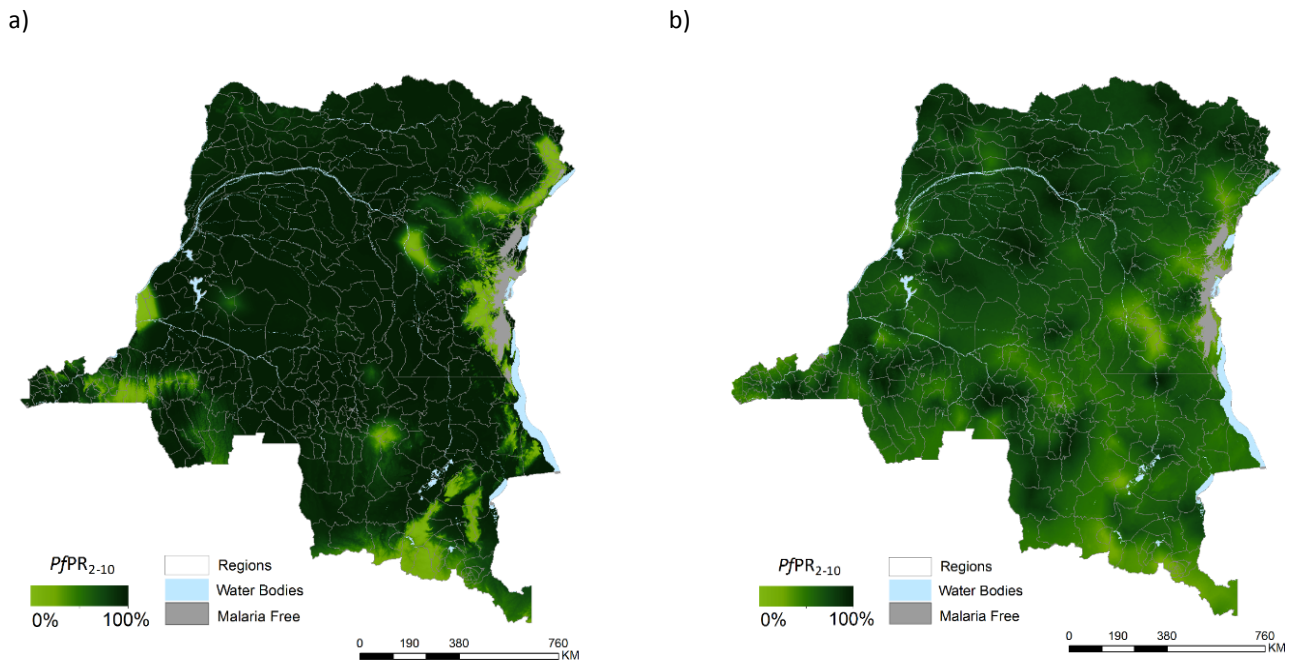
Thiessen polygon so that data located in densely surveyed regions had a lower probability of selection than those in sparsely surveyed regions setting a high threshold for model performance. Sampling and testing hold out sets was done for each regional and time-segmented tile. The Bayesian SPDE using 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.

Figure A.3 Continuous 1 x 1 predicted mean PfPR$_{2-10}$ for the year a) 1939; b) 2007; grey mask represents no malaria risk due to low ambient temperatures
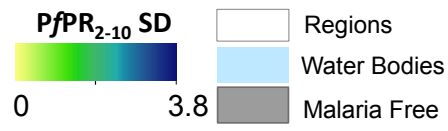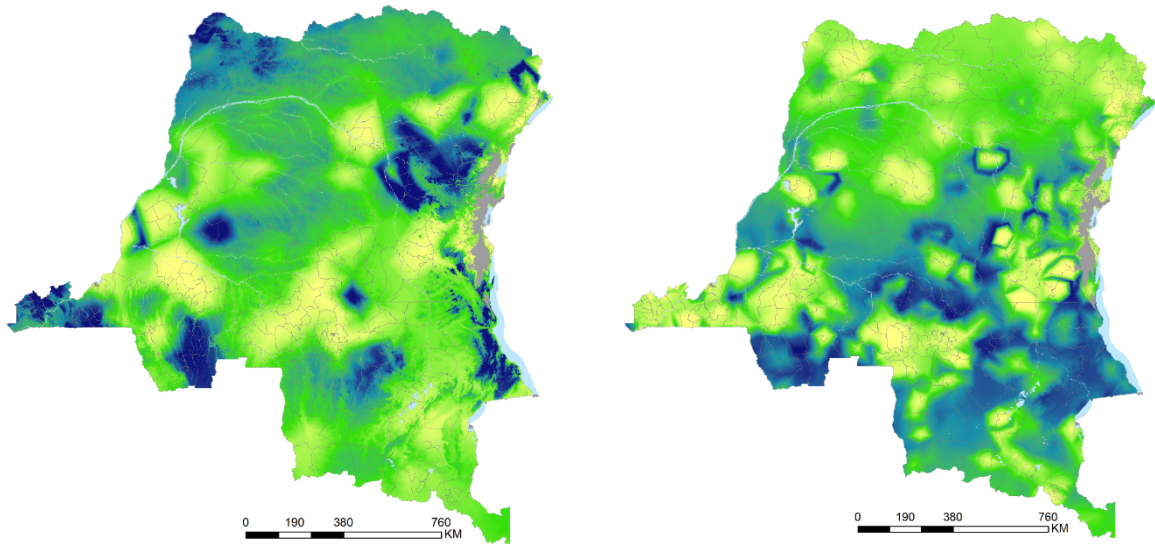
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