Eradicating Lymphatic Filariasis

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Prof Dr. Jörg Schibler
Dekan

To my mother, who relentlessly encourages me – no matter how far away my dreams take me.

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List of Acronyms

ADL	Acute adenolymphangitis
AFRO	African region
ALB	Albendazole
AMR	Region of the Americas
APOC	African Program for Onchocerciasis Control
bn	Billion
CDC	Centers for Disease Control and Prevention
CDDs	Community drug distributors
CHOICE	CHOosing Interventions that are Cost-Effective
CrI	Credible interval
Cx	Culex
DALY	Disability-adjusted life year
DEC	Diethylcarbamazine citrate
DEGA	Disease Eradication Governance Agency
dr	Discounting rate
DW	Disability weights
EIC	Eradication Investment Case
EMR	Eastern Mediterranean Region
GPELF	Global Program to Eliminate Lymphatic Filariasis
GSK	GlaxoSmithKline
HIV/AIDS	Human immunodeficiency virus infection/acquired immune deficiency syndrome
ICER	Incremental cost-effectiveness ratio
ICT	Immunochromatographic card test
IRS	Indoor residual spraying
ITNs	Insecticide treated nets
IUs	Implementation units
IVM	Ivermectin
kg	Kilogram
LLINs	Long lasting insecticidal nets
LF	Lymphatic filariasis
m	Million
MDA	Mass drug administration
M&E	Monitoring and evaluation
mf	Microfilariae
MNBs	Monetary net benefits
NTD	Neglected tropical disease
ODA	Overseas development assistance
PCT	Preventive chemotherapy

PELF	Program to eliminate lymphatic filariasis
PPP	Purchasing power parity
PSA	Probabilistic sensitivity analysis
SAEs	Severe adverse events
spp	Several species
SEAR	Southeast Asia Region
SD	Standard deviation
STH	Soil-transmitted helminths
Swiss TPH	Swiss Tropical and Public Health Institute
TAS	Transmission assessment survey
ToTs	Training of Trainers
USAID	United States Agency for International Development
USD	United States dollar
WHA	World Health Assembly
WHO	World Health Organization
WPR	Western Pacific Region
YLD	Years of life lived with disability

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Summary

Background

The neglected tropical disease (NTD), lymphatic filariasis (LF), is endemic in 73 countries, primarily among impoverished populations [1]. LF is caused by infection with the filarial nematodes *Wuchereria bancrofti, Brugia malayi,* or *B. timori,* which are transmitted to humans by a variety of mosquito genera, including *Anopheles*, *Culex*, and *Aedes* [2]. Infection with LF can damage the lymphatic system, causing permanent disability including hydrocele, lymphedema, and elephantiasis [3]. Though not all infections lead to disability, the health burden due to LF is considerable, estimated at 2.74 million disability-adjusted life years (DALYs) (1.73m-4.00m) [4]. The disfiguring disability associated with LF also causes stigma, social adversity, and economic hardship [5-7].

In 1997, LF was named by the World Health Assembly (WHA) as a potentially eradicable disease [8], in part because it is preventable through once yearly treatment administered through mass drug administration (MDA) using albendazole with ivermectin or diethylcarbamazine citrate (DEC). It is this prevention strategy that underlies the Global Program to Eliminate Lymphatic Filariasis (GPELF), which aims to globally eliminate LF as a public health problem by 2020 [9]. The efforts of the GPELF are supported through public and private partnerships, among which include the pharmaceutical companies Merck & Co., GlaxoSmithKline (GSK), and Eisai, which currently donate all of the medications used to carry out the MDA strategy [10,11].

In the 15 years since the inception of the GPELF, there has been great progress made against LF. In 2013 alone, over 410 million treatments were distributed to prevent LF transmission. Of the 73 LF-endemic countries, 59 have carried out MDA as part of the GPELF strategy, and 15 others are now conducting post-MDA surveillance to determine if local elimination has been achieved. However, 12 countries are yet to finish mapping and many countries are currently distributing treatments to relatively small percentages of their at-risk populations [12]. Problems with systematic non-compliance, contraindications of the antifilarials in some areas in Central Africa, and insecure funding also threaten the program [13,14].

Aims

This project has been undertaken in order to provide decision makers with evidence-based guidance on the rationale for investing in LF eradication. As such, this project aims to:

- Predict the duration of MDA necessary to reach local elimination for a variety of transmission archetypes using an existing model of LF transmission

- Develop plausible scenarios leading to global elimination and eradication under varying levels of MDA scale-up

- Project the number of treatments required for each scenario

- Estimate the time in which local elimination will be achieved in each country in each scenario

- Estimate the potential economic and financial investment needed to interrupt LF transmission and conduct surveillance activities under each of the scenarios

- Quantify the potential health impact of eradicating LF in terms of DALYs averted

- Estimate the cost-effectiveness of different intensities of MDA scale-up

- Project the potential health systems savings as a result of averted LF-related morbidity

- Monetarily value possible gains in worker productivity resulting from averted LF-related morbidity

Methods

In collaboration with a diverse group of stakeholders, decision-makers, and program experts, we developed a global elimination and three eradication scenarios. The global elimination scenario serves as the counter-factual case, mirroring the current geographic coverage and rate of MDA scale-up seen under the GPELF. In contrast, the three eradication scenarios include all LF endemic countries but differ in their rates of MDA scale-up. Eradication I extends MDA to all endemic countries under the average rate of MDA seen under the GPELF; eradication II assumes a more rapid scale-up, with 20% of each country's at-risk population added to the MDA schedule annually; and eradication III represents the ideal scenario, assuming all at-risk populations are treated with MDA immediately.

Using EpiFil [15], a deterministic model of LF transmission, we determined the number of annual rounds of MDA necessary to reach local elimination for a range of transmission archetypes. We then used the model estimates to assess the number of years of MDA and associated number of treatments required to interrupt LF transmission in each country in each scenario.

In order to assess the financial costs of interrupting LF transmission in each of the scenarios, we built a micro-costing model from the perspective of each LF endemic country's health system. We also considered the value of the donated pharmaceuticals and volunteer time in the assessment of economic costs. In order to account for the health impact of varying intensities of MDA scale-up, we simulated the amount of LF-related disability arising under each of the scenarios over a 50 year time

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horizon. The health impact estimates were then paired with the financial cost estimates in order to assess the cost-effectiveness of LF eradication. Using the WHO CHOICE database [16], we also determined the potential savings to health systems as a result of averted LF-related disability. Further, we monetarily valued the societal economic gains from LF eradication by pairing the potential increase in worker productivity due to averted LF-related disability with country or region specific daily per worker agriculture wage estimates taken from the World Bank [17].

Principal Findings

If MDA scale-up is maintained at the current rate, our model suggests that LF transmission will not be interrupted until 2050 (global elimination and eradication I scenarios). In contrast, providing MDA to all at-risk populations in all countries immediately (eradication III) is projected to result in the interruption of LF transmission by 2028. Providing treatments to all LF endemic countries at the current rate of scale-up (eradication I) is estimated to require 4,667 million treatments (95% CrI: 4,419m-4,904m). However, as population growth rates are taken into account, decreasing the time required to reach eradication is also projected to decrease the number of treatments required, with the eradication II scenario projected to require 4,369 million treatments (95% CrI: 4,133m–4,594m) and the eradication III scenario requiring 4,159 million treatments (95% CrI: 3,924m-4,382m). The financial cost of completing the current global elimination program is projected at 929.2 million US dollars (USD) (95% CrI: 883.5m-971.5m), while eradication I is projected to require a financial investment of 1,289 million USD (95% CrI: 1,227m-1,345m). Treating all populations in all endemic countries immediately (eradication III) will require a financial investment totaling 1,235 million USD (95% CrI: 1,172m-1,300m). The economic costs, which take into account the value of the donated pharmaceuticals and volunteer time together with the actual monetary expenditure required (financial costs), are projected at 5.21 billion USD (95% CrI: 4.91-5.45) under the global elimination scenario, 7.94 billion USD (95% CrI: 7.50bn-8.30bn USD) for eradication I, 8.00 billion USD (7.55bn-8.37bn) for eradication II and 7.57 billion USD (7.12bn-7.94bn) for eradication III. Approximately half of the economic costs are due to the value of the donated drugs.

