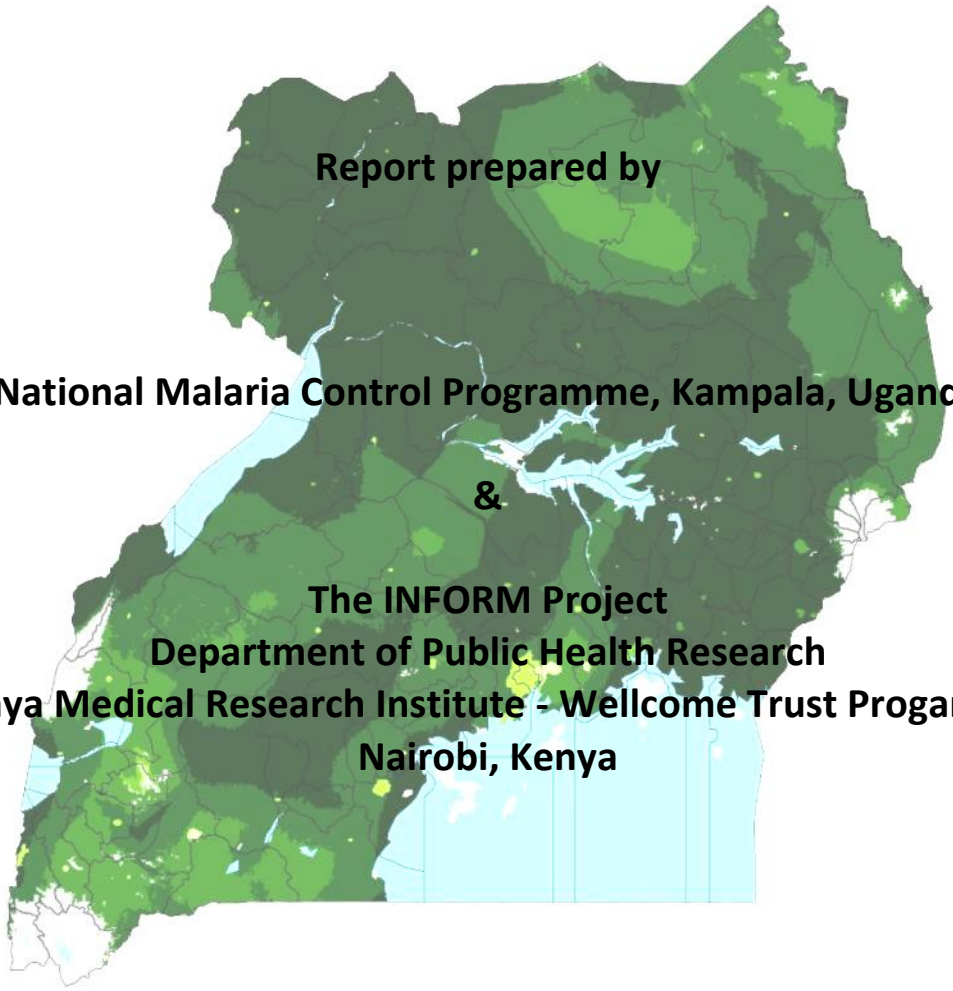
An epidemiological profile of malaria and its control in Uganda



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&

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October 2013

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Acknowledgments

The authors are indebted to the following individuals from the INFORM Project, KEMRI-Wellcome Trust programme: Emelda Okiro, Ngiang-Bakwin Kandala, Caroline Kabaria, Damaris Kinyoki, Stella Kasura and Jonesmus Mutua; We are also grateful to the help provided by Andrew Balyeku in geo-coding health facilities in July 2013, Didas Namanya of the ministry of health, planning department for help with administrative unit information, the WHO country office –mTRAC project for parts of the health facility inventory, and Catherine Linard for assistance on modelling human population settlement. We are grateful to the technical leadership of the Uganda Ministry of Health for agreeing to sign the MoU that facilitated this collaborative work.

We acknowledge in particular all those who have generously provided unpublished data, helped locate information or the geo-coordinates of data necessary to complete the analysis of malaria risk across Uganda: Jane Achan, Seraphine Adibaku, Miriam Akello, Paul Ametepi, Martha Betson, Teun Bousema, Simon Brooker, Clare Chandler, Jon Cox, Deborah DiLiberto, Grant Dorsey, Thomas Egwang, Allison Elliot, Francesco Grandesso, Jean-Paul Guthmann, Stephen Hillier, Narcis Kabatereine, Rita Kabuleta-Luswata, Mark Kaddumuka, Ruth Kigozi, Simon Kigozi, Macklyn Kihembo, , Catherine Maiteki-Sebuguzi, Fred Kironde, Steve Kiwuwa, Moses Kizza, Jan Kolaczinski, Steve Lindsay, Caroline Lynch, Godfrey Magumba, Edith Mbabazi, Catherine Maiteki, Dida Manya, Patrick Monami, Levi Mugenyi, Lawrence Muhangi, Charlotte Muheki, Halima Naiwumbwe, Zaria Nalumansi, Ruth Nanyonga, Florence Nankya, Sussann Nasr, Juliet Ndibazza, Gloria Oduru, Ambrose Onapa, Niels Ornbjerg, Erling Pedersen, Carla Proietti, Rachel Pullen, Denis Rubahika, John Rwakimari, Paul Simonsen, James Ssekitoleeko, Sarah Staedke, Claire Standley, Laura Steinhardt, Anna-Sofie Stensgaard, Rus Stothard, James Tibenderana, Henry Wannume, Emily Webb and Adoke Yeka.

The authors also acknowledge the support and encouragement provided by the Ugandan RBM partnership, Dr Alistair Robb, the UK government's Department for International Development (DFID) regional malaria advisor and Dr Thomas Teuscher of RBM. This work was supported by grants from The Wellcome Trust, UK to Professor Bob Snow (# 079080) and Dr Abdisalan Mohamed Noor (# 095127) and a contract between the University of Oxford and RBM with funds provided by DFID-UK.

Suggested citation

National Malaria Control Programme, Abt Associates and the INFORM Project (2013). *An epidemiological profile of malaria and its control in Uganda*. A report prepared for the Ministry of Health, the Roll Back Malaria Partnership and the Department for International Development, UK. October, 2013

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Abbreviations

ACT	Artemisinin Combination Therapy
AFRO	WHO Office for the Africa Region
AJOL	African Journals Online
AL	Artemether-Lumefanthrine
AMFm	Affordable Medicines Facility for malaria
ANC	Antenatal Clinics
ANVR	African Network for Vector Resistance
APRD	Arthropod Pesticide Resistance Database
AQ	Amodiaquine
ARI	Acute Respiratory Infections
BCC	Behavioural Change Communication
BIC	Bayesian Inference Criteria
BMGF	Bill & Melinda Gates Foundation
BOD	Burden of Disease
CAPSS	Consortium for ACT Private Sector Subsidy
CDC	Communicable Disease Control
CDD	Community Drug Distributors
CI	Confidence Interval
CMD	Community Medicine Distributors
CMS	Church Medical Society
CNDPF	Comprehensive National Development Planning Framework
CPC	Climate Prediction centre
CPHL	Central Public Health Laboratories
CQ	Chloroquine
CRDT	Constrained Refined Delaunay Triangulation
DCI	Development Cooperation of Ireland
DCW	Digital Chart of the World's Populated Places
DDT	Dichloro-Diphenyl-Trichloro-Ethane
DFID	Department for International Development
DHS	Demographic Household Surveys
DHSP	District Health Services Project
DHTs	District Health Teams
DVS	Dominant Vector Species
EA	Enumeration Area
EANMAT	East African Network for Monitoring Antimalarial Treatment
EAPHLNP	East Africa Public Health Laboratory Network Project
EAVRI	East Africa Virus Research Institute
EHP	Environmental Health Project
EIR	Entomological Inoculation Rates
ENSO	El Niño Southern Oscillation
EVI	Enhanced Vegetation Index
FAO	Food and Agriculture Organization

FAO	Food and Agriculture Organization
FBO	Faith Based Organizations
FEWS	Famine Early Systems Network
GAUL	Global Administrative Unit Layers
GFATM	Global Fund to Fight AIDs, Tuberculosis and Malaria
GIS	Geographic Information Systems
GLWD	Global lakes and Wetlands
GMEP	Global Malaria Eradication Programme
GMP	Global Malaria Programme
GPS	Global Positioning Systems
GRUMP	Global Rural Urban Mapping Project
GTZ	German Development Cooperation
HBMF	Home Based Management of Malaria Fevers
HC I	Health Centre level one
HC II	Health Centre level two
HC III	Health Centre level three
HC IV	Health Centre level four
HIPC	Heavily Indebted Poor Countries
HIS	Health Information Systems
HMIS	Health Management Information System
HMM	Home-based Malaria Management
HSD	Health Sub-District
HSSPII	Health Sector Strategic Plan II
IBEA	Indian British East African Company
ICCM	Inter-agency Coordinating Committee
IDP	Internally Displaced Persons
IDRC	Infectious Disease Research Collaboration
IDSR	Integrated Disease Surveillance and Response
IEC	Information, Education, Communication
IGME	Inter-Agency Group for Child Mortality Estimation
IMCI	Integrated Management of Childhood Illnesses
IMF	International Monetary Fund
INFORM	Information for Malaria Project - Africa
INLA	Integrated Nested Laplace Approximations
IPR	Infant Parasite Rate
IPTp	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Nets
IVM	Integrated Vector Management
KCC	Kampala City Council
Kdr	Knockdown Resistance
LGDPs	Local Government Development Plans
LLINs	Long Lasting Insecticidal Nets
LT50	Lethal Treatment dose 50% mortality

M&E	Monitoring and Evaluation
MAP	Malaria Atlas Project
MAPE	Mean Absolute Prediction Error
MARA/ARMA	Mapping Malaria Risk in Africa
MBG	Model Based Geo-Statistics
MC	Malaria Consortium
MCMC	Markov Chain Monte Carlo
MCU	Malaria Control Unit
MDA	Mass Drug Administration
MEDS	Malaria Epidemic early Detection System
MeSH	Medical Subject Headings
MEWS	Malaria Early Warning System
MIP	Malaria in Pregnancy
MIS	Malaria Indicator Survey
MODIS	MODerate-resolution Imaging Spectroradiometer
MoH	Ministry of Health
MP	Member of Parliament
MPE	Mean Prediction Error
MPR	Malaria Programme Performance Review
MSAT	Mass Screening and Treatment
MSP	Malaria Strategic Plan
MU-UCSF	Makerere University – University of California San Francisco
NDA	National Drug Authority
NDP	National Development Plan
NDVI	Normalised Difference Vegetation Index
NEMA	National Environmental Management Authority
NGOs	Non-Governmental Organizations
NHS	National Household Survey
NIH	National Institute of Health
NMCP	National Malaria Control Programme
NMS	National Malaria Strategic
NOAA	Night-time Lights Dataset
NPA	National Planning Authority
NRA	National Resistance Army
OA	Open Access
ODA	Overseas Development Assistance
PA $Pf\text{R}_{2\text{-}10}$	Population Adjusted Age-corrected *Plasmodium falciparum* parasite rate
PCR	Polymerase Chain Reaction
PEAP	Poverty Eradication Action Plan
$Pf\text{R}_{2\text{-}10}$	Age-corrected *Plasmodium falciparum* parasite rate
PHPs	Private Health Practitioners
PMI	Presidents Malaria Initiative
PPPY	Per Person Per Year
QAACTs	Quality Assured ACTs

RBM	Roll Back Malaria
RDTs	Rapid Diagnostic Tests
SAE	Small Area Estimations
SAFE	Sunlight Activated Formulated Plant Extract
SAM	Service Availability Mapping
SIMA	System-wide Initiative on Malaria and Agriculture
SMC	Seasonal Malaria Control
SP	Sulphadoxine-Pyrimethamine
SPDE	Stochastic Partial Differential Equations
SPR	Slide Positivity Rates
STG	Standard Treatment Guidelines
TDR	Tropical Disease Research
TPC	Tactical Pilotage Charts
TSI	Temperature Suitability Index
TWGs	Technical Working Groups
UBOS	Uganda Bureau of Statistics
UMRC	Uganda Malaria Research Centre
UMSP	Uganda Malaria Surveillance Programme
UN	United Nations
UNAS	Uganda National Academy of Science
UNBS	Uganda Bureau of Standards
UNCST	Uganda national Council of Science and Technology
UNHCR	United Nations High Commissioner for Refugees
UNICEF	United Nations Children's Fund
UNLA	Uganda National Liberation Army
UNLF	Uganda National Liberation Front
UPC	Uganda People's Congress
UPHOLD	Uganda Program for Human and Holistic Development
USAID	United States Agency for International Development
VCU	Vector Control Units
VHT	Village Health Teams
WHA	World Health Assembly
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme
WRBU	Walter Reed Biosystematics Unit
WWARN	Worldwide Antimalarial Resistance Network

Executive summary

This report is a product of collaboration between the Ugandan National Malaria Control Programme, national control partners and the INFORM Project of the KEMRI-Wellcome Trust Programme in Kenya.

The review has been developed to assist national level partners involved in malaria control to understand the impact of recent scaled intervention coverage, define what is required to achieve universal access and to prioritize future funding needs to meet unmet intervention ambitions or to revise recommendations to accelerate impact.

The report serves as a review of the epidemiological features of malaria in Uganda and how these relate to the context of historical and current malaria control activities.

Uganda has a rich legacy of carefully collected epidemiological data to design control. The skills and appetite for data-driven planning, however, were lost after the global malaria eradication era.

We have resurrected the need for epidemiological data to define malaria control priorities and monitor impact. We have assembled national spatially defined data on malaria parasite prevalence, vector species occurrence, human population settlement, health service location and vector control coverage. These databases should form a national data repository and that should be constantly updated.

Using model based geo-statistical methods we have produced two maps of malaria risk in Uganda, in 2000 and 2010. The maps are based on parasite prevalence in children aged 2-10 years ($Pf\mathrm{PR}_{2\text{-}10}$) and transformed into district population adjusted estimates of risk to review success and programme future control across each of the 112 health districts necessary to plan federal resources.

Malaria transmission in Uganda is best described as hyper-holoendemic, however important differences exist within the national borders. 84% of Uganda's population live in areas where $Pf\mathrm{PR}_{2\text{-}10}$ is greater than 50%.

Anopheles gambiae s.s is the dominant vector species and shows a sympatric distribution with *An. funestus* and less abundant *An. arabiensis*.

Plasmodium falciparum remains the dominant malaria infection, *P. malariae* may have significantly declined over the last 50 years and there is confirmed evidence of local transmission of *P. vivax* in a predominantly duffy-negative population.

Transmission is largely perennial and no areas within Uganda exist that would lend themselves to targeted seasonal malaria control (SMC).

There has been only a modest change in the national intensity of transmission over the last decade.

Transitional areas include areas located in the South Western districts of Uganda, Kampala and modest but perceptible changes in some areas where IRS has been initiated.

Triangulation with limited clinical surveillance and hospital admission data confirms the patterns described by the parasitological data: almost no change in disease burden across much of the country between 2000 and 2010, with the exception of fluctuating risks in the SW highlands and a decline in Kampala.

The mapped coverage of insecticide treated nets (ITN) shows only four districts have exceeded 50% coverage of their populations by 2010. Significant Indoor Residual Spraying (IRS) coverage has only been achieved in eight districts in 2010.

Resistance has been detected to insecticide classes used for IRS, including pyrethroids.

Unlike previous large national control programme activity during the 1960s, efforts to maintain a detailed epidemiological assessment of risk across Uganda, or in relation to specific vector control activities, have been poor over the last decade.

The next decade of control in Uganda must use the evidence provided in this report to define need, plan control and monitor future progress. The structures and policies are now in place to make a significant difference. Funding, however, will be harder to access and demonstrating changes in the epidemiology of malaria descried here for 2010 will be key to the business case for sustained investment as part of any revised national malaria strategic plan.

Chapter 1

Introduction

In 1929, Lt Col. SP James visited Kenya and Uganda and wrote in his report that "*.. there is, as yet, little or no knowledge even of the symptoms and effects of the chronic infestations with malaria parasites from which many native children and adults suffer, to say nothing of the wide gaps in knowledge of regarding the distribution, relative incidence and seasonal prevalence of different species of the malaria parasite*" [James, 1929]. An incomplete knowledge of the basic epidemiological features of malaria transmission has plagued the effective design, planning and measuring the impact of malaria control since these observations were made over 80 years ago.

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. Effective planning of malaria control depends on a reliable understanding of the temporal and spatial determinants of parasite transmission, its seasonal patterns and the dominant vectors implicated in transmission. Epidemiological profiling should form the cornerstone of any effective national malaria strategy planning cycle.

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 ($Pf\text{PR}_{2\text{-}10}$), 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].

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 Uganda in 2011, states that "*The programme has not adopted a system for routine and periodic monitoring of malaria risk in the country*" and that one of the key issues raised by the MPR was that "*The lack of risk mapping (including using routine data) makes it difficult to identify populations at highest risk and targeting of interventions to these populations*". As a result the MPR concludes as one of the key action points "*The malaria programme should plan for and conduct periodic risk assessments and mapping in order to assist intervention targeting*" [MoH, 2011]. This report attempts to fill this information void, focussing on parasite transmission and spatial descriptions of populations at risk, dominant vectors and intervention coverage. The report is developed against a background of how the Ugandan control programme has evolved from the period of the GMEP to present day.

The work is a collaborative effort between the NMCP of the Ministry of Health, the World Health Organization Country Office, Abt Associates and the INFORM Project, Department of Public Health Research, KEMRI-Wellcome Trust programme in Nairobi, Kenya.

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Chapter 2

Country context, administration, population distribution and health service provision

2.1 Location

Uganda, referred to as the "Pearl of Africa", is located along the central African Rift Valley within the Nile basin. It has borders with Kenya in the east, South Sudan to the north, the Democratic Republic of the Congo (DRC) to the west, Rwanda in the southwest and to the south with Tanzania. The country varies in topography ranging from high altitude areas including the Rwenzori Mountains (5,100 m), Mount Elgon (4,300 m) and the volcanic Virunga Mountains (> 4000 m) to the low lying Sudanese Plain in the north. The central region is dominated by the large shallow, inland Lake Kyoga, surrounded by extensive marshy areas. The Nile drains from Lake Victoria into Lake Kyoga and from there to Lake Albert on the DRC border. Other lakes include Lake Edward in the South West and Lake George. A small area on the eastern edge of Uganda is drained by the Turkwel River, part of the internal drainage basin of Lake Turkana. The north eastern Karamoja region has the driest climate and is prone to droughts. The climate in the south is heavily influenced by Lake Victoria that prevents temperatures from varying significantly but increases cloudiness and rainfall.

2.2 Political and social evolution

The Bantu migration expanded into the region from the west in the 4th century B.C. The earliest organized states may have been established in the 15th century by pastoral rulers called the Chwezi; probably ancestors of the modern Hima or Tutsi of Rwanda and Burundi [Kesby, 1977]. During the 15th century, the Chwezi were displaced by the Nilotic-speaking pastoral group called the Bito, including Luo and Ateker, who migrated from the north. As part of the Chwezi migration south, one group, the Banyoro, led by Prince Kimera, arrived in Buganda early in the 15th century. The prince became the first effective king (*kabaka*) of the Buganda state [Byrnes, 1990].

Protestant and Catholic missionaries entered the country between 1877 and 1879 and the United Kingdom placed the area under the charter of the Indian British East Africa (IBEA) Company in 1888 [Harlow et al., 1965]. Uganda was declared a British protectorate in 1894. In 1902, the Buganda, Busoga, Toro, Bunyoro, Ankole and Bukedi regions were brought under British rule. Kigezi was added to the protectorate in 1911, Acholi and Karamoja in 1913, and West Nile in 1914. By 1918, the British Protectorate of Uganda had attained its present shape and limits. The new commissioner of Uganda in 1900, Sir Harry H. Johnston, divided the country into the Northern, Eastern, and Western Provinces and Buganda, which itself was given a different status and made up of 17 districts. The colonial administrators decided to adopt an “indirect rule” system employing chiefs from Buganda posted to most districts with authority to maintain law and order. This special relationship with Buganda created animosity across other regions of the country [Byrnes, 1990].

Throughout the East Africa Campaign of World War I, Uganda prospered from wartime agricultural production. In 1921, a legislative council was set up to serve as the parliament of Uganda, but it was not until 1946 that the first Africans had any council presence; by 1956 this grew to 30 African representatives. The first attempts to establish African political leadership was mounted by I.K. Musazi as the Uganda African Farmers Union in 1947 that lasted only a few years. In 1952, Sir Andrew Cohen established the Uganda Development

Corporation to promote and finance new projects and reorganized the Legislative Council to include African representatives elected from all districts of Uganda. Uganda's approach to independence was different to other colonial territories; in Uganda parties were forced to cooperate with one another, with independence already assured [Byrnes, 1990].

Uganda gained independence from Britain on the 9th October 1962. The first President of Uganda was King Mutesa of Buganda with Milton Obote serving as the prime minister of a loose coalition. Obote seized the presidency in a coup in 1966 and his early reign was characterised by a growing prominence of the military; Obote selected a popular junior officer, Idi Amin Dada, and promoted him rapidly through the ranks. As the army expanded, it became a source of political patronage and power. Amin was used by Obote in 1966 to stage a coup d'état against his own government who had passed a vote of no confidence. Obote suspended the constitution, arrested the offending Uganda People's Congress (UPC) ministers, and assumed control of the state. He forced a new constitution through parliament; Buganda was divided into four districts and ruled through martial law; he issued the "Common Man's Charter", similar to the form of African Socialism proposed by Tanzanian President Julius Nyerere; despite this he appointed an Asian Millionaire to oversee economic nationalization; and he sent Idi Amin and loyal troops to attack the Bugandan *kabaka's* palace on Mengo Hill, driving the King into exile. The new republican 1967 constitution abolished the kingdoms altogether.

Obote created a system of secret police including paramilitary police, however, by 1971 his control over the military began to wane and he ordered the arrest of Idi Amin, who pre-empted this when he attacked Kampala and the airport at Entebbe on 25th January 1971 while Obote was away at the Commonwealth Conference of Heads of Government in Singapore. Amin immediately initiated mass executions of Acholi and Langi troops, whom he believed to be pro-Obote. Following his succession to president between 1971 and 1972, the Lugbara and Kakwa (Amin's ethnic group) from the West Nile slaughtered northern Acholi and Langi, the Kakwa fought the Lugbara and as ethic clashes continued Amin came to rely on mercenaries from southern Sudan. In September 1972, Amin expelled almost all of Uganda's 50,000 Asians and seized their property. Businesses were run into the ground, cement factories at Tororo and Hima in Kasese collapsed and sugar production came to a halt. Uganda's export crops were sold by government parastatals to raise foreign currency largely to fund the needs of the army.

By 1978, Amin's circle of allies had significantly diminished. Amin claimed that Tanzanian President Nyerere, had been the cause of his troubles and invaded Tanzanian territory (the Kagera salient), annexing a section across the Kagera River boundary in November 1978. Nyerere responded by mobilizing his citizen army reserves, joined by Ugandan exiles united as the Uganda National Liberation Army (UNLA) and fought Amin’s troops and those provided by Libya's Qadhafi until Tanzania and the UNLA took Kampala on 11th April 1979. Amin fled by air, first to Libya and later to Saudi Arabia where he died in 2003.

An interim government was established following the Moshi Unity Conference and established as the Uganda National Liberation Front (UNLF) headed by Yusuf Lule who became president in April 1979. However, he was forcibly removed from office after only a few months in power and replaced by Godfrey Binaisa. Binaisa was unable to gain control

over a growing military presence. By 1979 military leaders Yoweri Kaguta Museveni and David Oyite Ojok began to enrol thousands of recruits into private armies. When Binaisa sought to curb the use of these militias he was overthrown in a military coup in May 1980. The coup was engineered by Ojok, Museveni and Paulo Muwanga under the Military Commission; Muwanga effectively governed Uganda during the six months leading up to the elections of December 1980 (widely held to have been rigged) that returned to power Milton Obote with Paulo Muwanga as vice president and minister of defence. Shortly afterwards in February 1981 Yoweri Museveni established the National Resistance Army (NRA) and vowed to overthrow Milton Obote by means of a popular rebellion, "*the war in the bush*".

The following four years resulted in vast areas of devastation and more deaths than under the Amin regime. The overall death toll from 1981 to 1985 was estimated as high as 500,000. On the advice of the International Monetary Fund (IMF), Uganda devalued the Uganda shilling by 100%, and attempted to facilitate the export of cash crops. The government's inability to eliminate Museveni and win the civil war, however, sapped its economic strength. In July 1985, Obote and a large entourage fled the country for Zambia along with much of the national treasury.

A military government of General Tito Lutwa Okello ruled from July 1985 to 1986. On 26th January 1986, Museveni moved against Kampala. Yoweri Museveni was formally sworn in as president on 29th January 1986. Museveni restricted political parties from 1986 to a non-party "Movement" system where political parties continued to exist, but could only operate a headquarters office. A constitutional referendum canceled this ban on multiparty politics in July 2005; however the term limit for president was in September 2005, changed in the constitution from the two-term limit, in order to enable the current president to continue in active politics. Museveni was re-elected in 2006 and after 24 years of rule and was re-elected again in 2011.

2.3 Economy

The period of colonial rule saw a rapid expansion in agricultural economy of Uganda, mainly cotton, coffee, rubber, sugarcane, and tobacco. The rail line, completed in 1901, allowed the movement of crops within the country and to neighboring Kenya for export. Between 1948 and 1954, the Owens Falls Dam was constructed, but the expected dramatic growth of industries around Jinja did not take place [Harlow et al., 1965].

Agriculture continues to be the major source of foreign exchange, however, Uganda's mineral potential remains undeveloped. Areas identified for priority attention included the Busia goldfields in south-east Uganda (for gold, zinc, copper and lead), the area around Tororo and Mbale (for carbonatite) and the Buhweju and Kigezi goldfields (for gold, nickel and several other minerals). A Canadian company, Uganda Gold Mining, has claimed that there are diamond reserves in Bushenyi district. A French company Rhodia Chimie, in association with Madhvani International, was granted a license to mine phosphates at Sukulu, in eastern Uganda. Drilling for oil began in 2002 near Lake Albert following the link-up between Heritage Oil and Gas (Canada) and Energy Africa (South Africa).

During the decades of civil war and political strife, the country's economy was paralyzed and was regarded as one of the poorest countries in the world. In 1986, when Museveni took power, agriculture still dominated the economy, with coffee as its main export. The government, with donor assistance, rehabilitated the economy. Inflation ran at 240% in 1987, but was reduced to 42% by 1992, and further reduced to 5.1% in 2003. By 2007, the services sector had surpassed agriculture and accounted for 52% of GDP. In 2000, Uganda was included in the Heavily Indebted Poor Countries (HIPC) debt relief initiative worth US$ 1.3 billion and Paris Club debt relief worth US$ 145 million. The country was hailed by the IMF and the World Bank as a paragon of economic reform leading to substantive growth. In 2006 the Ugandan Government successfully paid all their debts to the Paris Club, which meant that it was no longer on the HIPC list. In 2008, Uganda recorded 7% growth despite the global downturn and regional instability. Uganda depends on Kenya for access to international markets via its rail and road networks, a dependence acutely felt during the post-election violence in Kenya in 2007/2008 when market access was virtually cut off.

In 2007, the government approved the Comprehensive National Development Planning Framework which provided for the development of a 30 year vision to be implemented through, National Development Plans, Sector Investment Plans and Local Government Development Plans. Later, cabinet approved the Uganda Vision 2040 Statement, *"A transformed Ugandan Society from a peasant to a modern and prosperous country within 30 years"* [NPA, 2013]. The Uganda Vision 2040 was launched in April 2013 and articulates strategies and policy directions to transform the country into a competitive upper middle income country with per capita income of US$ 9,500, currently standing at US$ 1,168 per person. This requires average real GDP to grow at the rate of 8.2% per annum translating into total GDP of about US$ 580.5 billion from US$ 17 billion in 2010. The vision incorporates emerging development prospects including the discovery of oil and gas reserves, green economy, e-revolution, globalization and regional economic integration among others. The Ministry of Health (MoH) is expected to contribute to this goal by working to improve the health status and life expectancy of the people of Uganda.

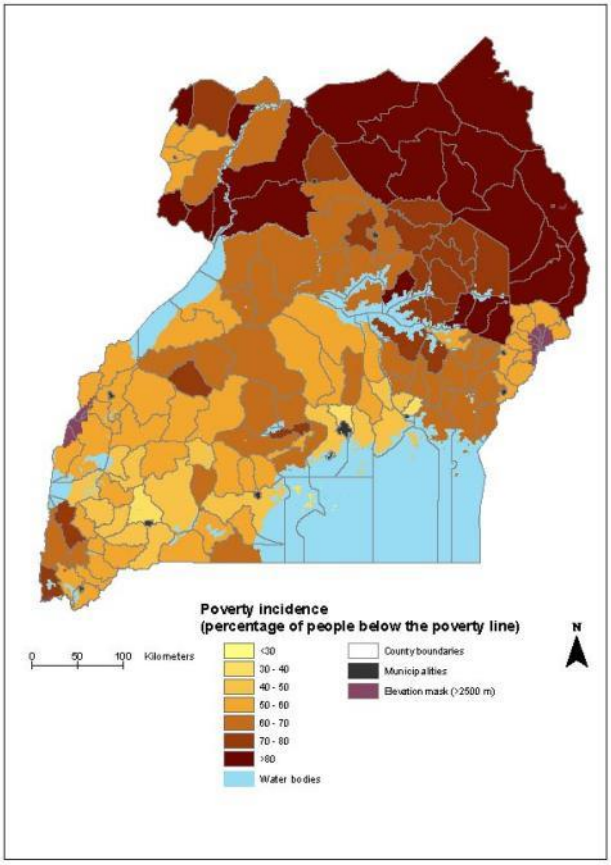
2.4 Poverty

The proportion of people living below the poverty line had declined from 52% in 1992 to 31% in 2005; however, Uganda remains one of the poorest countries ranking 161 on the 2012 global Human Development Index, with a human development index adjusted for inequality of 0.33 making it a very low development country [UNDP, 2013]. Per capita income is US$ 170.

Small area poverty mapping techniques have been applied to Ugandan survey and census data (1992/93 Integrated Household Survey and the 1991 Population and Housing Census) to produce baseline 1992 poverty estimates to district levels [Emwanu et al., 2003]. These estimates were updated, using information from the 1999/2000 UNHS, to show estimated poverty levels for 1999 and the relative changes in poverty levels over this time period [Emwanu et al., 2003]. The analysis showed extremes of poverty in the north and northeast in 1992 (Figure 2.1) and that between 1992 and 1999 there was little change. More data now exist from household budget surveys and the mapped evolution of poverty should be

undertaken as an important development measure for improved equitable targeting of resources in Uganda.

Figure 2.1: Small area estimates of poverty incidence in 1992 at county-level. Adapted from Emwanu et al. (2003).



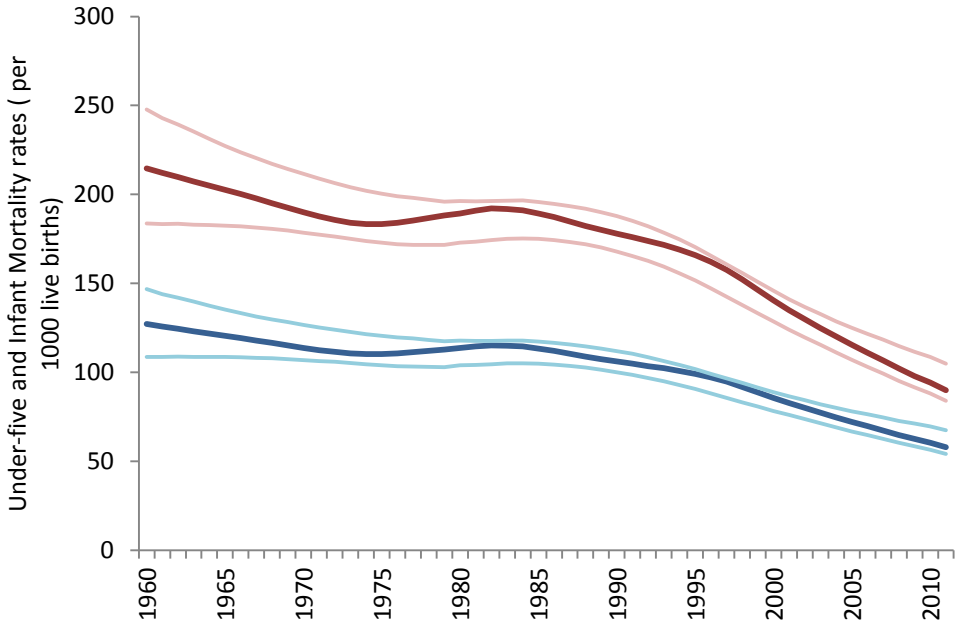
2.5 Child survival

Civil registration was made compulsory in Uganda in 1973. However, its coverage is incomplete and unsatisfactory as a source of reliable mortality data. The absence of credible civil and vital registration of childhood deaths has meant that changes in child survival have to be defined using indirect methods of estimating under-five mortality rates from birth histories reported by mothers that include information on the residence and survival of their live births [Hill & David, 1988]. These data are assembled within a life table to estimate the probabilities of dying between intervals derived from reported dates of birth and death and the numbers of children of a particular age exposed to the risk of dying during the period [Hill & David, 1988].

Data have been compiled by the Inter-Agency Group for Child Mortality Estimation (IGME), who used combinations of weighted LOESS regression techniques to fit smoothed mortality trends to estimate mortality between survey periods using sample survey data (Demographic and Health Surveys, Multiple Indicator Cluster Surveys and World Fertility surveys) and census data [UNICEF-IGME, 2011]. The IGME estimates of under-five mortality (the probability of dying between birth and the fifth birthday) and infant mortality (number deaths in the first year of life per 1000 pregnancies) for Uganda between 1960 and 2011 are

shown in Figure 2.2 [UNICEF-IGME, 2011]. Substantial declines in both infant and under-five mortality were witnessed from 1960 through to the early 1970s when modelled household survey data show the stagnation of progress and periods of high mortality over the two decades of civil strife and war and the emerging HIV epidemic. By the mid-1990s Infant and child mortality began to decline significantly. The recent 2011 national household DHS suggests that under-five mortality (5q0) is 90 per 1000 live births and infant mortality (1q0) is 54 per 1000 live births [UBOS, 2012].

Figure 2.2: Under-five mortality rates (red) and Infant mortality rates (blue) per 1000 live births for Uganda, 1960 to 2011 [UNICEF-IGME, 2011]



Legend: Under-five mortality rates (red) and Infant mortality rate (blue) per 1000 live births Uganda, 1960 to 2011. All rates are defined as per 1000 live births [UNICEF-IGME, 2011]. For IMR and U5MR, a country-specific local log-linear regression model is fitted to observations for one of the two indicators, within a model life table. Projections have been adjusted for projected mother-to-child HIV infection risks [You et al., 2009; Hill et al., 2012; UNICEF-IGME, 2011]. A loess line is produced with an uncertainty range (shown as boundaries to dark line in Figure 2.2).

Recent studies using a 1% sample of the 2002 national census data within a multivariate analysis framework indicate that the overall risk of child death in the first 5 years of life had decreased across Uganda (Hazards Ratio = 0.011; 95% CI 0.006 to 0.018) [Kazembe et al., 2012]. Through spatial Bayesian Gaussian random fields models the authors demonstrated significant spatial variations, highlighting inequalities in mortality by geographic location, for example, areas of high risk included the south-west and north-west regions while Kampala district showed the highest reduced risks. Risk factors associated with under-five mortality, within the spatial model, were identified to be number of under-five children in the household, marital status, education level of mother, ownership of electronic assets and shelter characteristics [Kazembe et al., 2012].

2.6 Administrative boundaries

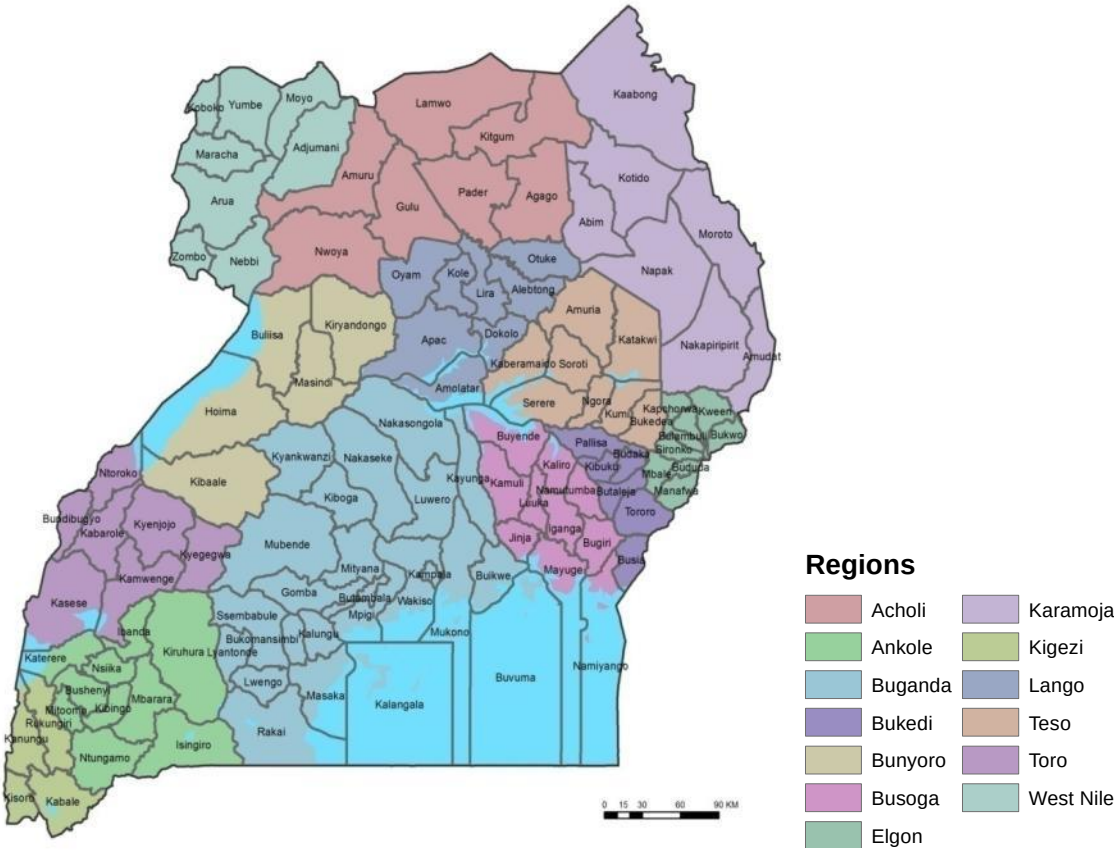
Over time, governments across Africa have embraced decentralization. Defining the health administrative units used by a country is central to resolving health information for planning and disease burden estimation. Most currently available malaria risk maps do not resolve information necessary for planning at units of decision making used by national governments, for example those most recently developed by the Malaria Atlas Project [http://map.ox.ac.uk] and used by the Global Malaria Programme of the WHO in its 2012 World Malaria Report [WHO, 2013]. Without congruence to accepted health decision making units at national levels the cartographic information of risk has diminished value [Omumbo et al., 2013]. Defining the second and third level administrative regions within each country poses perennial problems as these routinely change and are different for different national administrative purposes (e.g. census units do not always correspond to health planning units or political constituency units).

In Uganda, the provision of health services has, since 1993, been decentralized with districts and health sub-districts playing a key role in the delivery and management of health services. The 1995 Constitution and the 1997 Local Government Act mandates the District Local Government to plan, budget and implement health policies and health sector plans [MoH, 2010].

According to health sector strategic plans since 2008, the District Health System comprises "*a well-defined population living within a clearly delineated administrative and geographic boundary and includes all actors in the recognized spheres of health within the district. It is expected that the activities of the diverse partners in health are reflected in the District Health Sector Strategic Plan, which in turn is an integral part of the rolling District Development Plan. The National Health System established the Health Sub-District (HSD) as a functional subdivision or service zone of the district health system to bring good quality essential care closer to the people, allow for identification of local priorities, involve communities in the planning and management of health services, and increase the responsiveness to local needs*" [MoH, 2008]. At present there are 112 District Health Units.

District boundaries for 2012 were available in a mapped form and developed by the Uganda Bureau of Statistics (UBOS) [www.ubos.org/ provided by Didas Namanya of the MoH]. This digital shape file was compared to the Global Administrative Unit Layers (GAUL, 2008), an initiative of the Food and Agriculture Organization (FAO) that maintains global administrative layers with a unified coding system at country and updated annually, first (e.g. regions) and second administrative levels (e.g. districts). The UBOS district boundary had several anomalies at the national boundary and was re-digitized in *ArcGIS* [ArcMap 10.1, Esri Systems, Redland, CA, USA] to provide an exact match with approved global boundaries. The final delineation of the 112 health districts is shown in Figure 2.3. There is almost no regional level planning other than the regional referral hospital care system. There are 13 nominal regions Acholi, Ankole, Buganda, Bukedi, Bunyoro, Busoga, Central, Elgon, Karamoja, Kigezi, Lango, Teso, Toro, and West Nile. In parallel the six traditional Bantu kingdoms have remained, enjoying some degrees of mainly cultural autonomy. The kingdoms are Toro, Ankole, Busoga, Bunyoro, Buganda and Rwenzururu. These are however not used in service planning.

Figure 2.3: 112 health districts within 13 Administrative Regions in Uganda used in the present report



2.7 Population growth and distribution

The first censuses in Uganda were taken in 1911 (estimated 2.5 million people), 1921 (estimated 2.9 million people) and 1931 (estimated 3.5 million people) and used counts by 'huts' and not individuals [Kuncyzinski, 1948]. The slow growth rate in the first decade could have been explained by a series of sleeping sickness epidemics that were estimated to have killed more than 250,000 people; about two-thirds of the population in the affected lake-shore areas. The censuses undertaken in 1948 (5.07 million people) and in 1959 (6.54 million people) used modern *de facto* demographic methods following the formation of the East African Statistical Department, despite divisions into two separate enumerations, one for Africans, and one for the non-African population. The censuses since independence have been undertaken in 1969 (9.5 million people), 1980 (circa 12.6 million people, with significant uncertainty because of the loss of census data in subsequent outbreaks of violence), 1990/91 (16.6 million people), 2002 (24.2 million people) and 2012 (provisionally 39.2 million people).

The average annual population growth rate between 1991 and 2002 was 3.2%; higher than the growth rate of 2.5% between 1980 and 1991 and explained because of declining mortality and sustained high fertility.

Uganda was the focus of migration from surrounding African countries until 1970, with most immigrants coming from Rwanda, Burundi and Sudan. In the 1970s, immigrants were estimated to make up 11% of the population. About 23,000 Ugandans were living in Kenya, and a smaller number had fled to other neighboring countries. Emigration increased dramatically during the 1970s and was believed to slow during the 1980s. In 1989, Uganda reported 163,000 refugees to the United Nations High Commissioner for Refugees (UNHCR). Most of these were from Rwanda, but several other neighboring countries were also represented. At the same time, Zaire and Sudan registered a total of nearly 250,000 refugees from Uganda. The effects of the war in the north waged by the Lord's Resistance Army for over a decade from the mid-1990s led to large scale massacres, population displacement and refugee camps. The effects on human settlement have yet to be properly enumerated. In 2011, there was a surge in the number of refugees fleeing violence in the eastern parts of the Democratic Republic of the Congo and by 2012, had reached more than 40,000 seeking safety in Uganda. They joined other new arrivals, notably from South Sudan, Somalia, Burundi, Rwanda, Ethiopia and Eritrea, who were entering at a slower rate. By August 2012, Uganda was host to more than 190,000 registered refugees and asylum-seekers [UNHCR, 2013].

Uganda's population density was found to be relatively high in comparison with that of most of Africa, estimated to be 123 km^2 nationwide in 2002 [UBOS, 2006]. However, this figure masked a range from < 60 km^2 in the Northern region to more than 226 km^2 in Eastern region. The population density of the districts ranged from 22 persons per km^2 for Moroto district to 7,259 persons per km^2 in Kampala district. To effectively map population-attributable risks of any disease it is necessary to resolve the disease risks to high resolution population settlement.

Recently spatial modeling techniques for the spatial reallocation of populations within census units have been developed in an attempt to overcome the difficulties caused by input census data of varying, and often low, spatial resolutions [Linard et al., 2010; Linard et al., 2012; www.afripop.org]. In brief, a dasymetric modeling technique [Mennis, 2009] was used to redistribute population counts within the 6,255 spatially defined Parishes (Figure 2.4) used during the 2002 national census and land cover data sets derived from satellite imagery. A different population weight was assigned to each land cover class in order to shift populations away from unlikely populated areas, for example game reserves or arid deserts and concentrate populations in built-up areas. The net result was a gridded dataset of population distribution (counts) at 0.1 x 0.1 km resolution. The population distribution datasets were projected to 2000 and 2010 using UN national rural and urban growth rates [UN, 2011] and made to match the total national population estimates provided by the UN Population Division [UN, 2010] for these years. The resulting population density map is shown in Figure 2.5.

It is worth noting that the micro-data collected during the 2012 national census is expected to be released sometime later in 2013 and these would help improve population distribution modeling, age-sex compositions, projected populations per gridded count and definitions of urbanization.

Figure 2.4: 6,255 parish boundaries (2002) [Openmicrodata, 2013] and protected areas using the 2010 World Database on Protected Area [WDPA, 2013].

