

Spatial Epidemiology and the Integrated Control of Malaria and Lymphatic Filariasis in Africa

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Thesis submitted for PhD examination

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Declaration of own work

I declare that the thesis presented here is my own work, completed under the supervision of Professor Edwin Michael and Dr Simon Buckle. All sources used in this thesis have been cited appropriately. I would like to acknowledge that the co-infection model used in chapters five and six was developed collaboratively with Paul Parham and Manoj Gambhir. The work presented in chapter two has been published:

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Signed:.....

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Abstract

Malaria and lymphatic filariasis (LF) cause the largest public health burden of all vector-borne diseases worldwide. Some 350-500 million clinical episodes and 1 million deaths each year are caused by malaria, of which approximately 60% and 80% respectively occur in Africa. More than 50 million people are also thought to be infected with lymphatic filariasis in 39 endemic countries in sub-Saharan Africa, with approximately 14.6 million individuals living in these endemic countries estimated to suffer from the two major filarial debilitating conditions, lymphodema or hydrocele. These two infections are co-endemic in large parts of Africa and are transmitted by the same vector, namely the *Anopheles* mosquito.

The overall aim of the PhD was to develop a framework which could be used to evaluate the economic costs and benefits of different control strategies for reducing or eliminating the transmission of LF and malaria in Africa and, in particular, considering whether integrated control could offer a more effective approach for disease control. This problem was split into three key areas:

- 1) Mapping the geographic distribution of malaria and LF infection in Africa and identifying areas where the infections are co-endemic. Initially a maximum entropy modelling approach was used to identify areas at risk of LF based on environmental factors and population density. Then, a Bayesian spatial modelling approach was used to map the prevalence of malaria and LF in Africa, to estimate the number of people infected, and to identify areas of co-endemicity.
- 2) Developing a combined malaria-LF transmission model for humans and mosquitoes. This involved integrating a LF transmission model into a malaria transmission model. Interactions between the infections were captured using the model, specifically the increase in vector mortality as a result of LF larvae infection, and alterations in the host immune response as a result of co-infection. The model was used to investigate how the presence of one infection affected the prevalence of the other.
- 3) Finally, performing an economic evaluation of the economic costs and benefits of different control strategies, focusing on the potential for an integrated control approach. The economic benefits of the two primary control approaches (long lasting insecticidal nets for malaria and mass drug administration for LF) were modelled for a range of different scenarios using the co-infection model. The benefit of a control strategy was defined as the financial cost of the resulting reduction in treatment costs and work days lost due to infection and disease. The cost-benefit analysis was used to identify the optimal control strategy for different infection prevalence scenarios and the results were combined with the maps created in 1) to produce maps showing the optimal control strategy for different regions of Africa.

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Appendix A

Details of published data used in the Maxent analysis. The number of data points from each study or review is given in brackets. The list of study references for the data used are given below the table.

Appendix B

Further details on generalised linear spatial models and MCMC parameter estimation

Appendix C

Full co-infection model differential equations, descriptions of all state variables and model parameters, equations used to model the interaction effects in the host and vector, and equations for infection prevalence.

Appendix D

Details on modelling Ivermectin induced vector mortality post MDA

List of Abbreviations

ACT	Artemisinin-Combination Therapies
ADL	Adenolymphangitis
AFL	Acute Filarial Lymphangitis
AIC	Akaike Information Criterion
Alb	Albendazole
AUC	Area Under the Curve
CCC	Concordance Correlation Co-efficient
CI	Credible Interval
DALY	Disability Adjusted Life Year
DEC	Diethylcarbamazine
DIC	Deviance Information Criterion
EB	Economic Benefit
EB/\$1	Economic Benefit per \$1 control cost
EIR	Entomological Inoculation Rate
GAELF	Global Alliance to Eliminate Lymphatic Filariasis
GLSM	Generalised Linear Spatial Model
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GR	Gelman-Rubin
IPT	Intermittent Preventative Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Net
Iv	Ivermectin
IVM	Integrated Vector Management
LF	Lymphatic Filariasis
LLIN	Long Lasting Insecticidal Net
LTP	Least Training Presence
MCMC	Markov Chain Monte Carlo
MDA	Mass Drug Administration
MDG	Millennium Development Goals
mf	Microfilariae
MPL	Marginal Product of Labour
NDVI	Normalised Difference Vegetation Index
NTD	Neglected Tropical Disease
RBM	Roll Back Malaria
ROC	Receiver Operating Characteristic
SP	Sulfadoxine-Pyrimethamine
SSA	Sub-Saharan Africa
STH	Soil Transmitted Helminth
TB	Tuberculosis
TP	Training Presence
TPE	Tropical Pulmonary Eosinophilia
UN	United Nations
WHO	World Health Organisation

Chapter 1

Introduction and Literature Review

1.1 Background and aims of the thesis

Malaria and lymphatic filariasis (LF) cause the largest worldwide public health burden of all vector-borne diseases (Townson et al. 2005). These infections are thought to be co-endemic in large regions of sub-Saharan Africa (Molyneux and Nantulya 2004; Bockarie et al. 2009) and are transmitted by the same vector, the *Anopheles* mosquito (Muturi et al. 2008). Currently, separate intervention strategies are being implemented to control the transmission of each disease. The main methods of controlling malaria are insecticide spraying and insecticide treated bed nets together with drug therapy, whereas mass drug administration (MDA) is the primary prevention strategy for LF (Townson et al. 2005).

Recently there have been calls for an integrated approach to disease control (Manga 2002; Hotez et al. 2006). The focus of such calls have been largely predicated on the fact that the transmission of both diseases is dependent on the vector density and vector-human contact, and thus a reduction in either of these factors in a region can lead to a fall in the prevalence of each disease (Prasittisuk 2002; Michael et al. 2004; Townson et al. 2005; Burkot et al. 2006; Protopopoff et al. 2007). Therefore, implementing a policy that reduces the mosquito population or vector-human contact could serve to reduce both malaria and LF transmission levels. It is believed that this multi-disease control can be achieved via the targeted use of vector control methods alone or in combination with MDA to prevent or reduce transmission cost-effectively (Chanda et al. 2008). The current status of integrated control in Africa is discussed in section 1.4.

The control of vector-borne diseases is a deepening concern for Africa: any proliferation of malaria and LF can cause a huge burden on the economic potential of the continent. It is estimated that lymphatic filariasis currently causes a loss of \$1 billion annually in Africa as a result of lost productivity (Haddix and Kestler 2000) whilst the annual cost of malaria in Africa

is estimated at \$73 billion (Sachs and Malaney 2002). There are also the vast healthcare costs involved in the purchase and distribution of preventative and medicative treatments.

Recently, attempts have been made to calculate the cost-effectiveness of eliminating a single disease (Sachs and Malaney 2002; Michael et al. 2008), where the marginal effectiveness and marginal costs have been calculated for different interventions. However, there is currently no framework for assessing the cost-effectiveness of integrated control as a method for eradicating multiple diseases. Thus it is not clear when and where integrated intervention programmes for disease control or elimination will be most cost-effective.

Understanding how the presence of one parasite can affect the transmission of another parasite is of vital importance in the planning of control programmes. Co-infection with malaria and LF has been reported to alter the course of transmission of each infection in humans and vectors; specifically, vectors can experience increased mortality as a result of single LF, or combined LF and malaria infection (Hawley 1985; Michael et al. 2009), and changes in the host immunological response are thought to occur as a result of co-infection, leading to changes in immunity, susceptibility and disease severity (Su et al. 2005; Fenton et al. 2008; Graham 2008; Hillier et al. 2008; Fairlie-Clarke et al. 2010). Ignoring these interaction effects when investigating the potential effectiveness of a control programme could result in incorrect predictions, or 'unexpected' outcomes. A control programme targeted at one disease could alter the prevalence of another co-endemic infection.

The ultimate goal of this thesis is to produce an evidence-based policy framework for evaluating the costs and economic benefits of different malaria and lymphatic filariasis intervention strategies in different regions of Africa. This will allow us to establish the circumstances under which an integrated control programme could offer a more cost-effective means of reducing or eliminating the transmission of these two infections. This task can be sub-divided into three key aims:

- 1 To map the spatial distribution and prevalence of malaria and Lymphatic Filariasis (LF) in Africa and to identify areas of co-endemicity
- 2 To develop a malaria-LF co-infection transmission model for humans and mosquitoes that explicitly accounts for interaction effects between the two infections
- 3 To perform an economic evaluation of different control strategies, focusing on the costs and benefits of an integrated control approach where both infections are targeted simultaneously, and to investigate how the different pre-control prevalence levels in a given region will affect the optimal control option.

Firstly, the main topics covered in this thesis are introduced, namely: LF, malaria, integrated control, spatial mapping techniques, and transmission modelling.

1.2 Lymphatic Filariasis

Lymphatic Filariasis is a vector-borne disease caused by the nematode parasites *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. *Wuchereria bancrofti* is the only LF parasite present in Africa and causes 91% of all LF infections worldwide.

It has been estimated that 120 million people are infected with LF in 81 countries worldwide (Figure 1.1) (Michael et al. 1996a) and that 1.3 billion people are living in LF-endemic areas (WHO 2008a). LF is a disease which affects the poor disproportionately – of the 50 least developed nations, 43 are known to be LF-endemic (Goldman et al. 2007). In Africa, 382 million people are thought to live in areas at risk from LF and an estimated 50 million people are infected in 39 countries.



Figure 1.1: Lymphatic Filariasis endemic countries (Source: LF elimination programme)

1.2.1 LF Transmission

Adult filarial worms reside in the human lymphatic system where they live for 5-10 years (Vanamail et al. 1996). After mating, the female worm produces thousands of immature microfilariae (mf). These mf exhibit nocturnal periodicity – during the day they reside in the lungs but at night they move to the peripheral bloodstream which coincides with peak biting time of mosquitoes.

A mosquito biting a LF infected host may ingest some mf along with the bloodmeal. Once inside the mosquito, the mf shed their sheaths and migrate through the midgut to the thoracic muscles as stage one larvae (L1). Here they develop into stage three infective larvae (L3). This process takes approximately 10-14 days. These L3 larvae then travel through the hemocoel to the mosquito's proboscis; here they are ready to penetrate the skin and enter the bloodstream when the vector next bites a human host. Once inside the host, some of the L3 larvae will migrate to the lymphatic system and develop into mature adult worms, a process which takes around 6-12 months. The 'success' rate of an infectious mosquito bite leading to

infection in the host is low, and it can often take hundreds of thousands of bites to establish infection. The life cycle for *Wuchereria bancrofti* is shown in Figure 1.2.

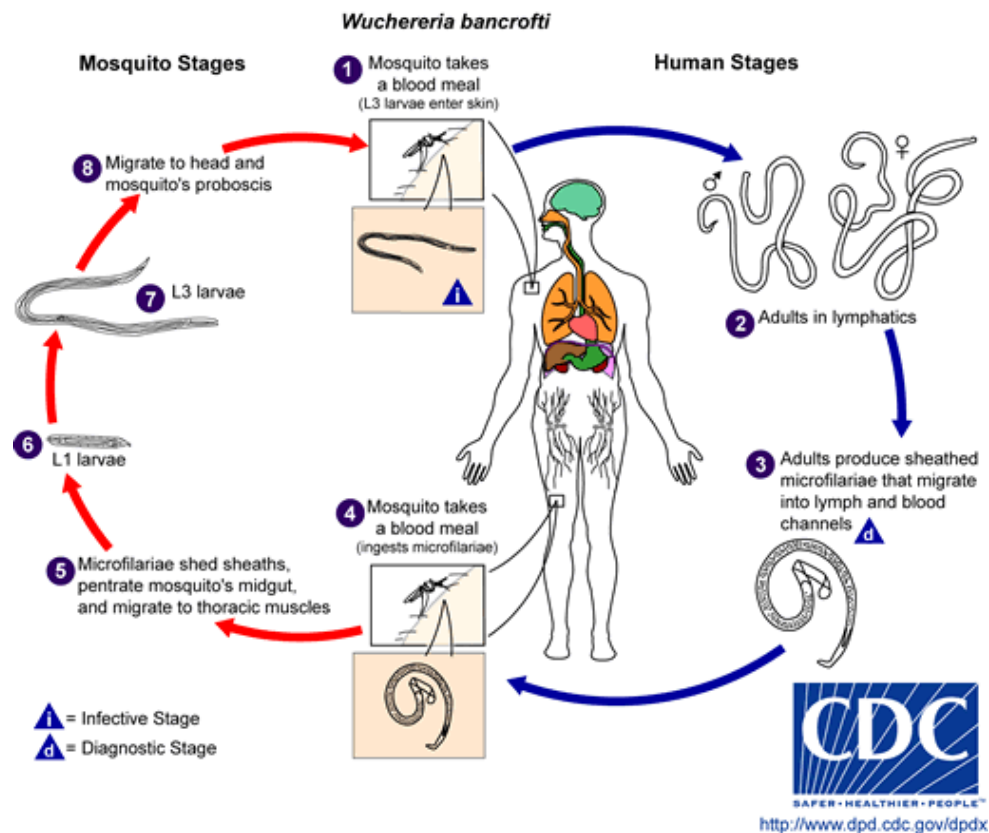


Figure 1.2: The life cycle of *Wuchereria Bancrofti*

1.2.2 Disease

Lymphatic filariasis is one of the leading causes of disability worldwide. The spectrum of disease severity can be divided into three broad categories: 1) asymptomatic infection, 2) acute disease and 3) chronic disease. Approximately one third of people infected with LF suffer from one of the associated chronic pathologies which include lymphodema which causes swelling of arms, legs, breasts and genitalia and hydrocele which causes swelling of the scrotum in males (Michael et al. 1996a; WHO 2004a). It has been estimated that approximately 13% of infected people suffer from the first condition while up to 21% of males living in endemic areas may experience hydrocele. Another chronic condition caused by LF infection is tropical pulmonary eosinophilia (TPE) – the effects include coughing, wheezing and breathlessness, and is caused by an increased immune response to the filarial worms and mf (Ottesen 1984).

Asymptomatic individuals have circulating microfilaria but experience no clinical symptoms of LF infection, even though filarial worms can still be causing damage to the lymphatic system. Acute infection usually consists of several episodes of fever or inflammation of the lymphatics per year, each of which lasts from three to five days (Pani et al. 1995). The two main causes

are acute adenolymphangitis (ADL), which is caused by bacterial infections in damaged tissues, and less commonly, acute filarial lymphangitis (AFL), caused by the death of adult filarial worms (Dreyer et al. 2000; Gyapong et al. 2005).

In addition to clinical disease, LF is also a socially debilitating condition – swellings are greatly disfiguring, which can lead to social stigma and impair marriage and sexual opportunities. Chronic LF sufferers can experience a lack of mobility often meaning that they are unable to work, or can only perform light duties (Ramaiah et al. 2000). Acute LF sufferers also have a reduced work capacity due episodes of illness leaving them bedridden to 3-5 days at a time (Ramaiah et al. 2000).

1.2.3 Vectors

Lymphatic filariasis is transmitted primarily by mosquitoes from the *Anopheles* and *Culex* genera and to a lesser extent from the *Aedes* and *Mansonia* genera. Vectors from the *Culex pipiens* complex, and in particular *Culex quinquefasciatus* (White 1989), are important LF vectors throughout the world. *Culex* mosquitoes are found primarily in urban and semi urban environments due to their high tolerance for breeding in polluted water sites such as cesspits, stagnant drains and septic tanks (Pedersen 2008; Manguin et al. 2010).

Mosquitoes of the *Anopheles* spp. are important LF vectors in Africa and Southern Asia, especially in rural areas. Within the *anopheles* genus, further distinctions are commonly made between *An. gambiae* complex and the *An. funestus* group. Within the *An. gambiae* complex there are three principal LF vector species, namely *An. gambiae* s.s., *An. arabiensis* and *An. merus*. Most *Anopheles* mosquitoes have a preference for open freshwater or muddy pools with little pollution. *An. funestus* vectors can breed in heavily vegetated water sites such as at the edge of a swamp or a river bank and can also breed in slow moving water (Gillies and de Meillon 1968). *An. merus* and *An. melas* are the only LF vector species that can breed in saltwater, meaning they are often found along the coast.

Focusing on LF vectors in Africa, *Anopheles* vectors are thought to account for approximately 90% of LF transmission (Molyneux 2003). There are thought to be different vector species transmitting LF in east and west Africa (Bockarie et al. 2009). In east Africa, LF is thought to be transmitted by mosquitoes from both the *Culex pipiens* complex and the *Anopheles* genus. However, in west Africa, *Anopheles* are the primary vector and although *Culex* vectors are present in relatively small numbers, they are largely not thought to transmit LF (Lenhart et al. 2007; Pedersen 2008). Maps are presented in Figure 1.3 showing where the different vector species are found in Africa.

A study conducted in inland Ghana found *An. gambiae* s.s. and *An. funestus* to be the first and second most common LF vectors respectively (Appawu et al. 2001). Although *An.*

arabiensis and *Cx. quinquefasciatus* were found, none had infective L3 larvae. Another study conducted in rural coastal Ghana found *An. gambiae* s.s. and *An. melas* to be the main LF vectors. In Nigeria *An. gambiae* s.s. was found to be the primary vector, but infective *An. arabiensis* and *An. funestus* vectors were also found. A small proportion of the mosquitoes caught were *Culex* but none of these were infective (Lenhart et al. 2007).

In east Africa, studies show *Culex* mosquitoes to be an important LF vector. In Tanzania *An. gambiae*, *An. funestus* and *Cx. quinquefasciatus* were identified as key LF vectors. The *Anopheles* vectors were found to have higher infectivity rates despite taking fewer bites (White 1971). *Culex* mosquitoes were found to be responsible for year round LF transmission but transmission by *Anopheles* mosquitoes tended to be seasonal, focused around the rainy season (Pedersen 2008). In Kenya, *Cx. quinquefasciatus* were found to be the principal vector and were shown to be equally effective vectors of LF as *An. gambiae* and *An. funestus* (Wijers and Kiilu 1977; Pedersen 2008). Studies in Uganda and Malawi showed *An. gambiae* and *An. funestus* to be the primary LF vectors (Onapa et al. 2001; Merelo-Lobo et al. 2003). *Mansonia* spp. were also identified but none were found to be infective. In Ethiopia, a study by McConnel and Schmidt (1973) also found *An. gambiae* and *An. funestus* to be the principal vectors, however no *Culex* mosquitoes were observed here. *Cx. quinquefasciatus* is thought to be the main LF vector on many of the Indian Ocean islands (Mauritius, Comoros, Maldives, Seychelles) apart from Madagascar where *An. funestus* and *An. gambiae* are the main vectors (Pedersen 2008).

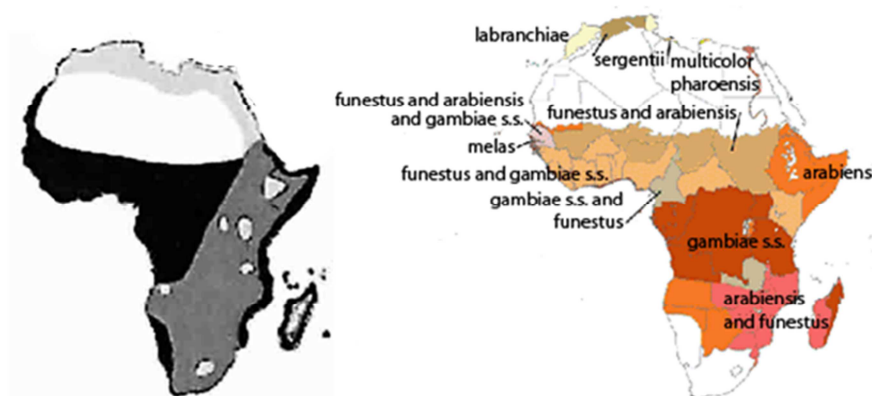


Figure 1.3: Published vector distribution maps. The left map shows *Culex* distribution in Africa. Light grey = *Culex pipiens*, Black = *Cx. quinquefasciatus*, dark grey = overlapping areas of *Cx. pipiens* and *Cx. quinquefasciatus* (Smith and Fonseca 2004). The map on the right shows the dominant *Anopheles* species in Africa (Kiszewski et al. 2004).

1.2.4 Control

In 1993, lymphatic filariasis was identified as one of only six infectious diseases that could be considered 'eradicable' or 'potentially eradicable' by the International Task Force for Disease Eradication. In 1997, this led to the World Health Assembly adopting resolution WHA 50.29 which calls for LF to be eliminated as a public health problem. Consequently, the Global

Programme to Eliminate Lymphatic Filariasis (GPELF) was set up in 2000 with the primary aims of 1) stopping the spread of infection and eliminating LF as a public health problem by 2020 and 2) alleviating the suffering of people experiencing LF induced morbidity.

The current strategy recommended by the WHO is to treat entire populations living in LF endemic areas through MDA. This involves an annual single-dose two-drug regimen of either albendazole (400mg) + Ivermectin (150-200µg/kg) for areas where onchocerciasis is co-endemic and albendazole (400mg) + diethylcarbamazine citrate (DEC) (6mg/kg) for individuals living in onchocerciasis free areas. There is much uncertainty regarding the number of rounds of treatment required to eradicate or reduce prevalence below some critical threshold, and this is currently the topic of much study and debate (Michael et al. 2006; Grady et al. 2007; Gambhir and Michael 2008). It is currently recommended that MDA is repeated for 4-6 years, although 6 or 7 rounds of treatment may be required (Molyneux 2009).

LF elimination programmes have been greatly aided by donations of these drugs - albendazole has been donated by GlaxoSmithKline and Ivermectin (Mectizan (R)) has been donated by Merck and Co., Inc. since 1997. Both companies have agreed to keep donating until LF is eliminated (Gustavsen et al. 2009). By 2008, 1.4 billion albendazole tablets and 1.2 billion Mectizan tablets had already been donated. More recently, in 2010 Eisai, Inc agreed to donate up to 2.2 billion DEC tablets starting in 2012.

Vector control has been identified as a potential tool to supplement MDA in LF eradication efforts, especially in areas where malaria is also endemic. The main methods used are indoor residual spraying (IRS), long lasting insecticide treated nets (LLINs) and the destruction of vector breeding sites (Bockarie et al. 2009).

In 2010, out of the 81 LF endemic countries in the world, 52 had begun MDA, and a further 10 were deemed to not have sufficiently high levels of transmission to require treatment. Approximately 496 million people worldwide had received treatment by 2008 - 38% of the at-risk population (Addiss 2010). Between 2000 and 2007, the work of GPELF has prevented an estimated 28 million people living with LF infection from progressing in LF disease (Chu et al. 2010). In Africa, only 26% of the at-risk population had been targeted by the end of 2009 and MDA programmes had were up and running in just 18 of the 34 endemic countries requiring treatment (Addiss 2010).

1.3 Malaria

Malaria is a vector-borne disease transmitted by parasites belonging to the *Plasmodium* genus. The four main *Plasmodium* species that can cause malaria are *Plasmodium falciparum* (which is responsible for 91% of all infections worldwide (WHO 2008b)), *P. vivax*, *P. malariae* and *P. ovale*.

It was reported that there were 229 million cases of malaria and 781,000 deaths caused by malaria in 2009 (WHO 2010a). Malaria is widely distributed throughout most tropical and subtropical regions including sub-Saharan Africa, Asia and the Americas (Figure 1.4). Approximately 78% of all malaria cases and 91% of all malaria deaths are in Africa (WHO 2010a).

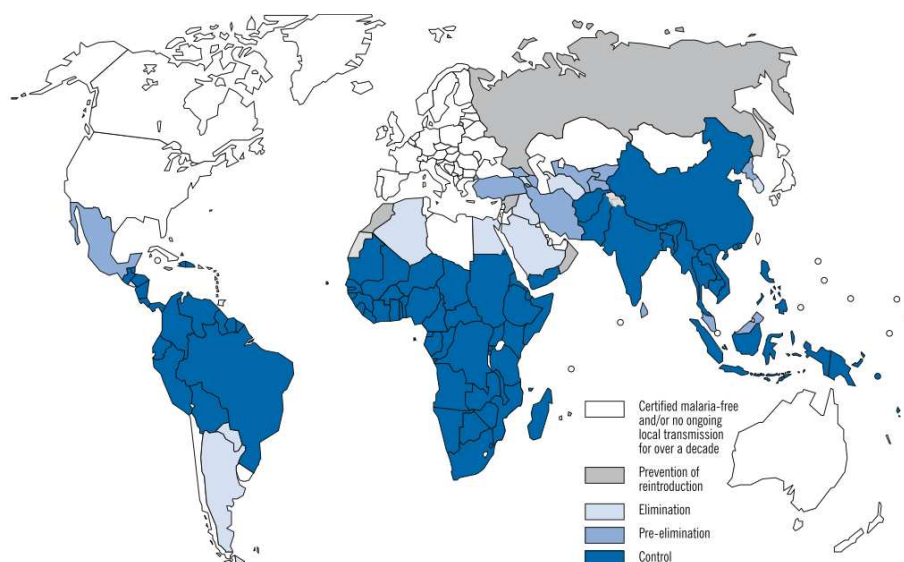


Figure 1.4: Malaria-endemic and malaria-free countries in 2007 (WHO 2008b)

1.3.1 Malaria Transmission

Malaria is transmitted when an *Anopheles* mosquito takes a bite from an infected host. The bloodmeal contains microscopic male and female gametocytes which move to the mosquito's midgut. There, the male gametocytes quickly develop and start to produce sperm-like microgametes that fertilise the female macrogamete, producing zygotes which become ookinetes. This all happens within 18-24 hours of blood feeding. Next, the ookinetes penetrate the stomach wall and become oocysts. The oocysts grow and divide to form hundreds of haploid sporozoite. Finally, the oocyst ruptures and releases the sporozoites which travel to the mosquito salivary gland. The process of the parasite development in the mosquito is known as the sporogonic cycle. The time taken to complete this cycle is highly dependent on the temperature, but is thought to take around 10 days at 28°C for *P. falciparum*.

When an infectious mosquito takes a blood meal the sporozoites leave the salivary glands and enter the blood stream of the host. From there they quickly infect the liver cells where they reproduce asexually (schizogony) to form a pre-erythrocytic schizont. This schizont ruptures releasing thousands of merozoites which invade red blood cells; this starts the erythrocytic cycle - here merozoites invade red blood cells and develop into trophozoites and then mature into schizonts which rupture, releasing more merozoites. Not all merozoites develop into schizonts upon invading a red blood cell; some produce male and female gametocytes which are then taken up by the female mosquito. The malaria transmission cycle is shown in Figure 1.5.

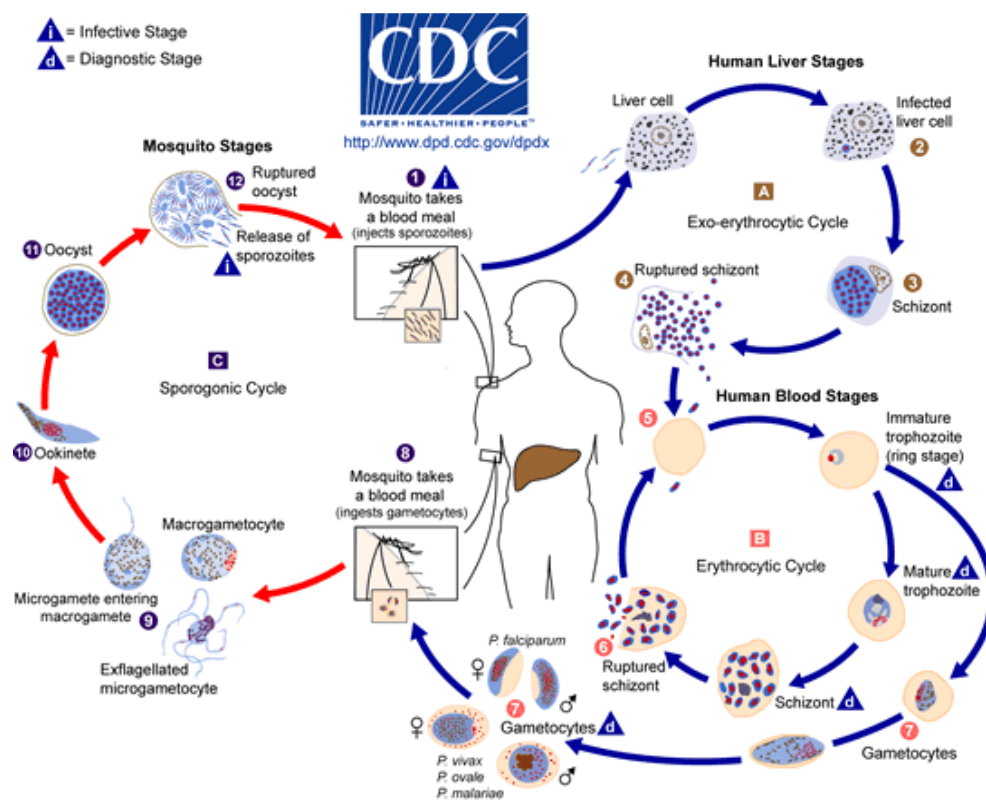


Figure 1.5: Malaria transmission cycle

1.3.2 Infection and Disease

The clinical manifestations of malaria are associated with the rupturing of the red blood cell schizonts. The first symptoms normally occur between 7 and 30 days after receiving a bite from an infectious mosquito. Malaria symptoms are broadly described as either uncomplicated or severe. Uncomplicated malaria symptoms include fever, joint pain, sweats, chills, vomiting, rapid breathing, coughing, diarrhoea and headaches. Generally, a bout of fever will begin with a cold stage characterised by shivering and a high temperature. This is followed by the hot stage where the temperature remains high and the patient is flushed and has a fast heart rate, and finally the sweating stage, where the patient sweats profusely and

the temperature drops (Gill and Beeching 2009). For *P. falciparum*, these episodes can occur as frequently as every 36-48 hours. Symptoms defined as severe malaria include anaemia, altered consciousness, splenomegaly, hypoglycaemia, hemoglobinuria, seizures and coma. *P. falciparum* is responsible for almost all cases of severe malaria and deaths. Severe malaria can affect the brain causing altered consciousness, seizures, coma and death. This is known as cerebral malaria. Untreated, cerebral malaria can be fatal within 24-72 hours. More long-lasting neurological conditions are experienced by around 10% of individuals that survive cerebral malaria.

Individuals repeatedly exposed to malaria acquire immunity. In endemic areas, typically children experience the most severe symptoms, but as immunity develops, the individual gains some level of protection against the development of new infections. Also, if infected, the severity of symptoms and the number of parasites in the blood decreases.

One of the groups most vulnerable to infection is pregnant women. During pregnancy, immunity is reduced, thus increasing susceptibility to infection. Infection during pregnancy can not only cause illness, anaemia and death, but can also result in low birth weight, prematurity, growth retardation, spontaneous abortion and stillbirth. Up to 200,000 newborns are thought to die each year due to malaria during pregnancy (Steketee et al. 2001).

Children are in the highest risk group for malaria (Taylor and Molyneux 2002) and tend to experience a more severe course of infection. Breman (2001) estimated that African children account for 75% of all malaria deaths worldwide. Individuals living in malarial areas develop some degree of immunity over time, meaning that symptoms tend to be less severe in older patients. However, a recent study suggested that adult mortality due to malaria may be higher than previously estimated, and may increase further as interventions roll out (Murray et al. 2012).

1.3.3 Vectors

Malaria is transmitted solely by female mosquitoes from the *Anopheles* genus. This genus has around 430 species of which around 100 can transmit malaria and 30-40 are thought to be significant vectors. In Africa, the main vector complex is *A. gambiae* which includes the species *A. gambiae* s.s., *A. arabiensis*, *A. bwambae*, *A. merus* and *A. melas*. The most efficient vector of malaria in Africa is thought to be *A. gambiae* s.s. (Coetzee 2004) which is distributed across the entire continent and is one of the primary vectors in most of central Africa and large parts of west Africa (Kiszewski et al. 2004). This vector prefers humid conditions whereas the second most important vector from the *A. gambiae* complex, *A. arabiensis*, is better equipped to survive in drier areas. *A. arabiensis* is one of the dominant vector species in southern and east Africa (Kiszewski et al. 2004). *A. melas* and *A. merus*

breed in saltwater so are normally found near the coast; *A. merus* is found on the east coast and *A. melas* is found on the west coast, especially in Gambia where it is considered one of the primary vectors. Another important vector complex in Africa is *A. funestus* which is present in most regions and is thought to be one of the primary species' in west, central and south-east Africa.

All three of the main vectors (*A. gambiae* s.s., *A. arabiensis* and *A. funestus*) are reported to be resistant to at least one of the insecticides used in vector control (Coetzee 2004).

1.3.4 Control

The Roll Back Malaria (RBM) initiative was set up in 1998 in conjunction with the World Bank, the UN development programme, WHO and UNICEF with the aim of significantly reducing malaria incidence (WHO 1998). The aims of the initiative were to improve access to effective treatments, increase bed net usage, offer preventative treatment to pregnant women in high transmission areas and to set up detection systems to enable quick responses to malaria epidemics (WHO 2005a).

In 2000, representatives from 44 of the 50 malaria affected countries in Africa convened in Abuja to discuss the implementation of the RBM initiative in Africa. This led to the Abuja Declaration which had the primary goal of halving malaria mortality by 2010. Additional goals were to ensure that:

- At least 60% of people with symptomatic malaria had access to effective and affordable treatment within 24 hours of symptoms first occurring
- At least 60% of people living in malarial areas, particularly high risk groups such as children and pregnant women, are protected by suitable community level vector control
- At least 60% of pregnant women living in malarial areas have access to preventative treatment.

These aims were reinforced by the millennium development goals (MDG) announced in 2000 and agreed by all 193 UN states. One of the goals, MDG 6C, aimed to "Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases" (UN 2012).

The current strategy WHO strategy focuses on both prevention and treatment of malaria. Prevention is recommended via Insecticide Treated Nets (ITNs), (specifically Long Lasting Insecticidal Nets (LLINs) that do not require respraying), Indoor Residual Spraying (IRS) and Intermittent Preventative Treatment (IPT) for high risk groups, particularly pregnant women and infants (WHO 2010a).

Mosquito nets are hung over the bed and protect the sleeper from bites during the night. LLINs have insecticides incorporated into the fibres, so as the bednets are washed old fibres are washed away and new fibres containing pyrethroid insecticides reach the surface meaning insecticides are constantly released. Although the LLINs are more expensive initially, in the long run they may work out to be more cost effective as they do not require retreatment. This is why they are preferable to traditional ITNs which are dipped in a synthetic pyrethroid insecticide before they are distributed and should be retreated every year or six months to remain fully effective. As of 2009, ITNs were distributed for free in 39 African countries and 23 countries were distributing nets to everyone living in malarial areas, not just people in high risk groups. Between 2008 and 2010, 254 million bed nets were distributed in sub-Saharan Africa (SSA), which is enough to protect 66% of people living in malarial areas. The proportion of households with at least one ITN has increased from 3% in 2000 to 42% in 2010.

IRS involves covering the walls and roofs of all houses with long-lasting insecticides. The aim is to kill all vectors resting on surfaces inside the house and to deter mosquitoes from entering the house. The most commonly used insecticides are DDT and pyrethroids, but the choice of insecticide in a region will depend on local vector susceptibility (N'Guessan et al. 2007). By 2009, IRS had been implemented by 27 countries in Africa and an estimated 73 million people were protected which is about 10% of the at-risk population (WHO 2010a).

Intermittent preventative treatment (IPT) for pregnant women involves taking doses of an antimalarial at set intervals during pregnancy (White 2005) and IPT for children involves taking antimalarials at set intervals for the first year of their lives (<http://www.ipti-malaria.org>). The most commonly used drug for IPT is sulphadoxine-pyrimethamine (SP), however, due to growing resistance to this drug, studies have looked at using other antimalarials, including artemisinin-combination therapies (ACTs) (Vallely et al. 2007; IPTi consortium 2012). IPT for pregnant women was adopted by 39 countries in SSA by the end of 2009 but so far none have implemented an IPT programme for infants. Just over half of the women that attended an antenatal clinic received a second dose of IPT (WHO 2010a).

The WHO treatment strategy is based around quick and accurate diagnosis and ACT for cases of uncomplicated malaria (WHO 2010a). WHO recommends the following ACTs: artemether-lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, and artesunate + sulfadoxine-pyrimethamine (WHO 2010b). Patients with severe malaria should be admitted to hospital and given artesunate intravenously or intramuscularly followed by a full course of antimalarials. By 2008, 33 countries in Africa had made it national policy to perform a diagnostic test for all suspected malaria cases (WHO 2010a) and by 2010 all malarial countries in Africa were using ACTs as first-line treatment (Snow and Marsh 2010).

Progress has been made since the RBM was established in 2000 (O'Meara et al. 2010; WHO 2010a). Incidence or mortality has been at least halved in 11 African countries as a direct result of control interventions. However, three countries have reported increases in incidence. Using the current tools available, malaria elimination may be an impossible task (Tanner and de Savigny 2008) and efforts may be better spent working towards a sustainable reduction in transmission and incidence (Snow and Marsh 2010).

1.4 Integrated Control

Malaria, tuberculosis (TB) and HIV/AIDS are the three most well-known and heavily funded diseases, as well as the only diseases mentioned by name in the Millennium development goals. Much effort has been focused on the prevention and control of these diseases (Molyneux 2008). However, in recent years increasing attention is being paid to a group of around 13 or 14 diseases known as NTDs – Neglected Tropical Diseases. The five most prominent of these being: schistosomiasis, lymphatic filariasis, onchocerciasis, Soil Transmitted Helminths (STHs) and Trachoma. Since 2006, there have been increasing calls for NTD programmes to be integrated with control programmes for malaria, TB and HIV/AIDS (Hotez et al. 2006). The reasoning behind this was that not only are NTDs thought to pose as big a health burden as the 'big three', but also they can be effectively treated at a relatively low cost and are co-endemic in large parts of Africa (Molyneux et al. 2005).

Funding for NTDs has increased significantly, and now many countries are carrying out mass drug administration programmes. Many of these programmes target two or more diseases; for example Ivermectin and Albendazole are widely distributed in LF and onchocerciasis endemic areas and are designed as treatments against both diseases (Molyneux et al. 2003). These drugs are also thought to have a beneficial effect on STHs (Molyneux et al. 2005). STHs and schistosomiasis control has been integrated in parts of Africa by giving school aged children doses of Praziquantel and Albendazole or Mebendazole (Kolaczinski et al. 2007).

Combining control programmes with similar treatment schedules appears to be a sensible way to achieve integrated control. Most NTDs control programmes involve targeting a single NTD with mass drug administration - integrating these is logistically simple and involves distributing a suitable combination of drugs, depending on which diseases are endemic in each area. Although side effects have been addressed, difficulties may arise due to organisational, political and funding complexities. The US agency for International Development set up the NTD control programme in 2006 to assist the integration of NTD

programmes (USAID 2006) - the initial plan was to help 15 countries initiate integrated control programmes. After three years, 7 countries had received support with setting up their programmes with assistance from locally-based non-governmental organisations (Linehan et al. 2011). In addition, more countries are looking at using existing structures or expertise developed from single disease control programmes to develop integrated NTD control strategies (Fenwick et al. 2009).

Integrated control programs specifically aimed at targeting LF and malaria are far more uncommon, although vector control aimed at controlling malaria is thought to have a beneficial impact on reducing LF transmission (Bøgh et al. 1998). There have been calls to adopt an integrated approach to controlling these two diseases (Manga 2002; Prasittisuk 2002). The two key reasons for this are: 1) they are transmitted by the same vector, the *Anopheles* mosquito, and 2) they are co-endemic in large parts of Africa. One way of tackling malaria and LF simultaneously is integrated vector management (IVM). This approach involves bringing together information on the local effectiveness on different vector control methods to identify an optimal strategy to manage vector populations and reduce the transmission of multiple diseases (WHO 2004b; Townson et al. 2005; van den Berg and Takken 2007; Chanda et al. 2008). IVM can be conducted alone or in combination with other interventions. It has been identified as a way of combining resources from LF and malaria control programmes to achieve a larger reduction in the transmission of both infections than if each one were conducted separately (Burkot et al. 2006; WHO 2011).

Despite approval from the WHO, few countries have adopted an IVM strategy. The few studies which exist have, to a large degree, focused on malaria alone. For example, the Zambian Malaria Control Programme introduced what proved to be a successful integrated vector management strategy in 2003 by conducting micro scale vector control based on local knowledge about prevalence and vector ecology. The result was a reduction in malaria incidence and deaths (Chanda et al. 2008). In a similar vein, Utzinger et al. (2002) explored the economic impact of an IVM programme - as well as averting large numbers of deaths and malaria incidences, the programme saved millions of dollars in medication costs and due to the increased productivity of having a healthier workforce.

In a practical sense, integrated LF and malaria control could be achieved by combining MDA for LF and bed net distribution. This could include utilising the infrastructure of MDA programmes to expand the distribution of bednets, training staff to carry out both vector control and MDA and by performing diagnostic testing for both parasites (WHO 2011). Another suggested synergy between LF and malaria control programmes is to distribute LF drugs to pregnant women receiving IPT, as filarial infection during pregnancy is

thought to worsen pregnancy outcomes such as birth weight and morbidity (Hotez et al. 2011).

Maxwell and colleagues investigated the impact of MDA and vector control (destruction of vector breeding sites) on LF prevalence versus just MDA (Maxwell et al. 1999) - they reported that in the long term, the combined approach is more successful. The study areas subject to combined interventions experience a drop in LF prevalence from 49% to 3% over six years whereas the study area just given drugs experienced an initial decline followed by a resurgence after 3-6 years (Maxwell et al. 1999). Distributing bed nets along with MDA has also been reported to increase the usage of bed nets (Blackburn et al. 2006).

A study in Zimbabwe looked at integrating schistosomiasis and STH deworming control with prompt malaria treatment for schoolchildren (Midzi et al. 2011). As well as providing the treatments, this intervention involved the study team going into schools and educating the teachers and children about the signs and symptoms of the infections, and the lifecycle of the parasites. This approach proved very efficient, reducing filarial worm infections by around 70% and *P. falciparum* infections by around 60% after one year.

1.5 Mapping

1.5.1 LF Mapping

The first estimates of LF prevalence in Africa were based on data obtained by Hawking (1940; 1957; 1977) and Jordan (1954; 1956a; 1956b; 1956c; 1960) for sub-Saharan Africa and by Shawarby et al. (1965) for Egypt. These data and more were collated in a review by Sasa (1976) to give the first indications of the extent and severity of LF in Africa. This study presents a map showing all the countries where LF transmission is thought to occur and the results of prevalence surveys or reported observations in LF pathologies for many African countries.

Attempts to produce LF maps intensified in the late 1960s and 1970s (Casaca 1966; Juminer et al. 1971; Lamontellerie 1972; Brinkmann 1976; Wijers 1977); these maps were created by displaying infected sites as points or ranges, or by interpolating between infection sites on local-level maps. Michael et al. (1996a) reviewed all published LF surveys and developed methods which allowed for generalisations between different survey methods, for example: accounting for different age and gender profiles, or for surveys that look at only infection or only chronic disease. Prevalence estimates were obtained by aggregating across all the available data in a country. This technique has also been applied using regional data to

produce national and region specific prevalence maps, either by direct application of the data or using simple probability mapping approaches (Michael and Bundy 1997; Meyrowitsch et al. 1998; Sabesan et al. 2000).

Recent mapping studies have adopted more advanced statistical modelling techniques. Lindsay and Thomas (2000) used published community LF prevalence data in conjunction with climate layers and a logistic regression model to predict the distribution of LF across sub-Saharan Africa, which helped refine first estimates of the at-risk population for this important endemic continent. Another technique used in disease mapping studies are generalised linear spatial models in combination with geostatistical methods (Gyapong et al. 2002; Srividya et al. 2002). This approach has been used to produce prevalence maps by finding correlations between LF prevalence data and climatic and environmental variables that are thought to influence transmission, with the exploration and adjustment of the effects of small-scale spatial correlation in the data (this will be discussed further in chapter 3).

1.5.2 Malaria Mapping

The first global malaria endemicity map was produced by Lysenko and Semashko (1968). Endemicity is defined in this study by the splenic index in children ages 2-9 (hypoendemic – 0-10%; mesoendemic – 11-50%; hyperendemic >50%; holoendemic – constantly >75% in children and either high or low for adults depending on the type of malaria). For the first time, a wide range of published literature on malaria was brought together to attempt to create a map of the “primary malaria distribution area”, i.e. the distribution of malaria at its maximum extent (Lysenko and Semashko 1968). This was achieved using information on the various malaria indicators including spleen rate, parasite rate and biting rate in combination with information on the suitability of the climatic conditions for both the malaria vector species and the development of the parasite (Lysenko and Semashko 1968).

Malaria infection was known to be widespread in Africa before Lysenko and Semashko produced maps of malaria distribution and endemicity (Russell 1952). The first estimates of the population living in at-risk areas and the population receiving some form of protection from malaria, both on a continental level and, in particular cases, on a national level were made in the 1950's (Russell 1952; Russell 1956). The first transmission map was produced for Kenya in 1959 (details in Lysenko and Semashko (1968)) detailing the length of the transmission period. This was estimated based on the climatic suitability for the parasites (climatic conditions suitable for parasite development) and some notion of the niche of the vector.

Between the late 1970s and the 1990s, the major public health bodies displayed a lack of interest in malaria control (Nájera et al. 2011), and the WHO's Global Malaria Eradication Programme was abandoned in 1969 (Tanner and de Savigny 2008). Even as late as 2006,

the only global map of malaria was the one produced by Lysenko and Semashko (1968). The late 1990s saw a revival in malaria eradication efforts with the creation of the Roll Back Malaria initiative in 1998 and the Millennium Development Goals in 2000. With this renewed enthusiasm came the call for new malaria maps to be created (Snow et al. 1996). Two important mapping projects were initiated, the Mapping Malaria Risk in Africa (MARA) project which began in 1997 (Le Sueur et al. 1997) and the Malaria Atlas Project (MAP) which was set up in 2005 (Hay and Snow 2006). The projects have collated malaria data from across Africa (MARA - over 10,000 data points) or the whole world (MAP - about 25,000 data points), and the data have been used widely to create a range of malaria maps (Kleinschmidt et al. 2000; Guerra et al. 2006a; Guerra et al. 2006b; Hay et al. 2009; Gething et al. 2010). The first map of malaria in Africa created using this data was by Craig et al. (1999) who adopted a fuzzy logic approach to classify the number of months suitable for transmission to occur based on the climatic suitability. Two of the most commonly used approaches to mapping malaria are: 1) by defining the climatic and environmental limits of the parasite and vector and working out the areas that fall within these limits (Omumbo et al. 1998; Grover-Kopec et al. 2006; Guerra et al. 2006a; Guerra et al. 2006b) or 2) a geostatistical approach. This second approach has been used widely to model malaria prevalence on a global scale (Hay et al. 2009; Noor et al. 2009; Haque et al. 2010; Riedel et al. 2010) and on a national scale (Kazembe et al. 2006). Another approach which has been used to map malaria is maximum entropy modelling (see chapter 2) (Moffett et al. 2007; Foley et al. 2008) which works by using environmental covariates and presence data to estimate the ecological niche of the malaria vector based on the relative suitability of each location in the study area.

1.5.3 Uses of Infection Maps

Infection maps are often produced as a first step in planning a control programme. Mapping exercises conducted in Gambia and Malawi were used to guide intervention programmes, and in the case of Malawi, infection was found to be higher and more widely spread than previously thought (Bøgh et al. 1998; Ngwira et al. 2007). Maps continue to be useful during later stages of a control programme - regular surveying during intermediate stages can help assess the effectiveness of the control strategy, and possibly highlight the need to upscale or downscale control efforts (Gemperli et al. 2006), or reassess the control methods in place (WHO 2010a).

Infection maps can be used to estimate the number of people living in at-risk areas, the number of people infected, or the number of people experiencing chronic disease pathology (Michael et al. 1996a). Estimations of the at-risk population for LF in Africa have varied significantly between studies, with recently reported figures appearing to increase over time possibly due to the effects of both increasing population and better surveillance efforts. In 1992, it was estimated that some 113 million individuals lived in LF endemic areas (WHO

1992), which increased first to 212 million (WHO 2005b) and then 396 million by 2009 (WHO 2009). These estimates, which are normally made by identifying infection positive districts and calculating the number of people in each of these districts, not only take little account of the spatial variation that exists at the local level (Gyapong et al. 2002) but are also highly dependent upon the existence of field surveys covering all relevant endemic areas.

Early reports estimate that 157 million people live in malaria endemic areas (Russell 1956). This figure increased to around 268 million by 1965 (Lysenko and Semashko 1968). The first global map of malaria extent produced since the advent of the RBM initiative estimated that 525 million people were at risk from *P.falciparum* in the WHO AFRO region and 50 million were at risk from *P.vivax* (Guerra et al. 2006a). The first malaria endemicity map estimates 657 million people are living in areas of stable malaria risk, and a further 22 million are living in areas of unstable risk (Hay et al. 2009).

Mapping will play a key role when villages treating with MDA start to reach the endpoint of their control programme. Mapping infection status on a national or regional level will allow programmes to monitor progress and determine whether prevalence has dropped below some threshold such that resurgence is highly unlikely. The WHO guidelines recommend the continuation of MDA whilst there is at least 1 in 3000 children born after the initiation of MDA with circulating filarial antigen (WHO 2005b), however this requires high levels of surveillance. Accurate prevalence maps could be used to make quicker and cheaper decisions about when to cease treatment.

An important consideration in malaria eradication is the resistance of vectors to insecticides (Chandre et al. 1999). Currently, some form of insecticide resistance monitoring is undertaken in 35 of the 43 malaria endemic countries in Africa (WHO 2010a), but maps detailing where different insecticides are used and the resistance levels of mosquitoes are needed for long term vector control programmes

Infection maps can also help us to develop a better understanding of the environmental factors affecting transmission (Brooker and Michael 2000; Lindsay and Thomas 2000), for example: the climatic limits of a species habitat, and the role of key environmental variables in governing ecological traits such as parasite development and survival. Using environmental factors as predictors to produce maps has been used widely for both infection maps (Sabesan et al. 2006; Craig et al. 2007) and vector distribution maps (Lindsay et al. 1998; Bayoh et al. 2001).

1.5.4 Environmental data

The use of interpolated climate data or remote sensing data in combination with advanced statistical techniques to map the distribution of vector-borne diseases has accelerated greatly over the last 25 years (Beck et al. 2000; Kalluri et al. 2007). Remote sensed data is collected by satellites and provides measurements of a collection of environmental factors, such as ground cover or humidity. The benefits of remote sensed data are that the same image can be collected frequently to create both temporal and spatial environmental datasets. The spatial scale of remote sensed data can be extremely fine, down to 1 metre, and the temporal scale can be as frequent as every 30 minutes (Kalluri et al. 2007), although a scale of about 1km collected every couple of days is far more common, and often there is a trade-off between spatial scale and frequency of collection (Kalluri et al. 2007). It has been thought that daily satellite data could be used to develop early warning systems for disease outbreaks (Beck et al. 2000; Zhou et al. 2009).

However, not all climate variables, such as precipitation, can be collected using remote sensing techniques. Proxy variables, such as Normalised Difference Vegetation Index (NDVI), may be more suitable. Although these variables are likely to be highly correlated, using proxy variables could miss some of the subtleties of the climate dependent transmission dynamics. Also, the climate data that is available will be hard to gather during cloudy periods. Infection data is seldom collected daily, or even weekly, so linking this to daily environmental data is not possible and often just one remote sensed image is used as a proxy for the surveying period (Bøgh et al. 1998). Another important issue affecting the use of remote sense data for making infection maps are the difficulties involved with obtaining temporal infection data, without which daily climate data is fairly meaningless.

Interpolated climate data layers are created by collecting large amounts of weather station data which are used to produce climate maps using a smoothing algorithm. One of the most commonly used interpolated climate data sets are WorldClim (www.worldclim.org, Hijmans et al. (2005)). This is a set of data layers of the whole world on a 1km resolution. The variables available are monthly mean, minimum and maximum temperature, monthly precipitation and a set of 19 bioclimatic variables (<http://www.worldclim.org/bioclim>). These maps were created using monthly averaged data over the period 1950-2000 from thousands of weather stations (47,554 locations for precipitation data, 24,542 for mean temperature, and 14,835 for minimum and maximum temperature – www.worldclim.org). The data were interpolated using a second-order spline with altitude, longitude and latitude as independent variables (Hijmans et al. 2005).

The worldclim dataset is useful for infection mapping as the data are freely available on a small spatial scale. The data can be used to create new data layers that describe factors which could be important for vector and parasite dynamics (Martens et al. 1997). For example

minimum temperature in the coldest month or maximum temperature in the hottest month could be used to represent the temperature extremes in a region. The data are averaged over 50 years, which removes the need for temporal infection data, however, the climate surfaces represent average temperature or precipitation and there is no indication of the annual variability which could have a major impact on transmission.

1.6 Malaria and LF transmission models

1.6.1 Brief history of transmission models for infectious diseases

Transmission models have long been used for describing the dynamics of various infections (Hethcote 1994), including HIV (Anderson and May 1992), malaria (Ross 1911), tuberculosis (Blower et al. 1995), measles (Schenzle 1984) and a range of helminth infections (Macdonald 1965; Plaisier et al. 1990; Chan et al. 1998). Models of this type allow us to develop a better understanding of the epidemiology of infection and disease as well as potentially providing insights into different aspects of transmission, such as host immunity or the parasite lifecycle. Importantly, transmission models have been widely used to investigate the impact of control interventions, which is a vital step in assessing their potential effectiveness and determining the best strategies for reducing transmission (Anderson and May 1992).

1.6.2 LF models

Models of LF transmission have been around since the 1960s (Hayashi 1962; Hariston and Jachowski 1968; Vanamail et al. 1989). However, these are all catalytic (compartmental) models where just the status of infection is modelled (Michael 2000). Chan and colleagues developed EPIFIL - the first LF model that captured the intensity of infection in hosts by modelling the worm and microfilaria populations using a set of differential equations (Figure 1.6) (Chan et al. 1998). This is important for modelling the relationship between infection and disease, as an individual's progression to disease is dependent on their worm burden. This model does not explicitly model the larvae stages in the vector - this is captured instead via the force of infection term which determines the number of new worms. Immunity is assumed to be a function of the 'experience' of worm infection which wanes over time, and affects the recruitment rate of new worms (Chan et al. 1998). This model assumes all infected individuals experience lymphatic damage (possibly asymptomatic) which can lead on to lymphodema and hydrocele. EPIFIL was developed further by Norman et al. (2000) to make it fully age structured and to include vector and larval populations. Explicitly modelling the larval population allowed researchers to investigate the impact of vector control on transmission dynamics for the first time. Further developments to this model have explored the immunoepidemiology of LF and how this affects transmission and the progression from infection to disease (Michael et al. 2001).

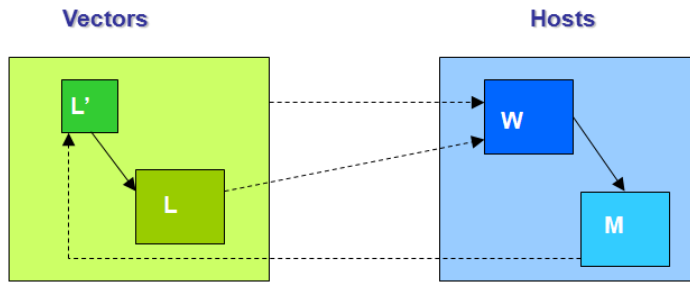


Figure 1.6: Simple LF transmission model. L' is the number of immature larvae, L is the number of mature larvae, W is the number of adult worms and M is the number of mf.

The second commonly used LF model is LYMFASIM (Plaisier et al. 1990) which is a stochastic microsimulation model. The individual life histories of the hosts and parasites are simulated allowing for heterogeneities in, for example, the biting rate. Both models produce similar results, although LYMFASIM predicts slightly fewer rounds will be needed to reduce prevalence below 0.5% possibly due to slightly different model assumptions regarding transmission biology (Stolk et al. 2006). Both these models were originally parameterised for LF transmission by *Cx. quinquefasciatus* mosquitoes in Pondicherry, India although both have now also been parameterised for *Anopheles* mosquitoes in the Pacific region and in Africa (Stolk et al. 2008; Gambhir et al. 2010).

Realistic models of LF transmission dynamics are important for determining the effectiveness of control strategies with different drug combinations and coverage levels, and for predicting the number of years of MDA required to reduce LF prevalence below some predefined elimination threshold (Michael et al. 2004; Michael et al. 2006; Gambhir and Michael 2008)

1.6.3 Malaria models

The first model of malaria transmission developed by Ross in 1911 (Ross 1911) and extended by Macdonald in 1957 (Macdonald 1957) is a compartmental model written as a pair of differential equations describing the number of infective humans and vectors. This model assumes constant host and vector populations and that there is no immunity and no incubation period. The change in infective humans is modelled as the number of people becoming infective minus the number of people clearing infection. The number of new infectives is described as the number of bites by infective vectors on susceptible hosts multiplied by the mosquito to host transmission probability. Similarly the change in infective vectors is modelled as the number of vectors becoming infective minus the number of vectors that die. The number of new infective vectors is described as the number of bites by susceptible mosquitoes on infective hosts multiplied by the human to mosquito transmission probability. This simple model allowed for the very first calculations of the basic reproduction

number (R_0) of malaria, which gave insights into intensity of transmission and the idea of critical threshold below which malaria would die out.

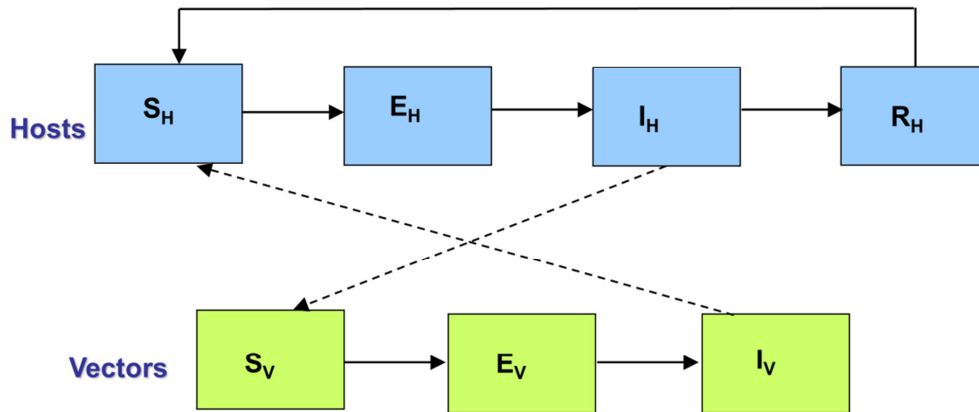


Figure 1.7: Simple malaria transmission model (Anderson and May 1992). S_h , E_h , I_h , R_h are the number of susceptible, exposed (infected but not infectious), infectious and recovered humans respectively. S_v , E_v , I_v are the number of susceptible, exposed (infected but not infectious) and infectious vectors respectively.

Many extensions and additions have been made to this basic model to attempt to more accurately capture different aspects of the epidemiology and control of malaria (Mandal et al. 2011) including the addition of exposed (infected but not infective) compartments for humans (Anderson and May 1992), the addition of an immune function (Aron 1988; Filipe et al. 2007), and the addition of age-dependencies (Anderson and May 1992). more detailed descriptions of immunity (Dietz et al. 1974; Aron 1988), the vector feeding cycle (Le Menach et al. 2007), the role of superinfection (Dietz et al. 1974), the impact of different interventions including mass drug administration (Macdonald et al. 1967), vaccines (Smith et al. 2006), ACTs (Okell et al. 2008), vector control (Worrall et al. 2007) and the modelling of within-host *P. falciparum* dynamics (McKenzie and Bossert 2005) to name but a few examples.

As with all models, there is a trade-off between complexity and simplicity. Complex models with more processes and variables may provide a more accurate representation of the actual biology of the system, however defining functional forms and parameterisation can be problematic. Simplified models may in fact provide a more realistic representation (Koella 1991).

1.6.4 Co-infection model

Modelling the co-transmission of multiple infections has become increasingly popular as evidence of meaningful within-host interactions between parasite species becomes better established (Petney and Andrews 1998; Cox 2001; Booth 2006; Brooker et al. 2007; Cattadori et al. 2008; Graham 2008).

Fenton (2008) developed the first hypothetical microparasite-macroparasite co-infection modelling framework. This combined a simple SI (susceptible – infected) model for the microparasite infection in the host with a macroparasite model that describes the number worms in hosts that are susceptible to and infected with the microparasite. These worms produce eggs that pass into the environment and may subsequently be passed to human hosts where they become adult macroparasites. In this thesis this basic framework is extended to capture the co-transmission of malaria and LF in humans and vectors (see chapter four).