Against the global elimination scenario, the health impact of the eradication I scenario is projected to result in approximately 1.72 million DALYs averted (95% CrI: 1.09m-2.61m), while the eradication III scenario is projected to result in 4.38 million DALYs averted (95% CrI: 2.79m-6.50m) over the same timeframe. The cost-effectiveness of LF eradication is also projected to be greatest when all LF at-risk populations are treated immediately, with an incremental cost-effectiveness ratio (ICER) under the eradication III scenario estimated at 72.9 USD/DALY averted (95% CrI: 47.7-110). Health systems savings also increase with increased rates of MDA scale-up, with the most savings expected under

the eradication III scenario (483 million USD (95% CrI: 219m-903m). Gains in worker productivity also increase with increased rates of MDA scale-up, estimated at about 14 billion USD (95% CrI: 8.58bn-22.0bn) under eradication III versus 3.41 billion USD (95% CrI: 2.03bn-5.36bn) in eradication I.

Conclusions

While pursuing LF eradication has many benefits, our analysis indicates reaching LF eradication in the shortest amount of time possible is preferred across a number of indicators. The results of our analyses indicate that eradicating LF could be among the best buy strategies in public health, though the success of eradicating LF will depend on the political engagement and enthusiasm at all levels.

1   Introduction

1.1.   Neglected Tropical Diseases

Neglected tropical diseases (NTDs) are a group of helminthic, bacterial, viral, fungal and protozoan infections that cause significant morbidity [18]. NTDs persist in areas where vector control, access to clean water, health care, and sanitation are limited. As such, they are most prevalent in low-income countries, particularly among impoverished populations [19]. NTDs are not just diseases that coexist in poverty, they reinforce the cycle of poverty by negatively impacting worker productivity, physical growth, cognitive development, and school attendance [20,21]. Additionally, the morbidity associated with some of the NTDs lead to stigma, thereby affecting social relationships [22].

One billion people are thought to be infected by at least one NTD [19]. By some estimates, the health burden due to NTDs account for nearly 48 million disability-adjusted life years (DALYs) [23]. In comparison, the health burden due to tuberculosis, malaria, and HIV/AIDs is 49 million DALYs, 83 million DALYs, and 82 million DALYs, respectively [23]. However, while HIV/AIDS, malaria, and tuberculosis account for more than 40% of the overseas development assistance (ODA) funding for health, collectively, NTDs receive just 0.6% of the ODA health funds [24]. Despite the disproportionate funding, investing in the control of NTDs is considered highly cost-effective, in part because many NTDs can be controlled or even eliminated through mass drug administration (MDA) to entire at-risk populations [25].

1.2.   Lymphatic Filariasis

Lymphatic filariasis (LF) is an NTD endemic in 73 countries, with over a billion people considered as being at-risk of infection and an estimated 120 million people infected by the filarial nematodes *Wuchereria bancrofti* (> 90%), *Brugia malayi,* or *B. timori* [26]. Though most people infected remain asymptomatic, LF infection can result in debilitating and irreversible morbidity, typically manifested as moderate to extreme swelling of the lower limbs (lymphedema and elephantiasis), swelling of the scrotum (hydrocele), and acute adenolymphangitis (ADL) [9]. Once infected, treatment options are limited. Simple hygienic measures, antibiotics, and antifungals are used for managing lymphedema and elephantiasis. Antibiotics, antipyretics, and analgesics are used to alleviate ADL. For men suffering from hydrocele, however, surgery is among the only options [27]. Recent estimates put the health burden due to LF-related morbidity at 2.74 million DALYs (1.73m-4.00m) [4]. This estimate, however, only accounts for the direct physical burden of LF. Upon incorporating the mental health problems that often accompany LF-related morbidity, the health burden increases to 5.09 million

DALYs [28]. Further, lymphatic filariasis impacts worker productivity and, despite limited options for care, burdens health systems in endemic countries [29].

1.2.1   Transmission of Lymphatic Filariasis

Mosquitoes serve as the vector for LF, transferring infective L3 larvae to humans during the course of a blood meal. Upon entry into humans, the larvae mature into male and female worms that mate in the lymph nodes of their human hosts. From this point on, female worms are fecund, producing millions of microfilariae (mf) throughout their lifespan (estimated at 4-6 years or longer). The mf circulate in the peripheral blood of infected humans at times that correspond to the peak biting patterns of their primary mosquito vector – the exact species primarily belonging to the genera *Anopheles, Culex, Mansonia*, or *Aedes*, depending on the geographic locale. Once taken up in a blood meal and inside the mosquito, the mf pass through the midgut and develop into an L2 larvae stage followed by an infective L3 larvae stage, before being passed on to the next host where the cycle continues (Figure 1) [30].

Figure 1: Transmission cycle of *Wucheria Bancrofti*
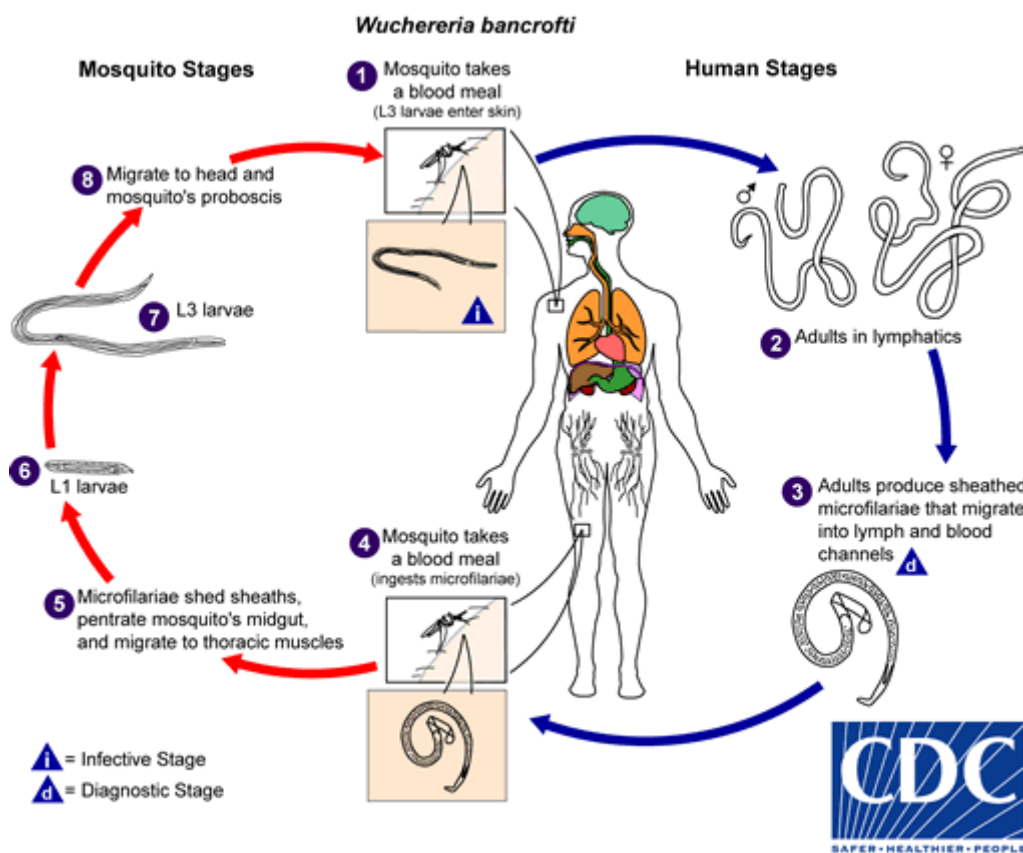
1.2.2   Determination of Lymphatic Filariasis Endemicity

The gold standard for determining populations at-risk for LF involves taking blood slides to assess the presence of circulating mf in a community [31]. However, the mf circulate in the blood at times that correspond to when the mosquitoes bite, which, in many areas, is only at night [32]. In such areas, blood slides to detect circulating mf need to be both collected and examined at night, which makes the use of blood slides for assessing endemicity highly inconvenient for both communities and mapping teams. Further, the sensitivity of blood slides vary by the accuracy of the person reading the slide, as well as the volume of blood collected [33]. To counter many of the challenges inherent in using blood slides, rapid tests have recently been introduced which allow for identification of infected individuals through blood samples that can be taken at any time of the day. In areas where *W. bancrofti* is thought to be endemic, the immunochromatographic card test (ICT) whole blood antigen card test can be used to detect infection, while the Brugia Rapid test can be used to detect antibodies from *Brugia* spp. infection [33,34].