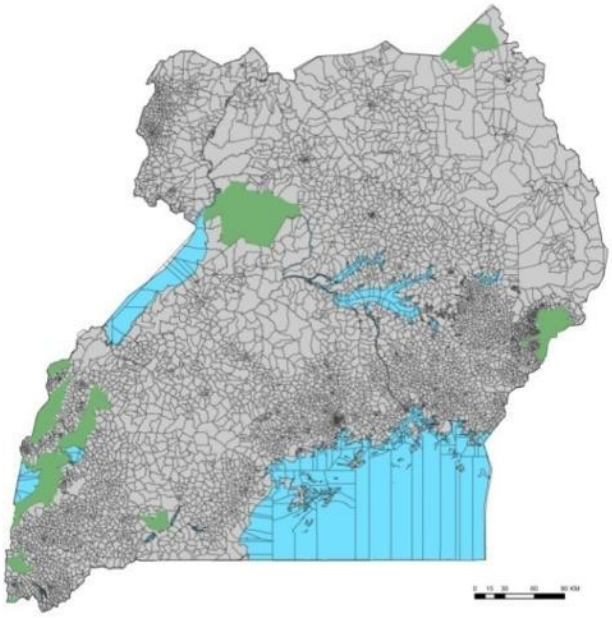
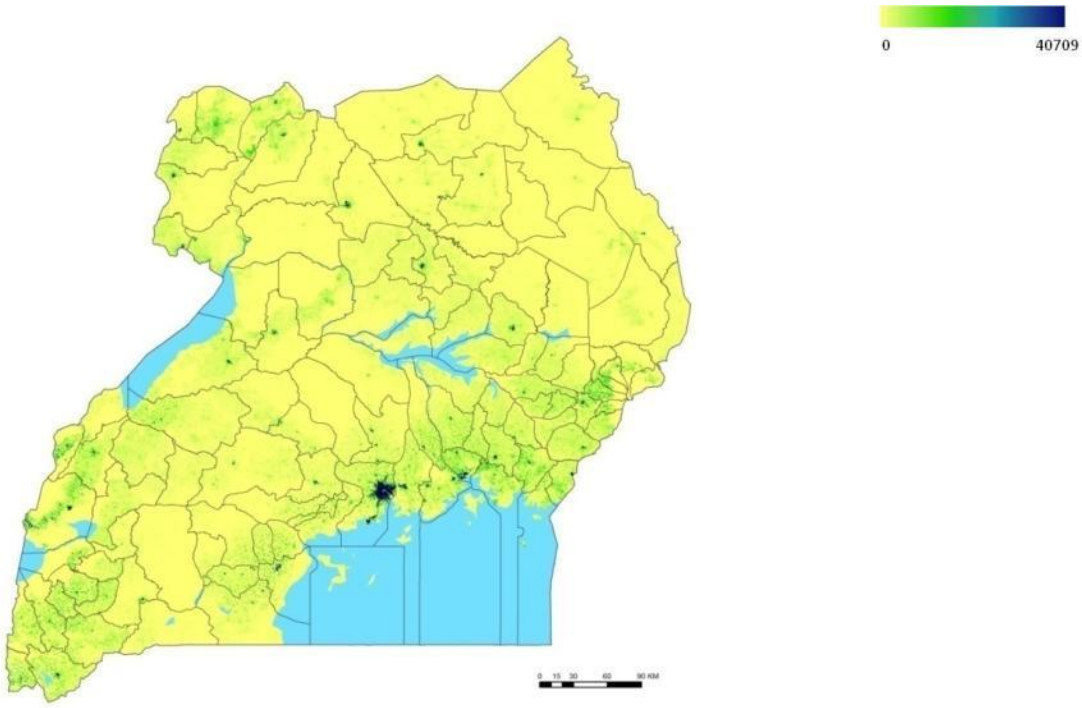


Figure 2.5: Modeled population density projected to 2010 using methods described in the text and represented as increasing density as shown in legend below. Ranging from zero to *c*. 41,000 per km^2

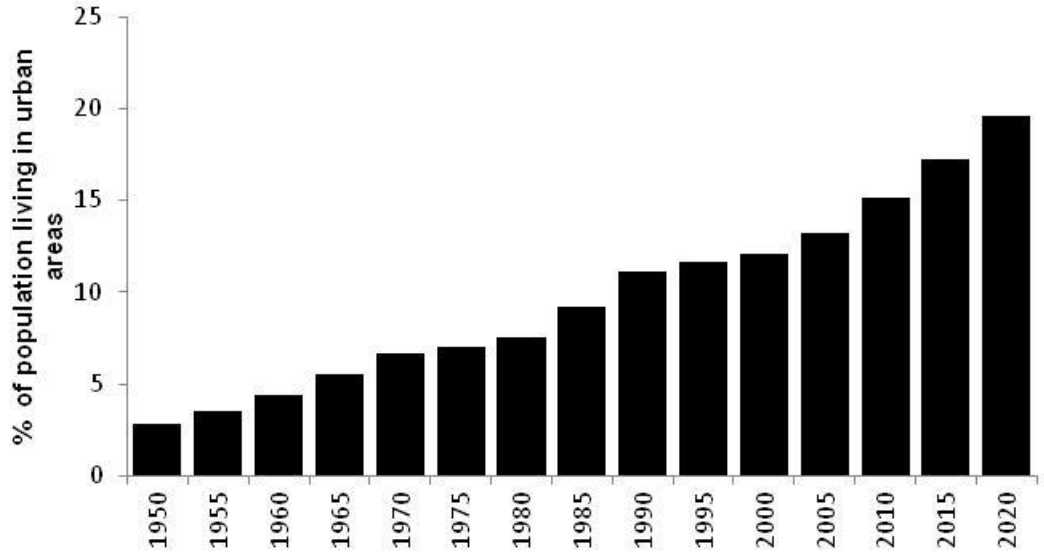


2.8 Urbanization

The proportion of the population living in urban areas has increased with each census year from 6.6% in 1969, 7.4% in 1980, 11.3% in 1991 and 12.3% in 2002. Rural-to-urban migration declined during the 1970s as a result of deteriorating security and economic

conditions. During the 1980s, Kampala accounted for almost 50% of the total urban population but recorded a population increase of only 3%. Jinja is the main industrial center and second largest city; six other cities Kabale, Fort Portal, Entebbe, Masaka, Mbarara, and Mbale had populations of more than 20,000 in 1989. The urban population in Uganda is estimated to reach close to 20% of the country's population by 2020 according to the UN's World Population Prospects of 2012 (Figure 2.6). These growth rates of urban populations are much lower than other neighbouring countries, highlighting the continued rural nature of Uganda.

Figure 2.6: Percentage of population residing in urban areas of Uganda between 1950 and 2020 [UN, 2012]

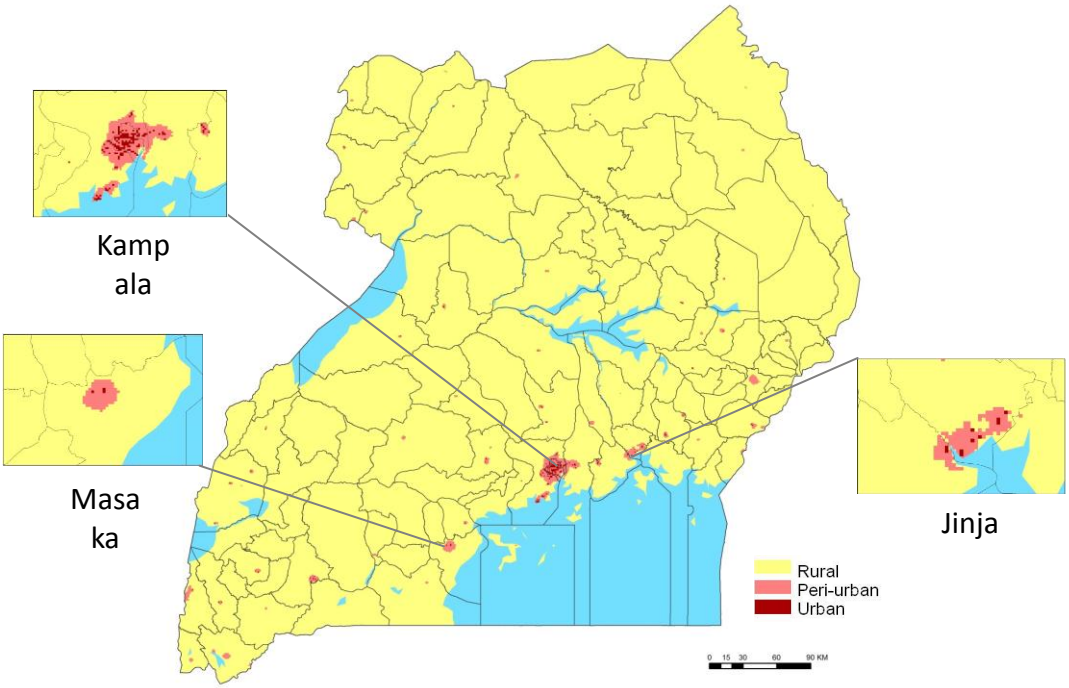


The definition of urban areas in Uganda has changed over the years. In the 1969 and 1989 census, trading centers with 100 and 400 people respectively were considered as urban. In the 1991 census, the classification was revised to include all cities, municipalities, town councils, town boards and trading centres with a population of over 1,000 persons. The 2002 population census however did not include a population threshold and only includes cities, municipalities and town councils gazetted in the Local Government Act of 2000 [UBOS, 2006].

These national definitions of urban settlements are vague and potentially inconsistent across the country. We have therefore used an urbanization classification that combines the spatial extent of urban settlements developed by the Global Rural Urban Mapping Project (GRUMP) and population density developed the AfriPop project [Linard et al., 2012]. GRUMP urban extent grids distinguish urban and rural areas based on a combination of NOAA's Night-time lights dataset [Elvidge et al., 1997], settlements data and population counts. Population counts used were derived from GRUMP spatial population database based on areal weighted census input data [Balk et al., 2006] while settlements data sources include ESRI's Digital Chart of the World's Populated Places (DCW), Tactical Pilotage Charts (TPC) from Australian Defense Imagery and Geospatial Organization and some LandSAT-derived polygons [Balk et al., 2004; CIESIN, 2013]. To define urban extents, a border was defined around each set of contiguous lighted pixels whose total population count was

greater than 5,000 persons. Because not all urban settlements are 'well-light' to be detected by satellite sensors, a buffer was drawn around settlement points to estimate spatial extents of the settlements. Similar to the Night-time lights-derived, urban extents, settlement extents with a total population count was greater than 5,000 persons were classified as urban with the rest of the grid define as rural. The GRUMP urban extent was further refined to produce a 'peri-urban' classification constrained by population density using the Afripop data [www.AfriPop.org]. 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 (Figure 2.7).

Figure 2.7: Urban and peri-urban settlements in Uganda (see text for definitions)



2.9 Evolution of the health system

Medical services were started by IBEA in 1895 when the company needed medical doctors for its employees. The IBEA transferred its functions and assets to the British foreign office, it also transferred its Medical services. The foreign office restructured the company's medical services into the medical department of the protectorates. The medical department was primarily focused on preventing health hazards for Europeans; second in priority were Indians who helped in building the railway and the promotion of trade. In 1901, there were seven doctors, seven hospital assistants, and three nurses serving the medical department. Numerous challenges faced the medical department in Uganda and led to a merger of the Kenya and Uganda medical departments in 1903, with Dr. Moffat as the principal medical officer for Kenya and Uganda. The combined medical staff at this time comprised of twenty-six doctors, seven European dispensers, and six nurses [Beck, 1970].

The first missionary hospital (Mengo Hospital) was established in 1897 by the Church Missionary Society (CMS) through Sir Albert Cook. The hospital was heavily over burdened

with 70 beds, serving 1,070 inpatients and 76,840 out-patients by 1901. It was at Mengo Hospital that the first case of sleeping sickness was diagnosed in 1901 [Berrang-Ford, 2007]. The missionary work introduced western medicine and accelerated its acceptance by local populations. World War I saw the formation of Uganda Medical Corps consisting of volunteers drawn from high schools and a government medical training center in Kampala. By 1915, the Uganda Medical Corps consisted of 1000 assistants [Berrang-Ford, 2007]. Between 1919 and 1925, the missions trained 60 hospital assistants and several "native" medical attendants at Makerere Technical College. Makerere College started in Kampala in 1921 as a technical college and changed its curriculum in 1922 when it began to teach medical courses formerly given at Mengo Hospital by CMS [Beck, 1970]. A dispensary system was introduced in 1924, which in later years these were upgraded to modern health centres [Beck, 1970].

Re-organization of medical services continued after the Second World War (1938 – 1945). In 1955, a committee was set up to review and examine health services in Uganda. The committee reported that lack of funds hindered expansion of medical services and recommended the introduction of user fees, adoption of a common policy to coordinate all medical resources in the country, and training of African personnel should be speeded up. The report also encouraged closer relationships between the medical department and mission medical work [Beck, 1970].

Uganda has a special place for medicine in the East Africa region. After many years of training medical auxiliaries and laboratory technicians, Makerere College became a University College for East Africa providing medical degrees from the University of London and eventually in 1963 as fully fledged regional degrees. The University was therefore responsible for the first cohorts of qualified doctors from Tanzania, Kenya and Uganda at independence [Beck, 1970].

The first decade following independence saw the growth of a national health system but by 1986 the health sector was in a state of near collapse, with dilapidated and very poorly equipped public health facilities. The country was thus dependent on foreign aid, and as a result donors and aid agencies influenced both health and development policy [Okuonzi et al., 1995]. There was a strong support for the role of user fees in encouraging community participation and ownership, and as a means to generate revenue. In the late 1980s, user fees were introduced against a backdrop of poor health system but did not spread widely until early 1990s. The fees were late abolished in 2001, with the exception of private wings as a health sector reform strategy [Kipp et al., 1999].

Uganda embarked on major reforms from 1986 both in the health sector and wider public arena. The immediate emphasis was on rehabilitation of the existing facilities to restore functional capacity, and a shift of emphasis to Primary Health Care. In the early 1990's the Ugandan government embraced decentralization as part of a cross-cutting public sector reform whereby the central government through the Ministry of Health mandate remained policy formulation, standard setting, quality assurance, resource mobilization, capacity development, technical support, provision of nationally coordinated services such as epidemic control, coordination of health research and monitoring and evaluation of overall sector performance. Local government was mandated to provide curative and rehabilitative

services, vector/communicable diseases control, health education, ensuring provision of safe water and sanitation and mobilize additional resources at the local (district) level. The health care delivery system in Uganda is devolved to districts, which are subdivided into counties and then into sub-counties. The sub-counties are self-contained service zones headed by a medical officer, but they are not considered distinct administrative units. According to the 1999 National Health Policy, the sub-counties are primarily responsible for health service delivery [Hutchinson et al., 1999]. Sub-counties are further divided into parishes, and parishes into villages.

Health care provision in Uganda is delivered through a tiered structure of facilities based on services they provide and catchment area they are intended to serve [MoH, 2006; MoH 2010]. The facilities are designated as Health Centre level one (HC 1) to Health Centre level four (HC IV); General Hospital, Regional Referral Hospital, and National Referral Hospital. The lowest level and first point of contact for someone living in a rural area is Health Centre level one (HC 1). These are owned by village health teams (VHT)/community medicine distributors who are largely volunteers targeting smaller populations of 1000. In most cases, they are non-existent or do not have basic drugs for diseases such as malaria. According to Uganda's health policy, every parish is supposed to have a Health Center II facility serving a target of about 5,000 people. A HC II is supposed to be staffed by an enrolled nurse, working with a midwife, two nursing assistants and a health assistant. It runs an out-patient clinic, treating common diseases and offering antenatal care. A HC III facility should be found in every sub-county in Uganda serving a target population of 20,000 people. These centers should have about 18 staff, led by a senior clinical officer, who runs a general outpatient clinic, inpatient health services and a maternity ward. HC III should also have a functioning laboratory. A HC IV serves a county, is the main facility for seven sub-counties. As a mini-hospital, a HC IV serves a target population of about 100,000 providing all services of HC III as well as emergency surgery and blood transfusion. HC IV facilities must have a senior medical officer and another doctor as well as a theatre for carrying out emergency operations. Ideally each district is supposed to have a hospital, which should have all the services offered at a health centre IV, plus specialized clinics – such as those for mental health and dentistry – and consultant physicians. Hospitals are grouped into three: General serving population of 100,000 – 1,000,000; Regional serving population of 1,000,000 - 2,000,000; and National serving population of over 24,000,000. Soroti's district hospital, in Soroti town, is also a regional referral hospital as it caters for the Teso and Karamoja regions, meaning it gets cases referred from other district hospitals. At the top of the healthcare chain is the national referral hospital located at Mulago in the capital Kampala, others are Butabika, and more recently Gulu and Mbarara.

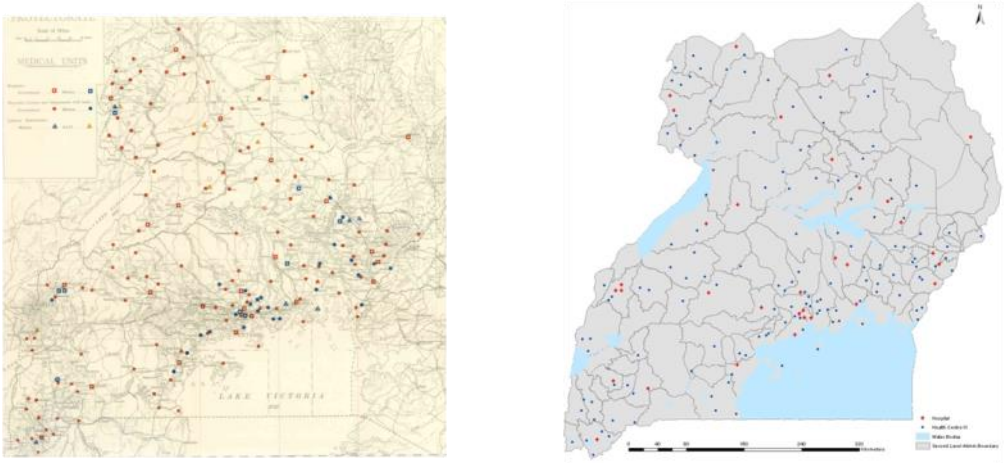
2.10 Health facility mapping

Accurate health information is the cornerstone of effective decision-making and reliable assessment of disease burden and resource needs [Detmer, 2003; WHO, 2007]. Efforts to tackle the enormous burden of ill-health in low-income countries are hampered by the lack of functioning health information structures to provide reliable health statistics [Osisobe, 1989; Boerma & Stansfield, 2007; WHO, 2008]. Central to a fully operational Health Information Systems (HIS) is a basic inventory of all functioning health facilities and the services they provide. Such an inventory requires a spatial dimension, allowing facilities to

be linked to the populations they serve by level of care and other proximate determinants of health such as environment, poverty and education. This spatial linkage can be provided by geographic information systems (GIS). The use of GIS for health services planning is widespread in developed countries [Bullen et al., 1996; Gatrell & Markku, 1998] but there are few examples of their development and operational use in resource poor settings in Africa [Noor et al., 2004; 2009; Kazembe et al., 2007; Lozano-Fuentes et al., 2008].

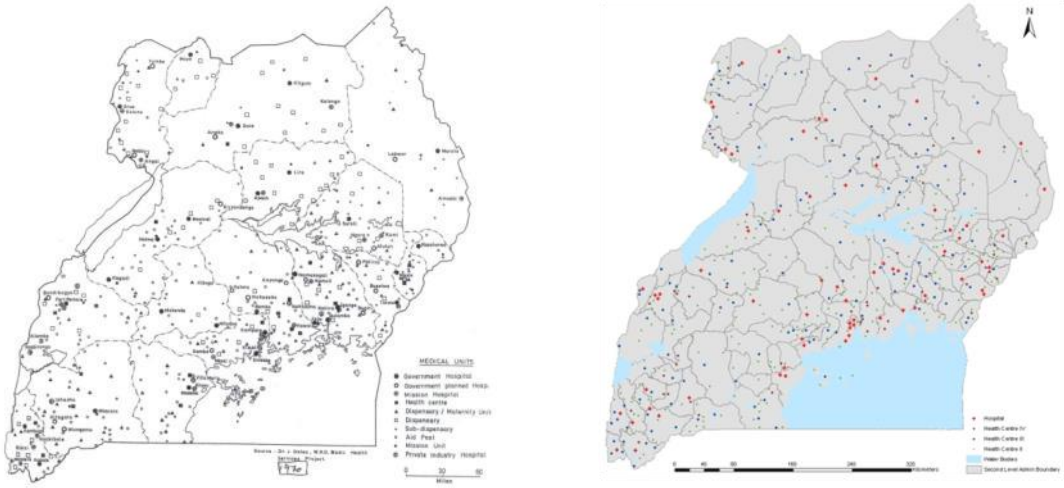
The first health facility mapping exercise began before independence by the medical department in 1956 and then soon after independence in 1968 by the Ministry of Health with the assistance of WHO [Galea, 1968]. The 1956 health facility map provided the positions of 33 hospitals and 142 maternity centres and dispensaries with beds. Of the 33 hospitals, 24 were maintained by the government while nine by missionaries. Of the 142 maternity centres and dispensaries with beds, 115 were maintained by the government while 27 by missionaries. We have recoded the facilities into Hospitals and Health Centre III (maternity centres and dispensaries with beds) for purposes of consistency with current service provision levels (Figure 2.8).

Figure 2.8: 1956 health service distribution a) The original maps and b) digitized by importing using *ArcGIS* [ArcMap 10.1, Esri Systems, Redlands, CA, USA] of each of the recoded 175 facilities (note leprosy settlements excluded)



The 1968 health facility map provided 29 government hospitals, 17 planned government hospitals, 21 mission hospitals, 18 health centres, 79 dispensaries / maternity units, 77 dispensaries, 92 sub-dispensaries, 154 aid posts, 37 mission units and four private industry hospitals. Here we have recoded the facilities into Hospitals (Government hospital, Government planned hospitals, mission hospitals, and Private industry hospitals); health centre IV (health centre and mission Unit); health centre III (dispensary and dispensary / Maternity Unit) and health centre II (Aid post and Sub-dispensary) (Figure 2.9).

Figure 2.9: 1968 health service distribution a) The original maps and b) digitized by importing using *ArcGIS* [ArcMap 10.1, Esri Systems, Redlands, CA, USA] of each of the recoded 504 recoded facilities (note four industry owned facilities excluded)



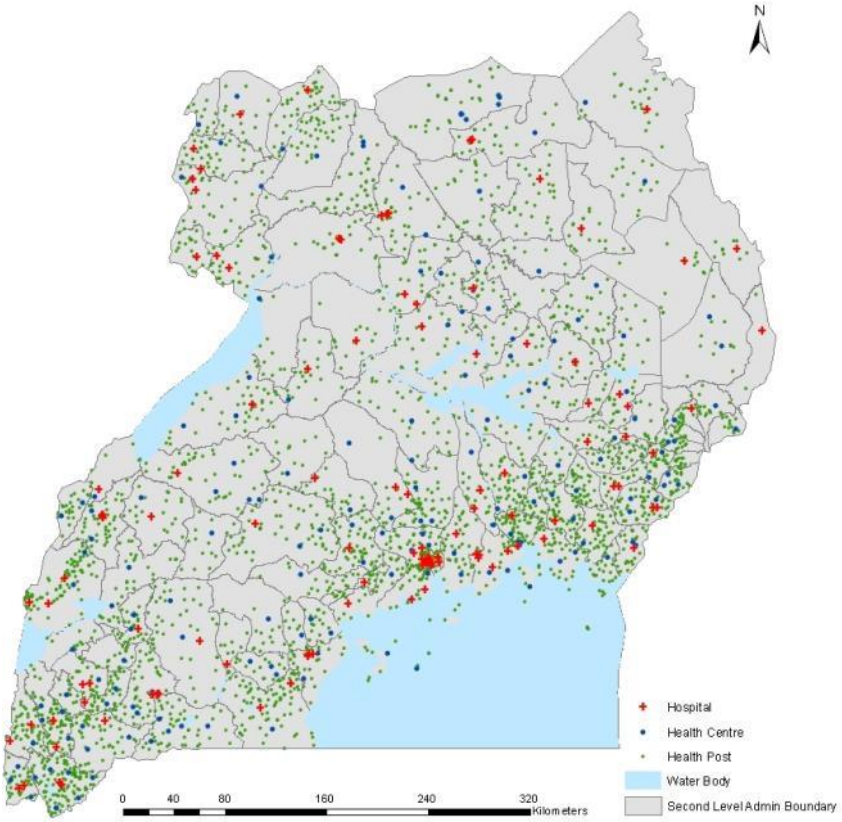
Recently a Service Availability Mapping Survey was carried out (March 2004) by the MOH and WHO which estimated the total number of health facilities were 2,731 managed by government, NGO, and private sectors. The composition of facilities included 108 hospitals, 160 health centre IVs, 873 health centre IIIs, and 1,593 health centre IIs [MOH & WHO, 2004].

Recently the Ministry of Health has compiled an updated version of a master health facility list using information supplied from district medical officers and partners in the health sector. This was provided to us by the Ministry in February 2013. The data file contained information on facility name, location information (district, county, parish), the service provider (NGO, Faith Based Organizations (FBO), public, private or a collection of providers we have classified as "other" (including prisons, armed forces, police, universities, industry owned clinics, counselling centres, youth centres, mental hospitals, maternity centres, and health offices that are unlikely to be providing routine curative services), whether the facility was functional or not and the level of services (Hospital, HC I, HC II etc). We first removed all facilities that were classified as closed, non-functional, under construction or could not be found following a more detail check with district level contacts in July 2013 (n=138). Private facilities (n=1436) were also excluded form the database. This does not deny the importance of private service providers but was a pragmatic decision based on how difficult it is to enumerate the private sector and the duality of the same public health professionals working in both sectors [Noor et al., 2004]. A study done in 2006 found that the number of Private Health Practitioners and their facilities accounted for 46% of service provision in Uganda. Dual employment was common and 54% of the doctors working in the private sector also worked in the government sector [Ssengooba et al., 2006; MoH, 2010]. 169 facilities classified as "other" were removed from the database; these included reproductive health clinics, TB centres, prison and other institution health facilities and maternity homes. The final list contained 3,357 facilities managed by the government or NGO/FBO agencies; and contained 2,561 facilities managed by the government and 796 facilities by NGO/FBO agencies. Overall there were 115 facilities with a designated hospital status, 184 Health Centre IVs, 1,112 Health centre IIIs and 1,946 Health Centre IIs. There

were no facilities specified as Health Centre I. We re-coded facilities into Hospitals, Health Centre (HC IV), and Health Post (HC III and HC II) for the purposes of display (Figure 2.10)

We then used a variety of Global Positioning Systems (GPS) databases and digital place name gazetteers to geo-locate each facility using the name and other administrative location data; the number of public facility coordinates obtained from these sources are: 1032 (GPS coordinates from WHO health facility database developed in 2004), 326 GPS locations (various MOH files), 543 GPS locations (Uganda Bureau of Statistics project village databases), 87 GPS locations (databases of various districts including Kabale and Gulu), 104 facility locations (Encarta), 274 facility locations (Google Earth), 92 facility locations (Geonames), 63 locations shifted in Google Earth or ArcMap, 230 facility locations from Global geodatabase cities [http://www.geodatasource.com/cities-platinum.html], 41 locations [http://www.diva-gis.org], 62 locations from parish centroids deduced in ArcMap, and finally 466 facility locations (Uganda national schools database developed in 2007). After exhausting all possible national and public domain geo-databases we were unable to identify 34 (1.0%) facilities. The location of 99% of public sector facilities is shown in Figure 2.10, the first of its kind since 1968.

Figure 2.10: Distribution of geo-coded hospitals, health centres and health posts managed as public sector in 2012/13



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Chapter 3

100 years of malaria control in Uganda

3.1 Background

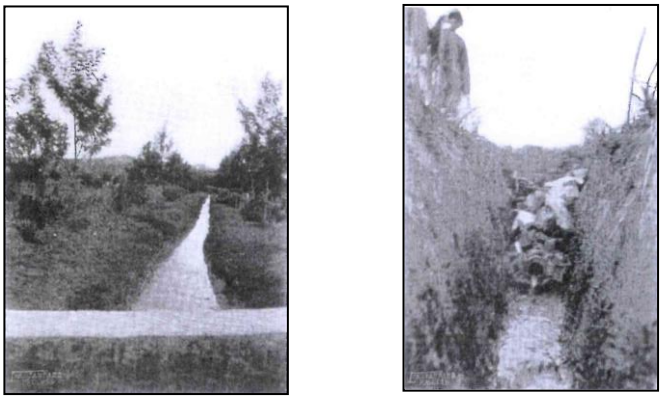
In this chapter we provide an overview of the evolution of malaria control in Uganda from the period before independence, through the era of the Global Malaria Eradication Programme (GMEP), from the abandonment of elimination to the present RBM control period. This chapter is motivated by a need to: 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 Uganda - who was involved, what was done, what worked and more importantly what did not work.

3.2 Malaria control 1900 to 1950 – the early years

The malaria control activities mounted from as early as during the First World War focussed on mosquito larval management. In many townships across the protectorate "*Anti-Malarial Gangs*" were employed to manage the conditions that supported mosquito breeding [Uganda Protectorate, 1917; 1919; 1921; 1923; 1928]. In 1917 this included grass cutting, drainage and filling in of breeding sites at Entebbe, Masindi, Hoima, Fort Portal, Mbale, Lira, Gulu, Kitgum and Soroti. The emphasis on environmental sanitation, followed Sir Ronald Ross's recommendations for "mosquito brigades" [Ross, 1902].

A significant effort was launched at the Nakivubo Swamp at Kampala, undertaken as a collaboration between departments - the Sanitary department and the Public Works Department. The head of Public Works, Mr. JD Milner, made this a special project using experiments of various mixtures of local clay, tile drain pipes, rubble contour drains and "seepage holes" marked with flags [Uganda Protectorate, 1917]. During the 1920s an average 116 labourers were employed daily to maintain the clearing of the Kampala swamps. Despite these efforts, the area affected by the swamp in Kampala remained malarious by 1920 and it was felt that only through the use of larvicides could risks be further reduced [Uganda Protectorate, 1921].

Figure 3.1: View from a railway bridge at lower end of valley showing portion of main channel cut through virgin swamp (left) and pipe and rubble drain under construction (right) Nakivubo swamp control in 1917.



Anti-malarial Gangs continued to be used for at least two decades in urban settlements; in Kampala this extended to include the filling in of extensive brick pits and improving conditions surrounding the railway. By 1928, there were reports of the use of crude oil and kerosene applied by spraying across water collections, and a few reports of the use of Paris Green. In 1928, the use of Dr. Horn's perforated plate trap was mentioned as a means of cleaning water collection tanks of larvae in Kampala and Entebbe [Uganda Protectorate, 1928].

Other measures employed before the Second World War included the routine distribution of quinine for prophylaxis, screening of houses and the insistence of using bed curtains around sleeping areas. However, these activities were largely restricted to the European administration and their families: "*In a tropical mosquito infested country like Uganda where the dominating cause of illness and disability among Europeans and Asiatics is malaria and its concomitants, too much stress cannot be laid upon the necessity for providing adequate housing accommodation of a permanent, commodious and mosquito-proof design for all officials*" [Uganda Protectorate, 1926].

Following Colonel SP James' visit to Uganda in 1929 [James, 1929], several important changes to malaria control operations were institutionalized: a) the appointment of an anti-malarial engineer (although funds soon ran out for this position); b) a new health ordinance that covered malaria was considered by the Government in 1931; c) enforcing screening of public buildings as part of the new ordinance; d) recommendations for housing personal servants at a distance from their employer's home and the removal of squatters from townships; e) improved housing for government labour, including the Labour Department Camp at Kololo, Kampala; f) the establishment of a Malaria Survey Unit, which was set up in 1929; and g) general approaches to continued drainage, township mosquito management and improved house screening, however the annual report highlights that these measures were bound by the efforts (or lack of them) by the Central Town Planning Board, Public Works Department, Land Office and the Forest Department [Uganda Protectorate, 1930].

The precise burden of disease and its distribution country-wide remained unclear to those responsible for health statistics between the two World Wars [James, 1929]. As stated in the 1927 annual report "*The very low number of deaths recorded under clinical malaria, i.e. malaria in which the diagnosis was not confirmed by the microscope, is explained by the fact that most of these cases were mild and attended as out-patients, when the facilities for microscopic diagnosis were not always possible*" [Uganda Protectorate, 1927].

By the mid-1930s, Paris Green was more regularly used in towns such as Kampala, Entebbe, Jinja and Kabale; it was estimated that UK£ 1,540 was spent on anti-malaria works in Eastern Province in 1933 [Uganda Protectorate, 1933]. Mosquito surveys across the country became more routine with the appointment of a Government Entomologist, who essentially worked for the Agricultural Department.

Following the Second World War it was reported that there was a general deterioration in the health of the European population. This was compounded by an increasing refugee population

(increasing to 6,114 in 1945) including transfers from neighbouring territories; refugees were principally Polish women and children accommodated at Koja in Buganda and Nyabeya in Bunyoro. These immigrants suffered from malaria attacks, but rates were "*no higher than could be expected from a non-immune population*" [Uganda Protectorate, 1945]. After the Second World War malaria epidemics were noted in township areas, even though they were said to be protected by permanent drainage schemes and routine oiling. At Kigezi, a highland area, reports emerged of malaria cases from areas previously considered free of the disease [Uganda Protectorate, 1945].

In 1948, it was reported that "*malaria continues to show the highest incidence of all diseases*": there were 105,751 cases and 261 deaths in 1947 and 101,899 cases with 320 deaths in 1948 reported throughout the Protectorate. In 1948, 11,204 cases were treated as in-patients. Table 3.1 shows the distribution of reported cases for the year 1948, although it is often stated this would have been a major under-estimate of the indigenous population's disease burden [Uganda Protectorate, 1949].

Table 3.1: Cases of malaria recorded at various stations in Uganda in 1948 [Uganda Protectorate, 1949]

Station	Total cases reported
Kampala	5,868
Masaka	6,480
Mbarara	4,670
Jinja	6,870
Tororo	4,962
Soroti	4,788
Lira	2,769
Gulu	4,992
Masindi	2,806
Arua	5,451
Mbale	7,001

In 1950, a review of statistics suggested that malaria mortality among hospital admissions had declined over the last 20 years among Europeans and Asians, and that "*It is now an unusual event to become infected with malaria in some of the major towns*". Entebbe reported six anopheline breeding sites, 259 breeding sites were recorded in Kampala Municipality with only 13 adult anophelines caught in dwellings during in 1950. Of 103 patients treated for malaria in the Government European and Asian Hospitals, only 10 were thought to have contracted the infection within the municipal boundaries [Uganda Protectorate, 1951]. Ten miles of new earth drains were dug in Kampala, while a mile and half of open concrete drains, three miles of sub-soil drains were constructed and numerous brick-pits were cleaned and stocked with *Lebistes* fish during 1950. Although it was noted that the remaining high risk areas included the Kabaka's Lake and adjacent swamp and pits used in the manufacture of bricks [Uganda Protectorate, 1951]. Although European settled areas had come under a degree of control the report goes on to say that "*the available evidence suggests that no appreciable change has taken place in its*

incidence among general African population". 80% of diagnoses of malaria at hospitals were unsupported by microscopic examination [Uganda Protectorate, 1951].

At Jinja, where a rapid industrial development had begun, housing schemes had brought residential areas into closer proximity with the peripheral breeding grounds such as brickfields and the lake shore swamps. In this township attempts at control by spraying gammexane powder on backwaters and spraying oil along the Lake edges were ineffectual. Despite a growth in vector breeding sites only 19 patients were treated for malaria at the Government Hospital during 1949, thought to be a result of the prophylactic use of proguanil (paludrine) by newly arriving expatriates [Uganda Protectorate, 1951].

From 1950 there were few specific reports of malaria activities in the pre-independence annual medical reports.

3.3 Malaria control 1950-1969: Pre-eradication planning

In 1950, the first malaria conference in Equatorial Africa, convened by the World Health Organization, was held in Kampala [WHO, 1951; Anon, 1951a; Dobson et al., 2000]. This historic conference was used to present and assess all the available information on the epidemiological aspects of malaria and attempted to coordinate the various methods of research and control of the disease. Its two main recommendations were: 1) that malaria should be controlled by all available methods, irrespective of the degree of endemicity of the disease; and 2) the benefits that malaria control might bring to the indigenous populations should be evaluated [WHO, 1951; Anon, 1951a; Anon 1951b, Dobson et al., 2000]. The role of research as a means to address the technical problems of control in tropical Africa was stressed at this meeting and was integral to the GMEP effort. The 1950 Kampala conference catalysed many studies in Africa, including a number of important field trials aimed at the “eradication” (appropriate term should have been elimination) of malaria in Uganda.

The Uganda malaria pre-eradication programme was established in 1964 as a joint Government of Uganda-WHO project with its headquarters at the malaria centre in Jinja (which later became the school of laboratory technology). In 1967, with the appointment of a Ugandan malariologist, Dr. G.W. Kafuko, as head of the programme, the WHO’s contribution was reduced to supporting the project to develop basic health services. After the abandonment of the eradication programme in 1969, Kafuko was to become the first Ugandan Director of the East Africa Virus Research Institute (EAVRI) in Entebbe, initially set up in 1936 as a yellow fever centre. After the collapse of the East African Community in 1977, EAVRI became the Uganda Virus Research Institute.

Building an epidemiological profile formed a major effort of the mid-1960s “pre-eradication” effort, resulting in intensive investigations in some areas and wider mapping of risk across the country (Section 4.1). The largest surveys were undertaken at Kigezi/Masaka [de Zulueta et al., 1963], Busoga (currently composed of ten districts - Bugiri, Buyende, Iganga, Kaliro, Kamuli, Luuka, Jinja, Mayuge, Namutumba and Namayingp) [Onori & Benthein, 1967] and Karamoja

[Onori, 1967; Onori, 1969; McCrae, 1975]. During these surveys, the field teams described the topography, the climate including temperature, humidity, winds, peak rainfall and the main agricultural pre-occupation of surveyed localities. Field operations were initiated in February 1964 and continued until the end of February 1965, while in other areas the surveys were conducted over the period 1966-67. They consisted of malariometric and entomological surveys carried out at regular intervals at 10 selected localities in each district (except Karamoja where 15 sites were selected) and monthly infant and fever surveys. School surveys were carried out at all the sites at approximately three monthly intervals, while general mass population surveys were conducted at eight of the 10 localities at six monthly intervals. Blood films were taken by medical assistants in charge of the medical units and collected every fortnight by project staff for examination at a central haematology laboratory at the district head quarters. Eight indicator localities were selected in each district for monthly entomological surveys; including: day time spray catches in eight fixed houses of different types of structures; all human and animal landing night catches indoors and outdoors for two consecutive nights (4 localities); window trap observations (4 localities); identification of the blood digestion stages and salivary gland dissections; identification of blood meals from samples collected in different types of structures [Onori & Benthein, 1967].

3.3.1 Malaria eradication experimental pilot projects

3.3.1.1 Northern Kigezi, Western Uganda, 1959-64: Kigezi district and parts of Masaka district were targeted for malaria "eradication" operations and experiments. Malaria prevalence in Kigezi district varied from meso to hyper-endemic with spleen rates in children 2-9 years of age as high as 92% in some localities [de Zulueta et al., 1961; de Zulueta et al., 1963]. *Anopheles gambiae* s.l. was the main vector throughout the area, with *Anopheles funestus* playing a secondary role in malaria transmission in a few localities [Garnham et al., 1948; de Zulueta et al., 1961; de Zulueta et al., 1963]. After the preliminary surveys conducted in 1957 and 1958 [De Rook & Cullen, 1957; Cullen, 1958], the pilot project was launched in January 1959. Initially the investigations were limited to North Kigezi at a government resettlement scheme. However, the project was extended toward the end of 1959 to the rest of Kigezi district (Section 3.3.1.2) [De Zulueta et al., 1964]. Interventions focussed on three annual rounds of IRS with Dichloro-Diphenyl-Trichloro-Ethane (DDT) and mass drug administration (MDA) with single doses of chloroquine-pyrimethamine (Chloroquine 200 mg base and Pyrimethamine 16.5 mg) (CQ/P).

Careful assessments of impact were undertaken. School surveys of infection and spleen prevalence; monthly infant parasite prevalence surveys at dispensaries and health posts before and after spraying; monthly fever surveys during visits to the health facilities; sampling adult indoor resting mosquitoes, outside resting traps were also used for outdoor catches, larval searches as part of reconnaissance surveys and the use of experimental huts in the Katoche area of Northern Kigezi [de Zulueta et al., 1961]. During the first year of the operations, there was an almost complete disappearance of malaria: parasite prevalence declined from 16.6% to 0.3%. Surveys carried out in other parts of Kigezi and Masaka district showed practically no reduction in malaria rates [de Zulueta et al., 1961]. By 1963, the malaria eradication experiment

in North Kigezi was deemed a success having eliminated malaria from almost the entire district [de Zulueta et al., 1964]. However, imported malaria led to localised outbreaks in the late stages of the scheme because malaria was never completely interrupted in the areas adjoining the protected areas in North Kigezi [Gillet, 1958; 1959].

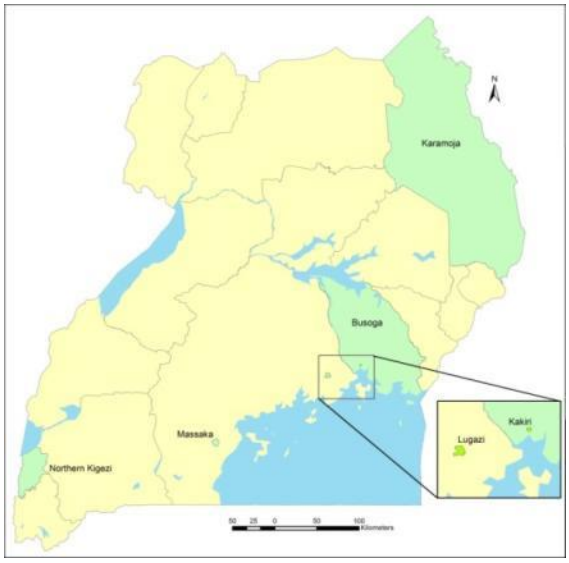
3.3.1.2 Kigezi highlands, Western Uganda, 1960-1964: The distribution of malaria in Kigezi district was closely related to the topography and climate. Before the Malaria Eradication Pilot Project started in Kigezi, there was malaria transmission in the whole of the North Kigezi, with hyper-endemic conditions in the flatlands near Lake Edward up to approximately 1128 m. However, beyond this attitude up to 1372 m, meso-endemic conditions prevailed. Further up in the highlands of central and southern Kigezi there were no permanent foci of transmission with the exception of the areas around Lake Bunyonyi (altitude 1920 m), Lake Mutanda (altitude 1798 m) and the small Lake Kimbugu (attitude 1600 m) near Kisizi. Following the success of the campaign in North Kigezi, and an attempt to prevent the rate of new infections being brought into the protected areas, it was decided to extend the eradication operations to the whole of Kigezi district.

The malaria "eradication" measures used in the Lake Bunyonyi area were the same as those used in the North Kigezi programme [de Zulueta et al., 1961] with the exception that there were only two rounds of MDA with CQ/P done during the spraying. Moreover, the first round of MDA covered only half of the target population due to delays in the delivery of the drugs. The results of the Lake Bunyonyi campaign were equally impressive. Not a single *An. funestus* was observed in six surveys conducted after DDT spraying in February 1961 up to May 1962. In spite of the complete elimination of *An. funestus* from the area, other less dominant anophelines were implicated in transmission *An. coustani*, *An. demellion*, *An. marshali* and *An. kingi* [de Zulueta et al., 1964]. Parasite prevalence declined from 21% in 1959 to 0.1 % in 1960 and 1961. De Zulueta and colleagues concluded "*the results so far obtained in Kigezi indicate the possibility of malaria eradication in the area within a short time. Preliminary surveys in other parts of Western and Central Uganda indicate that no more malaria is to be found there than in Kigezi, thus showing that the eradication of malaria in Central and Western Uganda is feasible*" [de Zulueta et al., 1964].

3.3.1.3 Field trial of Malathion in Masaka, Southern Uganda 1963-1964: Between 1963 and 1964, with the assistance of WHO, a large scale field trial of Malathion was carried out in Masaka district [Najera et al., 1967]. The areas of intervention covered 500 km^2 and a population of 26,000 inhabitants. All houses and animal shelters were sprayed with Malathion at 2 grams per square metre approximately every 4 months. Epidemiological evaluations were organised from November 1964 across a central area comprising 40% of the sprayed areas using parasitological and entomological methods developed during the Kigezi project. The average combined densities of *An. funestus* and *An. gambiae* declined from 66 per shelter per day in the pre-trial period-1960-1961 to 0.0011 at the end of 1964 in the sprayed area. No significant changes were noted in the non-sprayed areas. However, the persistence of malaria cases and the observation of some infections in infants born after the commencement of spraying were reported as not consistent with the entomological observations. Further

epidemiological investigations revealed that there were constant movements of the population in and out of the small intervention area and consequently a high importation rate of new infections. Moreover, the new entrants into the intervention area built new houses which remained unsprayed until the next spray round, leading to autochthonous cases from uncontrolled onward transmission of imported infections [Najera et al., 1967].

Figure 3.2: Map showing areas of 1960s malaria investigations and pilot projects



3.3.1.4 Chloroquine (CQ)-medicated salt for malaria suppression Lugazi & Kakira 1964-1965: A mixture of CQ with common salt had been proposed as an alternative method of MDA in situations where insecticide spraying was not effective [Pinotti, 1954; Clyde et al., 1964]. A trial began in Uganda between 1964 and 1965, involving the free distribution of CQ-medicated salt to workers and their dependants at two sugar estates, Lugazi and Kakira (48-87 km east of Kampala) [Hall & Wilks, 1966]. Prior to the launch of the trial it had been shown that IRS with DDT was unsuccessful in removing infection in the highly mobile immigrant labor force at these estates that recruited people from all over Uganda and Rwanda and employing circa 10,000 people on each estate. Weekly administration of CQ tablets had been tried but abandoned due to widespread objections to the bitter taste.

The effects of the MDA programme were assessed using mass blood examinations and morbidity data comparing recipient populations with similar populations on the estate not receiving the medicated salt. The results of this pilot experiment were inconclusive. There were no differences in infection or morbidity among children during 1964; larger differences were observed by 1965 notably among adults, a 30% decline in morbid events, but not among infants. There were problems with irregular distribution of CQ-medicated salt and some households bought alternative salt supplies from shops to avoid the bitter taste. Overall it was concluded that with satisfactory distribution of CQ medicated salt significant reductions in the crude parasite rates and morbidity could be achieved. Failure to achieve complete suppression

because of operational shortcomings, individual non-cooperation and inadequate uptake of the medicated salt per recipient meant that wider adoption was never pursued.