Individually, malaria and LF models have been studied extensively; however a malaria-LF co-infection model has not yet been developed. These two infections are very important in terms of the public health burden they pose and the efforts dedicated to controlling or eliminating their transmission. Any interactions between these infections in the host or the vector could impact the efficacy of any control programme, highlighting the importance of investigating the consequences of co-infection. In the following section we review the evidence of malaria-LF interactions.

1.7 Co-infection of malaria and LF

Studies report that interactions between malaria and LF parasites can affect transmission, both within the host and within the vector (Burkot et al. 1990; Muturi et al. 2008). Infection with both malaria and LF parasites is thought to alter the host immune response (Muturi et al. 2008), which can affect transmission, duration of infection as well as possibly altering the pathology or mortality of either disease (Briand et al. 2005; Graham et al. 2005; Booth 2006). Co-infection in the vector, on the other hand, has been reported to alter vector mortality (Rosen 1955), susceptibility to infection and development of infective parasites within the vector (Burkot et al. 1990; Albuquerque and Ham 1995).

More information about these interactions is needed to better understand the impacts of control strategies. It is thought that reducing the transmission of one disease could have unexpected knock-on effects on the transmission of other infections. For example, LF larvae infected vectors are thought to experience increased mortality, so eliminating LF could increase vector lifespan, allowing them more time to transmit malaria and therefore increase malaria prevalence (Muturi et al. 2008). Or that worm infection could skew the host immune response such that the ability to kill malaria parasite is reduced, prolonging malaria infection.

Despite the growing interest in understanding co-infections in general (Cox 2001; Brooker et al. 2007; Fenton 2008), and between malaria and LF in particular (Muturi et al. 2008; Manguin et al. 2010), a review of all available evidence for the latter is currently lacking. In this section we undertake a review of the literature on reported interactions between malaria and LF, and between malaria and other helminthic infections. We also consider how the host immune response alters as a result of single infection and co-infection, and we hypothesise how these changes could alter transmission and the course of each infection. Finally we consider how interactions between the parasites in the vectors could affect transmission.

1.7.1 Co-infection of malaria and LF in the human

Studies conducted looking at endemic human populations have found increased frequency of malaria attacks in malaria and schistosomiasis infected individuals (Nacher et al. 2002; Sokhna et al. 2004) and malaria and soil transmitted helminth infected individuals (Roussilhon et al. 2010). By contrast, it has been reported that people with schisto-malarial co-infections suffer from fewer attacks, and children with light intensities of schistosomiasis have significantly lower *p. falciparum* densities than worm-free individuals (Briand et al. 2005) (although this relationship did not hold for higher helminth loads). Muturi et al. (2006a) found that LF infection had no significant impact on malaria parasitemia.

The hypothesis that helminth infection increases the frequency of malaria is supported by a study in Madagascar where one cohort of children were treated with an anthelmintic drug and the second cohort were untreated; over two years, there was a 60% decrease in the incidence of malaria and the parasite density in the cohort that received treatment (Druilhe et al. 2005).

Data on the prevalence of concurrent infections of malaria and LF in humans is fairly sparse. Table 1.1 shows studies reporting LF, malaria and co-infection prevalence.

malaria (%)	LF (%)	co-infection (%)	Individuals tested	Source	Country
33.3	52.8	17.6	36	Chansiri et al. (2001)	Myanmar
66.9	33.9	25.0	517	Mehlotra et al. (2010)	PNG
36.4	16	4.3	94	Muturi et al. (2006a)	Kenya
17.4	2.8	0.0	107	Muturi et al. (2006a)	Kenya
10.1	9	0.33	1815	Ravindran et al. (1998)	India
35.3	18.3	11.1	578	Mboera et al. (2011)	Tanzania
35.8	0.5	0.15	51448	Ghosh and Yadav (1995)*	India

Table 1.1: Number of people infected with Malaria and *Wuchereria bancrofti* (*- daytime blood collection)

Studies investigating malaria and LF prevalence, but not co-infection prevalence, indicate a positive correlation between the two infections and that on average malaria prevalence is higher than LF prevalence (Wharton et al. 1963; Matola 1985)

Laboratory studies using murine models have been fairly widely used to investigate malaria-helminth interaction, and although no studies have been conducted looking at *wuchereria bancrofti* and *plasmodium falciparum*, we can look at studies between similar parasites.

A meta-analysis of 54 experiments using laboratory mice to investigate the effects of malaria parasite density with helminth infection which suggested that the direction of the effect is dependent on the parasite species pair (Graham 2008). There was no change in microparasite density in 27% of the studies, 23% found microparasite density decreased as a result of co-infection and 50% found an increase in density. *Brugia pahangi* and *Ascaris* infected mice have been found to experience protection against cerebral malaria (Yan et al. 1997; Nacher et al. 2000). However mice infected with *Plasmodium chabaudi chabaudi* and *Litomosoides sigmodontis* had a more severe course of infection (Graham et al. 2005). Similarly, mice with malaria-schistosomiasis infections were reported to have increased severity of the malaria infection and slower reduction in parasitemia (Legesse et al. 2004). Species pairs which induce anaemia in the host tended to have lower peak microparasite densities (Graham 2008) - we could find no evidence that LF induces anaemia.

1.7.2 Co-infection and host immunity

The altered immune response in co-infected human hosts is thought to be a result of interactions between the cytokines induced by malaria and filaria parasites. Cytokines are proteins secreted by the immune system that carry signals to cells, mediating and regulating immunity, inflammation and the development of blood cells. They are commonly divided into two categories: type 1 and type 2. Malaria is associated with a Th1 response, with increases in the production of type 1 cytokines, including IFN- γ and TNF- α (Graham et al. 2005), which stimulate immunity and can result in extreme inflammatory responses. When an individual becomes infected with malaria, IFN- γ production increases and a series of immune reactions are triggered which can result in the death of intracellular parasites (Malaguarnera and Musumeci 2002). Macrophages are stimulated which can kill protozoa and induce other cytokines such as TNF- α , IL-12 and IL-18; IL-12 stimulates the further production of IFN- γ and TNF- α as well as natural killer cells. It also helps build protection against parasitic infections. IL-18 can induce immunity as well as induce IFN- γ and TNF- α . TNF- α is anti-parasitic at low levels (Malaguarnera and Musumeci 2002).

For LF, the immune response is initially Th1 biased as a response to the incoming larval antigens (Pearce et al. 1991) with increased production of IFN- γ and parasite antigen which

causes inflammation and protects against the incoming larvae (Yazdanbakhsh 1999). The strength of this initial Th1 response depends on whether the individual is already infected, with uninfected individuals mounting a stronger response (Yazdanbakhsh 1999). Shortly after, a Th2 response is induced, in particular the cytokines IL-4, IL-10, IL-5, IL-13 and TGF- β , as well as increased levels of immunoglobulin E (IgE) which produces strong antibody responses and act to limit and contain infection (Maizels et al. 2004; Graham et al. 2005; Hartgers and Yazdanbakhsh 2006). Filarial worms can live for years in the human host; this is achieved by downregulating immune responses, meaning they are unable to mount an attack on the parasite (Maizels 2009). This allows the adult parasite to survive whilst restricting establishment of new infections and causing minimal damage to the host (de Almeida and Freedman 1999). In fact, most hosts infected with LF are asymptomatic, meaning they tolerate the parasite with no ill effects (Maizels et al. 2004).

The two arms of the host immune response, Th1 and Th2, are thought to be mutually inhibitory (Abbas et al. 1996), and the interaction between them could have a significant impact on the course of infection for LF and malaria. Helminth infections are thought to impair the type 1 dependent control of a malarial infection (Graham et al. 2005; Metenou et al. 2009) because the anti-inflammatory cytokines IL-10 and IL-13, which are associated with helminth infection (Hartgers et al. 2009), inhibit the production of Th1 cytokines such as IFN- γ (King et al. 2001; Doan et al. 2007) which can suppress the immune response against malaria (Su et al. 2005; Hartgers et al. 2009). Conversely, Th1 cytokine IFN- γ is also thought to inhibit the production of Th2 cytokine IL-4 (Malaguarnera and Musumeci 2002).

A Th2 response is induced by filarial worms and microfilariae (mf), so heavier worm burden could skew the immune system firmly in favour of a Th2 type response (King 2001). Anti-inflammatory cytokines IL-10 and TGF- β are up-regulated as a result of filarial infection (Lawrence and Devaney 2001; Hartgers and Yazdanbakhsh 2006) which protects the host against inflammatory impacts of disease, but may enable the prolonged survival of the worms, mf and malaria parasites, as well as potentially worsening the course of infection (Lawrence and Devaney 2001; Graham et al. 2005; Su et al. 2005; Hartgers et al. 2009).

Overproduction of the malaria induced Th1 cytokines IFN- γ and TNF- α can make the infected individual more likely to experience severe malaria pathology (Day 1999), so a LF induced downregulation in their production as a result of a proliferation in the Th2 response could protect against the most dangerous symptoms of malaria (Maizels et al. 2004). However, the development of antimalarial immunity is slowed down by helminth infections (Druilhe et al. 2005; Booth 2006), reportedly because co-infection suppresses the immune responses to malaria (Su et al. 2005). Studies on the production of immunity suppressing cytokines TGF- β and IL-10 in mice with a single infection or a co-infection of malaria and nematode parasite

Heligmosomoides polygrus show that co-infected mice had higher levels of TGF- β and IL-10 than mice with just malaria (Su et al. 2005).

Metenou and colleagues (2011) analysed T-cell responses of individuals with and without filarial infection that also had asymptomatic *plasmodium falciparum* infection. They found higher frequencies of CD4⁺ T cells producing IL-4, IL-10 and IL-17 in filarial patients. It is also reported that co-infected individuals had lower CD4⁺ cells producing IFN- γ , TNF- α and IL-17A, and lower malaria antigen specific Th1, Th17 and TNF- α than individuals with a single malaria infection.

Mice with *S. mansoni* that were infected with malaria were found to have higher parasitemia than mice with just malaria. Schistosome specific antigen, IgG and IgM levels were depressed for up to one month after infection and TNF- α levels were lower in co-infected mice, but IFN- γ levels were unaffected (Helmby et al. 1998).

Analysing antibody responses to co-infection has been used as an alternative to cytokine responses to explore the response of the immune system. It has been reported that worm infection could delay the development of malarial immunity by decreasing cytophilic antibodies IgG1 and IgG3 which are associated with protection from malaria, and an increasing in non-cytophilic antigen IgG4 which is non-protective (Roussilhon et al. 2010).

Fairlie-Clarke et al. (2010) investigated Th1 induced IgG2a and Th2 induced IgG1 antibodies in a murine model. Reduced IgG2a production was reported in co-infected mice compared to malaria infected mice, and was put down to Th1 suppression caused by the helminth. This study also found cross-reactive responses to both malaria and helminth antigens, suggesting that the antigen specific reactions must be carefully picked apart from the cross-reactions when using antibody responses as a proxy for Th1/Th2 responses. Elsewhere, worm infection has been reported to induce IgE and IgG1 responses, whereas mf are thought to induce all IgG subclasses as well as IgE (Lawrence et al. 1994).

The immune response to LF will be dependent on the disease state. Some individuals are microfilaremic, but have no clinical manifestations of infection, and at the other end of the spectrum there are individuals with chronic LF diseases who have no circulating microfilariae. Studies have shown that amicrofilaremic individuals with chronic pathologies have greater lymphocyte proliferation, and higher levels of IFN- γ and IgG antibodies than asymptomatic individuals (Ottesen 1989). In particular, chronically affected patients have higher levels of IgG1, IgG2 and IgG3 antibodies to filarial antigen than asymptomatic individuals, but have lower levels of anti-filarial IgG4 (Hussain et al. 1987). Also, the asymptomatics have higher levels of Th2 associated cytokines IL-4 and IL-5 (Ottesen 1992).

An unpublished study (reported by Maizels et al. (2004)) infected mice with *Litomosoides sigmodontis* and then *P.chabaudi* merozoites. Around half the mice were found to have fertile adult worms but no circulating mf (known as 'occult' filariasis). This amicrofilaremic group were found to experience a greater severity of malaria than mice with single malaria infection and mice with circulating mf (MF⁺). It was suggested that mf⁺ mice did not experience increased malaria severity as a result of co-infection because the pro-inflammatory response was downregulated.

Different cytokines are responsible for different aspects of the immune response to LF (Volkman et al. 2003; Maizels et al. 2004). A study looking at the roles of IL-4 and IL-5 in worm development in rodents reported that IL-5 deficient mice had increased development of L3 larvae to worms and increased worm mortality. IL-4 knockout mice experienced higher levels of mf (Volkman et al. 2003). A downregulation in the Th2 response as a result of malaria infection could therefore reduce IL-4 and IL-5 production and lead to increased worm development and mf in the blood, but also increased worm mortality. Lawrence et al. (1994) conducted a study looking at immune responses of mice to *Brugia malayi* worms and mf. They found that mf infected mice produced low levels of IL-4 initially, but this increased over time and mice implanted with worms had consistently high levels IL-4. Worm infected mice were reported to have low levels of IFN- γ production, but MF⁺ worms had high levels. The mf induced cytokine production was found to be independent of mf density.

A diagram outlining some of the possible interactions governing the host immune response to malaria and LF co-infection is presented in Figure 1.8.

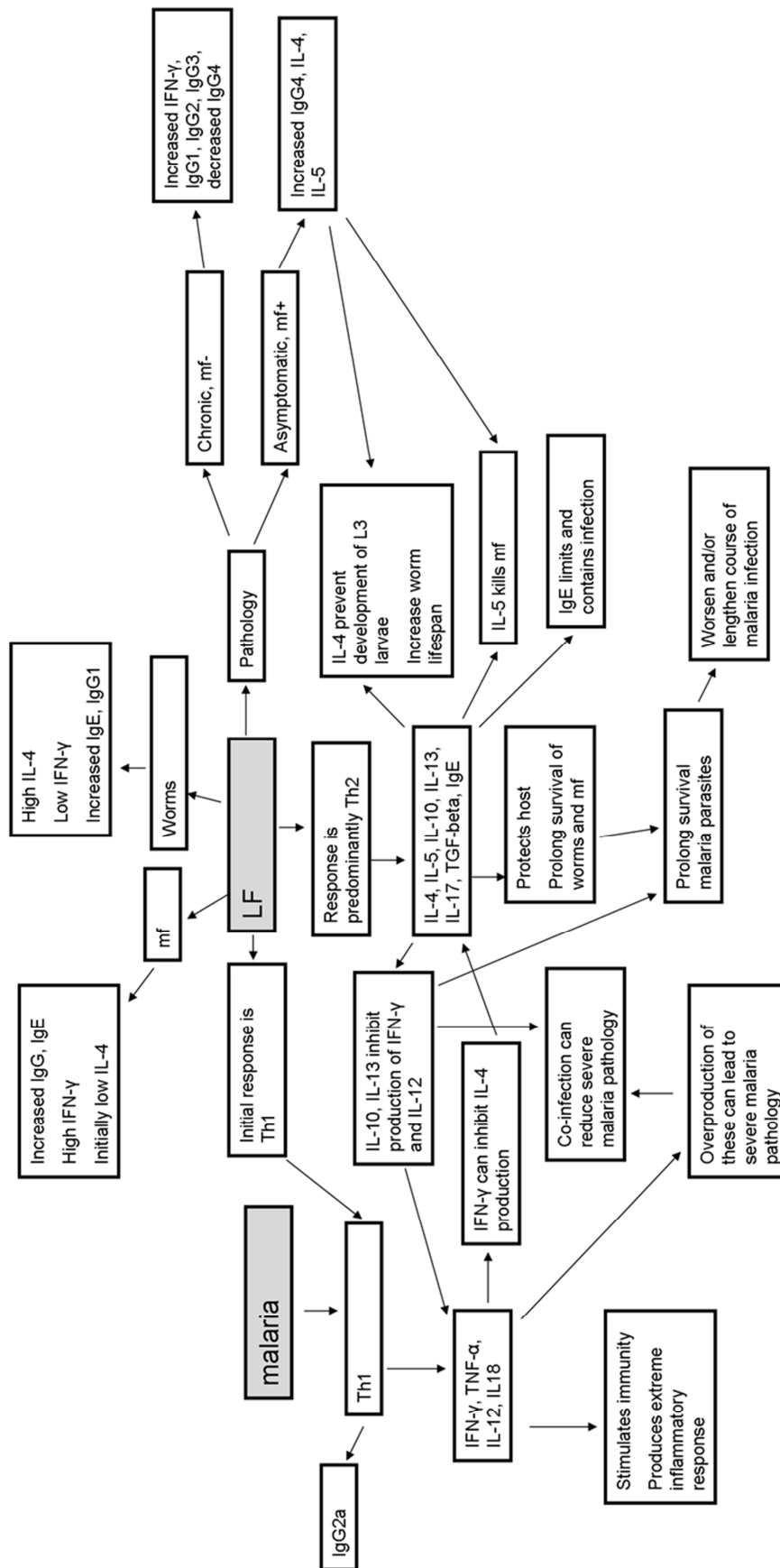


Figure 1.8: Diagram showing some of the possible Th1/Th2 interactions

The order in which a co-infected individual acquires malaria and LF could influence the immune response. If an individual is already infected with LF, for example, their immune response is Th2 skewed. If the individual then becomes infected with malaria, the immune system may not be able to instantly alter the response to become more Th1 biased, meaning the sufferer may experience more severe malaria symptoms and a longer course of infection, and also the filarial worms may survive longer. On the other hand, an individual with an existing malaria infection has a Th1 skewed response. A new LF infection initially causes a Th1 immune response – the immune system is already geared in this direction, meaning the individual may have a greater ability to kill off the LF parasites become infection is properly established. The level of acquired immunity to malaria will also have an impact on the host immune response; individuals with higher levels of acquired immunity are thought to have less Th1 skewed immune responses compared to malaria-susceptible individuals (Doolan et al. 2009). Therefore, new LF infections may be relatively more successfully established in malaria-immune individuals as the immune response is less Th1 skewed, and individuals with low acquired immunity to malaria (including children) may experience some degree of protection from LF infection.

1.7.2 Co-infection in the vector

Mosquitoes have been found carrying both infections simultaneously (Muirhead-Thomson 1953; Burkot et al. 1990) and *Anopheles* are thought to be the primary vector for both infections in rural and peri-urban environments (Manga 2002). Currently the effect of co-infection in these vectors is poorly understood, and a better understanding is needed because interactions between the parasites within the mosquito could have an impact on transmission cycles of both infections.

Co-infection is thought to affect the survivorship of the mosquito (Burkot et al. 1990), in particular LF vectors are reported to experience larval-dependent mortality (Rosen 1955; Lindsay and Denham 1986), implying that they have a shorter lifespan, and therefore a reduction in the probability that they will survive long enough to transmit malaria (Muturi et al. 2006b; Muturi et al. 2008). Malaria parasite–vector combinations commonly seen in the wild are not thought to induce excess mortality, however, sporozoite infected vectors have been reported to bite more frequently, increasing the risk of biting-related mortality (Anderson et al. 2000; Ferguson and Read 2002).

There is evidence that *Culex* mosquitoes experience increased mortality with increased larval density (Jordan and Goatly 1962; Samarawikrema and Laurence 1978; Hawley 1985). Krishnamoorthy et al. (2004) reported that *Culex* mosquitoes that fed on an microfilariae

positive host had a 21% higher mortality than mosquitoes that fed of a mf negative host. Another study reported increased mortality in LF infected *Culex* mosquitoes, where around 90% of uninfected vectors and 72% of infected vectors survived 16 days after taking a blood meal under laboratory conditions (Lindsay and Denham 1986).

There is little published data on larval dependent mortality in *Anopheles* mosquitoes. Michael et al. (Michael et al. 2009) identified only seven datapoints from three studies looking at vector survival and mf density per mosquito, and found no significant relationship.

A study in Papua New Guinea found that co-infected vectors are more common than would be predicted from the prevalence of single infections (Burkot et al. 1990), suggesting that infected vectors are more susceptible to other infections.

Infection with *wuchereria bancrofti* is thought to increase the susceptibility of the mosquito to *plasmodium* infection as the migration of the mf disrupts the midgut, allowing the *plasmodium* easier access through the midgut en route to the salivary glands (Burkot et al. 1990). Studies have found that *w.bancrofti* infected vectors have a higher malaria sporozoite rate than larvae-free vectors (Muturi et al. 2006b; Muturi et al. 2008) suggesting that malaria infections are enhanced by filarial infections. Similarly, there is also evidence suggesting that *plasmodium* infected mosquitoes have higher numbers of *w.bancrofti* parasites (Albuquerque and Ham 1995; Muturi et al. 2006b; Muturi et al. 2008).

On the contrary, laboratory experiments looking at helminth-*plasmodium* co-infections in *Armigeres subalbatus* and repeated in *Aedes aegypti* mosquitoes reported a lower intensity of oocysts in co-infected vectors (Aliota et al. 2010). When mosquitoes were fed on an LF and malaria infected gerbils, the development of the *plasmodium* was negatively affected and the mean intensity of oocysts was lower, possibly because the filarial larvae traverse the midgut much quicker than the *plasmodium*, activating an immune response that acts against the malaria parasites.

Another study looking at the distribution of oocyst in co-infected vectors found approximately 14% of vectors with just malarial infections had 10 oocysts, and 31% had 50 oocysts, whereas in coinfecting vectors, 31% had 10 oocysts and 14% had 50 oocysts (Albuquerque and Ham 1995), possibly indicating impaired development of the malaria parasites in co-infected vectors.

Co-infection has been reported to affect the size and development of both larvae and oocysts in the vector, with co-infection delaying the development of larvae by up to 30% (Albuquerque and Ham 1995). It can also lead to a reduction in the numbers of parasites; in particular, a study found the mean L3/mosquito in a vector with co-infection was 4.6, whereas the mean

L3/mosquito in a vector with just a filarial infection was 5.8 (Albuquerque and Ham 1995). It is fairly common to find mosquitoes with sporozoites and immature, deformed L1 or L2 larvae, but much less common to find mosquitoes with sporozoites and infective L3 larvae (Muirhead-Thomson 1953). A study conducted in Tanzania found that of 3242 *Anopheles* caught and dissected, 0.4% had sporozoites. 5.6% had filarial infections, but only 0.5% had infective L3 larvae (Mnzava et al. 1989). Most of the infective larvae were found in *A.gambiae* mosquitoes, where 1.4% of vectors had infective L3, much higher than *A.funestus* (0.5%) and *A.arabienis* (0%) (Mnzava et al. 1989). Muturi et al. (2006b) found similar results, whereby 3% of *A.gambiae* had infective larvae, but only 1% of *A.funestus* had infective larvae.

Vectors with infective sporozoites and filarial larvae are uncommon in nature. Of 426 *A.gambiae* dissected in Tanzania, 41 had sporozoites, 14 had infective larvae, but only 1 was coinfecting (Muirhead-Thomson 1953). A study in Papua New Guinea dissected 1454 mosquitoes, and although some had sporozoites and L1 or L2 larvae, none had sporozoites and infective L3 larvae (Burkot et al. 1990). Co-infections were found in 1.15% of vectors dissected as part of a study in Kenya (22 out of 1919), but only 10.5% of these co-infected vectors had sporozoites and L3 larvae (Muturi et al. 2006a).

It is possible for a vector to contract malarial and filarial parasites from a single bite and become infective for both diseases as shown by Muirhead-Thomson in (1953), where mosquitoes were fed upon a child infected with malaria and *w.bancrofti* and after 10 days, of the 49 surviving vectors, one had sporozoites and infective L3 larvae.

Generally, mosquitoes will only carry a single infection. However, as discussed above, a vector can carry both parasites – either by becoming infected with both parasites simultaneously (i.e. from a single bite on a co-infected host), or by becoming infected with each infection in successive bloodmeals. The order in which a co-infected vector becomes infected could alter the passage and development of the parasites. For example, a malaria parasite is likely to have an easier route to the mosquito salivary gland if the vectors midgut has already been disrupted by *wuchereria bancrofti* parasites compared to a malaria parasite making its way through the vector at the same time as LF parasites.

The findings discussed in this section will be used to define the interactions effects between LF and malaria in the vector and the host in the co-infection model presented in chapter four.

1.7 Structure of the PhD

In Chapter 2 a maximum entropy modelling approach is used to map the distribution of lymphatic filariasis in Africa. Predictions are made based on inferred relationships between environmental variables and LF occurrence data, and are used to estimate the number of people living in areas at-risk of LF currently and in 2050.

In chapter 4 a generalised linear spatial modelling approach is adopted to predict the prevalence of LF and malaria. These maps are then used to identify areas of co-infection in Africa. A Bayesian model selection procedure is used in this chapter to determine which predictive variables are used in the final analysis. The maps produced in this analysis are used to estimate the number of people with a single infection and the number of people with malaria and LF co-infections.

Chapter 4 shows the development of a malaria-LF co-infection transmission model. The model describes the individual dynamics of each infection and the interactions between the two. Various interaction scenarios between LF and malaria in the host and in the vector are considered and used to investigate how the presence of one infection affects the transmission of the other.

Finally in chapter 5 the co-infection model developed in chapter 4 is used to investigate the impact on prevalence and disease elimination of a range of control interventions. The costs of a control programme and the benefits of preventing infection and disease are estimated and cost-benefit measures are defined and applied to range of control strategies in an attempt to determine the 'optimal' strategy. Maps detailing the 'optimal' strategy for malaria and LF control are developed based on the cost-benefit estimates produced by the co-infection model and the pre-control prevalence levels given by the co-infection map presented in chapter three.

Chapter 2

Modelling the current and future distribution of Lymphatic Filariasis in Africa using Maximum Entropy Ecological Niche methods

2.1 Introduction

The role of risk mapping in describing the spatial patterns of infection and guiding the planning of parasite control is now well-established, and has been demonstrated for a range of major parasitic diseases, including malaria (Hay et al. 2000; Rogers et al. 2002), trypanosomiasis (Rogers and Randolph 1993; Robinson 1998), schistosomiasis (Brooker 2007; Clements et al. 2008), onchocerciasis (Richards 1993), and lymphatic filariasis. It has led to an increased understanding of the climatic and environmental ecology of parasitic infections (Brooker and Michael 2000; Lindsay and Thomas 2000), including improving appreciation of species thermal tolerances and the impact of key environmental variables on ecological traits that affect transmission, such as parasite development and survival rates. More recently, focus in parasite distribution modeling has expanded to evaluating the potential for the establishment and spread of invasive vector species (Hartley et al. 2006; Ward 2007; Roura-Pascual and Suarez 2008) and assessing parasite or vector species responses to global climate change (González et al. 2010).

Although attempts have been made in the past to map LF distribution in Africa, this has either been based on simply displaying infected sites as points or as ranges interpolated between such points on local-level maps (Casaca 1966; Juminer et al. 1971; Lamontellerie 1972; Brinkmann 1976; Wijers 1977; Thompson et al. 1996; Sowilem et al. 2006), geostatistical modelling of point prevalence data at regional levels (Sabesan et al. 2000; Srividya et al. 2002) or mapping of aggregated levels of infection at various within and between country or

regional levels (Michael and Bundy 1997; Meyrowitsch et al. 1998; Sabesan et al. 2000). The exception has been the work of Lindsay and Thomas (2000), who used published community LF prevalence data in conjunction with climate layers and a logistic regression model to predict the distribution of LF and refine the first estimates of the population at risk across sub-Saharan Africa (Michael and Bundy 1997).

These statistical modelling approaches have been important in describing and delimiting geographic ranges of species distributions, however, recent studies have highlighted several limitations of applying these models to mapping parasite distributions. First, simple statistical models, such as logistic regression, are restricted because they often fit linear functions between environmental variables and presence/absence data, when it is most likely that such associations are highly complex and non-linear (Brooker and Michael 2000; Lawler et al. 2006). Second, it is difficult using these methods to address complex interactions between such variables (Austin 2002; Pearce and Boyce 2006). Finally, using absence data in logistic regression modelling of LF distribution is complicated by the unreliability of such data owing to the use of variable blood volumes for diagnosing mf infection (Michael et al. 2008). The key problem here is that any “absence” record may either represent a true absence of infection (implying non-suitability of location) or arise as a limitation of parasite detectability, whereas if infection is recorded as being present in a location, it is fairly certain that it occurs there.

In this chapter, the distribution of LF in Africa is mapped using a machine learning approach. This method models complex non-linear dependencies between infection presence and predictor variables in multidimensional space, and allows us to better understand the ecological niche and to construct a more reliable map of the potential distribution of LF in Africa (Guisan and Thuiller 2005; Pearce and Boyce 2006; Peterson 2006; Peterson et al. 2007). Such ecological niche models predict the geographic range of a disease or species by: (1) finding correlations between presence data and environmental covariates, (2) using these relationships to characterise the environmental requirements of the species, and (3) deploying this information to predict suitable habitats over unsurveyed areas. This approach has traditionally been used to predict the geographic range of species (Soberon and Peterson 2005; Peterson 2006), but more recently it has been used to model the distribution of diseases (Anderson et al. 2003; Moffett et al. 2007; Holt et al. 2009).

There are currently a wide array of algorithms that can be used to model species' ecological niches using machine learning approaches (Segurado and Araújo 2004; Olden et al. 2008). In this study, we evaluated Maxent, a presence-only maximum entropy-based niche modelling technique (Phillips et al. 2006), to describe the ecological requirement and current potential distribution of LF in Africa, and to determine for the first time how future climate change may affect the distribution and burden of this disease on the continent so that better prevention and control efforts could be directed to mitigate against the effects of such change.

2.2 Methods and Materials

2.2.1 LF Occurrence Data

Point data for LF occurrence or presence were collated from community surveys published in the research literature dating from 1940 to 2009, using the online and manual search procedures described in Michael et al. (1996). Studies were selected if the surveys described the number of people surveyed, the number positive for microfilaraemia, and were conducted at a specific community site. We found a total of 664 community-specific datapoints of which 508 comprised presence data. These were used in the present analysis (see details of selected studies in Appendix A). Geo-coordinates for each chosen datapoint were either referenced from information given in the literature or by using Google Earth (see Figure 2.1). We were unable to find lat long data for 19 data points found in the literature review, and approximately 21% of the data locations used were only expressed to 2 decimal places (using decimal degrees).

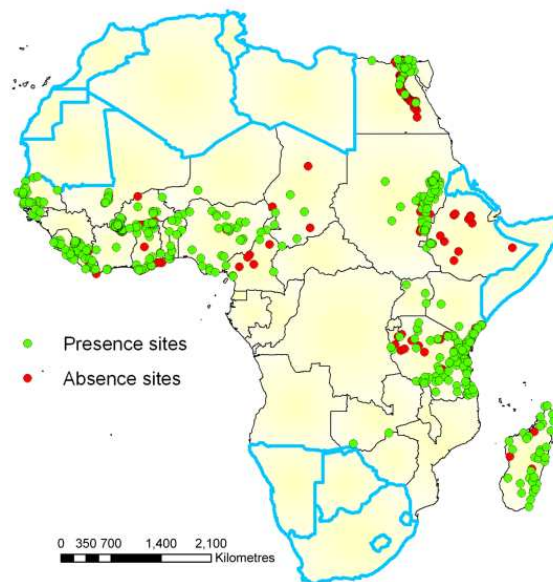


Figure 2.1: Locations of study sites. Green points show sites where LF infection was found to be present and red sites show sites where it was absent. Non-endemic countries are outlined in blue.

2.2.2 Environmental Layers

Initially ten environmental and demographic variables believed to influence the transmission of LF were selected for this analysis (Table 2.1) (Lindsay and Thomas 2000). Population density is not employed as a predictor in most previous studies of pathogen distribution modelling, however we view it as a key determinant of the potential distribution of LF for two

reasons: 1) is a component of the reproduction number for LF which determines the spread and prevalence of infection and 2) LF can only occur in habited places as the humans are the only host reservoir of the LF parasite in Africa (Anderson and May 1992; Hales et al. 2002; Moffett et al. 2007; Mills et al. 2010).

The use of interpolated climate data or remote sensing data in combination with advanced statistical techniques to map the distribution of vector-borne diseases has accelerated greatly over the last 25 years (Beck et al. 2000; Kalluri et al. 2007). In this chapter the worldclim data set is used (www.worldclim.org, Hijmans et al. (2005)) – see section 1.5.4 for more details. Uncertainty in the data can arise from inaccurate weather station data or from the interpolation method – this second effect will be magnified in areas with sparse weather station data. Precipitation data are fairly densely distributed in Africa; however, temperature data is much sparser. There are very few data points in areas with low population density, particularly in the Sahara and Central Africa (Hijmans et al. 2005). This uncertainty must be taken into consideration when assessing the accuracy of the predictions from the Maxent model.

The worldclim dataset is useful for infection mapping as the data are freely available on a small spatial scale. The data can be used to create new data layers, for example minimum temperature in the coldest month, or maximum temperature in the hottest month, to represent the temperature extremes in a region which could be important for vector and parasite dynamics (Lardeux and Cheffort 1997; Craig et al. 1999). One major drawback is that the climate surfaces represent average temperature or precipitation and hence there is no indication of the annual variability which could have a major impact on transmission dynamics.

Altitude data are from www.worldclim.org; these data were collected by <http://www2.jpl.nasa.gov/srtm/> and produced from data collected by a radar system circulating the earth to create a high resolution map of the globe.

NDVI data are downloaded from <http://edit.csic.es/GISdownloads.html>, these maps were originally obtained from satellite images (NOAA-AVHRR) over the entire globe. Twelve monthly NDVI maps are available, each of which represents the mean monthly NDVI over an 18 year period from 1982 to 2000. We averaged these maps to produce an annual mean NDVI map.

Population density data were obtained from <http://sedac.ciesin.columbia.edu/gpw/>. These data are created by interpolating global census data to create smooth population maps which are then scaled to match United Nations totals.

The data had slightly different scales (worldclim data ~ 9km x 9km, NDVI ~ 12km x 12km and population density ~ 5km x 5km), and so were resampled using ArcGIS to give all the layers the same grid size. This resulted in a scale of around 12km x 12km.

Environmental Variables	Source	Details
Altitude	http://www.worldclim.org	-
NDVI	http://edit.csic.es/GISdownloads.html	-
Annual mean temperature	http://www.worldclim.org	Mean of average monthly mean temperature across all 12 months
Mean maximum temperature	http://www.worldclim.org	Mean of average monthly maximum temperature across all 12 months
Mean temperature in warmest month	http://www.worldclim.org	Maximum of the 12 average monthly maximum temperature layers
Mean minimum temperature	http://www.worldclim.org	Mean of average monthly minimum temperature across all 12 months
Mean temperature in coldest month	http://www.worldclim.org	Minimum of the average monthly minimum temperature layers
Mean annual precipitation	http://www.worldclim.org	Mean of average monthly precipitation across all 12 months
Precipitation in wettest month	http://www.worldclim.org	Maximum of the 12 average monthly precipitation layers
Population density	http://sedac.ciesin.columbia.edu/gpw/	-

Table 2.1: Climate, altitude and population variables used in the analysis

2.2.3 Ecological Niche Modelling

The ecological niche of a species can be defined as those ecological conditions under which it can maintain populations without immigration (Grinnell 1917). Ecological niches and associated potential geographic ranges can be approximated using correlative approaches that relate known point-occurrence data to digital GIS data layers to summarize spatial variations in these layers in multidimensional environmental space (Guisan and Zimmermann 2000). Here, the maximum entropy method, as implemented by the Maxent software, is used to derive the ecological niche for LF occurrence in Africa. We initially compared the performance of Maxent with another widely used ecological niche modelling package GARP (Stockwell 1999).

Maxent is a general-purpose machine learning programme and has been widely used to predict species distributions (Phillips et al. 2004; Phillips et al. 2006; Peterson et al. 2007; Phillips and Dudik 2008). Maxent essentially builds ecological niche models by quantifying the unknown probability distribution defining a species' occurrence or distribution across a study area without inferring any unfounded information about the distribution. The approach aims to find the probability distribution of maximum entropy (that which is closest to uniform) subject to constraints imposed by the observed distribution of the species and environmental conditions across the study area. Maxent outputs the maximum entropy distribution that satisfies these constraints, thereby providing the least biased description for a given dataset (Jaynes 1957; Phillips et al. 2006). Here, Maxent models using version 3.3.1 of the software

developed by S. Phillips and colleagues were implemented to map LF (<http://www.cs.princeton.edu/~schapire/maxent/>). Selection of the convergence threshold and regularization values was carried out following default rules and the number of iterations was chosen such that all models converged. The default logistic model was used to ensure that predictions gave estimates between 0 and 1 of the probability of infection presence per map pixel.

2.2.4 Mathematical Formulation

Let the study area be denoted by X where $x_1, x_2, \dots, x_m$ are study sites or cells in X . There is a probability distribution π that fits a value $\pi(x)$ to every cell x in the study area. The maxent algorithm finds the distribution $\hat{\pi}$ that best approximates the actual distribution π . The best approximation $\hat{\pi}$ is the maximum entropy distribution. Entropy, $H(\pi)$, is given by

$$H(\pi) = - \sum_{x \in X} \pi(x) \ln(\pi(x))$$

So $\hat{\pi}$ is the distribution that maximises the above equation.

Denote the environmental variables $\underline{\theta} = (\theta_1, \theta_2, \dots, \theta_n)$ where each $\theta_i : X \mapsto \mathbb{R}$ is the vector of values for the i^{th} variable over the whole study area; so $\theta_i(x_j)$ is the values of the i^{th} variable at the j^{th} location.

The expected value of θ_i under the distribution π is denoted

$$\pi[\theta] = \sum_{x \in X} \pi(x) \theta_i(x)$$

We do not know $\pi[\theta_i]$ directly but it can be estimated by taking a sample of the known occurrence data points $x'_1, x'_2, \dots, x'_p$ from X according to π and calculating the mean value of the environmental variable θ_i at each x'_j according to

$$\tilde{\pi}[\theta_i] = \frac{1}{p} \sum_{j=1}^p \theta_i(x'_j)$$

so $\tilde{\pi}$ is the empirical distribution. We want the approximated distribution $\hat{\pi}[\theta_i]$ to be close to the empirical expectation $\tilde{\pi}[\theta_i]$.

When $\tilde{\pi}[\theta_i] = \hat{\pi}[\theta_i]$, i.e. the empirical distribution is equal to the best approximation distribution, then $\tilde{\pi}$ is the maximum entropy distribution. However, finding a distribution $\tilde{\pi}$ that satisfies this constraint can lead to overfitting, i.e. where the model is so closely fitted to the data used to build it that it doesn't generalise well over new data.

A more parsimonious model can be found by allowing an error band, β , known as the 'regularisation parameter'. The error of each individual environmental variable is controlled by this parameter β by the formula $\beta_j = \beta \sqrt{s^2[\theta_j]/m}$, so the difference between the estimated and the empirical expectations of variable i is constrained by β_i

$$|\tilde{\pi}[\theta_i] - \hat{\pi}[\theta_i]| \leq \beta_i$$

The maximum entropy distribution is equivalent to the maximum likelihood Gibbs distribution. If we assume, for simplicity, that we are only employing linear features to model the relationship, then

$$q_\lambda(x) = \frac{\exp\left(\sum_{j=1}^n \lambda_j \theta_j(x)\right)}{Z_\lambda} \quad [1]$$

So $q_\lambda(x)$ is the relative suitability of disease occurrence in each cell (rather than the actual probability of occurrence) at each location x , Z_λ is a normalising constant such that $\sum_{x \in X} q_\lambda(x) = 1$ and λ is a vector of weights corresponding to the environmental variables.

Maximising the likelihood of [1] with the regularisation parameter β_j is equivalent to finding the distribution q_λ that maximises the penalised log likelihood (Phillips and Dudik 2008)

$$\frac{1}{m} \sum_{i=1}^m \ln(q_\lambda(x_i)) - \sum_{j=1}^n \beta_j |\lambda_j| = \frac{1}{m} \sum_{i=1}^m \sum_{j=1}^n \lambda_j \theta_j(x_i) - \ln Z_\lambda - \sum_{j=1}^n \beta_j |\lambda_j| \quad [2]$$

So the distribution q_λ that maximises [2] is the best approximation, $\hat{\pi}$, of the maximum entropy distribution.

The value of λ that maximises [2] is found using a sequential update algorithm. One value λ_j of the vector $\underline{\lambda} = (\lambda_1, \lambda_2, \dots, \lambda_n)$ is updated at a time. Assume that we start with $\underline{\lambda} = (0, 0, \dots, 0)$, so $\hat{\pi}$ is a uniform distribution. Each λ_i is altered sequentially and the penalised log likelihood is calculated at each step, the iterative procedure on the λ 's

continues until the change in log likelihood falls below the convergence threshold or the maximum number of iterations has been performed.

The resulting distribution q_λ is the maximum entropy distribution. As stated above, $\sum_{x \in X} q_\lambda = 1$. The probability of occurrence in each cell is calculated by summing up the combined values in all cells that have equal or lower probabilities.

$$\pi(x) = \sum_{y \in Y} q_\lambda(y) \times 100 \quad \text{where } Y = \{y \in X : q_\lambda(y) \leq q_\lambda(x)\}$$

The value at each cell, $\pi(x)$ is the probability that the disease occurs at location x or it can be thought of as an index of environmental suitability (Phillips et al. 2006).

The above formulation is a slightly simplified version of the full model (only linear features are used). The more complex model takes into account a variety of functional forms to capture the relationship between the data points and the environmental variables.

2.2.5 Performance Measures

The performance of a model that predicts the potential distribution of species presence is traditionally assessed by calculating the area under the curve (AUC) of the receiver operator characteristic (ROC) (DeLong et al. 1988). This is a plot of the sensitivity (the proportion of correctly predicted known presences, also known as absence of omission error) vs. 1-specificity (the proportion of incorrectly predicted known absences, known as the commission error) over the whole range of threshold values between 0 and 1. The model AUC thus calculated is compared to the null model which is an entirely random predictive model with AUC=0.5; models with an AUC above 0.75 are normally considered useful (Elith 2006). Using this method, the commission and omission errors are therefore weighted with equal importance for determining the performance of the model. However, for a presence only ecological niche model this method may be unsuitable for two key reasons (Lobo et al. 2007; Peterson et al. 2008) : 1) we are less interested in the performance of the model over all the whole of the ROC space, for example, where the omission or commission error is very high, and 2) as we do not have absence data, Maxent simulates pseudo absence data which are drawn at random from the training region, so do not represent true absences, therefore mispredicting a known presence is a more serious failing of the model than mispredicting a possible absence, as the presences are known, whereas the absences are 'guessed'. In addition omission error has been shown to provide a better metric than commission errors for assessing model fit (Anderson et al. 2003).

For these reasons, we employed a model performance measure called partial AUC outlined by Peterson et al. (2008). The criticisms raised above are answered by: 1) using only presence data (no pseudo absence data) and 2) introducing a user defined variable E which refers to the maximum allowable level of omission error. The ROC curve is now a plot of sensitivity vs. the proportion of the study area predicted as present. Only the region where the omission error is less than E is considered – this area is called the restricted area, so the restricted ROC curve is the portion of the ROC curve that is present in the restricted area. The partial AUC is then a ratio of the AUC of the restricted ROC curve to the AUC of the restricted null model line (see Figure 2.2 and Peterson et al. (2008) for full details of this method). The partial AUC was calculated using Simpsons trapezium rule via routines implemented in R. Two levels of omission error were examined: $E=100$ which is essentially a traditional ROC plot as we are assessing the model over all levels of omission error (Figure 2.2A), and $E=10$ where we assume that 10% of the positive predictions are actually negative (Figure 2.2B), so we are only concerned with assessing models where omission error is less than 10%.

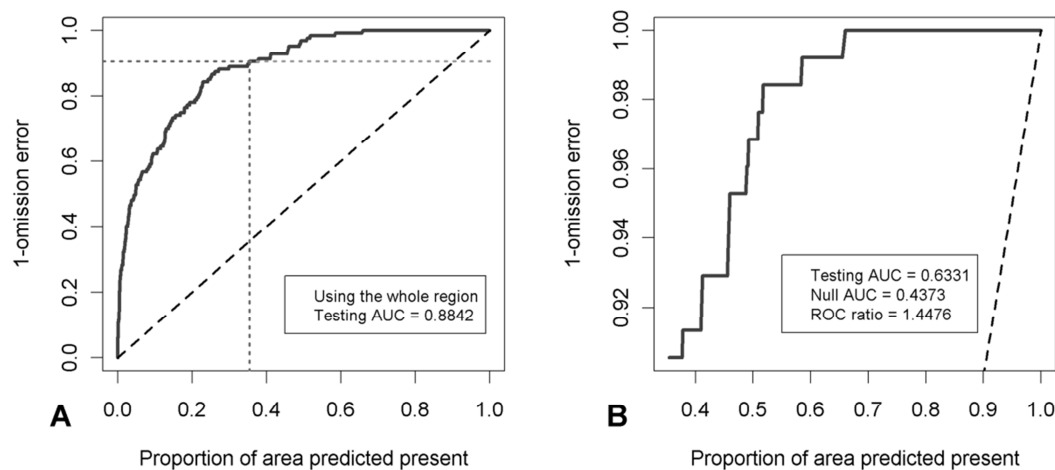


Figure 2.2: Comparison of traditional versus partial receiver operating characteristic (ROC) curves for the Maxent A model. A) Traditional ROC curve. The horizontal dotted line indicates the region of interest for the partial AUC plot – where the omission error is less than E (in this case $E=10$). B) The partial AUC plot – i.e. the region above the horizontal dotted line from Figure 2.2A. The dashed line indicates the null model.

2.2.6 Model Implementation

The data are split into two groups: 75% is used to construct the model and form the functional relationships between presence data and the environmental variables, and the remaining 25% are used to test the predictive ability of the model. The training region was chosen to be all the countries that are thought to be LF endemic and the resulting model was projected over the whole of Africa. The model performance was assessed by considering the partial AUC values of the testing data and the error associated with these values was estimated by

performing a bootstrap algorithm, where we sample with replacement from the testing data 200 times and calculate the partial AUC for each sample.

Maxent has five feature classes (linear (L), quadratic (Q), product (P), threshold (T) and hinge (H)) that can be used to model the functional response of presence probability to changes in the environmental variables (Phillips and Dudik 2008). We experimented with using different combinations of features to produce the best performing model. Some of the explanatory layers are also likely to be more predictive than others. We thus aimed to find a set of variables that are predictively powerful and independent as possible. Two techniques were employed to determine the most important variables: 1) considering the percentage contribution that each variable made to the total test gain; and 2) determining which variables caused the biggest lost in AUC when the data was resampled using a jackknife procedure where one variable was excluded at a time.

In addition, a quadratic discriminant analysis (QDA) was implemented in R to explore how interactions between the climate variables determine areas of LF presence or absence. QDA is a methods used to assign data into two groups based on the characteristics of each data point such that the probability of correct classification is maximised. In our case we use QDA to classify presence and absence data correctly based on the climatic conditions of each point.

2.2.7 Estimating populations at risk

The number of individuals at risk was estimated by overlaying a LF binary risk map on a population map and calculating the population in the 'positive' at-risk cells. The SEDAC 2010 population layer for Africa was used for calculating the current at-risk population (<http://sedac.ciesin.columbia.edu/gpw/global.jsp>). Note that climate data for 2010 was unavailable, and we were therefore forced to use the data averaged between 1950 and 2000 for making these estimations (Hijmans et al. 2005). We constructed a binary risk map by converting the continuous risk maps produced by Maxent into areas that are suitable and unsuitable by defining thresholds below which the probability of LF occurrence is considered to be zero and above which the probability is considered to be one.

Traditionally these classification thresholds are determined by selecting the value that: a) maximises the sum of sensitivity and specificity (Zweig and Campbell 1993), b) where commission error = omission error (Jimenez-Valverde and Lobo 2007) or c) is equal to the lowest predicted probability at a training presence site (Phillips et al. 2006; Pearson et al. 2007). However, methods a) and b) assume equal importance of omission and commission errors, and method c) is not suitable when we have an accepted level of omission error. When $E=100$ we adopt the lowest training presence threshold approach, and when $E=10$ we use a slightly modified version of c) suggested by A.T. Peterson (personal communication)

where we take the threshold to be the value of the predicted probability from the E^{th} quantile of the values at training data sites, so when $E=10$ we use the 10th percentile training presence value.

2.2.8 Future LF Predictions

The future potential distribution of LF was estimated by using the current Maxent model to make projections over projected climate and population density for 2050. The future climate data were downloaded from www.worldclim.org. These layers were constructed using data from general circulation models (GCMs). The IPCC report (IPCC 2007) considers around 25 GCMs and several emissions scenarios. The temperature projections amongst all the climate models are fairly consistent, however there is much more uncertainty regarding precipitation. The projections are made on a very coarse scale and are downscaled using current worldclim data. In this study we consider just two of these GCMs - the Hadley Centre global climate model HADCM3 and the Canadian Centre for Climate Modelling and Analysis model CCCMA under two IPCC climate scenarios – A2a and B2a (IPCC 2007). A2a is a more extreme scenario, assuming massive disparities between regions and high population growth and energy use, whereas B2a aims to capture a less disparate world with efforts focused towards social equity; this scenario also assumes lower population and economic growth than A2a. To account for differences in population growth between the two climate scenarios we multiplied the 2000 population data by country specific UN medium variant population growth rate predictions for the B2a scenario and by the high variant growth rate predictions for the A2a scenario (http://esa.un.org/unpd/wpp/unpp/panel_population.htm).

2.3 Results

2.3.1 Comparison of Maxent and GARP

A comparison of Maxent and GARP showed that Maxent performed better because it produced higher partial AUC values, therefore has a greater predictive ability. Therefore Maxent was thus used in all further analysis (Table 2.2).

	GARP		Maxent	
	E=10	E=100	E=10	E=100
Minimum	1.4167	1.5180	1.3331	1.6934
Maximum	1.4167	1.5628	1.5927	1.8336
Mean	1.4167	1.5437	1.4656	1.7622
Standard deviation	0.0000	0.0075	0.0655	0.0270
P-value	<0.00001	<0.00001	<0.00001	<0.00001

Table 2.2: Comparison of GARP and Maxent model fits. Partial AUC ratios taken across 200 bootstrap replications are shown for omission errors, E, of 10 and 100.

2.3.2 Model Selection

We initially ran a series of models using different combinations of the feature classes and selected three candidate models with the highest testing partial AUC values to investigate further. Model A employed the quadratic and threshold features, model B used the linear and threshold features, and model C used all the feature classes.

The relative importance and contribution of the original ten environmental, altitude and population density variables to the three initially selected niche models was assessed by considering the percentage contribution that each variable made to the total test gain, and by using a jackknife procedure to determine which of these variables caused the biggest lost in model AUC when each was excluded one at a time. This resulted in the selection of the following five variables: population density, mean maximum temperature, mean temperature in the coldest month, mean annual precipitation and altitude. Together they accounted for more than 88% of the total test gain. Specifically, these were selected by firstly excluding the variables which performed poorly using both methods: NDVI, annual mean temperature, mean temperature in the warmest month, and secondly, by identifying the most correlated variables (mean temperature in the coldest month and mean minimum temperature (0.92), and precipitation in the wettest month and mean annual precipitation (0.95)), and selecting the best performing variable from each pair. These were mean temperature in the coldest month as it contributed more than twice as much to the test gain and performed similarly using the jackknife test, and mean annual precipitation as it added slightly more to the test gain and caused a bigger loss in AUC when excluded using the jackknife test.

The three selected models were ran with the new set of five explanatory layers and the model performance was assessed using two different levels of acceptable omission error. Model A performed best and was used for all further analysis as it had a slightly higher combined testing partial AUC and the highest entropy. This model uses quadratic and threshold features (Table 2.3). The partial AUC plot for model A shows the modified AUC plot with 1- omission error on the y-axis and the proportion of area predicted positive on the x-axis. The whole AUC plot ($E=100$) is shown in Figure 2.2A and in Figure 2.2B we look at the AUC where we assume that we are only interested in the performance of the model when there is less than 10% omission error ($E=10$).

Model (Features)	E=10	E=100	Entropy	Environmental Variables (% contribution)	Features
A (Q+T)	1.4656 (1.3331, 1.5927)	1.7622 (1.6934, 1.8336)	8.2938	Population density 57.3	Q,T
				Altitude 26	Q,T
				Mean temp in coldest month 6.7	Q,T
				Mean annual precipitation 5.2	Q,T
				Mean max temp 4.8	Q,T
B (L+T)	1.4562 (1.3315, 1.6057)	1.7646 (1.6762, 1.8322)	8.2921	Population density 57.3	L,T
				Altitude 25.9	L,T
				Mean temp in coldest month 6.8	L,T
				Mean annual precipitation 5.3	L,T
				Mean max temp 4.8	L,T
C (All)	1.4227 (1.3278, 1.5600)	1.7455 (1.6461, 1.8249)	8.2577	Population density 57	All
				Altitude 25.4	Q,P,T,H
				Mean temp in coldest month 6.8	L,P,T,H
				Mean annual precipitation 5.9	L,P,T,H
				Mean max temp 4.7	L,P,T,H

Table 2.3: Summary results from the four Maxent models tested in the present analyses. See text for explanations of terms. Model A with quadratic and threshold features was selected as it performed the best using all three values of E – the acceptable level of omission error.

The relative contributions of the various explanatory data sets to the various Maxent models are shown in Table 2.3. The results indicate that population density contributed the most (around 57%) to each of the tested models, followed by altitude (around 26%) as the next most significant factor. For model A, the three climatic layers contributed in total to around 17% of the overall prediction of LF occurrence.

All our final models performed significantly better than the null model (all partial AUC's >1.42), re-emphasizing the high predictability that can result from ecological niche modelling using the Maxent programme (Phillips et al. 2006; Elith and Graham 2009).

2.3.3 Model Predictions

The distribution of LF occurrence in Africa predicted by the best performing Maxent model (A) is shown in Figure 2.3A. The map shows that LF in Africa occurs over a large area extending from the west to the east primarily across the middle region of the continent. The results also depict a high degree of heterogeneity in the probability of LF occurrence on the continent. There appears to be a large zone exhibiting a high probability of LF occurrence in the Western Africa region, whereas in Central and Eastern Africa and in Madagascar, large areas of medium probability are interspersed with smaller areas of high probability, especially along the coasts. All countries known to be LF-free (as shown in Figure 2.1) have been masked in this figure, but low probabilities of infection were predicted in these countries (not shown).

Most of the training data are located in west and east Africa and there are very few datapoints covering central Africa. Little is known about the state of LF in many of these countries, therefore we have no way to validate the model. For this reason we need to be cautious when interpreting the results from these countries compared to more densely sampled countries. Areas deemed at risk are presented in Figure 2.3B for two difference training presence thresholds.

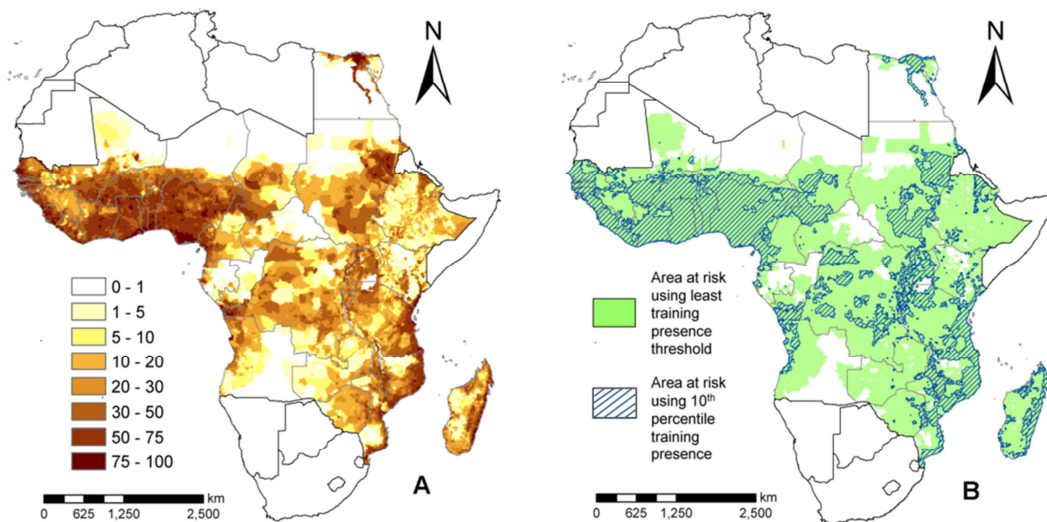


Figure 2.3: Probability map of the occurrence of LF in Africa (A) as predicted by the final Maxent A model containing the variables: mean annual precipitation, mean maximum temperature, and mean temperature in coldest month, altitude and population density, and quadratic and threshold features. Probability of occurrence is depicted in the form of percentages. Figure 2.3B shows areas that are at risk using two training presence thresholds.

Individual response curves (marginal responses obtained by keeping all other variables at their average sample value) of the relationships between each environmental variable and the probability of disease occurrence as estimated by model A are portrayed in Figure 2.4. There is a negative response observed between altitude and LF occurrence and positive responses observed for the rest of the variables. There also appears to be evidence for threshold effects in each of the estimated relationships (most clearly observed for the association between mean temperature in coldest month and probability of LF infection (Figure 2.4E)), wherein the probability of LF occurrence begins to increase only after about 10⁰C).

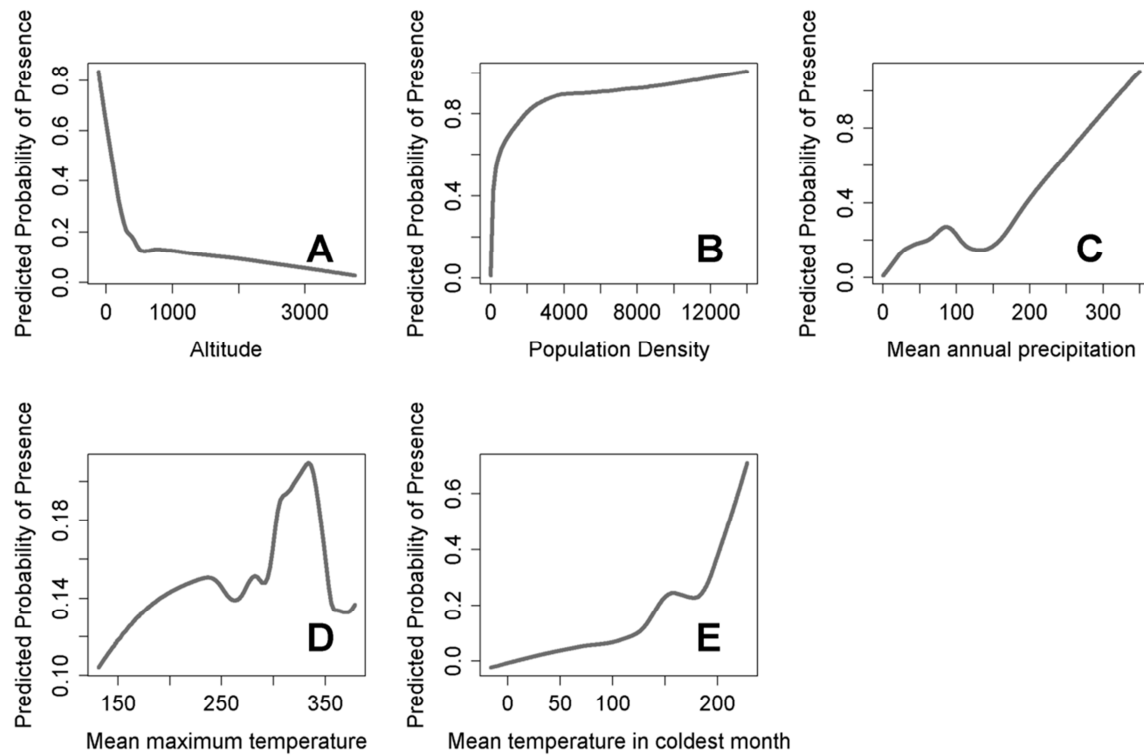


Figure 2.4: Marginal relationships between each environmental variable and the probability of LF occurrence. Temperature values are expressed in $\times 10^\circ\text{C}$, precipitation is in mm per month and altitude is in metres.

To visualise the LF ecological niche, the Maxent predictions were further related to environmental conditions at both presence sites and areas where the disease is known not to exist (Figure 2.5). Here we see that differences in the identified ecological conditions may strongly influence the probability of infection presence and absence in Africa. These results indicate that LF occurs mainly in the hot and wet regions of Africa, with non-endemic areas all having an annual rainfall level below around 100mm. The mean maximum temperature and mean temperature in the coldest month both need to be relatively high for the disease to occur, with no presence sites occurring when the temperature in the coldest month is 3.7 degrees and the mean maximum temperature in 22.4 degrees.