1.2.3   Global Distribution of Lymphatic Filariasis

Mapping in areas thought to be endemic for LF have been carried out using both blood slides and rapid tests [31]. As of 2013, 44 out of 73 endemic countries had finished mapping surveys. With the exception of Eritrea, mapping is underway or completed in all other endemic countries [12]. Lymphatic filariasis is most common in tropical and sub-tropical regions, including Sub-Saharan Africa, the Western Pacific Region, Southeast Asia, and parts of Central and South America [12,31]. Transmission intensity is highly focal, with risk of infection increasing with increased temperature and rainfall and decreasing with altitude [31]. Figure 2 depicts areas where the environment is suitable for LF transmission [31], while Table 1 provides a breakdown of at-risk populations by World Health Organization (WHO) region [12]. In rural Africa, LF is most commonly transmitted by *Anopheles* mosquitoes, while in urban areas of Africa, as well as throughout Asia, Central and South America, *Culex* mosquitoes serve as the primary vector [35].

Table 1: LF at-risk population by WHO Region, 2013

WHO Region	Population at-risk for LF	Percent of global at-risk population by region
SEAR	651,283,942	55%
AFRO	468,392,074	40%
WPR	26,499,057	2%
EMR	20,443,951	2%
AMR	12,048,009	1%
Total	1,178,667,033	

Figure 2: Map of environmental suitability for lymphatic filariasis transmission

Note: Transmission was predicted using boosted regression trees modelling on a range of climatic and population factors and data assembled in a global database of LF.
Cano et al. (2014) Parasit Vectors. 11;7(1):466. doi:10.1186/s13071-014-0466-x

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1.2.4   Prevention of Lymphatic Filariasis

Annual administration of albendazole paired with ivermectin or diethylcarbamizine citrate (DEC) reduces circulating mf to levels that cannot sustain transmission. The feasibility of preventing LF is improved by the fact that the antifilarials can be distributed as mass drug administration (MDA) to all at-risk populations [9], and through partnerships with Merck & Co., GlaxoSmithKline (GSK), and Eisai, which currently donate the ivermectin, albendazole, and DEC tablets used against lymphatic filariasis [10,11].

While not the primary strategy for prevention, vector control also plays a role in reducing LF transmission. The use of long-lasting insecticidal nets (LLINs) for the control of malaria has been shown to have an effect on LF transmission, especially where *Anopheles* mosquitoes serve as the primary vector [36]. Indoor residual spraying (IRS) in the Solomon Islands in the 1960s is also thought to have contributed substantially to the elimination of LF in the country [37]. The positive effects of vector control in combating LF are facilitated by the inefficiencies of LF transmission. In Yangon, Myanmar, where *Cx. Quinquefasciatus* is the primary vector, study teams estimated an average of 15,500 infective bites to be required to result in one transmittable LF infection [38]. However, the extent to which LF transmission is reduced as a result of vector control still needs to be quantified [36].

1.2.5 *The Global Program to Eliminate Lymphatic Filariasis*

In 1997, the International Task Force for Disease Eradication classified LF as a potentially eradicable disease due, in part, to the feasibility of interrupting transmission, the lack of a significant animal reservoir, and the availability of accurate diagnostic tools to assess infection [8,33,39]. Shortly thereafter, the World Health Assembly (WHA) adopted resolution WHA 50.29, which calls on Member States to develop national plans leading to the elimination of LF [9]. In response to the WHA resolution, the WHO began the Global Program to Eliminate Lymphatic Filariasis (GPELF) in 2000 with the overall goal of eliminating LF as a public health problem by 2020. The GPELF aims to accomplish this through two stated objectives: (1) to stop the spread of infection (interrupt transmission); and (2) to alleviate the suffering of affected populations (control morbidity). The GPELF strategy for accomplishing the first objective centers around annual MDA with albendazole and either ivermectin or DEC to entire eligible populations living in areas where LF is endemic (defined as areas where prevalence of circulating mf or antigenemia is ≥1%) [9]. With five years remaining to achieve the targets, the GPELF still considers global elimination by 2020 to be achievable if all countries scale-up MDA coverage to 100% of their at-risk populations within the next one year, and by assuming five rounds of annual MDA to be sufficient to interrupt transmission in all areas [40].

1.2.6 *Progress of and challenges facing the Global Program to Eliminate Lymphatic Filariasis*

The GPELF is among the most rapidly expanding public health programs ever undertaken [41]. In the 15 years since the GPELF began, more than five billion antifilarial treatments have been distributed, 58 out of 73 endemic countries have conducted at least one round of MDA, and 15 countries are

currently conducting post-MDA surveillance to assess the interruption of LF transmission [12]. Since the inception of the GPELF, China and South Korea have also certified local elimination [42,43]. By some estimates, the population at-risk for LF has decreased by 46% under the GPELF [44], while the economic benefits from the first eight years of the program could be up to 21.8 billion US dollars (USD) [29].

Though the GPELF has made great progress against LF, many at-risk populations remain untreated [12]. Issues with funding, logistics, community commitments and enthusiasm towards the program, natural and man-made disasters, civil and political unrest, and contraindications of the combination antifilarial treatments in areas where the parasitic disease *Loa loa* is highly endemic threaten the program [13,45,46]. Ensuring the timely distribution of the drugs used in the MDA program, achieving effective levels of treatment coverage, maintaining community support, and ensuring adequate numbers of trained community distributors to carry out the GPELF strategy pose additional challenge to achieving the program targets [46].

1.2.7 *EpiFil*

EpiFil is a deterministic model composed of partial differential equations, which aims to capture the dynamics of LF transmission [15]. EpiFil has been previously used to assess the impact of interventions for LF and has been validated against data sets for transmission with *Anopheles* spp. in East Africa and by *Culex* spp. in Pondicherry, India [15,47-49]. The model is fully age-structured and also takes into account the probability of adult worms remaining unmated.

The model incorporates changes in state parameters through the following partial differential equations:

$$\frac{\partial W}{\partial t} + \frac{\partial W}{\partial a} = \lambda \frac{V}{H} \psi_1 \psi_2 s_2 h(a) L^* e^{-\beta I} - \mu W$$

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = \alpha \phi(W,k)W - \gamma M$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = W - \delta I$$

which includes the mean adult worm burden in humans (W), the mean microfilariae density in humans (M), and the mean level of immunity (I). The model also takes into account natural death of mf and adult worms. Incidence of hydrocele and lymphedema, as well as damage to the lymphatic system as a result of LF infection, are accounted also for. A depiction of the model is shown in Figure 3.

Figure 3: EpiFil
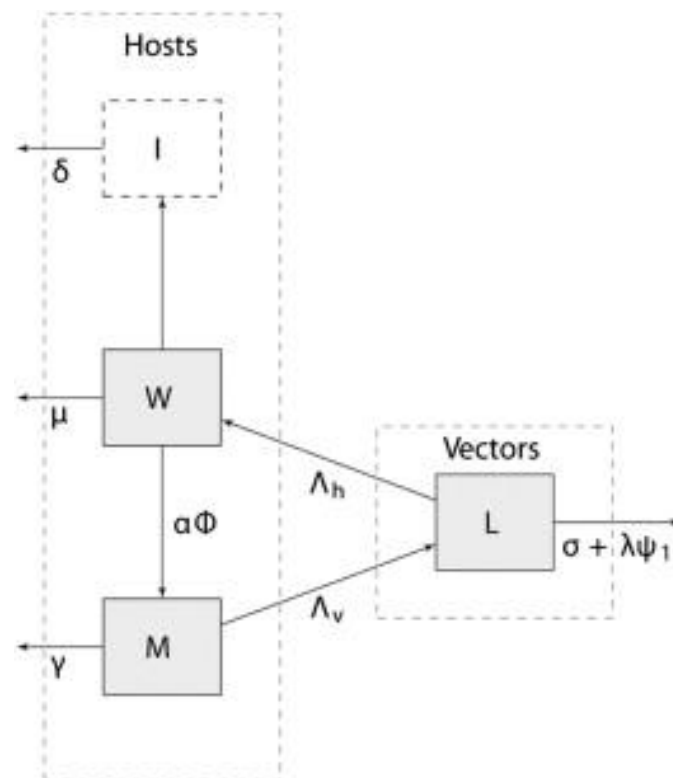
A schematic of the deterministic model, EpiFil. W represents the mean worm burden in humans, M the mean mf density, and L the mean intensity of L3 larvae. Diagram courtesy of Stolk et. al[50]

1.3   Disease eradication

Disease eradication has been considered to be a fundamental example of a global public good [51]. Successfully eradicating a disease also represents a significant triumph in public health. Indeed, the eradication of smallpox, which remains the only human disease that has been successfully eradicated, is heralded as one of the greatest achievements of the 20th century [52,53]. Eradicating an NTD in particular has additional benefits, including gains towards equity and social justice [22].