3.3.2 Other pre-eradication activities in Uganda 1950s-1960s

Larvicide control using drainage and oiling continued during the 1950s and 1960s in the urban areas of Uganda but the strategy was deemed not feasible in rural areas although partial measures such as the use of eucalyptus plantations was thought to be beneficial [Najera et al., 1967]. Reporting to the WHO malaria conference in Lagos in 1955, the Ugandan Government indicated that only 50,000 people were covered by malaria prevention activities [Anon, 1955]. Despite this low coverage, the report also mentions that the effects on the labour force were significant with an average daily malaria sick rate of 1.6 per 1000 [Anon, 1955]. Most control between 1950 and independence continued to focus on urban settlements where control formed part of the responsibilities of 13 urban councils, supported by the Ministry of Sanitation's Vector Control Units (VCUs) and activities eventually governed by the Public Health Act of 1964 [Uganda, Public Health Act, 1964]. Unfortunately, in spite of the locally appreciated services provided by the VCUs, they were all disbanded in 1983 due to financial constraints.

3.4 Malaria control 1970-1995: apathy to renewed interest

The malaria eradication experiments in Uganda, targeting adult vectors or parasites, provided in some cases impressive findings on the impact on transmission. However, following the abandonment of the eradication goal in Africa after the recommendation of WHO in 1969 [WHO, 1969], there was a general sense of disappointment and apathy globally and nationally and the latter was associated with a decline in resource allocation for malaria. Uganda's malaria program collapsed due to lack of human and financial resources. During the period 1970 to 1990, a period of great civil and political turmoil (Section 2.2), there was little effort made to control malaria, resulting in a resurgence of the disease across the country. The years of civil strife left the entire Ugandan health system in serious disrepair. The malaria control programme lost critical programme staff and the malaria centre at Jinja was left in disrepair. Efforts to revamp the Uganda health sector in the early 1980s were hampered by rampant insecurity and a de-motivated work force. The only semblance of malaria control was presumptive case management with chloroquine. There were no clear policies and no strategic plan. From 1986 onwards, Uganda as a country started making some recovery, including a gradual economic growth. However, there was no matched improvement in the health indicators during this period (Section 2.5).

It was not until the early 1990s, when global efforts to control malaria were re-started, that malaria gained some greater national prominence. In 1992, a global malaria control strategy aimed at preventing mortality and reducing morbidity was adopted by the ministerial conference held in Amsterdam. This strategy was adopted by the World Health Assembly (WHA) in 1993 as the global strategy for malaria control [WHO, 1993].

The only significant malaria research leading up to 1995 was undertaken in two districts,

Kabarole and Bundibugyo, supported by the German Development Cooperation (GTZ). These studies were important in providing contemporary data on the epidemiology and micro-epidemiology of malaria in Uganda, assessing the knowledge attitudes and practices towards malaria with an emphasis on how communities understood treatment and prevention and estimates of malaria specific mortality rates in different endemicity zones [Kilian, 1995].

3.5 Malaria control 1995-2001: defining the challenge

After the endorsement of the global malaria strategy by the WHA in 1993 [WHO, 1993], Uganda's malaria control efforts started gaining some visibility within the epidemiological division, communicable disease control (CDC) of the Ministry of Health, led by the late Dr. Alex Kamugisha. The division conducted an analysis of the malaria control problems in Uganda in the early 1990s and revealed the following challenges: lack of integration and inter-sectoral collaboration in control; problems with case management due to self-prescription and the wide availability of antimalarials on the open market; failure of vector control and environmental management, partly due to the efficient transmission characteristics of the major vectors and the multiplicity of breeding sites, but also due to lack of environmental management planning; absence of trained personnel; lack of an information system for monitoring and evaluation; inadequate early detection of malaria epidemics in vulnerable populations; escalating drug resistance of *Plasmodium falciparum* to CQ; and lack of resources [MOH, 1996].

In 1995, a burden of disease (BOD) study conducted in 13 of the districts supported by the World Bank District Health Services Project (DHSP) found that 75% of life years lost to premature death in Uganda were due to ten preventable diseases, including perinatal and maternal related conditions, malaria, acute respiratory infections, HIV/AIDS, tuberculosis, and diarrhoea [MOH, Epidemiology Unit CDC, 1996]. In Mukono and Kabale districts, for example, malaria contributed to 16.4% and 32.2% of the discounted life years lost respectively, suggesting that in the 1990s the largest number of life years lost was due to malaria. However, the resource allocation for malaria was not commensurate with this disease burden.

Faced with these statistics, the Ministry of Health, established the Malaria Control Unit (MCU) in 1995, under the division of epidemiology, communicable disease control. The MCU initially had three staff namely: the late Dr. Gilbert Mpigika as programme manager, Dr. Betty Mpeka as deputy programme manager and Dr. Tiberuis Muhebwa who briefly worked as the MCU medical officer before leaving for further studies overseas the same year. In 1996, a medical officer (Dr. Ambrose Talisuna) was posted to the MCU directly from further postgraduate studies in epidemiology. The MCU was then housed in two cargo containers at the back of the former Ministry of Health headquarters at Entebbe. The MCU, during 1998, moved to the former WHO offices near the botanical gardens in Entebbe. In 1999, when the entire Ministry of Health headquarters was relocated to a new structure, constructed with the support of the World Bank, the MCU offices relocated to its current offices at the headquarters in Kampala.

In 1996, two years prior to the launch of the RBM campaign, the World Bank initiated funding to support malaria control efforts in several African countries. Between 1996 and 1999 the

World Bank, WHO and UNICEF led missions to six countries: Kenya, Mozambique, Tanzania, Ethiopia, Malawi and Uganda. In Uganda, the team met with key stakeholders including government officials, health sector staff, researchers, non-governmental organizations (NGOs) and manufacturers. The mission highlighted the impact of malaria in Uganda and concluded that malaria control activities should be integrated within existing and proposed World Bank operations in the country. However, existing resources were being under-utilized, as the public health sector did not have the capacity to absorb available funding [Talisuna, 2008]. While these joint missions were a practical step towards creating a national partnership around malaria, it became very clear that partnerships would not establish themselves naturally and cross-sectoral approaches were not well-institutionalized.

After the 1996 joint country mission to Uganda, malaria did become more recognized as a national priority. The Minister for health, Dr. C.W.C.B Kiyonga, and the director general, Dr. Kihumuro Apuuli, directed the development of a five year Malaria Strategic Plan (MSP) (1996-2001) and a three year malaria policy. The plan was launched under the banner of "*the Uganda Intensified Malaria Control Initiative*" [MOH, 1996]. The goal was to reduce malaria morbidity and mortality to the lowest level possible using the available means. To achieve this goal the following priorities were identified: 1) improved management of malaria by the rational use of chemotherapy in the community, public and private health facilities; 2) improved community awareness; 3) reduction of human mosquito contact by encouraging personal protection; 4) strengthening and building management capacity centrally and at the district level; and 5) integration of malaria control activities within other health sector priorities. Specific targets were set, although no details on how these would be measured were offered, including the reduction of malaria mortality among children by 30% by 2001, 50% reductions in the incidence of severe malaria in children and 30% reductions in the incidence of malaria related complications in pregnancy.

The strategy emphasized the importance of early diagnosis and effective treatment of malaria in all areas, including improving laboratory components. Importantly, it was recognized that implementation had to be through the district care system in collaboration with other agencies within the communities. It was hoped that there would be significant investment in improving the information platform, through the Health Management Information System (HMIS), to provide evaluation metrics and help define epidemic thresholds for early detection.

At the time the intensified malaria control initiative was launched, a complimentary anti-malaria policy was developed in 1996 and passed by cabinet in 1998 [MoH, 1996]. The aims in the policy followed those of the MSP but retained several historic elements of malaria control including environmental sanitation and the destruction of breeding places where feasible. The policy guidelines also covered the treatment of malaria with CQ as the first line drug, sulphadoxine-pyrimethamine (SP) as the second line drug and quinine as the drug for severe malaria and for cases resistant to CQ or SP. The policy further stated that chemoprophylaxis could be useful for first and second time pregnancies, patients with sickle cell disease and visitors from non-endemic countries. The antimalarial policy recommended that legislation should be made on proper mosquito control especially in urban areas and identified priority

research, including monitoring treatment efficacy and drug sensitivity, monitoring the quality of antimalarial drugs present in the country and a broader economic, cost effectiveness analysis.

3.5.1 Restructuring of the malaria control unit and district management

After the development of the first MSP (1996-2001), the Minister for health directed the restructuring of the MCU. Consequently, Dr. Gilbert Mpigika (1995-1997) was replaced by Dr. Dawson Mbulamberi (1997), whose tenure was very short lived as he was quickly replaced by Dr. Peter Langi (1997-2004). In addition, a technical advisor (Dr. Albert Kilian) was seconded to the MCU from the GTZ project in Kabarole and Bundibugyo.

The first MCU organogram composed of the following sections: Program manager (Dr. Peter Langi), deputy Program Manager and in charge for case management (Dr. Betty Mpeka, later joined by Dr. Fred Kato in 1998), epidemiology, epidemic preparedness and control, research and data management (Dr. Ambrose Talisuna, replaced in 1999 by Dr. Nathan Bakyaita), vector control and environmental management (Mr. Michael Okia, Ms. Connie Balayo, the late Mr. Tom Byembabazi). Dr. Christopher Kigongo the Information, Education, Communication (IEC)/Behavioural Change Communication (BCC) focal person for the World Bank was seconded permanently to the NMCP in 1998. Finally, a supporting technical advisor (Ms. Jane Edmondson) was, in 2000, provided by the UK's Department for International Development (DFID).

In line with the 1993 policy of decentralization, the first anti malarial policy recommended the creation of a functional level called zonal coordination centres to support the decentralized districts in the implementation of malaria control. These coordination centres were based at the ten regional referral hospitals in Arua, Fort Portal, Hoima, Kabale, Lacor, Jinja, Masaka, Mbale, Mbarara, Kabale, Soroti and the the national referral hospital at Mulago. In the Karamoja region, because of the lack of a regional referral hospital, Moroto and Matany hospitals were selected. Public health specialists, physicians, obstetricians and paediatricians at the regional hospitals who had demonstrated a keen interest in malaria were assigned the additional responsibility of coordinating malaria control activities in their zones. At the district level an officer was assigned the additional responsibility of serving as the malaria focal person. The operation of the zonal coordinators system was initiated in 1998 and the overall objective of the zonal coordinators system was to assist the national level in providing support to districts with respect to the coordination, planning, implementation, supervision, monitoring and evaluation of malaria control activities. The support to malaria control in the districts was guided by the national MSP. This system of zonal coordination was to be jointly implemented from 1998 with the existing Integrated Management of Childhood Illnesses (IMCI) programme [Kolstad et al., 1997]. However, insufficient funds for the operational cost of this system of integrated support prevented its smooth functioning.

3.5.2 Assembling morbidity and mortality data and defining epidemics

In 1998, the Member of Parliament (MP) for Busia county Hon. Aggrey Awori requested on the floor of Uganda's parliament that the Minister for health, Hon. Dr. Crispus Kiyonga, provides the mortality estimates for malaria in Uganda disaggregated by sex for each of the then 39 districts. When the minister for health asked the MCU team to provide the information to help him repond to the MP's request, the first response to the minister was that it was not possible to provide such estimates with the available data. The health minister said *"Why does everyone report that malaria is the leading cause of morbidity and mortality in Uganda, yet there is no evidence to support that claim".* A team of epidemiologists and public health experts were assembled to provide a very crude model based on all-cause child mortality estimates in sub-Saharan Africa, the Burden of Disease (BOD) study of 1996 [MoH, CDC, 1996] and the mortality estimates from the GTZ project in Kabarole and Bundibugyo [Kilian A, 1995] which resulted in a crude annual death estimate attributable to malaria for all age groups of 70,000 (95% confidence interval (CI): 50,000-100,000). The Minister, when reporting back to parliament elected to use the upper limit of 100,000 deaths due to malaria per annum. The next day it was front page headline news in the main daily the New Vision *"Malaria kills 100,000 Ugandans every year"* [The New Vision, 1998]. This estimate, which is still widely quoted today in many programme documents, is definitely incorrect but a better defined estimate has yet to be produced. This early political plea for better data did however focus attention on assembling the evidence and marked the beginning of the re-establishment of the central malaria database and annual district morbidity data summaries [NCMP annual reports, 1998-2001; Talisuna, 2004; later reviewed by Yeka et al., 2012].

The need for better data was most urgent for the detection of malaria epidemics in the highland areas of Uganda, where a lack of an efficient surveillance system meant outbreaks were detected late, had a poor response or were missed entirely. The first epidemic waves began in July 1994 in the Kabale and Kisizi regions. In July 1994, 1,684 patients were admitted to the hospital of Kisizi with a confirmed diagnosis of malaria, compared to 200 in July 1993, and 225 in 1995 [Mouchet et al., 1998]. Later the El Niño Southern Oscillation (ENSO) unstable climate conditions in the Pacific during 1997–1998 led to exceptional rainfall patterns across East Africa [McPhaden, 1999] resulting in several dramatic malaria epidemics. At Kabale, the ENSO effect resulted in a malaria epidemic that lasted from February to April 1998 [Kilian et al., 1999; Lindblade et al., 1999] driven largely by excessive rainfall but compounded by changing land-use patterns near swamps [Lindblade et al., 2001]. Between 1990 and 2000 regular malaria epidemics occurred in Kisoro, Rukungiri and Kabale in the south-western part of the country [Talisuna, 2004].

Following these epidemics the MCU developed an epidemic preparedness guideline with technical assistance from a WHO consultant (Dr. Jose Najera). The guidelines included a malaria early warning sysetm (MEWS) and a malaria epidemic early detection system (MEDS) [MoH, NMCP, 1998]. The MEDS was proposed for the District Health Teams (DHTs), which involved close monitoring of critical malaria epidemic indicators at health facility, health sub-district and district levels in order to identify any abnormal patterns. In addition, any local reports of

upsurges of fever cases and any abnormal clustering of deaths were to be investigated using the existing integrated disease surveillance and response (IDSR) monthly/weekly data [Cox et al., 2007; Nsubuga et al., 2010; Lukwago et al., 2013].

The late 1990s identified a number of areas prone to epidemics: the arid North Eastern part of the country and the highland areas in the western and south western parts of the country. These areas include: in the South West region Kabale, Kisoro, Kanungu, Rukungiri, Ntungamo and Bushenyi districts, in the Western region Kasese, Bundibugyo Kamwenge and Kabarole districts, and in the Eastern region Bukwa, Kapchorwa, Sironko, Mbale, Manafa and Bududa districts.

3.5.3 Grappling with antimalarial drug resistance and the first antimalarial drug policy change

Effective malaria treatment during the mid-late 1990s was complicated by the emergence of resistance to widely used antimalarial drugs such as CQ. There had been no reports (suspected or confirmed) of *Plasmodium falciparum* strains resistant to CQ or amodiaquine (AQ) before 1969. In 1969, following a report of reduced CQ response from the missionary Hospital at Kuluva in West Nile, a field study was conducted. 160 children attending Eruba school, 180 children attending Vurra School and 90 children attending Kuluva missionary hospital were examined for the presence of parasites daily following standard body weight CQ three day dosing [Onori & Benthein, 1969]. The trial found that CQ eliminated parasitaemia before the 5th day post-treatment with a large majority clearing parasites on the 3rd day, suggesting normal sensitivity to CQ in Kuluva [Onori & Benthein, 1969].

Between 1970 and the early 1980s there were hardly any drug efficacy studies conducted. However, over the period 1988-2001, several *in vivo* efficacy studies were conducted with different protocols, different study populations and different outcome measures (Table 3.2). Many of the studies conducted before 1996 used asymptomatic subjects attending schools as recommended by the then WHO protocol [WHO, 1965], while those conducted after 1996 recruited symptomatic patients aged between 6 and 59 months or all age groups [WHO, 1996].

Faced with the lack of standardization of drug efficacy methodology and the limited sharing of data generated in the late 1990s, the East African Network for Monitoring Antimalarial Treatment (EANMAT) was conceived in 1997 in response to the sub-region's growing need for reliable information on the sensitivity of malaria parasites to antimalarial drugs. The goal of the network was to ensure that rational and evidence based malaria treatment policies were implemented in the East African Region. The network began in 1997 with Kenya, Uganda and Tanzania (mainland), and was joined later by Rwanda, Burundi and Zanzibar [EANMAT, 2001; EANMAT, 2003].

Initially the majority of the testing, data collection and analysis in Uganda was done by the MCU in collaboration with the staff at the sentinel health facilities at Aduku in Apac, Nangogera in Tororo, Kyenjojo in Kabarole (now Kenjojo), Cilio in Arua, Kihihi in Rukungiri (now Kanungu), Kasabya in Mubende, Mulago in Kampala and Walukuba in Jinja district (Figure 3.3) [Talisuna et

al., 2002; Bakyaita et al., 2005]. However, in view of the complexities required to conduct these studies, a model based on collaboration with local research partners was adopted after the formation of the Uganda Malaria Surveillance Programme (UMSP) later named Infectious Disease Research Collaboration (IDRC) [http://www.idrc-uganda.org/]. This collaboration has since produced the largest volume of drug efficacy data since 2005.

The data generated by the EANMAT/UMSP sentinel surveillance and several other studies conducted in Uganda confirmed that the prevalence of CQ resistance had become a major problem. For the period 1999-2001, CQ treatment failures had reached an average of 33% in the country, based on a 14 day follow up in children less than five years old (Table 3.2). While SP mono-therapy treatment failure had increased from 5.5% to 12% for the period 1995-1998 (Table 3.2). Paradoxically, faced with these data the Ministry of Health changed the first-line treatment policy at the end of 2000 to the combination of CQ+SP [MoH, 2000; Kamya et al., 2002], which had an average failure rate of 7% at the time the policy was launched.

This interim solution was selected because there was a perceived lack of practical alternatives. Treatment guidelines and other training and communication materials were updated, supplies of SP increased to support CQ co-administration and all health staff in the public sector trained on the new treatment guidelines. Following the 2000 decision, the actual launch of the policy took place in April 2002 and by 2003 practically all government health facilities used CQ+SP for malaria treatment. In contrast, uptake was significantly slower in the private sector where in September 2002 only 15% of all shops had both, CQ and SP available [Commercial Market Strategies Project Report, 2002].

After several studies trying to improve malaria case management at home [Kengeya-Kayondo et al., 1994; Kidane & Morrow, 2000; Ghebreyesus et al., 1999], in 1998, WHO-TDR spearheaded pilot studies to assess the feasibility of using pre-packaged medicines for home based management of malaria fevers (HBMF). The first pilot countries were Ghana, Nigeria and Uganda. In Uganda the pilot studies were conducted in three sub-counties in Masaka, Mubende and Mpigi districts between 1998 and 2000; the studies demonstrated that HBMF was feasible and could improve access to malaria treatment [Mpeka et al., 2000]. HBMF was adopted as a policy in 2001 [MoH, 2001]. In order to complement the availability of free malaria treatment through public health facilities and bring it closer to the home, the programme of HBMF for children less than 5 years of age was introduced initially in 10 districts in 2002 [MoH, 2005]. The blister packed combination treatment of CQ+SP was developed in two age-dependent and colour-coded packages; one for children 6 months to 2 years and another for the 2-5 year olds. The treatment was called “HOMAPAK” and was produced by a local pharmaceutical company. The medicines were initially distributed directly to the districts by the MCU but delivery was later integrated into the existing essential medicines supply system. Caretakers of children with fever accessed the treatment through volunteers called Community Drug Distributors (CDD) or *Community Medicine Distributors (CMD),* two of whom were selected and trained per village. These CDDs/CMDs reported to and received supplies from the nearest health facility which was also responsible for supervision.

A further growing concern during this period was the quality of medicines available in the private sector. In 1997, the drug regulatory body, the National Drug Authority (NDA), sampled 12 quinine mixtures/syrups from nine local manufacturers and found that none of them produced quinine in standard strengths (i.e. 100-mg quinine base/5 mls) [NDA, 1997]. A study on the quality of CQ reported that up to 30% of the tablet samples and 33% of the injectable CQ samples contained less than the normal amount of the active ingredient; only 45% of tablet samples and 38% of injectable samples of CQ contained the normal amount of active ingredient [Ogwal-Okeng et al., 1998]. A major challenge was that the system for post marketing surveillance and pharmacovigilance was inadequate [Talisuna et al., 2006].

3.5.4 Malaria prevention strategies and coverage 1996-2001 vs available funds

By the end of the 1990s there was overwhelming evidence of the clinical and child survival advantages of insecticide-treated nets (ITN) in Africa [Lengeler, 2004]. However, during the 2001 national DHS survey only 7% of children slept under a mosquito net [UBOS, 2001]. This low coverage was attributed to inadequate financial resources and the initial reluctance by senior level politicians in the Ministry of Health to scale up ITNs. Similarly despite a stated role of IRS in the MSP there was no documented evidence of its use. Weekly chemoprophylaxis for the prevention of malaria in pregnancy, targeting the first and second pregnancies had been identified as a strategy in the 1996-2001 strategic plan. However, again its implementation was affected by the lack of an infrastructure for the weekly delivery of drugs.

The 1996-2001 MSP had one glaring omission, it was never costed and funding agencies did not contribute to the plan. Consequently the activities identified in the plan were either not implemented or were implemented on an *ad hoc* basis because of lack of financial support. The main funding for the district based activities was from the World Bank through the district health services project, while the UK's Department for international development supported the response to malaria epidemics as well as drug resistance surveillance through support to EANMAT. EANMAT also received support from the Belgian Development Cooperation. The WHO provided technical assistance and the government of Uganda provided financial support to procure antimalarial medicines and salary support to MCU staff.

Table 3.2 CQ and SP resistance studies among children in Uganda (1988-2001)

Study districts	Year of study	Subjects recruited, Age group [follow-up duration]	Parasitological failure (%)		Clinical Treatment failure (%)		Source
			CQ	SP	CQ	SP	
Kampala	1988	Asymptomatic, 5-15 years [7 days]	39	0	-	-	Sezi et al., 1991
Jinja	1988	Asymptomatic, 5-15 years [7 days]	23	0	-	-	Sezi et al., 1991
Masaka	1988	Asymptomatic, 5-15 years [7 days]	38	0	-	-	Sezi et al., 1991
Masindi	1988	Asymptomatic, 5-15 years [7 days]	29	0	-	-	Sezi et al., 1991
Kasese	1988	Asymptomatic, 5-15 years [7 days]	21	0	-	-	Sezi et al., 1991
Arua	1988	Asymptomatic, 5-15 years [7 days]	3	0	-	-	Sezi et al., 1991
Kabarole	1992	Asymptomatic and uncomplicated, 0.5-60 years [7 days]	16	5	-	-	Kamugisha et al., 1994
Kampala	1993	Uncomplicated, 0.5-5 years [14 days]	12	2	-	-	Ministry of Health , 1993
Apac	1993	Uncomplicated, 0.5-5 years [14 days]	2	0	-	-	Ministry of Health , 1993
Tororo	1993	Uncomplicated, 0.5-5 years [14 days]	8	0	-	-	Ministry of Health, 1993
Hoima	1995	Asymptomatic, 7-10 years [7 days]	58	4	-	-	Ndyomugyenyi & Magnussen, 1997
Jinja	1996	Uncomplicated, 0.5-5 years [14 days]	36	5	12	6	Ministry of Health , , 1996
Bundibugyo	1996	Uncomplicated, 0.5-5 years [14 days]	40	13	33	5	Kilian et al., 1998 (unpublished)
Kabarole	1996	Uncomplicated, 0.5-5 years [14 days]	77	7	58	4	Kilian et al., 1998 (unpublished)
Jinja	1996	Uncomplicated, 0.5-5 years [14 days]	36	6	12	6	Mpeka & Ndezi, 1996 (unpublished)
Jinja	1998	Uncomplicated, 0.5-5 years [14 days]	33	3	28	2.4	Talisuna et al., 2002
Tororo	1999	Uncomplicated, 0.5-5 years [14 days]	88	72	21	15	Talisuna et al., 2002
Arua	1999	Uncomplicated, 0.5-5 years [14 days]	43	19	21	10	Talisuna et al., 2002
Apac	1998/99	Uncomplicated, 0.5-5 years [14 days]	41	14	15	10	Talisuna et al., 2002
Rukungiri	1998/99	Uncomplicated, 0.5-5 years [14 days]	10	0	10	0	Talisuna et al., 2002
Kabarole	1998/99	Uncomplicated, 0.5-5 years [14 days]	81	20	44	13	Talisuna et al., 2002
Moroto	1998	Uncomplicated, 0.5-5 years [14 days]	-	-	48	12	EANMAT/MoH

Study districts	Year of study	Subjects recruited, Age group [follow-up duration]	Parasitological failure (%)		Clinical Treatment failure (%)		Source
			CQ	SP	CQ	SP	
Moroto	1999	Uncomplicated, 0.5-5 years [14 days]	-	-	21	17	EANMAT/MoH
Hoima	1998	Asymptomatic, 4-10 years [7 days]	28	1	-	-	Ndyomugyenyi & Magnussen, 2000
Mbarara	1998/99	Uncomplicated, 0.5-5 years [14 days]	-	-	81	25	Legros et al., 2002
Kampala	1998/99	Uncomplicated, 0.5-5 years [14 days]	83	-	62	-	Dorsey et al., 2000
Kampala	1999	Uncomplicated, 0.5-5 years [14 days]	96	33	76	11	Kamya et al., 2001
Kampala	1999/2000	Uncomplicated, 0.5-5 years [14 days]	-	-	26	14	Staedke et al., 2001

Figure 3.3 Location of sites generating information on CQ and SP resistance 1988-2000

3.6 Malaria control 2001-2005: The early days of Roll Back Malaria (RBM)

3.6.1 National strategy 2001-2005

Hon. Dr. Chrispus Kiyonga, Minister for Health, and Professor F.G. Omaswa, Director General of Health Services, led several major health sector reforms during the early 2000s. Among these reforms was the formulation of the Uganda National Health Policy 1 in 1999 (UNHP1) and Health Sector Strategic Plan 1 (HSSP1), launched in 2000 and 2001 respectively [MoH, 1999, MoH, 2001a]. The NHP1 and the HSSP 1 identified malaria as one of the priority health programmes in the Uganda minimum healthcare package (UNMHCP). To be consistent with the HSSP1 and with global initiatives such as the RBM, the Abuja declaration and the Millennium Development Goals, a second MSP (2001-2005) was developed. This MSP defined the following key targets to be achieved during the 4-5 years of its operation, by 2005: 1) increase the proportion of the population at risk of malaria who receive appropriate treatment for malaria within 24 hours of symptom recognition to 60%; 2) increase the proportion of pregnant women receiving IPT to 60%; 3) increase the proportion of children aged less than 5 years, regularly sleeping under ITNs to 50%; and 4) reduce malaria case fatality rate in hospital level to 3% [MoH, 2001b].

3.6.2 Changing funding landscape for malaria prevention and control strategies

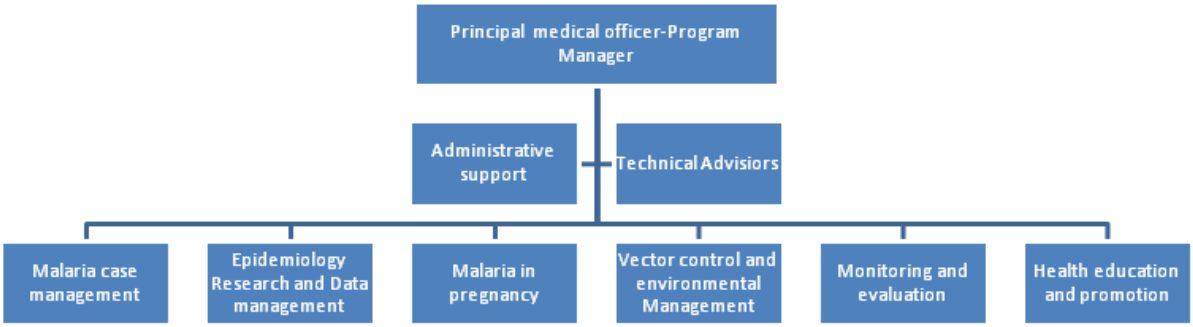
In 2002, the Global Fund to Fight AIDs, Tuberculosis and Malaria (GF) was initiated to alleviate the funding gap for the three diseases. In 2002, Uganda submitted a successful malaria proposal to the Round 2 call for proposals and another successful application to the Round 4 call in 2004. A significant part of the funding from the GF from these rounds financed the second MSP (2001-2005). The funding support from GF in Round 2 amounted to over US$ 23 million and was awarded to support the procurement of long-lasting Insecticide treated nets (LLINs). Round 4 GF funding, over US$ 150 million, was targeted at procuring ACTs and Rapid Diagnostic Tests (RDTs) and support to HBMF. Other external funders included the African Development Bank, USAID, UK's DFID, Development Cooperation of Ireland, WHO, UNICEF and many other donors and international NGOs who supported the implementation of the second MSP.

3.6.3 Changing staff and structure of the MCU

Dr. Peter Langi, who became programme manager in 1997, was replaced in 2004 by Dr. JB Rwakimari. Dr. Albert Kilian, who joined in 1998, left the programme in 2004, while Ms. Jane Edmondson, who was seconded by DFID in 2000 left the programme in 2003 and was replaced by Ms. Allison Bell who also left in 2005. The MCU organogram was reviewed and re-defined in 2001 (Figure 3.4) and four technical working groups (TWGs) were established to support case-management, insecticide treated materials & vector control, advocacy and IEC and research [MOH, 2001b]. These TWGs reported to the inter-agency coordinating committee (ICCM) that was responsible to the senior management within the Ministry of Health. In 2004, with support from various development partners including the GF (Round 2) and the Malaria Consortium [*www.malariaconsortium.org*] the zonal system was revitalized and the zonal coordinators played a significant role in supervision, training and in improving data collection and quality of malaria case management. At a consensus meeting in the later

part of 2004, it was agreed that: a) the concept of the zonal coordinators system be re-defined, the criteria for selection/ appointment of coordinators be set and resource requirements for zones; b) the terms of reference for zonal coordinators would be clearly stipulated and the 11 malaria control zones demarcated and all 17 vacant positions would be filled [Kato FK, 2012].

Figure 3.4: Revised MCU structure developed in 2001



3.6.4 Vector control

3.6.4.1 Urban malaria control: Urban malaria control received a renewed interest during the early 2000s. Following the principles of urban vector control established during the First World War (Section 3.3.2) a community-based environmental management program for malaria control was started in 2002 within two Ugandan cities (Kampala and Jinja) managed by the US based agency Environmental Health Project (EHP) and funded by USAID [Lindsay et al., 2003; Lindsay et al., 2004]. A detailed assessment of vector breeding sites was undertaken at two sites in Kampala (Kitebi & Kikulu) and two in Jinja (Police Barracks & Loco Estate). Workshops were held with local councils, brick makers and the wider community to explore the potential for vector breeding site management. The action plans in 2003 were specific to the ecology and social make-up in each site. In Kampala, the interventions included filling puddles, introducing larvivorous fish and improving drainage. In Jinja, the plans focused on building and repairing drainage channels and soak-pits. Larvicides were not used. Collections of adult mosquitoes from sentinel houses suggested that there was a reduction in malaria transmission, as indicated by a drop in the number of adult mosquitoes collected. Most important, the interventions were associated with reductions in malaria prevalence of 11% in the Police Barracks and 36% in Kitebi, providing evidence of the potential benefits of Environmental Management for reducing malaria transmission in these urban settings [Lindsay et al., 2004]. Due to public demand for mosquito control services, the Vector Control Units (VCUs) were re-introduced in 2006 in Kampala City Council (KCC) under the management of the Vector Control Division (VCD) of the Ministry of Health. However, faced with the perennial problem of inadequate funding, these units have not been able to perform targeted activities within the community. The VCD of the MoH, established in the 1925, has in recent years been advocating for integrated vector control of malaria (IVM).

3.4.6.2 Insecticide treated nets: During the late 1990s, private sector distributors, mainly Quality Chemicals and Safinet, began to enter the ITN market in Uganda. Sumitomo Corporation and Vestergaard Frandsen (Permanet brand) considered beginning sales and

distribution from 2003. In December 2000, Commercial Marketing Strategies (CMS), a USAID funded project, began social marketing of ITNs using the SmartNet brand (re-branded Permanet manufactured by Vestergaard Frandsen). A further USAID agency began working on nets in Uganda in 2001, with a heavy leaning toward sole private sector distribution, NETMARK. Most nets owned by households during this period were those obtained from commercial sector [NetMark, 2001; NetMark, 2006; Kilian, 2004].

In 2000, the government waived import taxes and tariffs on mosquito nets and netting materials, and USAID funded a Commercial Marketing Services (CMS) project with Population Services International (PSI) and other partners to develop effective social marketing programs for ITNs [Kilian et al., 2009]. However, in 2003, USAID scaled down social marketing and launched a more aggressive private sector approach with the Academy for Educational Development's NetMark project. This project was a partnership geared to create commercially sustainable ITN markets. NetMark established a system of matching private investments for marketing, expanding the distribution, facilitating branding and communications by local businesses for appropriate net use and generic nation-wide promotions of ITN use. Domestic net manufacturing remained nonexistent, although Cooper Uganda Limited developed a small factory in Kampala, employing about 25 women [NetMark, 2006]. NetMark and other groups created five ITN distributors and 1,747 outlets where nets were sold [NetMark, 2006]. Despite these initiatives increasing ITN use was too slow to have any immediate public health impact (Chapter 6).

In 2002, an ITN Working Group of the ICCM was established to address the dual challenge of rapidly scaling up coverage of ITNs among pregnant women and under-fives and supporting the development of a sustainable, commercial ITN market in Uganda. The group first began developing a blue-print for a National ITN Voucher scheme. The scheme was included in the Round 2 GF proposal [The Global Fund, 2002]. It was planned to pilot this concept as part of a USAID funded project with CMS in one district and by UNICEF in a further four districts.

During this period debates continued between partners on the balance between social marketing, private sector demand and supply creation versus subsidized or free net distribution through the public sector [AFM, 2007]. In view of the limited scale up of ITN distribution with the private sector model, the MoH initiated multiple public sector distribution strategies in an effort to increase household ITN ownership. In April 2004, Uganda signed a GF Round 2 grant, the majority of which was intended for the purchase and distribution of 1.8 million ITNs. The MoH decided that all GF funded ITNs and all future ITNs should be given free to ensure that they reached vulnerable groups. Commercial distribution was to be limited to populations that could afford nets. However, the GF grant was temporarily suspended due to mismanagement of funds by the Project Management Unit in the Ministry of Health [Kapiriri & Martin, 2006]. Consequently, ITNs did not arrive in the country until February 2007. By the end of 2006, all 1.8 million ITNs were distributed to 77 districts by the Malaria Consortium and PSI. An additional 650,000-700,000 were later distributed in 2007 through the public sector. These included 550,000 ITNs purchased by the NGO Malaria No More and delivered to 13 districts in April 2007. In 2007, NMCP was awarded US$ 125 million for 17 million nets by the Global Fund. Because of procurement problems by MoH only the first seven million nets were distributed 2010.

Despite the concerted efforts to increase coverage in 2007, the volume of nets remained too low to achieve 60% coverage of vulnerable groups. One consequence of a re-focussed effort on the public sector was that debates around integrating private, commercial sector sales came to an end. From 2007 the government concentrated on public sector delivery.

3.4.6.3 IRS: After the malaria eradication pilot experiments in Kigezi and Masaka districts in the late 1950s and early 1960s, only small and sporadic IRS campaigns were conducted, mainly as a response to malaria epidemics, notably in Kabale, Kisoro and Kanungu districts in 2004. In 2005, IRS was carried out in public institutions within the refugee camps in the northern Uganda districts, coordinated by the Malaria Consortium with funds from the UK's DFID [Malaria Consortium, 2007]. From 2004 there was a growing political pressure on the NMCP to expand IRS using DDT.

3.6.5 IPTp

The 2001-2005 MSP identified IPTp as a key intervention. However, it was realized very early during implementation that a more comprehensive and integrated package for malaria in pregnancy (MIP) was needed. This was reflected in the Malaria in Pregnancy Control Strategic Plan [MoH, 2000] which emphasized three elements: IPTp, clinical case management and prevention with ITNs. The implementation was coordinated principally through the Reproductive Health Programme with support from the MCU's malaria in pregnancy focal person. The objectives were by 2004 to have 60% of all pregnant women receiving two doses of SP as IPTp in their second and third trimesters; at least 80% of pregnant women would have access quality case management; and at least 60% using ITNs. The activities undertaken included: distribution of treatment guidelines (IPT and treatment) and other materials (flow charts, posters) to all government and NGO health facilities; sensitization of health workers. By the end of 2003, 35% of health workers in 40 districts had been trained, a training course on malaria in pregnancy for midwives and nurses had been developed, and SP had been procured and distributed to meet the increased demand [MoH, 2006]. National IPTp coverage of at least two doses, reported through HMIS increased from 22% in 2002 to 27% in 2003 and to 33% by 2004 [MoH, 2005]. However, during this period the routine distribution of ITNs through Antenatal clinics (ANC) remained limited and there was poor coordination between the Reproductive Health Division and the MCU [MoH, 2006]. Furthermore, stock outs of SP in ANC services reduced the potential coverage of IPTp. ITN coverage among recently pregnant women in 2006 remained low, only 16% of women had received two presumptive treatments with SP during ANC visits [UBOS, 2007].

3.6.6 Increasing access to malaria treatment in the home

Rolling out of the HBMF strategy continued between 2003 and 2006 and was assisted by the GF Round 2 and Round 4 funding. A 2003 evaluation of the HBMF program found an increase from 7% in 2001 to 39% of febrile children receiving malaria treatment within 24 hours in nine districts receiving the HBMF intervention. By 2005, HBMF had been scaled-up across communities in 47 districts, including the internally displaced persons (IDP) camps in the North [Malaria Consortium, 2003; Meek et al., 2005]. The approach was widely researched and it was generally felt to be an effective vehicle to ensure malaria medicines

were close to the household when needed for prompt treatment [Kilian et al., 2003; Nshakira et al., 2002; Nsungwa-Sabiiti et al., 2004].

However, HBMF faced many challenges, including: an inability to sustain the initial motivation of the volunteers due to lack of remuneration or other incentives; inability to ensure adequate supervision, data flows and drug supply management challenges; problems associated with being a vertical programme with inadequate integration with other community-based health activities such as IMCI; and finally an inability to transition to the new treatment policy in 2004-2007 using ACTs. The latter had regulatory challenges beyond the NMCP, for example whether community volunteers were allowed to handle the new drug whose safety remained uncertain and there was no pharmacovigillance linked to HBMF. An alternative became more popular, with a focus on integrated community case management (iCCM) and several assessment studies were conducted in the country that demonstrated that iCCM was feasible [Kallander et al., 2004; 2006a; 2006b].

3.6.7 The second antimalarial treatment policy change and implementation 2004-2007

As had been anticipated, resistance to SP as well as CQ+SP continued to rise and reached an average of 16% and 12% treatment failure at day 28 follow-up respectively during the period 2002-2004 [Talisuna et al., 2004; Bakyaita et al., 2005]. The announcement that CQ+SP would be abandoned in favour of Artemether-Lumefanthrine (AL) was first made on 17th May 2004. Interestingly at this stage the data available on AL efficacy from Epicentre at Mbarara were not used by the NMCP to arrive at this decision [JP Guttman, pers comm] and the decision seems to have been arrived as a default position using principally decisions made by neighbouring countries of Kenya, Tanzania and Rwanda, who were members of the sub-regional network EANMAT, and a general reluctance to adopt Amodiaquine (AQ) combinations.

The adoption of the new ACT policy was predominantly based on their good efficacy and the likely long useful life-expectancy with low probabilities of resistance; however, the affordability, acceptability, adherence and feasibility remained uncertain. The NMCP promoted a vision for ACTs of “learning while doing”. GF Round 4 provided approximately US$ 66 million within the US$ 158 million award to accelerate the implementation of the new AL treatment policy, this included funds to purchase AL for the public sector, strengthen distribution systems, train over 5,000 health workers in the new policy during the first year and maintain supervision in the second year. DFID-UK provided funds to the Malaria Consortium so they might support the MCU in this difficult drug policy transition and implementation.

Problems of effective national consensus following the announcement were similar to those faced by Kenya during this period [Amin et al., 2007]. These centred around the ability of the Ugandan Government to finance the long-term supply of AL, single source issues around the Novartis-WHO agreement, the reported global shortages of Artemisinin to produce AL and the possible interruption in manufacture by Novartis. In July 2005 the policy statement was revised to be more inclusive of other ACTs, notably AQ+Artesunate. The policy therefore stated: *“The recommended first line medicine is Artemether/Lumefantrine. This medicine (Artemether/Lumefantrine) is not recommended for children below 4 months of*

age or 5 kg body weight and pregnant women in the first trimester. Artesunate + Amodiaquine is the alternative when Artemether/ Lumefantrine is not available" [MoH, 2005a]. Oral Quinine was the second line treatment for all patients and also for pregnant women with clinical malaria.

It was not until 9th September 2005, that the NMCP organized a dissemination workshop to introduce the new policy to a wider set of stakeholders; 80 attendees including members of the iCCM, MoH senior staff members, National Drug Authority (NDA), Ugandan associations of paediatricians, private practitioners, medical associations, the research community, malaria zonal coordinators, IMCI and its zonal coordinators and MoH units responsible for reproductive health and health education. Various delays occurred in re-developing the national Standard Treatment Guidelines (STG) but the revised policy supporting AL in the public sector was eventually launched in facilities in May 2006 with the new STG, post-cascade training and emergency funding to procure AL. All implementation activities therefore started 24 months after the policy change was announced; complete roll out of the new policy for the first line treatment by the end of 2006 [Nanyunja et al., 2011].

3.7 Malaria Control 2005-2010: RBM going to scale

3.7.1 National Malaria Strategy 2005-2010

In 2005, Uganda developed a third MSP (2005-2010) with a goal to prevent and control morbidity and mortality and to minimize the social effects and economic losses attributable to malaria, embedded in the national efforts to enhance development, reduce poverty and improve health. The MSP 2005-2010 was aligned to the aspirations of the Health Sector Strategic Plan II (HSSPII) also developed in 2005 [MoH, 2005b].

The overall targets to which malaria control would contribute to the HSSP II were three-fold: 1) to reduce the infant mortality rate from 88 to 68 per 1,000 live births, 2) to reduce the under-five mortality rate from 152 to 103 per 1,000 live births, and 3) to reduce the maternal mortality rate from 505 to 354 per 100,000 live births. The specific malaria control targets included increasing the proportion of children under five years sleeping under an ITN to 80%, to roll-out IRS in all 15 epidemic prone districts, to increase the proportion of children receiving correct treatment according to the national treatment guidelines within 24 hours of the onset of symptoms to 80%, and to have 80% of pregnant women attending ANC services receiving two SP doses as IPTp [MoH, 2006].

3.7.2 Funding and staff changes 2005-2010

In August 2005 the GF suspended all funding (Rounds 2 and 4) to Uganda following a Pricewaterhouse Coopers financial audit highlighting gross mismanagement of funds [Kapiriri & Martin, 2006]. The Government of Uganda appointed Ernst & Young as GF managers including responsibilities for procurement of commodities. Following several months of lobbying and reorganizing the national GF management system, the GF ban was lifted in November 2005. The Malaria Consortium and the WHO were active participants in ensuring that the suspension would not interrupt activities deemed to be life-saving such as procurement of AL and the operational costs to support health worker training.

In 2005, the United States Government announced a new five-year, US$ 1.2 billion initiative to rapidly scale-up malaria prevention and treatment interventions in high-burden countries in sub-Saharan Africa, known as the President's Malaria Initiative (PMI) [http://www.fightingmalaria.gov/]. Fortunately, when GF funding had been suspended, the country became one of the first of three countries to benefit from this new PMI funding and began with "jump start" funding of *circa* US$ 500,000 in 2005. In 2006 PMI awarded US$ 9.5 million to Uganda, which increased to between US$ 19 million and US$ 35 million per annum between 2007 and 2011. In 2007, the GF awarded Uganda US$ 125.6 million as part of Round 7 support, largely for Long-Lasting Insecticide Treated Net (LLIN) distribution. In 2010, the GF awarded additional funds under Round 10, US$ 156 million, for the procurement of ACTs and Rapid Diagnostic Tests (RDTs). Therefore, between 2005 and 2010 Uganda had an unprecedented access to malaria development assistance, able to transform how successful the third MSP would be relative to its predecessors.

However, the third MSP was also characterised by a rapid turnover of staff within the malaria programme. In 2008, Dr. JB Rwakimari was replaced as head of the programme by Dr. Richard Ndyomugyenyi, who was replaced by Dr. Seraphine Adibaku in 2010, who was replaced by Dr. Albert Peter Okui in 2012. Between 2005 and 2012 all external technical advisors left the programme and MCU technical focal persons supporting all aspects of the programme also changed or moved to new jobs (Dr. Fred Kato, Dr. George Mukone, Dr. Nathan Bakyaita, Dr. Faustin Maiso, Dr. Petrobus Mufubenga, Ms. Maria Byangire, Ms Connie Balayo, Dr. Ebony Quinto and Dr. Myers Lugemwa). The only stable sections were vector control, where Mr. Michael Okia, a principal entomologist, served the MCU from 1997 until he retired in 2012. Mr. Tom Byembabazi, who joined the programme as a laboratory technician in charge of parasitology in 1997 served in that capacity until he passed away in 2013.

3.7.3 Vector control from 2007

3.7.3.1. ITN: Following the debates during the previous strategy on the optimal model for the delivery of ITN, a "mixed sector model" was finally adopted with a stronger emphasis on public sector delivery without complicated voucher schemes [MOH, 2004] and mass free distribution campaigns were recommended following successes in Kenya [Noor et al., 2007]. In 2009, Uganda shifted to universal coverage of the whole population with LLINs. In 2010, the program distributed over 7.3 million LLINs, with GF Round 7 support (Chapter 6). However, routine distribution of LLINs to pregnant women and children under 5 through the ANC and EPI services remained limited.