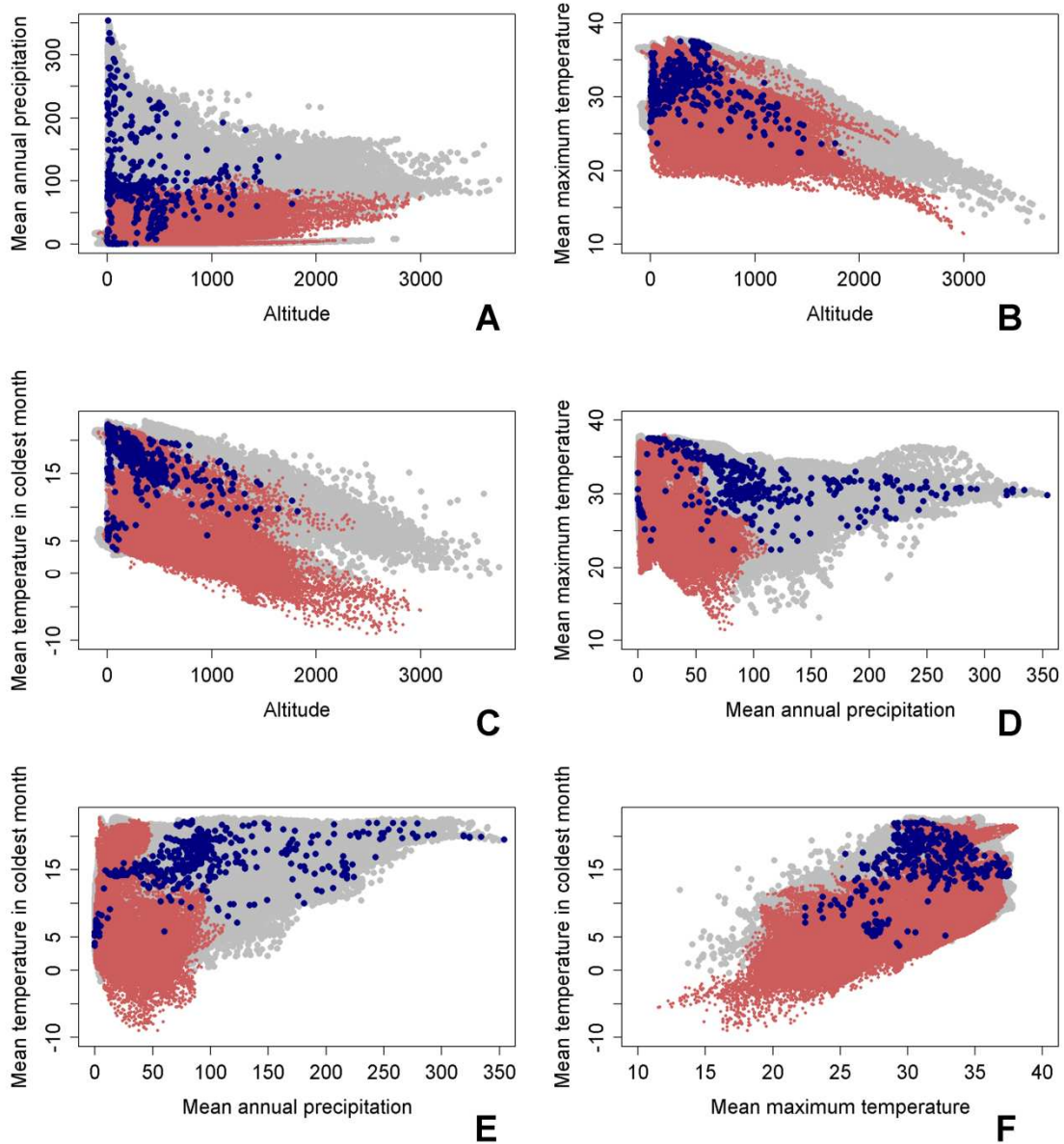


Figure 2.5: Visualisations of the modelled LF ecological niche in Africa. The grey points are the environmental conditions for every cell in Africa, the red points represent the conditions in non-endemic sites while the conditions underlying presence sites are shown in blue. Temperature values are expressed in $\times 10^{\circ}\text{C}$, precipitation is in mm per month and altitude is in metres.

A quadratic discriminant analysis was performed using just the climate variables (Figure 2.6). These highlight not only that different regions of each variable space can determine where LF is likely to occur and not occur, but also the dependency of such classification on variable interaction. Thus, the levels of rainfall and temperature required for the disease to occur are dependent on each other, whereby in warmer regions, less rainfall is needed to sustain parasite transmission. However, a key finding is that the minimum threshold for mean

temperature in the coldest month is around 11 degrees with apparently little variation in this value with increasing mean maximum temperature (Figure 2.6C).

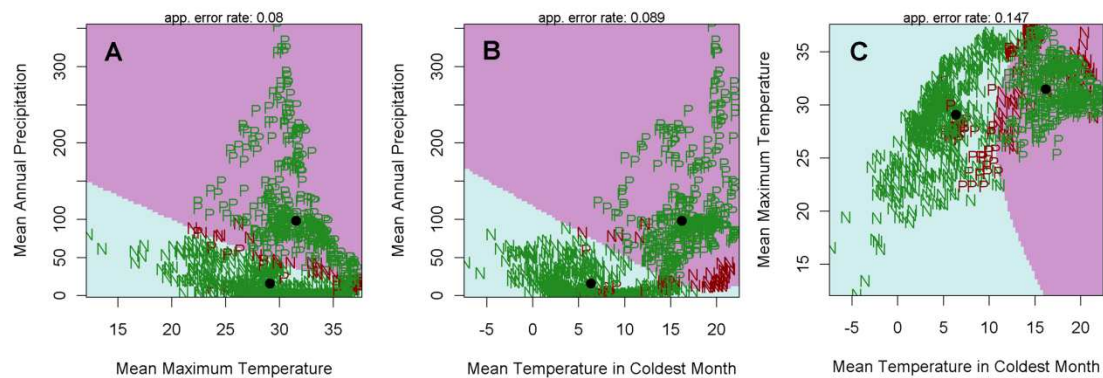


Figure 2.6: Results from the quadratic discriminant analysis carried out in this study to determine the importance of the climatic variables included in the final Maxent A model in classifying positive (P) and negative (N) LF occurrence sites in Africa. The purple area of the graph shows the area where infection is present, while the blue portion shows where it is absent based on the analysis. The green points represent correctly classified datapoints and the dark red points show incorrectly classified data points. 91% of the points were classified correctly.

2.3.4 Future LF Predictions

We used model A in conjunction with the four climate change projections and their associated population growth estimates outlined earlier to investigate how the potential distribution of LF could change between now and 2050, assuming that no control measures are implemented. Our model predictions shown in Figure 2.7 indicate that LF occurrence could increase in large parts of Africa with the highest increases expected in areas bordering the current northern extent of the disease (Figure 2.7C and D), particularly across regions of Mauritania, Sudan, and Somalia. LF occurrence is also predicted to increase in countries in the southern parts of the continent. The probability of disease occurrence could, however, decrease in other areas, mainly in the west near Ivory Coast and Nigeria and also the Democratic Republic of Congo (Figure 2.7). Overall, the mean change in probability of LF occurrence over the whole continent was found to be 0.1, suggesting that LF transmission is likely to increase in Africa with climate change and population growth.

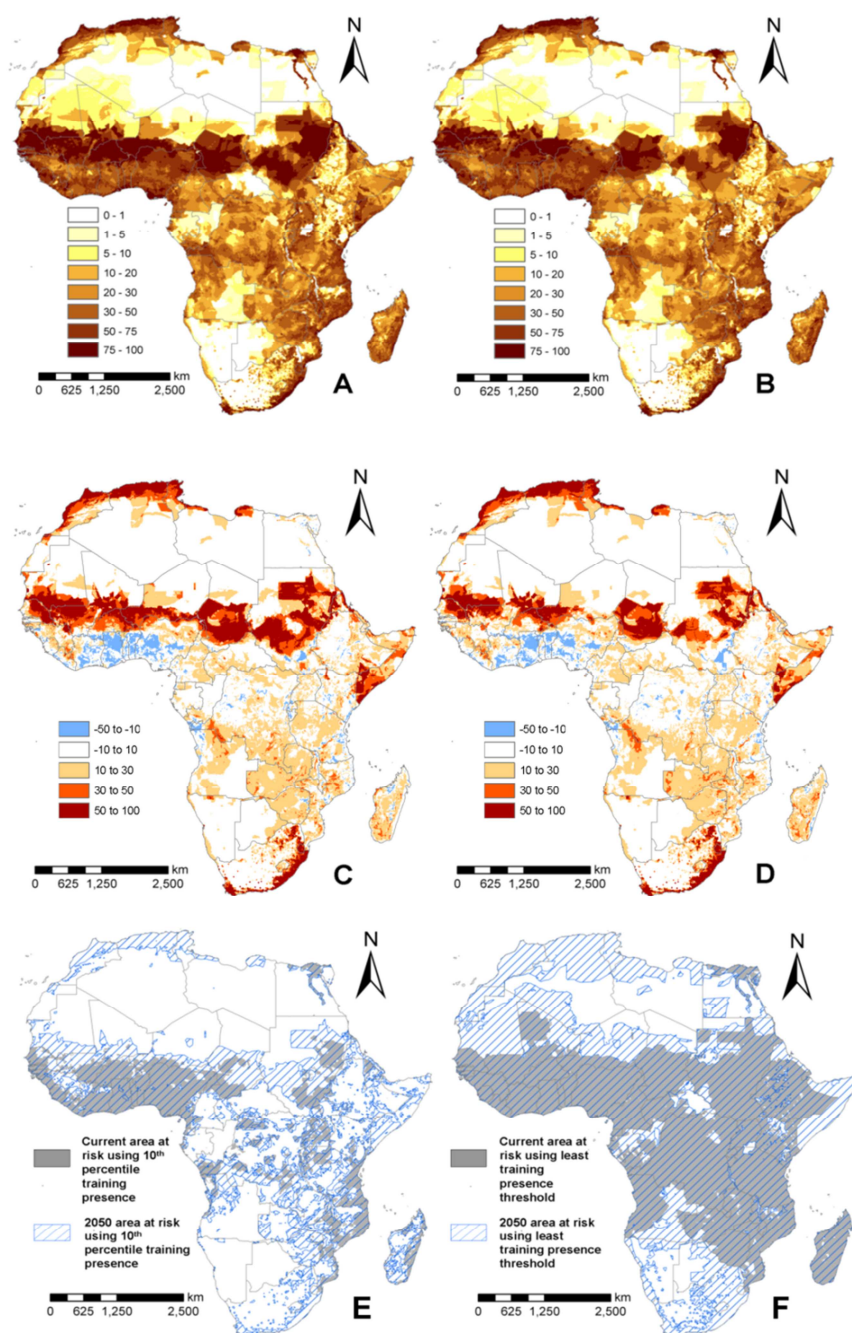


Figure 2.7: Predicted LF distribution in 2050 using HADCM3 A2a and high population increase scenario (A), and HADCM3 B2a and medium population increase scenario (B). Percentage point change between 2050 and current distribution (Fig 2.3) for A2a (C) and B2a (D). Model predictions for the CCCMA climate predictions are very similar so not shown here. The predicted at-risk areas in 2000 (grey) and in 2050 (shaded blue) for the a2a scenario (E) using a threshold of 33.4 given by setting the acceptable omission error to $E=10$. (F) shows the same but for a threshold of $E=100$.

2.3.5 Estimating current and future populations at risk to LF

The populations at risk were estimated by converting the Maxent prediction from model A into a binary map. Two thresholds are used – the value of the least training presence (LTP) prediction, which was 1.9%, and the value of the 10th percentile of the training presence (10% TP) predictions, which was 29.8%. For each threshold, each cell in the map with a value above these values was deemed to as having LF present. The threshold map for 2010 is shown in Figure 2.3B and for 2050 in Figure 2.7E and 2.7F.

Country name	Population increase (x) 2010 - 2050		Least training presence threshold			10th percentile training presence threshold		
	med	high	2010	2050 a2a	2050 b2a	2010	2050 a2a	2050 b2a
Angola	2.23	2.51	15.77m	42.34m	37.29m	4.27m	18.86m	17.56m
Benin	2.39	2.69	7.42m	20.86m	18.54m	7.38m	20.8m	18.53m
Burkina Faso	2.51	2.81	15.71m	45.07m	40.22m	15.26m	45.06m	40.22m
Burundi	1.74	1.97	8.76m	16.76m	14.8m	5.35m	9.16m	9.08m
Cameroon	1.84	2.1	18.13m	38.48m	33.79m	13.3m	31.29m	27.61m
Central African Rep.	1.69	1.95	4.04m	8.19m	7.1m	0.82m	4.13m	3.41m
Chad	2.41	2.7	10.51m	28.91m	25.78m	7.01m	28.28m	24.93m
Congo	1.83	2.08	3.96m	7.77m	6.94m	3.02m	6.14m	5.5m
Djibouti	1.67	1.89	0.57m	1.2m	1.07m	0.42m	1.01m	0.89m
Egypt	1.53	1.77	74.71m	136.27m	118.09m	74.11m	135.39m	117.34m
Equatorial Guinea	2.09	2.36	0.53m	1.23m	1.09m	0.37m	1.23m	1.09m
Ethiopia	2.05	2.31	78.08m	173.5m	156.7m	6m	29.9m	25.7m
Gabon	1.65	1.9	1.19m	2.57m	2.23m	0.68m	1.37m	1.21m
Gambia, The	2.15	2.44	1.36m	3.24m	2.88m	1.36m	3.24m	2.88m
Ghana	1.86	2.1	23.67m	47.64m	43.27m	23.67m	47.33m	43.07m
Guinea	2.32	2.62	9.83m	25.57m	22.68m	4.96m	22.61m	18.36m
Guinea-Bissau	2.16	2.42	1.43m	2.91m	2.65m	1.41m	2.88m	2.63m
Ivory Coast	2.01	2.29	18.3m	41.48m	36.99m	17.39m	40.37m	36.2m
Kenya	2.09	2.39	36.23m	93.34m	81.86m	12.21m	37.78m	36m
Liberia	2.16	2.45	4.52m	9.35m	8.41m	4.33m	9.28m	8.34m
Madagascar	2.12	2.42	20.44m	48.95m	42.91m	13.47m	41.57m	38.25m
Malawi	2.33	2.64	13.95m	39.34m	34.7m	12.68m	38.96m	34.25m
Mali	2.12	2.39	15.02m	34.32m	30.5m	11.52m	33.45m	29.29m
Mozambique	1.89	2.16	20.7m	47.2m	41.65m	16.71m	45.08m	39.86m
Niger	3.66	4.04	14.91m	62.34m	56.3m	10.57m	60.1m	52.75m
Nigeria	1.83	2.06	143.97m	288.68m	257.45m	139.88m	286.8m	255.36m
Rwanda	2.15	2.42	9.44m	23.8m	21.16m	3.7m	11.74m	11.67m
Senegal	2.03	2.3	9.75m	20.71m	19.03m	9.16m	20.71m	19.02m
Sierra Leone	2.13	2.42	5.9m	13.12m	11.67m	5.71m	13.03m	11.65m
Sudan	1.76	2	37.47m	75.98m	66.58m	20.24m	65.67m	53.55m
Tanzania	2.43	2.75	41.79m	120.35m	106.21m	24.05m	98.13m	88.77m
Togo	1.95	2.22	5.57m	12.39m	10.93m	5.57m	12.36m	10.93m
Uganda	2.7	3.04	32.52m	97.25m	86.75m	25.32m	83.56m	76.17m
Dem. Rep. of Congo	2.17	2.45	70.73m	165.66m	147.09m	33.99m	113.17m	97.77m
Zambia	2.18	2.48	12.67m	32.73m	28.84m	2.25m	21.99m	18.53m
Zimbabwe	1.75	2.04	14.9m	26.04m	22.44m	4.76m	21.38m	19.16m
Total			804.42m	1,855.52m	1,646.58m	542.88m	1,463.8m	1,297.54m

Table 2.4: Population at risk from LF in endemic countries in Africa estimated applying two different threshold values based on different levels of acceptable omission error, *E*, to the final Maxent model A predictions. 2010 populations at risk are calculated by projecting the derived Maxent model against 2000 climate data (but using 2010 population data (see text)) while the

2050 populations at risk are derived using the predicted 2050 environmental/population density data. The UN predicted increases in population are given, and show the factor by which population is expected to increase.

The current (2010) population at risk to LF in Africa is thus calculated to be 804 million using LTP threshold ($E=100$) and 542 million using the 10% TP ($E=10$) threshold. The 2050 estimates range from 1.86 billion to 1.46 billion using the LTP threshold and from 1.65 billion to 1.30 billion using the 10% TP threshold (Table 2.4). On average, the A2a scenarios predict a larger at-risk population, indicating that 13% more people would potentially live in at-risk areas when compared with the effects of the B2a scenario.

2.4 Discussion

We have used an ecological niche modelling approach based on infection presence-only data to firstly reveal the spatial distribution of LF in Africa, and the environmental determinants that underlie this pattern, and secondly to investigate how climate change and population growth may affect the future potential distribution and burden of this important parasitic disease on that continent. The performance of the Maxent models developed here were assessed using a newly developed partial AUC measure. The benefits of this method over a traditional AUC approach are that it: 1) eliminates the use of pseudo absence data in accuracy measurements and 2) allows the user to define an acceptable level of omission error.

The advantages of using machine learning approaches, such as the maximum entropy modelling algorithm implemented in the Maxent programme, over simpler statistical tools, such as logistic regression, for species distribution modelling have been thoroughly reviewed previously (Pearce and Boyce 2006; Phillips et al. 2006; Olden et al. 2008). Here, we highlight that two chief benefits of applying such methods to parasitic infection mapping arise from their flexibility in specifically accounting for: (1) the complex non-linear associations of infection occurrence with individual explanatory variables, and (2) the impact that interactions occurring among these variables may have on infection presence.

Here we are, in effect, defining the ecological niche of an 'average' LF vector, although in reality we would expect to see variation in the niches of different vector species. For example, *Anopheles arabiensis* are more suited to dry conditions than *An. gambiae* s.s (Lenhart et al. 2007), meaning drier areas where the former species are present might be able to sustain LF transmission, but areas where this species are not present may be LF free. Similarly, *An. gambiae* s.s prefer humid conditions so may facilitate LF transmission in regions too humid for other LF vectors (Lindsay and Bayoh 2004). As discussed in section 1.2.3, LF is

transmitted by mosquitoes from the *Culex pipiens* complex and the *Anopheles* genus in East Africa, but almost solely by *Anopheles* in west Africa. As a result, we would expect the ecological niche of LF to differ between east and west Africa, but due to a lack of data on the proportion of each vector species at each location, we make do with a 'general' ecological niche for an 'average' LF vector.

The complex and non-linear functional forms (Figure 2.4) allow us to explore how each climate variable influences LF presence. The relationship between the probability of LF presence and mean annual precipitation was the most linear (Figure 2.4C): its impact on infection probability is found to be low below a threshold of around 150mm per year. Biologically, this may be because a certain amount of water is needed to provide suitable laying sites for LF vectors. However, it has been suggested that vector survival can also be affected if there is too much rainfall as egg laying sites can get washed away (McMichael 2003). The LF occurrence - mean maximum temperature response curve (Figure 2.4D), by contrast, is increasing until it peaks between 25 °C and 32.5 °C, after which it begins to decrease suggesting this temperature range is the most suitable for LF transmission to occur. This result is consistent with experimental findings that both mosquito survival (Martens et al. 1997) and the development of LF larvae within the mosquito (Lardeux and Cheffort 1997) peak around 22-34°C. Although different measures of temperature were used, it is also consistent with the previous findings of Lindsay and Thomas (Lindsay and Thomas 2000), who found that the temperatures of sites in Africa with microfilaremic individuals lie within the range between 22-30°C. This comparability of results highlights the usefulness of ecological niche modelling based on machine learning methods as a possible first step in uncovering the functional forms of the climate variables that are thought to affect the ecological and physiological traits related to parasite transmission (Kearney and Porter 2009).

Figure 2.4E indicates that the probability of LF occurrence is very low at cold temperatures - this agrees with known temperature dependencies of LF vectors. *Anopheles* require a minimum temperature of around 10 °C for development (Martens et al. 1999). Above 22°C the predicted probability of presence increases rapidly, fitting in with known increasing development rates of LF parasites and vectors. (Lardeux and Cheffort 1997; Craig et al. 1999). In contrast to the effect of climate variables, the relationship between altitude and LF occurrence was found to be negative, although again the association was distinctly non-linear (Figure 2.4A). Such negative correlations between infection presence and altitude have been recorded previously in field studies (Onapa et al. 2005; Ngwira et al. 2007), and most likely reflect the negative effect of falling temperature with increasing altitude (ie. the lapse rate) on mosquito survival rate and the rate at which the parasite develops within the vector (Lardeux and Cheffort 1997; Ngwira et al. 2007).

Exploration of the Maxent modelling results in this study has also allowed a first depiction of how subtle interactions between key climatic variables may govern the suitability of a geographic region for transmitting LF. The key finding here is that levels of precipitation and temperature in particular could interact strongly to define the multivariate space required for the disease to occur, with generally less rainfall needed in warmer regions to sustain parasite transmission and vice versa (Figure 2.5 and 2.6). The biological significance of this finding is that such interactive effects could result in compensatory responses among vector and parasite ecological traits (vector birth, survival and biting rates, and larval development rate in the vector) that would not only dampen the effects of variations in individual key climatic variables but also allow the transmission of LF to occur over a much wider area than would be the case if habitat suitability is defined solely by each single variable.

A major finding of this study is that human population density was by far the most significant variable that may influence LF occurrence in Africa, accounting for 57% of the total test gain (Table 2.3). This supports not only theoretical expectations that host population density is a key driver of the transmission of vector-borne infections, such as LF (Anderson and May 1992), but is also biologically intuitive given that the adult parasites live in the host and mosquito vectors require human blood meals to be able to oviposit and reproduce. This result would suggest that climate variables *per se* may play a smaller though significant role in determining the ecological niche and hence the potential distribution of LF. A LF prediction model for 2050 was created using the climate and altitude variables, but setting the population layer equal to zero, thus allowing us to look at the contributions of these non-population density variables to the final projections (Figure 2.8). It is clear that the climate and altitude variables contribute in the region to the south of the Sahara, but much less so in other areas. These results thus suggest that both population density and environmental variables may contribute to the occurrence of vector-borne infections, and therefore that both sets of variables should to be taken into account when modelling the potential distribution of these and other parasitic infections (Hales et al. 2002; Moffett et al. 2007; Mills et al. 2010).

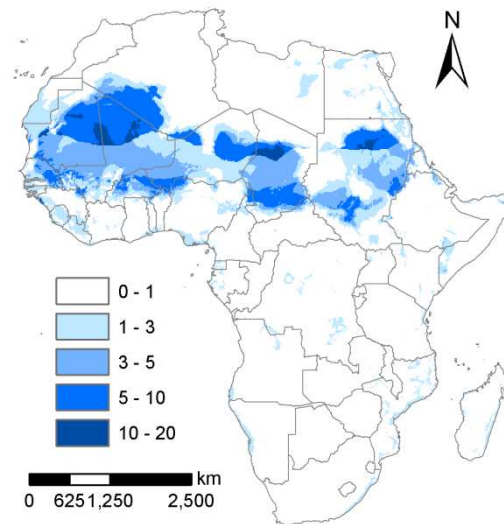


Figure 2.8: Probability of LF in 2050 as predicted using just the climate variables and altitude for the Hadley A2a climate model. It is clear that the climatic variables contribution strongly to the final LF predictions in the area to the south of the Sahara.

The Maxent model for LF occurrence across Africa generated a risk map giving a probability of infection presence in each location between 0 and 1, with a probability close to 1 indicating sites with the highest risk and possibly levels of infection. Thus, the map shown in Figure 2.2 provides not only information regarding the potential spatial extend of LF endemicity across Africa but also, crudely, data on variations in the intensity of transmission that can be expected in different parts of the continent. Based on the variation in relative risk shown in the figure, the highest LF transmission therefore appears to occur in the Western Africa region, whereas infection levels in large parts of Central and Eastern Africa and in Madagascar are predicted to be considerably more heterogeneous, with moderate levels interspersed with smaller areas of high infection occurring along the coasts. Despite the fact that the present Maxent results are based only on presence data, this conclusion is surprisingly well supported by the actual national LF prevalence values estimated for the endemic countries of Africa given in Michael et al. (Michael et al. 1996) and Michael and Bundy (Michael and Bundy 1997). This represents an important technical insight as it suggests that modelling of presence-only data may provide a good approximation to actual levels of parasite transmission intensity in an area (Lindsay and Thomas 2000). It may also support suggestions that the risk of a LF site as determined using climate/environmental variables (Lindsay and Thomas 2000) could be due to climate-derived variations in the abundance of the relevant transmitting vector species. This is highlighted by the remarkable similarity of the African ecological niche maps for *Anopheles funestus* and *A. gambiae*, the two principal anopheline vectors of LF in Africa, developed by Moffett and colleagues (Levine et al. 2004; Moffett et al. 2007), with the LF risk map shown in Figure 2.2.

Estimations of the at-risk population for LF in Africa have varied significantly between previous studies, with recently reported figures appearing to increase over time possibly due to the effects of both increasing population and surveillance. Thus, in 1992, it was estimated that some 113 million individuals lived in endemic areas (WHO 1992), which increased to 212 million (WHO 2005b) and 396 million by 2009 (WHO 2009). These estimates, which are normally made by identifying infection positive districts and calculating the number of people in each of these districts, not only take little account of the spatial variation that exists at the local level (Gyapong et al. 2002) but are also highly dependent upon the existence of field surveys covering all relevant endemic areas. By contrast, machine learning-based ecological niche models using presence-only data approximate the realised distribution of a disease (Phillips and Dudik 2008), and via the derivation of a continuous potential distribution map may offer a more accurate method to determine the true extent of infection and hence actual populations at risk. The predictions from our best fitting Maxent model are based on different assumptions regarding the omission error. Considering all levels of omission error, and a threshold equal to the least training presence we estimate 804m people living in at risk areas and assuming a 10% omission error and using the 10th percentile from the training presence predictions we estimate that there are 542m people at risk. Given that the average prevalence of LF (infection and disease) in African endemic countries has been estimated to be around 11% (Michael et al. 1996; Lindsay and Thomas 2000), our estimate of the population at risk suggests that we can expect between 60 and 89 million cases of LF in 2010 on that continent compared to the 51 million and 47 million estimated by Michael and Bundy (Michael and Bundy 1997) and Lindsay and Thomas (Lindsay and Thomas 2000) respectively for the years 1990 and 2000.

We also explore the impact of climate-induced change and population growth on the potential distribution and burden of a LF in Africa. These future projections were produced by using the best-fit Maxent model derived for 2000 and projecting the functional relationships therein onto the two 2050 climate scenarios, i.e. we consider that niche dynamics are static and that climate change will not affect either the form of the biotic relationships governing the vector and the parasite population dynamics or any adaptation by these populations to the new environment (Guisan and Thuiller 2005; Pearman et al. 2007). We examined the impact of two 2050 climate scenarios from two different global climate models. The more extreme scenario, A2a, predicted on average 13% more people living in at-risk areas than the B2a scenario. Predictions of the 2050 population at risk range from 1.30 to 1.86 billion (Table 2.4); although a large component of this increase is a result of population growth, changes in climate are also shown to increase the area of Africa that is suitable for LF transmission. Large regions below the Sahara desert and in Zambia, Zimbabwe and Angola are predicted to have increased probability of LF (Figure 2.7E,F), suggesting that the ecological niche of infection could increase and extend both northwards and southwards. This finding contradicts

the general assumption that future changes in climate will simply shift rather than increase the spatial extent of vector-borne diseases (Lafferty 2009). It is also predicted that the risk of LF could increase near the coast in northern Africa, possibly due to increasing temperature and decreasing rainfall, as well as predicted population increases. However, although this region may be suitable for transmission, LF will only spread to this area if infection carriers move to the region.

When analysing these results we must pay attention to the uncertainty and error associated with the future climate data – both from the GCMs and the downscaling procedures adopted, and the fact that we are only considering two GCMs and two emissions scenarios. There are large differences between the full range of 21 GCMs regarding future temperature and precipitation predictions. Temperature predictions are generally more coherent, with half the GCMs predicting within 0.5°C of the median value. However precipitation projections are considerably more disparate – in particular, the area directly below the Sahara appears to have vastly different predictions ranging from a 50% decrease to a 50% increase in precipitation. Projections made for the east of Africa are more consistent, generally showing an increase in precipitation. The majority of models predict also predict a decrease in precipitation for southern Africa (see figures S11.5 and S11.13 in the chapter 11 supplementary material of the IPCC Fourth Assessment Report (IPCC 2007)). It is important to take the different future prediction uncertainties into account when considering the future LF predictions – our predictions are likely to be more accurate in areas with more consistent climate predictions.

These results obviously do not take into account increases in disease control activities on the continent of Africa, which has accelerated greatly since the Global Alliance to Eliminate Lymphatic Filariasis was created in 2000. It also does not take account of the increase in vector control on that continent, primarily targeted at malaria, which will also have an impact on LF infection via reductions in vector biting rates and lifespans (Manga 2002). Indeed, our predictions of the likely future increase in LF burden argues strongly for strengthening and expanding these interventions even further as an important mitigation strategy to counter the predicted spread and intensifying of this debilitating disease in Africa as population density increases and climate changes.

Although our study has yielded several important and novel insights into the determinants and structuring of the ecological niche and the present and future spatial occurrence of LF in Africa, there are several limitations that need to be borne in mind when interpreting the present results. First, even though ecological niche modelling approaches based on occurrence data alone, such as the Maxent algorithm used in this study, are optimized for predicting the realised or actual (rather than the fundamental) distribution of a species (Phillips et al. 2006; Phillips and Dudik 2008), predictions of presence will still be dependent

on the sample locations of the available data with any deficiency in sample coverage of all suitable areas able to bias the results. Second, the crude scale of the environmental layers used to construct the Maxent model means that the validity of predictions on small focal spatial scales is questionable. Third, we have no error estimates associated with our predictions – in reality we would expect a heterogeneous error map of model predictions in Africa caused by different levels of error associated with the climate data and model fit, and from the biased distribution of presence data. However, it is hoped that our predictions are fairly robust on the district or country wide scales that are typically used in policy decisions regarding disease control and eradication strategies, especially in countries with more accurate climate data and more LF survey data. We have also used 50-year averaged climate layers to approximate a phenomenon that might have changed in the past decade or so to characterise “current” climate in our analyses. It might be possible to use remote-sensed data to overcome this limitation (Kalluri et al. 2007), forward projection of such data to future climates is not possible.

Combining correlative spatial modelling approaches with mechanistic models linking climate/environmental and population variables to parasite transmission processes in conjunction with regional climate models may provide a more useful solution to improving the detail of spatial predictions (Kearney and Porter 2009), although the practical modelling frameworks and tools required for successfully achieving this synthesis is still largely indeterminate. Nonetheless, the results presented here could be used to guide current LF elimination programmes in Africa and to improve estimates of the number of people living in areas at risk of LF. Maps stratifying at-risk areas could support the targeting of available interventions to where they are most needed and knowing which areas are most ecologically suitable for resilient LF transmission could help the planning of intervention strategies and post-intervention monitoring or vector management strategies to ensure that elimination efforts are successful.

Chapter 3

Mapping Malaria and Lymphatic Filariasis prevalence in Africa and identifying areas of co-endemicity

3.1 Introduction

Malaria and LF are thought to be co-endemic in large parts of Africa (Manga 2002; Muturi et al. 2006a; Manguin et al. 2010), and although the countries in which transmission occurs are known (Molyneux and Nantulya 2004), little is known about the spatial patterns of co-endemicity and co-infection prevalence. It has been suggested that targeting malaria and LF together could be a more successful and cost-effective approach for eliminating the transmission of these two important infections (Manga 2002; Muturi et al. 2008). The first step towards planning an integrated control program is to map the spatial extent and prevalence of each infection and to identify areas where they co-exist (Brooker and Clements 2009).

Maps detailing the distribution and severity of a disease, as opposed to mapping presence alone, are essential for guiding the planning and management of control programmes. Prevalence mapping methods have been widely used to model parasitic disease, including lymphatic filariasis (Michael et al. 1996a), schistosomiasis (Wang et al. 2006; Clements et al. 2008) and malaria (Kleinschmidt et al. 2000). In these studies, environmental data layers that are thought to influence transmission are used to try and explain some of the variation in prevalence across a region. This can aid our understanding of the relationships between transmission and the climatic/environmental ecology of parasitic infections (Brooker and Michael 2000; Lindsay and Thomas 2000; Noor et al. 2009). Commonly spatial models that take into account the spatial correlation of infection distribution are used (Wang et al. 2006; Diggle and Ribeiro Jr 2007; Ben-Ahmed et al. 2010). Identifying large scale spatial patterns in

the distribution of an infection can help uncover the environmental determinants of infection (Clements et al. 2006; Beck-Worner et al. 2007; Craig et al. 2007; Riedel et al. 2010).

The importance of explicitly accounting for spatial effects when mapping infection data has been explored (Diggle et al. 1998; Paterson and Lello 2003; Raso et al. 2005), and a variety of methods for dealing with spatially correlated data have been suggested, within both a frequentist framework (Dormann et al. 2007), and a Bayesian framework (Lunn et al. 2000; Christensen and Ribeiro Jr 2002; Belitz et al. 2009). Generalised linear models with spatially correlated random effects are commonly used in this context; models of this type are known as generalised spatial linear models (GLSMs) (Diggle et al. 1998) and have been used to map a wide range of phenomena, including germinating seeds (Breslow and Clayton 1993), root rot (Zhang 2002) and bird distribution (Buckland and Elston 1993). They have also been widely used to predict disease prevalence, including breast cancer (Breslow and Clayton 1993), schistosomiasis (Clements et al. 2006; Wang et al. 2008), pseudorabies virus (Staubach et al. 2002) and malaria (Kleinschmidt et al. 2000; Kazembe et al. 2006). Maps of prevalence or intensity of infection developed using this approach have been used to identify the worst affected areas to guide control strategies (Kazembe et al. 2006; Guerra et al. 2008) and to estimate the rate of spread of infection (Stevenson et al. 2005).

We attempt to map the prevalence of LF and malaria infection across Africa using a Bayesian generalised spatial linear model based on community-level infection data obtained from the published literature and environmental and population data layers. We use the package 'geoRglm' implemented in 'R' (Christensen and Ribeiro Jr 2002) to create a model to predict prevalence based on the data layers and spatially correlated random effects. The model parameters are estimated using Markov chain Monte Carlo (MCMC) techniques and a model selection procedure is used to identify a set of predictive non-correlated variables. The infection maps produced for LF and malaria will be overlaid to estimate the areas where both infections are present and also to estimate the number of people that are co-infected. The model is also used to assess how different environmental risk factors influence the distribution of LF and malaria.

3.2 Methods and Materials

3.2.1 Prevalence Data

Point data for LF was collated from published community surveys between 1950 and 2009 using the search procedures described in Michael et al. (1996a). The main selection criteria were that each study was based in a single community and detailed the number of people surveyed and the number positive for microfilariae (see details of LF studies in Appendix A).

Malaria prevalence data was taken from the MARA database for surveys conducted between 1991 and 2008 (Le Sueur et al. 1997). We used prevalence data for the whole population of each study site. Where prevalence had been stratified by age we aggregated all the study participants to get an overall prevalence. Studies not testing the range of age groups were discarded from the database. A longer time period was used for LF for two reasons: i) a lack of LF data and ii) less variability in LF prevalence than malaria prevalence over the last 60 years.

A total of 664 data points for LF and 642 for malaria were found, of which 508 and 472 were presence points respectively. Each survey site was georeferenced using information in the study literature or from the MARA database. Where this information was not available we performed online searches using Google Earth (with spatialepidemiology.net/user_maps/), geonames.org and fallingrain.com.

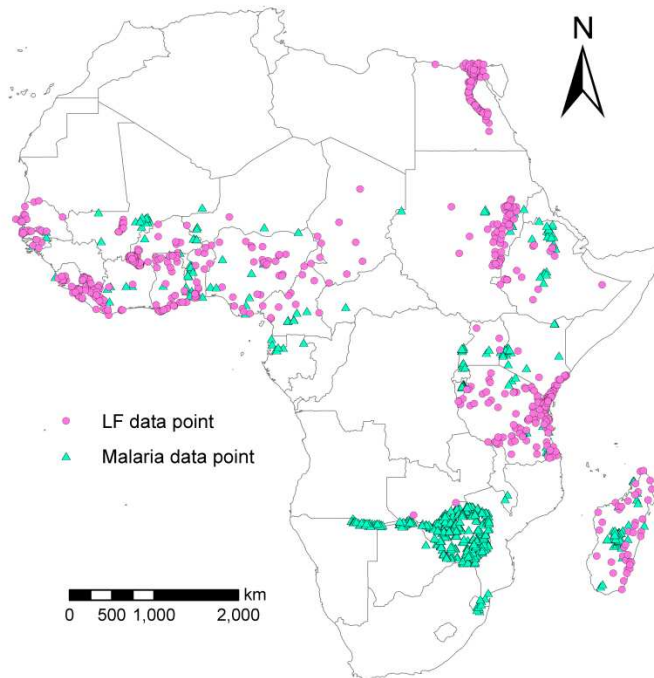


Figure 3.1: Data points showing the prevalence (%) of LF and malaria in Africa, shown as the proportion of people with mf or malarial parasites in their blood.

3.2.2 Environmental Layers

Initially ten environmental data layers believed to influence the transmission of LF and malaria were selected for the analysis. See table 2.1 in section 2.2.2 for further details.

3.2.3 Generalised Linear Spatial Model

Traditional geostatistical models attempt to model the value of some spatial process over a given region. Observations, Y_i , taken at each location, x_i , are assumed to be ‘noisy’ realisations of the underlying spatial process, $S(x_i)$ (Diggle et al. 2003). These models can also include a non-constant surface mean which is given by $\sum_{j=1}^k f_{ij}\beta_j$ where f_{ij} represents the value of the j^{th} environmental variable at the i^{th} location and β_j is the coefficient of the j^{th} variable. This model can now be denoted:

$$E(Y_i | S(x_i)) = \mu(x_i) = \sum_{j=1}^k f_{ij}\beta_j + S(x_i)$$

and $\mu(x_i)$ is the expected value of the process we are trying to estimate. However, models of this type assume that the observed data are Gaussian. Generalised linear spatial models offer a framework for non-Gaussian data. Our data are binomially distributed, where at each location, x_i , we have the total number of people tested, m_i , and the number of people testing positive for LF, Y_i . Now the model can be denoted:

$$E(Y_i | S(x_i)) = \mu(x_i)$$

$$h(\mu(x_i)) = \sum_{j=1}^k f_{ij}\beta_j + S(x_i)$$

where $h(\cdot)$ is a link function. For binomial data a logit function is used: $h(\mu) = \log(\mu/(1-\mu))$. The spatial process, $S(x_i)$, is modelled as a stationary Gaussian process with $S \sim MVN(0, \sigma^2 R + \tau^2 I)$, where σ^2 is the variance and τ^2 is the nugget effect which accounts for the additional non-spatial variation in the data. R is an $n \times n$ correlation matrix with $R_{l,m} = \rho(\|x_l - x_m\|, \phi)$. The correlation function, ρ , is assumed to be exponential, with $\rho(u) = \exp(-u/\phi)$, where u is the distance between two points and ϕ is a parameter that governs the rate of spatial decay (further details on the GLSM and the Markov chain Monte Carlo (MCMC) parameter estimation are presented in Appendix B).

3.2.4 Parameter Estimation

The likelihood function for the full GLSM cannot be solved directly, instead we look to a Markov Chain Monte Carlo (MCMC) approach in a Bayesian framework. It is assumed that the posterior distribution for each parameter of interest is equal to the likelihood of that parameter given the data and other model parameters, multiplied by the prior distribution. A prior distribution is defined for each of the parameters we are trying to estimate; a value is selected from each distribution using a sampling algorithm at each iteration, if a newly

selected value increases the value of the likelihood function, the value is retained, and if not it is rejected with some probability. This process continues for some pre-specified number of iterations after which we should have a Markov chain that converges to a stable posterior distribution from which we can calculate the mean, standard error, or the credible intervals. Further details on parameter estimation and prediction at new sites are given in Appendix B.

3.2.5 Variogram Analysis

A variogram is used to determine whether the data are spatially correlated. The association between a pair of datapoints is expressed as a function of the distance between them. If the association is greater for datapoints that are closer together, then we can say that they are spatially correlated and can be modelled using a regression model including a spatial correlation term. Specifically, for each pair of datapoints, x_i and x_j , the distance between them is calculated as $u = \|x_i - x_j\|$ and their semivariance is $\gamma = (y_i - y_j)^2 / 2$, where y_k is the value of the observation at location x_k . The distances, u , are grouped into distinct classes to produce a sample binned variogram

$$\hat{\gamma} = \frac{1}{2|N_u|} \sum_{i,j \in N_u} (y_i - y_j)^2$$

Where $\hat{\gamma}$ is the semi variance, u is the distance class, N_u is the set of pairs in class u and $|N_u|$ is the number of pairs in N_u . If the data are spatially correlated we would expect to see lower semivariances for points which are nearer together.

3.2.6 Model Selection

The aim of any variable or model selection procedure is to find a set of uncorrelated predictive variables that produce the best fitting model. In this chapter we adopt a model selection procedure rather than a variable selection procedure whereby all combinations of variables that fit the criteria of being non-correlated are considered. We still look at using both linear and quadratic functional forms. Now each possible set of variables is tested and compared with a spatial Bayesian framework. The process is conducted as follows:

Step 1 - Identify the best fitting functional form for each variable by running linear and quadratic univariate Bayesian GLSMs and comparing the model fit using the deviance information criterion (DIC) (Spiegelhalter et al. 2002).

Step 2 - Identify every possible combination of variables – i.e. find all the combinations of variables that satisfy the criteria of having no pairs of variables with a Spearmans correlation coefficient greater than 0.7.

Step 3 – For each possible set of variables, construct a GLSM. Use the functional forms identified as being the best fitting from step 1. Run the model five times and record the DIC value for each repetition. Initial testing suggests ‘good’ models will have DIC values less than 200 - if the DIC of one of the models is >200 skip the remaining repeated model runs. Repeat this step for all possible sets of variables.

Step 4 - Calculate the mean DIC of each model and select the best performing model for further analysis

3.2.7 Model Implementation

Functional form and model selection stages are run for 50,000 iterations after a burn-in of 50,000. Every 250th element is stored. The final models are run for 200,000 iterations after a burn-in of 200,000 and again every 250th element is stored. The β coefficients are assigned normal prior distributions with mean 0 and variance 5. The spatial parameter, ϕ , which controls the rate of exponential decay of the spatial correlation process, is assigned a reciprocal prior distribution between 5 and 6 for the LF model and between 30 and 40 for the malaria model. These values were informed by the range parameter estimated by the variogram. We assigned σ^2 a uniform prior and we assume τ^2 is proportional to σ^2 , with $\tau^2 = 0.005\sigma^2$, informed by the model variogram. The spatial correlation is modelled with an exponential function. Due to computational limitations we resampled the grid to create a coarser grid with cells of around 60km x 60km using arcGIS. This reduced the number of prediction sites from 500,000 to just under 20,000.

Predictions are only required in regions where LF and malaria exist, so we use two masks to reduce the whole of Africa to just the endemic region. The LF mask is simply the 32 countries in mainland Africa (plus Madagascar) that are still known to have LF (<http://www.filariasis.us/Toolkit-Eng/EndemicCountries.pdf>). The malaria mask is created by using the Seasonal Climatological Suitability for Malaria Transmission map (International Research Institute for Climate and Society - <http://iridl.ldeo.columbia.edu/maproom/Health/Regional/Africa/Malaria/CSMT/>) and described further in Grover-Kopec et al. (2006). This map shows the number of months that are suitable for malaria transmission to occur for each cell based on the climatic suitability of that location. We define the malaria transmission area to be all cells where at least one month per year is suitable for transmission to occur.

Model performance is assessed by testing its ability to make predictions at new sites. This is achieved using two tests: 1) testing if the model is able to predict in areas where there are few data points, and 2) testing if the model is able to predict areas where the prevalence is zero. We also construct a model with no covariates to test whether including covariates makes the model more predictively powerful. The first test was conducted by splitting the data into two

groups - one containing the densely distributed data points and the other containing the sparsely distributed data points. The groups were defined by calculating the cumulative distance to the 5 nearest neighbours of a data point – if this distance was less than 450km the data point was considered 'dense', and 'sparse' otherwise. Ten percent of the data points are removed from one of the groups, a model is then constricted using the all remaining data and used it to predict over the removed data points. The model is run five times, and for each run we obtain a posterior sample for each of the prediction points. We calculate the number of prediction points where the actual prevalence value falls within some specified credible interval of this posterior sample (Beck-Worner et al. 2007). This procedure is repeated for both 'sparse' and 'dense' data. Two models are used – one with just a spatial term and the full model with covariates and a spatial term.

The ability of the model to predict in areas where the prevalence is zero is assessed by comparing the number of 'correct' predictions at sites where prevalence is zero with predictions at sites with positive prevalence.

3.2.8 Convergence diagnostics

For the Bayesian spatial model, both within- and between-chain convergence is examined to assess the stability of the model. Within chain convergence is analysed using two methods, 1) visual checks using trace plots, 2) looking at the MCMC error as a percentage of the standard deviation. Spiegelhalter et al. (2007) suggest a MCMC error of less than 5% of the standard deviation indicates satisfactory convergence. The between chain convergence will be checked by running five identical models and comparing the DIC values and by using the the Gelman-Rubin diagnostic (Gelman and Rubin 1992). This second measure assesses convergence by running parallel chains from different starting values; in theory, when the chains converge, the within chain variance should dominate the between chain variance and all chains should converge to the same marginal distribution. This is measured by comparing the 50th and 97.5th quantiles of the sampling distribution of the shrink factor (the proportion by which the shape parameter of the distribution could reduce by if chain were to run to infinity). If both quantiles are around 1, then the chain has is said to have converged.

3.2.9 Estimating infected populations

The number of people infected with LF and malaria, and the number of people co-infected is estimated. This is achieved by firstly resampling the prevalence maps to the same scale at the population map, then overlaying the maps and multiplying prevalence by population on a cell-by-cell basis to estimate the number of people infected in each cell. The number of people co-infected is estimated by assuming that infection with malaria and LF are independent events, so the prevalence of co-infection in a given cell is defined as the prevalence of malaria multiplied the prevalence of LF.

The mean prevalence and the total number of people with LF, malaria and co-infection in each country can be calculated using the zonal statistics tool in the spatial analyst package in ArcGIS (ArcMap 9.3 ESRI 2009).

The number of people at risk of infection is estimated by assuming that if a cell has a prevalence $>1\%$, then all the people in that cell are at risk of infection. Using this approach we estimate the number of people at risk from malaria and LF. The co-infected population at risk is defined as the number of people living in areas where the prevalence of both malaria and LF is $>1\%$.

3.3 Results

3.3.1 Variogram analysis

The results of the variogram analysis show that for both malaria and LF there is spatial correlation, indicated by the lower semivariance at smaller distances. The range of spatial correlation for LF is much smaller than for malaria. For malaria, $u=60$, (using latlong co-ordinates) which equates to around 3000km and for LF, $u=4$, which corresponds to around 400km. This information is used to set the limits of the prior distribution of the range parameter in the Bayesian spatial model.

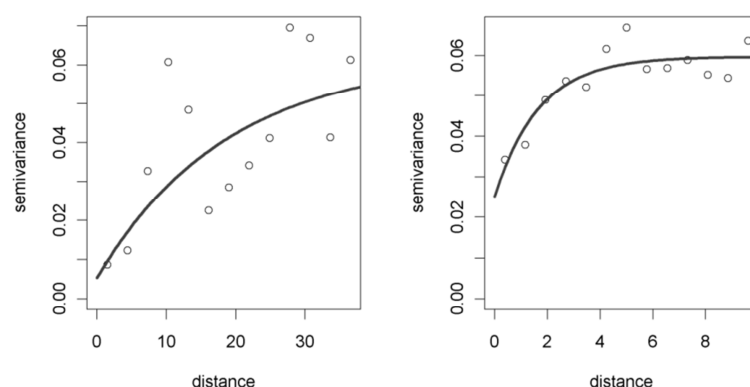


Figure 3.2: Variogram to show the spatial correlation in the data for Malaria (left) and LF (right). The distance at which line begins to flatten out represents the limit of the spatial correlation between data points.

3.3.2 Model selection

In both the malaria and LF models the quadratic functional forms were selected for all variables (Table 3.1).

	LF		Malaria	
	Linear	Quadratic	Linear	Quadratic
Altitude	364.70	325.64	263.66	243.74
NDVI	237.02	176.60	221.79	182.80
Population density	195.18	118.29	206.01	141.46
Mean annual precipitation	325.01	248.47	253.28	229.10
Precipitation in wettest month	326.41	324.17	199.81	159.75
Mean maximum temperature	188.57	136.16	197.54	152.38
Mean temperature in warmest month	172.52	129.05	186.73	152.07
Mean annual temperature	211.43	146.77	197.82	168.99
Mean temperature in coldest month	248.82	202.17	223.51	191.96
Mean minimum temperature	237.34	169.59	219.38	179.22

Table 3.1: DIC values for the linear and quadratic univariate Bayesian GLSM analysis. The quadratic model performed better in every case, so was used in the model selection.

All the possible combinations of uncorrelated variables were identified. There were 192 variable combinations for the malaria model and 288 for the LF model. A quadratic functional form was adopted for each variable. Each model was ran 5 times and the model with the lowest mean DIC was selected. The best performing models consisted of the following variables:

Malaria Model

- Mean temperature in coldest month
- Population density
- Mean temperature in the warmest month

LF model

- NDVI
- Population density
- Mean minimum temperature

3.3.3 Model Convergence

Firstly, the convergence of the model was checked. The trace plots for the parameters in both models are shown in Figure 3.3. The convergence of all the β parameters and σ^2 appears very stable, however, the convergence of ϕ is less stable. We tried running the model for more iterations, but this did not improve the convergence.

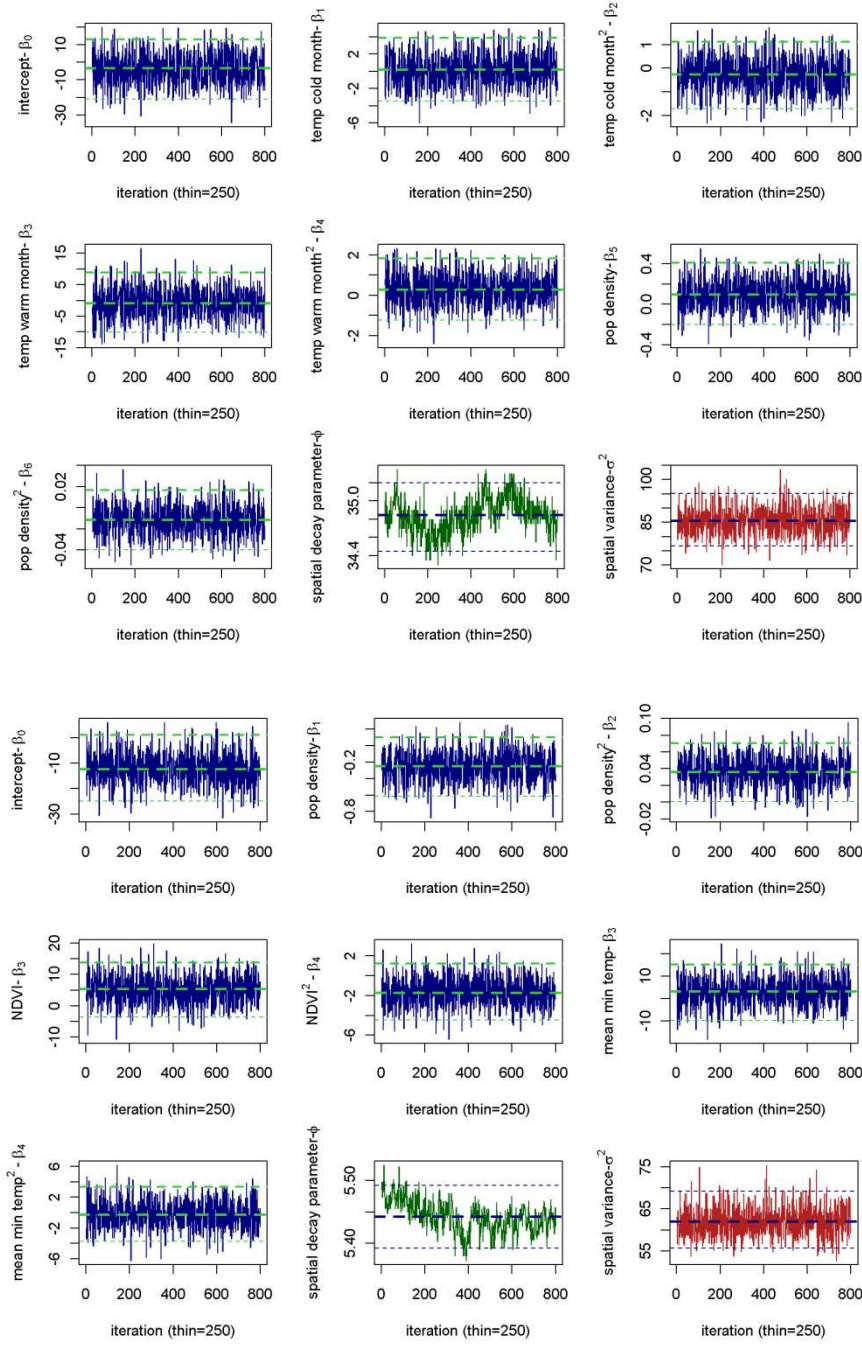


Figure 3.3: Trace plots for malaria (top 9 plots) and LF (bottom 9 plots) parameters. Models were run for 200,000 iterations and every 250th value was stored. The central dashed line in the mean and the upper and lower dashed lines are the 95% credible intervals. The plots with dark blue lines are the coefficients of the model parameter and those with the green and red lines are the spatial parameters.

The Geldman-Rubin (GR) diagnostic was around 1 for all the β s and σ^2 . This suggests that these parameters have converged (Table 3.2). However, ϕ did not converge, the GR statistic suggests that if the model was ran for more iterations the scale parameter (which controls the

variance) of the posterior distribution of ϕ would decrease. This is because the the within chain variance is small, but the between chain variance is larger. The within chain variance is smaller because the algorithm sampled from a discretised chain. The GR statistic is supposed to be ran using overdispersed starting values, however, as ϕ was assigned a very informative prior, this was not possible.

Malaria Model			LF Model		
Variable	Point est and 97.5% quantile	mcmc error as % of sd	Variable	Point est and 97.5% quantile	mcmc error as % of sd
β_0 - intercept	1, 1.01	3.536	β_0 - intercept	1, 1	3.419
β_1 - mean temp in cold month	1, 1	3.564	β_1 -population density	1, 1.01	3.620
β_2 - mean temp in cold month ²	1, 1	3.511	β_2 - population density ²	1, 1.01	3.538
β_3 - mean temp in warm month	1, 1	3.455	β_3 - NDVI	1, 1	3.525
β_4 - mean temp in warm month ²	1, 1	3.403	β_4 - NDVI ²	1, 1	3.526
β_5 -population density	1, 1	3.506	β_5 - mean minimum temp	1, 1	3.483
β_6 - population density ²	1, 1	3.461	β_6 - mean minimum temp ²	1, 1	3.487
phi	1.37, 1.84	12.47	phi	2.05, 3.17	11.01
sigma ²	1, 1	3.594	sigma ²	1, 1	3.506

Table 3.2: Within and between chain convergence is assessed using the Gelman Rubin (GR) statistic. If the point estimate and the 97.5% quantile are ≈ 1 , this indicates between chain convergence. An mcmc error of less that 5% of standard deviation is considered an indicator of sufficient within chain convergence (this was calculated for the best performing model).

3.3.4 Final LF and malaria models

The DIC values from 5 identical realisations of each model were compared. For the LF model, the mean DIC was 127.2 and the values had a range of 125.9 – 128.2. The mean DIC for the malaria model was 148.6 and the range was 146.0 – 153.5. The models with the lowest DIC values were used for all further analysis. The parameter estimates from these models are presented in Table 3.3. We also ran models with a spatial term but no covariates to see whether this improved the model fit. The DIC values for the models with no covariates are higher than the models with covariates (Table 3.3), suggesting including environmental covariates produces better fitting models.

A parameter can be considered significant if zero does not fall within the credible interval (CI) – for the LF model only the spatial parameters are significant using a 95% CI, but using a 50% CI population density and NDVI are significant, as well as the spatial parameters. For the malaria model again only the spatial parameters are considered significant at a 95% CI, and

at a 50% CI the only additional parameter becoming significant is the quadratic population density term.

Malaria model

	Full model with covariates			Model with no covariates	
	mean	95% CI	50% CI	mean	95% CI
β_0 - intercept	-3.966	(-20.941, 13.003)	(-10.63, 2.302)	-2.796	(-14.188, 9.350)
β_1 - mean temp in cold month	0.225	(-3.432, 3.884)	(-0.985, 1.552)		
β_2 - mean temp in cold month ²	-0.274	(-1.71, 1.113)	(-0.794, 0.228)		
β_3 - mean temp in warm month	-0.742	(-10.162, 8.819)	(-4.111, 2.737)		
β_4 - mean temp in warm month ²	0.282	(-1.246, 1.825)	(-0.277, 0.84)		
β_5 -population density	0.103	(-0.199, 0.41)	(-0.009, 0.21)		
β_6 - population density ²	-0.012	(-0.04, 0.017)	(-0.021, -0.002)		
phi	34.845	(34.45, 35.2)	(34.75, 34.95)	33.134	(30.448, 35.951)
sigma ²	85.402	(76.67, 95.054)	(82.196, 88.388)	85.535	(76.606, 96.762)
DIC	146.02			568.18	

LF model

	Full model with covariates			Model with no covariates	
	mean	95% CI	50% CI	mean	95% CI
β_0 - intercept	-11.981	(-24.828, 1.168)	(-16.295, -7.814)	-3.395	(-7.532, 0.654)
β_1 -population density	-0.249	(-0.612, 0.104)	(-0.377, -0.116)		
β_2 - population density ²	0.037	(0.001, 0.071)	(0.025, 0.048)		
β_3 - NDVI	5.163	(-3.633, 13.786)	(1.785, 8.523)		
β_4 - NDVI ²	-1.648	(-4.461, 1.202)	(-2.744, -0.582)		
β_5 - mean minimum temp	3.16	(-9.704, 15.341)	(-1.327, 7.596)		
β_6 - mean minimum temp ²	-0.201	(-3.703, 3.343)	(-1.487, 1.06)		
phi	5.443	(5.393, 5.492)	(5.425, 5.46)	5.84	(5.605, 5.995)
sigma ²	61.988	(55.626, 69.268)	(59.544, 64.091)	61.861	(55.411, 69.697)
DIC	126.62			1085.7	

Table 3.3: parameter values for the malaria (top) and LF (bottom) models including the 95% and 50% credible intervals and DIC values. The variable considered significant at different credible intervals are highlighted in bold.

3.3.5 Prevalence Maps

The model predictions are shown in Figure 3.4. Malaria prevalence is predicted to be highest in western Africa and Tanzania. The whole region below the Sahara and above Botswana is predicted have to have fairly high prevalence apart from Zimbabwe and in and around

Somalia. We predict fairly high malaria prevalence in west and central Madagascar but low prevalence in east Madagascar.

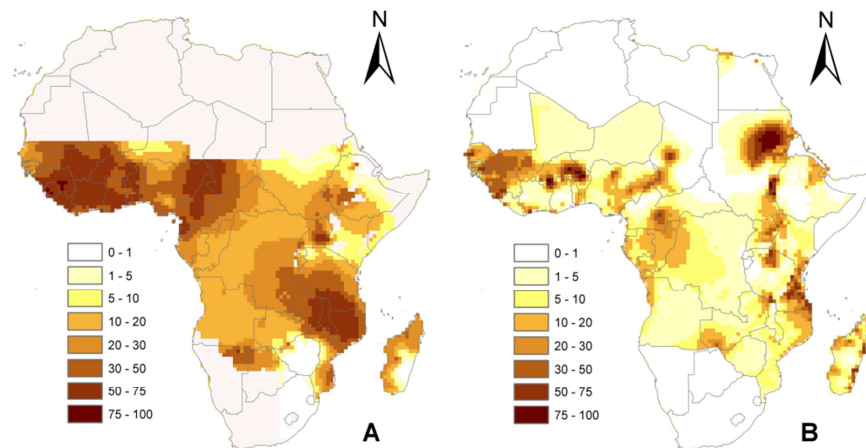


Figure 3.4: Maps showing the prevalence (%) of (A) malaria and (B) LF as predicted by the best performing GLSMs

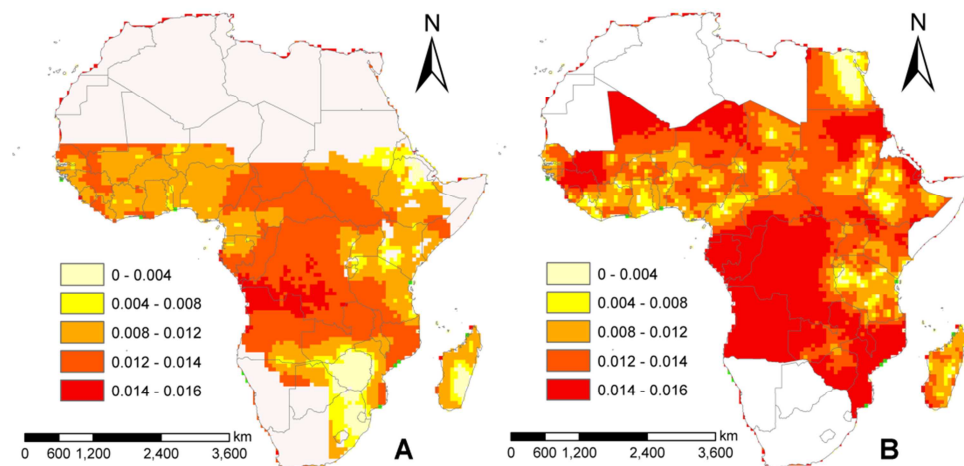


Figure 3.5: Error maps for malaria (A) and LF (B). Darker colours indicate larger error. The errors are largest in areas with no prevalence data.