Disease eradication requires a high degree of international collaboration and coordination over a long period of time [54]. Indeed, in the Global Burden of Disease study, Murray pointed out that

> *Whether eradication is achieved depends on the level of control adopted by the country that undertakes the least control. In practical terms, any country in which disease is endemic can prevent eradication from being achieved [55].*

Additional challenges facing disease eradication initiatives involve unforeseen circumstances, such as civil unrest, natural disasters, and disease epidemics that threaten the health systems' capacities to

deliver the intervention [45]. The evolution of resistance to the drugs used in the intervention, the realization that interrupting transmission in some areas is biologically unfeasible, and problems in maintaining the long term investments required all pose challenges to disease eradication initiatives [56-58]. Until the disease is eradicated, there also remains a continual risk of imported cases back into previously disease-free areas [59]. If unsuccessful, disease elimination and eradication campaigns could represent a poor use of resources and lead to donor fatigue [57].

1.4   Eradication Investment Cases

Given the many complex and interlinking issues involved in committing to a disease eradication initiative, decision makers, researchers, and thought leaders convened the 7th Ernst Strüngmann forum in 2009 in order to discuss the need for an evidence base in which to decide whether disease eradication initiatives should go forward. This meeting resulted in the concept of an Eradication Investment Case (EIC) [60].

Since the forum, guidelines for the development of an EIC have since been put into place, which specify that an EIC should describe four primary components: (1) the proposed investment, which includes an analysis of the significance of the disease; an understanding of the current state of efforts against the disease; and considerations for how eradication could be achieved, (2) the rationale for investing, which takes into account the feasibility or reaching eradication; the health, social, and economic burden of the disease; an assessment of total costs; an analysis of the cost-effectiveness of eradication; and considerations about the health systems; and (4) Issues to take into account when shifting to eradication, including partnerships and governance; monitoring and evaluation; and an operational research plan [61,62].

2   Study rationale and aims

Building from the momentum of successfully eradicating smallpox in 1980, the World Health Authority (WHA) called for the eradication of polio with resolution WHA 41.28 [63]. Three years later, resolution 39.21 was adopted, which called for the eradication of Dracunculiasis [64]. In response, global programs to reach eradication are underway for both diseases [65,66]. The campaigns for these initiatives were based on the realization that eradication was technically feasible, meeting three crucial objectives, including: the presence of a vaccine or other mode of preventing future infections, (2) lack of an animal reservoir, and (3) accurate diagnostics [67]. However, operational challenges encountered by both the polio and Dracunculiasis programs have underscored the importance of understanding a number of additional factors prior to undertaking an eradication program [62].

As such, this project was undertaken in order to create evidence for decision makers to determine whether to pursue LF eradication, and, if so, to what level of intervention intensity. Specifically, this work aimed to:

- Predict the duration of MDA necessary to reach local elimination for a variety of transmission archetypes using an existing model of LF transmission

- Develop plausible scenarios leading to global elimination and eradication under varying levels of MDA scale-up

- Estimate the number of treatments required for each scenario

- Estimate the potential economic and financial investment needed to interrupt LF transmission under each of the scenarios

- Quantify the potential health impact of eradicating LF

- Estimate the cost-effectiveness of different intensities of MDA scale-up

- Project the potential savings to the health system as a result of averted LF-related morbidity

- Value possible gains in worker productivity that could result from averted LF-related morbidity.

3   What is Needed to Eradicate Lymphatic Filariasis? A Model-Based Assessment on the Impact of Scaling up Mass Drug Administration Programs

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3.1   Abstract

Background

Lymphatic filariasis (LF) is a neglected tropical disease for which more than a billion people in 73 countries are thought to be at-risk. At a global level, the efforts against LF are designed as an elimination program. However, current efforts appear to aim for elimination in some but not all endemic areas. With the 2020 goal of elimination looming, we set out to develop plausible scale-up scenarios to reach global elimination and eradication. We predict the duration of mass drug administration (MDA) necessary to reach local elimination for a variety of transmission archetypes using an existing model of LF transmission, estimate the number of treatments required for each scenario, and consider implications of rapid scale-up.

Methodology

We have defined four scenarios that differ in their geographic coverage and rate of scale-up. For each scenario, country-specific simulations and calculations were performed that took into account the pre-intervention transmission intensity, the different vector genera, drug regimen, achieved level of population coverage, previous progress toward elimination, and potential programmatic delays due to mapping, operations, and administration.

Principal Findings

Our results indicate that eliminating LF by 2020 is unlikely. If MDA programs are drastically scaled up and expanded, the final round of MDA for LF eradication could be delivered before 2029 after 4,159 million treatments. However, if the current rate of scale-up is maintained, the final round of MDA to eradicate LF may not occur until 2050.

Conclusions/Significance

Rapid scale-up of MDA will decrease the amount of time and treatments required to reach LF eradication. It may also propel the program towards success, as the risk of failure is likely to increase with extended program duration.

3.2   Author Summary

Lymphatic filariasis (LF) is a disease caused by filarial worms transmitted by different types of mosquitoes that can lead to massive disability, including elephantiasis and hydrocele. LF has no significant zoonotic reservoir and is thought to be a potentially eliminable disease through once yearly treatment distributed by mass drug administration (MDA). In this study, we set out to determine how many treatments and over how much time it might take to globally eliminate and eradicate LF under different levels of treatment intensities. We created a model that took into account country-specific and disease-specific variables, and found that if the current intensity of MDA is maintained, 3,409 million treatments distributed over the next 37 years will be required. However, if treatment is rapidly expanded to the entire at-risk population in all endemic countries, eradication could be achieved with 4,159 million treatments and in less than half the time. While our estimates suggest more time may be needed to reach LF elimination than what is currently projected, with continued commitment, eradicating LF is within reach.

3.3   Introduction

Lymphatic filariasis (LF) is a neglected tropical disease (NTD) primarily prevalent in poor populations in 73 countries [1]. LF is caused by infection with *Wuchereria bancrofti, Brugia malayi,* or *B. timori* transmitted by a variety of mosquito genera [2]. Infection with the filarial nematodes can damage the lymphatic vessels, the main clinical manifestations being lymphedema, hydrocele, and elephantiasis [3]. In addition to disfigurement and disability, people affected by LF face stigma, social adversity, and economic hardship [5-7].

LF is spread by mosquitoes that take up circulating microfilarie (mf) in the peripheral blood of infected humans [68]. Administration of albendazole with ivermectin or diethylcarbamazine citrate (DEC) has been shown to reduce circulating mf to such low levels that transmission cannot be sustained [9]. For this reason, LF is one of six diseases considered to be potentially eliminable [8]. Accordingly, in 1997 the World Health Assembly (WHA) adopted resolution WHA 50.29, which calls for the elimination of LF as a public health problem and, in 2000, the World Health Organization (WHO) established the Global Program to Eliminate Lymphatic Filariasis (GPELF). The GPELF aims to eliminate LF in all endemic countries by 2020 through annual mass drug administration (MDA) maintained over multiple years [9]. The program benefits through donations from Merck & Co. and GlaxoSmithKline (GSK), which have pledged to provide enough ivermectin and albendazole, respectively, to achieve elimination, as well as from Eisai, which in 2010, pledged 2.2 billion DEC tablets [10,11].