3.7.3.2 IRS: Since the studies at Kigezi during the 1960s (Section 3.3.1), IRS had not been widely practiced in Uganda, with some exceptions of the use of lambda cyhalothrin (ICON™ 10% WP) during the epidemics in the late 1990s and 2004. In 2006, PMI funded activities in Uganda with a focus on IRS district-wide pilot IRS projects, the first of their kind since 1964. The NMCP chose the south-western highland district of Kabale to pilot IRS and build capacity for future epidemic surveillance. Under a cooperative agreement, Research Triangle Institute (RTI) was contracted by PMI to undertake environmental and entomological surveys, procure insecticides and equipment, coordinate community

education and implement IRS activities across the whole district. From April to May 2006, RTI trained nearly 50 supervisors, team leaders and other health officials and over 300 spray operators [MoH, 2006b]. IRS with lambda-cyhalothrin was carried out between June and August 2006 and post-IRS surveys were conducted in September 2006. Over 103,000 households were sprayed, constituting 96 % of the targeted structures [RTI, 2006]. Few adverse events were reported and data from the Kabale district hospital indicated a drop in malaria cases [AFM, 2007]. The following year 45,000 households were sprayed in neighbouring Kanungu district. With the exception of pre- post-spray slide positivity rates at one health centre [Bukirwa et al., 2009], there is very little detailed epidemiological impact data from these "pilot" IRS campaigns and in stark contrast to the level of survey detail generated during "pilots" in the 1960s (Section 3.3.1).

Based on RTIs growing regional experience with IRS implementation, the agency secured further contracts to manage all of the PMI's IRS programs in Uganda, PMI provided RTI over US$ 150 million between 2007-2012 [AFM, 2007]. IRS activities in Uganda began to expand in 2007 from Kanungu district to the high transmission northern districts of Apac, Pader, Gulu and Kitgum districts (Chapter 6). All 2006-2007 spraying operations were with lambda-cyhalothrin (Icon WP).

For several years, the MoH had been advocating for the use DDT for all IRS programs but this was met with significant reluctance from a broader set of lobbyists and development partners. In December 2006, the National Environmental Management Authority (NEMA) granted approval for the use of DDT on the condition that there would be strict adherence to Stockholm Convention rules and regulations on organic pollutants [New Vision; Stockholm Convention, 2001]. The MoH therefore started to use DDT in IRS programs in Apac and Oyam districts in 2008. Additional resources for testing and education were needed to facilitate its use. During 2008, NEMA approved the re-introduction of DDT for IRS following environmental impact assessment and public hearing in January 2008 [AFM, 2008; RTI, 2008a; 2008b; 2008c].

The European Union, the US and Japanese government's made it clear to agricultural exporters through the Ugandan media and that they would strictly enforce minimum DDT metabolite residue limits on any imports from Uganda and would reject any shipments if these standards were not met; despite this having never been an issue for produce from other countries using DDT to control malaria (Mozambique, South Africa, Swaziland and Zambia) [Wendo, 2004; Lewis, 2008]. The opposition to the use of DDT was heightened by Ugandan environmental activitists. Mr. Lukyamuzi, a member of parliament, continued to aggressively lobby against the use of DDT by implying that DDT caused blindness, kidney failure and was responsible for birth deformities in children in Vietnam [New Vision, 2006]. Activists accused the Museveni government of mixing DDT with ethanol and kerosene before spraying, making it deadly and they urged the citizens to exercise their constitutional right to protect themselves by using spears, pangas and sticks against spray men [New Vision, 2006]. A meeting of academics, policy makers and other interested parties was held in 2006 by the Uganda National Academy of Sciences [UNAS, 2006] and presented the Ugandan evidence of residual metabolites of DDT in soils of fish, soils, water sources and mother's breast milk in Uganda [Ejobi et al., 1998; Kasozi et al., 2006; Ssebugere et al., 2010; Wasswa et al., 2011]. The controversy was summed up in the Daily Monitor's story by

Emmanuel Kihaule of March 13, 2007 "*DDT: Survival Weapon or Threat?*". The environmental activists went to court and DDT spraying was temporarily stopped in Apac and Oyam.

In 2009, entomological monitoring in the PMI IRS districts showed resistance to DDT and pyrethroids [Verhaeghen et al., 2010; Section 5.6]. As a result, the IRS program switched to spraying with carbamate (Bendiocarb) insecticides [Abt, 2012; Steinhardt et al., 2013]. With respect to impact monitoring there have been few detailed routine analyses of long-term, detailed epidemiological data. One exception was that IRS was shown to be associated with a reduction in malaria infection prevalence and anameia, when two spray districts were compared to a single, unsprayed control district [Steinhardt et al., 2013]. Using routine health facility data from Apac district between March 2007 and October 2011, slide positivity rates (SPR) showed a significant reduction six months following the first round of DDT spraying in 2008, a further decline following the rounds of alpha-cypermethrin spraying in 2010 and a decrease during the six month period after spray activities with bendiocarb (August 2010 to June 2011) [Kigozi et al., 2012]. The greatest reductions in SPR were documented following bendiocarb spraying from 2010, suggesting greatest benefits after switching to the carbamate based insecticides [Kigozi et al., 2012].

3.7.3.3 Mass Drug Administration and Indoor Residual Spraying : Between 2008 and 2009, the NGO Pilgrim Africa [http://www.pilgrimafrica.org/] partnered with the Uganda MoH to assess the effectiveness of integrated vector management (IVM) combined with mass screening and treatment (MSAT) in two districts, Katakwi and Kumi in the Teso region. While the plan was to carry out the pilot experiment in the two districts, the intervention was carried out effectively only in Katakwi district. MSAT was conducted using RDTs and treatment initially with a donation of artemisinin-napthaquone (Arco®), a drug not on the WHO recommended list and thus later replaced with dihydroartemisinin–piperaquine (DUOCOTEXIN®). While the Pilgrim project refers to IVM [Pilgrim, 2012], what was actually implemented was IRS using lambda-cyalothrin (ICON). The average cost was estimated to be US$ 10.00 per capita covering approximately 500,000 people. For 6-8 months, the malaria cases recorded in the routine HMIS in Katakwi district are reported to have dropped by 92% in children under 5 years old to 4.9% of all outpatient attendances [Pilgrim, 2012]. No details are provided about any baseline and follow-up evaluations conducted for this project and the fidelity of these data have not been carefully analyzed. Despite the lack of carefully reviewed data, a draft proposal called the "*Accelerated National Scale-Up of Malaria Control in Uganda (2012 – 2016)*" to sustain this project was presented to the MoH with a cost projection of US$ 2.09 billion [Pilgrim, 2012].

3.7.3.4 Larviciding: Larvicide trials using Aquatain (an oil film), Sunlight Activated Formulated Plant Extract (SAFE) which kills mosquito larvae, possibly, by radiation and *Bacillus thuringiensis israelensis* (Bti) began to gain some wider interest in Uganda from 2009. Following presentations by the manufacturers of the SAFE larvicide, the Government of Uganda allocated Uganda Shs 5 billion (*c*. US$ 2 million) for larviciding, with SAFE. The initial application of SAFE larvicides was planned to be done in Wakiso and Nakasongola districts before the project extended to the other districts. In May 2012, Ms. Nambatya the MoH director of chemotherapeutics, representing the Health Minister, Dr Christine Ondoa, at the launch of larviciding in Wakiso District Headquarters is reported to have said that

larviciding would be part of the integrated vector management approach, using locally-available products such as Temophos (Abate), which has been used in the eradication of the Cyclops causing Guinea worms on in northern and North Eastern Uganda and is also currently being used for onchocerchiasis control in Hoima District. However, the funds earmarked for larviciding could not be utilized because all the candidate larvicides had to be subjected to rigorous evaluation for bio-efficacy, bio-safety, acceptability and cost-effectiveness by a National Task Force and a Technical Coordination Committee in the local Ugandan setting. This process has lasted for over a year since the launch. The results from this comprehensive assessment will guide the nation-wide larviciding decisions.

By 2010, vector control, combining the use of LLINs and IRS were beginning to improve their coverage (Chapter 6). However, according to the national household sample survey, undertaken between June and November 2011, only 34.5% of Ugandan's reported sleeping under a LLIN the night before the survey [UBOS & ICF, 2012]; and IRS covered approximately 3 million people in only a few selected districts [Abt, 2011].

3.7.4 IPTp from 2007

The implementation of the malaria in pregnancy (MIP) control strategy has continued to be carried out through the existing health care delivery structures from the national level through to the community level. Originally started as part of the MSP 2001-2005, community surveys have demonstrated progressive improvements of the MIP program in terms of IPTp - SP uptake, ITN use and correct knowledge on IPTp among pregnant women. By 2011, during the national household survey, it was reported that 68% of pregnant women had taken an antimalarial for prevention of malaria during the preceding two years, however, only 25% had taken two or more presumptive SP treatment courses [UBOS & ICF, 2012].

3.7.5 Malaria case management challenges during the AL era

3.7.5.1 Improving access: While the NMCP refers to “universal access to ACTs”, the private sector supports first treatment contact for an estimated 40-50% of fevers [MMV, 2007; 2008; Talisuna et al., 2012]. As HBMF is yet to be implemented for AL, engaging private sector providers was seen as a key element of improving AL access. In 2008, the Consortium for ACT Private Sector Subsidy (CAPSS) pilot project introduced a subsidized, first-line AL product in the private sector in Uganda. Four intervention districts (Kamuli, Kaliro, Pallisa, Budaka) were purposefully selected to receive branded subsidized medicines, while the fifth district (Kumi) acted as the control. Products in the intervention districts were branded “*ACT with a leaf*” to distinguish them from all other ACTs and antimalarials. A maximum recommended retail price for each age-pack was printed on the product. The final price per age-pack ranged from US$ 0.10 to US$ 0.40 [Talisuna et al., 2009; 2012]. At baseline, ACT accounted for less than 1% of anti-malarials purchased from licensed drug shops for children less than five years old at the end of the pilot "*ACT with a leaf*" accounted for 69% of anti-malarial purchased in the interventions districts [Talisuna et al., 2009; 2012; MMV, 2010].

A broader initiative to increase nation-wide AL availability through the private sector was launched in 2010 by the GF’s Affordable Medicines Facility for malaria (AMFm) initiative

[Global Fund, 2012; Tougher et al., 2012; Davis et al., 2013]. Uganda was part of the pilot 10-country study. AMFm negotiated with manufacturers to reduce the price of their ACTs, offered a co-payment of approximately 95%, reducing the factory price of ACTs to US$ 0.05 per adult dose. In-country national importers/wholesalers and retailers worked out an affordable profit margin to ensure affordable quality assured AL to consumers at the periphery through drug shops and general shops. Based on the CAPSS experience in Uganda, the AMFm products were branded "*ACT with a leaf*". However, AMFm elected not to print the maximum recommended retail price for each age-pack. The AMFm independent evaluation report for Uganda indicated a high achievement on the indicator for availability of Quality Assured ACTs (QAACTs) which rose from 21% to 67% and medium achievement on the indicator for market share of QAACTs, which rose from 40% to 57%. However, there was poor achievement on the indicator for price of QAACTs US$ 1.96 vs US$ 0.59 [Global Fund, 2012; Tougher et al., 2012; Davis et al., 2013].

The Uganda AMFm was not as successful as the CAPSS pilot project largely because the grant amendment was signed late because of an initial objection from the Government of Uganda that AMFm would "kill" local pharmaceuticals companies like Quality Chemicals. Further, the scope, scale and intensity of the demand generation under the Uganda AMFm was sub-optimal compared to that of the CAPSS pilot project. After the AMFm phase 1 independent evaluation report was presented to the Global Fund [Global Fund, 2012; Tougher et al., 2012], the Global Fund Board decided to integrate the AMFm into core Global Fund grant management and financial processes. AMFm phase 1 countries such as Uganda were encouraged to incorporate AMFm-like strategies within their broader funding requests and national strategies. How this might evolve as a true private sector integration continues to pose a challenge in Uganda. During the national household survey of 2011, 43% of febrile children took an antimalarial on the same/next day of symptom onset, with still only 30% of fevers treated with AL [UBOS & ICF, 2012].

3.7.5.2 Improving commodity tracking: Another initiative to improve malaria drug managment, malaria diagnosis and treatment in the public sector, mTRAC, was piloted in 2010 in two districts - Kabale and Gulu by the NMCP and the Foundation *for Innovative New Diagnostics-FIND* [http://www.finddiagnostics.org; Asiimwe et al., 2011]. mTRAC uses internet or mobile phone SMS based interfaces to enhance real time reporting on various malaria indicators including the availability of ACTs, Quinine and RDTs stocks, malaria cases confirmed by microscopy or RDTs, malaria cases treated and other health service delivery monitoring indicators. The project was supported by DFID, UNICEF and WHO. At the time of writing this report it was not clear to what extent mTRAC has been adopted beyond the pilot districts.

3.7.5.3 Improving diagnosis: Repeated attempts were made to improve the availability and the quality of laboratory diagnosis of malaria through training and provision of microscopes. The proportion of health facilities with functional microscopy services increased over the second MSP period, only 8% of all cases reported in the HMIS in 2004 were laboratory confirmed. In 2009 this had increased to 17% [UBOS & ICF, 2009] and to 24% by 2010 [HMIS report, 2010]. However, regular supervision and quality control of laboratory services in the public has been insufficient or absent. Rapid diagnostic tests (RDTs) for *Plasmodium falciparum* have been repeatedly investigated to assess their accuracy and feasibility at

peripheral health facilities in the public, private and community level [Asiimwe et al., 2012; Kilian et al., 1999; Mbonye et al., 2010; 2013; Mukanga et al., 2012a; 2012b; Cohen et al., 2012; Kyabayinze et al., 2008; 2010; 2011; 2012; Dhorda et al., 2012; Batwala et al., 2010; 2011; Hopkins et al., 2011). Most of the studies found RDTs to be useful in settings where no laboratories were available.

While RDTs have been routinely used for the investigation of suspected malaria outbreaks and by some NGOs in the context of clinical services in the IDP camps in Northern Uganda, their use at scale in the public health services remains a challenge for the NMCP. In 2007, the WHO and MoH with support from DFID to the Malaria Consortium provided an in-country forum to debate and provide a road map for scaling up the use of diagnostics for malaria [MoH, 2006b]. Late in 2009, a further consensus meeting proposed the scale-up of RDTs at lower level health facilities and the community level starting as operational research [MoH, 2010]. Numerous local and international NGO and agencies provided technical support in the development of implementation tools, including a trainers manual, users guide, job aids and quality control frameworks. A central coordination and steering committee was established and was responsible for planning, quantifying and providing leadership to the role-out of universal parasite diagnosis in Uganda. The steering committee was chaired by the Central Public Health Laboratories (CPHL), and had representatives from all NGOs involved in malaria diagnosis. The roll-out of diagnostics and large scale use of RDTs by Village Health Teams was launched in 2010 under the iCCM strategy supported by the Malaria Consortium, in mid western and central Uganda; this initiative led to a sharp rise in the use of malaria diagnostics for febrile patients from 8% to 30% during 2010 [MOH, 2010].

3.7.5.4: Monitoring ACT resistance: Between 2002 and 2008 13 site studies of AL day 28 efficacy have been undertaken at six sites [Piola et al., 2005; Staedke et al., 2004; Bukirwa et al., 2006; Bassat et al., 2009; Yeka et al., 2008; 2013; Kamya et al., 2007; 4 ABC Study, 2011; Clark et al., 2010; Arinaitwe et al., 2009]. Overall the median PCR adjusted day 28 efficacy was 98% (range: 71.9%–100%) showing that this drug remains effective. However, slow clinical and parasitological response with ACTs used for uncomplicated *P. falciparum* malaria has emerged in Western Cambodia and may have spread to other sites in the Mekong region [Noedl et al., 2010; Dondorp et al., 2009; White, 2010]. Tracking the evolution of artemisinin resistance is of paramount importance in Africa [Talisuna et al., 2012]. The WHO recommends that the proportion of patients remaining parasite positive at day 3 exceeding 10% should serve as a definition for suspected resistance [WHO, 2010] while others suggest this threshold should be 3% [Stepniewska et al., 2010].

The Worldwide Antimalarial Resistance Network (WWARN) [www.wwarn.org] has conducted a systematic review to search for the individual patient level data from clinical efficacy studies (available online). As of June 2013, there were 25 studies in the WWARN data repository from Uganda undertaken between 2000 and 2010, comprising 12,098 patients. Based on these data there seems to be no evidence suggesting artemisinin resistance (delayed parasite clearance) at any of the Ugandan sites. No site and no treatment regimen had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3%. However, the coverage of drug resistance surveillance studies needs to be further improved to reduce nationwide data gaps, especially in the North Eastern part of

the country. None of the existing studies employ rich parasite density sampling which might be required to detect emerging Artemisinin resistance. The later is now planned under the East Africa Public Health Laboratory Network project (EAPHLNP) which is supported by the World Bank [http://www.eac.int/health/index.php].

The use of counterfeit ACT drugs remains a very real threat to emerging resistance and the lack of effective pharmacovigliance is a weakness of existing drug monitoring. In a recent study between 2010 and 2011 at 93 drug stores in Bushenyi, Mbarara, Mpigi, Kampala and Mbale, 558 ACT products were tested using Raman spectroscopy and 38.9% were shown to be fakes [Björkman-Nyqvist et al., 2013].

3.7.6 Evolution of the monitoring, evaluation and operations research framework

The quality, completeness and timeliness of malaria related data from the HMIS slowly increased and improved over the third MSP period. An information officer was added to the MCU team and the MCP developed a data base of all available information and survey results including those from the commercial sector. In 2008, the MCU developed the first ever Monitoring and Evaluation (M&E) plan [MOH, NCMP, 2008] and the first Malaria Indicator Survey (MIS) was conducted in 2009 [UBOS, 2010]. However, data on in-patient malaria admissions and deaths, though systematically collected in the HMIS are rarely analysed. This has been partially addressed through the establishment of five sentinel hospitals with reasonably reliable data on paediatric admissions since 2000, and used in a more informed way to examine disease trends [Okiro et al., 2011; Section 4.6].

The UMSP was founded in 2001, initially as collaboration between researchers at the Makerere University College of Health Sciences, the Makerere University School of Public Health, the Ministry of Health and the University of California San Francisco. The first focus of UMSP was drug resistance surveillance, however the scope of the research, surveillance and the collaborators has rapidly expanded. In 2008, the UMSP was renamed the Infectious Disease Research Collaboration in Uganda-IDRC [http://idrc-uganda.org]. In 2010, the Program for Resistance, Immunology, Surveillance and Modelling (PRISM) of Malaria was set up as a dedicated East Africa International Center of Excellence for Malaria Research. The PRISM approach is designed to address the complexity of interactions between the mosquito vector, malaria parasite, and human host, and combine standard malaria surveillance techniques and metrics with cutting-edge methods designed to improve surveillance. The surveillance component covers entomology surveys, community and school surveys, cohort studies, outpatient and inpatient surveillance and measuring interventions and cost effectiveness modelling. The research and surveillance work is conducted at six sentinel districts: Apac, Jinja, Kabale, Kanungu, Mubende and Tororo [Francis et al., 2012].

In 2004, President Yoweri Museveni proposed the establishment of a Uganda Malaria Research Centre (UMRC), similar to the Joint Clinical Research Centre that handles HIV/AIDs research. Following the presidential directive, the Ministry of Health in 2005 appointed Dr. James Tibenderana of Malaria Consortium to head the UMRC and requested DFID for funding for a one year inception phase of the Centre (UK£ 274,490). The Centre had five strategic objectives: to set a national research agenda; to promote and carry out relevant

research; to facilitate research training and capacity development; to build strong and viable internal and external systems; and to disseminate and promote utilization of research findings. The centre has since developed a stakeholder meeting to shape the national research agenda, a grant writing workshop, awarded five competitive, local research grants, in collaboration with the Uganda National Council of Science and Technology (UNCST) set up an electronic database of malaria research in Uganda, and research findings discussion and dissemination of results (RFDD) workshop bringing together researchers, implementers, planners and policy makers. The anticipated funding from the government was not realised and in 2009 the operations of UMRC ceased. In 2012, Dr. Seraphine Adibaku, formerly the NMCP Programme Manager, was redeployed by the MoH to the UMRC to oversee the relocation of UMRC to a newly completed China-Uganda Friendship hospital at Naguru, Kampala. Later it was decided that the UMRC be positioned as a constituent institute of the Uganda National Health Research Organization (UNHRO) [Mbonye & Magnussen, 2013] and may relocate to a more permanent base in Entebbe.

3.8 Malaria control 2010-2015: sustaining the gains

3.8.1 The fourth national malaria strategic plan

A malaria programme review (MPR) was conducted in 2011 [RBM, 2011]. The MPR made several important recommendations to accelerate malaria control progress. Of note were the following: a new national malaria policy, strategic plan and annual work plans needed to be developed; the MOH should elevate the NMCP to the level of a Department; strengthen and improve routine malaria surveillance for both inpatients and outpatients; establish representative sentinel sites to monitor vector bionomics including insecticide resistance; finalize epidemic preparedness guidelines; procurement of malaria commodities should be guided by policies and quantification of malaria commodities should be strengthened by using malaria burden data; set up an NMCP composite malaria database and assign responsibilities for its routine and overall management; update a national malaria research agenda and the Parliamentary Malaria sub-committee of the Social Services Committee should be mobilized to raise the profile of malaria on the political agenda.

Following the MPR, Uganda defined its fourth MSP (2010-2015) [MoH, 2010], tied to Uganda's broader development context as detailed in its Vision 2040 [NPA, 2007] and the national development plan [NPA, 2010]. The Government of Uganda, with the stewardship of the MoH, developed the third National Health Policy (NHP III) that covers a five year period 2010/11-2014/2015 and includes malaria as part of the minimum essential package. The MSP has as its vision "*Malaria will no longer be the major cause of illness and death in Uganda and families will have universal access to malaria prevention as well as treatment by 2015*". The overall goals of the 2010-2015 MSP are two-fold: 1) to control and prevent malaria morbidity and mortality, and thereby minimize the social effects and economic losses attributable to malaria in the country; and 2) to contribute to the reduction of under five all-cause mortality rate, as a result of reduced malaria mortality. This is to be achieved by providing a definitive diagnosis to at least 85% of suspected malaria cases treated in the public sector; providing effective ACT treatment to at least 85% of people with uncomplicated malaria within 24 hours of onset of symptoms in the public or private sectors; provide universal coverage and utilization of LLINs, or IRS, singly or in combination;

provide presumptive treatment to pregnant women with at least two doses of IPT with a safe antimalarial; create an enabling environment for implementation of key malaria interventions through behavioural change initiatives, obtaining adequate financing and appropriate human resources, conducting relevant operational research, M&E and overall health systems strengthening [MOH, 2010]. The projected cost to implement the 2011-2015 MSP over five years is estimated to be US$ 785.5 million. Using commitments from various donors and the government the shortfall is estimated to be between US$ 500-600 million, requiring additional government support or to be raised from external sources.

Under vector control there is an emphasis on "integrated" but while this includes a reference to larviciding, the MSP sets targets and ambitions largely only around achieving universal coverage and replacement strategies for LLIN and expanding IRS coverage. The Global Fund [www.theglobalfund.org] announced on the 10th May 2013 that it was supporting Uganda in the distribution of over 15.5 million LLINs, making it the largest malaria prevention campaign, however despite a high profile launch, disputes over who would be the partners in delivery has delayed the mass campaigns. The vector control strategy makes no direct mention of urban, municipal malaria control, however where appropriate there is provision for "*reduction of vector breeding will be carried out either through physical reduction or alteration of sites (e.g. brick pits, drainage channels) or through larval control using larvicides, predators, or growth inhibitors*" involving other ministries [MoH, 2010]. A qualitative study of stakeholders in November 2010 explored the knowledge and possible role of IVM in Uganda; the study demonstrated how under-developed an inter-sectorial approach to IVM was and there was a long way to go to overcome the technical, policy and community-participation challenges [Mutero et al., 2012]. The MSP goes on to state that "*... NMCP and the Vector Control Division (VCD) will strengthen their expertise and capacity to effectively undertake IRS without technical assistance. This should be achieved by the end of 2012*". At the time of writing this report the IRS activities in Uganda continue to be managed by US funded RTI and Abt Associates.

One important strategic change in the current MSP includes the expansion of parasite diagnosis in the management of malaria in line with WHO recommendations for Test, Treat and Track [WHO, 2013]. The policy and STGs on malaria case-management were changed from presumptive treatment to parasite based diagnosis and treatment in 2009 [MoH, 2009]. With this new policy it is likely that RDT scale up will be rapid and the aim is to ensure that there shall be microscopy at all Health facilities from level III and above and RDTs at HC II and community levels and to fill the gaps at higher level health facilities whenever microscopy is not possible. At the time of writing this report, 16 million RDTs were available in the country and there are plans to train workers in the use of RDTs. Similarly there are plans to train health workers at the community level as part of the iCCM and VHTs role out. Quality assessments and lot testing for imported RDTs is now conducted by the NDA and the Uganda National Guidelines for Implementation of Parasite Based Diagnosis of Malaria (2013) have been developed [MoH, 2013]. Furthermore, an external quality assurance scheme is being implemented by the MoH and the central public health laboratories (CPHL) funded largely by CDC/PMI.

3.8.2 Elimination again?

Following the Bill and Melinda Gates call in 2007 to eliminate, and ultimately eradicate malaria [BMGF, 2007], there has been a gradual change in the political language used to describe malaria control in Uganda. The former Minister for health, Dr. Christine Ondoa, is quoted as saying "*To supplement efforts geared towards achieving a malaria-free Uganda, ongoing efforts such as indoor residual spraying, killing of mosquito larvae and distribution of mosquito nets should be scaled up",* adding *"to eradicate malaria, Uganda needs to create public awareness and participation among other interventions*" [The Observer, 2013]. The National Resistance Movement (NRM) Manifesto 2010-2016 on page 196 under the section malaria starts as follows "*It is the intention of NRM to totally eliminate malaria from Uganda through preventive methods"* [NRM, 2010]. Pilgrim Africa in their Facebook campaign are engaging the public on issues concerning malaria and its eradication [www.pilgrimafrica.org/malaria-free-uganda/resources]. Anthony Esenu, the vice president of the Pilgrim Africa International board posted "*We believe it is possible to eradicate malaria through engaging a critical mass. We encourage people to discuss issues that affect them, their solutions and we encourage them to take action".*

Whether the timing of this plea for elimination in Uganda is appropriate has been only provisionally discussed [Yeka et al., 2012]. Given the persistently high malaria burden and the continued challenges facing the NMCP to sustainably deliver protection, drugs and supporting health system requirements, an entirely vertical, re-focussed elimination strategy might be premature. Managing expectations of the public and wider stakeholder partnerships is key to the future success of the MSP 2010-2015. Posing elimination endpoints might run the risk of losing confidence and credibility.

3.9 Conclusion

One hundred years of malaria control in Uganda has been a journey mirrored by its social and political struggles (Chapter 2). The significance of malaria as a barrier to the country's development was evidenced by pre-independence urban control approaches and was resurrected as a development priority by the World Bank in the 1990s. There has been no shortage of timely research evidence that interventions such as ITN, IRS and replacing failing mono-therapies can reduce malaria risk and reverse trends in disease. These interventions of proven efficacy have all struggled to achieve ubiquitous and equitable coverage despite their promotion in national strategic plans since the late 1990s. Arguably, the slow progress was a direct consequence of poor funding and a rapid turn-over of staff leading to a constant loss of institutional memory within the national programme, seven NMCP heads since 1996. Significant overseas development assistance only became available from 2006. By 2011 there remains important gaps in national ambitions for universal coverage of prevention and reliable treatment services for malaria. Measuring impact was seen as a central part of malaria control during the 1950s and 1960s, guided by the principles of quality epidemiological surveillance. To a large extent recent efforts at scaled use of IRS have not been accompanied by an equivalent epidemiological assessment. The MSP 2010-2015 states that combinations of IRS and ITN might be used but the epidemiological and economic analysis to support this position is conspicuous by its absence. Whether the

Global Fund, PMI and other bi-lateral partners will continue to invest in the projected US$ 784.4 million five year plan without a detailed evidence-based platform remains unclear.

We believe this historical overview will provide a narrative that will accompany an analysis of changing risks presented in the subsequent chapters but also provide a form of institutional memory to the current and future players in malaria control in Uganda, highlighting some of the historical and current challenges. We were aware from the outset that the task at hand was ambitious and we might have missed out some relevant documents and milestones. Further, we believe such an overview should be a dynamic process that should be periodically updated. Finally, all the documents and materials used for this historical overview have been stored in both electronic and paper based form and should serve as the beginning of a comprehensive library (electronic and paper based) for malaria control in Uganda which should be readily accessible to all key players both online and at the national malaria control unit.

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Chapter 4

Mapping malaria transmission intensity

4.1 Previous malaria map use in Uganda

4.1.1 Historical malaria mapping efforts in the 1960s

One of the objectives of the malaria pre-eradication programme in Uganda was to assess the national malaria situation and investigate the epidemiological conditions prevailing in the country. Malariometric surveys were undertaken to provide a profile of risk, epidemiology and seasonality in preparation for the design of national elimination. This was one of the most significant national examinations of the epidemiology of malaria risk in Africa at the time. Despite recent, contemporary attempts at malaria indicator surveys (MIS), these older national surveys were more sophisticated, elaborate and large-scale investigations of age, parasite species and parasite density. Surveys were undertaken across Uganda, covering the examination of over 120,000 people between 1965 and 1967. The activities were conducted in all the regions of the country, except the central region [de Zulueta et al., 1961; 1963; 1964; Onori & Benthein, 1967; 1969]. Malaria endemicity was recorded following classifications formulated at the Malaria Conference in Equatorial Africa held in Kampala in 1950 [WHO, 1951] and later revised from spleen rates to parasite rates in children aged 2-9 years [Metselaar & Van Thiel, 1959]. The eradication headquarters at Jinja housed all the survey records until 2011 when they were destroyed. The assembled data provided an information platform necessary to produce a cartography of risk used for many years after data were assembled (Figure 4.1a) [MacRae, 1968; 1975].

MacRae's chapter on malaria in the book "*Atlas of disease in Uganda*", edited by Hall and Langlands, was first published in 1968 and revised in 1975. This was an example, over 30 years ago, where the cartography of disease distributions was regarded as a necessary public health tool. The book drew attention to the diversity of national risks, "*illustrates the complexity of the geographic pattern of disease in Uganda. The precise limits of the distribution of many diseases are set by environmental factors".* The atlases highlighted the interaction between altitude, open water and swamps, temperature and rainfall, vegetation, human geography, migration and immigrants, urbanisation, food crops, economics and population density as drivers of disease distribution. The geography of disease, including malaria, led to important observations, including the correspondence between Epstein Bar virus, malaria and Burkitt's Lymphoma [Burkitt & Wright, 1966; Kafuko et al., 1969; Kafuko & Burkitt, 1970; Morrow, 1985] and drivers of childhood diseases and malnutrition [Jellife et al., 1964]. Few attempts have since been made to describe the sub-national patterns of disease through multi-disciplinary studies conducted in collaboration with epidemiologists and geographers.

The pre-eradication national surveys and disease atlases intention was that assembled and mapped data would serve as a baseline for future monitoring; however, repeat national surveillance was not mounted at national or sentinel scales for another 50 years.

4.1.2 The use of epidemiological stratification in national strategic plans 1996-2011

The descriptions and cartography of malaria risk across the country developed in the 1960s formed the basis of the epidemiological characterization used as a prelude to the national malaria strategy 1996 to 2000 - "*Available information indicates that everyone in Uganda is at a risk of contracting malaria..... Malariometric studies done in the 1960s indicate that the*

northern region was hyper-endemic, the central and southern regions were meso-endemic and the highlands areas were hypo-endemic (epidemic prone)" [MOH, 1996]. No map was shown and the reported variations in malaria risk were not used to segment control approaches, with the exception of epidemic preparedness in the highlands.

The strategic plan 2001-2005 did not present any malaria stratification and stated that 95% of Uganda supports endemic transmission and only 5% of the population are located in epidemic prone areas [MOH, 2001]. The strategic plan did, however, highlight the paucity of current epidemiological data and referred to the need to extend sentinel site disease burden investigation in Apac, Tororo, Mubende and Kabale.

The 2005-2010 national strategy provided a similar narrative to the 2001-2005 strategy, "*In most of the country climatic conditions are suitable for transmission of malaria throughout the year. Consequently, approximately 95% of Uganda's territory is exposed to moderate to very high, mostly perennial transmission levels. Only few areas experience low or unstable malaria transmission and are prone to epidemics. This is mainly the Southwest at altitudes above 1,800 meters and the slopes of Mount Elgon in the East and the Rwenzori Mountains in the West*" [MOH, 2006]. The strategy, however, extended the epidemiological profile to consider seasonal and transmission variations across the country - "*The peak incidence of clinical malaria follows the peak of the rains with a delay of about 4-6 weeks and the most cases are therefore seen December to February and May to July except for the North where the malaria season is more between May and November..... Exposure to malaria transmission measured during entomological surveys has been found to be as high as 1,500 infective bites per person per year but is more in the range of 100-400 in the highly endemic areas (hyperendemic) and around 5-50 infective bites in the areas of moderate transmission (meso- and hyperendemic). In contrast to the seasonal variation of malaria incidence asymptomatic parasite prevalence rates in children vary very little throughout the year*" [MOH, 2006]. The entomological information had been assembled from sentinel sites [Okello et al., 2006], see Chapter 5. The strategic plan presents a comparison of the 1960s and current expected transmission, suggesting that changes may have occurred due to agricultural and development practices.

The map of contemporary risk used in the 2005-2010 plan is shown in Figure 4.1b. No quantification or description of high to very high, high, medium to high, low and very low no transmission was provided. This same figure has been used in various subsequent documents developed by the NMCP and partners as part of its monitoring and evaluation plan 2007-2012 [MoH, 2007], PMI annual programme annual reviews 2007-2012 [PMI, 2007-2012], the Global Fund Round 7 submission to scale up LLIN in 2007 [Global Fund, 2007], publications considering the potential for malaria elimination [Yeka et al., 2011], Malaria Programme Reviews in 2011 [MoH, 2011], that also provided a map summarizing the parasite prevalence among children aged less than five years across the nine regions recorded during the national Malaria Indicator Survey (MIS) in 2009, and the National Malaria Strategy 2011-2015 [MoH, 2012].

The strategic plan 2011-2015 did begin to spatially target interventions in areas requiring special attention, including the historic epidemic prone areas, border/conflict districts, urban areas and areas where IRS was to be targeted (Figure 4.1c) [MoH, 2012]. This is the

first evidence of spatial targeting of intervention, however few details are provided on how the cartography of risk was likely to guide intervention selection.

4.1.3 Other malaria risk maps of Uganda not used by Ministry of Health

Other maps that have been developed and available to the NMCP since 2000 include the maps developed under the MARA/ARMA collaboration on climate suitability for stable transmission (Figure 4.2a) [Craig et al., 1999; www.mara.org.za] and the length of malaria seasons [Tanser et al., 2003; www.mara.org.za] (Figure 4.2b), the maps generated by the Malaria Atlas Project for Uganda using sparse parasite prevalence data from 252 time-space locations surveyed between 1985 and 2010 using Bayesian methods with the inclusion of 14 covariates (urban, peri-urban, a temperature suitability index, land surface temperature (six variants), precipitation (six variants) and normalized difference vegetation index (NDVI, two variants) (Figure 4.2c) [Gething et al., 2011a; www.map.ox.ac.uk]; a map developed by Abt Associates that used a crude poison probability model based on malariometric data (for which no details of sources, types and fidelity are provided) and a selection of covariates case data, population density, density of clinics, density of water bodies, humidity, rainfall, NDVI and minimum and maximum temperature to provide six risk categories of low/low, low, moderate/low, moderate, high and high/high (Figure 4.2d) [Abt Associates, 2012]; and finally an interpolated map of school aged children malaria prevalence recorded at 71 locations between 2000 and 2003 using Bayesian regression techniques with the inclusion of NDVI, day and night-time land surface temperatures, altitude, and distance to permanent water bodies (Figure 4.2e) [Stensgaard et al., 2011]. None of these mapped products have been used by the NMCP or their national partners, data-driven maps have been developed on small numbers [Gething et al., 2011; Stensgaard et al., 2011], or the data input fidelity and sources are unknown [Abt Associates, 2012] and climate and seasonal maps developed by the MARA/ARMA collaboration do not provide sufficient transmission intensity data to distinguish the variations within Uganda at district levels [Craig et al., 1999; Tanser et al., 2003].

The MPR, undertaken in 2011, states that "*The programme has not adopted a system for routine and periodic monitoring of malaria risk in the country*" and that one of the key issues raised by the MPR was that "*The lack of risk mapping (including using routine data) makes it difficult to identify populations at highest risk and targeting of interventions to these populations*". As a result the MPR concludes as one of the key action point "*The malaria programme should plan for and conduct periodic risk assessments and mapping in order to assist intervention targeting*" [MOH, 2011].

In this chapter, we provide details of an extensive data assembly exercise and a robust Model Based Geostatistical (MBG) Bayesian method to provide malaria risk outputs that are resolved as district-levels to allow for pre- and post-scaled intervention prevalence to be assessed by the NMCP at decision-making units linked to its decentralized health policy.

Figure 4.1: a) Malaria endemicity regions obtained from surveys between 1965-1967 [McCrae, 1968; 1975]; b) Malaria risk map used in national malaria strategies and other MOH documents from 2007; c) Map showing targeted control/special areas used in 2011-15 national malaria strategy, red IRS districts, brown urban settlements, light purple epidemic prone areas and orange border/conflict areas [MOH, 2011]

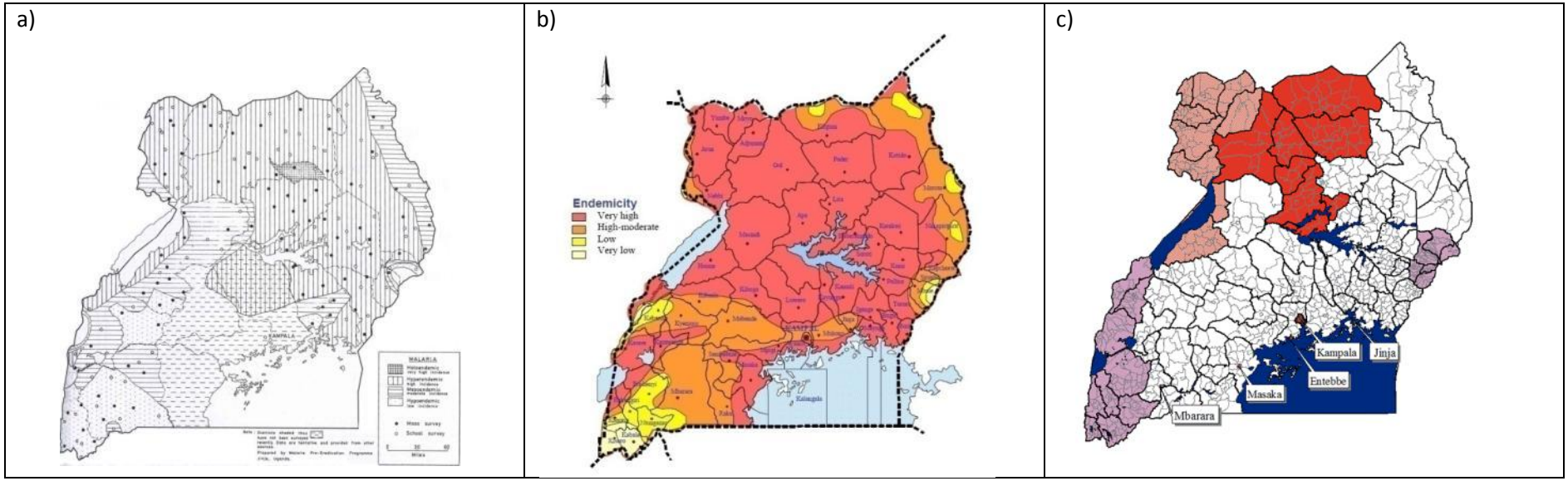
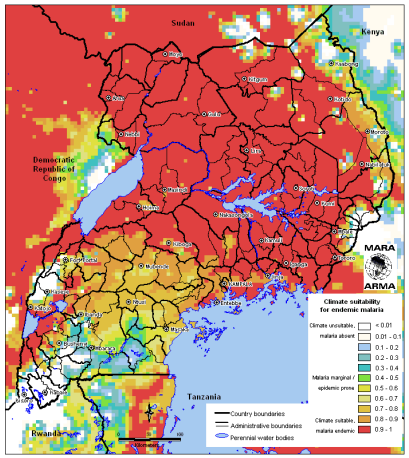
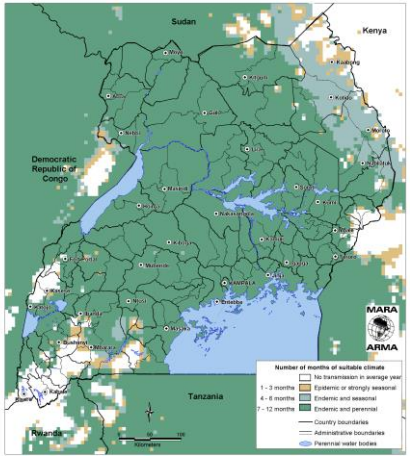


Figure 4.2: a) MARA climate suitability model for Uganda; b) MARA malaria seasons for Uganda; c) Modelled prediction of *Pf*PR_{2-10} in Uganda in 2010 attributed to four classes of risk: grey free, dark pink >=40%, mid pink 5-39% and light pink <5% [Gething et al., 2011b]; d) Risk map based on random effects hierarchical linear based malaria risk model [Abt associates, 2012]; e) Predicted *Plasmodium* parasitaemia risk for schoolchildren in the highest risk group (5-9 year old boys)in Uganda from 2000-2003 [Stensgaard et al., 2011]

a)



b)



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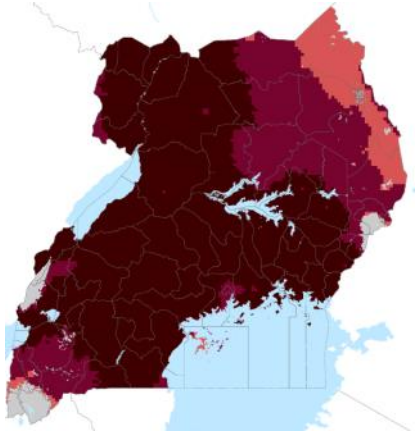
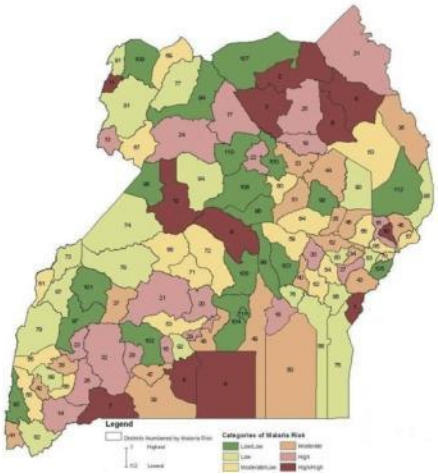
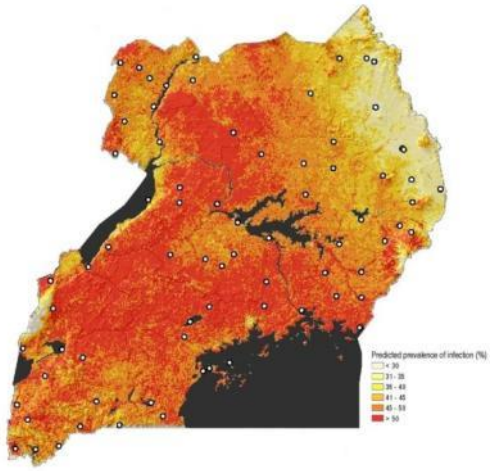


d)



e)



4.2 Malaria parasite prevalence data assembly, modelling and risk mapping

There are a variety of measures of the intensity of malaria transmission derived from field investigations of human populations or malaria vectors. The most ubiquitous measure, used for over 100 years in Africa, is the parasite rate - the proportion of individuals on a single cross-sectional survey among an entire or sampled community who have evidence of a peripheral blood stage malaria infection. This was the metric of choice for national risk mapping during the 1960s in Uganda and remains a key parameter to define transmission intensity in space and time. 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 parasite prevalence data in Uganda between 1980 and 2012; and therefore a reference source to the database. The following sections provide the details on how these data were modeled in time and space to provide district level estimates of malaria risk in 2000 and 2010. These data are then used to provide population-adjusted estimates of risk by district. We also describe, where possible, the distribution of parasite species in Uganda with time. Finally, given the importance of seasonality to previous NMCP malaria descriptions we revisit maps of seasonal malaria transmission in Uganda.

4.2.1 Parasite prevalence data search strategy

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

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

Publications with titles or abstracts suggestive of possible parasite data were either downloaded from journal archives where these have been made Open Access (OA) or

sourced from HINARI [http://www.who.int/hinari]. If publications were not available OA from HINARI we visited UK library archives at the London School of Hygiene and Tropical Medicine, the Liverpool School of Tropical Medicine and the Bodleian library at the University of Oxford. References not found following these searches were requested using world catalogue searches through the Oxford libraries at a per-page cost. All publications from which data were extracted were cross referenced using the bibliographies for additional sources that may have been missed or that may correspond to unpublished or 'grey' literature (i.e. not controlled by commercial publishers). In addition, tropical medicine and malaria meeting abstract books were identified from as many sources as possible produced as part of national and international conferences and congresses. These were used to signal possible data that were followed up through correspondence with abstract authors.

Unpublished archived survey reports: We undertook manual searches of archives at the World Health Organization (WHO) libraries in Geneva and Brazzaville at separate archive locations as Project, Country and Parasitology Department files. We also visited national libraries of Ministries of Health in Nairobi, Kenya (where sub-regional reports, including Uganda, were located) and Entebbe and Kampala in Uganda. As part of the RBM monitoring and evaluation initiative national, household surveys were resurrected as a means to monitor country-level progress [RBM-MERG; Corsi et al., 2012]. These surveys were initially embedded in the DHS as a malaria module and were largely focussed on intervention coverage measures until 2005 when it was agreed to include malaria infection prevalence into survey protocols. Data from the Ugandan DHS and malaria national sample surveys of 2007-08 and 2011-12. As a result of the help provided by the Ugandan Bureau of Statistics (UBOS) and the NMCP it was also possible to assemble a large volume of unpublished data from these national surveys.

We contacted malaria scientists based in Uganda many of whom generously provided unpublished, raw data from study sites, districts and wide-regions from investigations of malaria they were involved with, all acknowledged at the beginning of this report. Notable has been the provision of data by the Ugandan Malaria Surveillance Project (UMSP) from Jinja, Tororo and Kanungu districts; the Malaria Consortium from Hoima, Kibaale, Kiboga, Kyenjojo, Lira, Masaka, Masindi, Mpigi and Wakiso districts; the Medicine's for Malaria Venture School surveys in Kaliro, Kamuli and Pallisa districts; Epicentre Mbarara Malaria Research Centre surveys in Isingiro, Kiruhura and Mbarara districts; and the Liverpool School of Tropical Medicine's studies among the islands and coast line of Lake Victoria.