LF prevalence is predicted to be highest around Sudan, Tanzania and western Africa. Interestingly regions of some countries where we had no data, were found to be LF endemic – in particular areas of central Africa have prevalences up to 10% - however, when considering the predictions in unsampled regions we must bear in mind the huge distances over which the model is extrapolating, and the large prediction errors associated with these predictions.

Figure 3.5A shows the standard error for the malaria predictions and Figure 3.5B shows the standard error for the LF predictions. We see that the highest prediction errors for both

malaria and LF are in central Africa where we have almost no datapoints. The lowest errors are in western Africa where the data are more densely distributed.

Using the prevalence prediction maps (Figure 3.4) a malaria and LF co-infection map was created by highlighting the areas where the prevalence of both infections is above some threshold (Fig 3.6A). Here it is clear that most of sub-Saharan Africa is likely to have co-infection of malaria and LF. The worst affected areas are in western Africa and along the east coast near Tanzania. Figure 3.6B shows areas where the prevalence of one infection is high whilst the prevalence of the other infection is low. This shows that malaria tends to dominate over LF.

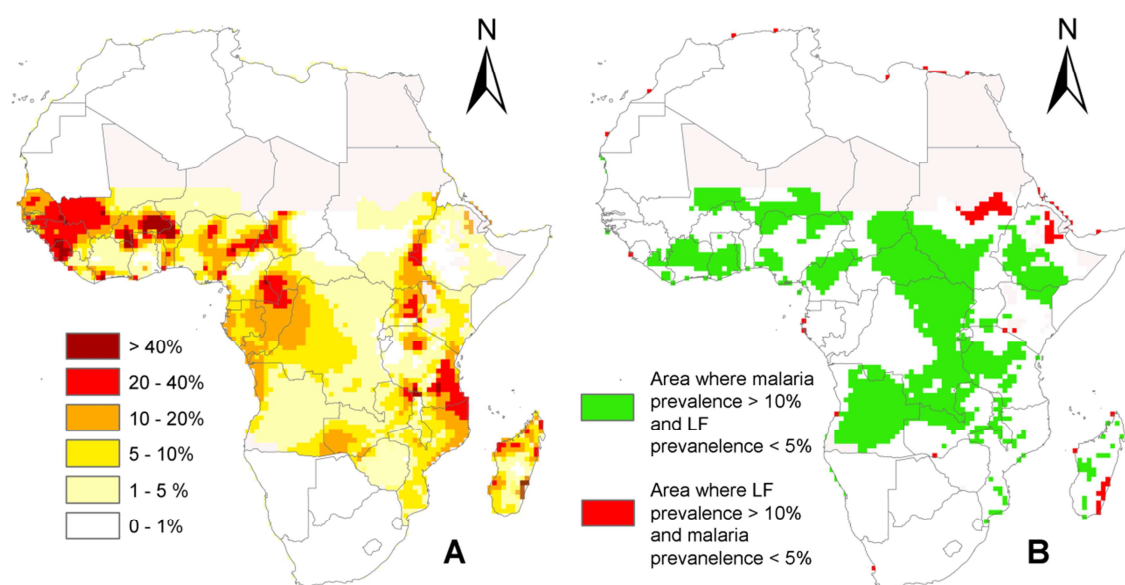


Figure 3.6: Co-infection maps showing A) where the prevalence of both infections are above certain thresholds. For example, the areas in orange are where the prevalence of LF and malaria are both above 10%. B) Regions where the prevalence of one infection is higher than the other.

3.3.6 Populations infected and at-risk

Using population data maps and the prevalence maps we estimate the number of people infected and the prevalence of malaria, LF and co-infection in each country (see Table 3.4) and the number of people living in areas at risk from each infections, and co-infection (see Table 3.5). An at-risk area is defined to be anywhere with prevalence >1%.

Country	Malaria		LF		Co-infection	
Angola	2.48m	(14.2%)	1.13m	(6.5%)	0.16m	(0.9%)
Benin	3.36m	(43.3%)	1.13m	(14.6%)	0.49m	(6.3%)
Botswana	0.06m	(3.6%)	0m	(0.0%)	0m	(0.0%)
Burkina Faso	8.87m	(56.5%)	4.07m	(25.9%)	2.3m	(14.6%)
Burundi	1.68m	(19.3%)	0.04m	(0.5%)	0.01m	(0.1%)
Cameroon	8.9m	(49.0%)	1.78m	(9.8%)	0.87m	(4.8%)
Central African Republic	1.32m	(29.8%)	0.43m	(9.7%)	0.13m	(2.9%)
Chad	4.32m	(40.4%)	0.98m	(9.1%)	0.39m	(3.7%)
Congo	0.76m	(17.5%)	0.44m	(10.2%)	0.08m	(1.8%)
Djibouti	0m	(0.0%)	0.07m	(11.3%)	0m	(0.0%)
Egypt	0m	(0.0%)	3.17m	(4.2%)	0m	(0.0%)
Equatorial Guinea	0.24m	(44.3%)	0.03m	(5.6%)	0.01m	(2.5%)
Eritrea	0.14m	(2.8%)	0m	(0.0%)	0m	(0.0%)
Ethiopia	10.43m	(13.1%)	1.94m	(2.4%)	0.25m	(0.3%)
Gabon	0.38m	(24.4%)	0.17m	(11.1%)	0.04m	(2.7%)
Gambia, The	0.29m	(21.1%)	0.2m	(14.1%)	0.04m	(3.0%)
Ghana	11.86m	(50.0%)	1.42m	(6.0%)	0.71m	(3.0%)
Guinea	5.98m	(60.4%)	2.3m	(23.2%)	1.39m	(14.0%)
Guinea-Bissau	0.31m	(21.8%)	0.36m	(25.4%)	0.08m	(5.5%)
Ivory Coast	9.9m	(53.2%)	1.39m	(7.4%)	0.74m	(4.0%)
Kenya	3.95m	(11.2%)	2.52m	(7.2%)	0.28m	(0.8%)
Liberia	2.67m	(57.7%)	0.49m	(10.7%)	0.29m	(6.2%)
Madagascar	2.24m	(10.9%)	2.19m	(10.7%)	0.24m	(1.2%)
Malawi	7.62m	(54.6%)	0.72m	(5.2%)	0.39m	(2.8%)
Mali	8.21m	(53.8%)	2.7m	(17.7%)	1.45m	(9.5%)
Mauritania	0.76m	(21.4%)	0m	(0.0%)	0m	(0.0%)
Mozambique	6.69m	(32.6%)	1.68m	(8.2%)	0.55m	(2.7%)
Namibia	0.19m	(10.0%)	0m	(0.0%)	0m	(0.0%)
Niger	2.63m	(16.9%)	0.48m	(3.1%)	0.08m	(0.5%)
Nigeria	48.57m	(34.0%)	13.53m	(9.5%)	4.6m	(3.2%)
Rwanda	0.9m	(9.6%)	0.09m	(1.0%)	0.01m	(0.1%)
Senegal	2m	(17.9%)	2.57m	(23.1%)	0.46m	(4.1%)
Sierra Leone	3.76m	(61.9%)	2.14m	(35.2%)	1.32m	(21.8%)
Somalia	0.61m	(5.0%)	0m	(0.0%)	0m	(0.0%)
South Africa	0.07m	(0.2%)	0m	(0.0%)	0m	(0.0%)
Sudan	2.58m	(6.7%)	9.31m	(24.3%)	0.63m	(1.6%)
Tanzania, United Rep. of	10.91m	(25.7%)	6.68m	(15.8%)	1.72m	(4.1%)
Togo	2.77m	(49.8%)	0.9m	(16.2%)	0.45m	(8.1%)
Uganda	11.43m	(34.9%)	4.3m	(13.1%)	1.5m	(4.6%)
Dem. Rep. of Congo	14.95m	(21.1%)	4.11m	(5.8%)	0.87m	(1.2%)
Zambia	3.45m	(26.6%)	0.97m	(7.4%)	0.26m	(2.0%)
Zimbabwe	0.22m	(1.5%)	0.41m	(2.7%)	0.01m	(0.0%)
TOTAL	208.49m	(21.6%)	76.84m	(8.0%)	22.79m	(1.7%)

Table 3.4: Number of people infected with malaria, LF and both infections and associated prevalences for countries in Africa.

Country	Malaria		LF		Co-infected	
Angola	17.24m	(98%)	17.58m	(100%)	17.24m	(98%)
Benin	6.41m	(83%)	5.85m	(76%)	5.85m	(76%)
Botswana	0.42m	(26%)	0m	(0%)	0m	(0%)
Burkina Faso	15.7m	(100%)	15.7m	(100%)	15.7m	(100%)
Burundi	8.68m	(100%)	0.69m	(8%)	0.69m	(8%)
Cameroon	18.01m	(99%)	14.74m	(81%)	14.74m	(81%)
Central African Republic	4.34m	(98%)	4.18m	(95%)	4.18m	(95%)
Chad	9.16m	(86%)	8.4m	(78%)	7.44m	(69%)
Congo	4.02m	(92%)	4.02m	(92%)	4.02m	(92%)
Djibouti	0m	(0%)	0.44m	(75%)	0m	(0%)
Egypt	0m	(0%)	20.4m	(27%)	0m	(0%)
Equatorial Guinea	0.45m	(85%)	0.43m	(81%)	0.43m	(81%)
Eritrea	3.74m	(74%)	0m	(0%)	0m	(0%)
Ethiopia	59.18m	(74%)	30.89m	(39%)	24.87m	(31%)
Gabon	1.44m	(93%)	1.46m	(94%)	1.44m	(93%)
Gambia, The	1.41m	(100%)	1.41m	(100%)	1.41m	(100%)
Ghana	22.56m	(95%)	18.73m	(79%)	18.73m	(79%)
Guinea	9.81m	(99%)	9.81m	(99%)	9.81m	(99%)
Guinea-Bissau	1.42m	(100%)	1.41m	(99%)	1.41m	(99%)
Ivory Coast	17.24m	(93%)	16.22m	(87%)	16.22m	(87%)
Kenya	27.93m	(79%)	33.81m	(96%)	26.64m	(75%)
Liberia	4.43m	(96%)	4.35m	(94%)	4.35m	(94%)
Madagascar	16.16m	(79%)	17.17m	(84%)	13.49m	(66%)
Malawi	13.95m	(100%)	13.52m	(97%)	13.52m	(97%)
Mali	14.74m	(96%)	15.27m	(100%)	14.73m	(96%)
Mauritania	1.92m	(54%)	0m	(0%)	0m	(0%)
Mozambique	20.18m	(98%)	19.88m	(97%)	19.77m	(96%)
Namibia	0.66m	(34%)	0m	(0%)	0m	(0%)
Niger	15.07m	(97%)	14.97m	(96%)	14.45m	(93%)
Nigeria	138.32m	(97%)	136.93m	(96%)	136.93m	(96%)
Rwanda	7.45m	(79%)	4.14m	(44%)	4.14m	(44%)
Senegal	8.39m	(75%)	8.39m	(75%)	8.39m	(75%)
Sierra Leone	5.17m	(85%)	6.12m	(100%)	5.17m	(85%)
Somalia	8.4m	(69%)	0m	(0%)	0m	(0%)
South Africa	0.93m	(2%)	0m	(0%)	0m	(0%)
Sudan	27.26m	(71%)	28.24m	(74%)	18.24m	(48%)
Tanzania, United Republic of	41.47m	(98%)	35.24m	(83%)	35.24m	(83%)
Togo	5.74m	(100%)	5.54m	(99%)	5.54m	(99%)
Uganda	32.48m	(99%)	31.94m	(98%)	31.86m	(97%)
Zaire	69.04m	(98%)	66.07m	(93%)	65.92m	(93%)
Zambia	12.93m	(100%)	12.93m	(100%)	12.93m	(100%)
Zimbabwe	2.97m	(20%)	14.78m	(99%)	2.97m	(20%)
TOTAL	676.82m	(77%)	641.65m	(73%)	578.46m	(66%)

Table 3.5: Number of people living in areas at-risk from malaria, LF and both infections and the percentage of people in each country living in at-risk areas.

3.3.7 Model Testing

Firstly the data is split into 'sparse' and 'dense' groups. For the malaria model there are 556 densely distributed data points and 86 sparsely distributed data points, so 56 and 9 data points were removed respectively (see Figure 3.7A).

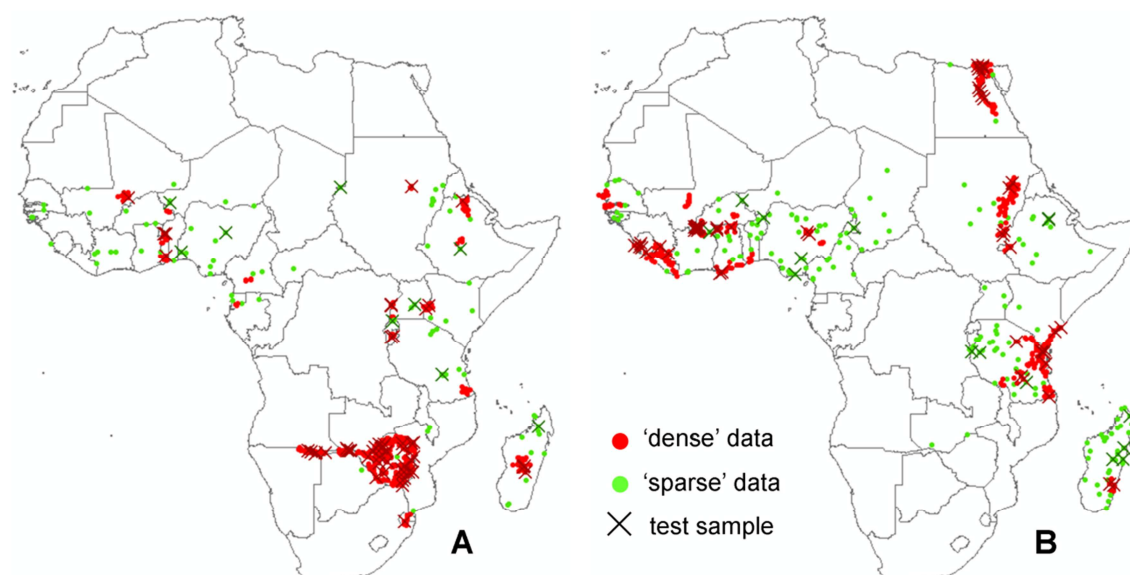


Figure 3.7: Maps showing the dense (red) and sparse (green) datapoints for malaria (A) and LF (B). The data used at the testing samples are identified with crosses.

Data	Model	Credible Interval				
		5%	25%	50%	75%	95%
Dense	covariates	4.6 ± 1	20 ± 0.7	38.9 ± 0.7	55.4 ± 0	68.9 ± 0.5
Dense	no covariates	6.1 ± 1	19.3 ± 1.3	37.9 ± 1	54.3 ± 0.5	68.6 ± 1.6
Sparse	covariates	6.7 ± 0.5	42.2 ± 0.4	71.1 ± 0.5	77.8 ± 0	100 ± 0
Sparse	no covariates	13.3 ± 1.1	44.4 ± 0	68.9 ± 0.7	77.8 ± 0	100 ± 0

Table 3.6: Malaria model – mean percentage of correctly predicted data points for difference credible intervals and associated 95% confidence interval. A point is deemed 'correctly predicted' if the actual (observed) value at that site falls within the specified credible interval. We predicted over 56 data points for the 'dense' data and 9 data points for the 'sparse' data.

The results for the malaria model testing are shown in Table 3.6 where we have the number of correctly predicted test sites for different models at sparse and dense test data sites for difference credible intervals. Interestingly the model is actually better at predicting sparsely distributed data. Of the data removed for testing the malaria model, 12 of the 65 data points had zero prevalence. Using a 95% credible interval and the model with covariates, approximately 88% of positive prevalence sites are predicted correctly, but 0% of the zero

prevalence sites are predicted correctly. For the model with no covariates these figures are 85% and 3% respectively. This shows that the model is particularly poor at predicted where prevalence is zero, but fairly good at predicting sites with positive prevalence.

For the LF data we had 503 and 161 densely and sparsely distributed data respectively; of these 50 and 16 were removed from each group for model testing. These are shown in Figure 3.7B.

Data	Model	Credible Interval				
		5%	25%	50%	75%	95%
Dense	covariates	6.4 ± 0.7	27.6 ± 1.4	45.6 ± 1.1	62 ± 0.6	80 ± 0.6
Dense	no covariates	5.6 ± 0.7	24.8 ± 1	46.8 ± 1.9	60.4 ± 1	78.8 ± 1
Sparse	covariates	1.3 ± 0.4	29.3 ± 0.5	60 ± 0	68 ± 0.4	84 ± 0.8
Sparse	no covariates	2.7 ± 0.5	32 ± 0.4	66.7 ± 1.2	78.7 ± 0.7	92 ± 0.4

Table 3.7: LF model – mean percentage of correctly predicted data points for difference credible intervals and associated 95% confidence interval. We predicted over 50 data points for the ‘dense’ data and 16 data points for the ‘sparse’ data.

The LF model testing results are shown in Table 3.7. Nine out of 50 of the data points had zero prevalence in dense test data for the LF model. Only 44% of these were correctly predicted using a 95% credible interval whereas for the data with positive prevalence 88% were correctly predicted using the model with covariates (42% and 87% correctly predicted using model with no covariates). The sparse testing data also contained zero prevalence sites for the LF model – here 3 out of 16 sites had zero prevalence. Just 53% of these were correctly predicted using the model with covariates. In contrast 92% of the sparse testing data with positive prevalence's were correctly predicted.

3.4 Discussion

In this chapter, Bayesian GLSMs were developed to map the prevalence of LF and malaria in Africa using environmental and demographic predictors. The resulting maps were used to estimate the number of people infected with LF and malaria and the number of people co-infected. The prevalence maps were also used to estimate, for the first time, the number of people living at areas at risk from LF, malaria and co-infection in Sub Saharan Africa.

The co-infection map (Figure 3.6A) shows areas where the prevalence of both infections is above some threshold. From this map we see that most of Africa below the Sahara and

above southern Africa has prevalence of both infections above 1%. The areas predicted to have the highest levels of co-infection are in western Africa, in particular Burkina Faso, southern Mali, Guinea, Senegal and Sierra Leone (Figure 3.6A). There are also smaller areas of high co-infection in western central Africa, along the east coast in Tanzania and Mozambique, and in Madagascar. These areas could be deemed the areas most suitable for integrated control as they have the highest levels of malaria and LF co-infection. We also estimate the number of people living in areas at risk from co-infection – we predict that in many countries, over 90% of the population is living in at-risk areas (Table 3.5). Figure 3.6B shows areas where malaria prevalence is over 10% and LF prevalence is under 5% and vice versa. Here we see large areas in central Africa and to a lesser extent west Africa have a relatively low LF prevalence and high malaria prevalence – indicating areas that might be areas more suited to a focus on malaria control.

Maps showing the errors associated with LF and malaria prevalence predictions were produced to help identify areas where we have the most and least confidence in our prevalence predictions, and also to identify areas where sampling is needed to make more assured predictions in the future. Areas more densely sampled, for example west Africa for the LF dataset, have lower standard error suggesting we can have more confidence in these predictions, whereas areas with little or no data, such as large parts of central Africa, have high associated standard error. One important way to test the validity of our model would be to obtain prevalence data for unsampled areas and compare with the model predictions.

There are two key reasons why a Bayesian MCMC approach is chosen for this analysis: firstly, it allows us to obtain estimates of the error associated with new predictions. Prediction error estimates using a frequentist framework are calculated by firstly estimating the model parameters, these resulting values are then taken as fixed and used to make new predictions, so any uncertainty regarding the parameter values is not taken into account when making the model predictions. This is not the case in the Bayesian framework where the uncertainty in the model parameters is accounted for in the model predictions. A frequentist approach can lead to underestimates of the error associated with predictions, whereas by using a Bayesian approach, more realistic error estimates are obtained. Secondly, the covariance structure of the spatial process is taken into account when predictions are made over new sites. The *geoRglm* package allows the spatial covariance structure of the data to be estimated within the parameter estimation process. Ignoring the spatial process can lead to overly tight confidence intervals around the coefficient estimations and underestimates of the uncertainty at model prediction sites (Thomson et al. 1999).

MCMC methods are used to approximate the likelihood function; the alternative to this involves making a simplifying approximation of the likelihood function which assumes the data

are normally distributed, a condition our data violates. This method leads to poorly fitting models and overly confident model predictions.

Typically, studies using GLSMs with predictive variables have either not attempted any sort of variable selection (Ben-Ahmed et al. 2010), just looked at a couple of different models (Beck-Worner et al. 2007; Gosoni et al. 2010; Riedel et al. 2010), or used a frequentist variable selection approach to determine the variables to be used in the Bayesian model (Clements et al. 2006; Craig et al. 2007; Brooker and Clements 2009; Noor et al. 2009). In this study we have, for the first time, implemented a full model selection procedure within a spatial Bayesian framework. The full set of acceptable models is initially defined as those with sets of variables that are not highly correlated. Each of these models is constructed and the best performing one is selected as the final model. Although computationally far more expensive, this method is far more rigorous than previous approaches as we are now examining the entire model space rather than just selecting one out of possibly many sets of predictive non-correlated variables.

The predictive ability of the model was tested by exploring, firstly, whether the model could predict accurately in areas with few training datapoints, and secondly, whether the model could make accurate predictions in areas with very low prevalence. To do this the data were split into two groups - 'dense' and 'sparse' data - and the model was used to predict over a random sample of the testing data from each group. The results from this show that in fact the model predicted more accurately over the 'sparse' data set for the malaria model (Table 3.6) and for the LF model there was no significant difference in performance (Table 3.7). The predictive ability of the model over zero prevalence sites was assessed by simply calculating the number of correctly predicted zero prevalence data points and positive prevalence data points out of the testing data. The malaria model correctly predicted 88% of positive prevalence sites but 0% of zero prevalence sites (using the 95%CI) - suggesting the model is poor at predicting malaria-free areas. Similarly the LF model correctly predicted 89% of positive prevalence sites and 46% of zero prevalence sites. This suggests the LF model predicts areas of zero prevalence better than the malaria model. One reason for this could be that LF prevalence levels are relatively constant throughout the year whereas malaria prevalence levels can be highly variable, especially in areas with seasonal malaria transmission - if the malaria prevalence survey was conducted at a time of low transmission the prevalence could have been measured as zero even though the area is suitable for transmission during other periods. Models with and without covariates were used to make predictions to see whether the addition of covariates made the model more predictively powerful (Tables 3.6 and 3.7). Both the malaria and the LF models without covariates predicts a slightly higher proportion of test data correctly, but this difference is not significant ($p < 0.05$). This result is unexpected as the DIC values for the models with no covariates are much higher than the DIC values for the full models.

This is a first attempt to identify the areas co-endemic with LF and malaria for the whole of Africa based on prevalence data and environmental and population covariates. Despite the fact that it is known that malaria and LF transmission are dependent on climate and altitude (Lardeux and Cheffort 1997; Craig et al. 1999; Onapa et al. 2001), including environmental covariates did not improve the predictive ability of the model. This could be due to the quality of the climate data, in particular the climate data used was averaged over the period 1960-2000, meaning all the interannual variability and temperature extremes would be missed, and the spatial scale of the data was fairly large meaning that we miss the microscale variations in LF and malaria prevalence. One previous study looking at LF and malaria co-endemicity found a negative spatial association between the two infections (Kelly-Hope et al. 2006). An explanation for this was that different vector species within the *Anopheles* genus have different competences and slightly different ecological niches, so, for example, malaria may dominate if the mosquitoes in that areas are relatively better vectors of malaria than LF. Seasonality was thought to be a factor – for example, LF could be inhibited in areas with higher and more prolonged malaria transmission. Although we did not uncover a negative spatial association between malaria and LF, this is likely to be due to the large spatial scale and the lack of vector species data. This study highlights the importance of understanding the niches, the distribution and the relative competences of the different vector species, particularly in areas where integrated control is used: the effectiveness of a vector control measure could vary depending on the vector make-up of an area.

The variograms (Figure 3.2) show different spatial scales for malaria and LF: prevalence data points are spatially correlated over greater distances for malaria than for LF. This could be because malaria is a faster moving disease – infection can be transmitted by a single vector bite, and R_0 values for malaria are typically higher than for LF, so infection could spread quicker and further. LF transmission is slower, so infection may tend to be more localised.

Many other sources of error are present in the data used in the analysis: the infection data are taken over a wide period of time and at different months of the year meaning we have no information on how infection changes throughout the year and between years, and the prevalence data are taken from many different studies which use different sampling methods and different testing techniques. Malaria control has been on-going for decades, as has LF control to a lesser extent – we do not have information on the control history of all our study sites, meaning that an area might be measured as having low prevalence, but actually the ecology of the region is suitable to support a higher level of transmission and higher prevalence in the absence of control.

Studies attempting to map prevalence over smaller areas with more consistent data may produce more accurate infection maps, and may prove to be more useful in the planning of

integrated control strategies (Clements et al. 2006). Stensgaard et al. (2011) mapped the prevalence of LF and malaria in Uganda using a Bayesian GLSM. Data were collected within a three year period, and the study sites were sampled across the region using existing procedures to ensure a non-biased spatial distribution (Onapa et al. 2005). Due to the smaller study area, environmental and demographic variables were available on a much smaller scale. The results from this study show that most of the environmental variables were statistically significant, suggesting that the relationships between the environmental predictors and prevalence are better defined for a smaller study area.

Mapping the distribution and severity of an infection is often thought to be this first step towards planning a control programme as well as acting as a useful tool for advocacy work for raising awareness of the scale and extent of a disease, particularly the neglected tropical diseases. Here we hope that estimates of the number of people living in areas where both malaria and LF transmission occurs could be used to highlight the massive potential for implementing integrated control programmes, as well as identifying candidate regions with a high prevalence of both infections that might be suitable for integrated control.

Chapter 4

Modelling the co-infection of Lymphatic Filariasis and Malaria

4.1 Introduction

As described in Chapter one, malaria and LF cause the largest public health burden of all vector-borne diseases worldwide (Townson et al. 2005). These infections are thought to be co-endemic in large regions of sub-Saharan Africa, as shown in chapter three (Molyneux and Nantulya 2004; Bockarie et al. 2009) and are transmitted by the same vector, the *Anopheles* mosquito (Muturi et al. 2008). Mosquitoes of this genus are the sole vector of malaria and are the predominant vector of LF in rural and semi-urban environments in Africa.

Malaria and LF parasites can co-exist in both the vector (Muirhead-Thomson 1953; Burkot et al. 1990) and host (Ghosh and Yadav 1995). Interactions between the malaria and LF parasites are thought to have an effect on the transmission cycle of each infection. Vectors are thought to experience increased mortality as a result of single LF, or combined LF and malaria infection (Hawley 1985; Michael et al. 2009). Changes in the host immunological response to each parasite as a result of co-infection have been reported to lead to changes in immunity, susceptibility and disease severity (Su et al. 2005; Fenton et al. 2008; Graham 2008; Hillier et al. 2008; Fairlie-Clarke et al. 2010).

If interactions between these infections exist, control programmes aimed at one of the infections could possibly have unexpected knock-on effects on the other infection. Here, we attempt to explicitly model the interactions between LF and malaria, and to understand how co-infection could impact the transmission and prevalence of each infection. Integrated control strategies, where both diseases are targeted simultaneously (Manga 2002), for example combining mass drug administration with bed net distribution (WHO 2011), have

been suggested as a way to reduce the transmission of both LF and malaria. However, it is thought that targeting only LF could actually increase malaria incidence; LF infected mosquitoes experience increased mortality due to their larval burden (Hawley 1985), so, eliminating LF would increase vector lifespan, meaning a mosquito would have more time to transmit malaria parasites. In this chapter we attempt to construct a framework which can be used to investigate how these effects could impact infection prevalence and control decisions.

A co-infection model is developed for malaria and LF that describes the individual transmission dynamics of each infection and the interactions between the two infections in the host and in the vector. The model is used to investigate the impact of co-infection on the transmission dynamics of each infection, in particular looking at how introducing one infection into a region already endemic with the other infection affects prevalence, how different interaction scenarios affect prevalence, and how the host and vector interaction effects combine to alter overall prevalence.

4.2 Mathematical Model Development

4.2.1 Background

Compartmental (catalytic) models are traditionally used for modelling microparasitic infections such as malaria (Macdonald 1957; Anderson and May 1981) and involve modelling multiple 'infection states' for the host (and the vector, for vector-borne diseases). Macroparasite infections, such as LF, are modelled slightly differently; the state of the infection is determined by the parasite burden in the host rather than just presence or absence of infection (Anderson and May 1985). Macroparasites do not reproduce within the host, so the effects of infection build up over time, and an individual can be infected for decades. Microparasites, on the other hand, do reproduce in the host and infections tend to have a much shorter duration.

Modelling the co-transmission of multiple infections has become increasingly popular as evidence of meaningful within-host interactions between parasite species becomes better established (Petney and Andrews 1998; Cox 2001; Booth 2006; Brooker et al. 2007; Cattadori et al. 2008; Graham 2008). The first framework for modelling the co-transmission of a microparasitic and a macroparasitic infection was developed by Fenton (2008). This consisted of a simple SI (susceptible-infected) model for the microparasites in the hosts and a macroparasite model that tracks the number of worms in hosts susceptible to and infected with the microparasite. These worms produce eggs that pass to the environment and can then pass back to either microparasite susceptible or infected humans, where they become adult macroparasites.

In this chapter the basic framework outlined by Fenton (2008) is adopted and developed to capture malaria and LF transmission dynamics. This involves several major new additions including: (1) explicitly modelling the vector population, with the external macroparasite infective stage modelled as larvae in the vector, (2) dividing the human and vector populations into different compartments depending on their malarial status and modelling the macroparasite populations in each of these compartments, (3) modelling three parasite stages in the host, namely developing LF worms, adult LF worms and microfilariae, (4) explicitly modelling the development of larvae in the vector and (5) capturing the effect of co-infection on host infection dynamics. Firstly, the single malaria and LF models are described, then the combined co-infection model is explained.

4.2.2 Malaria model

For the malaria component of the model a SEIRS (susceptible-exposed-infectious-recovered-susceptible) model is used for the humans and an SEI model is used for the vectors (see Figure 4.1). The state variables for the human population are denoted: S_H , E_H , I_H and R_H , and for the vector population: S_V , E_V and I_V . It is assumed that if a vector becomes infected, it does not recover (Macdonald 1957; Smith and Ellis McKenzie 2004).

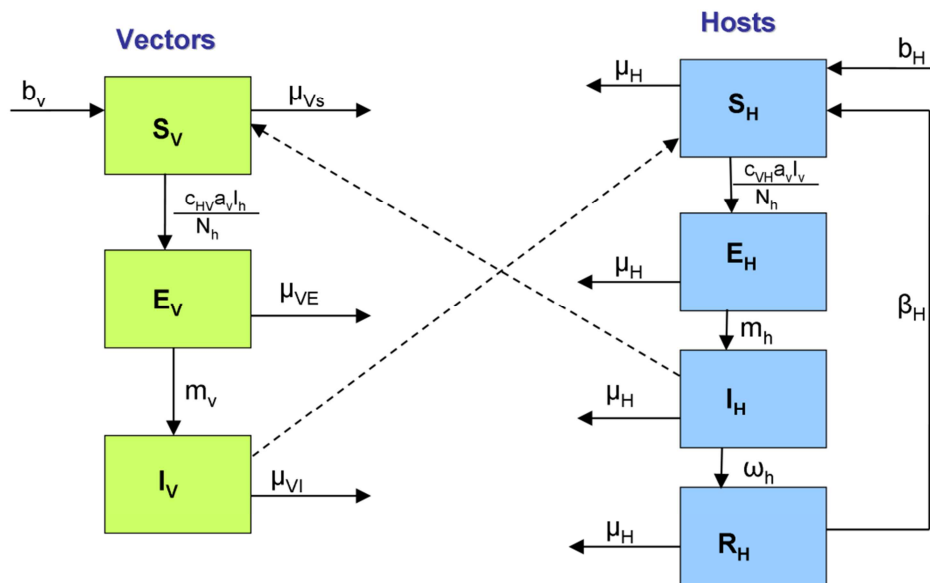


Figure 4.1: Basic structure of the malaria model (see Tables 4.2 and 4.3 for a summary of state variable and parameter definitions)

Susceptible humans become exposed (infected but not infectious) by receiving a bite from an infectious vector. Around 10 days after receiving the bite the host then becomes infectious. It takes around 200 days for the host to clear infection and move to the recovered compartment

– it is assumed that humans are temporarily immune from infection, so remain here for a short period before returning to the susceptible category. Vectors become exposed by taking a bite from an infectious host, they then become infectious around 10 days later. When an infectious vector then bites a susceptible host, infection is transmitted and the cycle continues.

The number of humans progressing from susceptible to exposed compartments is determined by the force of infection from infectious vectors to susceptible hosts. The rate at which humans move from exposed to infectious is determined by the duration of latency, and movement from infectious to recovered depends on the duration of infectiousness. The progression of vectors from susceptible to exposed is dependent on the force of infection from infectious hosts, and the progression from exposed to infectious states is determined by the length of the sporogonic cycle.

A variable vector birth rate is assumed such that the vector population is reduced when the vector mortality rate increases. The birth rate function used is given by:

$$b_v = b_v^* + b_v^* \left(1 - \frac{N_v}{K} \right)$$

The baseline birth-rate is given by b_v^* and is set equal to the total vector mortality rate. The total size of the vector population is N_v , and K is the carrying capacity - the maximum number of vectors in the model. When the mortality rate increases as a result of the larval burden in the vectors, the vector population starts to decrease; whilst $N_v < K$ the birth-rate b_v increases until the population equilibrates at a new lower equilibrium level and $b_v = \mu_v$ again.

4.2.3 LF model

The LF component of the model (see Figure 4.2) is a modified version of the LF model devised by Chan et al. (1998) and Norman et al. (2000) and developed further by Gambhir and Michael (2008). The LF model used in the co-infected model differs in three areas: 1) LF transmission is assumed to not be age-dependent, 2) a worm development stage is modelled in the host, and 3) a larval development stage is modelled in the vector.

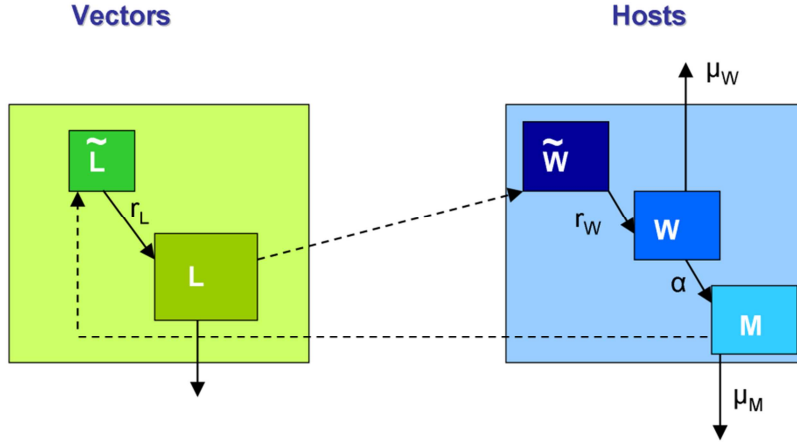


Figure 4.2: Basic structure of the lymphatic filariasis model (see Tables 4.2 and 4.3 for a summary of state variables and parameter definitions)

Six state variables are modelled relating to the LF model - the number of immature worms ($\tilde{W}$), reproductively active mature worms (W), microfilariae (M), immature larvae ($\tilde{L}$) and infective L3 larvae (L). A host gets infected when a LF infected vector takes a bloodmeal; L3 larvae enter the bloodstream before moving to the lymphatic system where they take around a year to develop into reproductively active mature worms. Once reproductively active, female worms produce microfilariae (mf) which circulate in the hosts' bloodstream. A vector taking a bite from this host can then ingest these microfilariae. The mf develop into L3 larvae inside the vector, and the transmission cycle continues.

4.2.4 Co-infection model formulation

A schematic for the full co-infection model is presented in Figure 4.3, and Tables 4.1 and 4.2 summarise the state variables and model parameters. The host population is modelled in four compartments corresponding to each of the four malarial states, and the basic LF model is split up, so we now track the number of immature and mature worms and mf in malaria susceptible, exposed, infectious and recovered hosts. We use the state variables M_S , M_E , M_I , M_R for the mf population, and $\tilde{W}_S$, $\tilde{W}_E$, $\tilde{W}_I$, $\tilde{W}_R$, and W_S , W_E , W_I , W_R for the immature and mature worm populations respectively.

The total number of immature worms is a function of the vector biting rate, the proportion of L3 larvae that leave the vector and successfully enter the host, the total L3 larvae population, and a term that captures the fact that worm development is lower at higher worm burdens due to greater individual level immunity. The number of mature worms in each malarial compartment is then calculated according to the proportion of hosts in each malaria

compartment. The immature worms state is in effect a ‘holding state’, where worms remain for a year before becoming mature worms that are reproductively active.

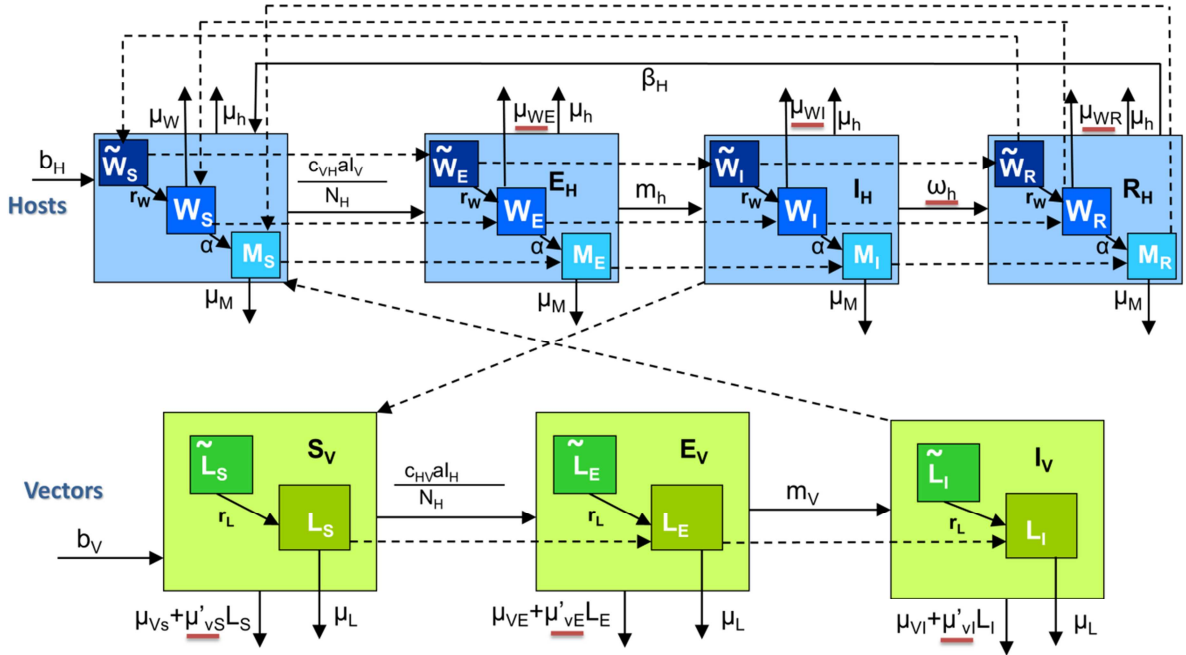


Figure 4.3: Schematic of the full malaria-LF co-infection model (see Tables 4.2 and 4.3 for a summary of state variables and parameter definitions). The parameters that govern the interactions between the infections are underlined in red.

The number of microfilariae in each malaria compartment is parameterised in terms of the number of mf per worm produced per unit time per $20 \mu\text{L}$ of blood, and is modelled as a function of the number of mature worms in that compartment and a term that represents the production of new mf. We assume mature worms, mature larvae and microfilaria all have a background mortality rate, denoted μ_W , μ_L and μ_M .

The vector population is divided into three compartments: susceptible, exposed and infectious. The number of immature ($\tilde{L}$) and mature (L) larvae in each compartment is denoted $\tilde{L}_S, \tilde{L}_E, \tilde{L}_I$ and L_S, L_E, L_I . The number of larvae in the immature stage is a function of the vector biting rate, the probability that an mf enters a vector and develops successfully, and a density dependent uptake term that determines the maximum amount of mf than can be taken up per mosquito. The immature larvae state is again a ‘holding state’ where larvae remain (for around 11 days) before developing into mature larvae.

‘Book-keeping’ terms are included in all the equations for microfilaria, immature and mature worms, and immature and mature larvae to account for hosts or vectors changing malaria

states. For example if a host moves from susceptible to exposed, the worms in that host move also from $\tilde{W}_S$ to $\tilde{W}_E$, or if a vector moves from exposed to infectious, the larvae in that vector also move from $\tilde{L}_E$ to $\tilde{L}_I$.

State variable	Definition
$\tilde{W}_i$	Number of immature worms in hosts with malaria status i (where $\tilde{W} = \tilde{W}_S + \tilde{W}_E + \tilde{W}_I + \tilde{W}_R$)
W_i	Number of mature worms in hosts with malaria status i (where $W = W_S + W_E + W_I + W_R$)
M_i	Number of microfilariae in hosts with malaria status i (where $M = M_S + M_E + M_I + M_R$)
$\tilde{L}_j$	Number of immature larvae in vectors with malaria status j (where $\tilde{L} = \tilde{L}_S + \tilde{L}_E + \tilde{L}_I$)
L_j	Number of mature larvae in vectors with malaria status j (where $L = L_S + L_E + L_I$)
H_i	Number of hosts with malaria status i (where $H = H_S + H_E + H_I + H_R$)
V_j	Number of vectors with malaria status j (where $V = V_S + V_E + V_I$)

Table 4.1: State variables in the full co-infection model (where $i = \{S, E, I, R\}$ and $j = \{S, E, I\}$)

A simplified version of the equations used in the co-infection model is shown below. The full equations for this model are given in Appendix C and a list of model parameters is given in Table 4.2. For the LF component of the model, let $i = \{S, E, I, R\}$ represent the different malaria states in the host, so $\tilde{W}_i$, W_i and M_i are the number of immature worms, mature worms and mf in a host of malaria state i . Let $j = \{S, E, I\}$ denote the malaria states in the vector, so $\tilde{L}_j$ and L_j are the number of immature and mature larvae in a vector with malaria state j . Stage-specific births and deaths are denoted B_k and D_k where $k = \{\tilde{W}, M, \tilde{L}, H, V\}$. The development of worms and larvae from immature to mature states is given by $dev(\tilde{W}_i)$ and $dev(\tilde{L}_j)$ respectively. The terms 'outflow' and 'inflow' refer to the 'book-keeping' terms, i.e. the transfer of worms and mf in hosts, or larvae in vectors due to changing malarial states. The simplified equations for the LF component of the model are given below (equations 1 - 5):

$$\frac{d\tilde{W}_i}{dt} = \tilde{B}_W(L, H_i) - \text{dev}(\tilde{W}_i) - \text{outflow} + \text{inflow} \quad (1)$$

$$\frac{dW_i}{dt} = \text{dev}(\tilde{W}_i) - D_W(W_i) - \text{outflow} + \text{inflow} \quad (2)$$

$$\frac{dM_i}{dt} = B_M(W_i) - D_M(M_i) - \text{outflow} + \text{inflow} \quad (3)$$

$$\frac{d\tilde{L}_j}{dt} = B_{\tilde{L}}(\tilde{L}_j) - \text{dev}(\tilde{L}_j) - \text{outflow} + \text{inflow} \quad (4)$$

$$\frac{dL_j}{dt} = \text{dev}(\tilde{L}_j) - D_L(L_j) - \text{outflow} + \text{inflow} \quad (5)$$

Similar notation is used to capture the malaria component of the co-infection model. Denote the process of new infection in hosts (H) and vectors (V) as ' new.inf_m ' where $m = \{H, V\}$. The process whereby hosts and vectors move from the exposed to the infectious compartment is denoted ' inf_m ', the process moving hosts from the infectious compartment to the recovered compartment is denoted ' recov ', and the process moving hosts from the recovered compartment back to the susceptible compartment is denoted ' lost.imm '. The simplified equations for the malaria component of the co-infection model are given below (equations 6 - 12).

$$\frac{dS_H}{dt} = B_H(H) - \text{new.inf}_H(V_I, H_S) - D_H(H_S) + \text{lost.imm}(H_R) \quad (6)$$

$$\frac{dE_H}{dt} = \text{new.inf}_H(V_I, H_S) - \text{inf}_H(H_E) - D_H(H_E) \quad (7)$$

$$\frac{dI_H}{dt} = \text{inf}_H(H_E) - D_H(H_I) - \text{recov}(H_I, W_I) \quad (8)$$

$$\frac{dR_H}{dt} = \text{recov}(H_I, W_I) - D_H(H_R) - \text{lost.imm}(H_R) \quad (9)$$

$$\frac{dS_V}{dt} = B_V(V) - D_V(L, V_S) - \text{new.inf}_V(H_I, V_S), \quad (10)$$

$$\frac{dE_V}{dt} = \text{new.inf}_V(H_I, V_S) - D_V(L, V_E) - \text{inf}_V(V_E), \quad (11)$$

$$\frac{dI_V}{dt} = \text{inf}_V(V_E) + D_V(L, V_I), \quad (12)$$

Parameter	Definition	Baseline value	Reference
a	Vector biting rate	Range from (1/14 – 1/2) bites per vector per day	(Filipe et al. 2007; Gambhir et al. 2010; Griffin et al. 2010)
b_h	Birth rate of humans	1/18,250 day ⁻¹	-
b_v	Birth rate of vectors	1/10 + 5 × 10 ⁻⁶ day ⁻¹	(Filipe et al. 2007)
μ_h	Death rate of humans	1/18,250 day ⁻¹	-
μ_w	Death rate of worms	13/37500 day ⁻¹	(Gambhir et al. 2010)
μ_M	Death rate of microfilariae	1/300 day ⁻¹	(Gambhir et al. 2010)
μ_{vj}	Death rate of vectors with malaria state $j = \{S, E, I\}$	1/10 + 5 × 10 ⁻⁶ day ⁻¹	(Filipe et al. 2007)
c_{vh}	Probability of infectious vectors transferring infection to susceptible hosts	1/25	(Chitnis et al. 2008)
c_{hv}	Probability of infectious hosts transferring infection to susceptible vectors	9/100	(Chitnis et al. 2008)
α	Production rate of mf per worm	1/15 day ⁻¹	(Gambhir et al. 2010)
r_L	Rate of development from immature to mature larvae	0.08 day ⁻¹	(Lardeux and Cheffort 1997)
m_h	Rate at which infected hosts become infectious	1/10 day ⁻¹	(Chitnis et al. 2008)
m_v	Rate at which infected vectors become infectious	0.1 ⁿ /n day ⁻¹	(Filipe et al. 2007)
β_h	Rate at which humans return to susceptible from recovered	1/7 day ⁻¹	(Chitnis et al. 2008)
$p_1 p_2$	Proportion of L3 leaving mosquitoes and entering the host per bite	1.497 × 10 ⁻⁵	(Gambhir et al. 2010)
μ_L	Death rate of larvae	0 day ⁻¹	(Gambhir et al. 2010)
μ'_v	Additional mortality rate of larval-infected vectors with malaria status (× by mean no. of larvae per vector)	0.1 day ⁻¹	(Michael et al. 2009)
$p_3 p_4$	Probability of mf entering the vector upon biting an LF-infected host and successfully developing into L3 larvae	0.37	(Gambhir et al. 2010)

Table 4.2: Parameters in the full co-infection model

4.2.5 Interactions between LF and malaria

In the host, the interaction between LF and malaria occurs via a modified immune response as a result of infection with malaria and LF parasites. See section 1.7 for a detailed review.

In this model we adopt a similar framework to that used by Fenton et al. (2008) for capturing the interaction between the micro and macroparasite. We assume that the Th1 and Th2 responses are antagonistic and that the Th1/Th2 bias is determined by the mean LF worm burden in the host. As worm burden increases, the Th2 response is up-regulated and the Th1 response is down-regulated. This effect is captured by altering key parameters in the model, namely, the malaria recovery rate and the worm mortality rate.

In the absence of LF, the malaria recovery rate in malaria infected individuals is at a maximum, as the immune response is totally Th1 skewed. Individuals with malaria and LF will have a comparatively weaker Th1 response, meaning that the immune system will be less able to kill malaria parasites and the recovery rate will decrease. This effect will be larger for higher worm burdens, as the immune response will become more Th2 biased. We therefore assume that malaria recovery rate is a decreasing function of the worm burden (see equation 13), so a co-infected individual will experience a longer recovery period than an individual with a single malaria infection (Figure 4.4B).

$$\omega_h = (\omega_h^{max} - \omega_h^{min}) \exp\left(-\varepsilon_1 \frac{W_I}{H_I}\right) + \omega_h^{min} \quad (13)$$

Where $\gamma_1 = 3$ per worm, $1/\omega_h^{min} = 200$ days, $1/\omega_h^{max} = 120$ days and $\varepsilon = 3$ per worm

The worm mortality rate is low in individuals susceptible to malaria as the immune response is Th2 skewed. When an individual with LF become infected with malaria the immune response becomes more Th1 biased, meaning a greater ability to kill LF worms. Therefore, we expect the worm mortality rate to be higher in co-infected individuals. In addition we assume a high worm burden will entail a lower mortality rate than a low worm burden as the immune response in an individual with a low worm burden will be more Th1 skewed (Figure 4.4A) (see equation 14 and 15).

$$\mu_{WS} = (\mu_{WS}^{max} - \mu_{WS}^{min}) \exp\left(-\gamma_1 \frac{W_I}{H_I}\right) + \mu_{WS}^{min}, \quad (14)$$

$$\mu_{WE} = \mu_{WI} = \mu_{WR} = (\mu_{WI}^{max} - \mu_{WI}^{min}) \exp\left(-\gamma_1 \frac{W_I}{H_I}\right) + \mu_{WI}^{min}, \quad (15)$$

where we assume the baseline values $1/\mu_{WS}^{min} = 10$ years, $1/\mu_{WS}^{max} = 8$ years, $1/\mu_{WI}^{min} = 8$ years, $\mu_{WI}^{max} = 6$ years.

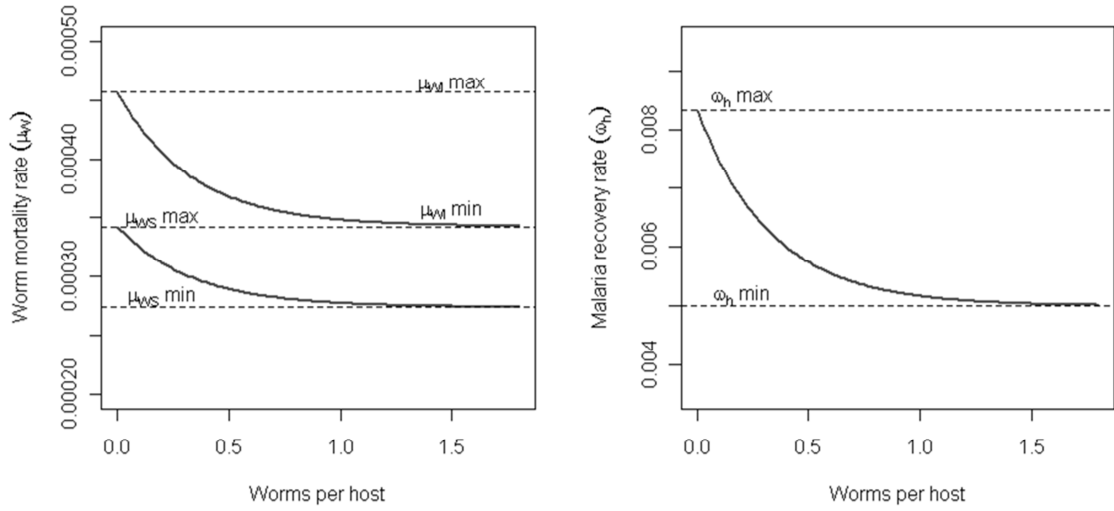


Figure 4.4: Worm mortality rate and malaria recovery rate as functions of mean worm burden (a). Increases in worm burden skew the immune system towards a Th2 response, meaning lower worm mortality rate and human recovery rate from malaria (b). In Figure 4.4A the two curves show the worm mortality rate in malaria infected (upper) and malaria uninfected (lower) hosts.

The interaction between LF and malaria in the vector population is assumed to occur via increased mortality in vectors as a result of larval infection. We assume an increasing mortality rate as a linear function of the mean larval burden per mosquito. Specifically, that there is a larval-dependent death rate in addition to the baseline mortality rate, so the daily vector mortality rate is $\mu_v = \mu_v^B + \mu_v' L / N_v$ where L / N_v is the mean number of larvae per vector, μ_v^B is the baseline death rate (i.e. with no larvae in the system) and μ_v' is a parameter scaling the magnitude of larval-induced excess mortality. This relationship is plotted in Figure 4.5.

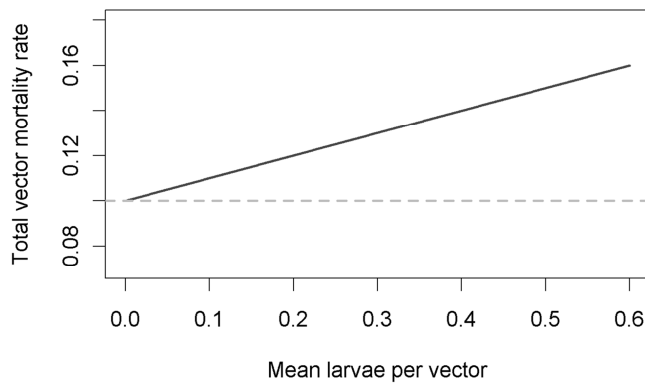


Figure 4.5: Relationship between the mean larval burden per vector and the overall vector mortality.

The model described above is used to investigate the impacts of co-infection on malaria and LF prevalence. In particular we consider the following questions:

- How is the prevalence of each infection altered when interaction effects are accounted for?
- How does the introduction of one infection into an area where the other infection is already endemic affect this equilibrium, and does the prevalence of the infection being introduced affect the new equilibrium level?
- How do the host interaction and the vector interaction effects impact prevalence individually, and what is their combined effect?
- How sensitive are the model results to changes in the parameter that determine the 'strength' of the interactions?
- When considering the impact of a vector control strategy on prevalence, how does modelling the interactions between malaria and LF affect the results?

4.3 Results

4.3.1 Infection prevalence of malaria and LF with and without the presence of the other infection

Firstly, we showed how the prevalence of each infection is affected by the presence of the other infection (Fig 4.6). When LF is present, the prevalence of malaria is higher in hosts, but lower in vectors. In hosts, when there is no LF infection, the immune response is Th1 biased, meaning an 'optimal' response to malaria, so infection is cleared quickly. When LF infection is present, the immune response becomes more Th2 skewed; the hosts ability to kill the malaria parasites is reduced, meaning a longer course of infection. LF infection in vectors increases their mortality rate due to larval induced excess mortality, so when LF is present, malaria prevalence is lower in vectors as they have a reduced lifespan, therefore less time in which to become infected with malaria (Figure 4.6B). Overall, these results indicate that the altered immune response in hosts outweighs the reduction in malaria prevalence in vectors, resulting in an overall increase in host prevalence.

In contrast, LF prevalence in hosts and vectors is lower when malaria is present. In the absence of malaria, the host immune response is predominantly Th2 skewed; this means worms live relatively longer as the immune system is not geared towards killing parasites. When malaria is present, however, the immune response becomes more Th1 skewed in malaria infected individuals, meaning that the worm mortality rate increases and LF

prevalence decreases. The same effect is exhibited in vectors, and is a result of the reduction in worm burden which reduces the larval burden in vectors.

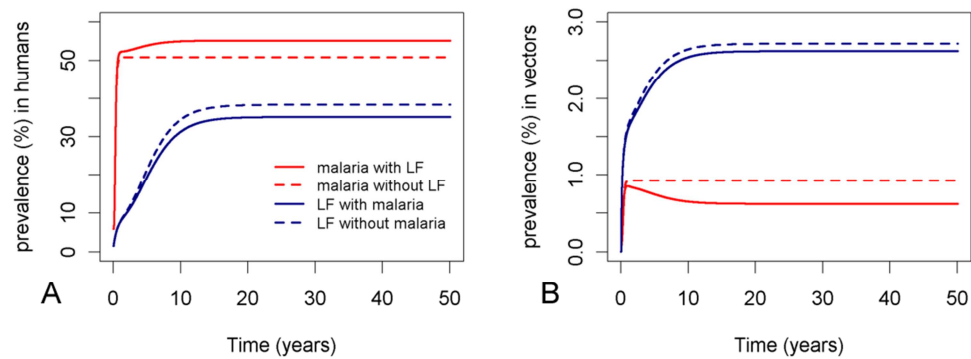


Figure 4.6: Prevalence of malaria with LF (red solid line) and without LF (red dashed line) in humans (A) and vectors (B). Prevalence of LF with malaria (navy solid line) and without malaria (navy dashed line) in humans (A) and vectors (B). The vector biting rate is 0.25

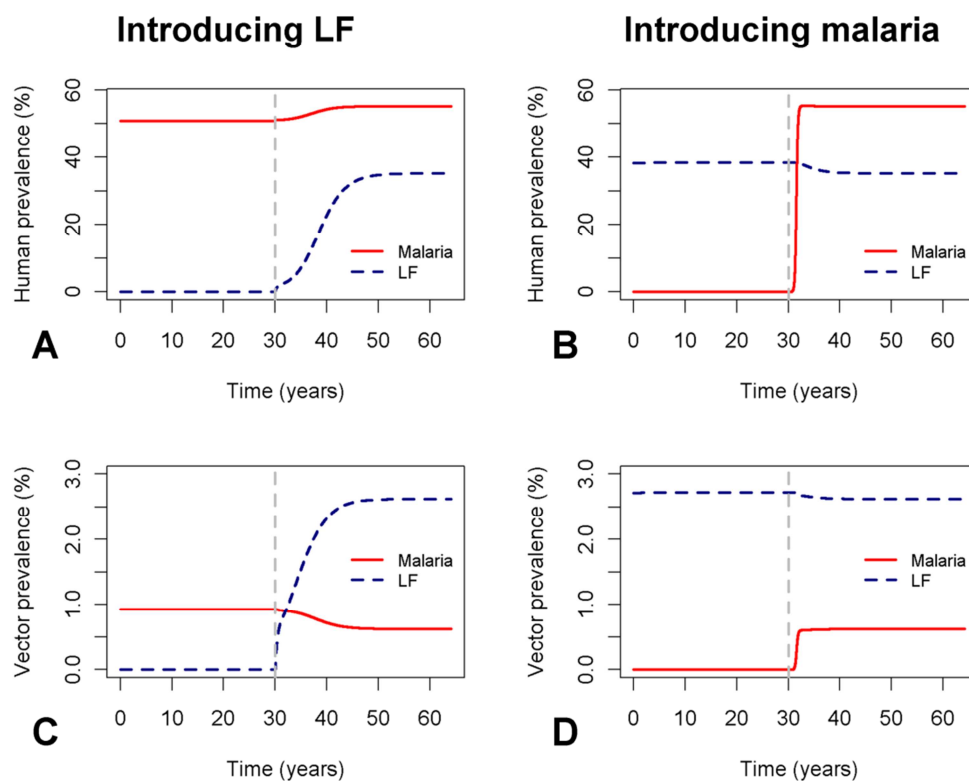


Figure 4.7: Time series plots showing how the prevalence of an existing infection is affected by the introduction of the other infection. The plots on the left show the effect of introducing LF when malaria is already established on hosts (A) and vectors (C). The plots on the right show the effect of introducing malaria when LF is already established on hosts (B) and vectors (D). The grey dashed line shows when infection is introduced.