The GPELF has scaled up rapidly and is among the fastest growing disease elimination programs in the world [41]. By the end of 2013, 56 LF-endemic countries had carried out MDA, of which 15 are now undertaking post-MDA surveillance. In 2013 alone, more than 410 million anti-filarial treatments were distributed under the GPELF. However, the program is not without its challenges: mapping is incomplete in 12 countries, 14 countries requiring MDA are yet to begin, and many of the other countries are targeting relatively small proportions of their at-risk populations [12]. Issues with compliance, contraindications of ivermectin and DEC in areas with hyper *Loa loa*-endemicity, and interruptions in funding also plague the program [13,14]. At a global level, the efforts against LF could be considered a global elimination program (elimination of infection in some but not all countries) as the name suggests, or an eradication program (permanent reduction to zero of the worldwide incidence of infection) as implied by the stated aims of the program [12,40,69].

In order to assist decision makers in determining whether efforts for LF should be scaled up to try to achieve eradication, it has been proposed to use an analytic and deliberate methodology to produce

evidence-based guidance on the rationale for investing [62,70]. As part of this endeavor, we herein predict the duration of MDA necessary to reach local elimination for a variety of transmission archetypes using an existing model of LF transmission, outline plausible scale-up scenarios leading to global elimination and eradication, and estimate the number of treatments required under each scenario. Potential delays in implementation, previous progress, and different intensities of infection and transmission are also taken into account. Studies on the economic and financial costs, the impact on disease burden, and cost-effectiveness of these scenarios are to be published as companion papers.

3.4   Methods

We have defined four hypothetical scenarios that differ in their geographic coverage and rate of scale-up. The global elimination scenario represents the case whereby countries continue with current practices. As such, it serves as the comparator against all other scenarios. The other three scenarios aim at reaching LF eradication through varying levels of MDA scale-up. Key assumptions and differences between the scenarios are outlined in Table 2. The number of years that each endemic country exceeded the minimum effective coverage rate of 65% in previous rounds of MDA, as well as the geographic coverage and rates of scale-up are provided in Table 3 (countries without previous rounds of MDA for LF) and Table 4 (countries that previously carried out MDA for LF). All scenarios were assumed to begin in 2014 and run until the final round of MDA has been distributed in each country under consideration. Though coverage rates above 65% are considered to be the lowest threshold necessary to be effective, the average programmatic coverage for countries that had previously achieved effective coverage was over 80%. Therefore, we assume that prospective MDA will continue to be performed at higher levels, and therefore assume MDA coverage to be fixed at 85%.

Table 2: Key features of the proposed scenarios for global elimination and eradication of LF

	Global Elimination (comparator)	Eradication I	Eradication II	Eradication III
Intervention	MDA	MDA	MDA	MDA
Coverage rate	85%	85%	85%	85%
Countries considered	All LF endemic countries that have previously conducted MDA[¥]	All LF endemic countries[¥], including all countries co-endemic for *L. loa*	All LF endemic countries[¥], including all countries co-endemic for *L. loa*	All LF endemic countries[¥], including all countries co-endemic for *L. loa*
Rate of scale-up	Countries with previous MDA continue at same rate as historically	Countries with previous MDA continue at same historical rate, countries without previous progress begin at an 'average' rate of MDA scale-up (schedule II)	Schedule I: All countries add 20% of their at-risk populations to the MDA schedule annually	All countries treat 100% of their at-risk populations annually

[¥]Assuming country requires MDA

Table 3: Countries without previous rounds of MDA for LF

Country	Primary vector	Treatment[α]	At-risk population, 2012[¤]	Population growth rate, 2012[¥]	Scale-up schedule[±]	Delay[§]
Angola	*Anopheles*	IVM + ALB	12,090,000	3.1%	-/2/1/0	4
Brunei Darussalam	*Culex**	DEC + ALB	15,000	1.4%	-/2/1/0	1
Chad	*Anopheles*	IVM + ALB	7,270,000	3.0%	-/2/1/0	4
Central African Republic	*Anopheles*	IVM + ALB	3,300,000	3.1%	-/2/1/0	4
Equatorial Guinea	*Anopheles*	IVM + ALB	420,000	2.8%	-/2/1/0	1
Eritrea	*Anopheles*	DEC + ALB	3,577,000	3.3%	-/2/1/0	4
Gabon	*Anopheles*	IVM + ALB	1,290,600	2.4%	-/2/1/0	1
Guinea	*Anopheles*	IVM + ALB	6,067,135	2.6%	-/2/1/0	1
New Caledonia	*Aedes*	DEC + ALB	12,378	1.6%	-/2/1/0	1
Palau	*Aedes*	DEC + ALB	20,044	0.7%	-/2/1/0	1

Republic of the Congo	*Anopheles*	IVM + ALB	2,600,000	2.6%	-/2/1/0	1
São Tomé and Príncipe	*Anopheles*	DEC + ALB	410,000	2.7%	-/2/1/0	1
South Sudan	*Anopheles*	IVM + ALB	1,659,558	4.3%	-/2/1/0	4
Sudan	*Anopheles*	IVM + ALB	19,893,779	2.1%	-/2/1/0	4
The Democratic Republic of Congo	*Anopheles*	IVM + ALB	49,140,000	2.7%	-/2/1/0	4
The Gambia	*Anopheles*	IVM + ALB	1,200,000	3.2%	-/2/1/0	1
Zambia	*Culex*	DEC + ALB	8,780,000	3.2%	-/2/1/0	4
Zimbabwe	*Culex*	DEC + ALB	6,000,000	2.7%	-/2/1/0	4

Treatment durations for Culex spp. were used for countries in which primary vector species was unknown.

[α]*Treatment assumed to occur once annually using diethylcarbamazine citrate (DEC) and albendazole, or in areas co-endemic with onchocerciasis, ivermectin (IVM) and albendazole (ALB)*

[¤] *Preventive Chemotherapy Databank Lymphatic Filariasis [Internet]. WHO. 2015 [cited 2015 January 20]. Available from: http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/.*

[¥] *United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP.227.*

[±] *Refers to MDA schedules assumed to be used by these countries for the purposes of our analysis, for the global elimination scenario, eradication I, eradication II, and eradication III scenarios, respectively. In schedule I, two deciles (20%) of the at-risk population are added to the MDA schedule annually. In schedule II, one decile is added annually. In schedule III, one decile is added every 2 years, and in schedule IV, one decile is added every 3rd year (see: Rate of Scale-Up and History of Control). '-' refers to a continued absence of an MDA program. '0' refers to instantaneous scale-up.*

[§]*A 4-year delay was assumed for countries that have not completed LF mapping, while a 1-year delay was assumed for those that have completed mapping but have not previously carried out MDA.*

Table 4: Countries that previously carried out MDA for LF

Country	Primary vector	Treatment[α]	At-risk population, 2012[¤]	Population growth rate, 2012[¥]	Previous effective years[¤]	Scale-up schedule[±]
>50% targeted						
Burkina Faso	*Anopheles*	IVM + ALB	16,779,208	2.9%	11	1/1/1/0
Cameroon	*Anopheles*	IVM + ALB	17,091,469	2.5%	5	1/1/1/0
Côte d'Ivoire	*Anopheles*	IVM + ALB	14,000,000	2.3%	1	1/1/1/0
Comoros	*Culex*	DEC + ALB	514,110	2.4%	5	1/1/1/0
Egypt	*Culex*	DEC + ALB	536,443	1.7%	11	1/1/1/0
Fiji	*Aedes*	DEC + ALB	529,984	0.8%	7	1/1/1/0
French Polynesia	*Aedes*	DEC + ALB	274,544	1.1%	10	1/1/1/0
Ghana	*Anopheles*	IVM + ALB	11,925,399	2.2%	11	1/1/1/0
Haiti	*Culex*	DEC + ALB	10,732,356	1.4%	10	1/1/1/0
India	*Culex*	DEC + ALB	617,170,000	1.3%	15	1/1/1/0
Kenya	*Culex**	DEC + ALB	3,421,741	2.7%	3	1/1/1/0
Lao PDR	*Culex**	DEC + ALB	132,644	1.9%	2	1/1/1/0
Liberia	*Anopheles*	IVM + ALB	3,600,000	2.7%	0	1/1/1/0
Malawi	*Anopheles*	IVM + ALB	14,807,685	2.9%	5	1/1/1/0
Mali	*Anopheles*	IVM + ALB	16,166,882	3.0%	7	1/1/1/0
Mozambique	*Anopheles*	IVM + ALB	17,114,949	2.5%	3	1/1/1/0
Nepal	*Culex*	DEC + ALB	15,755,990	1.2%	10	1/1/1/0
Niger	*Anopheles*	IVM + ALB	12,467,592	3.8%	4	1/1/1/0
Philippines	*Aedes*	DEC + ALB	29,383,286	1.7%	9	1/1/1/0