Search completeness: Our data searches have not used systematic, traditional evidence review strategies. These would have missed many unpublished sources of information. Rather, our strategy has used a cascaded, opportunistic approach. Authors of peer-reviewed papers were often asked about additional information within their paper and directions to other possible unpublished work in their geographic area or from their institution. Importantly, there are likely to be many post-graduate theses undertaken by students of the faculties of parasitology, public health and medicine in Uganda have not been adequately searched.

4.2.2 Data abstraction

The minimum required data fields for each record were: description of the study area (name, administrative divisions), the dates of start and end 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. The quality of slide reading [O'Meara et al., 2006; Gitonga et al., 2012], variations in sensitivity/specificity between RDTs [WHO-FIND, 2012] or the ability of field teams to reliably read RDTs [Rennie et al. 2007; Harvey et al., 2008] and selection of primers for PCR [Okell et al., 2009] all influence descriptions of prevalence and will have intrinsic variance between surveys included in the database. RDTs have been shown to yield higher false positive rates than microscopy [Endeshaw et al., 2008; Keating et al., 2009] but seem to stratify both the lowest (<1% parasite rate) and highest (>50% parasite rate) more accurately compared to microscopy [Gitonga et al., 2012].

For data derived from randomized controlled intervention trials, data 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 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. It was possible to establish the year of every survey however, the month of survey was occasionally not possible to define from the survey report. Here we used descriptions of "wet" and "dry" season, first or second school term or other information to make an approximation of the month of survey and included a record of this assumption. Some survey results were reported as an aggregate in space (e.g. a single *Pf*PR for a group of villages) or time (e.g. a mean *Pf*PR estimated from four different surveys conducted over time). In such cases, we either sought additional reports of the same surveys with higher spatial or temporal resolution. Where this was not possible and where clusters of villages exceeded 5 km^2 we excluded the record from the analysis (see below). Where additional information to provide unique time, village specific data was necessary we contacted authors to provide any missing information.

4.2.3 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". Where data were reported across communities that exceeded at 5 km grid we regarded these as too low a spatial resolution, with significant possible variation within the polygon of information to be excluded within the modeling phase. In practice, this was a difficult criterion to audit as most survey reports did not provide enough detail on the size of the area surveyed. 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]. We also used digital place name gazetteers developed for various Ugandan government ministries including a UBOS village data set [http://www.ugandaclusters.ug/geo-im.htm], a national schools database and available, incomplete health facility geo-coded data.

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 place names are replicated across a 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 off the coastline, located on the river or in incorrect administrative units, every anomaly was re-checked and re-positioned using small shifts in combination with Google Earth.

4.2.4 Database fidelity checks, exclusions and pre-processing

Data checks: 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 entered erroneously into the data assembly where multiple reviewed reports describing similar data. These were listed, checked and duplicates removed.

Data exclusions: The search strategy identified 1129 time-survey locations where malaria infection prevalence had been recorded between November 1980 and November 2012. This final data series was then subjected to various exclusion rules as defined below.

> *Location details*: Despite repeated efforts and multiple on-line digital gazetteers, national resources and personal communications we were unable to identify with sufficient precision the geo-coordinates for 21 survey data points at 18 locations. No survey data locations covered wide-areas beyond 5 km^2. In addition, there were 137 survey data points located on the islands of Bukooli, Bujumba, Bunya, Busiro, Buvuma, Kyamusua and Mukono parishes located in Lake Victoria; given the difficulties in matching environmental covariates to the island we have excluded these data points for the modelling work. These island communities were also excluded from model predictions and represent 0.6% of Uganda's population in 2010.
>
> *Ensuring sample precision*: Sample size is inversely related to prevalence where, at low sample sizes, biases in prevalence estimates are introduced, dependent on the true prevalence of the population and translates into large standard errors [Gregory & Blackburn, 1991]. There is a critical threshold of between 10 and 20 individuals sampled below which the standard error increases exponentially in most surveys of parasitic infections and the curve starts to flatten at a sample size of about 50 and reaches an asymptote at about 100 [Jovani & Tella, 2006]. The sample size of individual survey samples is also important in the derivation of correlations with covariates of endemicity, in testing plausible associations between say rainfall and prevalence during covariate selection small, imprecise samples can lead to over-fitting (section 4.3.2). We aimed to combine communities in close proximity where any village had less than 15 people sampled and where communities were within 5 km of each other, sampled at exactly the same time by the same investigators. Using these criteria we were unable to merge data from 20 time-space locations and these were excluded from the final analysis.

The final database contained 969 temporally unique data points at 830 survey locations.

4.2.5 Age standardization

There was a large diversity in the age ranges of sampled populations between studies. 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 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].

4.2.6 Parasite prevalence data summaries

Of the 969 unique time-space survey locations identified through the data search strategy described above, 789 (81%) were identified from unpublished sources, 95 (10%) were sourced from Ministry of Health reports, 64 (7%) from unpublished reports from organizations working in Uganda, 14 (1.4%) directly abstracted from journals, 6 (0.6%) from post-graduate theses and one (0.1%) from conference abstracts.

Of all samples identified we had to presume survey month for one study location based upon ancillary information in the report. In addition we had to estimate the minimum sample size based on information on total surveyed populations within the report for 53 (5.6%) data points. Survey data were located for time-space survey data points using GPS (285, 29%), Encarta (91, 9%), Google Earth (67, 7%), GeoNames (7, 0.7%), other digital place names sources, e.g. schools and village databases (245, 25%), coordinates provided by individual scientists for which sources not certain (20, 2%) and combinations of survey maps in reports, Google Earth, repositioned GPS coordinates and other sources (254, 26%). Of the time-space survey locational data, infection was recorded in 938 (97%) using microscopy alone, 25 (3%) used RDTs and 6 (0.6%) used microscopy with PCR confirmation.

The 1980 to 2012 data are unevenly distributed through time and in space. To explore the temporal (not spatial) variance in the age-standardized estimates of parasite prevalence we used a LOESS regression method that fits a best fitting curve using moving temporal windows on the data using information before and after the reference year in STATA (version 12). The results suggest that there may have been a rise in infection between 1980 and 2008, where after there is a suggestion that prevalence might have begun to decline (Figure 4.2). These data are however generated from different spatial locations with time and there this trend must be interpreted with extreme caution. The overall spatial distribution of *Pf*PR_{2-10} data is shown in Figure 4.3 and partitioned around 2005 in Figures 4.4a and 4.4b.

Figure 4.3: Loess regression line of 969 survey data points assembled between 1980 and 2012

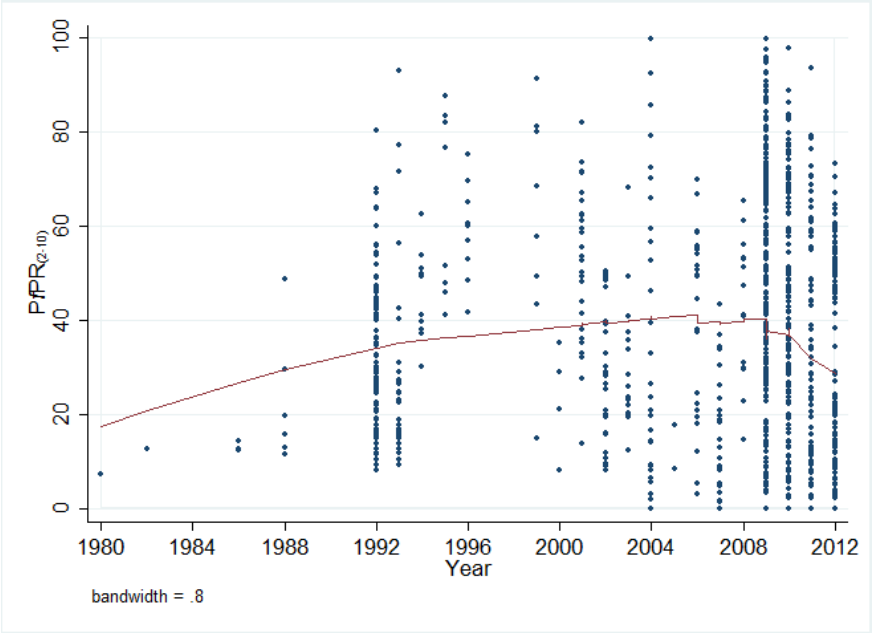
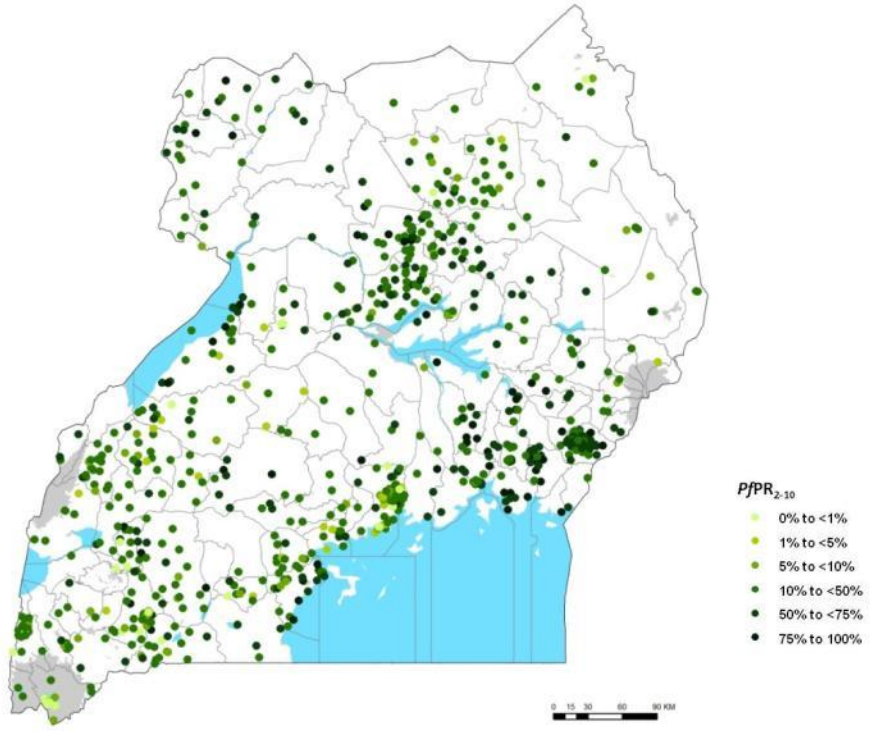


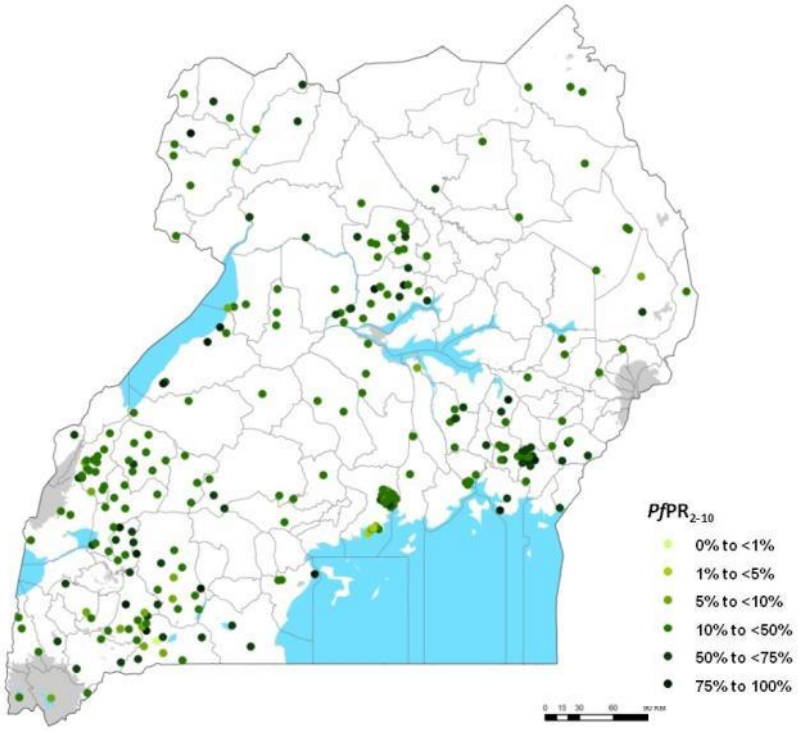
Figure 4.4 Data distribution of age-corrected *Pf*PR_{2-10} estimates in six categories: <1%, 1-4%, 5-9%, 10-49%, 50-74.9%, >=75% from 969 surveys at 830 unique locations conducted 1980-2012. We have masked out areas of Uganda that cannot support transmission by virtue of low temperature during non-epidemic years and not through imported infections (dark grey)[1] (Section 4.4).



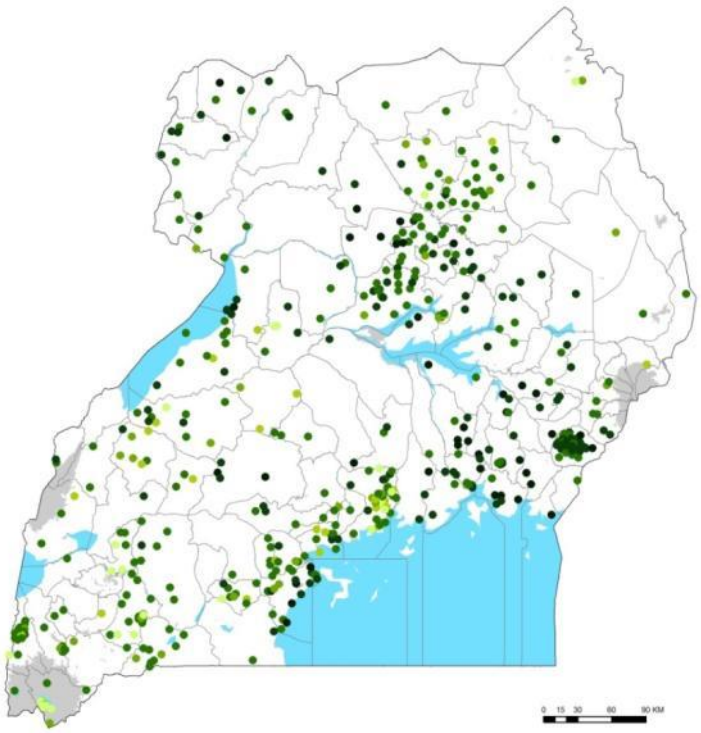
Footnote (1): To provide a plausible mask to eliminate the possibility of transmission across Uganda, we have used a recently developed temperature suitability index (TSI) [Gething et al., 2011]. The TSI model uses a biological framework based on the survival of vectors and the fluctuating monthly ambient temperature effects on the duration of sporogony that must be completed within the lifetime of a single generation of Anophelines. This was used to generate at each 1 x 1 km pixel, periods of an average year when a vector's lifespan would exceed the time required for sporogony, and hence when transmission was not precluded by temperature. If this time exceeded the maximum feasible vector lifespan, then the cohort was deemed unable to support transmission and the area classified as being at zero risk [Gething et al., 2011b].

Figure 4.5 a) Data distribution of age-corrected *Pf*PR_{2-10} estimates in six categories: <1%, 1-4%, 5-9%, 10-49%, 50-74.9%, >=75% from surveys conducted 1980-2005 (n=300); b) surveys conducted 2006-2012 (n=669). The data are shown against the 112 health districts described in Section 2.4. Areas masked dark grey malaria absent by virtue of temperature.

a)



b)



4.3 Model Based Geostatistical (MBG) modelling of age-corrected parasite prevalence

4.3.1 Model form

MBG methods interpolate from observed measures of interest of known locations in space and time to provide predictions of quantities and the empirical estimates of their uncertainty at locations and times where data do not exist [Diggle & Ribeiro, 2007]. MBG methods fit the data where the spatial and temporal covariance is used to generate samples of the predicted posterior distribution from which point estimates and the uncertainty around these estimates are computed simultaneously using Bayesian inference [Chilés & Delfiner, 1999; Diggle et al., 2002].

Data were used within a Bayesian hierarchical space-time model, implemented through an adapted Stochastic Partial Differential Equations (SPDE) approach using Integrated Nested Laplace Approximations (INLA)[1] for inference [Rue et al., 2009; Cameletti et al., 2012] to produce predictions of *Pf*$PR_{2\text{-}10}$. In the SPDE approach, the overall hierarchical space-time binomial model of the parasite prevalence was represented as the realization of a spatial-temporal process of the observed *Pf*$PR_{2\text{-}10}$ at the community location and survey year, selected covariates at sampled locations, the coefficient vector and the measurement error defined by the Gaussian white noise process. The realization of state process or the unobserved level of *Pf*$PR_{2\text{-}10}$ is defined by a spatial-temporal Gaussian field that changes temporally as a second-order autoregressive function. The space-time covariance matrix informs the spatial range and temporal lag of the prediction model for each tile such that observations have decreasing effect on the predictions at a given location the more distal in space and time they are to that location. Outside of the spatial and temporal range the autocorrelation of the contribution data becomes almost null. Continuous predictions of *Pf*$PR_{2\text{-}10}$ at 1×1 km spatial resolutions for the year 2000 and 2010 were made using the first and second data time-series. Full details of the model and prediction accuracies are provided in Annex A.1.

4.3.2 Selection of covariates

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

[1] Markov Chain Monte Carlo (MCMC) algorithms, although widely used in Bayesian inference in disease mapping, suffer from convergence and dense covariance matrices that increase computational time and cost significantly [Rue et al., 2009]. Integrated Nested Laplace Approximations (INLA) are alternative algorithms with faster computational speeds and can be undertaken in open source, easily adaptable R packages [R-INLA, project].

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 determinants of malaria transmission are climatic (rainfall and temperature), ecological (potential breeding sites and urbanisation) and control interventions (anti-vector and ant-parasitic measures) [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.

Temperature: Temperature plays a key role in determining the transmission of human malaria [Lunde et al., 2013]. Laboratory experiments have shown that high temperatures (> 34 ^{o}C) lead to almost 100% larval mortality and at lower temperatures (< 16 ^{o}C) they were unable to produce viable adults [Bayoh & Lindsay 2003; 2004]. The mortality of the anopheles mosquitoes also increase sharply at ambient temperatures approaching 40 °C [Muirhead-Thompson, 1951; Kirby & Lindsay 2004]. Temperatures of between 25 °C and 30 °C are considered optimum for *P. falciparum* sporogony [Molineaux 1988]. It is on the basis of these biological relationships that we have assembled two temperature metrics in order to test their statistical relationships with *Pf*PR_{2-10}. These were: annual mean temperatures, and a biologically modeled temperature suitability index (TSI). The annual mean temperature surface was developed from monthly average temperature raster surfaces at 1 × 1 km resolution which were downloaded from the WorldClim website [http://www.worldclim.org]. 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; Figure 4.5a]. TSI was developed as a quantitative value of optimal *P. falciparum* sporozoite development [Gething et al. 2011a]. The TSI model uses a biological framework based on the survival of vectors and the fluctuating monthly ambient temperature effects on the duration of sporogony that must be completed within the lifetime of a single generation of Anophelines. The TSI is constructed using long-term monthly temperature time series [Hijmans et al., 2005] and represented on a scale of increasing transmission suitability, from 0 (unsuitable) to 1 (most suitable) (Figure 4.5b).

Proxies of suitable conditions for larval development (precipitation and vegetation): Rainfall, combined with suitable ambient temperatures, provides potential breeding environments for *Anopheles* vectors while humidity is associated with vector longevity. Normally, proxies of rainfall such as precipitation and vegetation are used in malaria risk predictions [Schalermann et al., 2008]. This is because actual rainfall data, typically collected from weather stations, are sparse throughout Africa [Hijmans et al., 2005]. Monthly mean precipitation raster surfaces at 1 × 1 km resolution were downloaded from the WorldClim website [http://www.worldclim.org/] and used as a proxy for rainfall compiled over a similar period and weather as for mean temperature surfaces [Hijmans et al., 2005; Figure 4.5c]. These monthly surfaces were summed to generate a synoptic annual mean precipitation

surface and re-sampled 5x5 km resolutions. For vegetation, Fourier–processed enhanced vegetation index (EVI), derived from the MODerate-resolution Imaging Spectroradiometer (MODIS) sensor imagery and available at approximately 1 × 1 km spatial resolution [Scharlemann et al., 2008] 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) (Figure 4.5d). EVI, compared to the more commonly used Normalised Difference Vegetation Index (NDVI), is developed from satellite imagery of higher spatial and spectral resolution and corrects for some distortions in the reflected light caused by the particles in the air as well as the ground cover below the vegetation [NASA URL].

Urbanization: The availability of optimum environments for the development of the malaria transmitting anopheline populations become limited in urban areas resulting in reduced vector density, biting rates and transmission intensity. Overall malaria infection rates are lower in urban compared to rural areas of Africa [Hay et al., 2005]. To develop a consistently defined surface of urbanisation, information from the Global Rural Urban Mapping Project (GRUMP) [Balk et al*.,* 2006] and the Afripop project [www.AfriPop.org; Linard et al., 2010] was used (Section 2.5). 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 (Figure 4.5e).

Pre-processing covariate grids: There were internal and coastline spatial mismatches between the various assembled raster grid covariates due to the various geographic idiosyncrasies and projection problems of the source data. A process of carefully rectifying these spatial shifts was undertaken before the covariates selection process began to minimise any potential errors. The population surface was used as the template for correcting the distortions because it had a much closer match with the defined national administrative boundaries. Reconciliations were undertaken using the *Raster-to-Point Conversion* Tool in ArcGIS 10.1 (ESRI Inc., USA) and overlaid exactly on the template grid using the *shift* tool in ArcGIS 10.1.

Statistical selection process of covariates: To begin the covariate selection process the values of the assembled covariates were extracted to each *Pf*$PR_{2\text{-}10}$ survey location using ArcGIS 10 *Spatial Analyst* (ESRI Inc. NY, USA) tool. A correlation test was then undertaken to examine variable that were highly correlated (>0.85). Where two covariates had correlation >0.85, the aim was to select the one with the highest Bayesian Inference Criteria (BIC) for inclusion in the bootstrap and total set analysis using the results of a bivariate regression analysis (Table 4.1). 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. This analysis showed that four covariates contributed significantly, and independently, to the variation in *Pf*$PR_{2\text{-}10}$: TSI, EVI, precipitation and urbanisation (combined urban and peri-urban classes) comprised the best fit model (Table 4.1)

Figure 4.6: Climate and environmental covariates tested for Ugandan malaria prevalence model: a) mean ambient air temperature; b) Temperature Suitability Index; c) precipitation; d) EVI; e) urbanisation

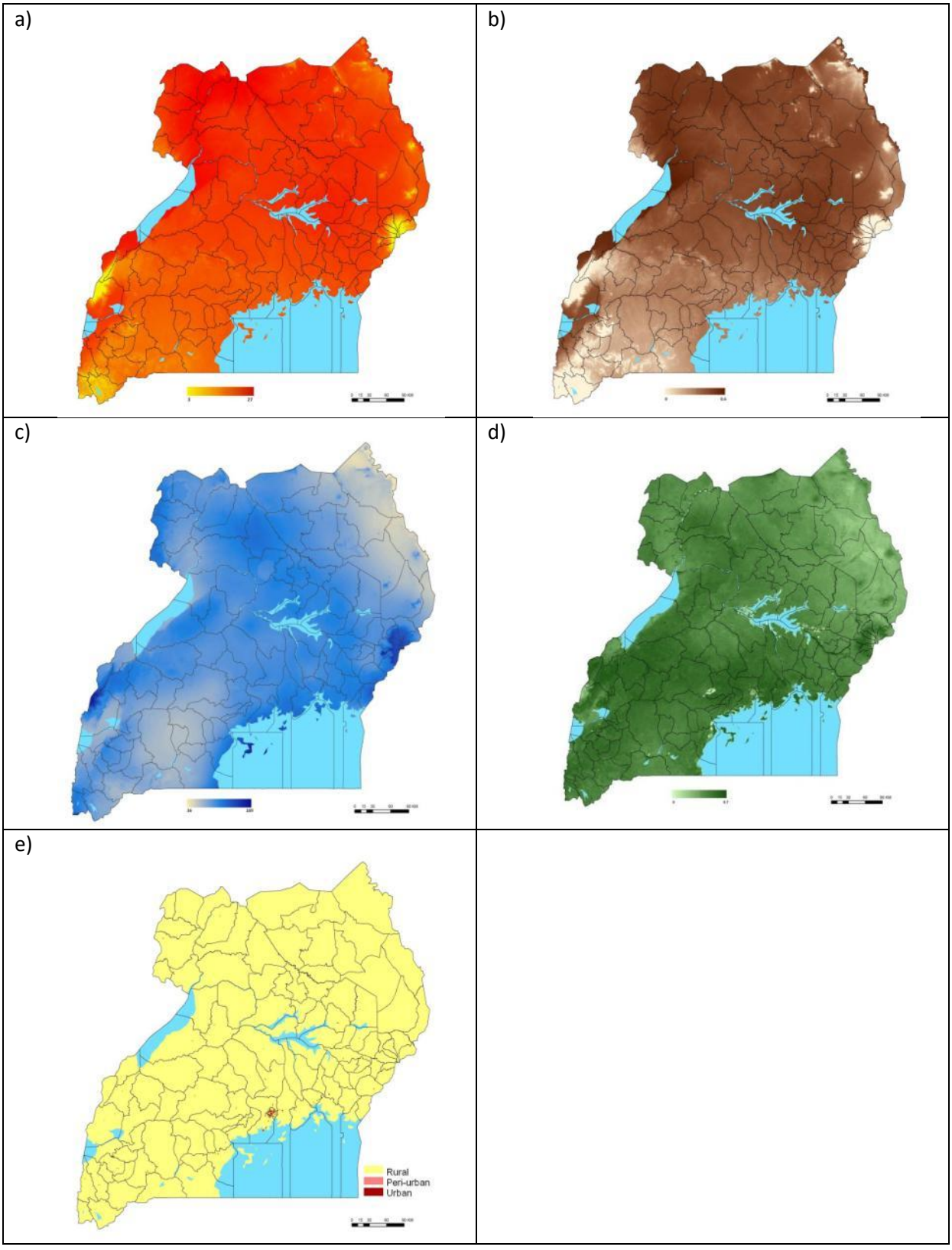


Table 4.1 The results of the bivariate generalised linear regression models of *Pf*PR_{2-10} and the climatic and ecological covariates

	Coefficient	95% Confidence Interval	P-value
Precipitation	0.0028	(0.0018, 0.0038)	<0.001
EVI	-0.3256	(-0.5253, -0.1260)	0.00143
TSI	0.5882	(0.4760, 0.7004)	<0.001
Urbanization	-0.2246	(-0.2651, -0.1840)	<0.001

4.4 Model predictions and populations at risk 2000 and 2010

We used the data from the age-corrected infection prevalence surveys (sample size, adjusted numbers positive) at known locations (longitude and latitude) and times (month and year) the minimal set of long-term climate and human settlement covariates within the Bayesian hierarchical space-time model, implemented through SPDE INLA for inference using a super-computing facility established in Kilifi, Kenya for proteomic analysis. The model took approximately 11 days to run for each prediction year and was repeated to provide precision metrics. The continuous predictions of mean *Pf*PR_{2-10} at each 1 x 1 km grid for 2000 and 2010 are shown in Figures 4.6a and 4.6b respectively.

The continuous *Pf*PR_{2-10} maps were then classified into adapted traditional endemicity classes and generated by computing the posterior probability of belonging to a range of *Pf*PR_{2-10} from the posterior marginal distribution of the predictions at each 1 x 1 km grid

- **Low stable endemic control**: areas supporting predicted *Pf*PR_{2-10} <1% which represent a pre-elimination transitional state [Cohen et al., 2010]
- **Hypoendemic 1**: areas supporting predicted *Pf*PR_{2-10} 1-<5%, separated from the below hypoendemic class to be able to distinguish finer resolution changes with time
- **Hypoendemic 2**: areas supporting predicted *Pf*PR_{2-10} 5-<10%
- **Mesoendemic**: areas supporting predicted *Pf*PR_{2-10} 10%-50%
- **Hyperendemic**: areas supporting predicted *Pf*PR_{2-10} >50%-74%
- **Holoendemic**: areas supporting predicted *Pf*PR_{2-10} ≥75%

We have included one additional class:

Malaria free: To provide a plausible mask to eliminate the possibility of transmission, we used the temperature suitability index (TSI) [Gething et al., 2011b]. This was used to generate at each 1 x 1 km pixel, periods of an average year when a vector's lifespan would exceed the time required for sporogony, and hence when transmission was not precluded by temperature. If this time exceeded the maximum feasible vector lifespan, then the cohort was deemed unable to support transmission and the area classified as being at zero risk. These areas are notably those parts of Uganda at exceptionally high altitude.

The final re-classified endemicity risks are shown for 2000 and 2010 in Figures 4.6c and 4.6d respectively.

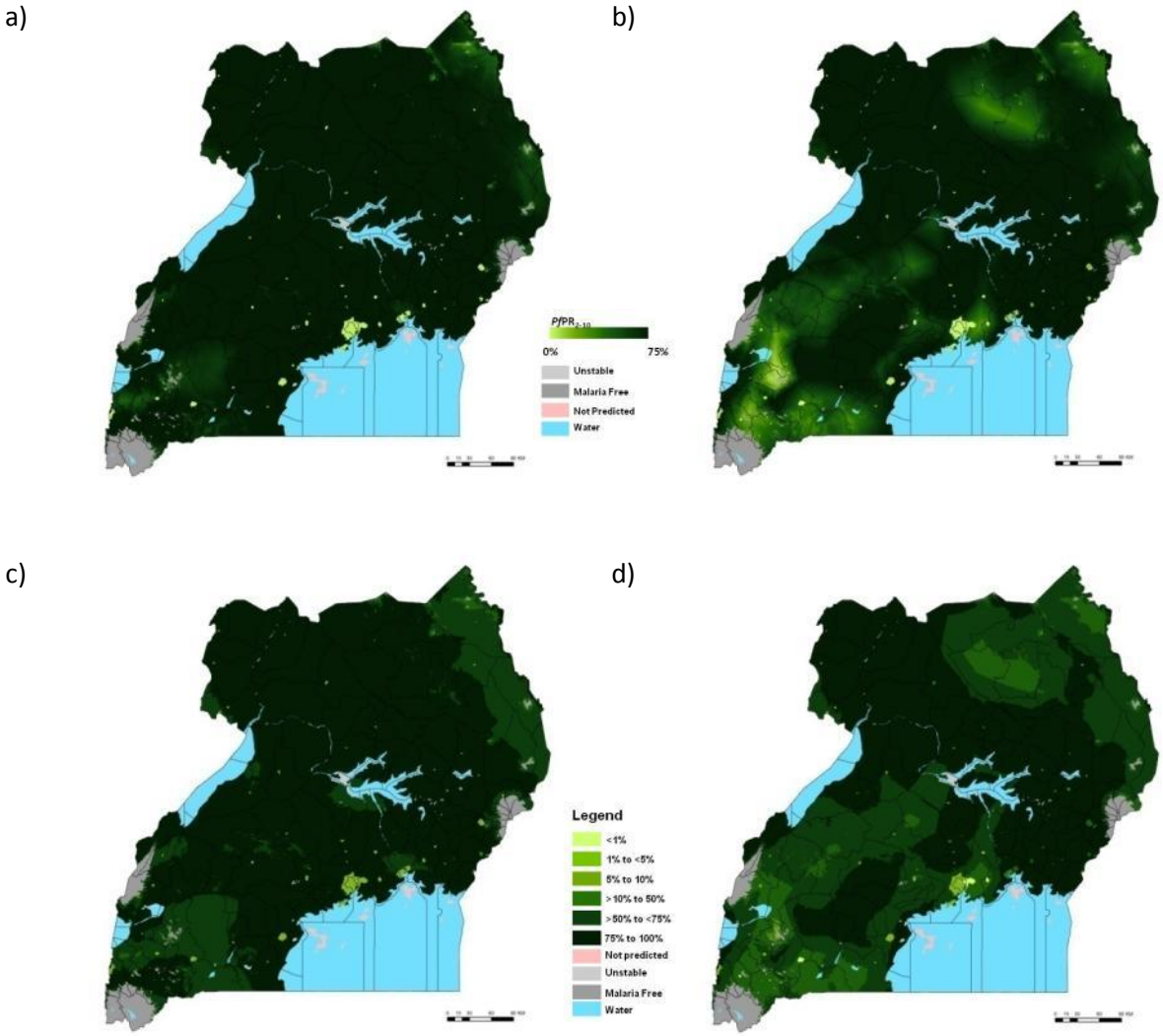
Since island data points were excluded from our analysis, it was necessary to zero the population within the Lake Victoria islands of Uganda. To do this, the population raster grid (Section 2.5) for each year was first converted to a point feature using the Raster to Point tool under Conversion Tools in ArcGIS 10.1. Under an edit session, all the points that corresponded to Uganda island pixels were highlighted and their values changed to zero. The edits were saved and edit session stopped. The point feature was then converted back to a raster grid using the Point to Raster Tool (Conversion Tools) and saved as a new raster. This newly edited population grid was then used to extract populations at risk by health district at each 1 × 1 km *Pf*PR_{2-10} grid location classified by predicted malaria risk class using the *Zonal Statistics* function in ArcGIS 10.1. The population totals (%) within each risk class for 2000 and 2010 for each of the 112 districts are shown in Tables 4.2a and 4.2b respectively.

Given the over-distribution of both population density (Figure 2.5) and malaria risk (Figures 4.6a-4.6b) within each district we computed a Population Adjusted *Pf*PR_{2-10} (PA*Pf*PR_{2-10}) for each district by first multiplying the *Pf*PR_{2-10} at each 1 × 1 km with the corresponding population at the same spatial resolution to compute the number of people who are likely to be positive for *P. falciparum*. This surface was then used to extract the number of people positive for *P. falcipraum* in each district which was divided by its total population in 2000 and 2010 to compute PA*Pf*PR_{2-10} for 2000 and 2010. The district values of the mean PA*Pf*PR_{2-10} in 2000 and 2010 and the differences across the interval are shown in Annex Tables A.2a and A.2b and Figures 4.7a-d.

Approximately 3.8% of Uganda's population live in areas that are essentially free of malaria based on temperature restrictions for parasite development in the mosquito vector. For Uganda as a whole, the mean PA*Pf*PR_{2-10} in 2000 was 72%, by 2010 the corresponding mean PA*Pf*PR_{2-10} was 66%, suggesting a drop in levels of transmission intensity over the ten year interval. In 2000, 84.6% of the Ugandan population lived in areas predicted to support hyper-holoendemic transmission (mean *Pf*PR_{2-10} >=50%), by 2010 this had reduced to 72.3% (Figures 4.8a &b). However, in 2000 70% of Ugandan's lived in areas of holoendemic transmission (mean *Pf*PR_{2-10} >=75%) but this had been substantially reduced to only 46% of Ugandan's living under these conditions by 2010. In 2000, 11.3% of the population lived in areas supporting a predicted mean *Pf*PR_{2-10} of less than 10% (traditional hypoendemic), by 2010 a similar proportion of the population lived under these conditions (12.8%) (Figure 4.8). Nevertheless this pattern was not universal, 25 districts achieved a greater than 20% reduction in mean PA*Pf*PR_{2-10} by 2010 compared to model predicted values in 2000 in the regions of Acholi, Ankole, Buganda, Bunyoro, Kigezi and Tororo (Figure 4.7c: Agago, Kitgum, Pader, Bushenyi, Ibanda, Isingiro, Katerere, Mbarara, Mitooma, Nsiika, Ntungamo, Bukomansimbi, Kampala, Mityana, Mukono, Rakai, Wakiso, Kibaale, Kanungu, Rukungiri, Kabarole, Kamwenge, Kasese, Kyegegwa and Kyenjojo). The greatest reductions (≥ 50%) were recorded in Mitooma, Nsiika and Ntungamo districts in Ankole region, Rukungiri in Kigezi region and Kampala (Figure 4.7c). Conversely, a greater than 10% rise in ten districts

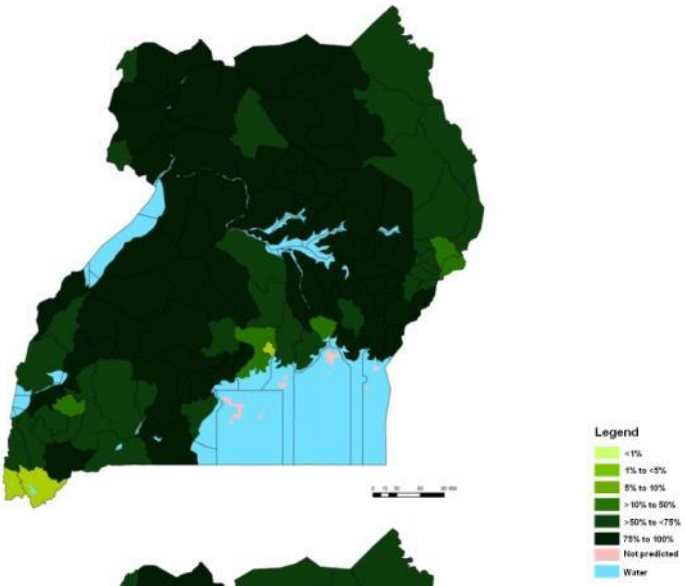
(Jinja, Mayuge, Iganga and Namutumba in Busoga region; Bududa, Mbale and Sironko in Elgon region; Budaka and Kibuku in the Bukedi region; and Kiruhura in Ankole).

Figures 4.7: a) continuous 1x1 predicted mean *Pf*PR_{2-10} for the year 2000; b) continuous 1x1 predicted mean *Pf*PR_{2-10} for the year 2010; c) re-classified endemicity classes using the posterior distribution for the year 2000; d) re-classified endemicity classes using the posterior distribution for the year 2010; dark grey areas masked based on inability of temperature to support stable transmission; light grey areas of unstable transmission constrained by aridity; pink areas showing Lake Victoria islands that were excluded from predictions.

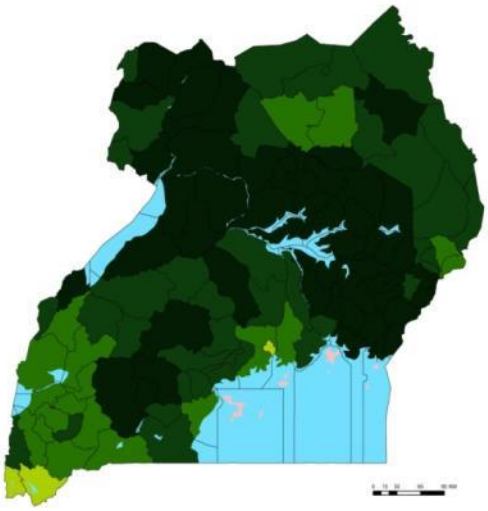


Figures 4.8: Population adjusted mean *Pf*PR_{2-10} in a) 2000, b) 2010 and c) figure showing percentage change 2000 to 2010 (light blue rise, no change or decrease within 20%; mid blue a decline of between 20% and 49% and dark blue a 50% or greater decline by 2000 compared to 2010 PA*Pf*PR_{2-10})

a)



b)



c)

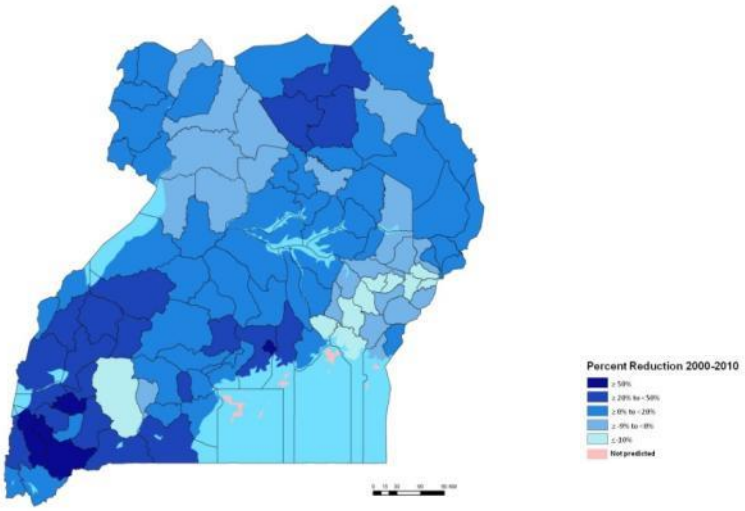
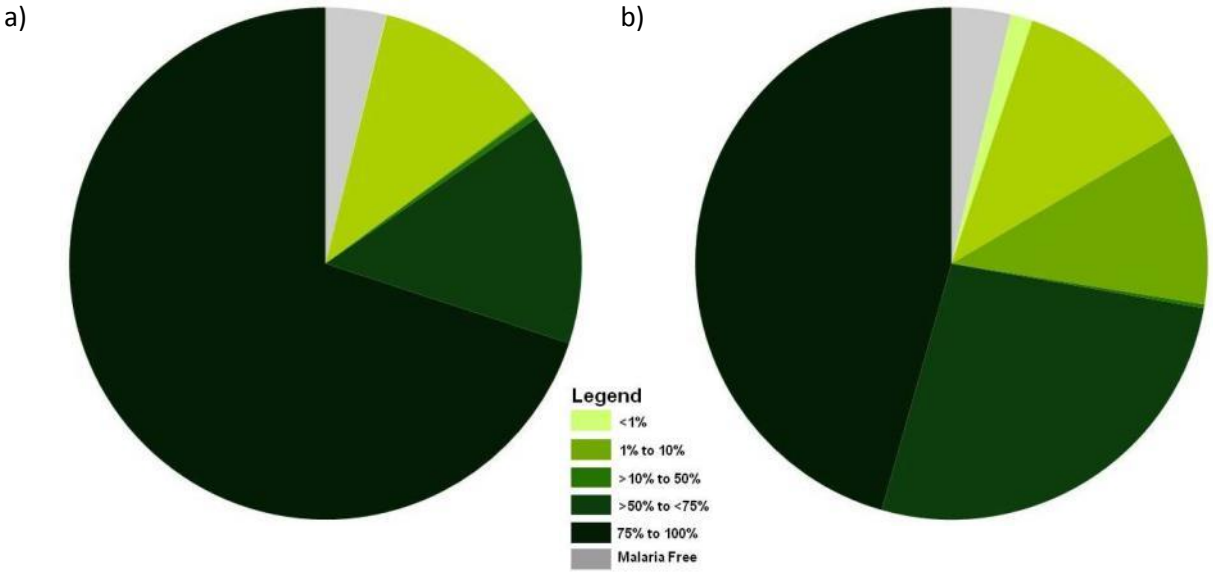


Figure 4.9: Percentage of Uganda's population at various classes of *P. falciparum* endemic risk in a) 2000 and b) 2010



4.5 Model uncertainty and validation statistics

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

The MPE, MAPE and the correlation coefficient of the observed and predicted *Pf*PR_{2-10} for the full space time *Pf*PR_{2-10} model for Uganda were -0.07%, 6.71% and 0.87 respectively indicating a good model accuracy. For both 2000 and 2000 mean predictions of *PfPR*$_{2-10}$ all pixels were within less than one standard deviation of the posterior mean *PfPR*$_{2-10}$ indicating good precision around estimates of risk.

4.6 Triangulating changing parasite prevalence with changing clinical incidence

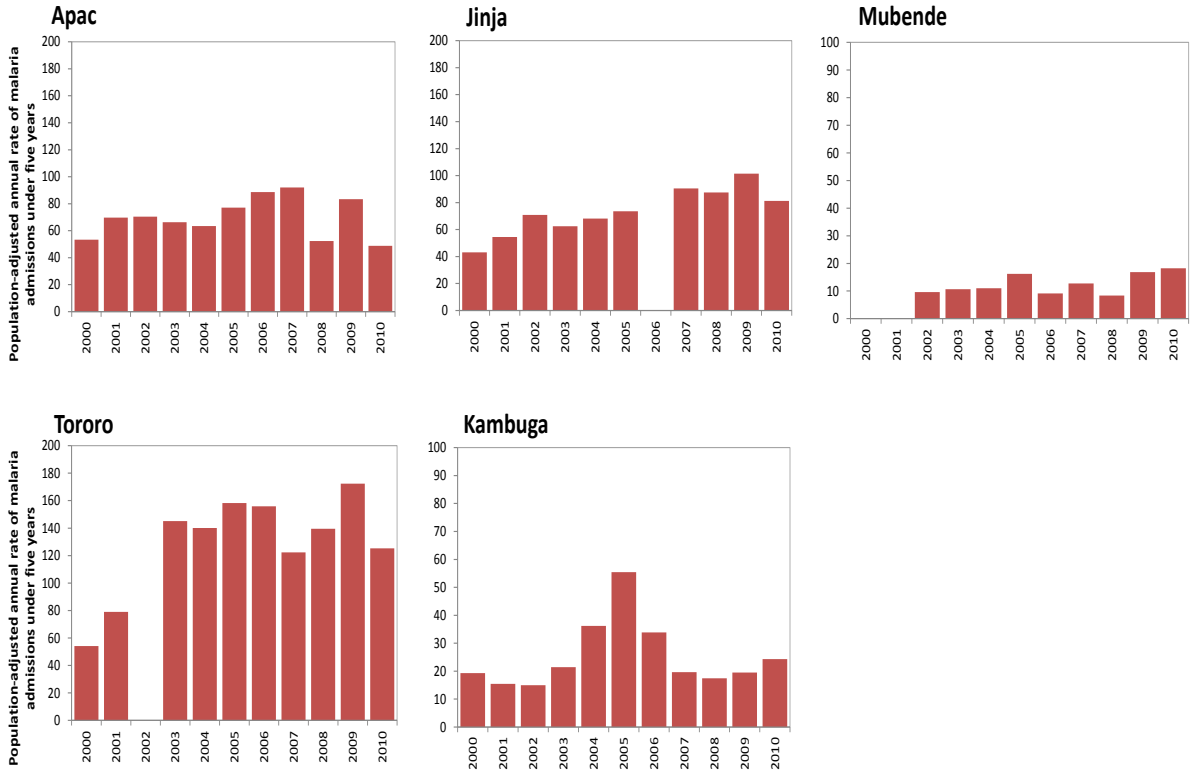
There have been attempts to re-construct HMIS out-patient data from across Uganda to demonstrate the rising malaria incidence during the 1990s [Adoke et al., 2012] and used by bilateral donors to define the burden in Uganda [PMI, 2010]. These, however, will have been imperfect representations of the national and sub-national trends given the problems associated with HMIS in Uganda. Completeness of district reporting was very poor in 2010-2011, only 9% of districts had complete health facility data and with regards to accuracy 18% of the district reports had a zero or missing values, 7% of the districts had extreme outliers, and 9% of the districts had major differences between the annual total and the sum of the monthly reports [WHO, 2011]. This is compounded by the inherent inaccuracies in the labelling of presumptive malaria cases based on clinical, "fever" diagnoses [Lubanga et al., 1997; Ndyomugyeni et al., 2007; Hopkins et al., 2008]. A more informed data series comes from careful reviews of hospitalized patients, who are more often than out-patients, parasitologically diagnosed as malaria and represent the severe, life-threatening end of the disease spectrum more closely related to the secular trends in community-based malaria mortality.