The effect of introducing one infection into an area where the other infection is already established is shown in Figure 4.7. Introducing LF leads to an increase in malaria prevalence in hosts (Fig 4.7A) - the increase is relatively slow, taking around twenty years to reach its new equilibrium level. This is caused by a slow switching of the host immune system towards a Th2 response and away from a Th1 response as the worm burden increases. This means individuals will experience a longer period of infection with malaria, and hence an increased malaria prevalence. In vectors, introducing LF infection increases the number of larvae; this causes a small decrease in malaria prevalence due to increased larval induced excess mortality, which reduces vector lifespan (Fig 4.7C). The introduction of malaria into a LF system results in a small decrease in LF prevalence in both hosts and vectors (Figure 4.7B and 4.7D) because malaria infection induces a more Th1 skewed immune response, meaning a higher worm mortality rate.

4.3.2 Prevalence malaria or LF infection with varying background levels of the other infection

Figure 4.8 shows how malaria prevalence changes when LF is introduced to the system with different underlying prevalence levels (10%, 40% and 70%). We see that when LF prevalence is at a low or medium level (10%, 40%), malaria prevalence increases. However, interestingly, when LF prevalence is very high (70%), malaria prevalence actually decreases. At low LF prevalence levels, the host immune effect dominates the dynamics and prevalence decreases, however at very high prevalence levels, the excess vector mortality dominates, meaning vectors have a greatly reduced lifespan and malaria prevalence decreases in both hosts and vectors.

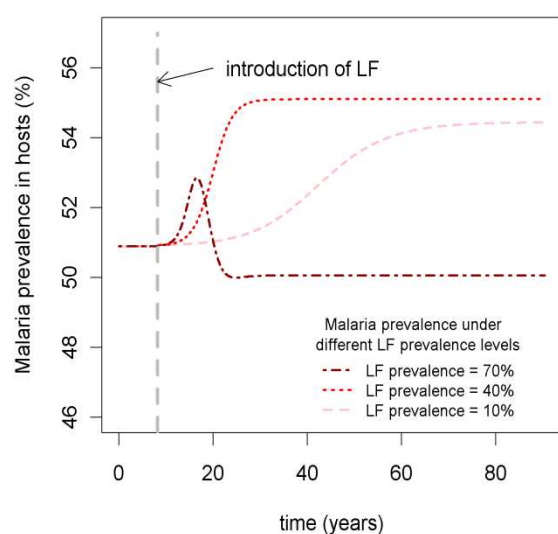


Figure 4.8: Time series plot showing the prevalence of malaria in hosts when LF is introduced at different prevalence levels

A similar treatment is applied to LF prevalence in Figure 4.9. Here malaria is introduced at different underlying prevalence levels (10%, 40%, 70%). It is clear that the higher the malaria prevalence, the greater the decrease in LF prevalence, as a larger proportion of the worms are in malaria infected hosts where worm mortality is higher.

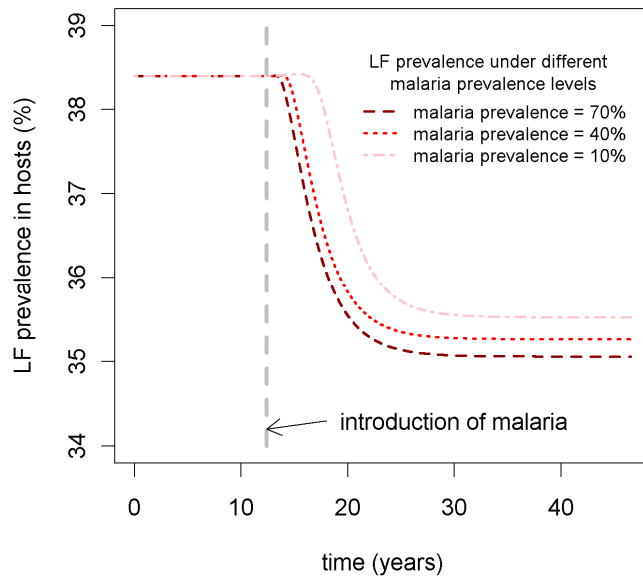


Figure 4.9: Time series plot showing the prevalence of LF in hosts when malaria is introduced at different prevalence levels

4.3.3 Contributions of interaction effects to overall prevalence

Figure 4.10 shows how each of the assumed interactions impacts prevalence. Firstly, the dotted lines show prevalence levels of malaria (red) and LF (dark blue) in hosts (A) and vectors (B) assuming there are no interactions between LF and malaria in the host and the vector. The dot-dashed lines assume just host th1/th2 interactions (host interaction), the dashed lines assume just larval induced excess vector mortality effects (vector interaction) and the solid lines assume both host and vector interaction. Assuming just vector interaction results in decreased malaria and LF prevalence in hosts and vectors (dashed lines below dotted lines in all plots). Comparing this host interaction only line (dot-dashed line) to the no interaction line (dotted line) we see that accounting for host interaction leads to a decrease in LF prevalence in hosts and vectors. For malaria, modelling host interaction (dot-dashed line) leads to an increase in prevalence in comparison to modelling no interactions (dotted line).

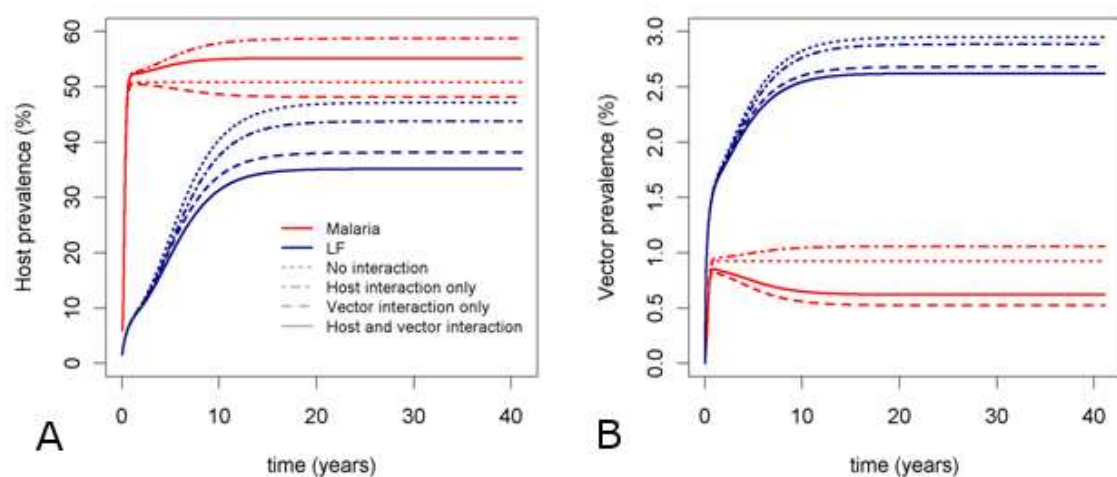


Figure 4.10: Time series plot showing the prevalence of malaria and LF in hosts (A) and vectors (B) with different assumptions regarding the interactions between the infections in the host and vector.

4.3.4 Sensitivity analysis of parameters governing the strength of the interaction effects

A range of values for the parameters controlling the worm lifespan in infected, infectious and recovered hosts is considered (Fig 4.11). It is clear that LF prevalence is far more sensitive to variation in this parameter than malaria prevalence.

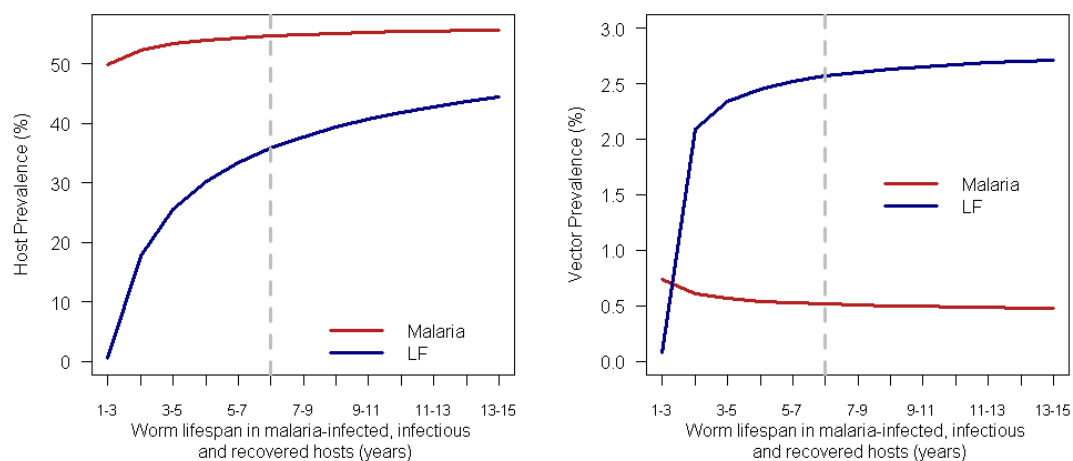


Figure 4.11: Parameter plots showing how varying the worm lifespan in malaria-infected, infectious and recovered hosts affects the prevalence of LF and malaria in hosts and vectors. The grey dashed line shows the parameter value normally used in the model.

A range of values for the maximum length of the malaria infectious period are also considered (Figure 4.12). Here it is assumed that the minimum period of being infectious is always 120 days. LF is almost entirely unaffected by changes in this parameter, but malaria prevalence increases slightly as the maximum infectious period increases. This shows that LF-induced changes in the malaria infectious period have a relatively small impact on transmission dynamics and prevalence.

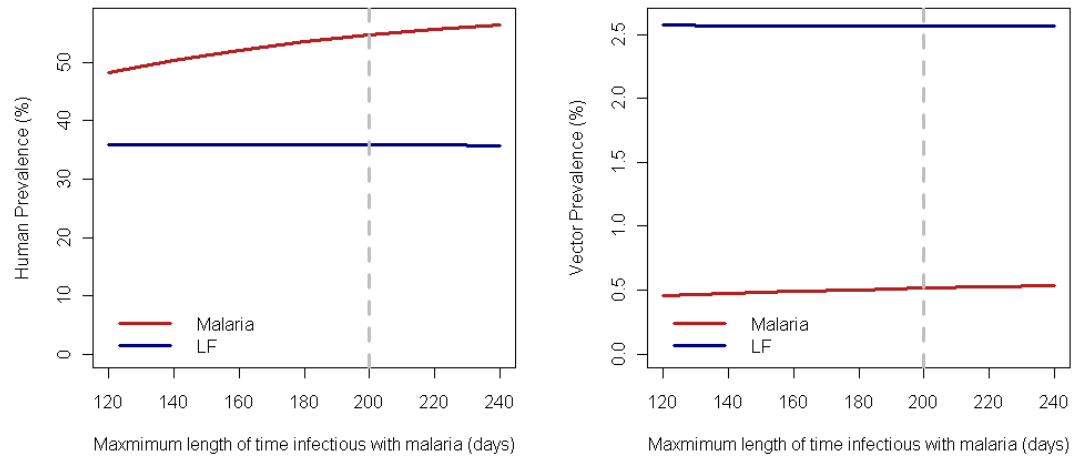


Figure 4.12: Parameter plots showing how changes in the maximum infectious period affect the prevalence of malaria and LF in hosts and vectors. The grey dashed line shows the parameter value normally used in the model.

Finally, the sensitivity of the additional larval induced mortality rate is considered. In Figure 4.13, it is clear that the higher the value of this parameter, the lower the prevalence of LF and malaria in both vectors and hosts. Again, compared to changes in the worm mortality rate (Fig. 4.12), infection prevalence is relatively insensitive to this parameter.

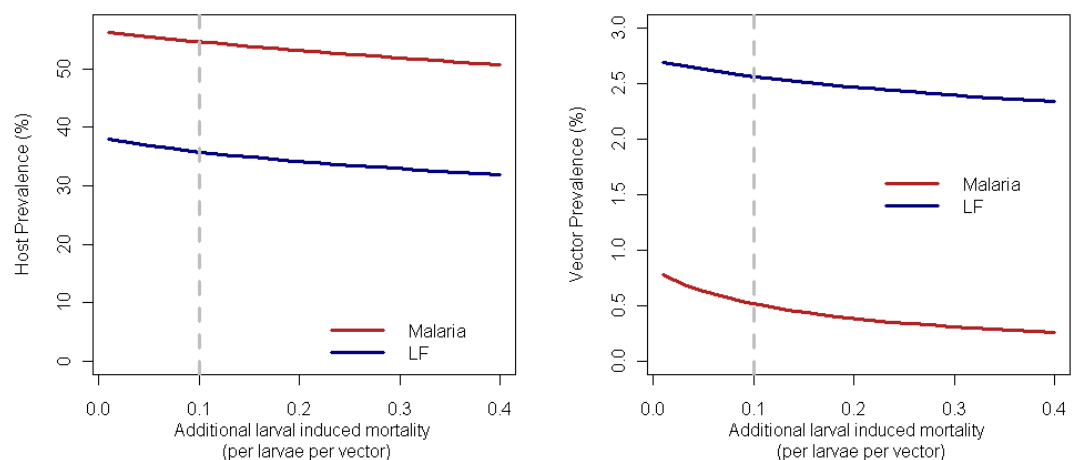


Figure 4.13: Parameters plots showing how changes in the additional larval induced vector mortality rate affect the prevalence of LF and malaria in humans and vectors. The grey dashed line shows the parameter value normally used in the model.

4.3.5 Effects on prevalence of a hypothetical vector control measure

In Figure 4.14 the impact of a hypothetical vector control measure that reduces the biting rate by 75% for a five year period is considered. Firstly, we notice that although the reduction in malaria prevalence is far greater than for LF, however the longevity of the intervention on LF prevalence is far greater. The second point to notice is that the predicted reduction in prevalence for both malaria and LF is greater when interactions between the infections into are taken account.

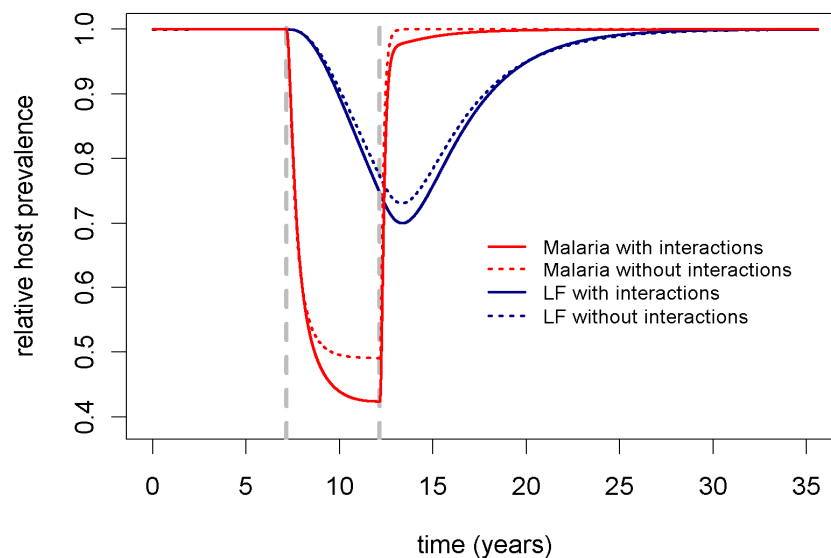


Figure 4.14: Time series plot of the relative host prevalence of malaria and LF given a 75% reduction in the biting rate that lasts for five years.

4.4 Discussion

Malaria and LF are co-endemic in large parts of Africa and co-infection is thought to be widespread (Bockarie et al. 2009). Understanding how co-infection impacts the transmission dynamics and pathology of each infection is vitally important for predicting how control strategies aimed at one infection might have a knock-on effect on the other infection, and for assessing whether an integrated control approach is the best strategy for effectively targeting both infections.

In this chapter a framework is developed for modelling the co-infection of malaria and LF. This has allowed us to investigate, for the first time, how interactions between the infections in the host and vector can impact transmission and prevalence, and how these results differ when considering a range of possible interaction scenarios.

Studies investigating the effects of multiple parasitic infections have found meaningful within-host interactions (Petney and Andrews 1998; Cox 2001; Booth 2006; Brooker et al. 2007; Cattadori et al. 2008; Graham 2008), suggesting that modelling single infections is too simplistic an approach, and that incorporating the interaction effects into transmission models could have a significant impact on model predictions.

The first microparasite-macroparasite co-infection model (Fenton 2008) was used to show that the introduction of a macroparasite into a microparasite model enabled the steady persistence of the microparasite, and that communities harbouring many low virulence parasites may actually be more healthy because more highly virulent parasites would be unable to establish. 'Unexpected' effects such as these could potentially have a large impact on the transmission dynamics of each infection.

Our results show that, in hosts, malaria prevalence is lower in the presence of LF, and that LF is higher in the presence of malaria. In vectors, prevalence is higher for both malaria and LF when the other infection is present (Figure 4.6). This means that if malaria is introduced into an LF-endemic area, LF prevalence will decrease. This implies that LF prevalence will increase if malaria is eradicated (Figure 4.7). However, if LF is introduced into a malaria-endemic area, malaria prevalence will increase, suggesting that if LF was eliminated, malaria prevalence could decrease slightly. However, this depends on the pre-elimination level of LF: eliminating LF in an area of high prevalence could increase malaria prevalence due to the increased lifespan of the vectors.

The speed at which malaria and LF infection take off after introduction varies greatly (Figure 4.7). Malaria prevalence quickly reaches its equilibrium level after just a year or two whereas LF takes around 20 years to equilibrate. This is because the infections have vastly different timescales and transmission efficiencies - the period of a malaria infection (the time from infection to recovery) is around nine months, and an individual can become infected with malaria from a single infective bite. However, becoming infected with LF can take hundreds or thousands of infective bites (Hairston and de Meillon 1968) as the probability of a L3 parasite successfully entering the bloodstream and becoming a mature worm is extremely low. Even when a worm does develop, it takes around a year for it to become reproductively active. This means malaria infection can spread rapidly across a population, but LF infection will take longer to reach equilibrium.

When LF is introduced into a malarial region, the underlying LF prevalence level (the prevalence level LF would reach in the absence of malaria) has an impact on the resulting malaria prevalence (Fig 4.8). At low and medium LF prevalence levels, malaria prevalence increases, but when LF prevalence is high, malaria prevalence decreases. This is because at low or medium LF prevalence levels the within host interaction dominates; the effect of the

increased infectious period outweighs the effect of the increase in larval mortality, and results in an increase in malaria prevalence. The larval mortality vs. worm burden relationship is linear whereas the infectious period vs. worm burden relationship is decreasing, meaning that as worm burden increases, there is a tipping point where the effect of increased larval mortality outweighs the increase in infectious period and malaria prevalence decreases. This result could have policy implications: reducing LF in a region with very high LF prevalence could actually lead to an increase in malaria prevalence.

Introducing malaria at different underlying prevalence levels to a LF endemic area has an impact on the resulting LF prevalence (Figure 4.9) - a higher underlying malaria prevalence level leads to a greater decrease in LF prevalence. This is because we assume that worms in malaria infectious hosts have a shorter lifespan, so a higher level of malaria implies more worms in infectious hosts, and thus a shorter mean worm lifespan and lower LF prevalence. Again, this result could have policy implications: reducing malaria prevalence in a co-endemic region could result in an increase in LF prevalence.

The different interaction effects were dissected in Figure 4.10 to examine how the vector and host interactions contributed to the overall prevalence level. If interaction in the vectors is assumed, the prevalence of both malaria and LF decreases; this is because vectors have a higher mortality rate, thus having less time to transmit both infections. If just interaction within the host is assumed, the prevalence of LF decreases in hosts and vectors; this is because larvae in malaria infected hosts experience an increased mortality rate, resulting in a lower worm burden and LF prevalence. The prevalence of malaria increases in both hosts and vectors if we assume host interaction. This is because malaria infected individuals harbouring LF parasites take longer to recover from infection.

Understanding the interactions between LF and malaria in the host and the vector is vitally important for predicting the impact of control programmes. The previous results examined how prevalence changes for a fixed set of interaction assumptions. Next, a brief sensitivity analysis was conducted, exploring the impact of different interaction assumptions. Firstly, the parameters controlling the worm lifespan in infectious hosts were varied (Figure 4.11). A shorter worm lifespan resulted in a lower LF prevalence; however the interesting feature here is the magnitude of the decrease in LF prevalence. We predict that if worms in malaria infected hosts only live 2-4 years, the prevalence of LF will more than halve. However, prevalence was less sensitive to changes in the other interaction parameters, the period of malaria infectiousness (Figure 4.12), and the larval induced mortality rate (Figure 4.13, suggesting that control aimed at reducing the lifespan of worms may have the greatest impact.

The model used in this study is overly simplified - both in terms of the underlying transmission models for LF and malaria, the fixed parameter values, and the interactions between the infections. In reality, more complex transmission models may be required to better capture the dynamics of each infection (Koella 1991; McKenzie and Bossert 2005; Stolk et al. 2006; Le Menach et al. 2007; Gambhir and Michael 2008). Assuming stochasticity in some of the key model parameters could also offer a more rigorous examination of model results, and allow us to examine the impact of parameter variability. Here, it is assumed that the vector population and biting rate are constant throughout the year, however, assuming season vector dynamics may be more realistic (Parham and Michael 2010) and could have a major impact on the potential eradicability of both infections: it may be easier to reduce the prevalence of an infection below some critical eradication threshold during a period of low transmission.

Another simplification is the fact that we assume that individuals do not acquire immunity to malaria - accounting for this could alter the dynamics of co-infection. Individuals with high levels of acquired immunity may have less Th1 skewed immune responses compared to individuals with less immunity (Doolan et al. 2009). Therefore co-infected individuals with high immunity are likely to be infected with malaria less frequently and have shorter periods of infectiousness. However, they would also have a lower ability to kill the LF worms due to the reduced Th1 response. This could result in increased LF prevalence and decreased malaria prevalence. This scenario could be explored more fully by developing an age-dependent model with immunity and Th1/Th2 immune responses that vary as a function of the level of age and acquired immunity.

The effect of co-infection is captured in terms of the 'mean' host immune response, i.e. all individuals mount the same immune response based on the mean worm burden in that malaria infection compartment. However, field studies have shown that host immune responses vary greatly between individuals (King 2001), possibly due to the fact that individuals harbour different numbers of filarial worms (Das et al. 1995), and that an individual's immune response is likely to be related to their worm burden (Ottesen 1992). The impact of variable immune responses between individuals cannot be captured by our model, but could potentially be explored further using an individual based microsimulation model. This could be an important area for future research.

The key to understanding how co-infection with malaria and LF affects the transmission and prevalence of each infection is to determine how the infections interact in the host and in the vector. In this chapter, assumptions regarding the interactions are formulated using: information from studies looking at how the immune system responds to a single infection, and studies affirming that the immune responses are mutually inhibitory. These were used to hypothesise how co-infection with malaria and LF could alter the host immune response. It is largely unknown which model parameters the altered immune response could affect, and by

how much. Here, we assume that increased worm burden causes an increased length of malaria infection and that worms residing in malaria infected hosts will experience a higher mortality rate. This is likely to be an oversimplification of the actual system, and in reality the altered immune response could manifest itself by altering several different aspects of the transmission cycle including the susceptibility to infection (Briand et al. 2005), severity of infection (Graham et al. 2005) or the development of malarial immunity (Druilhe et al. 2005; Booth 2006).

In vectors, we assume that the mortality rate is an increasing function of the mean larval burden. Studies have shown that vectors may also experience increased mortality due to infection with malaria parasites (Hogg and Hurd 1997; Koella 1999; Dawes et al. 2009). In particular, vectors carrying the infective sporozoite stage are thought to bit more, thus increasing the risk of biting-related mortality (Anderson et al. 2000). The non-infective parasite stages in the vector have been shown to increase mortality, although the effect is not usually observed in parasite-vector combinations commonly found in the wild (Ferguson and Read 2002). Vector co-infection could also affect the development of parasites (Albuquerque and Ham 1995) or vector susceptibility to infection (Burkot et al. 1990; Muturi et al. 2006a).

Overall, the present model offers a first attempt at describing and quantifying the impact of co-infection on the transmission dynamics. This study also highlights the great need for further research into how co-infection alters the host immune response and how vector mortality is affected when they are carrying malaria and LF parasites.

One key application of the co-infection model is to consider the impact of different intervention measures on prevalence levels. A hypothetical vector control measure is applied (see Figure 4.14) which shows that the drop in prevalence is greater for malaria, but is effective for a longer period of time for LF. Also, the decreases in prevalence are greater when co-infection effects are considered - this suggests that models describing a single infection could underestimate the impact of vector control.

This study demonstrates that, if within host and within vector interactions between malaria and LF exist, they could have a significant impact on the transmission dynamics of each infection and predictions of the efficacy of control programmes. In the next chapter we explore the impact of different control strategies further. In particular how each intervention affects the transmission cycle, and whether an integrated control approach could offer a more cost-effective way to reduce the transmission of both infections.

Chapter 5

Modelling the cost-benefit of malaria and LF control strategies and assessing the feasibility of an integrated control approach

5.1 Introduction

The integrated control of co-endemic infectious diseases has been frequently identified as a way to increase the coverage, effectiveness and efficiency of control programmes (Manga 2002; Prasittisuk 2002; Molyneux et al. 2005; Hotez et al. 2006). Vector control methods, such as insecticide treated bed nets, succeed in reducing the transmission of both malaria and LF (Choi et al. 1995; Bøgh et al. 1998; Lengeler 2004; Yukich et al. 2008), and in combination with Mass Drug Administration (MDA) could offer a quicker means of achieving LF elimination (Sunish et al. 2007) (see section 1.3 for a more in depth discussion on integrated control).

In this chapter, we aim to determine the conditions under which integrated control offers a 'better' means of eliminating LF, whilst also reducing or even eliminating malaria. Specifically, the co-infection model developed in chapter four is used to model to outcomes of different integrated control scenarios on infection prevalence. This model is used in combination with the co-infection map developed in chapter three to investigate whether the pre-control prevalence levels in a given region affects the 'optimal' control strategy. Two control methods are considered in this chapter: annual MDA and LLINs (Long Lasting Insecticidal Nets), either alone or in combination. The overall performance of each control programme is determined using a cost-benefit analysis. We also consider the number of years of control required to achieve LF elimination and the number of malaria and chronic LF disease cases prevented. A cost-benefit analysis was selected over a cost-effectiveness analysis for one key reason: to

assess the cost-effectiveness of a control programme aimed at reducing (or eliminating) the transmission of both malaria and LF a common metric would need to be identified, i.e. a single health outcome that captures reductions in both infections and allows a policy decision to be made regarding the best 'overall' control option. The problem with this approach is finding a common metric: malaria and LF have very different pathologies meaning that, for example, averting one case of malaria cannot be equated to averting one case of LF, and attributing weights to each disease is equally as problematic.

For this reason we look to a cost-benefit approach; this involves estimating the economic benefit of a control programme and using this, along with cost data, to determine the option which maximises the economic benefit per \$1 control cost. The main advantage of using cost-benefit analysis is that it allows us to separately define the economic benefits of preventing malaria and chronic LF disease cases, and then sum these values to produce an 'overall' economic benefit of the control programme.

Many studies have attempted to define the economic cost of a case of malaria, or the economic burden of malaria in a particular region (Leighton and Foster 1993; Ettling et al. 1994; Onwujekwe et al. 2000; Chima et al. 2003). Defining the economic benefit of preventing malaria cases can be complicated: studies tend to focus on and overestimate the costs associated with uncomplicated malaria, whereas the costs associated with severe malaria - malaria induced anaemia and malaria induced mortality - are ignored (Chima et al. 2003). One simple approach is to define the economic cost of a case of malaria as the sum of the direct costs of expenditure on prevention and treatment, plus the indirect costs of wages lost due to illness and premature mortality (Shepard et al. 1991; Chu et al. 2010). Therefore, the economic benefit of a control programme can be defined as the total sum of the economic costs of all the malaria cases prevented.

The direct costs to an individual can include both prevention and treatment costs. Prevention costs can include insecticide treated nets (although these are often distributed free of charge) as well as untreated nets and repellent sprays. Treatment costs include the cost of treatment at the health centre, the cost of travelling to the health centre and the cost of medicine. These costs can be highly variable depending on whether an individual is required to stay at the hospital, the locality of the health centre, and the medicines given (Asenso-Okyere and Dzator 1997; Chima et al. 2003; Wiseman et al. 2006).

Indirect costs include time lost due to malaria induced illness – this can include time spent unable to work, time spent seeking treatment, and time taken off work caring for ill household members. A day lost due to illness can either be valued as the mean daily wage rate or the marginal product of a day's labour. The marginal product of labour (MPL) is the opportunity cost of time lost due to being unable to work and time lost looking after an ill family member.

Commonly the MPL is assumed to be a fixed proportion of the mean daily wage rate (Chima et al. 2003).

Many other benefits may be observed as a result of reducing malaria, for example, increases in economic development, educational attainment and psychological well-being (Gallup and Sachs 2001; Sachs and Malaney 2002). However these factors are very difficult to measure, and will not be considered in this study.

A major study looking at the economic benefit of the first eight years of the Global Programme to Eliminate Lymphatic Filariasis was conducted by Chu and colleagues (2010). Here, for the first time, a formal framework was created which defined the 'benefit cohort population' - the groups of individuals benefiting from LF control, and estimated the benefits experienced by these different groups. Individuals at different stages of LF infection will face different costs of infection. Individuals with asymptomatic LF infection initially bear no economic losses due to infection, but a proportion will be expected to progress to chronic LF disease. Chronic LF disease sufferers experience economic losses due to reduced productivity annually as well as from bouts of acute disease. MDA is thought to prevent asymptomatic individuals developing chronic LF disease and also to prevent uninfected individuals from developing infection. It is largely unknown as to whether MDA alleviates the symptoms of these diseases (Chu et al. 2010).

Estimating the combined economic benefit of LF control on these groups involves estimating the direct costs (prevention and treatment) and indirect costs (work days lost due to illness) due to LF. Direct costs include the cost of treating acute disease (adenolymphangitis (ADL)) episodes and chronic disease cases – this includes a small proportion of hydrocele surgeries carried out. Indirect costs for acute disease consist of several days off for each ADL episode (Evans et al. 1993; Ramaiah et al. 2000), whereas for chronic disease, the indirect costs consist of a proportion of annual work hours lost due illness (Haddix and Kestler 2000; Chu et al. 2010).

In this study, a similar framework to that developed by Chu et al. (2010) is adopted and expanded to include the benefits of reducing malaria. Firstly, we begin by describing how the control interventions are implemented using the co-infection model, we then discuss how the cost of each control programme is calculated and finally we describe how the economic benefits of a control programme are defined.

5.2 Methods - Modelling control interventions

5.2.1 MDA for LF

The most commonly used drug regimens for LF in Africa are combinations of either Ivermectin (Iv) and Diethylcarbamazine (DEC), or Albendazole (Alb) and DEC. The Iv+DEC combination is generally used in areas where onchocerciasis is co-endemic and Alb+DEC is used elsewhere. Areas co-endemic with loa loa are usually treated with Alb+DEC even when onchocerciasis is present because Ivermectin can cause severe reactions in individuals with loa loa (Gardon et al. 1997).

In this study only the impact of the Iv+Alb combination is considered. The drugs primarily work by killing a proportion of microfilariae in the blood but are also thought to kill a smaller proportion of the adult worms and suppress mf production by worms for a short period post treatment (Michael et al. 2004). Doxycycline has been suggested as a new potential drug for MDA; it works by killing the adult worms rather than the microfilariae (Hoerauf 2008). The proportions of mf and worms killed due to MDA and the length of the mf suppression period are given in Table 5.1.

	Michael et al. (2004)			Stolk et al. (2006)	
	% Worm kill	% mf kill	Months mf suppression	% Worm kill	% mf kill
DEC	35	90	3	50	70
Iv	10	99	9	-	-
Iv+Alb	35	99	9	35	100
DEC+Alb	55	95	6	65	70
Doxycycline	-	-	-	80	0

Table 5.1: Parameter values describing the effects of different MDA drugs on worm mortality, microfilariae mortality and microfilariae production

The impact of MDA on the co-infection model is implemented as follows:

- 1) The number of rounds of MDA and the choice of drug(s) is defined
- 2) At the start of each round the total number of worms and microfilariae is reduced according to the mortality rates given in Table 5.1 (using values from Michael et al. (2004) for Iv+Alb)
- 3) The parameter controlling the rate of production of mf by worms is set to zero for the number of months given in Table 5.1
- 4) Steps ii),iii) are repeated for the number of rounds specified in i).

When Ivermectin is included in the drug combination, another effect is thought to occur: studies have shown that vectors taking a bloodmeal containing Ivermectin have an increased mortality rate, but that this increased mortality rate wanes with the number of days post-MDA

that the bloodmeal is taken (Cartel et al. 1991; Bockarie et al. 1999; Foley et al. 2000; Chaccour et al. 2010; Sylla et al. 2010). We define an approximation for an 'effective' mortality rate that takes into account that the fact that vectors taking bloodmeals at different times post-MDA will experience different mortality rates. The 'effective' mortality rate is dependent on the biting rate of mosquitoes and the MDA coverage level. Adopting this short-term increase in vector mortality rate causes a short term decrease in the vector population in the 30 or so days after each round of MDA is conducted. Full details of how this approximation was derived are presented in Appendix D.

5.2.2 Insecticide treated bed nets

For simplicity we choose to look at just one vector control method - Long Lasting Insecticidal Nets (LLINs), but to some extent, we expect the results presented here to generalise to other vector control methods such as larviciding or indoor residual spraying). Two types of bednets are commonly used in Africa - insecticide treated nets (ITNs), which are dipped in a synthetic pyrethroid insecticide before they are distributed, and should be retreated every year or six months. The other type of bed net used is a LLIN). These require no additional retreatment during their expected lifespan of 3-6 years and work by having insecticides incorporated into the fibres; when the bednets are washed old fibres are washed away and new fibres containing pyrethroid insecticides reach the surface meaning insecticides are constantly released. Although the LLINs are more expensive initially, in the long run they may work out to be more cost effective as they do not require retreatment. In this study we focus on LLINs as they are the bednet recommended by the World Health Organisation (WHO 2010a).

Bednets affect malaria transmission in two ways, they:

- i) reduce the number of bites each person receives
- ii) reduces the vector population due to the insecticidal qualities of the bednets

In our model, the biting parameter used is in terms of the number of bites on humans per vector per day, which is affected by both the above factors. Bednets have a repelling effect on vectors, so fewer vectors enter houses where nets are in use (Lindblade et al. 2006; Le Menach et al. 2007) meaning it will take longer to find a blood meal. Bednets have also been reported to increase the proportion of bites taken from non-humans (Takken 2002).

Vectors are thought to experience high levels of mortality as a result of landing on an ITN – mortality rates in the region of 80-100% are commonly reported (Guillet et al. 2001; N'Guessan et al. 2007) However, as mentioned above, ITNs have a repelling effect, so a large proportion of vectors will not land on the nets, so the overall level of vector mortality will be significantly lower than this. In fact studies have reported a decreases in total vector population of 72%, 77%, 80% or 90% found in or around houses (Curtis et al. 1998; Maxwell et al. 1999; Gimnig et al. 2003; Lindblade et al. 2004). Killeen et al. (2000) reported a 0-40%

reduction in vector survival per feeding cycle, and they used a conservative value of 15% in their model. We use this value, but it is converted into a new daily vector mortality rate which is calculated to be 11.7% per day (this value is scaled according to the LLIN coverage level).

Data on how bed nets directly affect the number of blood meals taken by a vector is sparse – however, there is plenty of data on the reduction in the entomological inoculation rate (EIR), see Table 5.2. The parameter for the reduction in the biting rate as a result of bed net usage is estimated by simulating model results for a variety of different values of this parameter and selecting the value that gave decreases in EIR that best reflects the empirical results (Table 5.3).

Study	Reduction in EIR
Maxwell et al. (2003)	69 - 75% reduction
Killeen et al. (2000)	7 - 13 fold decrease
Lindblade et al. (2004)	91% reduction
Maxwell et al. (1999)	95 - 97% reduction
Curtis et al. (1998)	42% increase in year 1, 90% reduction in year 2
Beach et al. (1993)	55% increase in year 1, 75% reduction in year 2
Hii et al. (1993)	94% reduction
Magesa et al. (1991)	86 - 100%

Table 5.2: Studies showing the reported reductions in EIR as a result of bed net usage

	coverage		
pre-control biting rate = 0.5	50%	75%	100%
80% reduction in biting rate	81%	92%	99%
<i>70% reduction in biting rate</i>	<i>78%</i>	<i>89%</i>	<i>96%</i>
60% reduction in biting rate	75%	84%	92%
50% reduction in biting rate	71%	80%	87%
40% reduction in biting rate	67%	74%	81%
pre-control biting rate = 0.25			
80% reduction in biting rate	84%	94%	99%
<i>70% reduction in biting rate</i>	<i>80%</i>	<i>91%</i>	<i>98%</i>
60% reduction in biting rate	77%	87%	94%
50% reduction in biting rate	73%	82%	89%
40% reduction in biting rate	69%	77%	84%

Table 5.3: Model output reduction in EIR for a range of different biting rates, coverage levels and reductions in the biting rate, used to select the value for reduction in biting rate.

Using data from Tables 5.2 and 5.3, it is now assumed that LLIN usage will reduce the biting rate by 70%. This value is scaled by the level of LLIN coverage.

5.3 Methods - Modelling the economic cost of control interventions

In this section, we detail how costs were estimated for MDA and LLINs. The cost of MDA per person includes office costs, transportation/delivery, cost of any non-donated drugs, and personnel costs (including wages and training) (Goldman et al. 2007). The cost of each LLIN distributed differs slightly from study to study but generally includes office costs, transportation/delivery, cost of the LLIN, personnel costs (training, wages and management), evaluation and monitoring, and storage space rental. All costs presented below have been converted into US\$ 2009.

5.3.1 MDA for LF

The reported costs for a range of MDA programmes are presented in Table 5.4. For programmes where financial data for more than one round is available, costs decrease after the initial start-up year, and in fact costs decrease between 12-53% in later years, with a mean reduction of a 38%. The mean cost for the initial year is \$1.46 and \$0.79 for subsequent years. These estimates are slightly higher than what has been used in the literature – Michael et al. (2008) used a fixed price of \$0.53 for treating one individual for one year in Tanzania (based on estimated from studies in Tanzania and Egypt) and \$0.45 was used by Brady and colleagues (2006) for sub-Saharan Africa. Considering only data from Africa, we find that mean cost per person treated for round 1 is \$0.82 and \$0.44 for subsequent years. One reason for this disparity might be the lower personnel costs in Africa. Mean personnel costs are estimated to be \$0.17 per person treated in African countries and \$0.66 elsewhere (Table 6 in Goldman et al. (2007)). There were no big differences in the other mean costs per person treated between African and non-African countries (equipment and facilities - \$0.08 in Africa, \$0.11 elsewhere, supplies - \$0.18 in Africa, \$0.20 elsewhere and transport - \$0.03 in Africa and \$0.12 elsewhere).

		Population at			
Drug combination and country	MDA round	risk in MDA areas	Population treated	Financial Cost (\$)	Cost per person treated (\$)
<i>Albendazole+Ivermectin</i>					
Burkina Faso	1	559,000	431,399	\$55,909	0.13
Burkina Faso	2	2,613,000	1,801,125	\$133,697	0.07
Ghana	2	1,650,000	1,223,122	\$1,650,553	0.21
Tanzania	1	40,800	37,000	\$24,308	0.66
Tanzania	2	182,000	118,220	\$60,771	0.51
Tanzania	3	537,000	437,698	\$143,420	0.33
Tanzania	4	687,000	511,671	\$161,652	0.32
<i>Albendazole+DEC</i>					
Dominican Republic	1	142,000	115,411	\$262,532	2.27
Dominican Republic	2	333,000	250,059	\$263,748	1.05
Egypt	1	2,088,000	1,795,553	\$2,931,617	1.67
Egypt	2	2,638,000	2,320,602	\$3,778,771	1.22
Haiti (Legolane)	1	150,000	105,750	\$286,841	2.71
Haiti (Legolane)	2	150,000	79,713	\$189,607	2.38
Haiti (Legolane)	3	150,000	121,139	\$192,037	1.59
Haiti (Milot)	1	126,000	100,376	\$133,697	1.33
Phillippines	3	691,000	556,912	\$128,643	0.23

Table 5.4: Financial costs and coverage of LF programmes (table taken from Goldman et al. (2007))

The final cost data for LF MDA used in further analysis is \$0.82 per person treated for the first year and \$0.44 per person treated in subsequent years.

The total cost of MDA is calculated using the following equation:

$$MDA \text{ cost} = pop \cdot cov.MDA \cdot \left(dc.Y1 + \sum_{t=1}^{nrounds-1} \frac{dc.Y2}{(1+r)^t} \right)$$

Where pop is the total population size, $cov.MDA$ is the proportion of the population treated with MDA, $dc.Y1$ is the cost of treating one person for a year in the first year of the MDA programme (\$0.82), $dc.Y2$ is the cost of treating one person in all subsequent years (\$0.44), $nrounds$ is the number of annual MDA rounds and r is the rate at which future costs are discounted (3%).

5.3.2 Vector control – LLINs

Similar to estimates of the costs of delivering MDA, the costs associated with providing LLINs varies across Africa (White et al. 2011). Collated data on the cost of LLINs in Africa shows that the costs per LLIN distributed ranges from \$3.23 - \$10.08 with a mean of \$6.90 (Table 5.5)

Study	Country	Cost per LLIN (\$)	LLIN lifespan (years)
Kolaczinski et al. (2010)	Uganda	6.61	3
Kolaczinski et al. (2010)	Uganda	7.55	3
Kolaczinski et al. (2010)	Uganda	7.03	3
Mueller et al. (2008)	Togo	6.96	3
Yukich et al. (2008)	Eritrea	7.75	3
Yukich et al. (2008)	Togo	3.47	3
Yukich et al. (2008)	Malawi	5.18	3
Yukich et al. (2008)	Senegal	7.58	3
Yukich et al. (2008)	Tanzania	6.04	3
Chanda et al. (2009)	Zanzibar	8.75	4
Chanda et al. (2009)	Zanzibar	8.03	4
Chanda et al. (2009)	Zanzibar	7.76	4
De Allegri et al. (2010)	Burkina Faso	7.94	5
De Allegri et al. (2010)	Burkina Faso	8.90	5
Yukich et al. (2007)	Eritrea	10.08	5
Yukich et al. (2007)	Togo	3.23	5
Yukich et al. (2007)	Malawi	5.05	5
Yukich et al. (2007)	Senegal	7.36	5
Yukich et al. (2007)	Tanzania	5.74	5

Table 5.5: Studies reporting different costs per LLIN distributed

A value of \$6.90 per LLIN distributed is used in all further analysis.

The total cost of LLINs is calculated using the following equation:

$$Total\ LLIN\ cost = \sum_{t=1}^{nLLIN} \frac{pop}{people.per.BN} \cdot cov.BN \cdot LLIN.cost \cdot \frac{1}{(1+r)^{LLINlifespan(t-1)}}$$

Where $nLLIN$ is the number of times that LLINs are distributed (only distributed when the lifespan of the previous LLIN ends), pop is the total population size, $people.per.BN$ is the number of people protected by (i.e. sleeping under) each LLIN, $cov.BN$ is the proportion of the population that are protected by a LLIN, $LLIN.cost$ is the cost of purchasing and distributed one LLIN (\$6.90), $LLIN.lifespan$ is the length of time in years that a LLIN is effective for, and r is the rate at which future costs are discounted (3%). This equation discounts future costs in the years that new LLINs are purchased. We estimate that an average 1.5 people sleep under each LLIN (Baume and Marin 2007) and that each net has a lifespan of 5 years (Table 5.5).

5.4 Methods - Modelling the economic benefit of a control intervention

The total economic benefit of a control programme is defined as the economic benefit of the malaria cases prevented plus the economic benefit of the chronic LF disease cases prevented. The economic benefit of preventing one case of malaria or LF disease is broadly defined to be the treatment costs saved plus the cost of wages that would have been lost due to illness. The number of malaria and LF disease cases prevented by a control programme is estimated using the co-infection model developed in chapter five.

5.4.1 Estimating the number of malaria infections prevented

The number of cases of malaria prevented as a result of control interventions is calculated as the total number of malaria cases without control minus the total number of malaria cases with control. We consider the number of malaria cases over a 50 year period. The number of malaria cases each day is given by:

$$New\ malaria\ infections\ per\ day = mal.NI(t) = a(t) \cdot c_{vh} \cdot I_v(t) \cdot \frac{S_h(t)}{N_h(t)}$$

where $a(t)$ is this biting rate at time t , c_{vh} is the infectivity rate from vectors to humans, $I_v(t)$ is the number of infective vectors, $S_h(t)$ is the number of susceptible hosts and $N_h(t)$ is the total number of hosts, all at time t (this equation is taken from the main co-infection model for the number of people moving from the susceptible to exposed compartments). Therefore the number of infections prevented by a control intervention is:

$$\text{Malaria infections prevented} = 365 \cdot \text{nyr} \cdot \text{mal.NI}^* - \sum_{t=1}^{365 \cdot \text{nyr}} \text{mal.NI}(t)$$

where *nyr* is the number of years malaria infections prevented are counted for and *mal.NI*^{*} is the steady state (pre-control) number of number of new infections each day.

NB: One problem with using this measure of malaria is that it does not fully capture the impact of control on malaria transmission - in some cases, when control leads to an overall decrease in malaria prevalence, the rate of new infections can actually increase. This happens when MDA is also being conducted; the worm burden in hosts decreases, skewing the host immune system towards a Th1 response, therefore malaria parasites are cleared more quickly and the duration of malaria infection decreases. Infected individuals return to the susceptible compartment quicker, and there is a larger pool of individuals to become infected. The effect of having an increased pool of susceptibles can outweigh the reduction in biting rate due to LLIN usage, and cause an overall increase in the number of new infections, even though prevalence decreases.

5.4.2 Estimating the economic benefit of preventing malaria cases

It is assumed that all malaria infected individuals will experience symptoms, normally febrile illness, at some point during their infection period. Of those individuals experiencing symptoms, 60% will seek treatment (Ruebush et al. 1995; Okell et al. 2008) and 100% will take time off work. The cost of treatment per malaria case is assumed to be \$8.22 which is made up of \$6.08 for health care provider costs and \$2.14 for drugs and transport (Wiseman et al. (2006), adjusted to 2009 prices). Therefore, if the number new malaria infections in year *n*, *mal.NI.yr(n)*, is denoted:

$$\text{mal.NI.yr}(n) = \sum_{i=1+(n-1) \cdot 365}^{365 \cdot n} \text{mal.NI}(i)$$

Where *mal.NI* is given in section 5.4.1. Then the total treatment costs saved for malaria over a 50 year period are:

$$TC_{\text{mal}} = \sum_{n=1}^{50} 0.6 \cdot 8.22 \cdot \text{mal.NI.yr}(n) \cdot \frac{1}{(1+r)^{n-1}}$$

It is also assumed that a bout of fever results in the affected individual taking four days off work, and the mean wage for a day's work in Africa is \$4.20 (Table 5.6), then the total wages that would have been lost due to malaria is defined as:

$$WC_{mal} = \sum_{n=1}^{50} 4 \cdot 4.20 \cdot mal.NI.yr(n) \cdot \frac{1}{(1+r)^{n-1}}$$

Malaria also causes fatalities; here we assume that 0.19% of malaria infections result in death. This figure was taken as a rough mean from the reported incidents and deaths from malaria in sub-Saharan Africa between 2000 and 2009 reported in the World Malaria Report 2010 (WHO 2010a). The majority of malaria deaths occur in under 5's - in this study we assume a mean age of death of 2 years old (Carneiro et al. 2010), and that individuals dying of malaria will avoid 30 years of working life (work from ages of 20 to 50). As we assume individuals die at the age of 2, the economic cost of wages lost will not be apparent for a further 18 years, at which point we assume 300 days are lost per year at a wage rate of \$4.20. Therefore the following equation gives the economic cost of malaria mortality in year n is given by:

$$MC_{mal}(n) = \begin{cases} \frac{1}{(1+r)^n} \sum_{i=1}^{n-17} mal.NI.yr(i) \cdot 300 \cdot 4.2 \cdot 0.0019 & \text{If } n \geq 18 \\ 0 & \text{If } n < 18 \end{cases}$$

And the total economic benefit of preventing malaria mortality over a 50 year period is:

$$MC_{mal}^{TOT} = \sum_{n=1}^{50} MC_{mal}(n)$$

The total economic benefit of preventing malaria cases is estimated as the sum of the wages lost due to illness and mortality, and the cost of treatment for the whole 50 year period.

5.4.3 Estimating the number of chronic LF disease cases prevented

Rather than estimating the number of LF infections prevented we choose to estimate the number of cases of chronic LF disease prevented. A large proportion of individuals infected with mf experience no clinical symptoms, so the number of chronic LF disease cases prevented is used to reflect the number of people who would actually benefit, health-wise, from the elimination/reduction of LF.

It is assumed that a proportion of LF infected individuals suffer from the two main chronic LF disease manifestations - lymphodema (here referred to as elephantiasis) and hydrocele, and that sufferers can continue to experience these diseases, even if then become clear of mf (Grenfell and Michael 1992) i.e. once an individual develops elephantiasis or hydrocele, they continue to be affected until they die. Once LF is eliminated there will be no new cases of chronic LF disease.

Prior to control, it is assumed that the number of people with elephantiasis is $E = N_h P_{LF}^* X$ where N_h is the total number of hosts, P_{LF}^* is the steady state LF prevalence level and X is the proportion of LF infected people that suffer from elephantiasis, here we use $X = 0.125$ (Ottesen et al. 2008). It is assumed that in a steady state, the number of cases of elephantiasis cases is constant. Therefore the number of new elephantiasis cases each day is equal to the number of people with elephantiasis that die that day. Then:

$$\begin{aligned} \text{Elephantiasis cases at time } t+1 - \text{Elephantiasis cases at time } t = \\ \text{new elephantiasis cases} - \text{deaths of elephantiasis cases} = 0 \end{aligned}$$

Let ρ_E be the rate at which LF infected individuals develop elephantiasis, and let μ_h be the host mortality rate, then:

$$\begin{aligned} E(t+1) - E(t) &= \rho_E N_h P_{LF}^* - \mu_h E = \rho_E N_h P_{LF}^* - \mu_h N_h P_{LF}^* X = 0 \\ \Rightarrow \rho_E &= \mu_h X \end{aligned}$$

It is assumed that ρ_E , the rate at which infected individual develop elephantiasis, is constant, even when the number of LF infected people is decreasing. It is also assumed that once an individual is cleared of mf they cannot go on to develop clinical disease. Therefore, substituting $\rho_E = \mu_h X$ into the above equation, the number of individuals suffering from elephantiasis at time $t+1$ is:

$$E(t+1) = \mu_h X N_h P_{LF}^*(t) + E(t)(1 - \mu_h)$$

The first part of this equation shows the number of new infections prevented at each time step, $NI_E(t)$, so we have:

$$NI_E(t) = \mu_h X N_h P_{LF}^*(t)$$

Then the total number of cases of elephantiasis disease prevented due to a control intervention in a time period T (days), DP_E , is:

$$DP_E = \mu_h X N_h \sum_{t=1}^T (P_{LF}^* - P_{LF}(t))$$

i.e. the number of cases that would of occurred without control minus the number of cases that did occur as a result of control.

Similarly, the number of hydrocele cases is estimated by assuming that the proportion of LF infected individuals experiencing hydrocele is 20.8% ($Y=0.208$) (Ottesen et al. 2008). Thus the total number of cases of hydrocele disease prevented in a time period T , DP_H , is:

$$DP_H = \mu_h Y N_h \sum_{t=1}^T (P_{LF}^* - P_{LF}(t))$$

The number of people suffering from chronic LF disease is then simply the sum of DP_E and DP_H . Typically the number of chronic LF disease cases prevented over a 50 year period is considered.

5.4.4 Estimating the economic benefit of preventing chronic LF disease cases

The economics benefits of preventing cases of hydrocele and elephantiasis are calculated separately and are based on the formulation presented in Chu et al. (2010). It is assumed that LF infected individuals start to develop chronic disease at the age of 30, and the mean lifespan of an individual is 50 years. Therefore, each individual protected from developing chronic LF disease experiences benefits for 20 years. The financial cost of each case of chronic disease is estimated by summing up the costs of treatment and the costs of wages lost due to illness. Following Chu et al. (2010), we assume an individual with chronic disease will experience treatment costs and loss of work hours due to the main chronic disease as well as several bouts of ADL each year, which also cause lost work hours and extra treatment costs. The parameters describing the proportion of people suffering from acute and chronic disease and the associated costs are presented in Table 5.6.

Employment data	Value	Range	Reference
Average wage per day for healthy individual	\$4.20	\$0.27 - \$13	IMF (2011)
Days worked per year	300		Chu et al. (2010)
Hydrocele			
<i>Chronic disease</i>			
% of individuals with hydrocele seeking treatment	40%	20-50%	Chu et al. (2010)
% of work hours lost each day due to hydrocele	15%	13-17%	Chu et al. (2010)
Average treatment costs per year	\$2.9	\$0.55-\$10.05	Chu et al. (2010)
<i>Acute disease</i>			
% of individuals with clinical LF with ADL	70%	45-90%	Chu et al. (2010)
% of ADL sufferers seeking treatment	65%	55-70%	Chu et al. (2010)
no. of ADL episode per affected individual per year	2	0-7	Chu et al. (2010)
Average duration of ADL episode (days)	4	0-9	Chu et al. (2010)
% of work hours lost during ADL episode	75%	50-93%	Chu et al. (2010)
Average treatment cost per ADL episode	\$1.50	\$0.25-\$5.20	Chu et al. (2010)
Lymphodema			
<i>Chronic disease</i>			
% of individuals with Lymphodema seeking treatment	50%	30-55%	Chu et al. (2010)
% of work hours lost each day due to Lymphodema	20%	15-22%	Chu et al. (2010)
Average treatment costs per year	\$4.3	\$0.85-\$15.00	Chu et al. (2010)
<i>Acute disease</i>			
% of individuals with clinical LF with ADL	95%	90-95%	Chu et al. (2010)
% of ADL sufferers seeking treatment	65	55-70%	Chu et al. (2010)
no. of ADL episode per affected individual per year	4	0-7	Chu et al. (2010)
Average duration of ADL episode (days)	4	0-9	Chu et al. (2010)
% of work hours lost during ADL episode	75%	50-93%	Chu et al. (2010)
Average treatment cost per ADL episode	\$1.50	\$0.25-\$5.20	Chu et al. (2010)

Table 5.6: Economic and epidemiological parameters used to estimate the cost of LF disease

The economic benefit of preventing one case of elephantiasis in one year, B_E , is given by:

$$\begin{aligned}
 B_E = & \begin{array}{ccccc} \text{Cost of} & & \text{Lost wages} & & \text{Cost of} \\ \text{treatment} & & \text{due to} & & \text{treatment} \\ \text{for chronic} & + & \text{chronic} & + & \text{for acute} \\ \text{disease} & & \text{disease} & & \text{disease} \end{array} \\
 B_E = & 4.3 * 0.5 + \frac{0.2 * \$4.20}{300} + 4 * 1.5 * 0.65 * 0.95 + 0.75 * 4 * 4 * \$4.20 * 0.95
 \end{aligned}$$

The total economic benefit of preventing one case of elephantiasis in year one is now defined as:

$$\sum_{t=1}^{20} \frac{1}{(1+r)^{t-1}} B_E$$

The total economic benefit up to a given year is defined as the economic benefit of preventing new disease cases in that year plus the economic benefit of preventing new cases in all preceding years up to a maximum of 20 years (as we assume individual develop chronic disease at the age of 30 and die at the age of 50). The economic benefit, in year n , of preventing new elephantiasis cases due to a control intervention can be expressed as:

$$\text{Economic benefit in year } n = EB_n^E = B_E \frac{1}{(1+r)^n} \sum_{i=\max\{1, n-19\}}^n DP_E(i)$$

Where $DP_E(t)$ is the number of infections prevented in year t defined in section 5.4.2. Hence, the total economic benefit of preventing elephantiasis cases by an intervention programme over the 50 year period following the initiation of MDA is:

$$EB_{TOT}^E = \sum_{k=1}^{50} EB_k^E$$

Similarly, for hydrocoele, the economic benefit of preventing one case of hydrocoele is defined as:

$$B_H = \begin{array}{ccccccc} \text{Cost of} & & \text{Lost wages} & & \text{Cost of} & & \text{Lost wages} \\ \text{treatment} & & \text{due to} & & \text{treatment} & & \text{due to} \\ \text{for chronic} & + & \text{chronic} & + & \text{for acute} & + & \text{acute} \\ \text{disease} & & \text{disease} & & \text{disease} & & \text{disease} \end{array}$$

$$B_H = \begin{array}{ccccccc} 2.9 * 0.5 & & 0.15 * \$4.20 & & 2 * 1.5 * & & 0.75 * 2 * 4 * \\ & + & * 300 & + & 0.65 * 0.70 & + & \$4.20 * 0.70 \end{array}$$

So, the total economic benefit in year n is given by:

$$\text{Total economic benefit in year } n = EB_n^H = B_H \frac{1}{(1+r)^n} \sum_{i=\max\{1, n-19\}}^n DP_H(i)$$

And the total economic benefit of preventing elephantiasis cases by an intervention programme over the 50 year period following the initiation of MDA is:

$$EB_{TOT}^H = \sum_{k=1}^{50} EB_k^H$$

The total economic benefit of preventing LF chronic disease is simply the sum of the economic benefit of preventing hydrocele cases plus the economic benefit of preventing elephantiasis cases.

In the result section, the economic benefit per \$1 control cost is used as the measure to determine the 'optimal' strategy. Then the time taken to eliminate LF, the number of disease cases prevented and the total economic benefit are also considered for a range of control scenarios. Specifically, we consider a range of MDA coverage levels with three different LLIN coverage levels. Initially, it is assumed that the pre-control (baseline) prevalence levels of malaria and LF are both 30%. We then go on to look at cases where the initial prevalence of both infections is 10%, and 50%. Finally, using the prevalence maps derived in chapter 4, the 'optimal' control strategy is predicted for each cell in the map based on its the pre-control prevalence levels. In all analyses we consider a 50 year period after control is first started, and the model contains 1667 humans and 1,000,000 vectors. It is assumed that LF is eliminated if prevalence falls below 0.1% (Michael et al. 2006).

5.6 Results

Initially, the baseline LF and malaria prevalence levels are assumed to be 30%. In Figure 5.1 we explore how long it takes to eliminate LF for a range of different MDA coverage levels (10%, 20%,...,100%) and LLIN coverage levels (0%, 40%, 80%). The dashed vertical lines in each colour demonstrate that LF elimination is not achieved for MDA coverage levels to the left of each point. It is clear that LF is eliminated quicker when LLIN coverage is higher and when MDA coverage is higher. Below 60% MDA coverage LF elimination is not possible unless LLINs are also used. However, when MDA coverage is 100% there is no difference in the time taken to eliminate LF between the three LLIN coverage levels.

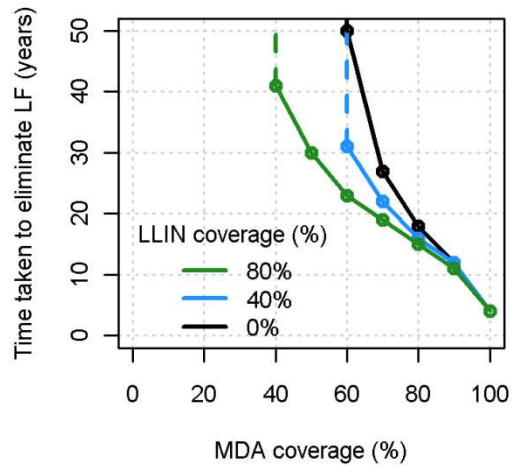


Figure 5.1: Time taken to eliminate LF for a range of different control programmes. Three LLIN coverage levels are considered (0%, 40%, 80%) and ten MDA coverage levels (10%, 20%,...,90%, 100%).

The total programme costs for each control package are shown in Figure 5.2. The LLIN costs are fixed for each coverage level, and the MDA costs are variable, depending on the coverage level and the required number of treatment rounds. Total programme costs initially increase as the MDA coverage level increases because people are treated, however, beyond the point at which LF elimination is first achieved, costs begin to decrease as fewer treatment rounds are required. For all LLIN coverage levels, the cheapest way to eliminate LF is by achieving a MDA coverage of 100%.