Samoa	*Aedes*	DEC + ALB	186,649	0.8%	5	1/1/1/0
Sierra Leone	*Anopheles*	IVM + ALB	6,667,687	1.9%	5	1/1/1/0
Thailand	*Aedes*	DEC + ALB	73,495	0.3%	11	1/1/1/0
Tuvalu	*Aedes*	DEC + ALB	10,373	0.2%	4	1/1/1/0
Uganda	*Anopheles*	IVM + ALB	14,464,244	3.4%	5	1/1/1/0
30-50% targeted						
Dominican Republic	*Culex*	DEC + ALB	249,803	1.3%	6	2/2/1/0
Guyana	*Culex*	DEC + ALB	690,869	0.6%	2	2/2/1/0
Indonesia	*Culex*	DEC + ALB	113,283,453	1.2%	7	2/2/1/0
Myanmar	*Culex*	DEC + ALB	41,666,403	0.8%	9	2/2/1/0
Timor Leste	*Anopheles*	DEC + ALB	1,180,067	2.9%	3	2/2/1/0
United Republic of Tanzania	*Culex*	IVM + ALB	45,173,251	3.0%	11	2/2/1/0
20-30% targeted						
Bangladesh	*Culex*	DEC + ALB	77,230,000	1.2%	14	3/3/1/0
Benin	*Anopheles*	IVM + ALB	3,747,913	2.7%	11	3/3/1/0
Guinea Bissau	*Anopheles*	IVM + ALB	1,582,496	2.4%	1	3/3/1/0
Malaysia	*Anopheles*	DEC + ALB	1,266,123	1.7%	7	3/3/1/0
Nigeria	*Anopheles*	IVM + ALB	108,526,381	2.8%	5	3/3/1/0
<20% targeted						
Brazil	*Culex*	DEC	1,700,000	0.9%	4	4/4/1/0
Ethiopia	**Culex*	IVM + ALB	30,000,000	2.6%	4	4/4/1/0
Kiribati	*Culex*	DEC + ALB	103,058	1.5%	5	4/4/1/0
Madagascar	*Anopheles*	DEC + ALB	18,602,379	2.8%	6	4/4/1/0
Micronesia	*Aedes*	DEC + ALB	11,241	0.1%	1	4/4/1/0

| Papua New Guinea | *Anopheles* | DEC + ALB | 5,602,188 | 2.2% | 1 | 4/4/1/0 |
| Senegal | *Anopheles* | IVM + ALB | 5,314,600 | 2.9% | 3 | 4/4/1/0 |

*Treatment durations for *Culex* spp. were used for countries in which primary vector species was unknown.

ᵅTreatment assumed to occur once annually using diethylcarbamazine citrate (DEC) and albendazole (ALB), or in areas co-endemic with onchocerciasis, ivermectin (IVM) and albendazole (ALB)

¤ Preventive Chemotherapy Databank Lymphatic Filariasis [Internet]. WHO. 2015 [cited 2015 January 20]. Available from: http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/.

¥ United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP.227.

± Refers to MDA schedules assumed to be used by these countries for the purposes of our analysis, for the global elimination scenario, eradication I, eradication II, and eradication III scenarios, respectively. In schedule I, two deciles (20%) of the at-risk population are added to the MDA schedule annually. In schedule II, one decile is added annually. In schedule III, one decile is added every 2 years, and in schedule IV, one decile is added every 3rd year (see: Rate of Scale-Up and History of Control).. '0' refers to instantaneous scale-up.

3.4.1   Scenario Development

Scenarios were developed by first reviewing the WHO preventive chemotherapy (PCT) databank to assess progress made towards LF elimination as of 2012 [12]. The scenarios were further refined, with key assumptions agreed upon in a series of technical advisory group meetings, including stakeholders from WHO, Centers for Disease Control and Prevention (CDC), funders, pharmaceutical companies, and program managers from endemic countries.

In the global elimination scenario, countries that have not yet started will not start, and countries that have started continue according to their assigned level of scale-up (see: *Rate of Scale-Up*). In the eradication I scenario, countries that have already started MDA continue as in the global elimination scenario and countries that have not yet started implement MDA following an 'average' level of scale-up. The eradication II scenario represents the case in which all countries scale-up MDA more quickly (fast). Eradication III serves as the 'best case' scenario, whereby all endemic countries provide MDA to their entire at-risk populations immediately. Thus, this analysis provides insight into the differences in the amount of time and treatments required to extend elimination efforts to all endemic countries (eradication I), increase MDA intensity (eradication II) and, most ideally, scale-up instantaneously (eradication III).

3.4.2   Assumptions Regarding Interventions and Loiasis Co-Endemicity

An important assumption underlying this study is that annual MDA using DEC with albendazole, or, in onchocerciasis-endemic countries, ivermectin and albendazole, will be sufficient to reduce circulating mf enough to interrupt the transmission cycle of LF if maintained for an appropriate number of years. Therefore, hardly predictable features that could undermine success, including systematic non-compliance with MDA, but particularly events such as civil unrest and humanitarian emergencies (e.g. earthquakes in Haiti and Nepal; Ebola epidemic in West Africa) that could compromise the health system's capacity, could not be accounted for. We also assume that countries undertake MDA without interruption.

Administration of ivermectin to communities with high prevalence (>40%) of L. loa is contraindicated, as the microfilaracidal actions of the drug poses an unjustifiably high risk of causing severe adverse events. As such, the WHO provisionally recommends the LF program to instead treat these areas with albendazole monotherapy distributed bi-annually and vector control [71]. Here we assume that this strategy will be equally efficacious as annual albendazole-ivermectin, and thereby assume the number of years of MDA required in areas co-endemic with *L. loa* to be equivalent to the number of years required with albendazole-ivermectin.

3.4.3   Rate of Scale-Up and History of Control

The GPELF advises LF endemic countries to conduct MDA for 4-6 years [9]. This duration only holds at a country level if all endemic areas are treated simultaneously. To incorporate scaling-up of geographic coverage for each scenario, we divided each country's at-risk population into deciles, and assumed MDA to start in subsequent deciles after varying durations according to four schedules of scale-up. In schedule I (fast), 20% of the at-risk population is added to the MDA schedule annually. In schedule II (average), one decile is added each year, in schedule III (slow) one decile is added every two years and in schedule IV (very slow) this period is three years.

In the global elimination scenario, scale-up is based upon the proportion of the at-risk population each country previously targeted. In order to be allocated to schedule I, the at-risk population targeted in the most recent round of MDA had to exceed 50%. Schedule II has been assigned to countries previously targeting 30-50%, schedule III to those targeting 20-29.9%, and schedule IV to those targeting <20%. Rather than attempting to recreate the progress of each country exactly, we used these categories to incorporate a range of scale-up levels encountered. Previous progress made towards local elimination was further taken into account by counting the number of previously effective years of MDA, which was considered as any year in which program coverage

within the targeted area (regardless of the at-risk population targeted) exceeded 65%. We then subtracted the number of effective years previously achieved from the number of years of MDA deemed necessary (see below: Transmission Archetypes; Table 5) in order to determine the number of years of MDA remaining.

3.4.4   Delays

For all scenarios, we assume that countries that have finished mapping but not begun MDA have a 1-year delay, whereas countries that have not completed mapping nor begun MDA have a 4-year delay. While countries face challenges of different magnitudes and require different durations to map, the 4-year delay assumed corresponds to the average number of years that mapping took in countries with available data to support the calculation [12].