The records of Hoima hospital from 1990 to 2001 and of Kabale hospital from 1994 to 2000 (Figure 4.9) were used to review the trends in initial diagnoses for all children aged less than five years; results showed a significant increase over the intervals at each hospital in malaria and anemia admissions [Ndyomugyenyi & Magnussen, 2004]. Between 1992 and 2004 admission records at St Mary's Mission Hospital at Lacor (Figure 4.9), a conflict area in Gulu, were reviewed. Over 59,000 malaria admissions were documented 1992-2004; malaria was the most frequent cause in the 0—14-year group (43.1%) and showed a rise across the interval 1992-1997 and continued to rise through to 2004 [Accorsi et al., 2001; Accorsi et al., 2007].

Figure 4.10: Location of Hoima (1990-2001), Kabale (1994-2000), Lacor (1992-2004), Apac (1999-2010), Jinja (1999-2010), Mubende (2002-2010), Tororo (1999-2010) and Kambuga (1999-2010) long-term hospital data in Uganda.

A larger review of hospitalized paediatric (0-14 years) malaria was undertaken at five hospitals covering 146,473 malaria admissions between 1999 and 2009: Apac, Jinja, Mubende, Tororo and Kambuga (Figure 4.9) [Okiro et al., 2011]. Attempts were made during this analysis to define catchments to the hospitals and populations-at-risk within these catchments. The monthly malaria admission, population-at-risk adjusted data were subjected to time-series analysis and all sites, except Kambuga, showed a significant rise in malaria admissions across the interval from January 1999 to December 2009 [Okiro et al., 2011]. These data have been extended to December 2010 and are shown in Figure 4.10 and demonstrate that there has been little change or evidence of a sustained rise in malaria admissions across most sites since the launch of RBM in 2000.

Figure 4.11: Annual paediatric admission rates from Apac, Jinja, Mubende, Tororo and Kambuga district hospitals 2000-2010



Slide positivity rates between 2007 and 2010 at health centres in Apac, Tororo, Mubende, Jinja, and Kabale confirm results of hospital admissions, that malaria burdens have remained the same over the four years of observation [Yeka et al., 2012]. Whereas at Kihihi Health Centre, Kanungu, close to the Kamguga hospital reviewed by Okiro et al. (2011), slide positivity rose between 2007 and 2010 [Yeka et al., 2012]. This area in south west Uganda is a marginal malaria transmission stability region and subject to large between year variations in climate driven malaria epidemics. The continued rise in malaria disease burden in Tororo has been also observed among cohorts of prospectively followed children aged 0-48 months using passive case detection methods for slide confirmed malaria. After adjusting for age and season, the risk of malaria increased in Tororo by 52% from 2008 to 2011 [Jagannathan et al. 2012]. Conversely, as part of an intensive study of ACT treatment accompanied by ITN provision in Kampala, the incidence of passively detected, slide confirmed malaria

decreased from 1.55 to 0.32 per child 1-10 years per year between 2004 and 2008 [Clark et al., 2010].

It seems reasonable to assume that if dramatic declines in parasite prevalence had occurred these would have impacted on disease burdens. We were not able in the previous sections to demonstrate significant changes in parasite prevalence between 2000 and 2010 in most areas of the country. This observation resonates with other less comprehensive or definitive data based on malaria hospital admissions and slide positivity at health centres across the same interval. Using prospective child cohorts clinical malaria rose in Tororo [Jagannathan et al. 2012] but in Kampala, where we have defined declining infection prevalence (Figures 4.6 & 4.7), independent data on clinical incidence also showed a decline [Clark et al., 2010].

4.7 Other parasite species

The current focus of control in Africa is justifiably *P. falciparum*, by far the most pathogenic of the five human malarias and contributes to over 95% of the world's mortality from malaria. However, it is not the only malaria parasite to affect man. *Plasmodium knowlesi,* the most recently discovered human malaria, has not been described in Africa. *Plasmodium vivax* is thought to have a restricted distribution in Africa owing to the refractory nature of duffy-negative red cells that lack a necessary receptor (Fy(a-b-)) for invasion. *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; Mueller et al., 2007]. There appears to be no duffy blood group restriction to infection for either of these parasites [Collins & Jeffery, 2005]. 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]. The non-falciparum human malarias are often susceptible to most antimalarial drugs including those that currently fail to treat *P. falciparum* [White, 2008], however most evade drug action as they are more often benign and/or relapse.

Investigations of non-falciparum infections were routinely done in national and specialized surveys during the 1960s. Between May and April 1960, Dr. Bagster Wilson and his wife surveyed 948 individuals living in communities in Bunyoro, Mubende and Karamoja regions; where they reported *P. malariae* prevalence rates ranging from 4-49%. Analysing national survey data, Jelliffe and Jelliffe (1963) between 1961 and 1962 reported extraordinary high prevalence of *P. malariae* among 2334 slides taken from children aged 0-4 years at Bukedi, Kasangati, the Orichinga Valley, Kayonza, Arua, Gulu on the Sudan border, and the Karamajong living in Moroto district. *P. malariae* was found as a single infection in 41% of all slides and 11.8% as a mixed infection; no *P. malariae* infections were found in children in Kayonza and an astounding 92% of slides among the Karamajong [Jelliffe & Jelliffe, 1963]. This was considerably higher than reported by Wilson and Wilson surveying in the same area one year earlier where overall *P. malariae* prevalence at four villages was less than 7% [Wilson & Wilson, 1962]. Among a larger sample at Mukuno during a health survey of the Buganda, Jelliffe found 33.7% of 1577 slides taken from people aged from birth to 50 years of age to harbor single *P. malariae* infections [Jelliffe, 1967]. The most extensive survey undertaken of parasite species was part of the national malariometric surveys between

1964 and 1967 and reported by Onori (1967). *P. malariae*'s contribution to malaria infections was highest in Karamoja, Acholi, West Nile and Lango districts in the north (Tables 4.2 and 4.3).

Quality-assured slide confirmation of parasite species was undertaken at large surveys in northern Uganda [NMCP/UMSP/UBOS, 2011] and as part of the national MIS survey undertaken in 2009 [UBOS, 2010], providing valuable information on the current distribution of non-falciparum plasmodium species. We have re-constituted the district boundaries reported by Onori (1967) and this boundary file was used in combination with the geo-coordinates of assembled community survey data described above to re-define the location boundaries of 368 surveys where species were identified between 1990 and 2012. The distribution of infections in accordance with Onori's regional descriptions is shown in Tables 4.2 and 4.3.

Over the last fifty years *P. falciparum* has remained the dominant parasite, accounting for over 90% of all infections. *P. ovale*, has remained constant as a small contributor to malaria infections detected in the community; 0.6% during the 1960s and 0.8% during the 1990s-2000s. Onori's nationwide investigation of *P. ovale* suggested highest prevalence in the north and west of the country (Tables 4.2 and 4.3) [Onori, 1967]. However, more recent investigations since the 1990s found an equivalent prevalence across the Eastern regions (Tables 4.2 and 4.3). Recently conventional and real-time quantitative PCR methods specifically designed to discriminate *P. o. curtisi* and *P. o. wallikeri*, were used to assess clinical samples from Apac and community-survey data from lakeside and island communities (Buliisa and Mayuge districts) where *P. ovale* infections ranged from 0-6.7% and both sub-species occurred simultaneously [Oguike et al., 2011]. *Plasmodium ovale* is a relatively benign parasite and induced infections with the *Donaldson* strain during the treatment of neuro-syphilis 50 years ago showed that only 15% of infections led to fever and that repeat infections were quickly sterilized [Collins & Jeffery, 2005].

Plasmodium malariae is a relatively easy parasite to observe with microscopy owing to a distinctive pigmented band forms in host cells [Collins & Jeffrey, 2007]. Most *P. malariae* infections also share similar properties as *P. ovale* and are rarely uniquely associated with clinical events but persist for decades at very low parasite densities and have been associated nephritic syndromes [Hendrickse, 1980; Collins & Jeffery, 2005], including clinical associated evidence in Uganda [Kibukamusoke et al., 1967; Kibukamusoke & Voller, 1970] and while relatively uncommon, *P. malariae*'s true burden has never been formally quantified. In Uganda there has been an interesting apparent drop in the proportion of all infections that include *P. malariae*; 8.5% 1960s to 4.5% in recent surveys (Tables 4.2 and 4.3) and dropped as a proportion of examined individuals infected from 2.5% to 1.7% across the two intervals (Table 4.2). However, in very high transmission areas, such as Apac, detailed investigations have shown focal high transmission of *P. malariae* infections [Proietti et al., 2011]. There is some suggestion of a suppressive effect of *P. falciparum* on *P. malariae* and a parasite density regulatory effect of *P. malariae* on *P. falciparum* clinical infections [Black et al., 1994; Mueller et al., 2007]. While the mechanisms and epidemiological significance of these potential interactions require further confirmation they might have a longer-term significance as prevalence of both parasites declines differentially with scaled prevention and treatment.

For *P. vivax* there are two dogmas that are not necessarily supported by any empirical data for sub-Saharan Africa. First, endemic *P. vivax* transmission is thought to be absent from much of the continent due to the presence of human genetic negativity for Duffy factor surface molecules required for invasion of *P. vivax* into red blood cells. Second, the dominant opinion has for many years been that *P. vivax* is clinically benign. There is a growing body of epidemiological and clinical evidence that suggests that *P. vivax* is far from benign directly causing, and not simply associated with, severe life-threatening disease, mortality and indirect consequences on pregnant women [Baird, 2007; 2013; Mendis et al., 2001; Price et al., 2007]. There is also growing epidemiological and molecular evidence that a parasite with characteristics of *P. vivax* is being transmitted among Duffy blood group–negative inhabitants in Kenya [Ryan et al., 2007], Congo [Culleton et al., 2009] and among travellers to central and west Africa [Gauret et al., 2001]. It would appear that vivax transmission is possibly routinely undetected and can persist in predominantly duffy-negative populations which may not be 100% refractive [Culleton et al., 2008; Rosenberg, 2007].

During the national surveys of the 1960s, 65 (0.2%) of all infections in the communities surveyed were identified as *P. vivax* (Table 4.2). Of infections documented during the assembly of parasite prevalence data, between 1990 and 2012, 50 (1.1%) of infected individuals were documented as harbouring *P. vivax* infections (Table 4.2). All infections were identified using microscopy and it should be noted that there is often a problem of misdiagnosis with *P. ovale* infections [Rosenberg, 2007]. However, there is supporting evidence of the persistence of *P. vivax* transmission in Uganda from clinical and epidemiological observations. Two unusual clinical presentations have been described associated with *P. vivax* in Uganda. First, a case report suggested a presentation of blackwater fever attributed to *P. vivax* infection in an HIV infected woman in the late 1980s [Katongole-Mbidde et al., 1988]. Second, an American missionary presenting with malaria and pulmonary odema was finally diagnosed with *P. vivax* infection acquired while in Uganda [Illamperuma & Allen, 2007]. Recent PCR investigations of a cohort of 68 pregnant women in Mbarara town identified three women infected with *P. vivax* and each were Duffy positive, as were nine other uninfected women randomly selected from the cohort [Dhorda et al., 2011].

Table 4.2: The relative contribution of parasite species among infections detected during community surveys in the 1960s and 1990s-2000s

	1964-1965						1990-2012					
District	Time of survey	Number Examined	Number of +ve *P. falciparum* (% of all +ve infections)	Number of +ve *P. malariae* (% of all +ve infections)	Number of +ve *P. ovale* (% of all +ve infections)	Number of +ve *P. vivax* (% of all +ve infections)	Time of survey	Number Exam	Number of +ve *P. falciparum* (% of all +ve infections)	Number of +ve *P. malariae* (% of all +ve infections)	Number of +ve *P. ovale* (% of all +ve infections)	Number of +ve *P. vivax* (% of all +ve infections)
Eastern												
Busoga	1964-65	39,789	13,699 (95.9)	577 (4.0)	7 (0.1)	1 (0.0)	2009-12	1,055	379 (95.5)	13 (3.3)	0 (0.0)	5 (1.3)
Bukedi	1964	1,716	1,096 (96.3)	42 (3.7)	0 (0.0)	0 (0.0)	2008-12	2,515	1,067 (96.0)	25 (2.3)	10 (0.9)	9 (0.8)
Bugisu	1964	648	272 (97.5)	6 (2.1)	1 (0.4)	0 (0.0)	2009	166	50 (94.3)	1 (1.9)	0 (0.0)	2 (3.8)
Sebei	1964	818	129 (96.4)	4 (2.9)	1 (0.7)	0 (0.0)	2009	21	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teso	1964	3,325	2,229 (94.0)	138 (5.8)	5 (0.2)	0 (0.0)	2009	285	126 (97.7)	1 (0.8)	0 (0.0)	2 (1.6)
Western												
Bunyoro	1964-66	3,813	972 (85.0)	130 (11.4)	39 (3.4)	2 (0.2)	1992-2009	271	116 (95.9)	1 (0.8)	2 (1.7)	2 (1.7)
Toro	1964	1,782	173 (91.8)	11 (5.6)	4 (2.0)	1 (0.6)	2009	211	69 (98.6)	0 (0.0)	0 (0.0)	1 (1.4)
Ankole	1965	2,929	209 (90.5)	19 (8.3)	3 (1.2)	0 (0.0)	2004-10	2,949	522 (88.2)	42 (7.1)	18 (3.0)	10 (1.7)
Kigezi	1964-66	49,809	3,736 (92.6)	254 (6.3)	12 (0.3)	32 (0.8)	2004-12	929	123 (91.1)	11 (8.1)	0 (0.0)	1 (0.7)
Northern												
Karamoja	1965-66	5,602	1815 (83.7)	347 (16.0)	2 (0.1)	4 (0.2)	2009	116	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acholi	1965	5,161	3,083 (82.5)	635 (17.0)	15 (0.4)	4 (0.1)	2009-11	806	203 (88.3)	24 (10.4)	3 (1.3)	0 (0.0)
West-Nile	1966	5,214	3,234 (83.7)	560 (14.5)	54 (1.4)	15 (0.4)	2009	397	193 (98.0)	3 (1.5)	0 (0.0)	1 (0.5)
Madi	1966	1,410	977 (92.1)	69 (6.5)	13 (1.2)	2 (0.2)	2009	81	41 (97.6)	0 (0.0)	0 (0.0)	1 (2.4)
Lango	1966	6,000	2,458 (83.1)	414 (14.0)	83 (2.8)	3 (0.1)	1992-2011	2,211	1,182 (91.3)	94 (7.3)	5 (0.4)	14 (1.1)
Central												
Central		NA	NA	NA	NA	NA	2004-09	842	332 (99.4)	0 (0.0)	0 (0.0)	2 (0.6)
Total		128,016	34,080 (90.7)	3206 (8.5)	238 (0.6)	65 (0.2)		12,855	4,434 (93.6)	215 (4.5)	38 (0.8)	50 (1.1)

Table 4.3: The prevalence of parasite species among infections detected during community surveys in the 1960s and 1990s-2000s

District	Time of survey	*Pf*PR (%)	*Pm*PR (%)	*Po*PR (%)	*Pv*PR (%)	Time of survey	*Pf*PR (%)	*Pm*PR (%)	*Po*PR (%)	*Pv*PR (%)
Eastern										
Busoga	1964-65	34.4	1.5	0.0	0.0	2009-12	35.9	1.2	0.0	0.5
Bukedi	1964	63.8	2.5	0.0	0.0	2008-12	42.4	1.0	0.4	0.4
Bugisu	1964	42.0	0.9	0.2	0.0	2009	30.1	0.6	0.0	1.2
Sebei	1964	15.7	0.5	0.1	0.0	2009	4.8	0.0	0.0	0.0
Teso	1964	67.0	4.1	0.1	0.0	2009	44.2	0.4	0.0	0.7
Western										
Bunyoro	1964-66	25.5	3.4	1.0	0.1	1992-2009	42.8	0.4	0.7	0.7
Toro	1964	9.7	0.6	0.2	0.1	2009	32.7	0.0	0.0	0.5
Ankole	1965	7.1	0.7	0.1	0.0	2004-10	17.7	1.4	0.6	0.3
Kigezi	1964-66	7.5	0.5	0.0	0.1	2004-12	13.2	1.2	0.0	0.1
Northern										
Karamoja	1965-66	32.4	6.2	0.0	0.1	2009	25.9	0.0	0.0	0.0
Acholi	1965	59.7	12.3	0.3	0.1	2009-11	25.2	3.0	0.4	0.0
West-Nile	1966	62.0	10.7	1.0	0.3	2009	48.6	0.8	0.0	0.3
Madi	1966	69.3	4.9	0.9	0.2	2009	50.6	0.0	0.0	1.2
Lango	1966	41.0	6.9	1.4	0.0	1992-2011	53.5	4.3	0.2	0.6
Central										
Central		NA	NA	NA	NA	2004-09	39.4	0.0	0.0	0.2
Total		26.6	2.5	0.2	0.1		34.5	1.7	0.3	0.4

4.8 Malaria seasonality

A dominant epidemiological characteristic of malaria across much of Africa is its seasonal profile. Relationships between climate, seasonal parasite transmission and disease outcomes are complex and have been poorly defined for many years [Gill, 1938]. There is a suggestion that areas with acute transmission represent settings that are more adapted to synchronized infections leading to higher host parasite densities [Mckenzie et al., 2001]. Acutely seasonal malaria exposure areas may lead to poorly "designed" immunization for new-born children, resulting in different disease-severity profiles compared to settings with equivalent annual parasite exposure more evenly distributed throughout a year (spaced immunization) [Caniero et al., 2010; Greenwood et al., 1991].

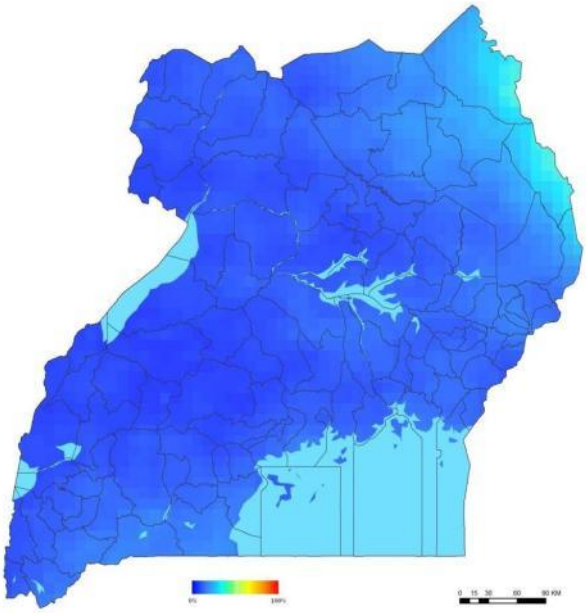
The description of seasonality represents an important operational information platform to target the timing of vector control, most notably IRS and larval control operations, and the renewed interest in pulsed mass drug administration or restricted chemoprophylaxis in the Sahel, known as Seasonal Malaria Control (SMC) [Cairns et al., 2012; WHO, 2012].

The climate suitability maps developed by the MARA collaboration are based on the likelihood of stable transmission using a rules-based approach [Craig et al., 1999; Tanser et al., 2003; http://www.mara.org.za/] (Figure 4.2b). A more robust approach has recently been developed using empirical data to define extremes of seasonality for SMC using Fourier processed daily rainfall data since 2000 [http://www.cpc.noaa.gov/products/fews/rfe.shtml] and tested against monthly clinical incidence data from 55 sites across sub-Saharan Africa. The optimal model was one where 60% of annual rainfall occurred within 3 months and best fitted the seasonal clinical profiles of >60% of cumulative cases occurring in 4 consecutive months [Cairns et al., 2012]. Using this rainfall profile, areas with incidence patterns suitable for SMC were identified, with a sensitivity of 95.0% and a specificity of 73.5% [Cairns et al., 2012].

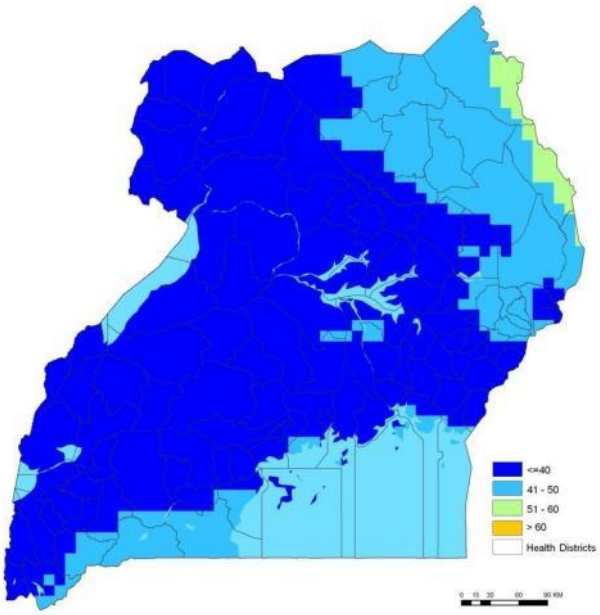
Here, we have used daily rainfall estimates from the African Rainfall Estimates version 2 (RFE 2.0) dataset developed as a collaborative programme between NOAA's Climate Prediction centre (CPC), USAID/Famine Early Systems Network (FEWS). The RFE 2 gridded dataset combines gauge and satellite information on a near-real time basis to provide daily rainfall estimates over the African continent and is archived from January 2000 at 10 km spatial resolution [NOAA CPC, 2001; Novella & Thiaw, 2012]. To match work done by Cairns and colleagues we have selected daily-accumulated rainfall data between 2002 to 2009 per 10 km pixel to define the maximum percentage of the total annual rainfall occurring in a period of consecutive months (Figures 4.11a and 4.11b). These predictions are more tangibly rooted in current models of disease risk and are used here in preference to MARA models described in Figure 4.2b. As can be seen from Figures 4.11a and 4.11b there are no areas within Uganda that would constitute areas where SMC might be appropriate and the majority of the landmass experiences rainfall patterns best described as supporting more perennial transmission.

Figure 4.12: a) NOAA rainfall/seasonality concentration index in Uganda in continuous form and b) classes of rainfall seasonality

a)



b)



Footnotes: The gridded daily rainfall estimates at 0.1 degree resolution from the RFE 2.0 dataset between January 2002 and December 2009 was acquired from the NOAA CPC/FEWS archive [NWS, 2012; ftp://ftp.cpc.ncep.noaa.gov/fews/newalgo_est/]. The daily rainfall estimates were then aggregated to calculate total monthly and annual rainfall. For each pixel, the maximum percentage of the total annual rainfall occurring in three month-iterations was then calculated for each year using spatial analyst tool in ArcGIS 10.1 (ESRI, USA). The average pixel value between 2002 and 2009 was then calculated and the resulting image reclassified to give a binary output of areas where rainfall in three consecutive months was < 60% or > 60%

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Chapter 5

Dominant malaria vectors in Uganda

5.1 Background

Africa is home to the most effective and efficient vectors of human malaria [Coluzzi, 1984]: *An. gambiae*, with its sibling, *An. arabiensis* [Coetzee, 2004; White, 1974], both form part of the *An. gambiae* complex which also includes the salt water tolerant, coastal species *An. melas* and *An. merus* [Gillies & Coetzee, 1987; Gillies & DeMeillon, 1968; Harbach, 2004; White, 1974]. Other members of the *An. gambiae* Giles complex are not regarded as dominant vectors because of their restricted, focal (*An. bwambae* [White, 1985]) or zoophilic nature (*An. quadriannulatus* A and *An. quadriannulatus* B [Coluzzi, 1984]), or because they cannot, by themselves, sustain malaria transmission in an area. In addition to the four dominant vector species (DVS) within the *An. gambiae* complex, large parts of Africa are also home to other DVS including the *An. funestus* Giles, *An. nili* and *An. moucheti*. Others such as *An. rivulorum, An. coustani and An. pharoensis,* although not considered DVS in Africa, appear to play a significant minor role as weaker, but nevertheless important vectors, in some selected areas [Kawada et al., 2012; Mwangangi et al., 2013; Wilkes et al., 1996].

All national malaria strategies across Africa implement interventions aimed at reducing human exposure to infectious malaria vectors. These include insecticides on mosquito 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 composition linked to their intrinsic behavioural bionomics and their resistance to currently available 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 currently used vector control strategies [Ferguson et al., 2010; Gatton et al., 2013; Pates & Curtis, 2005; Ranson et al., 2011]. Furthermore, a lack of reliable entomological monitoring systems that capture all major relevant phenotypes and their effect on vector population dynamics on national scales limit capacity of malaria control programs to manage ongoing vector control efforts or adapt to changing vector behaviour and insecticide susceptibility [Govella et al., 2013].

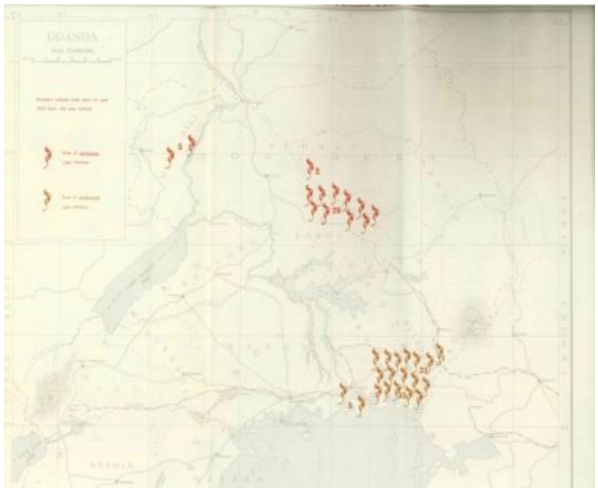
5.2 Historical vector surveillance

The entomologist, MF Fiske, worked in Uganda from 1917 and provided much needed support to the government on defining the vector challenges faced by human trypanosomiasis and malaria [Uganda Protectorate, 1919]. His principal responsibilities included the reclamation and sanitation of the Victoria Nyanza infected areas for both diseases. In addition he supported the reconnaissance of Anopheline vector breeding within the municipalities and major towns country-wide.

Colonel SP James's visit in April 1929, with the help Dr. H Bennet, assessed the malaria situation and collected mosquito specimens in Kampala, Masindi, Lira, Siroti, Mbale and Tororo [James, 1929]. Later in 1932, major entomological work was carried out by Dr. EG Gibbins, the government entomologist, who conducted infectivity surveys in four physically distinct towns

across Uganda. *An. gambiae (costalis)* and *An. funestus* were found resting in most human dwellings with other vectors identified to be *An. moucheti, An. pharoensis, An. hancocki, An. marshalli* and *An. mauritanius* [Uganda Protectorate, 1933; Gibbins, 1932]. The sporozoite rates of *An. funestus* were 13-17% in Kampala and 1.4% in Fort Portal. The sporozoite rate of *An. moucheti* varied from 1.6-4.3%; that of *An. pharoensis* was 0.7% and that of *An. hancocki* was 0.2% in the central-southern part of the country. In 1934, local entomologists conducted extensive mapping of principal breeding sites in Kampala area [Uganda Protectorate, 1935; Hopkins, 1934; Uganda Protectorate, 1956]. Crude maps were assembled from various surveys through to the 1950s (Figure 5.1).

Figure 5.1: Map of breeding sites for *An. gambiae* and *An. rhodesiensis* [Uganda Protectorate, 1956]

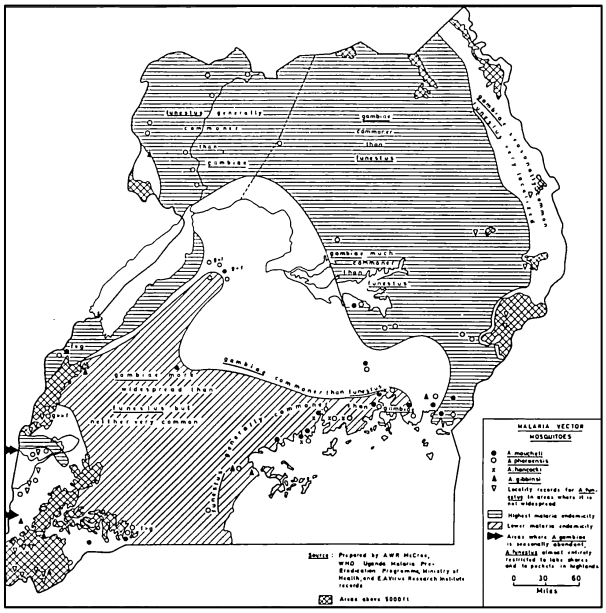


Following the division of the *An. gambiae* Complex, three species were identified in Uganda: *An. gambiae* s.s. in the humid regions on the shores of Lake Victoria [Onori & Benthein, 1969]; *An. arabiensis* in the drier savannah regions of the north [Onori, 1969]; and *An. bwambae*, an endemic species of Uganda described by White (1985) whose larvae developed in mineral springs of the Semliki National Park [Harbach et al., 1997], and abundant in Bwamba District, particularly anthropophilic but did not appear to play an important role in transmission.

The maps developed as part of the geography of disease, edited by Hall & Legands, between 1968 and 1975, (Section 4.1.1) presented a distribution map of major malaria vectors, *An. gambiae* (with it sibling species *gambiae A* and *gambiae B*) and *An. funestus* (Figure 5.2). The chapter also confirms the minor roles played by four other vectors: *An. pharoensis* found to inhabit grassy swamps near the shores of Lake Victoria and other lakes, *An. moucheti moucheti* in the flooded grasslands, *An. hancocki* sharing similar habitats to *An. funestus* and *An. gibbinsi* a sibling of *An. marshalli* found indoors at higher altitudes [McCrae, 1975].

In this chapter, we attempt to update the knowledge base of DVS in Uganda as part of an extended literature search and compilation of unpublished data.

Figure 5.2: Map of the distribution of major and minor vectors across Uganda before independence [McCrae, 1975]



5.3 Data assembly

Detailed inventories of species distribution began during elimination campaigns launched in the 1950s, but continued in earnest only in North Africa where elimination efforts continued through the 1970s. The notion of mapping vector species was resurrected during the mid 1990s as part of the Mapping Malaria Risk in Africa (MARA/ARMA) project [Coetzee et al., 2000]. There have been several recent attempts to model the distributions of DVS in Africa using sparse data and climatic determinants notably, temperature, soil moisture and other environmental drivers of vector species presence and abundance [Lindsay, 1998; Moffett et al., 2007; Sinka et al., 2010; Lunde et al., 2013a; Lunde et al. 2013b]. These model predictions have used different statistical approaches and different data sets and are hard to systematically compare.

The coincidental growth of geo-located databases of vector species has, however, provided some unique resources for countries to access, augment and adapt to local planning needs; notably AnoBase [http://skonops.imbb.forth.gr/], VectorBase [https://www.vectorbase.org], MARA/ARMA collaboration [https://www.mara.org.za], Walter Reed Biosystematics Unit (WRBU) Mosquito Catalog [http://www.mosquitocatalog.org], Malaria Atlas Project (MAP) [http://www.map.ox.ac.uk], and the Disease Vectors database [https://www.diseasevectors.org]. The database on insecticide resistance, the Arthropod Pesticide Resistance Database (APRD) [http://www.pesticideresistance.org/], covers a large variety of arthropods, but only reports instances of occurrence of resistance, without any precision on geographic location nor actual data. The African Network for Vector Resistance (ANVR) was established in 2000, and amongst its objectives was the important goal of improving dissemination of resistance data [ANVR, 2005]. Over the last 10 years, a database has

been developed to store the results of resistance monitoring activities by ANVR members. This database has now been integrated for open access with the launch of IRBase [Dialynas et al., 2009].

The most comprehensive available, geo-coded species-specific data is currently held on the MAP database [Sinka et al., 2010]. We have augmented this database for Uganda with additional systematic on-line searches of medical literature databases including PubMed, Google Scholar and Web of Science using search terms “Anopheles AND Uganda“ for all study publications after December 1970 and post the last searches undertaken by MAP. We also included data identified during searches of reports held at the WHO library in Geneva that related to vector studies in Uganda, unpublished reports from the MCU libraries in Kampala and recent extensive vector studies undertaken by Research Triangle International (RTI) and other partners across Uganda.

Each study site was geo-coded using methods described in section 4.2.3. Data abstracted from each report included the start and end of the entomological survey, species identified at complex or species member levels, methods of sampling (animal bait catches, bed net traps, CDC light traps, human landing catches, indoor resting searches, pyrethrum spray catches, exit traps, larval searches), methods of species detection (Polymerase chain reaction (PCR), Chromosome Banding Sequences, Morphology, DNA probes), estimates of numbers of vectors sampled and the full citation source. For older survey data it is recognized that there is a degree of taxonomic ambiguity, for example the *Anopheles gambiae* complex was only fully categorised in 1998 and *An. quadrimaculatus* species B designated a separate species after this date [Harbach, 2004; Hunt et al., 1998]; furthermore the exact composition of the *An. funestus* complex remains unclear [Costantini et al., 1999]. In addition, we developed two addition sub-databases on recorded entomological inoculation rates (EIR) and any information of insecticide susceptibility testing documented since 1970.

5.4 Occurrence with time and bionomics

Here we present only a mapped distribution of DVS, however, with a complete spatial and temporal database it is planned to develop a more mathematical approach to defining species distribution in Uganda with the geo-located species data and using Boosted Trees Regression methods [Elith et al., 2008]. The mapped presentation of species distribution derived from the assembled data is shown in Figures 5.3a-c with a comment on each vectors traditional bionomics [Sinka et al., 2010]. On the whole *An. gambiae s.s*. *An. arabiensis* and *An. funestus* show a sympatric, universal distribution across Uganda. It is however notable that there have been very few investigations of DVS in the north, west or north eastern regions of the country.

Figure 5.3: Maps of a) *An. gambiae s.s.*, b) *An. arabiensis* and c) *An. funestus* sampled across Uganda between 1970 and 2013

	***a.Anopheles gambiae s.s*:** *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, 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.
	***b. Anopheles arabiensis:*** *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. Its larval habitats are generally small, temporary, sunlit, clear and shallow fresh water pools, although *An. arabiensis* is able to utilize a variety of habitats including slow flowing, partially shaded streams, large and small natural and man-made habitats, turbid waters and there are reports of larval identification in brackish habitats. *Anopheles arabiensis* is described as a zoophilic, exophagic and exophilic species but has a wide range of feeding and resting patterns, depending on geographical location. This behavioural plasticity allows *An. arabiensis* to adapt quickly to counter indoor residual spraying control showing behavioural avoidance of sprayed surfaces depending on the type of insecticide used. Blood feeding times also vary in frequency; peak evening biting times can begin in the early evening (19:00) or early morning (03:00). This species usually has a greater tendency than *An. gambiae s.s.* to bite animals and rest outdoors.
	***c. Anopheles funestus:*** A typical *An. funestus* larval habitat is a large, permanent or semi-permanent body of fresh water with emergent vegetation, such as swamps, large ponds and lake edges. *An. funestus* is a highly adaptable species, allowing it to occupy and maintain its wide distribution and utilise and conform to the many habitats and climatic conditions. *An. funestus* is considered to be highly anthropophilic with a late-night biting pattern (after 22.00 hours). Endophilic resting behaviour is also commonly reported, and these characteristics are responsible for rapid disappearance of this vector following expanded indoor residual spraying and insecticide-treated nets. Compared to other dominant vector species in Africa, *An. funestus* shows fairly consistent behaviour (generally anthropophilic and endophilic) throughout its range. In the absence of insecticide use, the endophilic resting behaviour of *An. funestus* combined with a relatively high longevity, makes it as good a vector, or better in some areas, as *An. gambiae s.s*.

Anopheles nili was detected in 2002 in Maracha, West Nile [Okello et al., 2006]. Isolated observations of *An. pharoensis* have been made between 1992 and 2010 at Buganda, Kigezi and Toro regions [Lutwama et al., 1999; CDCD/MoH, 1992; Kamugisha, 1992; Mutebi et al., 2012]. Multiple observations in the mid-1990s were made of *An. bwambae* in Bundibugyo [Harbach et al., 1997].

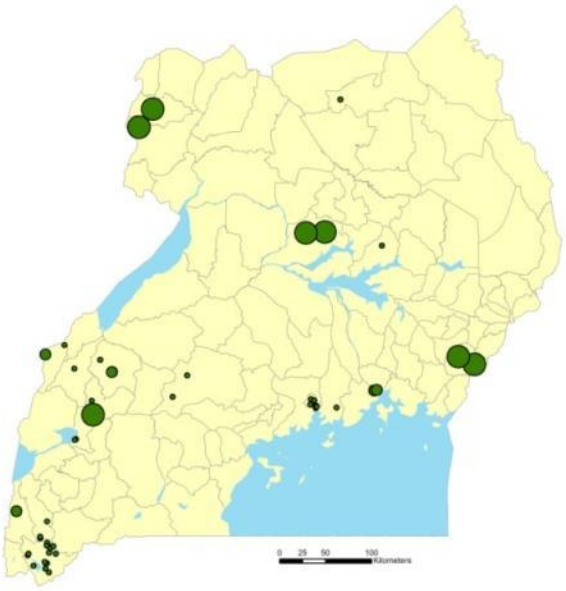
An entomological study conducted as part of the System-wide Initiative on Malaria and Agriculture (SIMA) in Nyabushozi (Kihurura District, western Uganda) in 2006 found *An. gambiae s.s.* and *An. funestus* were the only vectors despite the dryness of the area and setting up of CDC light traps next to cattle kraals and outside occupied houses [Onen, unpublished observations]. This could be attributed to the fortnightly application of acaricides/insecticides onto cattle for the control ticks and other cattle disease vectors which could have eliminated *An. arabiensis* from the area.

Provisional information from Apac in 2012 indicates that a population replacement of endophilic and endophagic *An. gambiae s.s.* by exophilic and exophagic *An. arabiensis* may have taken place because of use of LLINs and intense IRS in the area since 2008 [Craig Wilding, unpublished observations]. However, more comprehensive studies are needed to define species replacement in areas where IRS have been used in Uganda.

5.5 EIR

One vector based measure of transmission intensity is the Entomological Inoculation Rates (EIR); the number of infective bites per person per time unit expressed across species or individually by species. In 2002, Dr. Paul Okello and colleagues undertook a detailed examination of EIRs in seven areas of Uganda [Okello et al., 2006]. *An. gambiae s.s.* was responsible for over 80% of malaria transmission in Tororo and Arua sentinel sites, whist *An. funestus* contributed 88% of infective bites in the Apac region. The study showed both seasonal and spatial variability in transmission intensity across the country. Sporozoite rates detected in Kyenjojo, Kanungu and Jinja were negligible, resulting in annual EIR tending to 0, in other sites annual EIRs ranged from 4 infective bites per person per year (Mubende) to > 1,500 infective bites per person per year (Apac) [Okello et al., 2006]. The EIR recorded in Apac is possibly the highest documented EIR in Africa. These EIR data have been subsequently used in multiple malaria risk maps presented by the NMCP in various strategic plans. Between 1997 and 2009, there have been a total of 34 site-time estimates of EIR in Uganda [Lindblade et al., 2000; Okello et al., 2006; Kristan et al., 2008; Okia et al., 2013a] and these are summarized in Figure 5.4 highlighting the huge variation in EIRs across relative short distances and possibly a consequence of variations in sampling methods or intrinsic heterogeneity in vector based estimates of transmission.

Figure 5.4: Annual Entomological Inoculations rates observed between 1970 and 2013 across Uganda 0 to 4 infective bite per person per year (pppy) 4 to 50 infective bites pppy 50 to 250 infective bites pppy and 250 to 1586 infective bites pppy



5.6 Resistance

The two single base substitutions in the sodium channel commonly referred to as knockdown resistance (*kdr*) mutations confer cross-resistance to DDT and pyrethroids and are associated with resistance in *An. gambiae* s.l populations [Ranson et al., 2011]. The gene mainly responsible, the *1014F* alleles (West), are at high frequency in West Africa and have only rarely been reported in East African populations including historically at a very low frequency in Ugandan *An. gambiae* s.s. [Verhaeghen et al., 2006].

Between April and May 2008 in the districts of Tororo and Butaleja, eastern Uganda, *Anopheles gambiae s.l.* adults were raised from wild-caught larvae sampled from two ecologically distinct breeding sites and exposed to WHO discriminating concentrations of DDT, permethrin, deltamethrin, bendiocarb and malathion. Survival rates to DDT were as high as 85.4%, however it was noted that there were significant resistance levels to permethrin (38.5%), reduced susceptibitity to deltamethrin, but full susceptibility to bendiocarb and malathion. In both ecological settings the *kdr* L1014F ('kdr west') alleles were absent, however the *kdr* L10145 ('kdr east') allele was present.

WHO bioassays indicated that *An. funestus* in Tororo was resistant to pyrethroids (62% mortality after 1 h exposure to 0.75% permethrin and 28% mortality to 0.05% deltamethrin) in 2009. Suspected DDT resistance was also observed with 82% mortality. However, *An. funestus* was fully susceptible to bendiocarb (carbamate), malathion (organophosphate) and dieldrin with 100% mortality observed after exposure to each of these insecticides. There was a poor correlation between the bioassay results and presence of the L1014F *kdr* mutation [Morgan et al., 2010].

Field-collected *An. gambiae s.s.* and *An. arabiensis* were tested using bioassays from Jinja in 2010, and only *An. gambiae* exhibited high pyrethroid resistance (permethrin LT50 > 2 h; deltamethrin LT50 > 5 h). *An. arabiensis* were resistant to permethrin and exhibited reduced susceptibility to deltamethrin. However, while *An. gambiae* were DDT resistant, *An. arabiensis* were fully susceptible. Both species were fully susceptible to bendiocarb and fenitrothion. The *Kdr 1014S* has increased rapidly in the Jinja population of *An. gambiae s.s.* and now approaches fixation (*Circa* 95%), consistent with insecticide-mediated selection, but is currently at a low frequency in *An. arabiensis* (0.07%) [Mawejje et al., 2012]

The shift from the use of DDT and pyrethroids to carbamates in 2010 (Section 3.7.3.2) was a result of generating resistance data from entomological monitoring. Insecticide resistance monitoring conducted in 2009 showed vector resistance on bioassays to both DDT and pyrethroids, specifically λ-cyhalothrin but not α-cypermethrin [Okia & Protopopoff, 2009; Okia, 2010], Bioassays conducted in the Apac district in 2009 indicated only 52% *An. gambiae* mortality to DDT after 24 hours and 68%, 72%, and 71% mortality to λ-cyhalothrin 0.05%, etofenprox 0.5%, and permethrin 0.75%, respectively [Okia, 2010]. Resistance mechanisms are likely to be caused by the *kdr* mutation, as evidenced by the cross-resistance between pyrethroids and DDT [Verhaeghen et al., 2010].

In 2011, an extensive investigation was undertaken of 11 World Health Organization Pesticide Evaluation Scheme approved public health insecticides including DDT (Organochlorine), α-cypermethrin, Cyfluthrin, Deltamethrin, Etofenprox, λ-cyhalothrin, Permethrin (Pyrethroids), Malathion and Pirimiphos-Methyl (Organophosphates), Bendiocarb and Propoxur (Carbamates) in six districts (Apac, Hoima, Kanungu, Kitgum, Tororo and Wakiso) using standard WHO tube test using *An. gambiae* s.l. only [Okia et al., 2013b].

For DDT, mortality was under 80% in the three sites of Wakiso, Tororo and Kanungu, while in Apac and Kitgum where IRS with carbamates have been conducted, mortality was 91.5% and 94%, respectively. The susceptibility of *An. gambiae* s.l. to pyrethroids varied by site. Susceptibility for Deltamethrin was <80% in Apac, Tororo, Wakiso and 86% in Kanungu, but varied from 23%-86%, with the lowest mortality rate in Apac District and the highest mortality rate in Kanungu District. Susceptibility for Cyfluthrin was <80% in Apac and Tororo where testing produced mortalities of 40% and 27% respectively. Mortality for Etofenprox was <80% in Apac, Hoima, Kanungu, Tororo, and Wakiso Districts. λ-Cyhalothrin susceptibility was <80% in Apac, Kanungu, Tororo, and Wakiso, varying between 36% to 53%. Mortality for Permethrin was <80% in Tororo and Apac standing at 40% and 31%, respectively. α-cypermethrin mortality was <80% in Apac but test mosquitoes were susceptible in Kanungu and Wakiso, but had reduced susceptibility of 89% in Tororo. Malathion treated mosquitoes were susceptible with mortality between 99-100% in Apac and Tororo. All tested mosquitoes were 100% susceptible to Pirimiphos-Methyl in all the 6 districts tested. Bendiocarb treated mosquitoes were all susceptible (99%-100%) in Apac, Hoima, and Wakiso, however, it had a slightly reduced mortality varying from 84% and 97% in Tororo and Kanungu Districts, respectively. Propoxur was fully (100%) susceptible in Apac and Kanungu but had reduced susceptibility of 81% in Tororo District.

The report concluded that "*An. gambiae s.l. in Uganda is resistant to DDT and most pyrethroids but susceptible to organophosphates and carbamates. However, data from Tororo and Kanungu Districts indicates that there is reduced susceptibility to carbamates which strongly indicates the need for routine monitoring of insecticide susceptibility. These results may also indicate that it may be possible to use Carbamates and Organophosphates for IRS in the management of DDT- and pyrethroid resistance, and thus, maintain the effectiveness of Long-Lasting Insecticide-Treated Nets (LLINs)*" [Okia et al., 2013a; 2013b]

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Chapter 6

Modelling the coverage of ITNs/IRS 2000-2010

6.1 Background to ITN distribution 1999-2011

Surveys done in 1995 and 1996 by AMREF and GTZ indicated that less than 1% of the population used mosquito nets [Balayo, 2005]. From 2003, strategies to increase ITN coverage promoted a market segmentation model, where commercial distribution was promoted among populations who could afford to pay, and government and donor funds dedicated to distributing free nets in the conflict-affected areas of the north and subsidizing social-marketing nets elsewhere [Section 3.4.6.2; MoH, 2003].