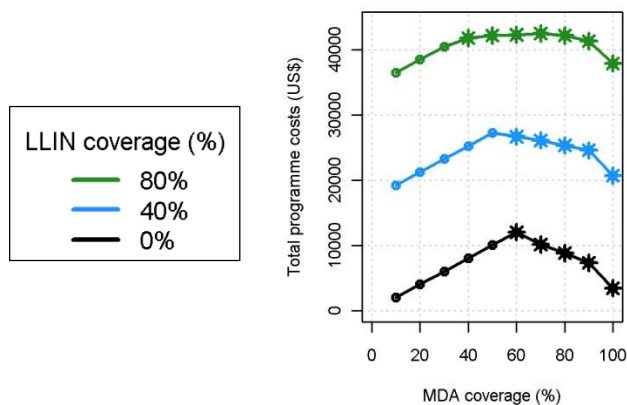


Figure 5.2: Total programme costs of each control package (US\$). The starred points indicate scenarios where LF elimination is achieved.

The number of disease cases prevented as a result of the different control strategies is shown in Figure 5.3. The numbers of elephantiasis and hydrocele cases prevented are shown in Figures 5.3A and 5.3B. At high levels of MDA coverage, there is little difference between the number of cases prevented for the different LLIN coverage scenarios, but at lower MDA coverages, a greater LLIN coverage level results in a higher number of chronic LF disease cases prevented. Conducting MDA without LLINs actually increases the number of malaria cases (Figure 5.3C), and more cases occur when MDA coverage is higher. Incorporating LLINs into the control package greatly reduces the number of malaria cases; 80% LLIN coverage prevents around double the number of cases compared to when LLIN coverage is 40%. When LLIN coverage is 40%, the number of malaria cases prevented decreases with increasing MDA coverage.

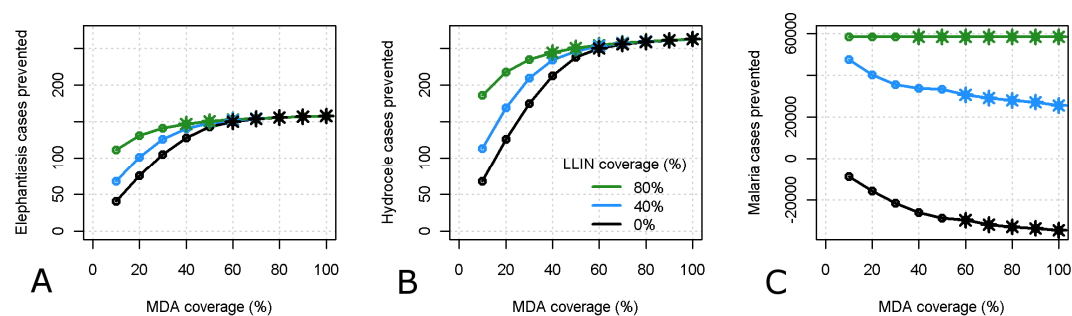


Figure 5.3: Number of elephantiasis, hydrocele and malaria cases prevented as a result of a range of different control interventions. The green, blue and black lines represent different levels of LLIN coverage (80%, 40% and 0% respectively).

The economic benefit of preventing chronic LF disease cases (the sum of preventing hydrocele and elephantiasis cases) is calculated using the formulae described in section 5.4.4. For low MDA coverage levels, including LLINs in the control package greatly increases the economic benefit of preventing LF cases, but at higher MDA coverage levels there is little difference in the economic benefit with and without LLINs (Figure 5.4A).

The economic benefit of preventing malaria cases is calculated using the formulae shown in section 5.4.2 and the results are shown in Figure 5.4B. LLIN coverage of 0% results in a negative economic benefit. When LLIN coverage is 40% there is a large positive economic benefit which decreases as MDA coverage increases. When LLIN coverage is 80% the economic benefit is almost constant for all MDA coverage levels.

Figure 5.4C shows the combined economic benefit of preventing chronic LF disease and malaria cases. It is clear that not including LLINs in the control package results in an overall negative economic benefit. The greatest overall economic benefit is achieved when LLIN

coverage is 80% and MDA coverage is 100%. A LLIN coverage level of 80% results in around 1.5x the benefit of having a LLIN coverage of 40%.

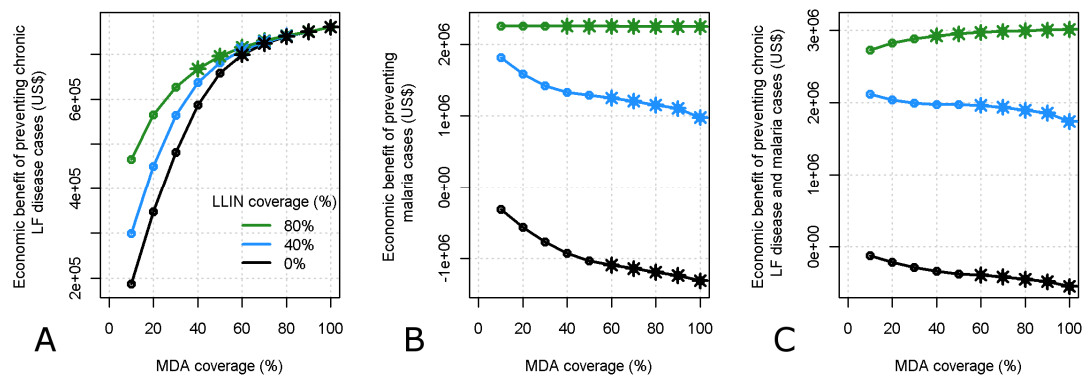


Figure 5.4: The estimated economic benefit of preventing chronic LF disease cases (A), malaria cases (B) and combined LF and malaria cases (C).

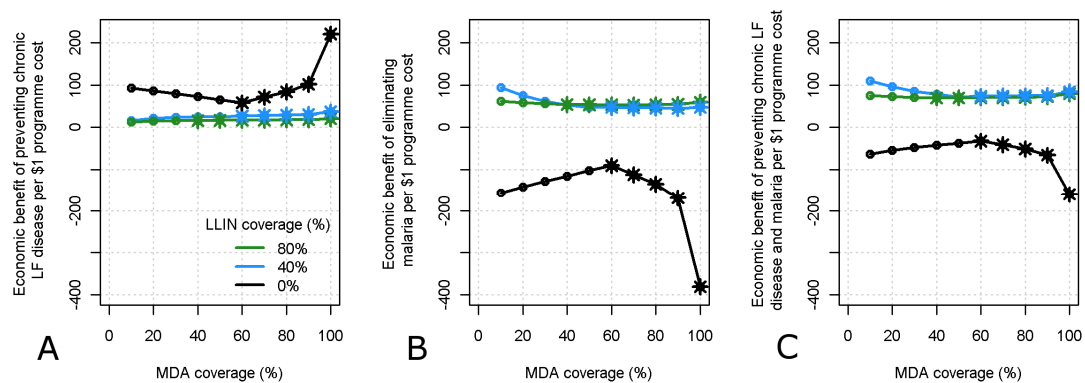


Figure 5.5: Economic benefit of preventing chronic LF disease cases (A), malaria cases (B) and combined LF and malaria cases (C) per \$1 spent on the control programme.

The economic benefit of preventing chronic LF disease per \$1 programme cost (EB/\$1) (Figure 5.5A) is highest when LLIN coverage is 0%, and is slightly higher for when LLIN coverage is 40% compared to when it is 80%. However, this is not the cases for malaria (Figure 5.5B). The highest EB/\$1 for preventing malaria (and where LF elimination is achieved) is when LLIN coverage is 80% and MDA coverage is 100%, but the EB/\$1 is almost identical for LLIN coverages of 40% and 80%. The EB/\$1 is negative when LLIN coverage is 0%.

Figure 5.5C shows the combined EB/\$1 of preventing chronic LF disease and malaria cases. Here it is clear that the EB/\$1 is very similar for LLIN coverage levels of 40% and 80%, but is marginally higher when LLIN coverage is 40%. We also note that the combined EB/\$1 when LLIN coverage is 0% is negative. This shows that given baseline malaria and LF prevalence levels of 30%, the strategy that produces the highest EB/\$1 is where LLIN coverage is 40%

and MDA coverage is 100%. A control package consisting of MDA with no LLINs actually results in an overall negative economic benefit.

Figures 5.1-5.5 show how different control packages consisting of MDA and LLINs at different coverage levels affect malaria and LF, and which strategies are 'optimal' in terms of the cost-benefit. It is assumed that malaria and LF prevalence levels are initially at a pre-control level of 30%. In Figures 5.6 and 5.7, the above analyses are repeated but we now assume the pre-control (baseline) levels of malaria and LF are 10% (Figure 5.6) and 50% (Figure 5.7).

The time taken to eliminate LF is lower when baseline prevalence is lower (Figures 5.6A, 5.7A). When the baseline prevalence is 10%, LF elimination can be achieved in 33 years with MDA coverage of 50% with no LLINs, in 25 years when LLIN coverage is 40% and 21 years with a LLIN coverage of 80% (Figure 5.6A). In contrast, when the baseline prevalence is 50% (Figure 5.7A) and MDA coverage is 50% it takes 40 years to eliminate LF if LLIN coverage is 80%, and elimination is not possible in less than 50 years if LLIN coverage is 40% or 0%. MDA coverage must exceed 80% for LF elimination to be achieved when there are no LLINs.

The total programme costs are almost identical when baseline prevalence levels are 10% (Figure 5.6B) and 50% (Figure 5.7B). The only difference is that LF is eliminated quicker when baseline prevalence is lower meaning the MDA costs are lower, and therefore overall costs are lower.

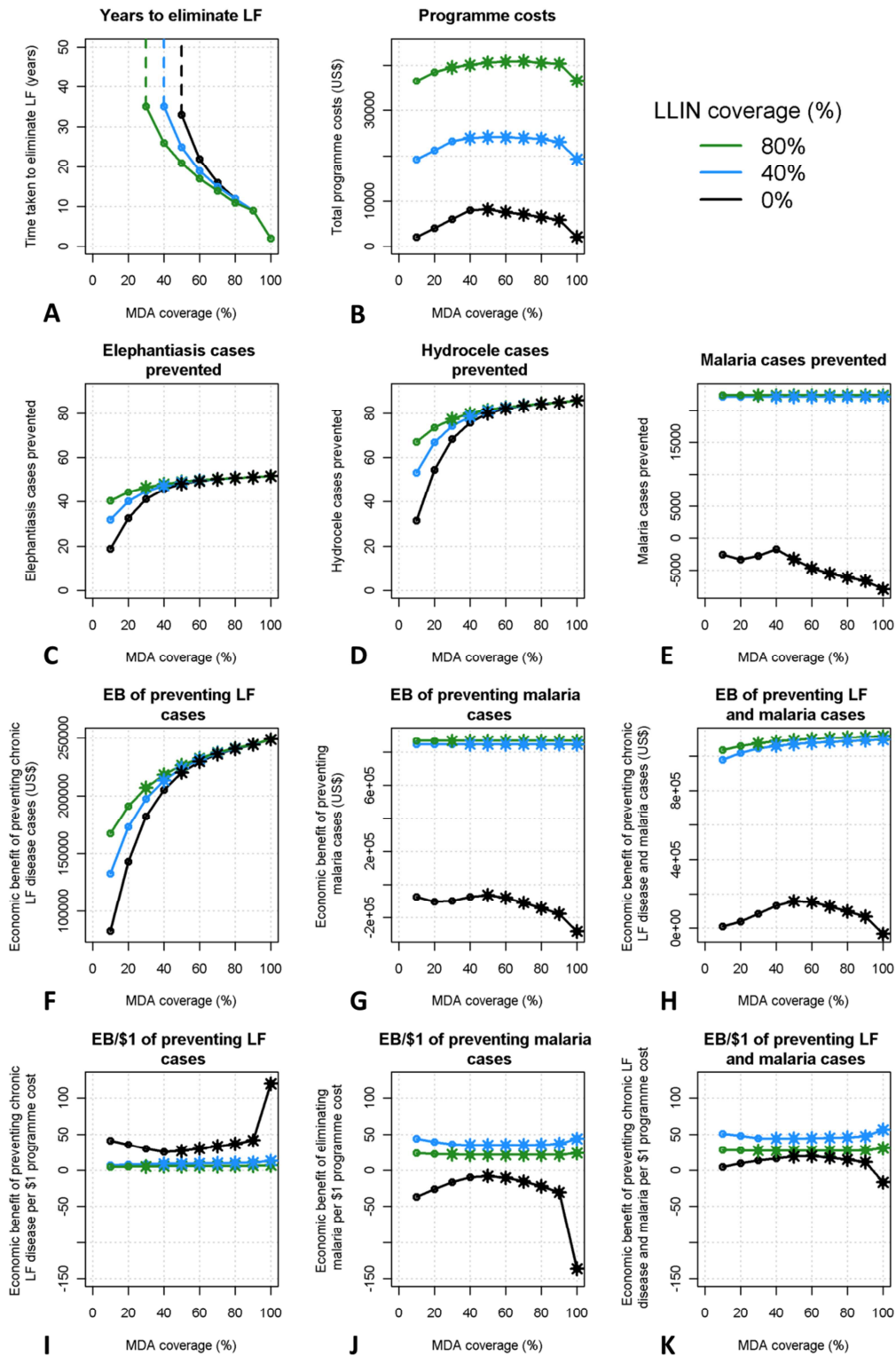


Figure 5.6: The time taken to eliminate LF (A), total programme costs (B), Elephantiasis, Hydrocele and malaria cases prevented (C,D,E), economic benefit of preventing chronic LF cases, malaria cases and combined LF and malaria cases (F,G,H) and the economic benefit of preventing chronic LF cases, malaria cases and combined LF and malaria cases per \$1 spent on control (I,J,K) assuming baseline pre-control malaria and LF prevalence levels of 10%.

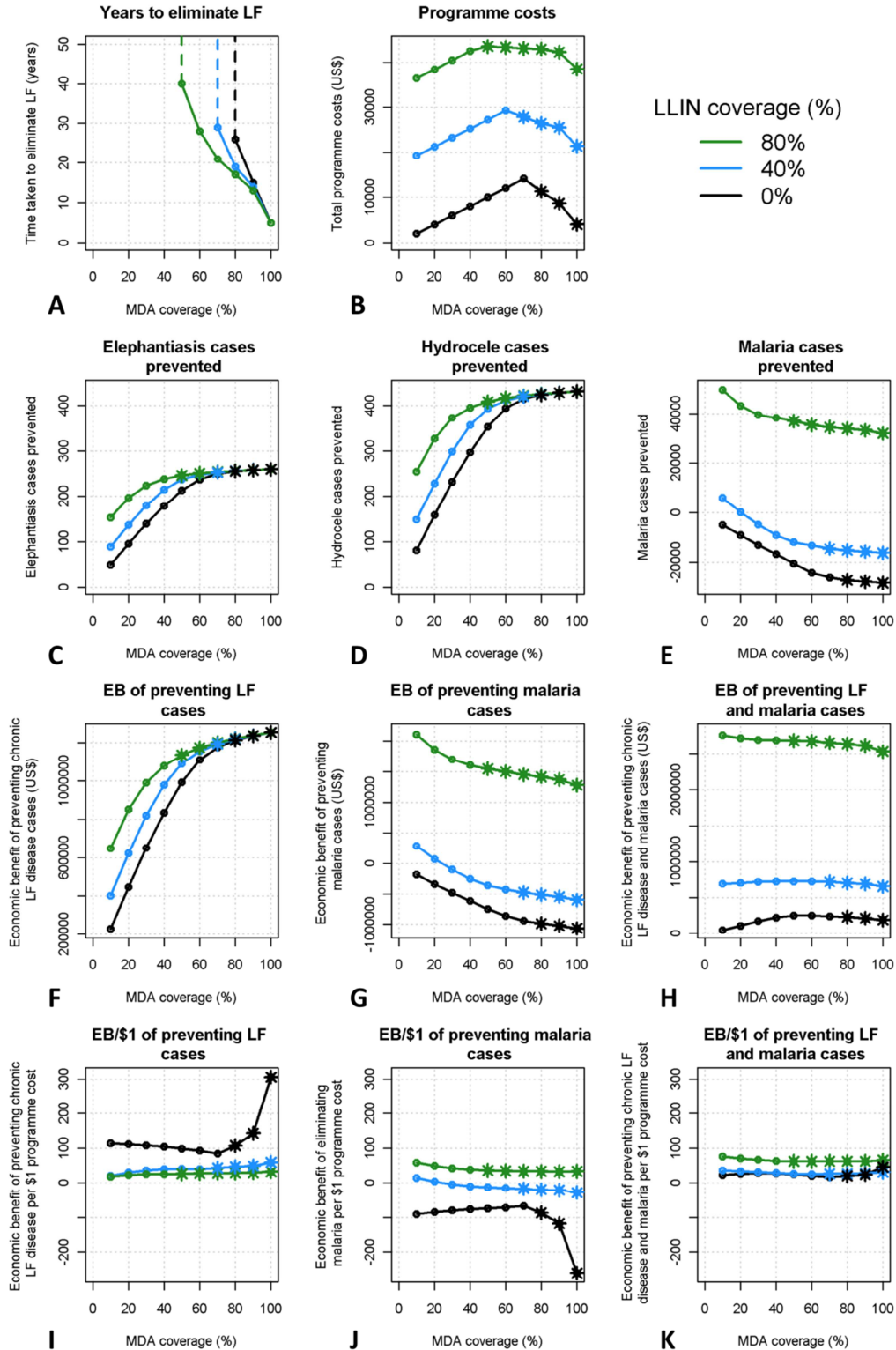


Figure 5.7: The time taken to eliminate LF (A), total programme costs (B), Elephantiasis, Hydrocele and malaria cases prevented (C,D,E), economic benefit of preventing chronic LF cases, malaria cases and combined LF and malaria cases (F,G,H) and the economic benefit of preventing chronic LF cases, malaria cases and combined LF and malaria cases per \$1 spent on control (I,J,K) assuming baseline pre-control malaria and LF prevalence levels of 50%.

When the baseline prevalence levels of LF and malaria are 10%, the number of malaria cases prevented is maximised when LLIN coverage is 40% or 80% (Figure 5.6E), but when LLIN coverage is 0% there is an increase in the number of malaria cases. However, when baseline prevalence is 50%, LLIN coverages of 0% and 40% both result in an increase in the number of malaria cases (Figure 5.7E). Only a LLIN coverage of 80% manages to achieve a reduction in the number of malaria cases. This shows that at low baseline prevalence levels, LLIN coverages of 40% and 80% are equally effective, but when the baseline prevalence is high, a high LLIN coverage level is required when MDA is being performed in order to reduce the number of malaria cases. The number of hydrocele and elephantiasis cases prevented (Figures 5.6C,D and 5.7C,D) is clearly highest when baseline prevalence is 50%, and the general shape of each curve is consistent with the description given for Figures 5.3A,B.

The economic benefit of preventing chronic LF disease cases is clearly highest when baseline prevalence is high. Figures 5.6F and 5.7F exhibit the same behaviour as described for Figure 5.4A. The economic benefit of preventing malaria cases is maximised for LLIN coverages of 40% and 80%, and is negative when LLIN coverage is 0% when the baseline prevalence is 10% (Figure 5.6G). However when baseline prevalence is 50%, the economic benefit of preventing malaria cases is negative for LLIN coverage levels of 0% and 40%. Only when LLIN coverage is 80% is there a positive economic benefit (Figure 5.7G).

Figures 5.6H and 5.7H show the combined economic benefit of preventing LF and malaria cases for baseline prevalence levels of 10% and 50% respectively. Here, we see that the total economic benefit is almost identical for LLIN coverage levels of 40% and 80% when the baseline prevalence is 10% (Figure 5.6H). However, when the baseline prevalence is 50% the total economic benefit is around 3.5x higher when LLIN coverage is 80% compared to 40% (Figure 5.7H). When the baseline prevalence is 30%, this figure is around 1.5 (Figure 5.4C).

Finally, the economic benefit of preventing LF and malaria per \$1 programme costs is considered. Figure 5.6I shows that when the baseline prevalence is 10%, looking at just the prevention of chronic LF disease cases, the optimal strategy is to treat with MDA at 100% coverage and provide no LLINs.

However, looking at the economic benefit of preventing malaria per \$1 spent on control (Figure 5.6J), this is actually the worst strategy. Here the best option is to have still treat with MDA at 100%, but also have LLINs with 40% coverage.

The overall 'best' strategy given the baseline prevalence conditions is presented in Figure 5.6K. The strategy that maximises the EB/\$1 is where MDA coverage is 100% and LLIN

coverage is 40%. The figure also shows that treating with MDA and no LLINs does give a positive EB/\$1.

This is not the case when the baseline prevalence is 50%; treating with MDA coverage at 100% and no LLINs maximises the economic benefit of preventing LF per \$1 spent is considered (Figure 5.7I), but now looking at the EB/\$1 of preventing malaria (Figure 5.7J), the 'best' control package would be one including LLINs with a 80% coverage level, and MDA coverage at any level above 50%. The 'optimum' control package that maximises the EB/\$1 for preventing both malaria and LF cases would be one with LLIN coverage of 80% and again MDA coverage at any level above 50% (Figure 5.7K). The EB/\$1 for preventing LF and malaria is almost identical for LLIN coverages of 0% and 40% showing that, unless LLIN coverage reaches some threshold level, their inclusion in a control package adds almost no gain to the EB/\$1.

The key finding from these results is that the strategy that maximises the economic benefit of preventing LF and malaria per \$1 spent on the control programme and achieves LF elimination varies depending on the baseline pre-control prevalence levels. When the baseline prevalence is 10% the clear 'optimum' strategy is to have 40% LLIN coverage and 100% MDA coverage (Figure 5.6K). For a baseline prevalence of 30% the 'optimum' strategy is to have LLINs with coverage of 40% and MDA coverage of 100%, although there is very little difference in the EB/\$1 between 40% or 80% LLIN coverage, and also very little difference between any MDA coverage level above 50% (Figure 5.5C). Finally, when the baseline prevalence is 50% the clear 'optimum' strategy is to have LLIN coverage of 80% and MDA coverage at any level above 50% (Figure 5.7K).

In the final analyses, the methods and results described thus far are used to predict the optimal strategy in different regions of Africa. Infection prevalence maps developed in chapter 4 are used to determine the pre-control prevalence levels of LF and malaria. These maps are then used to split the continent into categories based on LF and malaria prevalence levels. For each infection, four prevalence categories are defined - zero (0%), low (0-20%), medium (20-40%) and high (40+%). Therefore, in total, there are 16 categories, which are shown in Figure 5.8 (2 categories do not appear on the map: mal=ZERO, LF=MED and mal=ZERO, LF=HIGH). For each infection category, a model is defined with the pre-control prevalence set to the mid-point of the category, for example, a model with mal=LOW and LF=MED has pre-control prevalence levels of mal=10% and LF=30%. In total there are fifteen models (the model with zero prevalence of both infections is discarded as no control is clearly the optimum strategy in this case), and for each model, the impact of five control interventions are tested; these are described in Table 5.7.

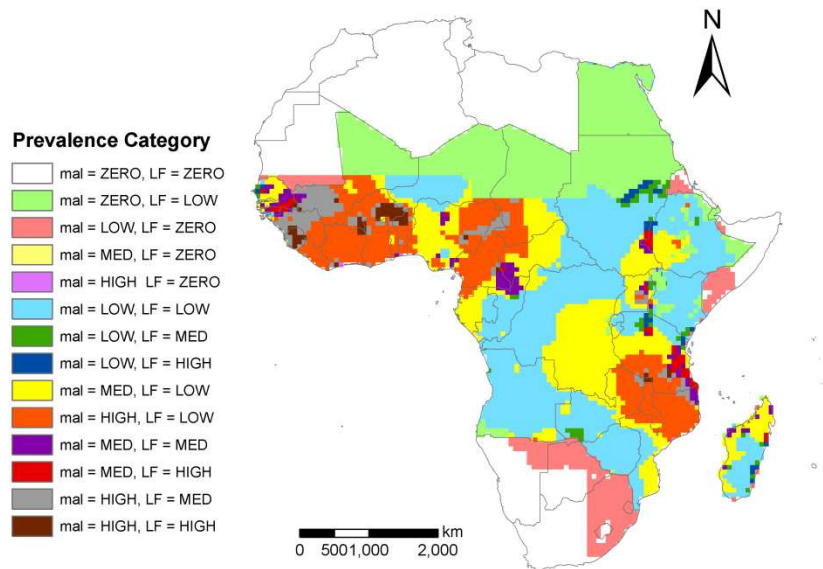


Figure 5.8: Map of Africa split into categories according to the malaria and LF prevalence in each cell. LOW indicates that prevalence is 0-20%, MED indicates that prevalence is 20-40% and HIGH shows areas where prevalence is greater than 40%.

Control	MDA	
Intervention	coverage	LLIN coverage
A	HIGH 80%	NONE 0%
B	NONE 0%	MEDIUM 40%
C	NONE 0%	HIGH 80%
D	HIGH 80%	MEDIUM 40%
E	HIGH 80%	HIGH 80%

Table 5.7: Details of the five control interventions tested

It is assumed that MDA is repeated annually for 50 years or until LF is eliminated, and that LLINs have a lifespan of five years and are re-distributed every five years for the whole 50 year period. The 'optimal' strategy is defined as the one which maximises the economic benefit per \$1 programme cost for a given set of baseline prevalence levels.

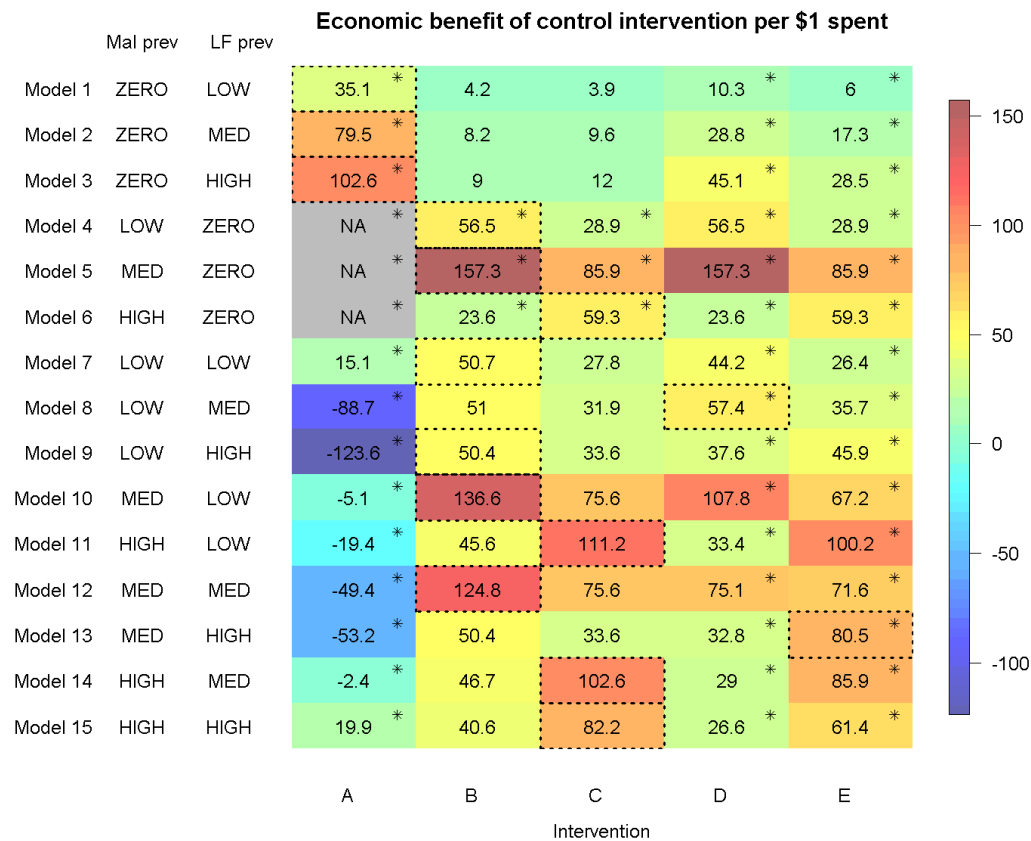


Figure 5.9: Economic benefit of preventing chronic LF and malaria cases per \$1 spent on the control programme. The colour ramp indicates the EB/\$1 of each control strategy for each model - the warmer colours represent higher EB/\$1 values. The strategy with the highest EB/\$1 value for each model is shown with a dotted line round it. Boxes with a star in the top right corner indicate models and control strategy combinations where LF elimination is achieved.

The economic benefit per \$1 programme costs for each model and control intervention is shown in Figure 5.9. The strategy with the highest EB/\$1 value for each model is shown with a dotted box, and the strategies which achieve LF elimination are identified with a star in the top right corner. In some cases, the strategy with the highest EB/\$1 value does not achieve LF elimination (see model 11 on Figure 5.9 for example) - here intervention C has the highest EB/\$1 value, but LF is not eliminated (no star in top right corner). In this situation intervention E may be the preferred strategy as it is the one with the highest EB/\$1 value that also manages to eliminate LF. The 'best' strategy when malaria prevalence is zero (models 1-3) is to just use MDA (intervention A). When LF prevalence is 0% (models 4-6), the best strategy is to just use LLINs with a coverage of 40% for medium and low malaria prevalence, and 80% LLIN coverage when malaria prevalence is high. The best strategy for many of the models (models 7, 9-12, 14,15) with both infections endemic is to have just LLINs (interventions B,C), however these strategies do not succeed in eliminating LF. For these models a combination

of LLINs and MDA (interventions D,E) achieve the highest cost-benefit ratios whilst managing to eliminate LF. For models 8 and 13, the strategy with the highest EB/\$1 value is also one that manages to eliminate LF (interventions D and E respectively).

Using the map presented in Figure 5.8 and the data from Figures 5.9, maps were created showing the optimal control strategy for different areas of Africa. Figure 5.10A shows the 'optimal' strategy – the one that maximises the EB/\$1 - given the prevalence conditions defined in Figure 5.8. Figure 5.10B shows the strategy with the highest EB/\$1 that also manages to achieve LF elimination. The best strategy in most of Africa for just maximising the EB/\$1 value is to have LLINs with coverage of 40%, and LLINs with coverage of 80% in areas where malaria prevalence is particularly high (Figure 13A). However, if LF elimination is also desired, the 'best' strategy is to have MDA with coverage at 80% and LLINs with coverage of 40% in most of Africa and both LLINs and MDA with coverage of 80% in areas with high malaria prevalence.

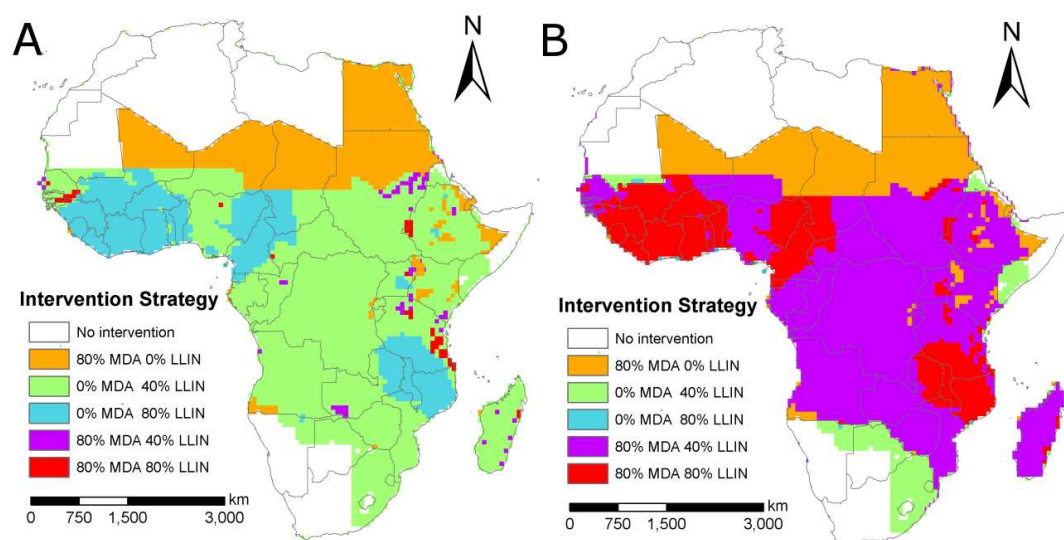


Figure 5.10: 'Optimal' strategy for controlling LF and malaria i.e. the strategy that (A) maximises the economic benefit per \$1 programme cost and (B) maximises the economic benefit per \$1 programme cost and achieves LF elimination

5.7 Discussion

In this chapter, we investigated whether an integrated control policy consisting of both MDA and LLIN distribution offered a more effective means of controlling the transmission of LF and malaria. Economic benefit per \$1 control cost was used as the metric to define the optimum strategy. The primary finding was that the optimum strategy for controlling LF and malaria depended on the pre-control prevalence levels of each infection, suggesting a universal integrated control programme would not be the most cost-effective way of tackling infection on a national or continental scale. Specifically, in areas of low LF and malaria prevalence the clear optimum strategy is to have a high MDA coverage and a medium LLIN coverage (Figure 5.6K). However, in areas of high prevalence, the best strategy is to have high coverages of both MDA and LLINs, and in fact, providing LLINs at a lower level offers almost no benefit (Figure 5.7K). For medium levels of LF and malaria prevalence the benefit of having a medium or a high LLIN coverage is almost identical, however, in this case, treating with MDA with no LLINs actually results in a negative economic benefit (Figure 5.5C).

Another key result is that the inclusion of LLINs alongside MDA reduces the number of annual treatment rounds required to eliminate LF (Figures 5.1, 5.6A, 5.7A), when MDA coverage is less than 80%. In the field, MDA coverage levels rarely exceed 90%; mean coverages of 80.3% and 83.4% were reported in Kenya (Njenga et al. 2008) and 77% in Tanzania (Simonsen et al. 2010). Elsewhere in the world, MDA coverage has been reported at around 85% in India (Addiss 2010), 70% in Philippines (Addiss 2010) and 52-93% in Haiti (De Rochars et al. 2005). Coverage will never reach 100% because pregnant women are not treated during MDA (Ottesen et al. 2008), nor are young children below some prescribed age or weight limit (Gyapong et al. 2005), additionally some individuals experience adverse reactions to taking the drugs, meaning they are less likely to participate in subsequent treatment rounds (McLaughlin et al. 2003) or simply do not believe that the drugs will benefit them (Talbot et al. 2008).

Our results also highlight the importance of considering both malaria and LF when planning and predicting the benefit of a control programme. The optimal strategy for LF control is to just use MDA at a high coverage level (Figures 5.5A, 5.6I, 5.7I), however, this strategy has a negative impact on malaria control. Therefore, a control programme just focusing on LF could actually lead to an increase malaria transmission.

MDA is currently the primary control measure for targeting LF in Africa. Many countries have been treating for 5+ years but none have achieved complete LF elimination. This is thought to be for a variety of reasons: the obvious reason is the high pre-control prevalence levels, but other factors such as coverage, compliance, the drug regimen and the competence of local LF vectors will also determine the success of a control programme (Kyelem et al. 2008).

Michael et al. (2004) modelled the number of annual MDA rounds required to eliminate LF and found that at pre-control prevalence levels above 15% (with 100% coverage), at least 6 years of treatment are required. However, if coverage levels are 80% (which is commonly observed for MDA), 8 annual rounds will be required. There is much uncertainty regarding these predictions as the actual number of rounds required will be specific to the local epidemiological conditions of each village or town. A study conducted in Egypt agrees with this hypothesis - here ten villages were treated with ten MDA rounds. They found that transmission was interrupted in some, but not all, of the villages (Ramaiah et al. 2007).

Conducting MDA, but not achieving elimination will initially decrease prevalence, but after control is ceased, prevalence will either level off (Simonsen et al. 2010) or bounce back towards its initial pre-control level (Gyapong et al. 2005). The uncertainty in the number of MDA rounds required to eliminate LF and the thresholds below which prevalence must decrease past in order to achieve elimination has increased calls for integrating vector control into MDA programmes (Michael et al. 2004; Burkot et al. 2006). Vector control can reduce the number of MDA rounds required to achieve elimination (Bockarie et al. 2009) and it can suppress transmission such that re-emergence of infection after MDA has ceased is less likely. However, as of yet, few studies have demonstrated how the addition of vector control can aid LF elimination. Maxwell et al. (1999) showed that using vector control after MDA ensured prevalence was maintained at a low level of around 3%. Similarly, in India, villages with MDA and vector control experienced a sustained decrease in transmission whereas villages with just MDA did not (Sunish et al. 2007).

Finally, we created the first maps showing 'optimal' control strategies for different regions of Africa based on the pre-control prevalence levels. If the target of the control programme is to maximise the EB/\$1 whilst achieving LF elimination (Figure 5.10B), the best strategy in most of Africa (where the prevalence of both infections is low) is to treat with a high MDA coverage and a medium LLIN coverage. In areas where malaria prevalence is very high, such as around Tanzania and western Africa, the best strategy is to treat with high LLIN and MDA coverage levels. However, if the aim is solely to maximise EB/\$1, the best strategy is to treat with just a medium LLIN coverage and no MDA in low prevalence areas and a high LLIN coverage and no MDA in higher prevalence areas (Figure 5.10A). This is because MDA increases malaria prevalence, so the economic benefits achieved by reducing LF are offset by the increases in malaria. Only in regions where malaria is non-endemic is MDA alone the best strategy (dark yellow shaded areas in Figure 5.10).

The results presented in the chapter represent a high speculative and theoretical attempt to understand how the optimal control strategy might vary in areas with different pre-control prevalence levels. We have made many assumptions in order to produce these results, and as such, there is great uncertainty associated with these predictions. Firstly, the nature of the

interactions between LF and malaria are still largely unknown - here we have accounted for LF induced vector mortality, and alterations in the host immune response as a result of co-infection. In reality the interactions between these infections is likely to be far more complex, and could potentially impact transmission in unexpected ways. More studies looking at how the immune response of a co-infected individual differs from that of an individual with single malaria or LF infection are needed to better understand this question. Secondly, quantifying the benefits of a control programme is a complicated task. In this chapter we assume that the benefits of eliminating a case of malaria consist of the treatment/drug costs saved, the hours of work not lost to illness or mortality. However, many other factors could be considered, such as the benefits to child health from reducing maternal malaria or economic growth due to having a healthy population (Goodman et al. 1999; Gallup and Sachs 2001). Similarly, many of the benefits of preventing a case of chronic LF disease are difficult to quantify, such as the social stigma attached to infection (Evans et al. 1993).

All results presented in this chapter are based on single point estimates for all the model parameters. As an extension to this work, a full sensitivity analysis would provide a more rigorous assessment of the optimum control strategies. Parameters that would be key candidates for a sensitivity analysis include: the MDA worm and mf kill rates, (Table 5.1) and the effectiveness of LLINs (Table 5.2) including the assumption the effectiveness wanes over the lifespan of the net. One fixed average wage rate is assumed for the whole of Africa, whereas in reality wages are likely to vary within countries, by age group, and by season depending on the type of work available. Assuming different wage rates could affect the optimal strategy, for example if the wages in a country were particularly high, a strategy that minimised the days lost due to illness might perform better. Treatment costs are also likely to vary between different countries, and between urban and rural areas.

Estimates of the total costs of each control programme used in this analysis are based on the separate costs of MDA and LLIN programmes, however in practice these costs may be reduced due to economies of scale from carrying out nationwide programmes, and from synergies achieved by integrating the programmes where possible (WHO 2011). Similarly, estimates of the benefits of the control programmes might be underestimates; here we consider just the beneficial impact of control on malaria and LF, however other infections are likely to benefit from the control measures implemented. Ivermectin is also used to treat onchocerciasis, and vector control could help reduce the transmission of other vector-borne diseases such as leishmaniasis (Molyneux 2004).

In this chapter, we have demonstrated a methodology for assessing the relative performance of different control strategies. In particular, we show that conducting MDA alone in areas co-endemic with malaria and LF could have actually increase malaria prevalence. This highlights the need to take a multi-disease control approach when designing control programmes. This work could be furthered by including the transmission of other infectious diseases commonly

found in Africa (such as HIV/AIDS, schistosomiasis or onchocerciasis) to allow better informed decisions regarding the 'best' strategies for controlling all infections, and how to maximise the economic benefit per \$1 control cost.

Chapter 6

Final Discussion

The aim of this thesis was to investigate whether integrated LF and malaria control is a more effective approach for reducing infection and disease in Africa. The primary result was that the 'optimal' control strategy in a specific area is dependent on the local infections conditions, in particular, the pre-control prevalence of each infection. For this reason, we developed maps showing how the prevalence of each infection varies over Africa. These maps were used, in combination with a malaria-LF co-infection transmission model, to explore how the effectiveness of different control strategies varied given different malaria and LF prevalence levels and how a control measure aimed at one infection impacted the transmission of the other infection.

Maps of infection prevalence have been used widely to guide control programmes, but they will never be entirely accurate representations due to the uncertainties that exist in all stages of the construction, from the lack of current prevalence data and the temporally averaged environmental data layers to the model parameterisation and the spatial scale of predictions. A trade-off exists between accuracy and computational speed. Increasing the resolution of the prediction maps greatly increases the computing time, however, a finer spatial scale may be required to identify smaller scale heterogeneities in prevalence (Onapa et al. 2001; Craig et al. 2007). The environmental predictive layers used to create the maps are interpolated from weather station data, so obtaining these on a finer spatial scale may just add more uncertainty to the predictions as these are inherently less accurate at higher resolutions. Environmental layers derived from satellite imagery could offer a way to sidestep this latter problem. Much of the variation in the actual infection prevalence across the continent may be as a result of factors not captured by the environmental and population variables used in the model. In addition, the environmental variables used in the analysis represent average conditions, whereas LF and malaria transmission are known to vary within the year and between years (Molineaux et al. 1980; Rwegoshora et al. 2005; Mabaso et al. 2006).

Producing up-to-date prevalence maps is a complicated task, primarily because the factors

that control transmission, and therefore transmission itself are constantly changing. In particular, vector population vary throughout the year, depending on the climate and season. Not only will the size of the vector population have a large impact on transmission, but the relative proportions of the different vector species will also affect transmission. Each vector species has a slightly different ecological niche, so, for example, in some regions, the vector population, and thus transmission, may plummet during the dry season, but another region with the same climatic conditions but more resilient vector species' may experience more sustained transmission. Many parts of Africa are currently using some form of LF or malaria control. Including this information in infection maps is key to capturing the actual prevalence rather than what prevalence would be in the absence of control. However, obtaining continent-wide data on the timing and location of all control would be a sizeable task.

Quantifying the uncertainty, accounting for the unknown factors that affect transmission and understanding how the inaccuracies in the model predictions affect control decisions are important jobs for map-makers. particularly if infection maps are to be a useful tool in planning and implementing control programmes.

The development of the malaria-LF co-infection model is presented in chapter four. This model describes the transmission dynamics of each infection and the interactions between the two. This is the first attempt to develop a model framework that quantifies how co-infection with malaria and LF affects the course of each infection in the host, and how the vectors ability to transmit one infection may be altered if they are already carrying the other infection. The co-infection model is clearly a simplification of the system in terms of the transmission dynamics of each infection and the effect of the interactions. However, we hope it offers insight into the potential impacts of co-infection, and highlights the need for more studies to be conducted that investigate how co-infection alters the host immune response. Although the interaction effects assumed in this chapter were hypothetical, we have shown that small changes in the transmission parameters induced by co-infection can have a significant impact on prevalence and the efficacy of control interventions.

Data relating to the impact of co-infection on hosts and vectors are sparse. Here we have hypothesised one set of LF-malaria interactions, but in reality the effects are likely to be far more complex. Fully understanding how co-infection impacts transmission dynamics is of vital importance for planning control interventions. As we have shown, eliminating one infection can lead to increases in the prevalence of the other infection.

Transmission models have a long history in epidemiology, and although no model can claim to be 'right', most can offer insights into different aspects of the transmission. The novel co-infection modelling framework developed in this thesis does just this: the model has helped to identify the gaps in current knowledge and data, as well as to highlight the potential

importance of adopting a multi-disease approach to transmission modelling. Not just for LF and malaria, but all co-infections that alter the host immune response, and in particular HIV/AIDS, tuberculosis and malaria, which are three of the most devastating diseases in Africa (Hotez et al. 2006).

In the penultimate chapter of the thesis, the prevalence maps and the co-infection model were brought together to produce maps detailing how the 'optimum' control strategy varies across Africa. We found that that 'optimal' control strategy in a specific area is dependent on the pre-control malaria and LF prevalence levels. This work again emphasises the importance of having accurate prevalence maps to help design control programmes, and also highlights the potential for integrated control as a more effective policy option.

The predictions of the 'optimal' strategies are based on estimates of the costs and benefits associated with each control programme. Estimating the benefits of reducing the prevalence of an infection is notoriously difficult (Chima et al. 2003; Chu et al. 2010). In this chapter, a fixed economic benefit of preventing one case of malaria or LF disease is assumed. However, in reality, the economic benefit of preventing a case of malaria or LF is likely to vary greatly, depending on the age, employment status, country of residence, level of treatment required and the proximity to a health facility of the sufferer, as well as the length and severity of the attack.

The estimates of the benefits of preventing both LF and malaria cases fail to include any social or economic development factors. A high malaria burden can impede the development of human capital due to children missing school as well as impairing cognitive ability due to illness (Sachs and Malaney 2002). Chronic LF disease can lead to social stigma and exclusion (Evans et al. 1993). Both diseases are associated with poverty (Haddix and Kestler 2000; Gallup and Sachs 2001) and can impair the economic development and acquisition of physical capital as a result of lost productivity and earnings, health sector spending on treatment, and a lack of foreign investment (Sachs and Malaney 2002). Estimating these factors is complex, and as a result, we excluded them from our calculations. However, by ignoring them, we could be grossly underestimating the total economic benefits of disease control.

Cost-benefit analysis was used in this thesis because it offered a means to compare and aggregate the benefits of LF control and malaria control. This allowed us to predict which strategy was 'optimal' for a given set of malaria and LF pre-control prevalence levels. However, this approach does not take into account the objectives of the policy makers and the logistical/financial constraints faced by programme managers. For example, the policy objective could be to reduce child mortality, in which case the control emphasis should be on malaria elimination rather than LF elimination. Also, we predicted the 'optimal' control strategy

over a 50 year period, whereas, in reality, programme managers may be expected to deliver results on a much smaller time scale. Funding for disease control in Africa is finite, and ideally should be spent in a way that maximises some definable health outcomes. However, a framework for quantifying the relative burden of different diseases and deciding the best way to allocate these resources has not been established.

The co-infection model presented in chapter four and the associated cost-benefit analysis presented in chapter five are not intended to be a comprehensive guide on the best control strategies for targeting LF and malaria across Africa. Rather, it is intended to highlight the importance of modelling the co-transmission of co-endemic infections and to provide a framework for investigating how co-infection with malaria and LF can affect the prevalence of each infection and the 'optimal' control strategy.

In order for the model presented here to provide a useful tool for policy makers, further work would be needed to better describe the transmission dynamics, including: an age-structured model to account for differences in transmission and disease severity for different age groups, seasonal vector dynamics, and a more accurate description of how co-infection alters the host immune response and vector mortality. Another potentially important addition to the model would be the acquisition of immunity to malaria - the immune response to malaria is different for individuals with and without acquired immunity, so the malaria immunity status of an individual is likely to affect their response to LF. Better estimates of the economic benefits of preventing chronic LF and malaria disease cases are needed to improve the accuracy of the cost-benefit predictions. In particular, location-specific estimates of the costs of control and the benefits of disease prevention would enable policy makers to make better informed decisions specific to the regions they are operating within. In addition, finer scaled prevalence maps would be required in order to ensure each area targeted by the control programme was receiving the correct level of control. Finally, a sensitivity analysis exploring all model parameters, especially those with large uncertainty (i.e. parameters that capture the impact of co-infection), would be needed to assess the stability of the model results.

Despite these caveats, this thesis offers a first attempt to define the spatial distribution and prevalence of malaria and LF co-infection in Africa, and to investigate how co-infection can affect the transmission dynamics of each infection. We also explore the effectiveness of different control strategies and quantify the potential benefits of adopting an integrated approach to disease control. Although much of this work is theoretical, we hope it can be used to guide future research questions and to provide an initial framework for modelling the co-transmission of important infectious diseases.

Appendix A

Details of studies used in LF mapping

Details of published LF data used chapters 2-4. The number of data points from each study or review is given in brackets. The references for the data used are given below the table.

Country	References
Benin	(Hawking, 1977) (7), (Myung <i>et al.</i> , 1998) (3)
Burkina Faso	(Bregues, 1975) (3), (Gidel <i>et al.</i> , 1969) (2), (Guigemde <i>et al.</i> , 1983) (2), (Gyapong <i>et al.</i> , 2002) (6), (Hawking, 1977) (1), (Lamontellerie, 1972) (73)
Cameroon	(Languillon, 1957) (10), (Moyou-Somo <i>et al.</i> , 2003) (1)
Chad	(Hawking, 1977) (6)
D.R.Congo	(Fain <i>et al.</i> , 1974)(1)
Egypt	(El-Setouhy <i>et al.</i> , 2007) (1), (McConnell & Dennis, 1976) (17), (Sasa, 1976) (2), (Shawarby <i>et al.</i> , 1965)(90) (Weil <i>et al.</i> , 1999) (3)
Ethiopia	(Hawking, 1977) (1), (McConnell & Dennis, 1976) (1)
Gambia	(Knight, 1980) (11), (Sasa, 1976) (2)
Ghana	(Dunyo <i>et al.</i> , 1996) (6), (Gbakima <i>et al.</i> , 2005) (3), (Gyapong <i>et al.</i> , 1996a) (10), (Gyapong <i>et al.</i> , 1996b) (6) (Gyapong <i>et al.</i> , 1998) (4), (Gyapong <i>et al.</i> , 2002) (11)
Guinea-Bissau	(Sasa, 1976) (4)
Ivory Coast	(Bregues, 1975) (3), (Hawking, 1977) (2)
Kenya	(Aburu, 1974) (5), (Mukoko <i>et al.</i> , 2004) (9), (Njenga <i>et al.</i> , 2000) (4), (Wamae <i>et al.</i> , 2001) (20)
Liberia	(Brinkmann, 1976) (3), (Burch & Greenville, 1955)(3), (Chlebowski & Zielke, 1980) (3), (Hawking, 1957) (1) (Hawking, 1977) (1), (Kuhlow & Zielke, 1976) (46), (Poindexter, 1950) (3), (Sasa, 1976) (1)
Madagascar	(Brunhes <i>et al.</i> , 1972) (2), (Brygoo, 1958) (34), (Coulanges, 1982) (2), (Rakotomalala <i>et al.</i> , 1995) (1)
Malawi	(Ngwira <i>et al.</i> , 2002) (6), (Ngwira <i>et al.</i> , 2007) (47)
Mali	(Bregues, 1975) (11)
Niger	(Hawking, 1977) (1), (Sasa, 1976) (1)
Nigeria	(Anosike & Onwuliri, 1994) (3), (Anosike <i>et al.</i> , 2005) (1), (Engelbrecht <i>et al.</i> , 2003) (1), (Onwuliri & Anosike, 1989)(5) (Sasa, 1976) (1), (Terranella <i>et al.</i> , 2006) (1), (Udonsi, 1986) (4), (Ufomadu <i>et al.</i> , 1990) (12), (Wijeyaratne <i>et al.</i> , 1982) (2)
Senegal	(Diallo <i>et al.</i> , 1977) (2), (Diallo <i>et al.</i> , 1983) (1), (Hawking, 1977) (6), (Juminer <i>et al.</i> , 1971)(1)
Sierra Leone	(Gbakima <i>et al.</i> , 1996) (3), (Gbakima & Sahr, 1996) (5), (Hawking, 1957) (1)
Sudan	(Satti & Abdel Nur, 1974) (3)
Tanzania	(Hawking, 1940) (1), (Hawking, 1977) (13), (Jordan, 1954) (15), (Jordan, 1956c, a, b) (56), (Sasa, 1976) (4), (Wegesa <i>et al.</i> , 1979) (2), (Southgate, 1992) (1), (Simonsen <i>et al.</i> , 1995) (2), (Meyrowitsch <i>et al.</i> , 1996) (2), (Massaga <i>et al.</i> , 2000) (2), (Meyrowitsch <i>et al.</i> , 2004) (1), (Jaoko <i>et al.</i> , 2007) (1)
Togo	(Hawking, 1977) (1), (Scheiber & Braun-Munzinger, 1976) (3)
Uganda	(Hawking, 1940) (1), (Onapa <i>et al.</i> , 2001)(2)
Zambia	(Roberts <i>et al.</i> , 1973) (1)
Zimbabwe	(Hawking, 1977) (2)

References

- Aburu, D.E. (1974) Studies on filarial infections at the East African coast. Annual report of East African Institute of Malaria and vector-borne diseases, Jan 74 - Dec 75.
- Anosike, J.C. & Onwuliri, C.O. (1994) Studies on filariasis in Bauchi state, Nigeria. II. The prevalence of human filariasis in Darazo local government area. *Parasitology*, **35**, 242-250.
- Anosike, J.C., Nwoke, B.E., Ajayi, E.G., Onwuliri, C.O., Okoro, O.U., Oku, E.E., Asor, J.E., Amajuoyi, O.U., Ikpeama, C.A., Ogbusu, F.I. & Meribe, C.O. (2005) Lymphatic filariasis among the Ezza people of Ebonyi state, Eastern Nigeria. *Annals of Agricultural and Environmental Medicine*, **12**, 181-186.
- Bregues, J. (1975) La filariose de Bancroft en Afrique de l'Ouest. *Memoires d'ORSTOM*, **79**, 1-299.
- Brinkmann, U.K. (1977) Epidemiological investigations of Bancroftian filariasis in the coastal zone Liberia. *Tropenmedizin Und Parasitologie*, **28**, 71-76
- Brunhes, J., E. , Rajaonarivelo, E. & Nelson, G.S. (1972) Epidemiologie de la filariose de Bancroft a Madagascar. *Cahiers ORSTOM Serie Entomologie Medicale et Parasitologie*, **10**, 193-205.
- Brygoo, E.R. (1958) La filariose humain a Madagascar. *Archives de l'Institute Pasteur de Madagascar*, **26**, 23-39.
- Burch, T.A. & Greenville, H.J. (1955) Filariasis in Liberia. *American Journal of Tropical Medicine and Hygiene*, **4**, 47-51.
- Chlebowski, H.O. & Zielke, E. (1980) Studies on Bancroftian filariasis in Liberia, West Africa. III. Efficacy of repeated treatment with diethylcarbamazine and vector control on the microfilarial reservoir in a rural population. *Tropenmedizin Und Parasitologie*, **31**, 181-193.
- Coulanges, P. (1982) Data on lymphatic filariasis caused by *w. bancrofti* in Madagascar. *Archives de l'Institut Pasteur de Madagascar (Tananarive)*, **50**, 23-33.
- Diallo, S., Sarr, M., Diagne, S. & Konate, L. (1977) Filariasis in the Nianing region, Senegal. Prevalence, clinical aspects, entomological findings. *Medecine Afrique Noire*, **24**, 233-242.
- Diallo, S., Bah, I.B., Victorious, A., N'dir, O. & Diouf, F. (1983) Effects of diethylcarbamazine on the transmission of *Wuchereria bancrofti* in a Senegalese reservoir of lymphatic filariasis. *Dakar Medical*, **28**, 179-186.
- Dunyo, S.K., Appawu, M., Nkrumah, F.K., Baffoe-Wilmot, A., Pedersen, E.M. & Simonsen, P.E. (1996) Lymphatic filariasis on the coast of Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **90**, 634-638.
- El-Setouhy, M., Abd Elaziz, K.M., Helmy, H., Farid, H.A., Kamal, H.A., Ramzy, R.M., Shannon, W.D. & Weil, G.J. (2007) The effect of compliance on the impact of mass drug administration for elimination of lymphatic filariasis in Egypt. *American Journal of Tropical Medicine and Hygiene*, **77**, 1069-1073.
- Engelbrecht, F., Oettl, T., Herter, U., Link, C., Philipp, D., Edeghere, H., Kaliraj, P. & Enwezor, F. (2003) Analysis of *Wuchereria bancrofti* infections in a village community in northern Nigeria: Increased prevalence in individuals infected with *Onchocerca volvulus*. *Parasitology International*, **52**, 13-20.
- Fain, A., Elsen, P., Wery, M. & Maertens, K. (1974) Human filariases in the Mayumbe region and adjacent areas (Zaire republic). Evaluation of the microfilarial density. *Annales de la Societe Belge de Medecine Tropicale*, **54**, 5-34.
- Gbakima, A.A. & Sahr, F. (1996) Filariasis in the Kaiyamba chiefdom, Moyamba district Sierra Leone: an epidemiological and clinical study. *Public Health*, **110**, 169-74.

- Gbakima, A.A., Pessima, J. & Sahr, F. (1996) Parasitological and clinical studies on *Wuchereria bancrofti* infection in Moyamba district, Sierra Leone. *African Journal of Health Sciences*, **3**, 37-40.
- Gbakima, A.A., Appawu, M.A., Dadzie, S., Karikari, C., Sackey, S.O., Baffoe-Wilmot, A., Gyapong, J. & Scott, A.L. (2005) Lymphatic filariasis in Ghana: Establishing the potential for an urban cycle of transmission. *Tropical Medicine & International Health*, **10**, 387-392.
- Gidel, R., Brengues, J. & Rodhain, F. (1969) Evaluation of 2 immunological tests (skin test and complement fixation test) for the detection of filariasis in populations of Upper Volta where *Wuchereria bancrofti*, *Onchocerca volvulus* and *Dipetalonema perstans* occur together. *Bulletin of the World Health Organization*, **40**, 831-842.
- Guigemde, T.R., Sokal, C.D. & Roux, J. (1983) Study of filarial associations in two villages in south-western Upper Volta. *Medecine Afrique Noire* **30**, 411-417
- Gyapong, J.O., Adjei, S. & Sackey, S.O. (1996a) Descriptive epidemiology of lymphatic filariasis in Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **90**, 26-30.
- Gyapong, J.O., Omane-Badu, K. & Webber, R.H. (1998) Evaluation of the filter paper blood collection method for detecting og4c3 circulating antigen in bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **92**, 407-410.
- Gyapong, J.O., Adjei, S., Gyapong, M. & Asamoah, G. (1996b) Rapid community diagnosis of lymphatic filariasis. *Acta Tropica*, **61**, 65-74.
- Gyapong, J.O., Kyelem, D., Kleinschmidt, I., Agbo, K., Ahouandogbo, F., Gaba, J., Owusu-Banahene, G., Sanou, S., Sodahlon, Y.K., Biswas, G., Kale, O.O., Molyneux, D.H., ROUNGOU, J.B., Thomson, M.C. & Remme, J. (2002) The use of spatial analysis in mapping the distribution of Bancroftian filariasis in four west African countries. *Annals of Tropical Medicine and Parasitology*, **96**, 695-705.
- Hawking, F. (1940) Distribution of filariasis in Tanganyika territory, East Africa. *Annals of Tropical Medicine and Parasitology*, **34**, 107-119.
- Hawking, F. (1957) The distribution of Bancroftian filariasis in Africa. *Bulletin of the World Health Organization*, **16**, 581-592.
- Hawking, F. (1977) The distribution of human filariasis throughout the world. Part iii. Africa. *Tropical Diseases Bulletin*, **74**, 649-679.
- Jaoko, W.G., Michael, E., Meyrowitsch, D.W., Estambale, B.B., Malecela, M.N. & Simonsen, P.E. (2007) Immunoepidemiology of *Wuchereria bancrofti* infection: Parasite transmission intensity, filaria-specific antibodies, and host immunity in two east African communities. *Infection and Immunity*, **75**, 5651-5662.
- Jordan, P. (1954) Filariasis in the southern province of Tanganyika. *East African Medical Journal*, **31**, 537-542.
- Jordan, P. (1956) Filariasis in the eastern, Tanga and northern provinces of Tanganyika. *East African Medical Journal*, **33**, 225-233.
- Jordan, P. (1956) Filariasis in the lake province of Tanganyika. *East African Medical Journal*, **33**, 237-242.
- Jordan, P. (1956) Filariasis in the western province of Tanganyika. *East African Medical Journal*, **33**, 233-236.
- Jordan, P. (1960) Bancroftian filariasis in Tanganyika: Observations on elephantiasis, microfilarial density, genital filariasis and microfilaraemia rates. *Annals of Tropical Medicine and Parasitology*, **54**, 132-140.
- Jumier, B., Diallo, S. & Diagne, S. (1971) A focus of filariasis in Sandiara (Senegal). I. *Archives de l'Institut Pasteur de Tunis*, **48**, 231-246.
- Knight, R. (1980) Current status of filarial infections in The Gambia. *Annals of Tropical Medicine and Parasitology*, **74**, 63-68.