3.4.5   Prevalence Data

To account for heterogeneity in transmission intensity within countries, we obtained paired baseline circulating filarial antigenemia prevalence, measured through immunochromatographic test (ICT), and mf prevalence data from sentinel site surveys from program countries across the AFRO region. As specified by the WHO, these surveys involve collecting fingertip blood, between 10 p.m. and 2 am. from at least 300 participants aged five years and above [72]. We gained additional access to ICT prevalence data from mapping studies in 17 African countries. The relationship between mf and ICT prevalence was estimated using the non-parametric regression proposed by Passing and Bablock, which assumes linearity and uncertainties in both variables [73]. The regression equation calculated from the paired prevalence data was then used to infer mf prevalence from the ICT mapping data.

We determined the percentage of the at-risk population that fell into prevalence quartiles: <5%, 5-10%, 10.1-15%, >15%, for each country that provided district level prevalence data. To account for uncertainties in this approach, we took 500 random draws from a multinomial distribution with probabilities based on weighted averages from the dataset and assumed these to be the possible ranges of pre-intervention prevalence distributions for all countries in our analysis.

3.4.6   Transmission Archetypes

It has been theoretically demonstrated that the required duration of MDA is region-specific and dependent on various factors, including drug regimen and level of coverage, vector species, and pre-intervention transmission intensity [74-76]. In order to broadly capture the heterogeneous transmission patterns of LF, we defined transmission archetypes (Table 5). In addition to prevalence levels and drug regimens, we accounted for differences in transmission between *Anopheles* spp. and

Culex spp., which notably differ in their mf-density dependent likelihood of becoming infected [77]. Predicting regional anopheline- or culicine-mediated LF transmission has been shown to require different model formulations and parameterizations [78]. For our analysis we made several simplifications: we assumed transmission of *W. bancrofti* by *Aedes* spp. was similar to transmission efficacy by *Culex* spp., while transmission of *Brugia* spp. was assumed to be comparable to *W. bancrofti* transmission by *Anopheles* spp. Where the primary vector was unclear, infection by *Culex* spp. was assumed in order to avoid underestimating the number of MDA rounds required.

Table 5: Estimates of the number of annual MDA rounds needed to reach local LF elimination by transmission archetypes, based on sets of 500 simulations using EpiFil and assuming 85% coverage.

Primary vector	Treatment[α]	Baseline MF prevalence			
		5%	10%	15%	20%
Anopheles spp.	DEC + ALB	6	6	7	7
	IVM + ALB	7	9	11	11
Culex spp.	DEC + ALB	9	10	11	11
	IVM + ALB	11	13	15	15

[α]Treatment assumed to occur once annually using diethylcarbamazine citrate (DEC) and albendazole (ALB), or in areas co-endemic with onchocerciasis, ivermectin (IVM) and albendazole (ALB)

The number of rounds corresponds to the minimum at which at least 97.5% of simulations went to elimination.

3.4.7   Modeling the Number of MDA Rounds Required to Reach Local Elimination

The duration of MDA required to eliminate LF was predicted for the transmission archetypes using a deterministic model of LF transmission, EpiFil [15]. The model used for the current analysis has been described in detail, validated against multiple data sets for both transmission settings with *Anopheles* spp. and *Culex* spp., and used extensively to predict LF intervention outcomes [15,47,49,79]. Details on model structure, equations, and the approach to obtaining parameter estimates are provided in Supplementary material 1.

For all transmission archetypes, we ran 500 simulations of once-yearly MDA of varying total durations, drawing from a range of parameter estimates. The lowest number of rounds at which the 95th percentile range of the simulations resulted in an mf prevalence below 1% 50 years after the start of the MDA program was taken as a conservative measure of the number of rounds required to ensure elimination.

3.4.8   Calculating the Number of Future Treatments Required

Population at-risk figures were taken from the WHO PCT database for 2012 and adjusted for population growth using country-specific 2012 United Nations estimates [12,80]. MDA coverage rates were assumed to be 85% for all countries. Except for areas co-endemic with *L. loa*, treatments are assumed to occur annually.   Based on the pre-intervention prevalence distributions, we developed 500 estimates of the number of treatments needed for each country and scenario. Results are reported as the mean number of treatments by region and scenario, along with 95% credible intervals.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

3.5   Results

Our results indicate that interrupting LF transmission in all countries by 2020 is unlikely, though if MDA is drastically scaled-up and expanded, the final round of MDA to eradicate LF could be carried out by 2028 (eradication III; Figure 4). If scale-up continues at the current rate, as modeled in our global elimination and eradication I scenarios, the last round of MDA will not be given until 2050, largely due to slow scale-up in areas where transmission occurs through *Culex* spp. The eradication II scenario reaches the last round of MDA by 2032. As this scenario assumes that all countries add 20% of their at-risk populations to MDA annually, the last countries to reach local elimination are those that were delayed due to mapping, and whose vector and treatment combination included *Anopheles* spp. and ivermectin or *Culex* spp. and DEC, including: Angola, Chad, the Democratic Republic of Congo, South Sudan, Sudan, Zambia, and Zimbabwe. Figure 5 provides a visual representation of the impact different intensities of scale-up and expansion have on time to reach local elimination for each country.

Figure 4: Cumulative number of treatments by year

Figure 5: Maps depicting the final year of MDA per country for the four scenarios

Since the scenarios take into account population growth, rapid scale-up of MDA also decreases the number of treatments required. As depicted in Figure 6, the eradication III scenario initially requires substantially more treatments, but by 2024, the treatments under this scenario are projected to be less than that required under all other scenarios. The global elimination scenario is projected to

require approximately 3,409 million treatments (95% CI: 3,185m–3,538m). Expanding the program to all endemic countries will increase the number of treatments to 4,666 million (95% CI: 4,419m–4,904m). Scaling-up MDA more rapidly, as under the eradication II scenario, results in savings of nearly 300 million treatments compared to the eradication I scenario. Under the most optimistic scenario (eradication III), eradication could be achieved with 4,159 million treatments (95% CI: 3,924m–4,382m). As shown in Figure 4, this represents nearly 750 million treatments more than the global elimination scenario but 210 million treatments less than the intensified eradication scenario (eradication II). Owing to the largest burden, the AFRO region requires the majority of treatments, followed by Southeast Asia. With the shift from global elimination to eradication, the number of treatments required in the Eastern Mediterranean region increases by more than 380 fold due to treatments required for Sudan, which is not considered under the elimination scenario (Table 6).

Figure 6: Incremental treatment projections by year (elimination as comparator)

Table 6: Projected treatment needs (in millions) by WHO region with 95% credible intervals

	Global Elimination (comparator)	Eradication I	Eradication II	Eradication III
AFRO	2,117 (2,011–2,223)	3,202 (3,048–3,355)	2,930 (2,788–3,074)	2,746 (2,605–2,889)
SEAR	1,148 (1,102–1,190)	1,148 (1,102–1,190)	1,141 (1,096–1,183)	1,139 (1,096–1,181)
WPR	109.3 (104.5–114.0)	109.7 (104.9–114.4)	100.1 (95.6–104.7)	98.55 (94.25–102.94)
AMR	34.66 (33.07–36.27)	34.66 (33.07–36.27)	33.43 (31.87-35.00)	33.10 (31.60–34.62)
EMR	0.3729 (0.3380–0.4095)	173.0 (165.2–180.9)	164.1 (156.6–171.5)	142.0 (134.2–150.2)
Total	3,409 (3,185–3,538)	4,667 (4,419–4,904)	4,369 (4,133–4,594)	4,159 (3,924–4,382)

3.6   Discussion

As not all LF endemic countries are considered under the global elimination (comparator) scenario, any eradication campaign will require a massive increase in treatments. However, if LF is to be eliminated in all endemic countries, then rapid scale-up as soon as possible will lead to increased savings – both in terms of time and treatments. Accelerated MDA may also propel the program towards success, as risk of failure (due to lapses in funding, donor fatigue, or occurrence of calamitous events) potentially increases with extended program duration [81]. It is conceivable that a decrease in program duration may also decrease the likelihood of drug resistance evolution [56].