Between 1999 and 2004, four main distribution strategies were used to promote ITN sales and use across Uganda: a) commercial sale of nets at full cost; 2) sale of subsidized ITN through the private sector; 3) free distribution to vulnerable groups through small targeted campaigns; and latterly 4) free distribution through ANC/EPI clinics [PMI,2011]. Although, the policy for free distribution at ANC clinics began in 2004 less than 200,000 nets were distributed through this channel [Kilian, 2004]. Notable in 2004 was the distribution of 169,840 free LLINS across six districts (Kitgum, Gulu, Pader, Katakwi, Soroti and Kaberamaido) by various NGO's (Oxfam, Malaria Consortium, CARE, Medair and Concern) [Balayo, 2005]. Two rounds of free mass net re-treatment campaigns were reported as conducted in twenty districts starting May 2004 [Balayo, 2005]. A survey undertaken in 2006 at five urban and rural sites in Eastern, Central and Western regions found that 78% of nets had been purchased from commercial sources [NetMark, 2006]. The total annual sales of mosquito nets increased from an estimated 40,000 nets in 1999 to about 600,000 in 2004 [Balayo, 2005], 50% channeled through 20 NGOs, the remainder sold in the commercial market. The price of a family sized net was between US$ 6.6-10.3 US$ in 1998/99 and had declined to between US$ 4.3-7.7 $ by 2002 [Balayo, 2005].

Between December 2005 and March 2006, the Uganda Program for Human and Holistic development (UPHOLD) launched a free distribution campaign across nine districts (Bugiri, Bushenyi, Gulu, Katakwi, Kitgum, Lira, Mayuge, Mubende and Rukungiri). The UPHOLD project, supported by USAID through funds to JSI Research & Training Institute, Inc., used the existing systems established for Home-based Management of Fever (HBMF) to target children below the age of five years with over 200,000 LLIN. The nine districts were selected on the basis that the ITN coverage in children under the age of 5 within the districts was below 10% before the mass campaign and of the nine districts, four were conflict-affected and the rest non-conflict affected [Mpeka et al., 2007].

In 2007, the MoH was awarded a grant from the Global Fund to provide 17.7 million LLINs to pregnant women and children below five years of age. In 2009, the agreement was reprogrammed to provide two, large-scale campaigns: the first was to distribute LLINs to pregnant women and children under five through a network of NGO partners. The second phase was to distribute a balance of LLINs as a "fill-in" campaign in 2010 to reach universal coverage (defined as one net per two people).

The use of NGO partners to deliver LLIN was critical from 2009, as part of the first phase of Global Fund and supplementary PMI support. Between July 2009 and June 2010 a total of 5.32 million "Global Fund" LLINs were distributed through various organizations. Between July and October 2009, AFFORD distributed 282,236 LLINS in Kaberamaido, Kumi, Manafwa,

Soroti and Mabale districts. In July 2009, the Malaria Consortium distributed 66,342 LLIN in Moyo and Yumbe districts and extended in October 2009, to support the distribution of 17,525 LLINs in Nebbi and Adjumani districts. The Stop Malaria Project and Program for Accessible Health, Communication and Education (PACE; a transitional NGO from PSI) distributed 1.48 million LLINS in 13 central region districts and 2.85 million LLINs in western districts, Kampala and Wakiso regions [MOH, 2009]. During this period the Malaria Consortium received funding from the UK's Comic Relief and distributed 600,034 free LLINs in Hoima (November 2009), Bullisa (December 2009) and Kiboga (March 2010) districts. Nets distributed through commercial sales totalled 12,540 in 2009, 90% lower than commercial sales in 2000 [Kilian, 2004].

The second phase, that involved nationwide mass-campaigns between May 2010 and ended in January 2011, led to the distribution of 7.3 million LLINs. This was managed as a collaboration between the MCU and PSI's PACE project with a nationwide involvement of political leaders, district health teams, transporters, parish and village leaders and village health teams. Distribution costs amounted to *circa* US$ 1 million. An evaluation of the costs through routine ANC delivery versus mass campaigns in Jinja and Adjumani districts showed that economic costs for ANC distribution were higher (US$ 2.27) compared to campaign costs (US$ 1.23) [Kolaczinski et al., 2010]. By the end of the first round of the mass campaign, there was a gap from projected to actual needs of 678,476 LLINs in eight districts [Muzaki & Mukasa, 2011].

6.2 Enumerating ITN distribution

ITN distribution data by district were assembled from databases provided by the MCU and partners described above. Data were provided by year and were re-assembled to match each of the 112 health district described in earlier chapters. According to these ITN registers, between 2005 and 2010, about 15.1 million ITNs have been documented as distributed in Uganda. Over 65% of ITN distributions happened during the period 2008-2010. 75% of these nets were distributed in 2010 and remain within the 3-year effective operational life-span of LLINs (Figure 6.1). However, there are gaps in the data and we are not sure how well these ITN distribution registers were assembled within the MCU, despite support to establish them from WHO in 2007. For example, it is reported that 17.1 million LLINs have been distributed since 2005 in Uganda [MoH, 2009] but this does not tally with registered data. This remains a serious issue for the NMCP as it cannot define spatially distribution volumes against distribution targets. While we present these data here, for the purposes of modelling coverage we have elected not to use the process data as a covariate to improve precision in 2010 coverage estimates. Distribution data have been expressed as nets delivered and per capita projected populations for each district for the intervals 2005-2008 and 2009- 2010 (Figure 6.2).

Figure 6.1 Annual and cummulative total distributions of ITNs from 2005 to 2010. ITN distribution per year (light green) and cummulative net distributions 2005-2010 (dark green)

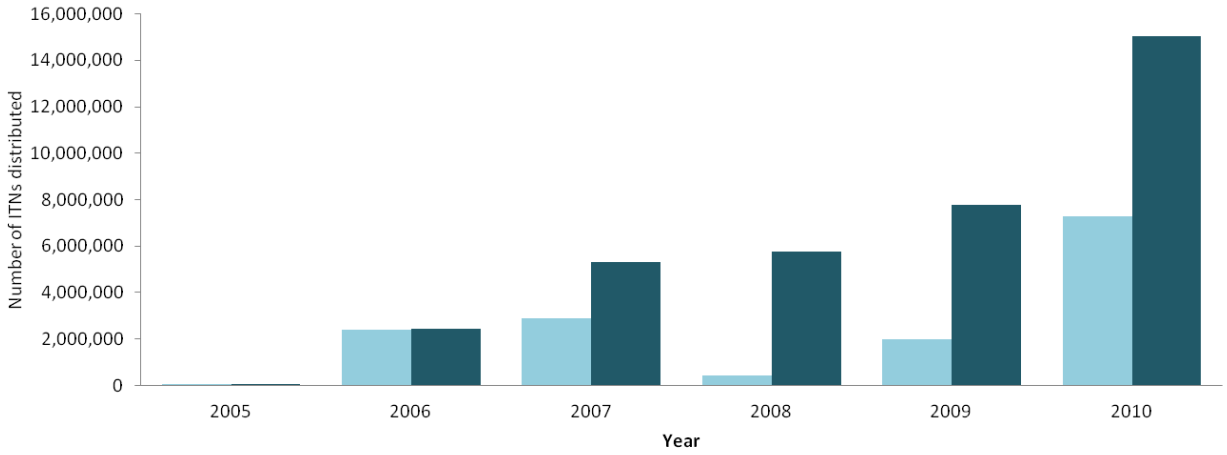
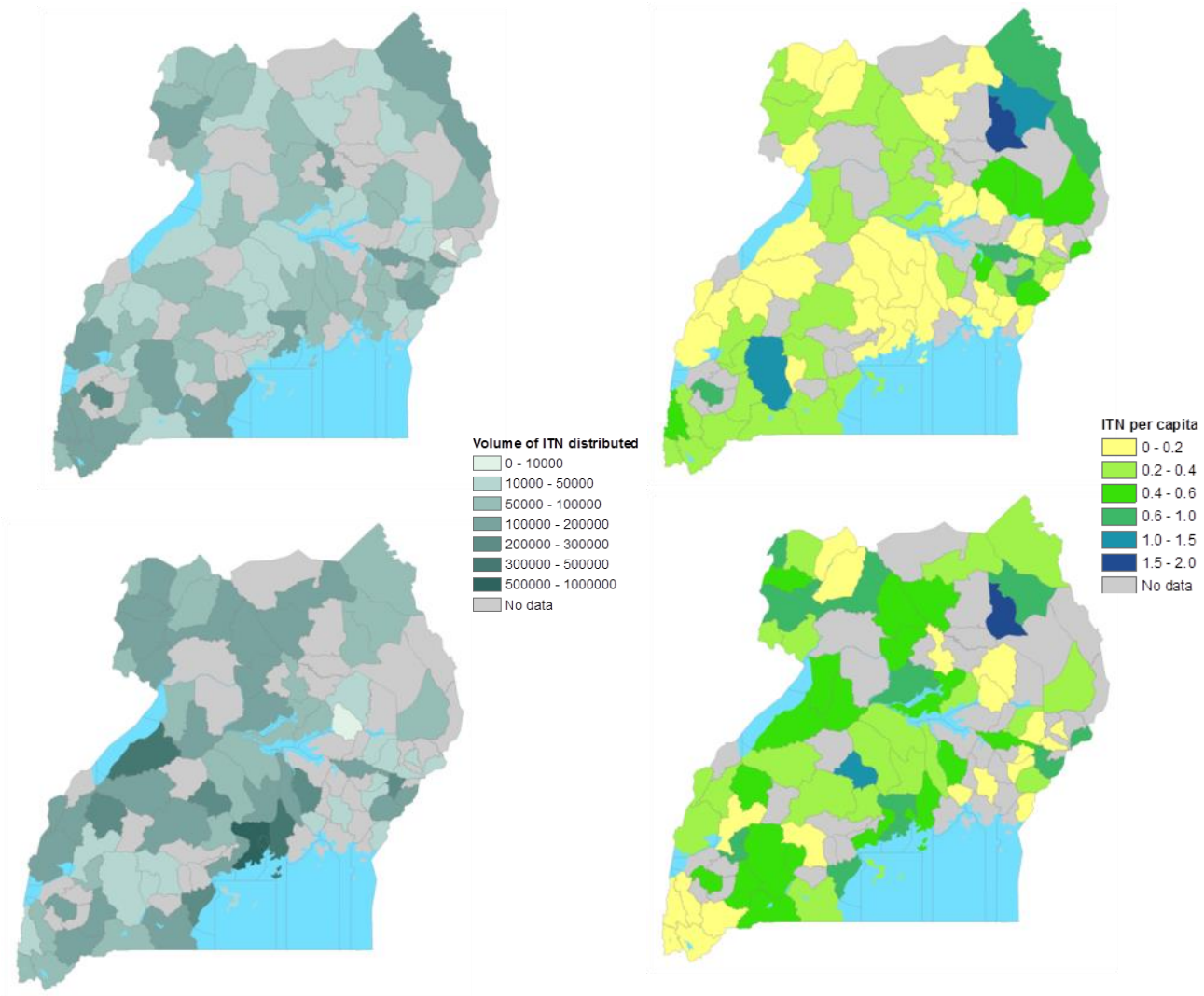


Figure 6.2 Annual total distributions of ITNs from 2005-2008 and 2009-2010 by district (left) and per capita (right)



From 2011, it was intended to start routine distribution for "keep up" in 32 out of 112 districts with support from PMI and begin planning for a further catch-up mass campaign in 2012 using funds from the Global Fund Round 10. The Global Fund announced on its website on May 17th 2013 that it was supporting Uganda in the distribution of over 15.5 million long lasting insecticide-treated nets, making it the largest malaria prevention campaign in 2013. Present at the launch included the President, the Minister of Health and PMI's Admiral Tim Ziemer. The campaign was planned to start in the eastern part of the country and continue to the central, western, and northern regions. However, following this high profile launch event there was a lack of consensus as to whether the NGOs, civil society or the security agencies in should be the main distributors of the LLINs, leading to delays in the 2013 mass campaigns.

6.3 Assembling ITN coverage data

Since 2000, five large scale, sample household surveys, with information on the proportion of persons sleeping under an ITN the night before survey, have been undertaken in Uganda (Table 6.1). The details of the survey sampling procedures and sample sizes are provided in Annex A3.1. During the DHS in 2000/01 only children below the age of five years were investigated about ITN use, however among 14,428 children surveyed only 0.5% were reported using an ITN the night before the survey. Combining the National Household Survey (NHS) and the Demographic and Health Survey (DHS) undertaken between 2005 and 2006, of the 87,666 household members of all ages interviewed, only 6,041 (6.9%) reported sleeping under an ITN the night before the survey. The Malaria Indicator Survey (MIS), undertaken between November and December 2009, showed that approximately 26% of Ugandans were reporting to have slept under an ITN. Following several NGO partner led ITN campaigns across the country in 2009 and 2010, the total proportion of Ugandans reported as sleeping under an ITN had increased to 34.5% according to the DHS undertaken between June and November 2011.

Table 6.1 Summary of large scale household survey data with information on persons sleeping under an ITN the night before survey

Survey	Clusters	Households	Persons	Age group for ITN coverage information	Source
DHS 2000-01	298	7,885	14,428	0-4 & 14-49	UBOS, MEASURE
NHS 2002-03	973	9,711	50,513	all ages	UBOS
NHS 2005-06	762	7,426	42,227	all ages	UBOS
DHS 2006	368	8,870	45,439	all ages	UBOS, MEASURE
MIS 2009	170	4,421	21,606	all ages	UBOS, MEASURE
DHS 2011	404	9,033	31,068	all ages	UBOS, MEASURE

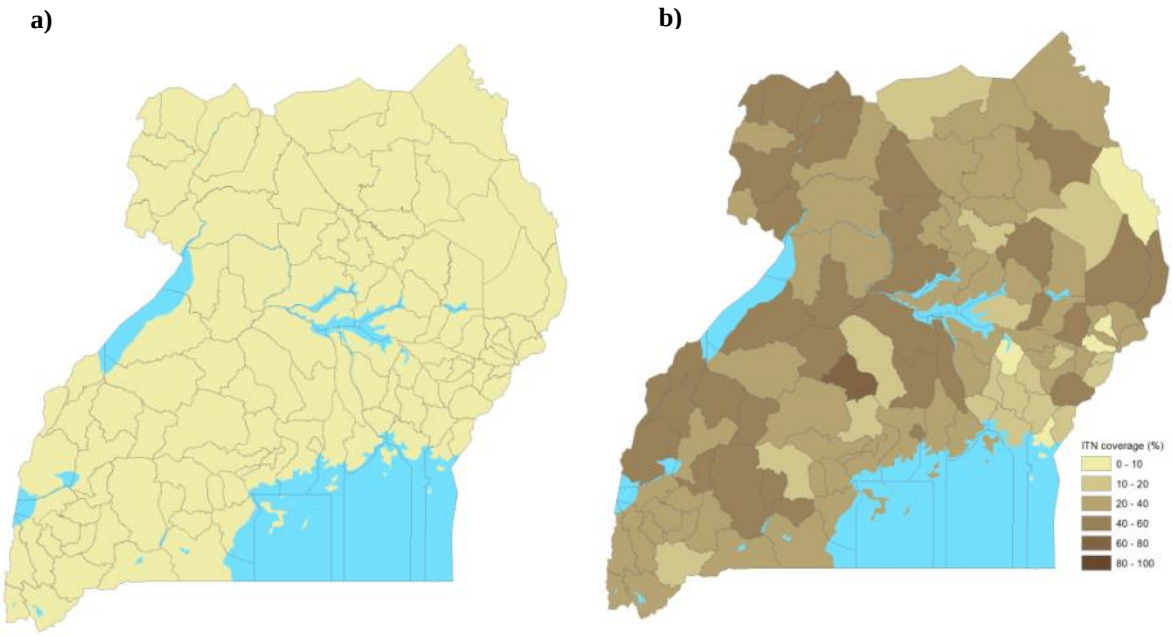
6.4 Modelling spatial aggregates of ITN coverage using Small Area Estimation

Typically, national household surveys are designed to be precise at national and regional levels and rarely at lower levels such as districts. Therefore, simply aggregating survey data to provide district level estimates of an outcome of interest will lead to values of low precision. District level estimates, however, are more important to planners in order to

accelerate policy interventions, optimise inputs and improve coverage of health interventions. Small Area Estimation (SAE) methods handle the problem of making reliable estimates of a variable at these areal units under conditions where the information available for the variable, on its own, is not sufficient to make valid estimates [Rao et al., 2003; BIAS, 2007]. We have used hierarchical Bayesian spatial and temporal SAE techniques [Banerjee et al., 2004; Best et al., 2005] to estimate the ITN coverage by district for the years 2000 and 2010; and a prediction of ITN coverage in all age groups, that now represents the important indicator for universal coverage and necessary when computing likely impacts on malaria transmission [Smith et al., 2009; Griffin et al. 2010].

To model ITN coverage a fully Bayesian geo-additive regression approach [Fahrmeir & Lang 2001; Kamman & Wand 2003] was applied. Details of model procedures and accuracy metrics are presented in Annex A3. The data-driven, modelled predictions of the proportions of all age groups sleeping under an ITN for the years 2000 and 2010 are shown in Figure 6.3. Sensitivity of district level predictions are shown in Annex Figure A.3.1 as standard deviations of predicted means.

Figure 6.3: The mean ITN coverage predictions in Uganda (using neighbouring information: MRF prior) for the years: a) 2000 b) 2010



In 2000, almost all districts had a predicted mean ITN coverage below 1 % among all age groups. Only three districts Kabale, Oyam and Katakwi had an ITN coverage among its population on more than 1% (Figure 6.3a). Katakwi had the highest ITN predicted coverage of 3.3% in 2000. By 2010 the modelled data from household surveys suggested a very different pattern of coverage (Figure 6.3b). 70 districts had predicted coverage estimates in excess of 30% of their population protected; 36 of these districts had over 40% of the population protected. Four districts, Kiruhura, Kiboga, Lyantonde and Masindi had over 50% of the population protected; Kiboga had the highest percentage of the population protected, 71%. Conversely, 21 districts still had overall predicted coverage below 20% with

four districts having less than 10% predicted ITN coverage (Kaliro, Namiyango, Kapchorwa and Moroto districts).

While the coverage data are based on reported use the night before the survey, there remains the issue of actual versus reported use. In the MIS of 2009, 17% of households had at least one net that was not slept under the previous night. Among households with a net that was not slept under the previous night, the most common reason cited for non-usage was that the net was not hung (58%), especially in North East region (99%) and 16% reported that the net was not used because it was too hot [UBOS & ICF, 2010].

6.5 Indoor Residual House-spraying coverage

IRS was re-introduced in a large scale in 2006 following its adoption as a major malaria control intervention in the Uganda Malaria Control Strategic Plan 2005/06 – 2009/10 [MOH, 2005]. IRS was first mounted in Kabale and Kanungu districts in 2006 using lambda-cyhalothrin (ICON^{TM} (10%) WP) [Section 3.7.3.2; RTI, 2006]. During February and March 2007, approximately 45,000 households in Kanungu District, covering a population of 190,000 people were sprayed with lambda-cyhalothrin (ICON 10% WP). IRS was targeted to cover *circa* 70% households that were situated in areas below an altitude of 1,200 and thus resulted in an estimated coverage of 90% of targeted households. Pre- and post slide positivity rates were collected at Kihihi Health Centre, slide positive rates declined immediately following IRS but soon rose after a year [Bukirwa et al., 2009]. Based on RTIs successful implementation in Uganda, as well as in Angola and Tanzania, RTI secured a contract to spearhead all of the PMI's IRS programs, with a US$ 150 million ceiling over the period 2007-2012. The focus of IRS activities in Uganda shifted from the epidemic prone districts to the high transmission districts in northern Uganda - initially in the areas of Apac, Pader, Gulu and Kitgum: subsequently divided into the current 10 PMI, IRS supported districts - Lamwo, Kitgum, Pader, Agogo, Kole, Oyam, Apac, Gulu, Amuru and Nwoya

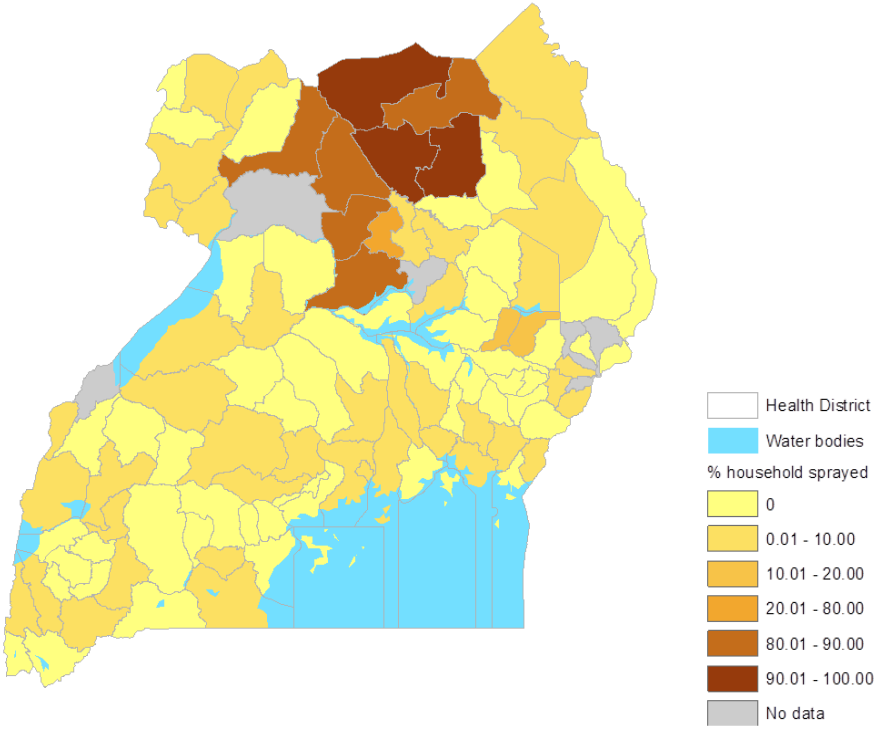
Lambda-cyhalothrin (ICON 10% WP) was also used in Katakwi and Kumi as part of integrated control with MSAT during 2008 and 2009 [Section 3.7.3.3; Pilgrim Africa, 2012]. In 2008, DDT was introduced in Apac and Oyam districts [RTI, 2008c] (Section 3.7.3.2). However, in 2009 DDT was substituted with alpha-cypermethrin for the first round spray and later Bendicarb (Carbamate) in the consequent rounds following an entomological surveillance that showed increased DDT resistance [Abt, 2010; Chapter 5]. From 2010-11 only Bendicarb insecticide has been used in the spray operations. Two spray rounds were carried out per year [Abt, 2010].

Detailed inventories and coverage data were maintained by the operational teams and these have been used here to estimate the household coverage in 10 districts for the year 2010/11 (Lamwo, Kitgum, Pader, Agogo, Kole, Oyam, Apac, Gulu, Amuru and Nwoya) [Abt, 2011]. 2010-11 as a prediction year was selected as representing a period of sustained operations, but importantly was coincidental with other household survey data available from the national household surveys undertaken as part of the UDHS indicator survey in 2011 [UBOS & ICF, 2012].

We have selected as the indicator the proportion of households reporting or documented as sprayed (at least once) in the last 12 months. Data from household surveys only using DHS

data, without SME methods described above for ITN coverage interpolation, is shown in Figure 6.4 for the period June - November 2011. Coverage ranged from reported spraying in last 12 months from 72% in Kole to 95% in Lamwo districts among the ten target districts in the North. However, in 2011 reported household IRS was only 8% in Katakwi and 18% in Kumi districts where the NGO Pilgrim had supported IRS with MSAT (Section 3.7.3.3). The two south western districts of Kabale and Kanungu, where IRS operations were started several years previously, reported less than 3% IRS coverage in 2011.

Figure 6.4: a) Proportion of households sprayed in last 12 months using only national household survey data (2011)



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Chapter 7

Summary, recommendations and action points

7.1. Background

In 1996, Uganda developed the first malaria strategic plan (MSP), post the malaria pre-eradication era and subsequently developed three further MSPs which were in line with broad WHO recommendations to scale up ITN and effective treatment coverage universally. As with so many other countries in the region Uganda struggled with implementation of interventions, despite policy recommendations, during the early phase of Roll Back Malaria due to inadequate funding. By 2007, substantial overseas development assistance was made available to Uganda to ensure universal coverage of proper treatment in public facilities, ITN use and selected districts protected by IRS (Section 3.7). There has never been an attempt, however, to use a cartography of malaria risk to target resources nor an attempt to measure the impact of scaled intervention. This lack of epidemiological intelligence in Uganda was signaled as a significant programming gap in the 1920s and again more recently in the malaria programme review in 2011.

7.2 Mapping malaria risk in Uganda

We have assembled the largest ever repository of community based malaria infection studies in Uganda covering surveys undertaken from 1980 to 2012 (Section 4.2). These geo-coded data have been combined with traditional determinants of malaria transmission (temperature, rainfall, surface water and urbanization) within a Bayesian time-space model to predict malaria transmission intensity at un-sampled locations in 2000 and 2010 (Section 4.3). The model had a high predicted accuracy (R^2 = 0.87; Section 4.5). Population-adjusted estimates of risk for each of Uganda's 112 districts have been generated to allow for a sub-national district level analysis (Annex A2).

Less than 4% of Uganda's population lives in areas that are essentially free of malaria. Overall the changes in malaria transmission were very modest between 2000 and 2010. The mean *Plasmodium falciparum* parasite rate in the age group 2-10 years old ($Pf\mathrm{PR}_{2\text{-}10}$) dropped from 72% (2000) to 66% (2010). In 2000, 84.6% of the Ugandan population lived in areas predicted to support hyper-holoendemic transmission (mean $Pf\mathrm{PR}_{2\text{-}10} \geq 50\%$), by 2010 this had only reduced to 72.3%; making Uganda one of the highest transmission countries in Africa, and supported by entomological data over the last 15 years (Section 5.5). However, some districts (25) did show evidence of declining transmission intensity by more than 20% by 2010. The greatest reductions (≥ 50%) were recorded in Mitooma, Nsiika, Ntungamo, Rukungiri and Kampala districts. Conversely, ten districts showed a greater than 10% increase in transmission during the same period (Section 4.4).

7.3 Intervention coverage

We have not directly analyzed the reasons for district level declines, rises or stability over the last decade. The reasons are likely to be complex and multifaceted. However, using small area estimation techniques and 2011 household survey data (Section 6.3) we were able to show that most districts after 2010 had only 30% of their total populations protected by an ITN, many had lower coverage, and only four districts had ITN coverage in excess of 50% (Kiruhura, Kiboga, Lyantonde and Masindi). Uganda had not invested in mass free net distribution campaigns until 2010. Previously there had been an emphasis on public-private

sector initiatives that failed to reach the majority of the population. Despite attempts at catching-up with coverage, the 2010 campaigns fell short of what would be required to impact on transmission and has not translated into changing disease incidence across much of Uganda (Section 4.6). Post-2010 campaigns have been plagued by disagreements on distribution costs and partners. The failure to distribute over 15 million LLINs by September 2013 should be a major concern at all levels. If targeting is required the maps provided in Chapter 6 highlight the most vulnerable.

One limitation to modelling LLIN coverage, has been the inadequacy of detailed distribution data (Section 6.2). All future distributions must be accompanied by accurate, detailed distribution records at parish levels, this is a relatively simple and essential accountability task, but additionally assists in modelling coverage from household observation studies [***Action Point 7.1***].

Success with IRS was first documented in Uganda during the 1960s. While never achieving an interruption of transmission, carefully recorded data on prevalence dropped substantially (Section 3.1.1). IRS was resurrected again in 2006/7 as a vector control strategy through funding from PMI in Kabale and Kanugu districts using the pyrethroid lambda-cyhalothrin (Section 3.7.3.2). This was expanded to more northern districts from 2008 using either lambda-cyhalothrin, alpha-cypermethrin and switched with DDT. By 2009, resistance to both classes of insecticides had emerged (Section 5.6) and the carbamate, bendocarb is now used.

Detailed entomological and environmental assessments were undertaken by partners delivering IRS, but striking by its absence was a detailed epidemiological impact analysis. There remains inadequate data to enumerate the impact of IRS, or combined IRS with mass-drug administration, in districts where these interventions have been applied. This is in stark contrast to the first IRS and drug trials in Uganda and does not allow the NMCP to decide on the future of IRS and/or ITN in high transmission districts of Uganda. We would strongly recommend that infant/school children parasitological and serological surveys be conducted in these areas to provide some additional data to modeled predictions from sparse data provided in this report [***Action Point 7.2***].

7.4 Sustaining a nationwide parasite, vector and resistance surveillance

During the pre-independence malaria control period, reconnaissance and detailed research formed the basis of decision making (Section 3.3). The need to assess the malaria situation and investigate the epidemiological conditions prevailing nationwide was a core strength of the malaria programme. Malariometric surveys were undertaken to provide a profile of risk, epidemiology and seasonality in preparation for the design of national elimination and was one of the most significant nation-wide examinations of the epidemiology of malaria risk in Africa at the time.

Despite recent, contemporary attempts at a malaria indicator survey in 2009, the national surveys during the 1960s were more sophisticated, elaborate and large-scale epidemiological investigations of age, parasite species and parasite density. Surveys were undertaken across Uganda, covering examinations of over 120,000 people between 1965 and 1967 accompanied by more detailed epidemiological and entomological investigations

in areas where interventions were piloted. This contrasts the low sensitivity of sampling a few young children per village during current national malaria indicator surveys and the lack of detailed epidemiological data accompanying the roll-out of IRS and MSAT (Section 3.7.3.3) in Uganda since 2006.

A continued emphasis on assembling malariometric data from the community should provide a cornerstone of any planning metrics. We have demonstrated the value of parasite prevalence to define risk across the country, there is no equivalent, unambiguous data to provide this cartography. This should extend to data on vectors (Chapter 5). We have identified available vector species data to provide a contemporary repository but this must remain constantly updated and reviewed to identify what we don't know and where across Uganda.

Rapid sampling of infection prevalence and vector species abundance and ecology must become a priority. Current designs of malaria indicator surveys or demographic and health surveys provide valuable information on intervention coverage but are inadequately designed to provide reliable spatial data on infection. Uganda has invested in sentinel sites but these are few and have yet to provide any nationally representative information on parasite prevalence or vector distributions.

School surveys for rapid, powerful infection prevalence surveillance have been undertaken in neighboring Kenya. Similar protocols have been used in several sites in Uganda. These should be resurrected to be a more systematic approach to tracking the future epidemiological transition in Uganda and could be combined, as is being proposed in Tanzania, with satellite community vector sampling [***Action Point 7.3***].

Surveillance extends to more intensive sampling of resistance alleles in vectors, changing binomics and vector composition, and rich parasite sampling for the detection of artemisinin resistance. Both vector control and treatment will continue to be the mainstay of future malaria policy in Uganda and thus maintaining an intelligence of potential behavioural and resistance threats is essential. Such sampling is, however, more complex and best undertaken at carefully selected sentinel sites using the transmission and vector cartography developed in this report [***Action Point 7.4***].

7.5 Using current evidence to target control

Clearly Uganda has a long way to go to achieve levels of intervention coverage likely to impact on transmission in most of the country. Areas where IRS and ITNS have been used intensively show some evidence of gradual reduction in infection prevalence but these data are weak. The cartography of risk, coverage and population can however be used to better target limited resources and meet the unmet needs of intervention poor districts [***Action Point 7.5***].

There are also two areas of the change 2000-2010 maps that merit additional comment for future targeted control.

Urban malaria control: Over the last 100 years, interest in urban malaria control has waxed and waned. Colonial interests were focused on protecting Europeans (Section 3.2). Today these early urban settlements have grown to account for over 12% of the national population and projected to reach 20% of the country's population by 2020. Urban malaria control provides several challenges, but it is notable that the few areas which have been identified as transitional epidemiological sites are located in Kampala (Section 4.4) and coincidentally the only sites where disease incidence shows some evidence of decline (Section 4.6). Targeted urban malaria control might be one approach that merits further attention in Uganda where experimental efforts at environmental management have already proven successful (Section 3.6.4.1). For this to be successful, requires higher resolution mapping exercises and more detailed epidemiological profiling within major town and city limits. An agenda to begin exploring approaches to urban malaria mapping and control should be considered [***Action Point 7.6***].

Epidemic prone South East regions: Other areas of transition have been districts located in the South Eastern borders with Rwanda. These districts have historically represented areas of malaria epidemic potential and have recently been the target for early IRS. The IRS campaigns have not continued in these areas. Should there be further rainfall anomalies, as witnessed during the later 1990s (Section 3.5.2), these areas may be highly exposed to rebound, epidemic conditions. Careful monitoring of intervention coverage and secular clinical burdens is particularly important in these districts [***Action Point 7.7***].

7.6 Re-visiting the malaria burden estimates for Uganda

The precise burden of the disease and its distribution country-wide has remained uncertain since the 1920s (Section 3.1) only marginally, and controversially, improved through modeling efforts during the 1990s (Section 3.5.2). Here we provide several data platforms that might be used to triangulate with HIMS to better define the malaria burden in Uganda. Disease outcomes are critically dependent on transmission intensity, the diversity in parasite exposure that does exist within Uganda's borders must therefore be used to model burden. More recently, updating the national malaria burden has fallen to external agencies and research groups. There is now a research opportunity to improve estimates of malaria morbidity and mortality using combinations of population, malaria risk, disaggregated census estimates of child mortality, triangulated against HMIS data, sentinel site hospital admission data and community surveillance data. We therefore recommend this be developed and led by the national research community. Creating the business case to sustain overseas and domestic investment in malaria control demand credible, plausible national data [***Action Point 7.8***].

The spatial distribution of human settlement is also critical to understanding attributable risk, notably from over-distributed vector-borne diseases, but also in terms of understanding accessibility to services. We have not had access to the most recent national census data at the highest possible resolution (enumeration area). Access to this information would massively improve the precision of human settlement mapping in Uganda [***Action Point 7.9***].

In an ideal world, a fully operational and complete HMIS would provide reliable estimates of disease risk per district in Uganda. Most cases, however, are not treated in the formal health sector and those that are do not always receive parasitological confirmation. The latter, in theory, will change with the expansion of RDT testing nationwide. The basic principles of model based geo-statistics can provide some solutions to handling imperfect and incomplete data. This does however demand that events are recorded spatially. To this end we have invested, as part of this report, in updating the spatial platform of health facilities in Uganda (Section 2.10). This new platform should be integrated with malaria surveillance and reporting, slide positivity, health service accessibility models and peripheral data to increase the spatial value of routine HMIS, possibly to become, with time, a real-time epidemiological tool [***Action Point 7.10***].

7.7 Conclusion and perspectives for the future

It is now over twelve years since the 2000 Abuja commitment to fight malaria and just a few years away from the landmark year, 2015, when Uganda should assess it progress towards the achievement of the Millennium Development Goals (MDGs). Despite substantial financial investment for malaria control over the last decade (close to US$ 600 million from the Global Fund and PMI alone) and clear policies and strategic plans, malaria remains highly endemic across most of the country.

This report "*An epidemiological profile of malaria and its control in Uganda*" is the first attempt to build an evidence platform to understand the context of control nationwide. Understanding change, enumerating current risks and predicting the future of the malaria burden in Uganda requires a detailed assembly and examination of national data. This report should serve as the basis by which the malaria programme in Uganda establishes a culture of national data ownership and use, to set the framework for future evidence-based evaluations and planning.

As the resource landscape for malaria changes, there will be a need for the malaria control programme in Uganda to improve its evidence-based programming to maximize investments and accelerate the scale up of universal coverage of interventions. We have developed a series of important data repositories, models to handle sparse data and maps of where people live, covered by interventions and the patterns of malaria risk over the last decade. This process of data assembly and analysis is by definition dynamic and there is a need to document the changing landscape of risks, climate, population and intervention coverage over the next decade.

The Ugandan NMCP will have to invest in data management capabilities to serve as the custodians of this national data repository. The report provides the description of these data, the metadata that should accompany these databases. Maintaining a national malaria data repository will require funding and technical skills [***Action Point 7.11***].Funding alone will not be enough. Over the next 5-10 years, accountability, impact analysis, financial business cases supported by a culture of data use will have to become the new paradigm by which malaria programmes, governments and their development partners operate.

Annexes

Annex A.1: Parasite prevalence model development

A.1.1 *Pf*PR$_{2\text{-}10}$ Model specification

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

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

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

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

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

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

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

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

Where K_V is the modified Bessel function of the second kind, $\|\cdot\|$ denotes the Euclidean distance and order $\nu > 0$. $k > 0$ is a scaling parameter and σ^2 is the marginal variance. For the stationary model, k and ν 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

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

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

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

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

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

This model is characterised by a GF ***y(s, t)*** built from covariate information ***z(s, t)***, measurement error ***ε(s, t)***, and a second order autoregressive dynamic model for the latent process ***ξ(s, t)*** with spatially correlated innovations ***ω(s, t)***. The *Pf*PR$_{2\text{-}10}$ survey data were modelled as realizations of this spatial process (random field) changing in time. These realizations were used to make inference about the process and predict it at desired

locations and at a specified time. This is where $y(s_i,t)$ was the realization of a spatial-temporal process representing the *Pf*PR$_{2\text{-}10}$ at the community location s_i, where $i=1...n$, and year t_j where $j=1...m$, $z(s_i,t_j)=(z_1(s_i,t_j)\dots z_p(s_t,t_j))$ represents fixed effect from the covariates for cluster s_i at time t_j, $\beta=(\beta_1\dots,\beta_p)'$ 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.1.2 Constructing a suitable MESH

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

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

and in the outer extension. The inner maximum edge value was made small enough to allow the triangulation to support representing functions with small enough features, and typically smaller than the spatial correlation range of the model. Therefore this value was adjusted to fit the range of the area domain in the model.

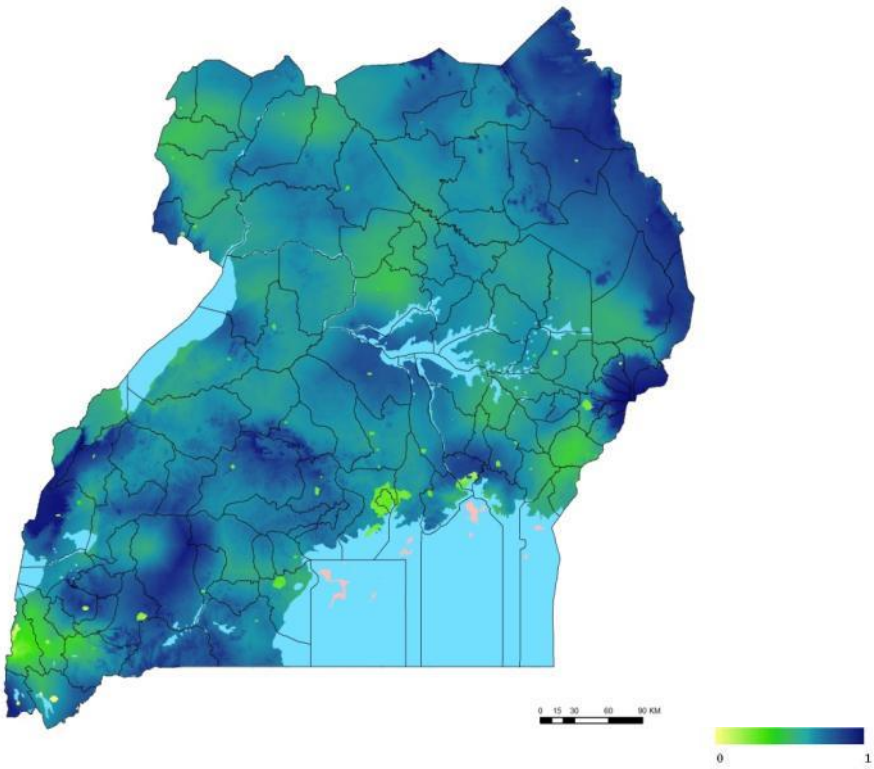
A matrix was then constructed to link the $PfPR_{2\text{-}10}$ input locations to the triangles on the mesh defined by ŋ* as $\eta^* = A(x + 1\beta_0)$ and in the inla code in the following *inla.spde.make. A* function. This makes each row in the matrix to have three non-zero elements since every data point is inside a triangle and the corresponding columns are expected to have non-zero elements. In order to obtain a square matrix for the model, the response was linked to the index of the random field, where the length of the index vector was the same as the length of the projection matrix. In order to estimate the intercept, the stack function introduces a vector of ones in the matrix and this is removed in the formula by putting [-1] [Lindgren 2013].

A.1.3 Prediction accuracy

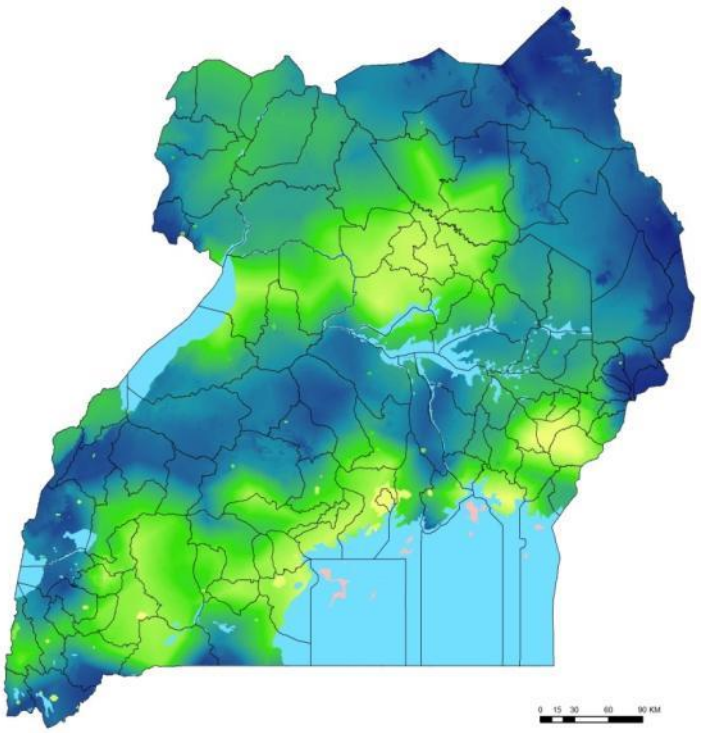
The standard deviation is a measure of the variability or dispersion of an expected value of a variable from its mean. High/low standard deviations indicate that data points are far/close to the mean. In scientific measurements it can be used as a measure of uncertainty. Of particular importance is the distance of the standard deviation (SD) from the mean. This is because the absolute value of the standard deviation could be both because of uncertainty but also a function of generally high base (mean) values of the measure under consideration. In this study, the distance (number) of the standard deviations of the mean $Pf\text{PR}_{2\text{-}10}$ were computed for the years 2000 and 2010. Both predictions were highly accurate with no where greater than one SD. For purposes of display we have shown gradations of less than 1 SD in Figure A.1.1.