- Kuhlow, F. & Zielke, E. (1976) Distribution and prevalence of *Wuchereria bancrofti* in various parts of Liberia. *Tropenmedizin Und Parasitologie*, **27**, 93-100.
- Lamontellerie, M. (1972) Results of surveys on the filariasis in western Upper Volta (cercle de banfora). *Annales de Parasitologie Humaine et Comparee*, **47**, 783-838.
- Languillon, P. (1957) Carte des filaires du Cameroun. *Bulletin de la Société de Pathologie Exotique*, **3**, 417-427.
- Massaga, J.J., Salum, F.M. & Savael, Z.X. (2000) Clinical and parasitological aspects of Bancroftian filariasis in Hale, northeast Tanzania. *Central African Journal of Medicine*, **46**, 237-241.
- McConnell, E. & Dennis, D.T. (1976) A survey for *Wuchereria bancrofti* in Ethiopia. *Ethiopian Medical Journal*, **14**, 31-36.
- Meyrowitsch, D.W., Simonsen, P.E. & Magesa, S.M. (2004) A 26-year follow-up of Bancroftian filariasis in two communities in north-eastern Tanzania. *Annals of Tropical Medicine and Parasitology*, **98**, 155-169.
- Meyrowitsch, D.W., Simonsen, P.E. & Makunde, W.H. (1996) Mass diethylcarbamazine chemotherapy for control of Bancroftian filariasis: Comparative efficacy of standard treatment and two semi-annual single-dose treatments. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **90**, 69-73.
- Moyou-Somo, R., Antoine Ouambe, M., Fon, E. & Bema, J. (2003) Enquete sur la filariose lymphatique dans sept villages du district de sante de Bonassama dans l'estuaire du Wouri, province du Littoral, Cameroon. *Médecine Tropicale*, **63**, 583-586.
- Mukoko, D.A., Pedersen, E.M., Masese, N.N., Estambale, B.B. & Ouma, J.H. (2004) Bancroftian filariasis in 12 villages in Kwale district, coast province, Kenya - variation in clinical and parasitological patterns. *Annals of Tropical Medicine and Parasitology*, **98**, 801-815.
- Myung, K., Massougbdji, A., Ekoue, S., Atchade, P., Kiki-Fagla, V. & Klion, A.D. (1998) Lymphatic filariasis in a hyperendemic region: A ten-year, follow-up panel survey. *American Journal of Tropical Medicine and Hygiene*, **59**, 222-6.
- Ngwira, B.M., Tambala, P., Perez, A.M., Bowie, C. & Molyneux, D.H. (2007) The geographical distribution of lymphatic filariasis infection in Malawi. *Filaria Journal*, **6**, 12.
- Ngwira, B.M., Jabu, C.H., Kanyongoloka, H., Mponda, M., Crampin, A.C., Branson, K., Alexander, N.D. & Fine, P.E. (2002) Lymphatic filariasis in the Karonga district of northern Malawi: A prevalence survey. *Annals of Tropical Medicine and Parasitology*, **96**, 137-144.
- Njenga, S.M., Muita, M., Kirigi, G., Mbugua, J., Mitsui, Y., Fujimaki, Y. & Aoki, Y. (2000) Bancroftian filariasis in Kwale district, Kenya. *East African Medical Journal*, **77**, 245-249.
- Onapa, A.W., Simonsen, P.E., Pedersen, E.M. & Okello, D.O. (2001) Lymphatic filariasis in Uganda: Baseline investigations in Lira, Soroti and Katakwi districts. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **95**, 161-167.
- Onwuliri, C.O.E. & Anosike, K. (1989) Filariasis in some parts of Bauchi state of Nigeria. In: *Epidemiology in Health Care Delivery*, Proc. 4th African Reg. Conf. of the IEA, pp. 91-98, Harare, Zimbabwe.
- Poindexter, H.A. (1950) Filariasis Bancrofti studies in Liberia. *American Journal of Tropical Medicine and Hygiene*, **30**, 519-523.
- Rakotomalala, R., Comolet, T., Rajonson, R. & Rakoto, B. (1995) Prevalence of Bancroftian filariasis in the region of Sainte Marie: Implications in public health. *Archives de l'Institut Pasteur de Madagascar*, **62**, 124-127.
- Roberts, C.J., Whitehall, J. & Gelfand, M. (1973) W. Bancrofti in the Kanyemba area. *Central African Journal of Medicine*, **19**, 13-14.
- Sasa, M. (1976) Human filariasis. A global survey of epidemiology and control. University Park Press: Baltimore.

- Satti, M.H. & Abdel Nur, O.M. (1974) Bancroftian filariasis in the Sudan. *Bulletin of the World Health Organization*, **51**, 314-315.
- Scheiber, P. & Braun-Munzinger, R.A. (1976) Bancroftian filariasis in Togo 1. A comparative field study of the membrane filtration concentration technique and conventional blood films. *Tropenmedizin Und Parasitologie*, **27**, 224-228.
- Shawarby, A.A., Mahdi, A.H., Naguib, K. & Moharran, A. (1965) Incidence of filariasis in Egypt. *Journal of the Egyptian Public Health Association*, **40**, 267-282.
- Simonsen, P.E., Meyrowitsch, D.W., Makunde, W.H. & Magnussen, P. (1995) Selective diethylcarbamazine chemotherapy for control of Bancroftian filariasis in two communities of Tanzania: compared efficacy of a standard dose treatment and two semi-annual single dose treatments. *American Journal of Tropical Medicine and Hygiene*, **53**, 267-272.
- Simonsen, P.E., Meyrowitsch, D.W., Jaoko, W.G., Malecela, M.N., Mukoko, D., Pedersen, E.M., Ouma, J.H., Rwegoshora, R.T., Masese, N., Magnussen, P., Estambale, B.B. & Michael, E. (2002) Bancroftian filariasis infection, disease, and specific antibody response patterns in a high and a low endemicity community in East Africa. *American Journal of Tropical Medicine and Hygiene*, **66**, 550-559.
- Southgate, B.A. (1992) Intensity and efficiency of transmission and the development of microfilaraemia and disease: their relationship in lymphatic filariasis. *Journal of Tropical Medicine and Hygiene*, **95**, 1-12.
- Terranella, A., Eigiege, A., Gontor, I., Dagwa, P., Damishi, S., Miri, E., Blackburn, B., Mcfarland, D., Zingeser, J., Jinadu, M.Y. & Richards, F.O. (2006) Urban lymphatic filariasis in central Nigeria. *Annals of Tropical Medicine and Parasitology*, **100**, 163-172.
- Udonsi, J.K. (1986) The status of human filariasis in relation to clinical signs in endemic areas of the Niger delta. *Annals of Tropical Medicine and Parasitology*, **80**, 425-432.
- Ufomadu, G.O., Nwoke, B.E., Akoh, J.I., Sato, Y., Ekejindu, G.O., Uchida, A., Shiwaku, K., Tumbau, M. & Ugomo, K.K. (1990) The occurrence of loiasis, mansonellosis and wuchereriosis in the Jarawa river valley, central Nigeria. *Acta Tropica*, **48**, 137-147.
- Wamae, C.N., Mwandawiro, C., Wambayi, E., Njenga, S. & Kiliku, F. (2001) Lymphatic filariasis in Kenya since 1910, and the prospects for its elimination: A review. *East African Medical Journal*, **78**, 595-603.
- Wegesa, P., McMahon, J.E., Abaru, D.E., Hamilton, P.J., Marshall, T.F. & Vaughan, J.P. (1979) Tanzania filariasis project. Survey methodology and clinical manifestations of Bancroftian filariasis. *Acta Tropica*, **36**, 369-377.
- Weil, G.J., Ramzy, R.M., El Setouhy, M., Kandil, A.M., Ahmed, E.S. & Faris, R. (1999) A longitudinal study of Bancroftian filariasis in the Nile delta of Egypt: baseline data and one-year follow-up. *American Journal of Tropical Medicine and Hygiene*, **61**, 53-58.
- Wijeyaratne, P.M., Singha, P., Verma, O.P. & Motha, B. (1982) Evaluation of the diethylcarbamazine provocative test in the diagnosis of *Wuchereria bancrofti* infections in the Nigerian savanna and the effects on *Dipetalonema perstans*. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **76**, 387-389.

Appendix B

Generalised Linear Spatial Models and MCMC parameter estimation

Generalised linear models (GLM) were developed by Nelder and Wedderburn (1972) to provide a regression modelling framework for data that are distributed according to one of the members of the exponential family. One example is binomial data which has a response variable Y_i , the number of positive outcomes out of a given number of trials, m_i . In a GLM the responses Y_i are assumed to be mutually independent and to have expectation μ_i which is given by $h(\mu_i) = \sum_{j=1}^k f_{ij}\beta_j$, where $F = [f_{ij}]$ is a matrix of covariates and f_{ij} is the value of the j^{th} predictive covariate at the i^{th} location. A link function is denoted by $h(\cdot)$; for binomial data we use the logit function $h(\mu) = \log(\mu/(1-\mu))$.

This theory was extended by Breslow and Clayton (1993) to allow for dependent responses, whereby a latent variable U with a multivariate normal distribution with mean zero was introduced. The responses are now independent conditionally on the latent variables (Diggle and Ribeiro Jr 2007; Ben-Ahmed et al. 2010), so now $\mu_i = E[Y_i | U_i]$ and the model is denoted $h(\mu_i) = \sum_{j=1}^k f_{ij}\beta_j + U_i$. Models of this type are called generalised linear mixed models (GLMM).

A further extension to this is the introduction of spatially correlated latent variables $S(x_i)$ (Diggle et al. 2003); these models are called generalised linear spatial models (GLSM). S is modelled as a stationary Gaussian process with $S \sim MVN(0, \sigma^2 R + \tau^2 I)$ where σ^2 is the variance and τ^2 is the nugget effect which accounts for the additional non-spatial variation in the data. R is an $n \times n$ correlation matrix with $R_{ij} = \rho(\|x_i - x_j\|)$. We employ an exponential correlation function: $\rho(u; \phi) = \exp(-u/\phi)$ and $u = (\|x_i - x_j\|)$ and x_i is the location of the i^{th} observation. The model is now:

$$h(\mu_i) = \sum_{j=1}^k f_{ij}\beta_j + S(x_i)$$

where the response variables $Y_1, \dots, Y_n$ are conditionally independent given S and the conditional expectation is $\mu_i = Y_i | S(x_i)$ which can be expressed as $\mu(x_i) = m(x_i)h^{-1}(S(x_i))$ where $m(x)$ is the number of trials and h^{-1} is the inverse of the link function.

Denote the spatial parameters $\theta = \{\phi, \sigma^2\}$ (for simplicity we assume τ^2 is fixed). The likelihood of the model is given by

$$\ell(\beta, \theta) = \int \prod_{i=1}^n f(y_i; \mu_i) p(s; \beta, \theta) ds$$

where $f(y, \mu)$ is the density of the error distribution parameterised by μ and $p(s; \beta, \theta)$ is the multivariate normal density for S .

The high dimensionality of this function prevents us from evaluating it directly, instead we look to Markov chain Monte Carlo (MCMC) methods to approximate the integral.

Markov Chain Monte Carlo Inference

We adopt a Bayesian Framework for estimating the model parameters and the target process, which is the process we are trying to model, $h^{-1}(\mu(x))$. MCMC methods are also adopted for estimating the target process over new prediction sites; S^* is the values of the spatial process S at new prediction sites.

Parameter Estimation

The algorithm outlined by Diggle and Ribeiro (2007) and Christensen and colleagues (2006) is as follows: each iteration of the MCMC algorithm first samples from $[S | \beta, \theta, Y]$, then from $[\theta | S]$ and finally from $[\beta | S, Y]$. Repeating this process sufficiently many times gives us samples from $[S, \beta, \theta | Y]$. We use the open source software package geoRglm (Christensen and Ribeiro Jr 2002) in R to run the MCMC simulations.

For a Bayesian analysis with priors $\pi(\beta | \theta)$ and $\pi(\theta)$, the conditional distribution $[S, \beta, \theta | Y]$ has density

$$f(s, \beta, \theta | Y) \propto \prod_{i=1}^n f(y_i | \mu_i) f(s | \beta, \theta) \pi(\beta | \theta) \pi(\theta)$$

A Langevin-Hastings (LH) algorithm is used to simulate S and β (Christensen 2000). This algorithm uses information about the gradient of the posterior distribution to help direct it away

from the tails of the distribution by tending to propose values in the ‘uphill’ direction i.e. values towards the median of the distribution.

The data are transformed in such a way that the new transformed parameters are standardised and uncorrelated. Denote the transformation: $S \mapsto \tilde{S}(S; \beta; \theta; y)$ and $\beta \mapsto \tilde{\beta}(\beta; \theta; y)$

For a target density $f(s | \beta, \theta)$ where the proposal density for state $\tilde{s}$ is multivariate normal with mean

$$\xi(\tilde{s}) = \tilde{s} + \frac{h}{2} \nabla \log(p(\tilde{s} | \tilde{\theta}, \tilde{\beta}))$$

and variance $h\mathbf{I}$. The proposal s' is accepted with probability

$$\alpha(s, s') = \min \left\{ \frac{p(s') \exp(-\frac{1}{2h} \|s - \xi(s')\|^2)}{p(s) \exp(-\frac{1}{2h} \|s - \xi(s)\|^2)}, 1 \right\}$$

where h is the proposal variance. This value should be tuned when running the model until the acceptance rate is around 60% as this is optimal for the algorithm (Christensen et al. 2006). The posterior for β , $\pi(\beta | \theta)$ is calculated in the same way.

The spatial parameters $\theta = \{\phi, \sigma\}$ are updated using a Metropolis-Hastings algorithm (Christensen et al. 2006). Again, the parameters are transformed to reduce the correlation between the posterior distributions: $\sigma \mapsto \tilde{\sigma}$ and $\phi \mapsto \tilde{\phi}(\sigma, \phi)$. If σ is the current state and σ' is a proposal generated from a multivariate normal distribution with mean σ and covariance $h\mathbf{I}$, then this proposal is accepted with probability

$$\alpha(\sigma, \sigma') = \min \left\{ 1, \frac{f(\sigma' | y)}{f(\sigma | y)} \right\}$$

For the spatial parameters we tune h such that approximately 25% of the proposals are accepted, as this is optimal for the metropolis algorithm (Ribeiro et al. 2003).

The parameters are all updated during each iteration of the model. Once we have estimated $f(s, \beta, \theta | y)$, it is used to predict over new locations.

Prediction

Prediction of the process at new sites is performed by adding an additional step to the algorithm (Diggle et al. 1998; Diggle and Ribeiro Jr 2007). The value of the spatial process at new sites S^* is dependent on S and θ and is found by drawing a sample from $[S^* | S, \theta]$ in each iteration where

$$[S^* | S, \theta] \sim MVN(\Sigma_{12}^T \Sigma_{11}^{-1} S, \Sigma_{22} - \Sigma_{12}^T \Sigma_{11}^{-1} \Sigma_{12})$$

with $\Sigma_{11} = \text{Var}(S)$, $\Sigma_{12} = \text{Cov}(S, S^*)$, $\Sigma_{22} = \text{var}(S^*)$ and using the values of S generated by the algorithm.

The target process we are trying to predict $T = T(S^*)$ is found by using the samples generated by the algorithm to form a sample from the predictive distribution $[T | Y]$ and taking the sample mean.

References

- Ben-Ahmed, K., A. Bouratbine, et al. (2010). "Generalized linear spatial models in epidemiology: A case study of zoonotic cutaneous leishmaniasis in Tunisia." Journal of Applied Statistics **37**(1): 159 - 170.
- Breslow, N. E. and D. G. Clayton (1993). "Approximate Inference in Generalized Linear Mixed Models." Journal of the American Statistical Association **88**(421): 9-25.
- Christensen, O. F., Møller, J., and Waagepetersen, R. (2000). Analysis of spatial data using generalized linear mixed models and Langevin-type Markov chain Monte Carlo. Research Report R-00-2009, Department of Mathematical Sciences, Aalborg University.
- Christensen, O. F. and P. J. Ribeiro Jr (2002). "geoRglm: A package for generalised linear spatial models." R News **2**(2): 26-28.
- Christensen, O. F., G. O. Roberts, et al. (2006). "Robust Markov chain Monte Carlo Methods for Spatial Generalized Linear Mixed Models." Journal of Computational and Graphical Statistics **15**(1): 1-17.
- Diggle, P. J. and P. J. Ribeiro Jr (2007). Model-Based Geostatistics. New York, Springer.
- Diggle, P. J., P. J. Ribeiro, et al. (2003). An introduction to model-based geostatistics. Spatial statistics and computational methods. Lecture notes in statistics. J. Møller. New York, Springer: 43-86.
- Diggle, P. J., J. A. Tawn, et al. (1998). "Model-based geostatistics." Journal of the Royal Statistical Society: Series C (Applied Statistics) **47**(3): 299-350.
- Nelder, J. A. and R. W. M. Wedderburn (1972). "Generalized Linear Models." Journal of the Royal Statistical Society. Series A (General) **135**(3): 370-384.
- Ribeiro, P. J., O. F. Christensen, et al. (2003). Geostatistical software - geoR and geoRglm. DSC 2003 Working Papers.

Appendix C

Full co-infection model equations

Host Malaria Equations

$$\frac{dS_h}{dt} = b_h N_h - \frac{ac_{vh}}{N_h} I_v S_h - \mu_h S_h + \beta_h R_h$$

$$\frac{dE_h}{dt} = \frac{ac_{vh}}{N_h} I_v S_h - m_h E_h - \mu_h E_h$$

$$\frac{dI_h}{dt} = m_h E_h - \mu_h I_h - \gamma_{hm} I_h - \omega_h I_h$$

$$\frac{dR_h}{dt} = \omega_h I_h - \mu_h R_h - \beta_h R_h$$

Vector Malaria Equations

$$\frac{dS_v}{dt} = b_v N_v - \left(\mu_{vs} + \mu'_v \frac{L}{N_v} \right) S_v - \frac{ac_{hv}}{N_h} I_h S_v$$

$$\frac{dE_v}{dt} = \frac{ac_{hv}}{N_h} I_h S_v - \left(\mu_{ve} + \mu'_v \frac{L}{N_v} \right) E_v - m_v E_v$$

$$\frac{dI_v}{dt} = m_v E_v - \left(\mu_{vi} + \mu'_v \frac{L}{N_v} \right) I_v$$

Immature Worm Equations (in hosts)

$$\frac{d\tilde{W}_S}{dt} = a p_1 p_2 L \frac{H_S}{H} g(Y) - \mu_h \tilde{W}_S - r_w \tilde{W}_S - \frac{ac_{vh}}{H} V_I \tilde{W}_S + \beta_h \tilde{W}_R$$

$$\frac{d\tilde{W}_E}{dt} = a p_1 p_2 L \frac{H_E}{H} g(Y) - \mu_h \tilde{W}_E - r_w \tilde{W}_E + \frac{ac_{vh}}{H} V_I \tilde{W}_S - m_h \tilde{W}_E$$

$$\frac{d\tilde{W}_I}{dt} = a p_1 p_2 L \frac{H_I}{H} g(Y) - \mu_h \tilde{W}_I - r_w \tilde{W}_I + m_h \tilde{W}_E - \omega_h \tilde{W}_I - \gamma_{hm} \tilde{W}_I$$

$$\frac{d\tilde{W}_R}{dt} = a p_1 p_2 L \frac{H_R}{H} g(Y) - \mu_h \tilde{W}_R - r_w \tilde{W}_R + \omega_h \tilde{W}_I - \beta_h \tilde{W}_R$$

Mature Worm Equations (in hosts)

$$\frac{dW_S}{dt} = r_w \tilde{W}_S - (\mu_{wS} + \mu_h) W_S - \frac{ac_{vh}}{H} V_I W_S + \beta_h W_R$$

$$\frac{dW_E}{dt} = r_w \tilde{W}_E - (\mu_{wE} + \mu_h) W_E + \frac{ac_{vh}}{H} V_I W_S - m_h W_E$$

$$\frac{dW_I}{dt} = r_w \tilde{W}_I - (\mu_{wI} + \mu_h) W_I + m_h W_E - \omega_h W_I - \gamma_{hm} W_I$$

$$\frac{dW_R}{dt} = r_w \tilde{W}_R - (\mu_{wR} + \mu_h) W_I + \omega_h W_I - \beta_h W_R$$

Microfilaria Equations (in hosts)

$$\frac{dM_S}{dt} = \alpha \frac{W_S}{N_h} - \mu_M M_S - \mu_h M_S - \frac{ac_{vh}}{N_h} I_v M_S + \beta_h M_R$$

$$\frac{dM_E}{dt} = \alpha \frac{W_E}{N_h} - \mu_M M_E - \mu_h M_E + \frac{ac_{vh}}{N_h} I_v M_S - m_h M_E$$

$$\frac{dM_I}{dt} = \alpha \frac{W_I}{N_h} - \mu_M M_I - (\mu_h + \gamma_{hm}) M_I + m_h M_E - \omega_h M_I$$

$$\frac{dM_R}{dt} = \alpha \frac{W_R}{N_h} - \mu_M M_R - \mu_h M_R + \omega_h M_I - \beta_h M_R$$

Immature Larva Equations (in vectors)

$$\frac{d\tilde{L}_S}{dt} = a\eta(M) p_3 p_4 S_v - r_L \tilde{L}_S - \frac{ac_{hv}}{N_h} I_h \tilde{L}_S$$

$$\frac{d\tilde{L}_E}{dt} = a\eta(M) p_3 p_4 E_v - r_L \tilde{L}_E + \frac{ac_{hv}}{N_h} I_h \tilde{L}_S - m_v \tilde{L}_E$$

$$\frac{d\tilde{L}_I}{dt} = a\eta(M) p_3 p_4 I_v - r_L \tilde{L}_I + m_v \tilde{L}_E$$

Mature Larva Equations (in vectors)

$$\frac{dL_S}{dt} = r_L \tilde{L}_S - \mu_L L_S - \left(\mu_{VS} + \mu'_V \frac{L}{N_V} \right) L_S - a p_1 L_S - \frac{ac_{hv}}{N_h} I_h L_S$$

$$\frac{dL_E}{dt} = r_L \tilde{L}_E - \mu_L L_E - \left(\mu_{VE} + \mu'_V \frac{L}{N_V} \right) L_E - a p_1 L_E + \frac{ac_{hv}}{N_h} I_h L_S - m_v L_E$$

$$\frac{dL_I}{dt} = r_L \tilde{L}_I - \mu_L L_I - \left(\mu_{VI} + \mu'_V \frac{L}{N_V} \right) L_I + m_v L_E$$

State variable	Definition
$\tilde{W}_i$	Number of immature worms in hosts with malaria status i (where $\tilde{W} = \tilde{W}_S + \tilde{W}_E + \tilde{W}_I + \tilde{W}_R$)
W_i	Number of mature worms in hosts with malaria status i (where $W = W_S + W_E + W_I + W_R$)
M_i	Number of microfilariae in hosts with malaria status i (where $M = M_S + M_E + M_I + M_R$)
$\tilde{L}_j$	Number of immature larvae in vectors with malaria status j (where $\tilde{L} = \tilde{L}_S + \tilde{L}_E + \tilde{L}_I$)
L_j	Number of mature larvae in vectors with malaria status j (where $L = L_S + L_E + L_I$)
H_i	Number of hosts with malaria status i (where $H = H_S + H_E + H_I + H_R$)
V_j	Number of vectors with malaria status j (where $V = V_S + V_E + V_I$)

Table C.1 (from chapter 5) – Description of model state variables

Parameter	Definition	Baseline value
a	Vector biting rate	0.25 or 0.5 bites per vector per day
b_h	Birth rate of humans	1/12,000 day ⁻¹
b_v	Birth rate of vectors	1/10 + 5×10 ⁻⁶ day ⁻¹
μ_h	Death rate of humans	1/12,000 day ⁻¹
μ_{Wi}	Death rate of worms in hosts with malaria state $i = \{S, E, I, R\}$	defined below
μ_M	Death rate of microfilariae	1/300 day ⁻¹
μ_{Vj}	Death rate of vectors with malaria state $j = \{S, E, I\}$	1/10 + 5×10 ⁻⁶ day ⁻¹
μ'_V	Additional mortality rate of larval-infected vectors with malaria status (× by mean no. of larvae per vector)	0.1 day ⁻¹
μ_L	Death rate of larvae	0 day ⁻¹
c_{vh}	Probability of infectious vectors transferring infection to susceptible hosts	1/25
c_{hv}	Probability of infectious hosts transferring infection to susceptible vectors	9/100
ω_h	Rate at which infectious host become recovered	defined below
α	Production rate of mf per worm	1/15 day ⁻¹
r_L	Rate of development from immature to mature larvae	1/13 day ⁻¹
r_W	Rate of development from immature to mature worm	1/365 day ⁻¹
m_h	Rate at which infected hosts become infectious	1/100 day ⁻¹
m_v	Rate at which infected vectors become infectious	0.1 ⁿ / n day ⁻¹
β_h	Rate at which humans return to susceptible from recovered	1/7 day ⁻¹
γ_{hm}	Human mortality rate due to malaria infection (virulence of plasmodium parasite in humans)	0.00000001 day ⁻¹
p_1	Proportion of L3 leaving mosquitoes per bite	0.414
p_2	Proportion of leaving mosquitoes that enter host	3.616×10 ⁻⁵
μ_L	Death rate of larvae	0 day ⁻¹
p_3	Probability of mf entering the vector upon biting an LF-infected host	0.37
p_4	Probability of mf entering the vector developing into L3 larvae	1

Table C.2 (from chapter 5) – model parameter and values used

The death rate of worms μ_{wi} in hosts with malaria state $i = \{S, E, I, R\}$ is defined as follows:

$$\mu_{ws} = (\mu_{ws}^{max} - \mu_{ws}^{min}) \exp\left(-\gamma_1 \frac{W}{N_h}\right) + \mu_{ws}^{min}$$

$$\mu_{we} = \mu_{wi} = \mu_{wr} = (\mu_{wi}^{max} - \mu_{wi}^{min}) \exp\left(-\gamma_1 \frac{W}{N_h}\right) + \mu_{wi}^{min}$$

where we assume baseline values $1/\mu_{ws}^{min} = 10$ years, $1/\mu_{ws}^{max} = 8$ years, $1/\mu_{wi}^{min} = 8$ years, $\mu_{wi}^{max} = 6$ years and $\gamma_1 = 3$.

The rate at which infectious hosts recover ω_h is defined as follows:

$$\omega_h = (\omega_h^{max} - \omega_h^{min}) \exp\left(-\varepsilon_1 \frac{W}{N_h}\right) + \omega_h^{min}$$

where $1/\omega_h^{min} = 200$ days, $1/\omega_h^{max} = 120$ days and $\varepsilon_1 = 3$.

The function $g(Y)$ is an immunity term for worms given by:

$$g(Y) = \exp(-cY)$$

where $c = 0.2$ and Y is a variable that models the change in immunity over times given by:

$$\frac{dY}{dt} = \frac{W}{N_h} - \frac{1}{30}Y$$

This can be thought of as the 'experience of infection'.

The function $\eta(M)$ is a mf uptake function given by:

$$\eta(M) = \kappa \left(1 - \exp\left(-\frac{\rho}{\kappa} M\right) \right)$$

where $\kappa = 4.5$ and $\rho = 0.19$

The prevalence of malaria in hosts is defined as:

$$prev.MAL.h = 100 \frac{I_h}{N_h}$$

The prevalence of malaria in vectors is defined as:

$$prev.MAL.v = 100 \frac{I_v}{N_v}$$

The prevalence of LF in hosts is defined as:

$$prev.LF.h = 100 \left(1 - \left(1 + \frac{M}{k_0 + k_1 M} \right)^{-(k_0 + k_1 M)} \right)$$

where $k_0 = 0.0029$ and $k_1 = 0.0236$

The prevalence of LF in vectors is defined as:

$$prev.LF.v = 100 \left(1 - \left(1 + \frac{L}{N_v k_2} \right)^{-k_2} \right)$$

where $k_2 = 0.007$.

Appendix D

Modelling Ivermectin induced vector mortality

In this section, the impact of vectors taking bloodmeals containing ivermectin on overall vector mortality is modelled. Ivermectin bloodmeals are taken from individuals in areas where MDA has recently been conducted. Specifically, data from studies looking at the effect of Ivermectin on vector mortality is used to determine:

- 1) how vector mortality is altered when vectors take a bloodmeal containing ivermectin
- 2) whether the number of days after MDA has been conducted that a vector takes a bloodmeal on has an effect on its mortality rate

In this appendix we attempt to develop an equation to estimate the mean vector mortality rate that takes into account the varying mortality rates of vectors which have taken a bloodmeal at different time points post-MDA. This new equation was formulated as follows:

Studies were collated that looked at how vector mortality is affected by the number of days post-MDA that a vector takes a bloodmeal containing Ivermectin (table 1). For each study the pre and post MDA mortality rates were calculated by using a non-linear least squares method to estimate the value of the daily probability of mortality, μ_v , for the following equation:

$$s_d = 100(1 - \mu_v)^d$$

Where s_d is the proportion of mosquitoes surviving to day d . The new mortality rates were then converted to give the mean lifespan for each data point.

Study	Vector species	Wild or Lab	Control (or pre MDA) mortality rate	days post MDA	new mortality rate	mean lifespan	new mean lifespan	mean days post MDA	% change in mean lifespan
Bockarie et al. (1999)	<i>An. punc.</i>	Wild	0.0216	< 4	0.3844	46.296	2.601	2	94.381
Bockarie et al. (1999)	<i>An. punc.</i>	Wild	0.0216	28	0.0211	46.296	47.393	28	-2.370
Sylla et al. (2010)	<i>An. gambiae</i>	Wild	0.0365	1-6	0.1644	27.397	6.083	3	77.798
Sylla et al. (2010)	<i>An. gambiae</i>	Wild	0.0365	7-14	0.0559	27.397	17.889	10	34.705
Sylla et al. (2010)	<i>An. arabiensis</i>	Wild	0.0451	1-6	0.1763	22.173	5.672	3	74.419
Sylla et al. (2010)	<i>An. arabiensis</i>	Wild	0.0451	7-14	0.0723	22.173	13.831	10	37.621
Chaccour et al. (2010)	<i>An. gambiae</i>	Lab	0.1357	1	0.4007	7.369	2.496	1	66.134
Cartel et al. (1991)	<i>Ae. polynesiensis</i>	Lab	0.011	30	0.1491	90.909	6.707	30	92.622
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	0	0.47	90.090	2.128	0	97.638
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	7	0.3078	90.090	3.249	7	96.394
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	10	0.1913	90.090	5.227	10	94.198
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	14	0.0467	90.090	21.413	14	76.231
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	26	0.0196	90.090	51.020	26	43.367
(Foley et al. 2000)	<i>An. farauti</i>	Lab	0.0111	44	0.02	90.090	50.000	44	44.500

Table D.1: Summary data on the effect on Ivermectin on vector mortality for blood engorged vectors. Full data showing the percentage of vectors surviving to different time points are shown in the papers.

An example of the model fits are shown in fig 1 where we fit to the data in Bockarie et al. (1999)

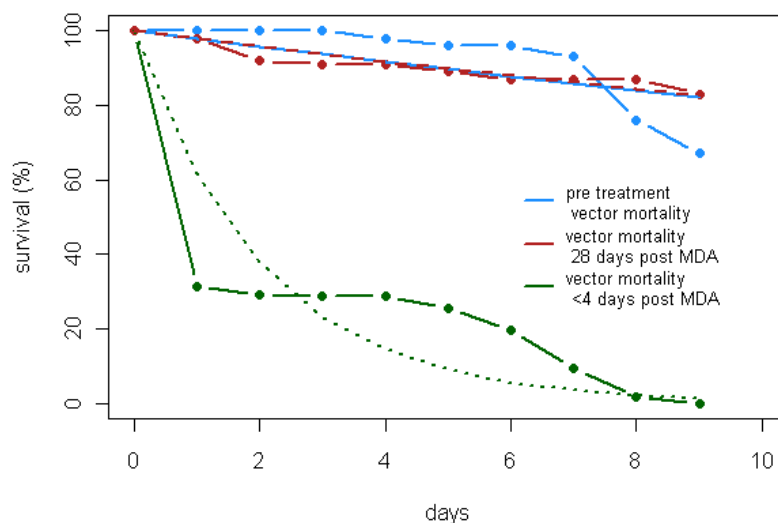


Fig D.1: Survival curves fitted to the vector mortality data presented in Bockarie et al. (1999). The solid lines with points are the data from the study and the dashed lines are the fitted lines.

Using the pre-MDA mean lifespan and post-MDA lifespan, the percentage change in mean lifespan after a mosquito has taken a bloodmeal containing ivermectin is calculated for each data point. These data are plotted against the number of the days post MDA that the vectors were caught (fig 2). The 'wild mosquito only' data was used in all further analysis.

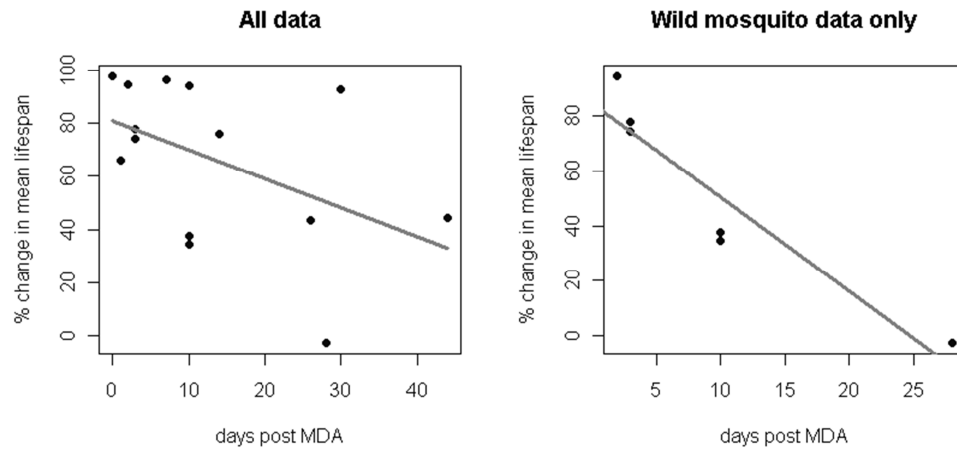


Figure D.2: Percentage change in mean lifespan against the number of days post MDA the mosquitoes were captured. Light grey line is the line of best fit.

Using a pre-MDA vector mortality rate of 0.1, the '% change in mean lifespan' was converted back into new mean lifespan and new mean mortality rate (fig 3). Ivermectin is assumed to have an effect of vector mortality for 24 days post-MDA, after which mortality returns to its original level.

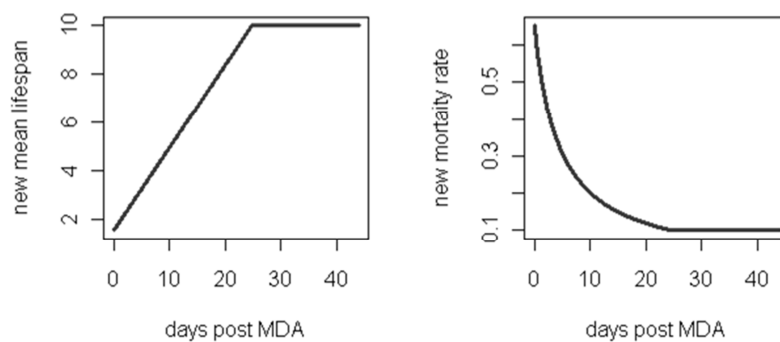


Figure D.3: New mean lifespan and new mortality rates for vectors caught post MDA. For example, on day 5 is the mortality rate is 0.31, so a vector taking a blood meal 5 days after MDA would survive to day 1 post capture with a probability $(1-0.31)^1$, and to day 2 post capture with probability $(1-0.31)^2$, and so on.

The new mortality rate function shown in fig 3b is explained further in fig 4 where we show the survival curves of vectors taking bloodmeals 0, 6 and 15 days after MDA.

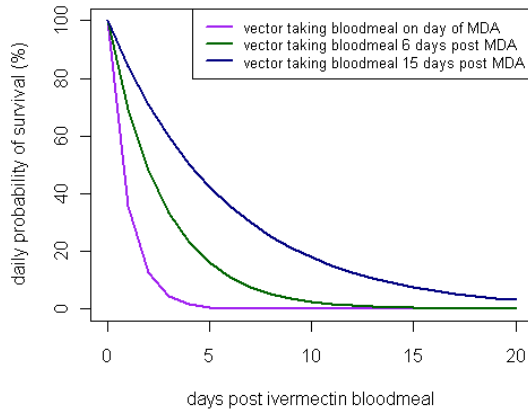


Fig D.4: Survival curves for mosquitoes taking an ivermectin blood meal 0, 6 and 15 days after MDA. The daily probability of survival is larger the longer post MDA the vector takes a bloodmeal showing the waning effect ivermectin has on vector mortality.

The next step is to estimate a 'combined' mortality rate. For example, on day three after MDA the mean mortality rate has to account for the fact that mosquitoes that are not blood engorged are just dying at the background vector mortality rate, vectors that took a bloodmeal containing ivermectin on day 1 after MDA are dying at some high mortality rate, vectors that took an ivermectin blood meal of day 2 after MDA are dying at some slightly lower rate, and so on.

We achieve this by constructing a simple discrete vector birth and death model with variable mortality rates (fig 5). The vector population is split into two categories: V_B = blood engorged vectors (post MDA) and V_N = non-blood engorged vectors (post MDA). It is assumed that non-blood engorged vectors die at the normal background mortality rate, and that the carrying capacity does not change. It is also assumed that if a vector takes a blood meal on day X post MDA, then the daily probability of mortality will be μ_{vX} , regardless of whether another blood meal is taken.

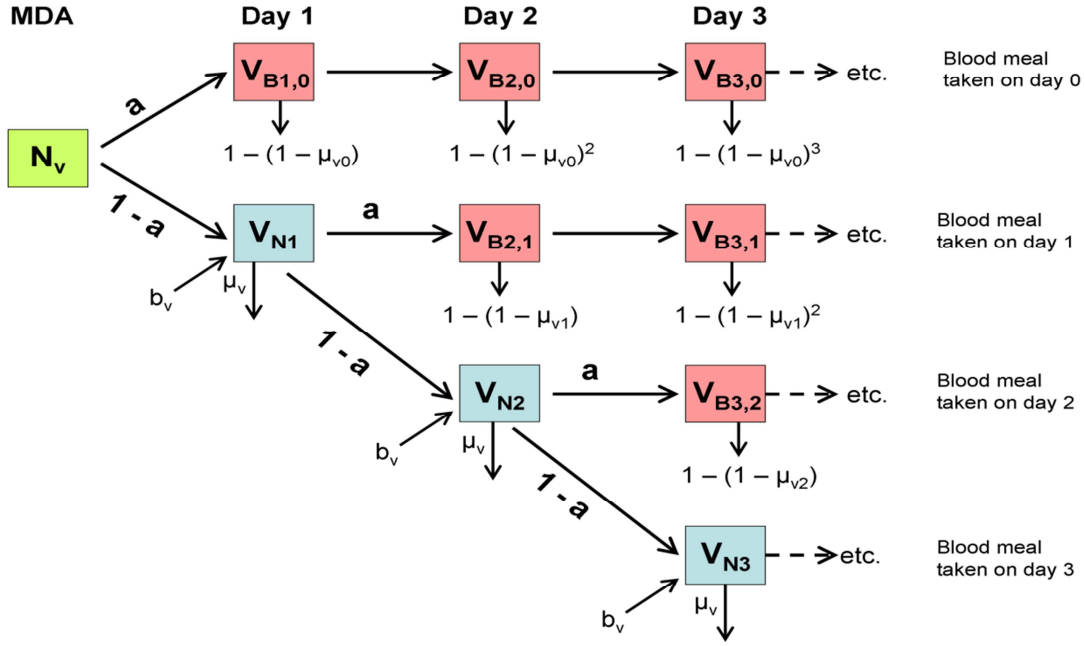


Figure D.5: Schematic of the vector birth and death model accounting for the day on which the blood meal was taken post MDA and the day of biting specific mortality rates. $V_{Bi,j}$ represents the number of blood engorged vectors on day i that took a blood meal on day j . V_{N1} represents the number of vectors that have not taken a blood meal post MDA. Initially all vectors start in the green box. Vectors taking a blood meal from a treated host on day 1, for example, move to $V_{B1,0}$, where they experience a mortality rate of μ_{v0} . These vectors then die out such that $1 - (1 - \mu_{v0})^n$ die on day n .

The blood engorged vectors are denoted as $V_{Nj,k}$ where j is the day post MDA and k is the day on which the vector took the blood meal. For a given day, t , the total number of blood engorged vectors is: $V_B(t)$. The number of non-blood engorged vectors on a given day, t , is denoted $V_N(t)$. The total number of vectors on day t is given as: $N_v(t) = V_B(t) + V_N(t)$.

Here we present a sub-model to describe the blood engorged and non-blood engorged vector population post-MDA as a discretised set of equations. They are written as follows:

$$V_B(t+1) = ca \sum_{i=1}^{t-1} V_N(i) E(i) (1 - \mu_{IV}(i))^{t+2-i} \quad (1)$$

$$V_N(t+1) = (1 - ca) + (1 - E(t))ca + V_N(t)(1 - \mu_v) + b_v N_v(t) \quad (2)$$

Where a is the biting rate, $\mu_{IV}(i)$ is the vector mortality rate for vectors that fed on an Ivermectin treated human i days after MDA, b_v is the vector birth rate, c is the MDA coverage level, μ_v is the normal vector mortality and $E(t)$ is an indicator function (as we only want increased mortality to effect vectors biting up to 24 days post MDA) given by:

$$E(t) = \begin{cases} 1 & \text{if } t \leq 24 \\ 0 & \text{if } t > 24 \end{cases}$$

These equations are modelled in fig 6.

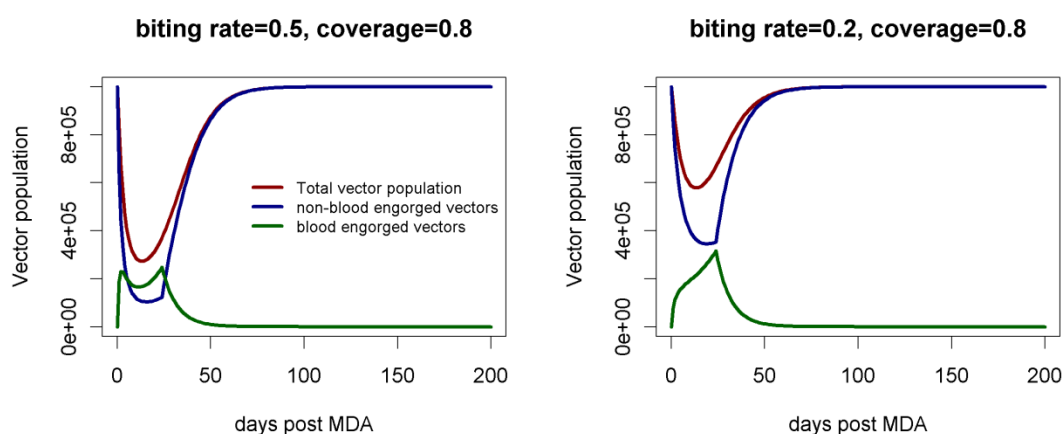


Fig D.6: Vector population dynamics after Ivermectin MDA simulated using equations (1) and (2).

We account for the increased mortality in the model by defining a new 'effective' mortality rate which is essentially a 'mean' mortality rate that accounts for the fact that after Ivermectin has been administered to a host population, different vectors experience different mortality rates based on the number of days post MDA that they take a bloodmeal.

The new 'effective' mortality rate is calculated from the time at which ivermectin is administered by taking the model parameters for biting rate, MDA coverage and baseline vector mortality and simulating the values of V_B , V_N and N_V for the next 200 days using equations (1) and (2). The value for N_V at each time step is then used to calculate the 'effective' mortality rate which is defined as:

$$\mu_{ve}(t) = \frac{N_v(t) + b_v(t)N_v(t) - N_v(t+1)}{N_v(t)}$$

(because the basic vector population model is $N_v(t+1) = N_v(t) - \mu_v(t)N_v(t) + b_v(t)N_v(t)$). Here we are in effect approximating the overall mortality rate given that post MDA vectors die at a variety of different mortality rates.

The new effective mortality rates are calculated for the 200 day period post-MDA and replace the baseline mortality rate in the model (fig 7).

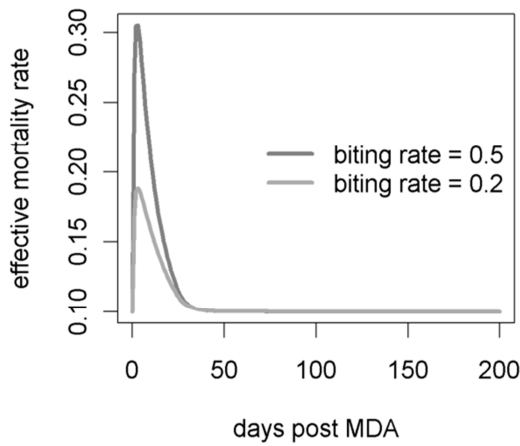


Fig D.7: effective mortality rate over time due to Ivermectin induced vector mortality for two different biting rates

Notes:

- We calculate N_v to 200 days because after experimentation, the mortality rate was always round to have returned to its baseline rate after 200 days (and normally considerably less)
- We assume larval induced excess mortality is independent of this process, and overall mortality post MDA is given by $\mu_{vTOT} = \mu_{ve} + \mu'_v L / N_v$. We use this simple assumption because after MDA the larval level decreases greatly, so the effect of this larval induced excess mortality is small
- Mosquito lifespan is reduced post MDA, so therefore the lifespan of the larvae in these mosquitoes is also reduced. This is included in the model by altering the larval mortality rate by the same amount as for the vector mortality rate.

The impact of this additional Ivermectin induced vector mortality shows that although there is a very small effect on the LF prevalence, there is a large, but short term impact on malaria prevalence, in both humans and vectors (fig 8).

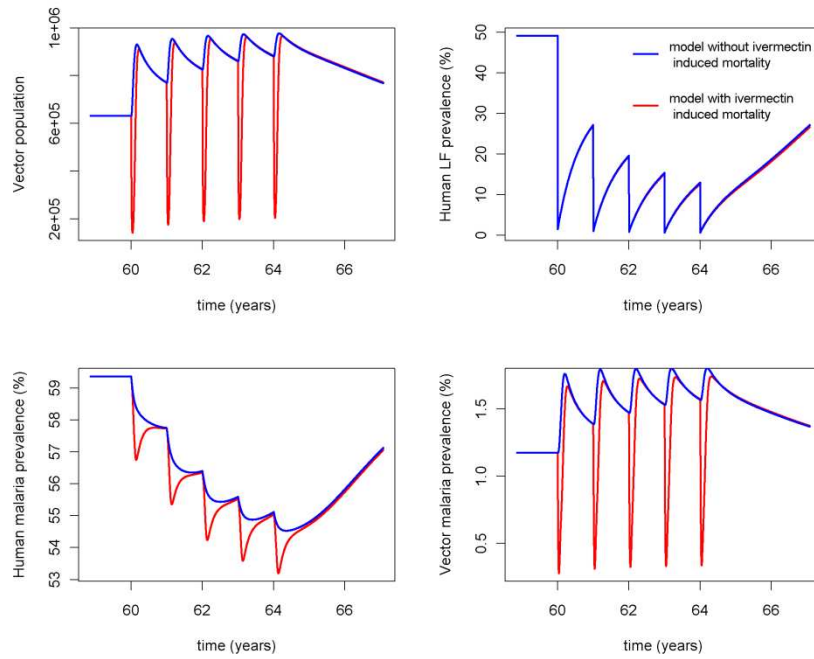


Fig D.8: Effect on vector population, human LF prevalence, human malaria prevalence and vector malaria prevalence of including the additional ivermectin induced vector mortality. The blue lines show the model output without this effect and the red lines show the model output with this effect. Here we assume a biting rate of 0.5.

This new vector mortality model is incorporated into the co-infection model by recalculating the vector mortality rate for a 200 day period after each time a round of MDA is implemented.

References

- Abbas, A. A., K. M. Murphy, et al. (1996). "Functional diversity of helper T lymphocytes." Nature **383**(6603): 787-793.
- Addiss, D. (2010). "The 6th Meeting of the Global Alliance to Eliminate Lymphatic Filariasis: A half-time review of lymphatic filariasis elimination and its integration with the control of other neglected tropical diseases." Parasites & Vectors **3**(1): 100-100.
- Albuquerque, C. M. R. and P. J. Ham (1995). "Concomitant malaria (*Plasmodium gallinaceum*) and filaria (*Brugia pahangi*) infections in *Aedes aegypti*: effect on parasite development." Parasitology **110**(01): 1-6.
- Aliota, M. T., J. F. Fuchs, et al. (2010). "Mosquito Transcriptome Profiles and Filarial Worm Susceptibility in *Armigeres subalbatus*." PLoS Neglected Tropical Diseases **4**(4): e666-e666.
- Anderson, R. A., B. G. Knols, et al. (2000). "Plasmodium falciparum sporozoites increase feeding-associated mortality of their mosquito hosts *Anopheles gambiae* s.l." Parasitology **120** (Pt 4): 329-333.
- Anderson, R. M. and R. M. May (1981). "The Population Dynamics of Microparasites and Their Invertebrate Hosts." Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences **291**(1054): 451-524.
- Anderson, R. M. and R. M. May (1985). "Helminth Infections of Humans: Mathematical Models, Population Dynamics, and Control." Advances in Parasitology **24**: 1-101.
- Anderson, R. M. and R. M. May (1992). Infectious Diseases of Humans. Dynamics and Control. Oxford, Oxford University Press.
- Anderson, R. P., D. Lew, et al. (2003). "Evaluating predictive models of species' distributions: criteria for selecting optimal models." Ecological Modelling **162**: 211-232.
- Appawu, M. A., S. K. Dadzie, et al. (2001). "Lymphatic filariasis in Ghana: entomological investigation of transmission dynamics and intensity in communities served by irrigation systems in the Upper East Region of Ghana." Tropical Medicine & International Health **6**(7): 511-516.
- Aron, J. L. (1988). "Acquired immunity dependent upon exposure in an SIRS epidemic model." Mathematical Biosciences **88**(1): 37-47.
- Asenso-Okyere, W. K. and J. A. Dzator (1997). "Household cost of seeking malaria care. A retrospective study of two districts in Ghana." Social Science & Medicine **45**(5): 659-667.
- Austin, M. P. (2002). "Spatial prediction of species distribution: an interface between ecological theory and statistical modelling." Ecological Modelling **157**: 101-118.
- Baume, C. A. and M. C. Marin (2007). "Intra-household Mosquito Net Use in Ethiopia, Ghana, Mali, Nigeria, Senegal, and Zambia: Are Nets Being Used? Who in the Household Uses Them?" The American Journal of Tropical Medicine and Hygiene **77**(5): 963-971.
- Bayoh, M. N., C. J. Thomas, et al. (2001). "Mapping distributions of chromosomal forms of *Anopheles gambiae* in West Africa using climate data." Medical and Veterinary Entomology **15**(3): 267-274.
- Beach, R. F., T. K. Ruebush, et al. (1993). "Effectiveness of Permethrin-Impregnated Bed Nets and Curtains for Malaria Control in a Holoendemic Area of Western Kenya." The American Journal of Tropical Medicine and Hygiene **49**(3): 290-300.
- Beck-Worner, C., G. Raso, et al. (2007). "Bayesian spatial risk prediction of *Schistosoma mansoni* infection in western Côte d'Ivoire using a remotely-sensed digital elevation model." The American Journal of Tropical Medicine and Hygiene **76**(5): 956-963.
- Beck, L. R., B. M. Lobitz, et al. (2000). "Remote Sensing and Human Health: New Sensors and New Opportunities." Emerging Infectious Diseases **6**(3): 217-227.
- Belitz, C., A. Brezger, et al. (2009). "BayesX - Software for Bayesian inference in structured additive regression models." Version 2.0.1. Available from <http://www.stat.uni-muenchen.de/~bayesx>.
- Ben-Ahmed, K., A. Bouratbine, et al. (2010). "Generalized linear spatial models in epidemiology: A case study of zoonotic cutaneous leishmaniasis in Tunisia." Journal of Applied Statistics **37**(1): 159 - 170.

- Blackburn, B. G., A. Eigege, et al. (2006). "Successful integration of insecticide-treated bed net distribution with mass drug administration in Central Nigeria." The American Journal of Tropical Medicine and Hygiene **75**(4): 650-655.
- Blower, S. M., A. R. McLean, et al. (1995). "The intrinsic transmission dynamics of tuberculosis epidemics." Nature **1**(8): 815-821.
- Bockarie, M., E. Pedersen, et al. (2009). "Role of vector control in the global program to eliminate lymphatic filariasis." Annu Rev Entomol **54**: 469 - 487.
- Bockarie, M. J., J. L. K. Hii, et al. (1999). "Mass treatment with ivermectin for filariasis control in Papua New Guinea: impact on mosquito survival." Medical and Veterinary Entomology **13**(2): 120-123.
- Bøgh, C., E. M. Pedersen, et al. (1998). "Permethrin-impregnated bednet effects on resting and feeding behaviour of lymphatic filariasis vector mosquitoes in Kenya." Medical and Veterinary Entomology **12**(1): 52-59.
- Booth, M. (2006). "The role of residential location in apparent helminth and malaria associations." Trends in Parasitology **22**(8): 359-362.
- Brady, M. A., P. J. Hooper, et al. (2006). "Projected benefits from integrating NTD programs in sub-Saharan Africa." Trends in Parasitology **22**(7): 285-291.
- Breman, J. G. (2001). "The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden." The American Journal of Tropical Medicine and Hygiene **64**(1 suppl): 1-11.
- Breslow, N. E. and D. G. Clayton (1993). "Approximate Inference in Generalized Linear Mixed Models." Journal of the American Statistical Association **88**(421): 9-25.
- Briand, V., L. Watier, et al. (2005). "Coinfection with *Plasmodium falciparum* and *schistosoma haematobium*: protective effect of schistosomiasis on malaria in senegalese children?" The American Journal of Tropical Medicine and Hygiene **72**(6): 702-707.
- Brinkmann, U. K. (1976). "Epidemiological investigations of Bancroftian filariasis in the Coastal Zone of Liberia " Tropenmedizin Und Parasitologie **28**: 71-76.
- Brooker, S. (2007). "Spatial epidemiology of human schistosomiasis in Africa: risk models, transmission dynamics and control." Transactions of the Royal Society of Tropical Medicine and Hygiene **101**(1): 1-8.
- Brooker, S., W. Akhwale, et al. (2007). "Epidemiology of Plasmodium-Helminth Co-Infection in Africa: Populations at Risk, Potential Impact on Anemia, and Prospects for Combining Control." The American Journal of Tropical Medicine and Hygiene **77**(6 Suppl): 88-98.
- Brooker, S. and A. C. a. Clements (2009). "Spatial heterogeneity of parasite co-infection: Determinants and geostatistical prediction at regional scales." International Journal for Parasitology **39**(5): 591-597.
- Brooker, S. and E. Michael (2000). "The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections." Advances in Parasitology **47**: 245-288.
- Buckland, S. T. and D. A. Elston (1993). "Empirical Models for the Spatial Distribution of Wildlife." Journal of Applied Ecology **30**(3): 478-495.
- Burkot, T. R., D. N. Durrheim, et al. (2006). "The argument for integrating vector control with multiple drug administration campaigns to ensure elimination of lymphatic filariasis." Filaria Journal **5**: 10-10.
- Burkot, T. R., L. Molineaux, et al. (1990). "The prevalence of naturally acquired multiple infections of *Wuchereria bancrofti* and human malarias in anophelines." Parasitology **100 Pt 3**: 369-375.
- Carneiro, I., A. Roca-Feltrer, et al. (2010). "Age-Patterns of Malaria Vary with Severity, Transmission Intensity and Seasonality in Sub-Saharan Africa: A Systematic Review and Pooled Analysis." PLoS ONE **5**(2): e8988.
- Cartel, J. L., Y. Sechan, et al. (1991). "Cumulative mortality rates in *Aedes polynesiensis* after feeding on polynesian *Wuchereria bancrofti* carriers treated with single doses of ivermectin, diethylcarbamazine and placebo." Tropical Medicine and Parasitology **42**(4): 343-345.
- Casaca, V. M. R. (1966). "Contribuicao para o estudo da filariase *bancrofti* em Angola." Anais do Instituto de higiene e Medicina Tropical **23**: 127-132.
- Cattadori, I. M., B. Boag, et al. (2008). "Parasite co-infection and interaction as drivers of host heterogeneity." International Journal for Parasitology **38**(3-4): 371-380.

- Chaccour, C., J. Lines, et al. (2010). "Effect of ivermectin on *Anopheles gambiae* mosquitoes fed on humans: the potential of oral insecticides in malaria control." Journal of Infectious Diseases **202**(1): 113-116.
- Chan, M. S., A. Srividya, et al. (1998). "Epifil: a dynamic model of infection and disease in lymphatic filariasis." The American Journal of Tropical Medicine and Hygiene **59**(4): 606-614.
- Chanda, E., F. Masaninga, et al. (2008). "Integrated vector management: the Zambian experience." Malaria Journal **7**: 164-164.
- Chanda, P., M. Castillo-Riquelme, et al. (2009). "Cost-effectiveness analysis of the available strategies for diagnosing malaria in outpatient clinics in Zambia." Cost Effectiveness and Resource Allocation **7**(1): 5.
- Chandre, F., F. Darrier, et al. (1999). "Status of pyrethroid resistance in *Anopheles gambiae sensu lato*." Bulletin of the World Health Organisation **77**(3): 230-234.
- Chansiri, K., P. Kwoasak, et al. (2001). "Detection of *Plasmodium falciparum* and *Wuchereria bancrofti* infected blood samples using multiplex PCR." Pharmacia **15**(4): 201-207.
- Chima, R. I., C. A. Goodman, et al. (2003). "The economic impact of malaria in Africa: a critical review of the evidence." Health Policy **63**(1): 17-36.
- Chitnis, N., J. M. Hyman, et al. (2008). "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model." Bulletin of mathematical biology **70**(5): 1272-1296.
- Choi, H. W., J. G. Breman, et al. (1995). "The effectiveness of insecticide-impregnated bed nets in reducing cases of malaria infection: a meta-analysis of published results." The American Journal of Tropical Medicine and Hygiene **52**(5): 377-382.
- Christensen, O. F., Møller, J., and Waagepetersen, R. (2000). Analysis of spatial data using generalized linear mixed models and Langevin-type Markov chain Monte Carlo. Research Report R-00-2009, Department of Mathematical Sciences, Aalborg University.
- Christensen, O. F. and P. J. Ribeiro Jr (2002). "geoRglm: A package for generalised linear spatial models." R News **2**(2): 26-28.
- Christensen, O. F., G. O. Roberts, et al. (2006). "Robust Markov chain Monte Carlo Methods for Spatial Generalized Linear Mixed Models." Journal of Computational and Graphical Statistics **15**(1): 1-17.
- Chu, B. K., P. J. Hooper, et al. (2010). "The economic benefits resulting from the first 8 years of the Global Programme to Eliminate Lymphatic Filariasis (2000-2007)." PLoS Neglected Tropical Diseases **4**(6): e708-e708.
- Clements, A. C., S. Brooker, et al. (2008). "Bayesian spatial analysis of a national urinary schistosomiasis questionnaire to assist geographic targeting of schistosomiasis control in Tanzania, East Africa." International Journal for Parasitology **38** (3-4): 401-415.
- Clements, A. C., N. J. Lwambo, et al. (2006). "Bayesian spatial analysis and disease mapping: tools to enhance planning and implementation of a schistosomiasis control programme in Tanzania." Tropical Medicine & International Health **11**(4): 490-503.
- Coetzee, M. (2004). "Distribution of the African Malaria Vectors of the *Anopheles Gambiae* Complex." Tropical Medicine **70**(2): 103-104.
- consortium. (2012). "<http://www.ipti-malaria.org>." Retrieved 13th February 2012.
- Cox, F. E. G. (2001). "Concomitant infections, parasites and immune responses." Parasitology **122**: S23-S38.
- Craig, M., B. Sharp, et al. (2007). "Developing a spatial-statistical model and map of historical malaria prevalence in Botswana using a staged variable selection procedure." International Journal of Health Geographics **6**(1): 44.
- Craig, M. H., R. W. Snow, et al. (1999). "A climate-based distribution model of malaria transmission in sub-Saharan Africa." Parasitology today (Personal ed.) **15**(3): 105-111.
- Curtis, C. F., C. A. Maxwell, et al. (1998). "A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors." Tropical Medicine & International Health **3**(8): 619-631.
- Das, P. K., S. Subramanian, et al. (1995). "Frequency distribution of *Wuchereria bancrofti* infection in the vector host in relation to human host: evidence for density dependence." Acta Tropica **60**(3): 159-165.