Figure A.1.1: Standard deviation maps from posterior distributions of predicted mean *Pf*PR $_{2\text{-}10}$ for a) 2000; and b) 2010: darker blue the less precise the predictions; however all predictions highly accurate.

a)



b)



A.1.4 References

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Annex A2. a: Population (%) in 2000 exposed to various classes of malaria and population-adjusted *Pf*PR_{2-10} for the year 2000 by 112 health districts

Region/District	Total Pop 2000	Malaria Free	Unstable Transmis-sion	*Pf*PR_{2-10} <1%	*Pf*PR_{2-10} 1-4.9%	*Pf*PR_{2-10} 5-10%	*Pf*PR_{2-10} >10-50%	*Pf*PR_{2-10} >50- 74.9%	*Pf*PR_{2-10} 75%+	Population-weighted mean *Pf*PR_{2-10}
Acholi										
Agago	260,419	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	257,517 (98.9%)	83.31
Amuru	95,434	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	95,391 (100%)	85.11
Gulu	219,471	0 (0%)	0 (0%)	0 (0%)	28,599 (13%)	0 (0%)	0 (0%)	0 (0%)	190,872 (87%)	73.08
Kitgum	215,102	0 (0%)	0 (0%)	0 (0%)	9,289 (4.3%)	0 (0%)	338 (0.2%)	3,121 (1.5%)	202,345 (94.1%)	78.61
Lamwo	153,187	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	87 (0.1%)	2,927 (1.9%)	150,141 (98%)	81.20
Nwoya	30,058	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30,058 (100%)	84.60
Pader	201,271	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	201,271 (100%)	85.15
Ankole										
Bushenyi	225,499	294 (0.1%)	0 (0%)	0 (0%)	7,674 (3.4%)	0 (0%)	1,071 (0.5%)	190,382 (84.4%)	26,078 (11.6%)	63.88
Ibanda	70,407	1,678 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2,665 (3.8%)	59,298 (84.2%)	6,766 (9.6%)	63.87
Isingiro	114,213	43 (0%)	0 (0%)	0 (0%)	284 (0.2%)	0 (0%)	0 (0%)	102,264 (89.5%)	11,618 (10.2%)	69.99
Katerere	107,502	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	53,302 (49.6%)	54,201 (50.4%)	75.32
Kibingo	197,059	5,292 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	85,109 (43.2%)	106,659 (54.1%)	74.21
Kiruhura	74,741	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	71,064 (95.1%)	3,677 (4.9%)	66.80
Mbarara	135,332	1,569 (1.2%)	0 (0%)	0 (0%)	25,361 (18.7%)	0 (0%)	425 (0.3%)	77,239 (57.1%)	30,737 (22.7%)	56.13
Mitooma	176,197	364 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19,176 (10.9%)	125,465 (71.2%)	31,192 (17.7%)	63.99
Nsiika	91,479	18,713 (20.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23,434 (25.6%)	49,263 (53.9%)	69 (0.1%)	43.93
Ntungamo	428,143	25,942 (6.1%)	0 (0%)	0 (0%)	289 (0.1%)	0 (0%)	226 (0.1%)	72,352 (16.9%)	329,335 (76.9%)	75.88

Region/District	Total Pop 2000	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Buganda										
Buikwe	367,990	0 (0%)	0 (0%)	0 (0%)	67,125 (18.2%)	0 (0%)	0 (0%)	23,877 (6.5%)	276,988 (75.3%)	68.41
Bukomansimbi	135,054	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	135,054 (100%)	83.60
Butambala	87,918	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2,662 (3%)	85,256 (97%)	78.37
Buvuma	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Gomba	138,177	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,515 (1.1%)	136,662 (98.9%)	78.68
Kalangala	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Kalungu	155,312	0 (0%)	0 (0%)	0 (0%)	3,721 (2.4%)	0 (0%)	0 (0%)	0 (0%)	151,591 (97.6%)	81.13
Kampala	1,124,710	0 (0%)	0 (0%)	0 (0%)	1,124,570 (100%)	0 (0%)	0 (0%)	0 (0%)	140 (0%)	3.28
Kayunga	316,688	0 (0%)	0 (0%)	0 (0%)	9,257 (2.9%)	0 (0%)	0 (0%)	65,281 (20.6%)	242,151 (76.5%)	77.13
Kiboga	143,849	0 (0%)	0 (0%)	0 (0%)	194 (0.1%)	0 (0%)	0 (0%)	19,540 (13.6%)	124,114 (86.3%)	79.94
Kyankwanzi	160,971	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,417 (0.9%)	159,554 (99.1%)	81.33
Luwero	271,864	0 (0%)	0 (0%)	0 (0%)	29,613 (10.9%)	0 (0%)	0 (0%)	0 (0%)	242,251 (89.1%)	73.65
Lwengo	201,375	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19,896 (9.9%)	181,480 (90.1%)	80.16
Lyantonde	60,984	0 (0%)	0 (0%)	0 (0%)	4,362 (7.2%)	0 (0%)	0 (0%)	9,646 (15.8%)	46,975 (77%)	73.25
Masaka	252,233	0 (0%)	0 (0%)	0 (0%)	77,906 (30.9%)	0 (0%)	0 (0%)	0 (0%)	174,327 (69.1%)	59.21
Mityana	204,906	0 (0%)	0 (0%)	0 (0%)	23,449 (11.4%)	0 (0%)	0 (0%)	4,192 (2%)	177,266 (86.5%)	70.69
Mpigi	194,122	0 (0%)	0 (0%)	0 (0%)	1,935 (1%)	0 (0%)	0 (0%)	2,803 (1.4%)	189,384 (97.6%)	79.21
Mubende	322,914	0 (0%)	0 (0%)	0 (0%)	3,059 (0.9%)	0 (0%)	0 (0%)	14,130 (4.4%)	305,725 (94.7%)	78.75
Mukono	459,108	0 (0%)	0 (0%)	0 (0%)	89,933 (19.6%)	0 (0%)	0 (0%)	0 (0%)	369,176 (80.4%)	66.66
Nakaseke	109,458	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	109,458 (100%)	83.88
Nakasongola	138,816	0 (0%)	0 (0%)	0 (0%)	3,222 (2.3%)	0 (0%)	0 (0%)	65,153 (46.9%)	70,441 (50.7%)	74.67
Rakai	367,403	0 (0%)	0 (0%)	0 (0%)	1,207 (0.3%)	0 (0%)	0 (0%)	60,522 (16.5%)	305,673 (83.2%)	78.37
Ssembabule	196,674	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17,864 (9.1%)	178,810 (90.9%)	83.55
Wakiso	1,023,540	0 (0%)	0 (0%)	0 (0%)	626,397 (61.2%)	0 (0%)	0 (0%)	473 (0%)	396,668 (38.8%)	33.80

Region/District	Total Pop 2000	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Bukedi										
Budaka	124,962	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	124,962 (100%)	81.49
Busia	258,154	0 (0%)	0 (0%)	0 (0%)	25,954 (10.1%)	0 (0%)	0 (0%)	0 (0%)	229,402 (88.9%)	78.49
Butaleja	124,293	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	124,293 (100%)	85.58
Kibuku	117,311	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	117,311 (100%)	82.15
Pallisa	235,656	0 (0%)	0 (0%)	0 (0%)	4,056 (1.7%)	0 (0%)	0 (0%)	0 (0%)	231,601 (98.3%)	81.37
Tororo	298,387	0 (0%)	0 (0%)	0 (0%)	123 (0%)	22,097 (7.4%)	0 (0%)	0 (0%)	276,120 (92.5%)	84.59
Bunyoro										
Buliisa	128,122	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25,635 (20%)	102,487 (80%)	80.76
Hoima	470,894	0 (0%)	0 (0%)	0 (0%)	18,485 (3.9%)	0 (0%)	0 (0%)	32,878 (7%)	419,531 (89.1%)	79.60
Kibaale	590,450	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19,010 (3.2%)	571,440 (96.8%)	81.75
Kiryandongo	235,258	0 (0%)	0 (0%)	0 (0%)	122 (0.1%)	0 (0%)	0 (0%)	0 (0%)	235,137 (99.9%)	85.25
Masindi	211,890	0 (0%)	0 (0%)	0 (0%)	16,149 (7.6%)	0 (0%)	0 (0%)	199 (0.1%)	195,542 (92.3%)	76.67
Busoga										
Bugiri	402,715	0 (0%)	0 (0%)	0 (0%)	8,860 (2.2%)	0 (0%)	0 (0%)	86 (0%)	393,769 (97.8%)	82.33
Buyende	182,730	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27,104 (14.8%)	155,627 (85.2%)	81.68
Iganga	328,742	0 (0%)	0 (0%)	0 (0%)	51,610 (15.7%)	0 (0%)	0 (0%)	9,729 (3%)	267,403 (81.3%)	68.19
Jinja	410,560	0 (0%)	0 (0%)	0 (0%)	147,294 (35.9%)	0 (0%)	0 (0%)	252,779 (61.6%)	10,487 (2.6%)	45.47
Kaliro	147,271	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	147,271 (100%)	86.92
Kamuli	345,730	0 (0%)	0 (0%)	0 (0%)	3,696 (1.1%)	0 (0%)	0 (0%)	13,328 (3.9%)	328,706 (95.1%)	80.43
Luuka	171,376	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	22,650 (13.2%)	148,726 (86.8%)	80.89
Mayuge	393,955	0 (0%)	0 (0%)	0 (0%)	2,061 (0.5%)	0 (0%)	0 (0%)	117,946 (29.9%)	273,948 (69.5%)	79.66
Namiyango	129,846	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	129,846 (100%)	87.02
Namutumba	156,347	0 (0%)	0 (0%)	0 (0%)	286 (0.2%)	0 (0%)	0 (0%)	0 (0%)	156,060 (99.8%)	83.12

Region/District	Total Pop 2000	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Elgon										
Bududa	64,088	567 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	45,235 (70.6%)	18,287 (28.5%)	69.86
Bukwo	43,427	9,981 (23%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	580 (1.3%)	32,688 (75.3%)	160 (0.4%)	41.45
Bulambuli	112,123	11,808 (10.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	58,310 (52%)	42,005 (37.5%)	63.59
Kapchorwa	72,152	2,320 (3.2%)	0 (0%)	8,674 (12%)	0 (0%)	0 (0%)	0 (0%)	54,776 (75.9%)	6,382 (8.8%)	55.03
Kween	71,332	27,552 (38.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	38,158 (53.5%)	5,622 (7.9%)	37.04
Manafwa	140,558	503 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	34,444 (24.5%)	105,599 (75.1%)	79.10
Mbale	175,743	964 (0.5%)	0 (0%)	0 (0%)	54,206 (30.8%)	0 (0%)	0 (0%)	29,226 (16.6%)	91,348 (52%)	55.21
Sironko	213,015	3,606 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	99,915 (46.9%)	109,494 (51.4%)	72.57
Karamoja										
Abim	18,176	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,963 (10.8%)	16,213 (89.2%)	79.13
Amudat	95,202	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	65,774 (69.1%)	28,753 (30.2%)	69.73
Kaabong	130,766	298 (0.2%)	0 (0%)	0 (0%)	827 (0.6%)	0 (0%)	12,977 (9.9%)	109,245 (83.5%)	7,090 (5.4%)	61.23
Kotido	50,718	0 (0%)	0 (0%)	0 (0%)	696 (1.4%)	0 (0%)	5 (0%)	41,925 (82.7%)	8,092 (16%)	72.01
Moroto	121,196	1,853 (1.5%)	0 (0%)	0 (0%)	4,564 (3.8%)	0 (0%)	6,219 (5.1%)	102,100 (84.2%)	5,880 (4.9%)	61.58
Nakapiripirit	140,749	2,200 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,947 (1.4%)	57,619 (40.9%)	78,983 (56.1%)	73.40
Napak	166,545	257 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	809 (0.5%)	109,478 (65.7%)	56,000 (33.6%)	73.95
Kigezi										
Kabale	442,390	425,996 (96.3%)	0 (0%)	377 (0.1%)	0 (0%)	0 (0%)	6,830 (1.5%)	9,126 (2.1%)	0 (0%)	1.89
Kanungu	224,709	28,800 (12.8%)	0 (0%)	0 (0%)	10,295 (4.6%)	0 (0%)	0 (0%)	40,768 (18.1%)	144,792 (64.4%)	66.26
Kisoro	225,207	214,394 (95.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10,111 (4.5%)	702 (0.3%)	2.90
Rukungiri	284,810	44,842 (15.7%)	0 (0%)	0 (0%)	7,477 (2.6%)	0 (0%)	5,544 (1.9%)	94,581 (33.2%)	132,366 (46.5%)	61.73
Lango										
Alebtong	143,570	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	143,570 (100%)	85.63
Amolatar	75,550	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8,491 (11.2%)	67,059 (88.8%)	80.10
Apac	183,214	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3,244 (1.8%)	0 (0%)	27 (0%)	179,942 (98.2%)	86.66
Dokolo	118,133	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	118,133 (100%)	86.24
Kole	133,690	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	133,690 (100%)	89.11
Lira	243,460	0 (0%)	0 (0%)	0 (0%)	14,165 (5.8%)	0 (0%)	0 (0%)	0 (0%)	229,295 (94.2%)	83.12
Otuke	46,955	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	123 (0.3%)	46,832 (99.7%)	84.48
Oyam	194,545	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	194,545 (100%)	87.46

Region/District	Total Pop 2000	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Teso										
Amuria	92,967	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	92,967 (100%)	85.85
Bukedea	113,180	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	113,180 (100%)	81.14
Kaberamaido	174,459	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	174,459 (100%)	86.33
Katakwi	62,642	0 (0%)	0 (0%)	0 (0%)	1,048 (1.7%)	0 (0%)	0 (0%)	105 (0.2%)	61,488 (98.2%)	83.59
Kumi	152,141	0 (0%)	0 (0%)	0 (0%)	7,544 (5%)	0 (0%)	0 (0%)	0 (0%)	144,596 (95%)	77.81
Ngora	93,731	0 (0%)	0 (0%)	0 (0%)	3,319 (3.5%)	0 (0%)	0 (0%)	0 (0%)	90,412 (96.5%)	81.20
Serere	250,152	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	250,152 (100%)	86.65
Soroti	279,131	0 (0%)	0 (0%)	0 (0%)	14,057 (5%)	0 (0%)	0 (0%)	0 (0%)	265,074 (95%)	82.85
Toro										
Bundibugyo	222,701	21,533 (9.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17,938 (8.1%)	183,230 (82.3%)	76.57
Kabarole	370,965	25,377 (6.8%)	0 (0%)	0 (0%)	9,125 (2.5%)	0 (0%)	0 (0%)	201,630 (54.4%)	134,832 (36.3%)	66.23
Kamwenge	295,098	974 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,512 (0.5%)	73,309 (24.8%)	219,303 (74.3%)	76.37
Kasese	649,870	37,170 (5.7%)	0 (0%)	472 (0.1%)	23,846 (3.7%)	0 (0%)	19,558 (3%)	216,559 (33.3%)	352,266 (54.2%)	67.34
Kyegegwa	140,208	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3,638 (2.6%)	136,570 (97.4%)	79.00
Kyenjojo	336,068	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	47,929 (14.3%)	288,139 (85.7%)	79.77
Ntoroko	76,198	1,581 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6,516 (8.6%)	68,081 (89.3%)	83.72
West Nile										
Adjumani	318,833	0 (0%)	0 (0%)	0 (0%)	4,539 (1.4%)	0 (0%)	0 (0%)	2,902 (0.9%)	314,295 (98.6%)	83.81
Arua	229,543	0 (0%)	0 (0%)	0 (0%)	20,426 (8.9%)	0 (0%)	0 (0%)	4,756 (2.1%)	204,361 (89%)	78.88
Koboko	75,637	0 (0%)	0 (0%)	0 (0%)	11,247 (14.9%)	0 (0%)	0 (0%)	0 (0%)	64,380 (85.1%)	74.35
Maracha	178,510	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	178,510 (100%)	88.75
Moyo	348,985	0 (0%)	0 (0%)	0 (0%)	5,756 (1.6%)	0 (0%)	0 (0%)	0 (0%)	343,170 (98.3%)	82.13
Nebbi	297,796	0 (0%)	0 (0%)	0 (0%)	10,956 (3.7%)	0 (0%)	0 (0%)	31,555 (10.6%)	255,286 (85.7%)	80.31
Yumbe	459,899	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	459,859 (100%)	86.87
Zombo	194,526	0 (0%)	0 (0%)	0 (0%)	21,465 (11%)	0 (0%)	0 (0%)	149,181 (76.7%)	23,880 (12.3%)	61.47

Annex A2. b: Population (%) in 2010 exposed to various classes of malaria and population-adjusted *Pf*PR_{2-10} for the year 2010 by 112 health districts

Region/District	Total Pop 2010	Malaria Free	Unstable Transmis-sion	*Pf*PR_{2-10} <1%	*Pf*PR_{2-10} 1-4.9%	*Pf*PR_{2-10} 5-10%	*Pf*PR_{2-10} >10-50%	*Pf*PR_{2-10} >50- 74.9%	*Pf*PR_{2-10} 75%+	Population-weighted mean *Pf*PR_{2-10}
Acholi										
Agago	348,786	0 (0%)	0 (0%)	0 (0%)	0 (0%)	205,452 (58.9%)	4,343 (1.2%)	138,992 (39.9%)	0 (0%)	48.59
Amuru	128,276	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	127,759 (99.6%)	85.72
Gulu	304,184	0 (0%)	0 (0%)	0 (0%)	45,533 (15%)	0 (0%)	0 (0%)	17,776 (5.8%)	240,875 (79.2%)	74.94
Kitgum	288,109	0 (0%)	0 (0%)	0 (0%)	12,441 (4.3%)	36,543 (12.7%)	8,591 (3%)	223,827 (77.7%)	6,677 (2.3%)	57.59
Lamwo	205,221	9 (0%)	0 (0%)	0 (0%)	0 (0%)	281 (0.1%)	23 (0%)	165,126 (80.5%)	39,695 (19.3%)	68.62
Nwoya	40,258	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	40,258 (100%)	87.27
Pader	269,568	0 (0%)	0 (0%)	0 (0%)	0 (0%)	148,499 (55.1%)	849 (0.3%)	119,811 (44.4%)	409 (0.2%)	49.87
Ankole										
Bushenyi	303,914	394 (0.1%)	0 (0%)	0 (0%)	12,079 (4%)	148,819 (49%)	3,023 (1%)	133,827 (44%)	5,772 (1.9%)	48.33
Ibanda	94,298	2,248 (2.4%)	0 (0%)	0 (0%)	5,712 (6.1%)	46,067 (48.9%)	1,020 (1.1%)	37,939 (40.2%)	1,313 (1.4%)	42.86
Isingiro	152,975	58 (0%)	0 (0%)	380 (0.2%)	0 (0%)	131,293 (85.8%)	2,458 (1.6%)	18,781 (12.3%)	0 (0%)	41.32
Katerere	143,981	0 (0%)	0 (0%)	0 (0%)	0 (0%)	129,330 (89.8%)	1,578 (1.1%)	12,983 (9%)	89 (0.1%)	39.15
Kibingo	263,926	7,088 (2.7%)	0 (0%)	0 (0%)	0 (0%)	43,062 (16.3%)	541 (0.2%)	140,246 (53.1%)	72,990 (27.7%)	62.64
Kiruhura	100,103	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2,680 (2.7%)	106 (0.1%)	36,341 (36.3%)	60,975 (60.9%)	75.19
Mbarara	189,760	2,101 (1.1%)	0 (0%)	42,359 (22.3%)	0 (0%)	64,506 (34%)	695 (0.4%)	78,434 (41.3%)	1,665 (0.9%)	40.46
Mitooma	235,985	487 (0.2%)	0 (0%)	0 (0%)	0 (0%)	217,357 (92.1%)	586 (0.2%)	17,554 (7.4%)	0 (0%)	29.64
Nsiika	122,520	25,063 (20.5%)	0 (0%)	0 (0%)	32,319 (26.4%)	61,132 (49.9%)	567 (0.5%)	3,438 (2.8%)	0 (0%)	16.09
Ntungamo	573,423	34,744 (6.1%)	0 (0%)	387 (0.1%)	0 (0%)	428,793 (74.8%)	7,193 (1.3%)	102,306 (17.8%)	0 (0%)	37.12

Region/District	Total Pop 2010	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Buganda										
Buikwe	513,068	0 (0%)	0 (0%)	60,155 (11.7%)	48,039 (9.4%)	50,422 (9.8%)	1,533 (0.3%)	163,089 (31.8%)	189,830 (37%)	55.67
Bukomansimbi	180,881	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	162,501 (89.8%)	18,381 (10.2%)	64.95
Butambala	117,751	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	117,694 (100%)	57 (0%)	65.90
Buvuma	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Gomba	185,065	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	125,622 (67.9%)	59,443 (32.1%)	71.17
Kalangala	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	197,244 (0%)	0
Kalungu	209,206	0 (0%)	0 (0%)	0 (0%)	6,168 (2.9%)	0 (0%)	0 (0%)	160,996 (77%)	0 (0%)	68.19
Kampala	1,946,410	0 (0%)	0 (0%)	58,700 (3%)	1,887,520 (97%)	164 (0%)	0 (0%)	23 (0%)	0 (0%)	1.40
Kayunga	427,507	0 (0%)	0 (0%)	0 (0%)	14,875 (3.5%)	0 (0%)	0 (0%)	362,559 (84.8%)	50,073 (11.7%)	68.56
Kiboga	192,661	0 (0%)	0 (0%)	0 (0%)	260 (0.1%)	664 (0.3%)	159 (0.1%)	158,345 (82.2%)	33,232 (17.2%)	66.94
Kyankwanzi	215,593	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	194,642 (90.3%)	20,951 (9.7%)	67.02
Luwero	376,252	0 (0%)	0 (0%)	0 (0%)	50,464 (13.4%)	0 (0%)	0 (0%)	12,944 (3.4%)	312,843 (83.1%)	70.82
Lwengo	269,707	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	156,442 (58%)	113,265 (42%)	73.69
Lyantonde	83,398	0 (0%)	0 (0%)	0 (0%)	7,081 (8.5%)	0 (0%)	0 (0%)	13,447 (16.1%)	62,871 (75.4%)	76.25
Masaka	364,167	0 (0%)	0 (0%)	0 (0%)	129,665 (35.6%)	0 (0%)	0 (0%)	148,514 (40.8%)	85,988 (23.6%)	48.50
Mityana	282,870	0 (0%)	0 (0%)	0 (0%)	39,364 (13.9%)	5,106 (1.8%)	1,984 (0.7%)	219,549 (77.6%)	16,867 (6%)	54.00
Mpigi	260,790	0 (0%)	0 (0%)	0 (0%)	3,002 (1.2%)	0 (0%)	0 (0%)	193,480 (74.2%)	64,308 (24.7%)	69.96
Mubende	436,430	0 (0%)	0 (0%)	0 (0%)	4,510 (1%)	0 (0%)	0 (0%)	148,975 (34.1%)	282,944 (64.8%)	76.08
Mukono	643,696	0 (0%)	0 (0%)	144,123 (22.4%)	4,903 (0.8%)	259,742 (40.4%)	2,916 (0.5%)	231,441 (36%)	570 (0.1%)	37.49
Nakaseke	146,600	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2,136 (1.5%)	307 (0.2%)	20,852 (14.2%)	123,306 (84.1%)	81.37
Nakasongola	187,038	0 (0%)	0 (0%)	0 (0%)	5,283 (2.8%)	0 (0%)	0 (0%)	65,293 (34.9%)	116,462 (62.3%)	73.90
Rakai	492,742	0 (0%)	0 (0%)	0 (0%)	1,941 (0.4%)	122,951 (25%)	4,307 (0.9%)	361,033 (73.3%)	2,510 (0.5%)	56.79
Ssembabule	263,411	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	81,852 (31.1%)	181,558 (68.9%)	79.43
Wakiso	1,599,870	0 (0%)	0 (0%)	132,586 (8.3%)	932,665 (58.3%)	78 (0%)	0 (0%)	405,550 (25.3%)	128,994 (8.1%)	24.62

Region/District	Total Pop 2010	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Bukedi										
Budaka	167,365	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13,283 (7.9%)	167,365 (100%)	90.31
Busia	355,022	0 (0%)	0 (0%)	0 (0%)	43,531 (12.3%)	0 (0%)	0 (0%)	0 (0%)	307,592 (86.6%)	75.89
Butaleja	166,469	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	166,469 (100%)	92.85
Kibuku	157,118	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	157,118 (100%)	90.40
Pallisa	317,705	0 (0%)	0 (0%)	0 (0%)	6,732 (2.1%)	0 (0%)	0 (0%)	0 (0%)	310,973 (97.9%)	87.20
Tororo	408,375	0 (0%)	0 (0%)	0 (0%)	165 (0%)	36,000 (8.8%)	0 (0%)	0 (0%)	372,152 (91.1%)	84.92
Bunyoro										
Buliisa	171,597	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	171,597 (100%)	88.60
Hoima	638,660	0 (0%)	0 (0%)	0 (0%)	31,313 (4.9%)	0 (0%)	0 (0%)	107,381 (16.8%)	499,966 (78.3%)	78.32
Kibaale	790,805	0 (0%)	0 (0%)	0 (0%)	0 (0%)	31,043 (3.9%)	1,674 (0.2%)	721,569 (91.2%)	36,520 (4.6%)	64.99
Kiryandongo	315,124	0 (0%)	0 (0%)	0 (0%)	187 (0.1%)	0 (0%)	0 (0%)	239 (0.1%)	314,698 (99.9%)	92.81
Masindi	289,991	0 (0%)	0 (0%)	0 (0%)	25,700 (8.9%)	0 (0%)	0 (0%)	47,406 (16.3%)	216,884 (74.8%)	76.06
Busoga										
Bugiri	543,742	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14,616 (2.7%)	0 (0%)	0 (0%)	529,127 (97.3%)	88.85
Buyende	244,735	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	36,042 (14.7%)	208,694 (85.3%)	81.68
Iganga	458,785	0 (0%)	0 (0%)	0 (0%)	0 (0%)	87,513 (19.1%)	0 (0%)	0 (0%)	371,272 (80.9%)	77.07
Jinja	593,938	0 (0%)	0 (0%)	0 (0%)	147,352 (24.8%)	90,860 (15.3%)	0 (0%)	34,574 (5.8%)	321,152 (54.1%)	53.75
Kaliro	197,244	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	42,042 (21.3%)	87.79
Kamuli	464,393	0 (0%)	0 (0%)	0 (0%)	6,216 (1.3%)	0 (0%)	0 (0%)	51,996 (11.2%)	406,180 (87.5%)	79.14
Luuka	229,528	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	229,528 (100%)	87.52
Mayuge	528,948	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3,446 (0.7%)	0 (0%)	0 (0%)	525,502 (99.3%)	93.61
Namiyango	173,906	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	173,906 (100%)	88.74
Namutumba	209,518	0 (0%)	0 (0%)	0 (0%)	0 (0%)	443 (0.2%)	0 (0%)	0 (0%)	209,075 (99.8%)	92.23

Region/District	Total Pop 2010	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Elgon										
Bududa	85,835	759 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	71,793 (83.6%)	80.73
Bukwo	58,161	13,368 (23%)	0 (0%)	0 (0%)	0 (0%)	41,758 (71.8%)	435 (0.7%)	2,579 (4.4%)	0 (0%)	34.60
Bulambuli	150,169	15,815 (10.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	67,209 (44.8%)	67,145 (44.7%)	67.78
Kapchorwa	99,862	3,107 (3.1%)	0 (0%)	0 (0%)	14,656 (14.7%)	0 (0%)	0 (0%)	66,679 (66.8%)	15,419 (15.4%)	54.50
Kween	95,537	36,900 (38.6%)	0 (0%)	0 (0%)	0 (0%)	28,105 (29.4%)	1,642 (1.7%)	24,803 (26%)	4,087 (4.3%)	32.09
Manafwa	188,251	673 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4,287 (2.3%)	183,276 (97.4%)	86.01
Mbale	249,182	1,291 (0.5%)	0 (0%)	0 (0%)	1,593 (0.6%)	84,744 (34%)	0 (0%)	0 (0%)	161,555 (64.8%)	62.06
Sironko	285,297	4,830 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	51,242 (18%)	229,225 (80.3%)	80.73
Karamoja										
Abim	24,344	0 (0%)	0 (0%)	0 (0%)	0 (0%)	604 (2.5%)	42 (0.2%)	18,504 (76%)	5,194 (21.3%)	67.97
Amudat	127,441	0 (0%)	0 (0%)	0 (0%)	0 (0%)	22 (0%)	0 (0%)	126,420 (99.2%)	160 (0.1%)	66.69
Kaabong	175,107	399 (0.2%)	0 (0%)	0 (0%)	1,107 (0.6%)	80,521 (46%)	2,973 (1.7%)	83,415 (47.6%)	6,283 (3.6%)	52.15
Kotido	67,928	0 (0%)	0 (0%)	0 (0%)	932 (1.4%)	0 (0%)	0 (0%)	13,253 (19.5%)	53,744 (79.1%)	75.24
Moroto	162,265	2,481 (1.5%)	0 (0%)	0 (0%)	6,113 (3.8%)	8,537 (5.3%)	311 (0.2%)	139,758 (86.1%)	4,343 (2.7%)	59.31
Nakapiripirit	188,509	2,946 (1.6%)	0 (0%)	0 (0%)	0 (0%)	2,308 (1.2%)	319 (0.2%)	83,119 (44.1%)	99,817 (53%)	71.90
Napak	223,058	345 (0.2%)	0 (0%)	0 (0%)	0 (0%)	773 (0.3%)	190 (0.1%)	175,231 (78.6%)	46,520 (20.9%)	70.30
Kigezi										
Kabale	601,513	579,516 (96.3%)	0 (0%)	171 (0%)	355 (0.1%)	8,390 (1.4%)	666 (0.1%)	12,314 (2%)	1,548 (0.3%)	1.84
Kanungu	302,311	38,573 (12.8%)	0 (0%)	0 (0%)	15,054 (5%)	43,445 (14.4%)	2,432 (0.8%)	174,109 (57.6%)	28,577 (9.5%)	51.31
Kisoro	305,298	290,817 (95.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14,482 (4.7%)	0 (0%)	2.88
Rukungiri	384,711	60,058 (15.6%)	0 (0%)	12,406 (3.2%)	0 (0%)	262,537 (68.2%)	753 (0.2%)	47,039 (12.2%)	1,919 (0.5%)	27.90
Lango										
Alebtong	192,288	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	192,288 (100%)	87.02
Amolatar	101,186	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27,335 (27%)	73,851 (73%)	77.97
Apac	245,964	0 (0%)	0 (0%)	0 (0%)	4,883 (2%)	5 (0%)	8 (0%)	13,609 (5.5%)	227,459 (92.5%)	81.01
Dokolo	158,218	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	769 (0.5%)	157,449 (99.5%)	84.93
Kole	179,055	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	179,055 (100%)	82.84
Lira	332,244	0 (0%)	0 (0%)	0 (0%)	23,054 (6.9%)	0 (0%)	0 (0%)	15,907 (4.8%)	293,284 (88.3%)	80.21
Otuke	62,888	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	21,311 (33.9%)	41,577 (66.1%)	76.58
Oyam	260,559	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	260,559 (100%)	90.62

Region/District	Total Pop 2010	Malaria Free	Unstable Transmis-sion	*Pf*PR$_{2-10}$ <1%	*Pf*PR$_{2-10}$ 1-4.9%	*Pf*PR$_{2-10}$ 5-10%	*Pf*PR$_{2-10}$ >10-50%	*Pf*PR$_{2-10}$ >50- 74.9%	*Pf*PR$_{2-10}$ 75%+	Population-weighted mean *Pf*PR$_{2-10}$
Teso										
Amuria	124,513	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	124,513 (100%)	84.79
Bukedea	151,586	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	151,586 (100%)	86.67
Kaberamaido	233,658	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13,438 (5.8%)	0 (0%)	81.71
Katakwi	84,436	0 (0%)	0 (0%)	0 (0%)	1,761 (2.1%)	0 (0%)	0 (0%)	158 (0.2%)	82,517 (97.7%)	83.68
Kumi	205,822	0 (0%)	0 (0%)	0 (0%)	12,066 (5.9%)	0 (0%)	0 (0%)	0 (0%)	193,756 (94.1%)	79.58
Ngora	126,665	0 (0%)	0 (0%)	0 (0%)	5,480 (4.3%)	0 (0%)	0 (0%)	0 (0%)	121,185 (95.7%)	80.52
Serere	335,035	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26,146 (7.8%)	308,889 (92.2%)	80.70
Soroti	378,632	0 (0%)	0 (0%)	0 (0%)	23,351 (6.2%)	0 (0%)	0 (0%)	0 (0%)	355,282 (93.8%)	77.12
Toro										
Bundibugyo	300,458	28,840 (9.6%)	0 (0%)	0 (0%)	0 (0%)	3,245 (1.1%)	0 (0%)	51,473 (17.1%)	216,901 (72.2%)	71.81
Kabarole	499,840	33,988 (6.8%)	0 (0%)	0 (0%)	14,808 (3%)	99,045 (19.8%)	7,372 (1.5%)	343,079 (68.6%)	220,220 (44.1%)	47.70
Kamwenge	395,232	1,304 (0.3%)	0 (0%)	0 (0%)	7,586 (1.9%)	235,392 (59.6%)	1,304 (0.3%)	149,645 (37.9%)	0 (0%)	38.37
Kasese	879,606	49,810 (5.7%)	0 (0%)	5,723 (0.7%)	34,169 (3.9%)	322,915 (36.7%)	6,656 (0.8%)	411,607 (46.8%)	48,726 (5.5%)	48.74
Kyegegwa	187,784	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26,363 (14%)	4,726 (2.5%)	156,695 (83.4%)	0 (0%)	57.34
Kyenjojo	450,104	0 (0%)	0 (0%)	0 (0%)	0 (0%)	37,984 (8.4%)	4,936 (1.1%)	407,184 (90.5%)	0 (0%)	54.94
Ntoroko	102,077	2,118 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12,373 (12.1%)	87,537 (85.8%)	82.71
West Nile										
Adjumani	431,580	0 (0%)	0 (0%)	0 (0%)	6,998 (1.6%)	0 (0%)	0 (0%)	0 (0%)	424,582 (98.4%)	83.34
Arua	317,521	0 (0%)	0 (0%)	0 (0%)	33,711 (10.6%)	761 (0.2%)	0 (0%)	20,999 (6.6%)	262,049 (82.5%)	73.35
Koboko	107,534	0 (0%)	0 (0%)	0 (0%)	19,187 (17.8%)	0 (0%)	0 (0%)	0 (0%)	88,311 (82.1%)	69.43
Maracha	239,084	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	239,084 (100%)	83.87
Moyo	467,515	0 (0%)	0 (0%)	0 (0%)	7,709 (1.6%)	0 (0%)	0 (0%)	0 (0%)	459,617 (98.3%)	84.10
Nebbi	401,240	0 (0%)	0 (0%)	0 (0%)	17,067 (4.3%)	0 (0%)	0 (0%)	67,044 (16.7%)	317,129 (79%)	76.51
Yumbe	616,081	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	615,901 (100%)	86.87
Zombo	265,751	0 (0%)	0 (0%)	0 (0%)	33,966 (12.8%)	0 (0%)	0 (0%)	220,588 (83%)	11,197 (4.2%)	57.85

Annex A3: Survey data with information on ITN utilisation and Bayesian mapping procedures

A.3.1 ITN coverage data for Uganda

The national household sample surveys where data are available on household and individual net ownership and use are described here.

Demographic and Health Survey (DHS) 2000-01: The data collection was carried out within the period September 28th 2000 to March 3rd 2001. A three-stage sample design was used and overall, 298 census enumeration areas (EA) were selected from the 1991 Population census list of EAs. The survey covered 41 out of the then 45 districts in the country due to insecurity in a few areas. The districts of Kasese and Bundibugyo in the Western Region and Gulu and Kitgum in the Northern Region were excluded. In the second stage, a complete listing of household exercise was carried out within all the selected EAs. From these lists, households were selected to be interviewed. A total of 8,792 households were selected in the sample, of which 8,234 were occupied. Of the existing households, 7,885 were successfully interviewed [UBOS, 2001]. Information on usage of ITNs was collected for children under the age of 5 years, women aged 15-49 and pregnant women aged 15-49.

National Household survey (NHS) 2002-03: Data collection took place from May 2002 to April 2003. The UNHS 2002-03 covered 55 districts of Uganda, with some parts of Gulu and Kitgum districts not fully covered due to insecurity. Pader District was not covered at all. The UNHS sample was drawn through a stratified two-stage sampling design. The EA was used as the first stage sampling unit and the household as the second stage-sampling unit. The sampling frame used for selection of first stage units (FSUS) was the list of EAs with the number of households based on the cartographic work of the 2002 Population and Uganda NHS 2005-06 Housing Census. A total of 972 EAs (565 in rural and 407 in urban areas) were covered. In order to select the second stage units, which are the households, a listing exercise using listing schedules was done in all selected EAs. UNHS 2002/03 covered a sample of 9,711 households of the 10,000 households that had been identified. ITN usage information was not collected but bed net usage information was collected for all ages.

National Household survey (NHS) 2005-06: Data collection took place from May 2005 to April 2006. The UNHS 2005-06 covered all the districts in Uganda. A two stage sampling design was used to draw the sample. At the first stage, EAs were drawn with Probability Proportional to Size (PPS), and at the second stage, households which are the Ultimate Sampling Units, were drawn using Simple Random Sampling (SRS). The sample of EAs for the UNHS 2005/06 was selected using the Uganda Population and Housing Census Frame for 2002. A total of 762 EAs representing both the general household population and displaced population was selected for the UNHS 2005-06. The UNHS 2005-06 covered a sample size of about 7,400 households. 10 households were targeted per EA with two visits per household [UBOS, 2006]. ITN usage information was available for all ages.

DHS 2006: The survey started in May and continued through to October 2006. The sample was selected in two stages. In the first stage, 321 clusters were selected from among a list of clusters sampled in the 2005-2006 Uganda National Household Survey. For the UDHS 2006,

an additional 17 clusters were selected from the 2002 Census frame in Karamoja in order to increase the sample size to allow for reporting of Karamoja specific estimates in the UDHS. Finally, 30 IDP camps were selected from a list of camps compiled by the United Nations Office for the Coordination of Human Affairs (UN OCHA) as of July 2005, completing a total of 368 primary sampling units. In the second stage, households in each cluster were selected based on a complete listing of households. In the 321 clusters that were included in the UNHS sample, the lists of households used were those generated during the UNHS listing operations April-August 2005. The UNHS sampled ten households per cluster. An additional 15 to 20 households were randomly selected in each cluster. The 17 additional clusters in Karamoja were listed, and 27 households were selected in each cluster. The listing operation was also carried out in the camps and 30 households were selected in each camp. A total of 9,864 households were selected for the sample, of which 9,099 were found to be occupied during data collection. Of these existing households, 8,870 were successfully interviewed [UBOS & Macro, 2006]. ITN usage information was available for all ages.

Malaria Indicator Survey (MIS) 2009: The 2009 UMIS was implemented by the Uganda Bureau of Statistics (UBOS) and the Uganda Malaria Surveillance Project (UMSP) on behalf of the National Malaria Control Program (NMCP). Data collection was carried out in the period November and December 2009. The survey utilized a two-stage sample design. The first stage involved selecting sample points or clusters from a list of EAs covered in the 2002 Population Census. A total of 170 clusters (26 urban and 144 rural) with probability proportional to size were selected. Several months prior to the main survey, a complete listing of all households in the 170 selected clusters was carried out. This provided a sampling frame from which households were then selected for the survey. The second stage of selection involved the systematic sampling of households from the list of households in each cluster. Twenty-eight households were selected in each cluster. Of the 4,760 households selected in the sample, 4,536 were found to be occupied at the time of the fieldwork of these 4,421 were successfully interviewed [UBOS, 2010]. ITN usage information was available for all ages.

DHS 2011: Data collection was carried out between June and December 2011. The sample was selected in two stages. In the first stage, 404 EAs were selected from among a list of clusters sampled in the 2009/10 Uganda National Household Survey (2010 UNHS). This matching of samples was done in order to allow for linking of the 2011 UDHS health indicators to poverty data from the 2009/10 UNHS. The clusters in the UNHS were selected from the 2002 Population Census sample frame. In the second stage, households in each cluster were selected based on a complete listing of households. In all clusters new lists of the households were generated for the purpose of updating the sample list. Households were systematically selected from the households listed during the listing exercise. All the households covered in 2010 UNHS were purposively included in the UDHS sample. A total of 10,086 households were selected for the sample, of which 9,480 were found to be occupied during data collection. Of these, 9,033 households were successfully interviewed [UBOS, 2012].

A 3.2 Bayesian geo-additive regression models

The presentation of ITN coverage data is often limited only to the lowest sampling precision estimates of national surveys, regions in the case of Uganda. Here, we use the properties of intervention coverage at geo-coded cluster levels combined data within a regression framework using a geo-additive semi-parametric mixed model constructed within a Bayesian framework [Kammann & Wand, 2003]. Here, we use a fully Bayesian approach based on Markov priors that uses MCMC techniques for inference and model checking [Fahrmeir & Lang, 2001; Lang & Brezger, 2004] where the classical linear regression model forms are as follows

$$y_i = w_i'\gamma + \varepsilon_i, \qquad \varepsilon_i \sim N(0,\sigma^2), \qquad \text{(Equation A.3.1)}$$

for observations $(y_i, w_i), i = 1,....,n,$ on a response variable *y* and a vector *w* of covariates assume that the mean $E(y_i \mid w_i)$ can be modeled through a *linear predictor* $w_i'\gamma$. In our application to ITN coverage no covariate was used. The geographical small-area information was given in form of a location variable *s*, indicating the areal unit to which predictions of ITN coverage are to be made. In our study, this geographical information is given by the health districts of Uganda. Attempts to include such small-area information using district-specific dummy-variables would in our case entail more than 100 dummy-variables and using this approach we would not assess spatial inter-dependence. The latter problem cannot also be resolved through conventional multilevel modeling using uncorrelated random effects [Goldstein, 1999]. It is reasonable to assume that areas close to each other are more similar than areas far apart, so that spatially correlated random effects are required.

To overcome these difficulties, we replace the strictly linear predictor through a *geo-additive predictor*, leading to the *geo-additive regression model*

$$y_i = f_{spat}(s_i) + \varepsilon_i \qquad \text{(Equation A.3.2)}$$

here, f_{spat} is the spatial effect $s_i \in \{1,...,S\}$ labelling the districts in Uganda. Regression models with predictors as in (2) are sometimes referred to as geo-additive models.

In a Bayesian approach unknown functions f_j and parameters γ as well as the variance parameter σ^2 are considered as random variables and have to be supplemented with appropriate prior assumptions. In the absence of any prior knowledge we assume independent diffuse priors $\gamma_j \propto const, j=1,...,r$ for the parameters of fixed effects. Another common choice is highly dispersed Gaussian priors.

Several alternatives are available as smoothness priors for the unknown functions $f_j(x_j)$ [Fahrmeir & Lang, 2001; Fahrmeir et al., 2004]. We use Bayesian (Penalized) – Splines, introduced by Eilers and Marx in a frequentist setting. It is assumed that an unknown smooth function $f_j(x_j)$ can be approximated by a polynomial spline of low degree. The usual choices are cubic splines, which are twice continuously differentiable piecewise cubic

polynomials defined for a grid of k equally spaced knot *p* on the relevant interval $[a,b]$ of the x-axis; written in terms of a linear combination B-spline basis functions $B_m(x)$,

$$f(x)=\sum_{m=1}^{l}\beta_m B_m(x) \qquad \text{(Equation A.3.3)}$$

These basis functions have finite support on four neighbouring intervals of the grid, and are zero elsewhere. A comparably small number of knots (usually between 10 and 40) is chosen to ensure enough flexibility in combination with a roughness penalty based on second order difference of adjacent B-spline coefficients to guarantee sufficient smoothness of the fitted curves. In our Bayesian approach this corresponds to second order random walks

$$\beta_m = 2\beta_{m-1} - \beta_{m-2} + u_m, \qquad \text{(Equation A.3.4)}$$

with Gaussian errors $u_m \sim N(0,\tau^2)$. The variance parameter τ^2 controls the amount of smoothness, and is also estimated from the data. More details on Bayesian P-Splines can be found in Lang and Brezger (2004). Note that random walks are the special case of B-Splines of degree zero.

For the spatially correlated effect f_{str} (s), s = 1, … S, we have chosen Markov random field priors common in spatial statistics [Besag et al., 1991]. These priors reflect spatial neighbourhood relationships. For geographical data one usually assumes that two sites or regions *s* and *r* are neighbours if they share a common boundary. Then a spatial extension of random walk models leads to the conditional, spatially autoregressive specification

$$f_{str}(s) \mid f_{str}(r), r \neq s \sim N(\sum_{r\in\partial_s} f_{str}(r)/N_s, \tau^2/N_s) \qquad \text{(Equation A.3.5)}$$

where N_s is the number of adjacent regions, and $r \in \partial_s$ denotes that region r is a neighbour of region s. Thus the (conditional) mean of $f_{str}(s)$ is an average of function evaluations $f_{str}(s)$ of neighbouring regions. Again the variance τ^2_{str} controls the degree of smoothness. For a spatially uncorrelated (unstructured) effect f_{unstr} a common assumption is that the parameters $f_{unstr}(s)$ are i.i.d. Gaussian

$$f_{unstr}(s) \mid \tau^2_{unstr} \sim N(0, \tau^2_{unstr}) \qquad \text{(Equation A.3.6)}$$

Variance or smoothness parameters τ^2_j, $j=1,...,p, str, unstr,$ are also considered as unknown and estimated simultaneously with corresponding unknown functions f_j. Therefore, hyper-priors are assigned to them in a second stage of the hierarchy by highly dispersed inverse gamma distributions $p(\tau^2_j) \sim IG(a_j,b_j)$ with known hyper-parameters a_j and b_j. For model choice, we routinely used the Deviance Information Criterion (DIC) as a measure of fit and model complexity [Spiegelhalter et al., 2002].

A.3.3 Model selection

The spatial effects were modelled through the Markov random field prior (MRF) with penalized splines (P-spline) with second-order random walk penalty. With MRF prior, it was possible to predict ITN coverage in districts with no coverage data based on information of neighbouring districts. Two model forms were explored: a spatial model with district as random effect and with MRF priors (Model A); and geo-spline model with weights applied as inverse proportional to the distance of the centroids of neighbouring districts (Model B). Table A.2.1. summarises the comparison of the DIC and prior sensitivities for the three models.

Table A.3.1 Summary of the DIC & sensitivity analysis of the choice of spatial priors for model selection

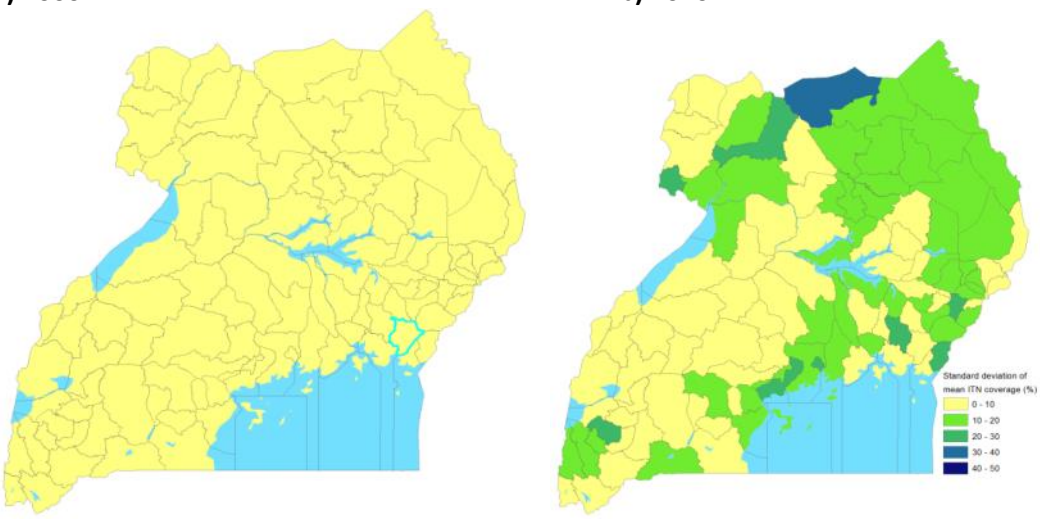
Hyper-parameters	Year	Diagnostics	Spatial With MRF	Spatial With geo-spline
a=1, b=0.005	2000	Deviance	1014.6	1017.3
		pD	10.1	9.8
		DIC	1034.8*	3563.1
a=1, b=0.005	2010	Deviance	357.8	360.9
		pD	49.2	44.8
		DIC	456.2	450.5*

Models with asterisks (*) is the best.

The results indicate for the year 2000 Model B (albeit without ITN per capita) was most accurate and for 2010 and 2012 the geo-spline provided the best fit (Model C). In addition to the sensitivity analysis (Table A.3.1), the standard deviations (SD) of the mean ITN coverage predictions per district were computed for each year with higher values of the SD indicating greater uncertainty (Figure A.3.1).

Figure A.3.1: standards deviations of mean ITN coverage predictions in Uganda for the years: a) 2000; b) 2010

a) 2000 **b) 2010**



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