- Dawes, E., T. Churcher, et al. (2009). "Anopheles mortality is both age- and *Plasmodium*-density dependent: implications for malaria transmission." Malaria Journal **8**(1): 228.
- Day, K. P. (1999). The Epidemiology of Malaria. Malaria: Molecular and Clinical Aspects. M. Wahlgren and P. Perlmann. The Netherlands, Harwood Academic Publishers: 57-86.
- De Allegri, M., P. Marschall, et al. (2010). "Comparative cost analysis of insecticide-treated net delivery strategies: sales supported by social marketing and free distribution through antenatal care." Health Policy and Planning **25**(1): 28-38.
- de Almeida, A. B. and D. O. Freedman (1999). "Epidemiology and immunopathology of bancroftian filariasis." Microbes and Infection **1**(12): 1015-1022.
- De Rochars, M. B., S. Kanjilal, et al. (2005). "The Leogane, Haiti Demonstration Project: Decreased Microfilaremia and Program Costs and Three Years of Mass Drug Administration." The American Journal of Tropical Medicine and Hygiene **73**(5): 888-894.
- Delong, E. R., D. M. Delong, et al. (1988). "Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach " Biometrics **44**: 837-845.
- Dietz, K., L. Molineaux, et al. (1974). "A malaria model tested in the African savannah." Bulletin of the World Health Organization **50**(3-4): 347-357.
- Diggle, P. J. and P. J. Ribeiro Jr (2007). Model-Based Geostatistics. New York, Springer.
- Diggle, P. J., P. J. Ribeiro, et al. (2003). An introduction to model-based geostatistics. Spatial statistics and computational methods. Lecture notes in statistics. J. Moller. New York, Springer: 43-86.
- Diggle, P. J., J. A. Tawn, et al. (1998). "Model-based geostatistics." Journal of the Royal Statistical Society: Series C (Applied Statistics) **47**(3): 299-350.
- Doan, T., R. Melvold, et al. (2007). Lippincott's illustrated reviews: immunology.
- Doolan, D. L., C. Dobaño, et al. (2009). "Acquired Immunity to Malaria." Clinical Microbiology Reviews **22**(1): 13-36.
- Dormann, C. F., J. M. McPherson, et al. (2007). "Methods to account for spatial autocorrelation in the analysis of species distributional data: a review." Ecography **30**(5): 609-628.
- Dreyer, G., J. Norães, et al. (2000). "Pathogenesis of Lymphatic Disease in Bancroftian Filariasis: A Clinical Perspective." Parasitology Today **16**(12): 544-548.
- Druilhe, P., A. Tall, et al. (2005). "Worms can worsen malaria: towards a new means to roll back malaria?" Trends in Parasitology **21**(8): 359-362.
- Elith, J. (2006). "Novel methods improve prediction of species' distributions from occurrence data." Ecography **29**(2): 129-151.
- Elith, J. and C. Graham (2009). "Do they? How do they? WHY do they differ? On finding reasons for differing performances of species distribution models." Ecography **32**: 1-12.
- Ettling, M., D. A. McFarland, et al. (1994). "Economic impact of malaria in Malawian households." Tropical medicine and parasitology : official organ of Deutsche Tropenmedizinische Gesellschaft and of Deutsche Gesellschaft fur Technische Zusammenarbeit (GTZ) **45**(1): 74-79.
- Evans, D. B., H. Gelband, et al. (1993). "Social and economic factors and the control of lymphatic filariasis: A review." Acta Tropica **53**(1): 1-26.
- Fairlie-Clarke, K., T. Lamb, et al. (2010). "Antibody isotype analysis of malaria-nematode co-infection: problems and solutions associated with cross-reactivity." BMC Immunology **11**(1): 6.
- Fenton, A. (2008). "Worms and germs: the population dynamic consequences of microparasite-macroparasite co-infection." Parasitology **135**(13): 1545-1560.
- Fenton, A., T. Lamb, et al. (2008). "Optimality analysis of Th1/Th2 immune responses during microparasite-macroparasite co-infection, with epidemiological feedbacks." Parasitology **135**(Special Issue 07): 841-853.
- Fenwick, A., Y. Zhang, et al. (2009). "Control of the Neglected Tropical Diseases in sub-Saharan Africa : the unmet needs." Tropical Medicine.
- Ferguson, H. M. and A. F. Read (2002). "Why is the effect of malaria parasites on mosquito survival still unresolved?" Trends in Parasitology **18**(6): 256-261.
- Filipe, J. A. N., E. M. Riley, et al. (2007). "Determination of the Processes Driving the Acquisition of Immunity to Malaria Using a Mathematical Transmission Model." PLoS Comput Biol **3**(12): e255.

- Foley, D. H., J. H. Bryan, et al. (2000). "The potential of ivermectin to control the malaria vector *Anopheles farauti*." Transactions of the Royal Society of Tropical Medicine and Hygiene **94**(6): 625-628.
- Foley, D. H., T. a. Klein, et al. (2008). "Malaria risk assessment for the Republic of Korea based on models of mosquito distribution." U.S. Army Medical Department journal: 46-53.
- Gallup, J. L. and J. D. Sachs (2001). "The economic burden of malaria." The American Journal of Tropical Medicine and Hygiene **64**(1 suppl): 85-96.
- Gambhir, M., M. Bockarie, et al. (2010). "Geographic and ecologic heterogeneity in elimination thresholds for the major vector-borne helminthic disease, lymphatic filariasis." BMC Biology **8**(1): 22.
- Gambhir, M. and E. Michael (2008). "Complex ecological dynamics and eradicability of the vector borne macroparasitic disease, lymphatic filariasis." PLoS ONE **3**(8): e2874.
- Gardon, J., N. Gardon-Wendel, et al. (1997). "Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection." The Lancet **350**(9070): 18-22.
- Gelman, A. and D. B. Rubin (1992). "Inference from Iterative Simulation Using Multiple Sequences." Statistical Science **7**(4): 457-472.
- Gemperi, a., P. Vounatsou, et al. (2006). "Malaria mapping using transmission models: application to survey data from Mali." American Journal of Epidemiology **163**(3): 289-297.
- Gething, P. W., A. P. Patil, et al. (2010). "Quantifying Aggregated Uncertainty in *Plasmodium falciparum* Malaria Prevalence and Populations at Risk via Efficient Space-Time Geostatistical Joint Simulation." PLoS Computational Biology **6**(4): e1000724.
- Ghosh, S. K. and R. S. Yadav (1995). "Naturally acquired concomitant infections of bancroftian filariasis and human plasmodia in Orissa." Indian Journal of Malariology **32**(1): 32-36.
- Gill, G. and N. Beeching (2009). Tropical Medicine (Lecture Notes), Wiley-Blackwell. p55-72.
- Gillies, M. and B. de Meillon (1968). "The Anophelinae of Africa South of the Sahara." The South African Institute for Medical Research.
- Gimnig, J. E., J. M. Vulule, et al. (2003). "Impact of permethrin-treated bed nets on entomologic indices in an area of intense year-round malaria transmission." The American Journal of Tropical Medicine and Hygiene **68**(4 suppl): 16-22.
- Goldman, A. S., V. H. Guisinger, et al. (2007). "National mass drug administration costs for lymphatic filariasis elimination." PLoS Neglected Tropical Diseases **1**(1): e67-e67.
- González, C., O. Wang, et al. (2010). "Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species." PLoS Neglected Tropical Diseases **4**(1): e585.
- Goodman, C. A., P. G. Coleman, et al. (1999). "Cost-effectiveness of malaria control in sub-Saharan Africa." The Lancet **354**(9176): 378-385.
- Gosoni, L., A. M. Veta, et al. (2010). "Bayesian geostatistical modeling of Malaria Indicator Survey data in Angola." PLoS ONE **5**(3): e9322-e9322.
- Grady, C. a., M. B. de Rochars, et al. (2007). "Endpoints for lymphatic filariasis programs." Emerging Infectious Diseases **13**(4): 608-610.
- Graham, A. L. (2008). "Ecological rules governing helminth-microparasite coinfection." Proceedings of the National Academy of Sciences of the United States of America **105**(2): 566-570.
- Graham, A. L., T. J. Lamb, et al. (2005). "Malaria-filaria coinfection in mice makes malarial disease more severe unless filarial infection achieves patency." Journal of Infectious Diseases **191**(3): 410-421.
- Grenfell, B. T. and E. Michael (1992). "Infection and disease in lymphatic filariasis: an epidemiological approach." Parasitology **104**(SupplementS1): S81-S90.
- Griffin, J. T., T. D. Hollingsworth, et al. (2010). "Reducing *Plasmodium falciparum* Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies." PLoS Med **7**(8): e1000324.
- Grinnell, J. (1917). "The niche-relationships of the California Thrasher." Auk **34**: 427-433.
- Grover-Kopce, E. K., M. B. Blumenthal, et al. (2006). "Web-based climate information resources for malaria control in Africa." Malaria Journal **5**: 38-38.

- Guerra, C. A., P. W. Gikandi, et al. (2008). "The Limits and Intensity of *Plasmodium falciparum*. Transmission: Implications for Malaria Control and Elimination Worldwide." PLoS Medicine **5**(2): e38.
- Guerra, C. a., R. W. Snow, et al. (2006a). "Mapping the global extent of malaria in 2005." Trends in Parasitology **22**(8): 353-358.
- Guerra, C. A., R. W. Snow, et al. (2006b). Defining the Global Spatial Limits of Malaria Transmission in 2005. Advances in Parasitology, Academic Press. **62**: 157-179.
- Guillet, P., R. N'Guessan, et al. (2001). "Combined pyrethroid and carbamate 'two-in-one' treated mosquito nets: field efficacy against pyrethroid-resistant *Anopheles gambiae* and *Culex quinquefasciatus*." Medical and Veterinary Entomology **15**(1): 105-112.
- Guisan, A. and W. Thuiller (2005). "Predicting species distribution: offering more than simple habitat models." Ecology Letters **8**(9): 993-1009.
- Guisan, A. and N. E. Zimmermann (2000). "Predictive habitat distribution models in ecology." Ecological Modelling **135**: 147-186.
- Gustavsen, K. M., M. H. Bradley, et al. (2009). "GlaxoSmithKline and Merck: private-sector collaboration for the elimination of lymphatic filariasis." Annals of Tropical Medicine and Parasitology **103** (Suppl): S11-15.
- Gyapong, J. O., V. Kumaraswami, et al. (2005). "Treatment strategies underpinning the global programme to eliminate lymphatic filariasis." Expert opinion on pharmacotherapy **6**(2): 179-200.
- Gyapong, J. O., D. Kyelem, et al. (2002). "The use of spatial analysis in mapping the distribution of bancroftian filariasis in four West African countries." Annals of Tropical Medicine and Parasitology **96**(7): 695-705.
- Haddix, A. C. and A. Kestler (2000). "Lymphatic filariasis: economic aspects of the disease and programmes for its elimination." Transactions of the Royal Society of Tropical Medicine and Hygiene **94**(6): 592-593.
- Hairston, N. G. and B. de Meillon (1968). "On the inefficiency of transmission of *Wuchereria bancrofti* from mosquito to human host." Bulletin of the World Health Organisation **38**(6): 935-941.
- Hales, S., N. de Welt, et al. (2002). "Potential effect of population and climate changes on global distribution of dengue fever: an empirical model." Lancet **360**: 830-834.
- Haque, U., R. Magalhaes, et al. (2010). "Spatial prediction of malaria prevalence in an endemic area of Bangladesh." Malaria Journal **9**(1): 120.
- Hariston, N. G. and L. A. Jachowski (1968). "Analysis of the *Wuchereria bancrofti* population in the people of American Samoa." Bulletin of the World Health Organization **38**(1): 29-59.
- Hartgers, F. C., B. B. Obeng, et al. (2009). "Responses to malarial antigens are altered in helminth-infected children." Journal of Infectious Diseases **199**(10): 1528-1535.
- Hartgers, F. C. and M. Yazdanbakhsh (2006). "Co-infection of helminths and malaria: modulation of the immune responses to malaria." Parasite Immunology **28**(10): 497-506.
- Hartley, S., R. Harris, et al. (2006). "Quantifying uncertainty in the potential distribution of an invasive species: climate and the Argentine ant." Ecology letters **9**: 1068-1079.
- Hawking, F. (1940). "Distribution of filariasis in Tanganyika territory, East Africa." Annals of Tropical Medicine and Parasitology **34**: 107-119.
- Hawking, F. (1957). "The distribution of Bancroftian filariasis in Africa." Bulletin of the World Health Organisation **16**(3): 581-592.
- Hawking, F. (1977). "The distribution of human filariasis throughout the world. Part III. Africa." Tropical Disease Bulletin **74**(8): 649-679.
- Hawley, W. A. (1985). "The Effect of Larval Density on Adult Longevity of a Mosquito, *Aedes sierrensis*: Epidemiological Consequences." Journal of Animal Ecology **54**(3): 955-964.
- Hay, S. I., C. A. Guerra, et al. (2009). "A World Malaria Map: *Plasmodium falciparum* Endemicity in 2007." PLoS Medicine **6**(3): e1000048.
- Hay, S. I., J. A. Omumbo, et al. (2000). "Earth observation, geographical information systems and *Plasmodium falciparum* malaria in sub-Saharan Africa." Advances in Parasitology **47**: 174-215.
- Hay, S. I. and R. W. Snow (2006). "The malaria Atlas Project: developing global maps of malaria risk." PLoS Medicine **3**(12): e473.

- Hayashi, S. (1962). "A mathematical analysis on the epidemiology of Bancroftian and Malayan filariasis in Japan." The Japanese Journal of Experimental Medicine **32**: 13-43.
- Helmby, H., M. Kullberg, et al. (1998). "Altered Immune Responses in Mice with Concomitant *Schistosoma mansoni* and *Plasmodium chabaudi* Infections." Society **66**(11): 5167-5174.
- Hethcote, H. W. (1994). A thousand and One Epidemic Models. Frontiers in Mathematical Biology, Springer-Verlag: 504-515.
- Hii, J. L. K., L. Kanai, et al. (1993). "Impact of permethrin-impregnated mosquito nets compared with DDT house-spraying against malaria transmission by *Anopheles farauti* and *An.punctulatus* in the Solomon Islands." Medical and Veterinary Entomology **7**(4): 333-338.
- Hijmans, R., J., S. Cameron, E., et al. (2005). "Very high resolution interpolated climate surfaces for global land areas." International Journal of Climatology **25**(15): 1965-1978.
- Hillier, S. D., M. Booth, et al. (2008). "*Plasmodium falciparum* and helminth coinfection in a semi urban population of pregnant women in Uganda." Journal of Infectious Diseases **198**(6): 920-927.
- Hoerauf, A. (2008). "Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis." Current Opinion in Infectious Diseases **21**(6): 673-681.
- Hogg, J. C. and H. Hurd (1997). "The effects of natural *Plasmodium falciparum* infection on the fecundity and mortality of *Anopheles gambiae* s. l. in north east Tanzania." Parasitology **114** (Pt 4): 325-331.
- Holt, A., D. Salkeld, et al. (2009). "Spatial analysis of plague in California: niche modeling predictions of the current distribution and potential response to climate change." International Journal of Health Geographics **8**(1): 38.
- Hotez, P. J., N. Mistry, et al. (2011). "Integrating neglected tropical diseases into AIDS, tuberculosis, and malaria control." The New England Journal of Medicine **364**(22): 2086-2089.
- Hotez, P. J., D. H. Molyneux, et al. (2006). "Incorporating a Rapid-Impact Package for Neglected Tropical Diseases with Programs for HIV / AIDS , Tuberculosis , and Malaria A comprehensive pro-poor health policy and strategy for the developing world." PLoS Medicine **3**(5): 576-584.
- Hussain, R., M. Grogl, et al. (1987). "IgG Antibody Subclasses in Human Filariasis. Differential Subclass Recognition of Parasite Antigens Correlates with Different Clinical Manifestations of Infection." Pathology(8): 2794-2798.
- IMF. (2011). "World Economic Outlook Database." Retrieved 14th October 2011, from <http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/index.aspx>. Institute), E. E. S. R. (2009). ArcMap 9.2. ESRI. Redlands, California.
- IPCC, Ed. (2007). Climate Change 2007: The Physical Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, UK, Cambridge University Press.
- IPCC (2007). Climate Change 2007; The Physical Science Basis - Summary for Policymakers. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, Cambridge University Press.
- Jaynes, E. T. (1957). "Information theory and statistical mechanics." Physics Review **106**: 620-630.
- Jimenez-Valverde, A. and J. M. Lobo (2007). "Threshold criteria for conversion of probability of species presence to either -or- presence-absence." Acta Oecologica **31**: 361-369.
- Jordan, P. (1954). "Filariasis in the Southern Province of Tanganyika." East African Medical Journal **31**(12): 537-542.
- Jordan, P. (1956a). "Filariasis in the western province of Tanganyika." East African Medical Journal **33**(6): 233-236.
- Jordan, P. (1956b). "Filariasis in the eastern, Tanga and northern provinces of Tanganyika." East African Medical Journal **33**(6): 225-233.
- Jordan, P. (1956c). "Filariasis in the Lake Province of Tanganyika." East African Medical Journal **33**(6): 237-242.

- Jordan, P. (1960). "Bancroftian filariasis in Tanganyika: observations on elephantiasis, microfilarial density, genital filariasis and microfilaraemia rates." Annals of Tropical Medicine and Parasitology **54**: 132-140.
- Jordan, P. and K. D. Goatly (1962). "Bancroftian filariasis in Tanganyika: a quantitative study of the uptake, fate and development of microfilariae of *Wuchereria bancrofti* in *Culex fatigans*." Annals of Tropical Medicine and Parasitology **56**: 173-187.
- Juminer, B., S. Diallo, et al. (1971). "A focus of filariasis in Sandiara (Senegal). I. ." Archives de l'Institut Pasteur de Tunis **48**(3): 231-246.
- Juminer, B., S. Diallo, et al. (1971). "Le foyer de filariose lymphatique du secteur de Sandiara (Senegal). 1. Evaluation de l'endemicite." Achives de l'Institut Pasteur de Tunis **48**: 231-246.
- Kalluri, S., P. Gilruth, et al. (2007). "Surveillance of Arthropod Vector-Borne Infectious Diseases Using Remote Sensing Techniques: A Review." PLoS Pathogens **3**(10): e116.
- Kazembe, L., I. Kleinschmidt, et al. (2006). "Spatial analysis and mapping of malaria risk in Malawi using point-referenced prevalence of infection data." International Journal of Health Geographics **5**(1): 41.
- Kearney, M. and W. Porter (2009). "Mechanistic niche modelling: combining physiological and spatial data to predict species' ranges." Ecology Letters **12**(4): 334-350.
- Kelly-Hope, L. a., P. J. Diggle, et al. (2006). "Negative spatial association between lymphatic filariasis and malaria in West Africa." Tropical medicine & international health : TM & IH **11**(2): 129-135.
- Killeen, G. F., F. E. McKenzie, et al. (2000). "The potential impact of integrated malaria transmission control on entomologic inoculation rate in highly endemic areas." The American Journal of Tropical Medicine and Hygiene **62**(5): 545-551.
- King, C. L. (2001). "Transmission intensity and human immune responses to lymphatic filariasis." Parasite Immunology **23**(7): 363-371.
- King, C. L., M. Connelly, et al. (2001). "Transmission Intensity Determines Lymphocyte Responsiveness and Cytokine Bias in Human Lymphatic Filariasis." The Journal of Immunology **166**(12): 7427-7436.
- Kiszewski, A., A. Mellinger, et al. (2004). "A global index representing the stability of malaria transmission." The American Journal of Tropical Medicine and Hygiene **70**(5): 486-498.
- Kleinschmidt, I., M. Bagayoko, et al. (2000). "A spatial statistical approach to malaria mapping." International Journal of Epidemiology **29**(2): 355-361.
- Koella, J. C. (1991). "On the use of mathematical models of malaria transmission." Acta Tropica **49**(1): 1-25.
- Koella, J. C. (1999). "An evolutionary view of the interactions between anopheline mosquitoes and malaria parasites." Microbes and infection / Institut Pasteur **1**(4): 303-308.
- Kolaczinski, J., K. Kolaczinski, et al. (2010). "Costs and effects of two public sector delivery channels for long-lasting insecticidal nets in Uganda." Malaria Journal **9**(102).
- Kolaczinski, J. H., N. B. Kabatereine, et al. (2007). "Neglected tropical diseases in Uganda : the prospect and challenge of integrated control." Trends in Parasitology **23**(10).
- Krishnamoorthy, K., S. Subramanian, et al. (2004). "Vector survival and parasite infection: the effect of *Wuchereria bancrofti* on its vector *Culex quinquefasciatus*." Parasitology **129**(01): 43-50.
- Kyelem, D., G. Biswas, et al. (2008). "Determinants of Success in National Programs to Eliminate Lymphatic Filariasis: A Perspective Identifying Essential Elements and Research Needs." The American journal of tropical medicine and hygiene **79**(4): 480-484.
- Lafferty, K. D. (2009). "The ecology of climate change and infectious diseases." Ecology **90**(4): 888-900.
- Lamontellerie, M. (1972). "Resultats d'enquetes sur les filarioses dans l'Ouest de la Huate-Volta (Cerle de Banfora)." Annales de Parasitologie Humaine et Comparee (Paris) **47**: 743-838.
- Lamontellerie, M. (1972). "Results of surveys on the filariasis in western Upper Volta (Cercle de Banfora)." Annales de Parasitologie Humaine et Comparee **47**(6): 783-838.
- Lardeux, F. and J. Cheffort (1997). "Temperature thresholds and statistical modelling of larval *Wuchereria bancrofti* (Filariidea:Onchocercidae) developmental rates." Parasitology **114** 123-134.

- Lawler, J. J., D. White, et al. (2006). "Predicting climate-induced range shifts: model differences and model reliability." Global Change Biology **12**: 1568-1584.
- Lawrence, R. a., J. E. Allen, et al. (1994). "Adult and microfilarial stages of the filarial parasite *Brugia malayi* stimulate contrasting cytokine and Ig isotype responses in BALB/c mice." Journal of Immunology (Baltimore, Md. : 1950) **153**(3): 1216-1224.
- Lawrence, R. A. and E. Devaney (2001). "Lymphatic filariasis: parallels between the immunology of infection in humans and mice." Parasite Immunology **23**(7): 353-361.
- Le Menach, A., S. Takala, et al. (2007). "An elaborated feeding cycle model for reductions in vectorial capacity of night-biting mosquitoes by insecticide-treated nets." Malaria Journal **6**(1): 1-12.
- Le Sueur, D., F. Binka, et al. (1997). "An atlas of malaria in Africa." African Health **19**(2): 23-24.
- Legesse, M., B. Erko, et al. (2004). "Increased parasitaemia and delayed parasite clearance in *Schistosoma mansoni* and *Plasmodium berghei* co-infected mice." Acta Tropica **91**(2): 161-166.
- Leighton, C. and R. Foster (1993). Economic Impacts of Malaria in Kenya and Nigeria, Health Financing and Sustainability (HFS) Project.
- Lengeler, C. (2004) "Insecticide-treated bed nets and curtains for preventing malaria." In The Cochrane Database of Systematic Reviews
- Lenhart, A., A. Eigege, et al. (2007). "Contributions of different mosquito species to the transmission of lymphatic filariasis in central Nigeria: implications for monitoring infection by PCR in mosquito pools." Filaria Journal **6**(1): 14.
- Levine, R. S., A. T. Peterson, et al. (2004). "Geographic and ecologic distributions of the *Anopheles gambiae* complex predicted using a genetic algorithm." The American Journal of Tropical Medicine and Hygiene **70**(2): 105-109.
- Lindblade, K. A., T. P. Eisele, et al. (2004). "Sustainability of Reductions in Malaria Transmission and Infant Mortality in Western Kenya With Use of Insecticide-Treated Bednets." The Journal of the American Medical Association **291**(21): 2571-2580.
- Lindblade, K. A., J. E. Gimnig, et al. (2006). "Impact of Sustained Use of Insecticide-Treated Bednets on Malaria Vector Species Distribution and Culicine Mosquitoes." Journal of Medical Entomology **43**(2): 428-432.
- Lindsay, S. W. and M. N. Bayoh (2004). "Mapping members of the *Anopheles gambiae* complex using climate data." Physiological Entomology **29**(3): 204-209.
- Lindsay, S. W. and D. A. Denham (1986). "The ability of *Aedes aegypti* mosquitoes to survive and transmit infective larvae of *Brugia pahangi* over successive blood meals." Journal of Helminthology **60**(03): 159-168.
- Lindsay, S. W., L. Parson, et al. (1998). "Mapping the ranges and relative abundance of the two principal African malaria vectors, *Anopheles gambiae sensu stricto* and *An. arabiensis*, using climate data." Proceedings of the Royal Society of London. Series B: Biological Sciences **265**(1399): 847-854.
- Lindsay, S. W. and C. J. Thomas (2000). "Mapping and estimating the population at risk from lymphatic filariasis in Africa." Transactions of the Royal Society of Tropical Medicine and Hygiene **94**: 37-45.
- Linehan, M., C. Hanson, et al. (2011). "Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: proving the feasibility at national scale." The American Journal of Tropical Medicine and Hygiene **84**(1): 5-14.
- Lobo, J. M., A. Jimenez-Valverde, et al. (2007). "AUC: a misleading measure of the performance of predictive distribution models." Global Ecology and Biogeography **17**: 145-151.
- Lunn, D. J., A. Thomas, et al. (2000). "WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility." Statistics and Computing **10**: 325-337.
- Lysenko, A. Y. and I. N. Semashko (1968). A medical-geographical study of an ancient disease. Medical Geography. Moscow, Academy of Sciences, USSR: 25-146.
- Mabaso, M. L. H., P. Vounatsou, et al. (2006). Spatio-temporal analysis of the role of climate in inter-annual variation of malaria incidence in Zimbabwe, BioMed Central Ltd.
- Macdonald, G. (1957). "The epidemiology of malaria." London, Oxford University Press.
- Macdonald, G. (1965). "The dynamics of helminth infections, with special reference to schistosomes." Transactions of the Royal Society of Tropical Medicine and Hygiene **59**(5): 489-506.

- Macdonald, G., C. V. Foll, et al. (1967). The Potential Value of Mass Treatment in Malaria Eradication.
- Magesa, S. M., T. J. Wilkes, et al. (1991). "Trial of pyrethroid impregnated bednets in an area of Tanzania holoendemic for malaria Part 2. Effects on the malaria vector population." Acta Tropica **49**(2): 97-108.
- Maizels, R. M. (2009). "Parasite immunomodulation and polymorphisms of the immune system." Journal of Biology **8**(7): 62-62.
- Maizels, R. M., A. Balic, et al. (2004). "Helminth parasites – masters of regulation." Immunological Reviews **201**(1): 89-116.
- Malaguarnera, L. and S. Musumeci (2002). "The immune response to *Plasmodium falciparum* malaria." The Lancet Infectious Diseases **2**(8): 472-478.
- Mandal, S., R. R. Sarkar, et al. (2011). "Mathematical models of malaria - a review." Malaria Journal **10**(1): 202-202.
- Manga, L. (2002). "Vector-control synergies between 'Roll Back Malaria' and the Global Programme to Eliminate Lymphatic Filariasis in the African Region." Annals of Tropical Medicine and Parasitology **96**: S129-S132.
- Manguin, S., M. J. Bangs, et al. (2010). "Review on global co-transmission of human *Plasmodium* species and *Wuchereria bancrofti* by *Anopheles* mosquitoes." Infection, Genetics and Evolution **10**(2): 159-177.
- Martens, P., R. S. Kovats, et al. (1999). "Climate change and future populations at risk of malaria." Global Environmental Change **9**, **Supplement 1**(0): S89-S107.
- Martens, W. J. M., T. H. Jetten, et al. (1997). "Sensitivity of Malaria, Schistosomiasis and Dengue to global warming." Climatic Change **35**(2): 145-156.
- Matola, Y. G. (1985). "Prospects of human malaria and Bancroftian filariasis infections in the Lower Rufiji Basin, Tanzania. I. Malaria." Tropical and Geographical Medicine **37**(2): 102-107.
- Maxwell, C., W. Chambo, et al. (2003). "Variation of malaria transmission and morbidity with altitude in Tanzania and with introduction of alphacypermethrin treated nets." Malaria Journal **2**(1): 28.
- Maxwell, C. a., K. Mohammed, et al. (1999). "Can vector control play a useful supplementary role against bancroftian filariasis?" Bulletin of the World Health Organization **77**(2): 138-143.
- Maxwell, C. A., J. Myamba, et al. (1999). "Comparison of bednets impregnated with different pyrethroids for their impact on mosquitoes and on re-infection with malaria after clearance of pre-existing infections with chlorproguanil-dapsone." Transactions of the Royal Society of Tropical Medicine and Hygiene **93**(1): 4-11.
- Mboera, L. E. G., K. P. Senkoro, et al. (2011). "*Plasmodium falciparum* and helminth coinfections among schoolchildren in relation to agro-ecosystems in Mvomero District, Tanzania." Acta Tropica **120**(1-2): 95-102.
- McConnel, E. and M. L. Schmidt (1973). "Bancroftian filariasis in Gambela, Illubabor Province, Ethiopia." Tropical and Geographical Medicine **25**(3): 300-303.
- McKenzie, F. E. and W. H. Bossert (2005). "An integrated model of *Plasmodium falciparum* dynamics." Journal of Theoretical Biology **232**(3): 411-426.
- McLaughlin, S. I., J. Radday, et al. (2003). "Frequency, severity, and costs of adverse reactions following mass treatment for lymphatic filariasis using diethylcarbamazine and albendazole in Leogane, Haiti, 2000." The American Journal of Tropical Medicine and Hygiene **68**(5): 568-573.
- McMichael, A. J. (2003). "Global climate change: will it affect vector-borne infectious diseases?" Internal medicine journal **33**(12): 554-555.
- Mehlota, R. K., L. R. Gray, et al. (2010). "Short Report : Molecular-Based Assay for Simultaneous Detection of Four *Plasmodium* spp. and *Wuchereria bancrofti* Infections." Tropical Medicine **82**(6): 1030-1033.
- Merelo-Lobo, a. R., P. J. McCall, et al. (2003). "Identification of the vectors of lymphatic filariasis in the Lower Shire Valley, southern Malawi." Transactions of the Royal Society of Tropical Medicine and Hygiene **97**(3): 299-301.
- Metenou, S., B. Dembele, et al. (2009). "Patent Filarial Infection Modulates Malaria-Specific Type 1 Cytokine Responses in an IL-10-Dependent Manner in a Filaria/Malaria-Coinfected Population." The Journal of Immunology **183**(2): 916-924.

- Metenou, S., B. Dembele, et al. (2011). "Filarial Infection Suppresses Malaria-Specific Multifunctional Th1 and Th17 Responses in Malaria and Filarial Coinfections." The Journal of Immunology **186**(8): 4725-4733.
- Meyrowitsch, D. W., D. T. Nguyen, et al. (1998). "A review of the present status of lymphatic filariasis in Vietnam." Acta Tropica **70**(3): 335-347.
- Michael, E. (2000). The Population Dynamics and Epidemiology of Lymphatic Filariasis. T. Nutman, Imperial College Press: 41-82.
- Michael, E. and D. A. Bundy (1997). "Global mapping of lymphatic filariasis." Parasitology Today **13**: 472-476.
- Michael, E., D. A. Bundy, et al. (1996). "Re-assessing the global prevalence and distribution of lymphatic filariasis." Parasitology **112**(Pt 4): 409-428.
- Michael, E., M. N. Malecela-Lazaro, et al. (2006). "Mathematical models and lymphatic filariasis control: endpoints and optimal interventions." Trends in Parasitology **22**(5): 226-233.
- Michael, E., M. N. Malecela-Lazaro, et al. (2004). "Mathematical modelling and the control of lymphatic filariasis." The Lancet Infectious Diseases **4**(4): 223-234.
- Michael, E., M. N. Malecela, et al. (2008). "Global eradication of lymphatic filariasis: the value of chronic disease control in parasite elimination programmes." PLoS ONE **3**: e2936.
- Michael, E., P. E. Simonsen, et al. (2001). "Transmission intensity and the immunoepidemiology of bancroftian filariasis in East Africa." Parasite Immunology **23**(7): 373-388.
- Michael, E., L. C. Snow, et al. (2009). "Ecological Meta-Analysis of Density-Dependent Processes in the Transmission of Lymphatic Filariasis: Survival of Infected Vectors." Journal of Medical Entomology **46**(4): 873-880.
- Midzi, N., S. Mtapuri-Zinyowera, et al. (2011). "Efficacy of integrated school based deworming and prompt malaria treatment on helminths-*Plasmodium falciparum* co-infections: A 33 months follow up study." BMC International Health and Human Rights **11**(1): 9-9.
- Mills, J. N., K. L. Gage, et al. (2010) "Potential influence of climate change on vector-borne and zoonotic diseases: a review and proposed research plan." Environmental Health Perspectives DOI: 10.1289/ehp.0901389.
- Mnzava, a. E., W. L. Kilama, et al. (1989). "Application of a biochemical key to study transmission of malaria and Bancroftian filariasis in sibling species of the *Anopheles gambiae* complex in north-eastern Tanzania." Acta Tropica **46**(5-6): 323-333.
- Moffett, A., N. Shackelford, et al. (2007). "Malaria in Africa: vector species' niche models and relative risk maps " PLoS ONE **2**: e824.
- Molineaux, L., J. Storey, et al. (1980). "A longitudinal study of human malaria in the West African Savanna in the absence of control measures: relationships between different *Plasmodium* species, in particular *P. falciparum* and *P. malariae*." The American Journal of Tropical Medicine and Hygiene **29**(5): 725-737.
- Molyneux, D. H. (2003). "Lymphatic Filariasis (Elephantiasis) Elimination: A public health success and development opportunity." Filaria journal **2**(1): 13-13.
- Molyneux, D. H. (2004). ""Neglected" diseases but unrecognised successes?challenges and opportunities for infectious disease control." The Lancet **364**(9431): 380-383.
- Molyneux, D. H. (2008). "Combating the "other diseases" of MDG 6: changing the paradigm to achieve equity and poverty reduction?" Transactions of the Royal Society of Tropical Medicine and Hygiene **102**(6): 509-519.
- Molyneux, D. H. (2009). "Filaria control and elimination: diagnostic, monitoring and surveillance needs." Transactions of the Royal Society of Tropical Medicine and Hygiene **103**(4): 338-341.
- Molyneux, D. H., M. Bradley, et al. (2003). "Mass drug treatment for lymphatic filariasis and onchocerciasis." Trends in Parasitology **19**(11): 516-522.
- Molyneux, D. H., P. J. Hotez, et al. (2005). ""Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor." PLoS Medicine **2**(11): e336.
- Molyneux, D. H. and V. M. Nantulya (2004). "Linking disease control programmes in rural Africa: a pro-poor strategy to reach Abuja targets and millennium development goals." BMJ (Clinical research ed.) **328**(7448): 1129-1132.

- Mueller, D., V. Wiseman, et al. (2008). "Cost-effectiveness analysis of insecticide-treated net distribution as part of the Togo Integrated Child Health Campaign." Malaria Journal **7**(1): 73.
- Muirhead-Thomson, R. C. (1953). "Inter-relations between filarial and malarial infections in *Anopheles gambiae*." Nature **172**(4372): 352-353.
- Murray, C. J. L., L. C. Rosenfeld, et al. (2012). "Global malaria mortality between 1980 and 2010: a systematic analysis." The Lancet **379**(9814): 413-431.
- Muturi, E. J., B. G. Jacob, et al. (2008). "Are coinfections of malaria and filariasis of any epidemiological significance?" Parasitology Research **102**(2): 175-181.
- Muturi, E. J., C. M. Mbogo, et al. (2006a). "Concomitant infections of *Plasmodium falciparum* and *Wuchereria bancrofti* on the Kenyan coast." Filaria Journal **5**: 8.
- Muturi, E. J., C. M. Mbogo, et al. (2006b). "Relationship between malaria and filariasis transmission indices in an endemic area along the Kenyan Coast." Journal of Vector Borne Diseases **43**(2): 77-83.
- N'Guessan, R., V. Corbel, et al. (2007). "Reduced efficacy of insecticide-treated nets and indoor residual spraying for malaria control in pyrethroid resistance area, Benin." Emerging Infectious Diseases **13**(2): 199-206.
- Nacher, M., F. Gay, et al. (2000). "Ascaris lumbricoides infection is associated with protection from cerebral malaria." Parasite Immunology **22**(3): 107-113.
- Nacher, M., P. Singhasivanon, et al. (2002). "Intestinal helminth infections are associated with increased incidence of *Plasmodium falciparum* malaria in Thailand." Journal of Parasitology **88**(1): 55-58.
- Nájera, J. a., M. González-Silva, et al. (2011). "Some lessons for the future from the Global Malaria Eradication Programme (1955-1969)." PLoS Medicine **8**(1): e1000412-e1000412.
- Nelder, J. A. and R. W. M. Wedderburn (1972). "Generalized Linear Models." Journal of the Royal Statistical Society. Series A (General) **135**(3): 370-384.
- Ngwira, B., P. Tambala, et al. (2007). "The geographical distribution of lymphatic filariasis infection in Malawi." Filaria Journal **6**(1): 12.
- Njenga, S. M., C. N. Wamae, et al. (2008). "Impact of two rounds of mass treatment with diethylcarbamazine plus albendazole on *Wuchereria bancrofti* infection and the sensitivity of immunochromatographic test in Malindi, Kenya." Transactions of the Royal Society of Tropical Medicine and Hygiene **102**(10): 1017-1024.
- Noor, A. M., P. W. Gething, et al. (2009). "The risks of malaria infection in Kenya in 2009." BMC Infectious Diseases **9**: 180-180.
- Norman, R. A., M. S. Chan, et al. (2000). "EPIFIL: the development of an age-structured model for describing the transmission dynamics and control of lymphatic filariasis." Epidemiology and Infection **124**(3): 529-541.
- O'Meara, W. P., J. N. Mangeni, et al. (2010). "Changes in the burden of malaria in sub-Saharan Africa." The Lancet Infectious Diseases **10**(8): 545-555.
- Okell, L. C., C. J. Drakeley, et al. (2008). "Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity." PLoS Medicine **5**(11): e226.
- Olden, Julian D., Joshua J. Lawler, et al. (2008). "Machine Learning Methods Without Tears: A Primer for Ecologists." The Quarterly Review of Biology **83**(2): 171-193.
- Omumbo, J., J. Ouma, et al. (1998). "Mapping malaria transmission intensity using geographical information systems GIS: an example from Kenya." Annals of Tropical Medicine and Parasitology **92**(1): 7-21.
- Onapa, A. W., P. E. Simonsen, et al. (2005). "Rapid assessment of the geographical distribution of lymphatic filariasis in Uganda, by screening of schoolchildren for circulating filarial antigens." Annals of Tropical Medicine and Parasitology **99**(2): 141-153.
- Onapa, A. W., P. E. Simonsen, et al. (2001). "Lymphatic filariasis in Uganda : baseline investigations in Lira, Soroti and Katakwi districts." Transactions of the Royal Society of Tropical Medicine and Hygiene **95**(2): 161-167.
- Onwujekwe, O., R. Chima, et al. (2000). "Economic burden of malaria illness on households versus that of all other illness episodes: a study in five malaria holo-endemic Nigerian communities." Health Policy **54**(2): 143-159.

- Ottesen, E. A. (1984). "Immunological aspects of lymphatic filariasis and onchocerciasis in man." Transactions of the Royal Society of Tropical Medicine and Hygiene **78**(Suppl): 9-18.
- Ottesen, E. A. (1989). "Filariasis Now." The American Journal of Tropical Medicine and Hygiene **41**(3 Suppl.): 9-17.
- Ottesen, E. A. (1992). "The Wellcome Trust Lecture Infection and disease in lymphatic filariasis an immunological perspective." World Health.
- Ottesen, E. A., P. J. Hooper, et al. (2008). "The Global Programme to Eliminate Lymphatic Filariasis: Health Impact after 8 Years." PLoS Neglected Tropical Diseases **2**(10): e317.
- Pani, S. P., J. Yuvaraj, et al. (1995). "Episodic adenolymphangitis and lymphoedema in patients with bancroftian filariasis." Transactions of the Royal Society of Tropical Medicine and Hygiene **89**(1): 72-74.
- Parham, P. E. and E. Michael (2010). "Modeling the effects of weather and climate change on malaria transmission." Environmental Health Perspectives **118**(5): 620-626.
- Paterson, S. and J. Lello (2003). "Mixed models: getting the best use of parasitological data." Trends in Parasitology **19**(8): 370-375.
- Pearce, E. J., P. Caspar, et al. (1991). "Downregulation of Th1 Cytokine Production Accompanies Induction of Th2 Responses by a Parasitic Helminth, *Schistosoma mansoni*." Journal of Experimental Medicine **173**(January): 159-166.
- Pearce, J. L. and M. S. Boyce (2006). "Modelling distribution and abundance with presence-only data." Journal of Animal Ecology **43**(3): 405-412.
- Pearman, P. B., A. Guisan, et al. (2007). "Niche dynamics in space and time." Trends in Ecology and Evolution **23**: 149-158.
- Pearson, R. G., C. J. Raxworthy, et al. (2007). "Predicting species distributions from small numbers of occurrence records: a test case using cryptic geckos in Madagascar." Journal of Biogeography **34**(1): 102-117.
- Pedersen, E. M. (2008). Vectors of lymphatic filariasis in Eastern and Southern Africa. Lymphatic filariasis: research and control in Eastern and Southern Africa. P. Simonsen, M. Malecela, E. Michael and C. Mackenzie. Denmark, DBL - Centre for Health Research and Development: 77-110.
- Peterson, A. T. (2006). "Ecologic niche modeling and spatial patterns of disease transmission." Emerging Infectious Diseases **12**(12): 1822-1826.
- Peterson, A. T., M. Papes, et al. (2007). "Transferability and model evaluation in ecological niche modeling: a comparison of GARP and Maxent." Ecography **30**: 550-560.
- Peterson, A. T., M. Papes, et al. (2008). "Rethinking receiver operating characteristic analysis applications in ecological niche modeling." Ecological Modelling **213**: 63-72.
- Petney, T. N. and R. H. Andrews (1998). "Multiparasite communities in animals and humans: frequency, structure and pathogenic significance." International Journal for Parasitology **28**(3): 377-393.
- Phillips, S. J., M. Dudik, et al. (2004). A maximum entropy approach to species distribution modeling. Proceedings of the 21st International Conference on Machine Learning. Banff, Alberta, Canada, ACM.
- Phillips, S. J., R. P. Anderson, et al. (2006). "Maximum entropy modeling of species geographic distributions." Ecological Modelling **190**: 231-259.
- Phillips, S. J. and M. Dudik (2008). "Modeling of species distributions with Maxent: new extensions and a comprehensive evaluation." Ecography **31**: 161-175.
- Plaisier, a. P., G. J. van Oortmarssen, et al. (1990). "ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis." Computer methods and programs in biomedicine **31**(1): 43-56.
- Prasittisuk, C. (2002). "Vector-control synergies, between 'Roll Back Malaria' and the Global Programme to Eliminate Lymphatic Filariasis, in South-east Asia." Annals of Tropical Medicine and Parasitology **96**(8): 133-137.
- Protopopoff, N., W. Van Bortel, et al. (2007). "Spatial targeted vector control in the highlands of Burundi and its impact on malaria transmission." Malaria Journal **6**(1): 1-10.
- Ramaiah, K. D., P. K. Das, et al. (2000). "The Economic Burden of Lymphatic Filariasis in India." Parasitology Today **16**(6): 251-253.
- Ramaiah, K. D., P. K. Das, et al. (2007). "Impact of 10 years of diethylcarbamazine and ivermectin mass administration on infection and transmission of lymphatic filariasis." Transactions of the Royal Society of Tropical Medicine and Hygiene **101**(6): 555-563.

- Raso, G., B. Matthys, et al. (2005). "Spatial risk prediction and mapping of *Schistosoma mansoni* infections among schoolchildren living in western Côte d'Ivoire." Parasitology **131**(01): 97-108.
- Ravindran, B., P. K. Sahoo, et al. (1998). "Lymphatic filariasis and malaria: concomitant parasitism in Orissa, India." Transactions of the Royal Society of Tropical Medicine and Hygiene **92**(1): 21-23.
- Ribeiro, P. J., O. F. Christensen, et al. (2003). Geostatistical software - geoR and geoRglm. DSC 2003 Working Papers.
- Richards, F. O. (1993). "Use of geographic information systems in control programs for onchocerciasis in Guatemala." Bulletin of the Pan American Health Organization **27**: 52-55.
- Riedel, N., P. Vounatsou, et al. (2010). "Geographical patterns and predictors of malaria risk in Zambia: Bayesian geostatistical modelling of the 2006 Zambia national malaria indicator survey (ZMIS)." Malaria Journal **9**(37).
- Robinson, T. P. (1998). "Geographic Information Systems and the selection of priority areas for control of tsetse-transmitted trypanosomiasis in Africa." Parasitology Today **14**: 457-461.
- Rogers, D. J. and S. E. Randolph (1993). "Distribution of tsetse and ticks in Africa, past, present and future." Parasitology Today **9**: 266-271.
- Rogers, D. J., S. E. Randolph, et al. (2002). "Satellite imagery in the study and forecast of malaria." Nature **415**(6872): 710-715.
- Rosen, L. (1955). "Observations on the epidemiology of human filariasis in French Oceania." The American Journal of Tropical Medicine and Hygiene **61**: 219-248.
- Ross, R. (1911). The prevention of Malaria. London, John Murray.
- Roura-Pascual, N. and A. V. Suarez (2008). "The utility of species distribution models to predict the spread of invasive ants (hymenoptera: Formicidae) and to anticipate changes in their ranges in the face of global climate change." Myrmecological News **11**: 67-77.
- Roussilhon, C., P. Brasseur, et al. (2010). "Understanding Human-*Plasmodium falciparum* Immune Interactions Uncovers the Immunological Role of Worms." PLoS ONE **5**(2): e9309.
- Ruebush, T. K., M. K. Kern, et al. (1995). "Self-treatment of malaria in a rural area of western Kenya." Bulletin of the World Health Organisation **73**(2): 229-236.
- Russell, P. F. (1952). "The Present Status of Malaria in the World." The American Journal of Tropical Medicine and Hygiene **1**: 111-123.
- Russell, P. F. (1956). "World-wide Malaria Distribution, Prevalence and Control." The American Journal of Tropical Medicine and Hygiene **5**: 937-956.
- Rwegoshora, R. T., E. M. Pedersen, et al. (2005). "Bancroftian filariasis: patterns of vector abundance and transmission in two East African communities with different levels of endemicity." Annals of Tropical Medicine and Parasitology **99**(3): 253-265.
- Sabesan, S., M. Palaniyandi, et al. (2000). "Mapping lymphatic filariasis at the district-level in India." Annals of Tropical Medicine and Parasitology **94**: 591-606.
- Sabesan, S., H. K. K. Raju, et al. (2006). "Delimitation of lymphatic filariasis transmission risk areas: a geo-environmental approach." Filaria Journal **5**: 12-12.
- Sachs, J. and P. Malaney (2002). "The economic and social burden of malaria." Nature **415**(6872): 680-685.
- Samarawikrema, W. A. and B. R. Laurence (1978). "Loss of filarial larvae in a natural mosquito population. ." Annals of Tropical Medicine and Parasitology **72**(6): 561-566.
- Sasa, M. (1976). Human Filariasis. A Global Survey of Epidemiology and Control, University Park Press: Baltimore.
- Schenzle, D. (1984). "An Age-Structured Model of Pre- and Post-Vaccination Measles Transmission." Mathematical Medicine and Biology **1**(2): 169-191.
- Segurado, P. and M. Araújo, B. (2004). "An evaluation of methods for modelling species distributions." Journal of Biogeography **31**(10): 1555-1568.
- Shawarby, A. A., A. H. Mahdi, et al. (1965). "Incidence of Filariasis in Egypt." Journal of the Egyptian Public Health Association **40**(4): 267-282.
- Shepard, D. S., M. B. Ettling, et al. (1991). "The economic cost of malaria in Africa." Tropical Medicine and Parasitology : official organ of Deutsche Tropenmedizinische Gesellschaft and of Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) **42**(3): 199-203.

- Simonsen, P. E., E. M. Pedersen, et al. (2010). "Lymphatic Filariasis Control in Tanzania: Effect of Repeated Mass Drug Administration with Ivermectin and Albendazole on Infection and Transmission." PLoS Neglected Tropical Diseases **4**(6): e696.
- Slater, H. and E. Michael (2012). "Predicting the Current and Future Potential Distributions of Lymphatic Filariasis in Africa Using Maximum Entropy Ecological Niche Modelling." PLoS ONE **7**(2): e32202.
- Smith, D. and F. Ellis McKenzie (2004). "Statics and dynamics of malaria infection in *Anopheles* mosquitoes." Malaria Journal **3**(1): 13.
- Smith, J. L. and D. M. Fonseca (2004). "Rapid Assays for Identification of Members of the *Culex* (*Culex*) *Pipiens* Complex, their hybrids, and the other sibling species (Diptera Culicidae)." The American Journal of Tropical Medicine and Hygiene **70**(4): 339-345.
- Smith, T., G. F. Killeen, et al. (2006). "Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: Overview." The American Journal of Tropical Medicine and Hygiene **75**(2 Suppl): 1-10.
- Snow, R. W. and K. Marsh (2010). "Malaria in Africa : progress and prospects in the decade since the Abuja Declaration." Tropical Medicine **376**(9735): 137-139.
- Snow, R. W., K. Marsh, et al. (1996). "The need for maps of transmission intensity to guide malaria control in Africa." Parasitology Today **12**: 455-457.
- Soberon, J. and A. T. Peterson (2005). "Interpretation of models of fundamental ecological niches and species' distributional areas." Biodiversity Informatics **2**: 1-10.
- Sokhna, C., J.-Y. Le Hesran, et al. (2004). "Increase of malaria attacks among children presenting concomitant infection by *Schistosoma mansoni* in Senegal." Malaria Journal **3**(1): 43.
- Sowilem, M. M., I. M. Bahgat, et al. (2006). "Spectral and landscape characterization of filarious and non-filarious villages in Egypt." Journal of the Egyptian Society for Parasitology **36**: 373-388.
- Spiegelhalter, D. J., N. G. Best, et al. (2002). "Bayesian measures of model complexity and fit." Journal of the Royal Statistical Society. Series B (Statistical Methodology) **64**(4): 583-639.
- Spiegelhalter, T. D., N. Best, et al. (2007). "WinBUGS User Manual Version 1.4.3. ." [Online] Available from: <http://www.mrc-bsu.cam.ac.uk/bugs>.
- Srividya, A., E. Michael, et al. (2002). "A geostatistical analysis of the geographic distribution of filariasis infection prevalence in Southern India." The American Journal of Tropical Medicine and Hygiene **67**(5): 480-489.
- Staubach, C., V. Schmid, et al. (2002). "A Bayesian model for spatial wildlife disease prevalence data." Preventive Veterinary Medicine **56**(1): 75-87.
- Steketee, R., B. Nahlen, et al. (2001). "The burden of malaria in pregnancy in malaria-endemic areas." The American journal of tropical medicine and hygiene **64**(1 suppl): 28-35.
- Stensgaard, A.-S., P. Vounatsou, et al. (2011). "Bayesian geostatistical modelling of malaria and lymphatic filariasis infections in Uganda: predictors of risk and geographical patterns of co-endemicity." Malaria Journal **10**(1): 298.
- Stevenson, M. A., H. Benard, et al. (2005). "Spatial epidemiology of the Asian honey bee mite (*Varroa destructor*) in the North Island of New Zealand." Preventive Veterinary Medicine **71**(3-4): 241-252.
- Stockwell, D. (1999). "The GARP modelling system: problems and solutions to automated spatial prediction." International Journal of Geographical Information Science **13**(2): 143 - 158.
- Stolk, W., S. de Vlas, et al. (2006). "Advances and challenges in predicting the impact of lymphatic filariasis elimination programmes by mathematical modelling." Filaria Journal **5**(1): 5.
- Stolk, W. a., S. J. de Vlas, et al. (2008). "LYMFASIM, a simulation model for predicting the impact of lymphatic filariasis control: quantification for African villages." Parasitology **135**(13): 1583-1598.
- Su, Z., M. Segura, et al. (2005). "Impairment of protective immunity to blood-stage malaria by concurrent nematode infection." Infection and Immunity **73**(6): 3531-3539.
- Sunish, I. P., R. Rajendran, et al. (2007). "Vector control complements mass drug administration against bancroftian filariasis in Tirukoilur, India." Bulletin of the World Health Organization **85**(2): 138-145.

- Sylla, M., K. C. Kobylinski, et al. (2010). "Mass drug administration of ivermectin in south-eastern Senegal reduces the survivorship of wild-caught, blood fed malaria vectors." Malaria Journal **9**(1): 365.
- Takken, W. (2002). "Do insecticide-treated bednets have an effect on malaria vectors?" Tropical Medicine & International Health **7**(12): 1022-1030.
- Talbot, J. T., A. Viall, et al. (2008). "Predictors of Compliance in Mass Drug Administration for the Treatment and Prevention of Lymphatic Filariasis in Leogane, Haiti." The American journal of tropical medicine and hygiene **78**(2): 283-288.
- Tanner, M. and D. de Savigny (2008). "Malaria eradication back on the table." Bulletin of the World Health Organization **86**(2): 82-82.
- Taylor, T. and M. Molyneux (2002). Clinical features of malaria in children. Essential Malariology. D. Warrell and H. Gilles, Arnold. **Fourth Edition**: 206-218.
- Thompson, D. F., J. B. Malone, et al. (1996). "Bancroftian filariasis distribution and diurnal temperature differences in the southern Nile delta." Emerging Infectious Diseases **2**: 234-235.
- Thomson, M. C., S. J. Connor, et al. (1999). "Predicting malaria infection in Gambian children from satellite data and bed net use surveys: the importance of spatial correlation in the interpretation of results." The American Journal of Tropical Medicine and Hygiene **61**(1): 2-8.
- Townson, H., M. B. Nathan, et al. (2005). "Exploiting the potential of vector control for disease prevention." Bulletin of the World Health Organization **83**(12): 942-947.
- UN. (2012). "Millenium developmet goals. <http://www.un.org/millenniumgoals/aids.shtml>." Retrieved 13th February 2012.
- USAID (2006). Neglected tropical disease program. Acta Tropica.
- Utzinger, J., Y. Tozan, et al. (2002). "The economic payoffs of integrated malaria control in the Zambian copperbelt between 1930 and 1950." Tropical Medicine & International Health **7**(8): 657-677.
- Vallely, A., L. Vallely, et al. (2007). "Intermittent preventive treatment for malaria in pregnancy in Africa: what's new, what's needed?" Malaria Journal **6**(16).
- van den Berg, H. and W. Takken (2007). "A framework for decision-making in integrated vector management to prevent disease." Tropical Medicine & International Health **12**(10): 1230-1238.
- Vanamail, P., K. D. Ramaiah, et al. (1996). "Estimation of the fecund life span of *Wuchereria bancrofti* in an endemic area." Transactions of the Royal Society of Tropical Medicine and Hygiene **90**(2): 119-121.
- Vanamail, P., S. Subramanian, et al. (1989). "Estimation of age-specific rates of acquisition and loss of *Wuchereria bancrofti* infection." Transactions of the Royal Society of Tropical Medicine and Hygiene **83**(5): 689-693.
- Volkman, L., O. Bain, et al. (2003). "Murine filariasis: interleukin 4 and interleukin 5 lead to containment of different worm developmental stages." Medical microbiology and immunology **192**(1): 23-31.
- Wang, X.-H., X.-H. Wu, et al. (2006). "Bayesian estimation of community prevalences of *Schistosoma japonicum* infection in China." International Journal for Parasitology **36**(8): 895-902.
- Wang, X. H., X. N. Zhou, et al. (2008). "Bayesian Spatio-Temporal Modeling of *Schistosoma japonicum* Prevalence Data in the Absence of a Diagnostic 'Gold' Standard." PLoS Neglected Tropical Diseases **2**(6): e250.
- Ward, D. F. (2007). "Modelling the potential geographic distribution of invasive ant species in New Zealand." Biological Invasions **9**: 723-735.
- Wharton, R. H., A. B. Laing, et al. (1963). "Studies on the Distribution and Transmission of Malaria and Filariasis among Aboriginies in Malaya." Annals of Tropical Medicine and Parasitology **57**: 235-254.
- White, G. (1971). "Studies on transmission of bancroftian filariasis in North-eastern Tanzania." Transactions of the Royal Society of Tropical Medicine and Hygiene **65**(6): 819-829.
- White, G. (1989). Lymphatic filariasis. Geographic Distribution of Arthropod-borne Diseases and Their Principal Vectors. W. H. Organisation. Geneva, Vector Biology Control Division: 23-34.
- White, M., L. Conteh, et al. (2011). "Costs and cost-effectiveness of malaria control interventions - a systematic review." Malaria Journal **10**(1): 337.

- White, N. J. (2005). "Intermittent presumptive treatment for malaria." PLoS Medicine **2**(1): e3-e3.
- WHO (1992). Lymphatic Filariasis: The Disease and Its Control. WHO Technical Report Series 821. Geneva, WHO.
- WHO (1992). Lymphatic Filariasis: The disease and its control. Fifth report of the WHO Expert Committee on Filariasis. Geneva, World Health Organization. **Technical Report Series No.: 821**.
- WHO (1998). Four International Organisations Unite to Roll Back Malaria. <http://www.who.int/inf-pr-1998/en/pr98-77.html>, Press Release WHO/77. World Health Organisation.
- WHO (2004a). Lymphatic filariasis elimination in the African region: progress report. Geneva, World Health Organisation.
- WHO (2004b). Global Strategic Framework for Integrated Vector Management. Geneva, World Health Organisation.
- WHO (2005a). World Malaria Report 2005. Geneva, World Health Organisation.
- WHO (2005b). "Global Programme to Eliminate Lymphatic Filariasis: Progress report for 2004." Weekly Epidemiological Record(80): 202-212.
- WHO (2008a). "Global programme to eliminate lymphatic filariasis." Weekly Epidemiological Record(83): 333-348.
- WHO (2008b). World Malaria Report 2008. Geneva, World Health Organisation.
- WHO (2009). "Global programme to eliminate lymphatic filariasis. Progress report on mass drug administration in 2008." Weekly Epidemiological Record **84**: 437-444.
- WHO (2010a). World Malaria Report 2010. Geneva, World Health Organisation.
- WHO (2010b). Guidelines for the treatment of malaria. Geneva, World Health Organisation.
- WHO (2011). "WHO position statement on integrated vector management to control malaria and lymphatic filariasis." Weekly Epidemiological Record **86**(13): 121-128.
- Wijers, D. J. and G. Kiilu (1977). "Bancroftian filariasis in Kenya III. Entomological investigations in Mambui, a small coastal town, and Jaribuni, a rural area more inland (Coast Province)." Annals of Tropical Medicine and Parasitology **71**(3): 347-359.
- Wijers, D. J. B. (1977). "Bancroftian filariasis in Kenya. I. Prevalence survey among adult males in the Coast Province." Annals of Tropical Medicine and Parasitology **71**(3): 313-331.
- Wiseman, V., M. Kim, et al. (2006). "Cost-Effectiveness Study of Three Antimalarial Drug Combinations in Tanzania." PLoS Medicine **3**(10): e373.
- Worrall, E., S. J. Connor, et al. (2007). "A model to simulate the impact of timing, coverage and transmission intensity on the effectiveness of indoor residual spraying (IRS) for malaria control." Tropical Medicine & International Health **12**(1): 75-88.
- Yan, Y., G. Inuo, et al. (1997). "Down-regulation of murine susceptibility to cerebral malaria by inoculation with third-stage larvae of the filarial nematode *Brugia pahangi*." Parasitology **114**(04): 333-338.
- Yazdanbakhsh, M. (1999). "Common features of T cell reactivity in persistent helminth infections: lymphatic filariasis and schistosomiasis." Immunology letters **65**(1-2): 109-115.
- Yukich, J., C. Lengeler, et al. (2008). "Costs and consequences of large-scale vector control for malaria." Malaria Journal **7**(1): 258.
- Yukich, J., F. Tediosi, et al. (2007). Operations, Costs and Cost-Effectiveness of Five Insecticide-Treated Net Programs (Eritrea, Malawi, Tanzania, Togo, Senegal) and Two Indoor Residual Spraying Programs (Kwa-Zulu-Natal, Mozambique). Basel, Switzerland, Swiss Tropical Institute.
- Zhang, H. (2002). "On estimation and prediction for spatial generalized linear mixed models." Biometrics **58**(1): 129-136.
- Zhou, X.-N., S. Lv, et al. (2009). Spatial epidemiology in zoonotic parasitic diseases: insights gained at the 1st International Symposium on Geospatial Health in Lijiang, China, 2007. Parasites & Vectors.
- Zweig, M. H. and G. Campbell (1993). "Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine." Clinical Chemistry **39**: 561-577.