Noticeably missing from our analysis is India. While India has the greatest burden of LF [4], it has made substantial progress against the disease, having distributed nearly 3.5 billion antifilarial treatments since 2001 [12]. As such, our model suggests that further rounds may not be necessary for India. However, previous studies have found pockets of systematic non-compliance in India, leading to MDA coverage in those areas to fall below effective coverage [82]. It is therefore possible that transmission of LF may still occur in India. However, in order to remain consistent in our approach, and in recognizing that to provide global estimates we cannot take into account all eventualities, additional treatments for India have not been considered.

We sought data from a number of diverse sources. Due to the inherent structure of the LF program, however, our analysis relies heavily on data that have been collected and reported directly by each country. While this arrangement raises a number of issues, discrepancies in the data could also decrease the validity of our estimates. Inconsistencies in coverage data may affect the number of years required to interrupt transmission, while inaccuracies in at-risk estimations would directly impact the number of treatments projected to reach our scenario endpoints. Whether these issues would result in underestimates or overestimates is dependent upon the direction and magnitude of the error.

While we avoided underestimating scale-up potential through our eradication III scenario, it is possible that we overestimated the capacity of some countries to scale-up. It is possible that we also overestimated the effectiveness and ability to proceed with rapid scale-up in areas co-endemic with *L. loa*. While WHO has provisional guidelines for dealing with LF and *L. loa* co-endemicity, no such areas have been broadly targeted for LF elimination as yet, and thus the effectiveness and feasibility of the strategy remains unclear. At the same time, the mass distribution of long-lasting insecticidal nets (LLINs) in many malaria endemic sites is likely to have a large impact on LF transmission by anophelines [36,83]. Because the impact remains difficult to quantify, and uncertainty remains regarding the duration LLINs have to remain in place, we have not included this here. The time and treatment estimates in this study are based on data and model formulations and parameterizations currently available to the authors. Many of the assumptions and simplifications inherent to our scenarios are in need of closer investigation. Ideally, models would be fit to specific transmission settings within and between countries, as parameter values have been shown to differ by region [47]. Other aspects equally deserving of more attention, but likewise beyond the scope of this project, are the effectiveness of twice-yearly albendazole in concert with vector control for areas co-endemic with *L. loa*, and the consequences of mid-program delays, [84,85]. Care should thus be taken when interpreting these results, particularly at a country-specific level.

Our duration estimates are considerably longer than those proposed under the GPELF, which envisages all endemic countries to reach full geographic coverage by 2016, with post-MDA surveillance in all countries anticipated by 2020 [40]. While this level of scale-up is similar to that proposed under our eradication III scenario, we project the last round of MDA to occur nearly a decade later, in 2028. This divergence arises from differences in the assumed number of rounds of MDA required to interrupt transmission. Depending on baseline prevalence and vector-treatment combinations, our model estimates interruption in transmission to occur after 6-15 rounds of MDA (Table 4). In contrast, the GPELF assumes five years of MDA in all areas [40]. It is worth noting that the durations in this study represent a potentially conservative measure, as they were based on the 95th percentile range of simulations leading to elimination, accounting for the uncertainty in our parameter estimates. This measure was taken to represent the time that could guarantee elimination with a reasonable level of certainty, but does not preclude that shorter durations may be sufficient in many areas. However, the discrepancy between predicted MDA durations and those advocated by GPELF was also evident in previous estimates with both deterministic and stochastic LF transmission models [50]. While aggressive goals for disease elimination and eradication potentially propel campaigns forward, overly optimistic projections could stifle innovations and further investment, ultimately hindering the initiative.

This study adds to the growing body of evidence on the feasibility of eliminating LF. While our estimates suggest more time may be needed to reach LF elimination than what is currently projected, the treatment estimates for our scenarios represent 66-89% of that which has already been distributed under the GPELF. Thus, our analysis indicates that with continued commitment, eliminating LF is within reach.

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Figures

Figure 4: Cumulative number of treatments by year
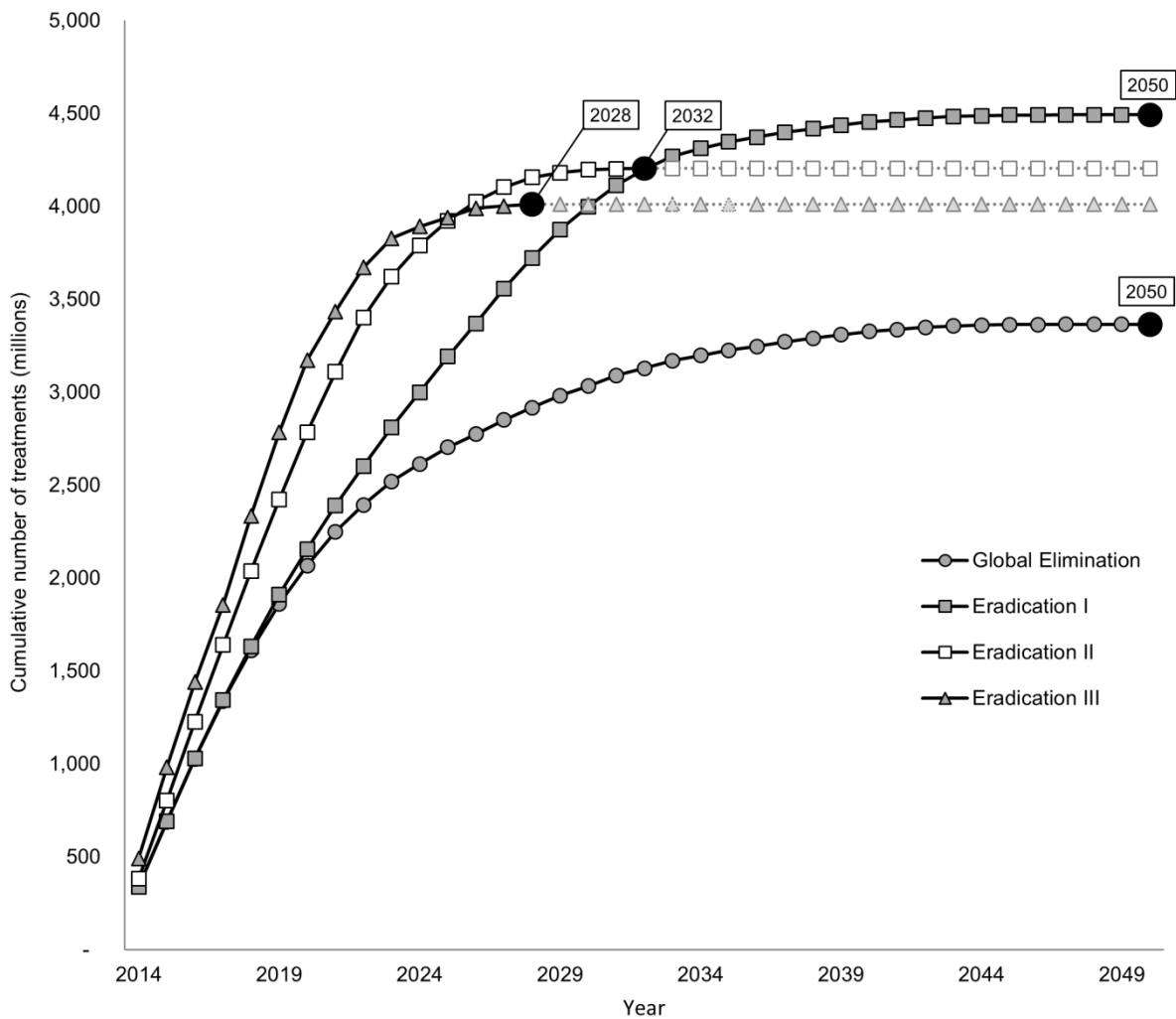
The line with circular markers represents the global elimination (comparator) scenario. As highlighted in the text boxes, both the global elimination and eradication I scenario are estimated to conclude MDA after 37 years of MDA. Eradication II, the intensified scale-up scenario, sees the last round of MDA to occur by 2032, after 19 years of MDA. Eradication III is estimated to require 15 years of MDA, concluding in 2028.

Figure 5: Maps depicting the final year of MDA per country for the four scenarios
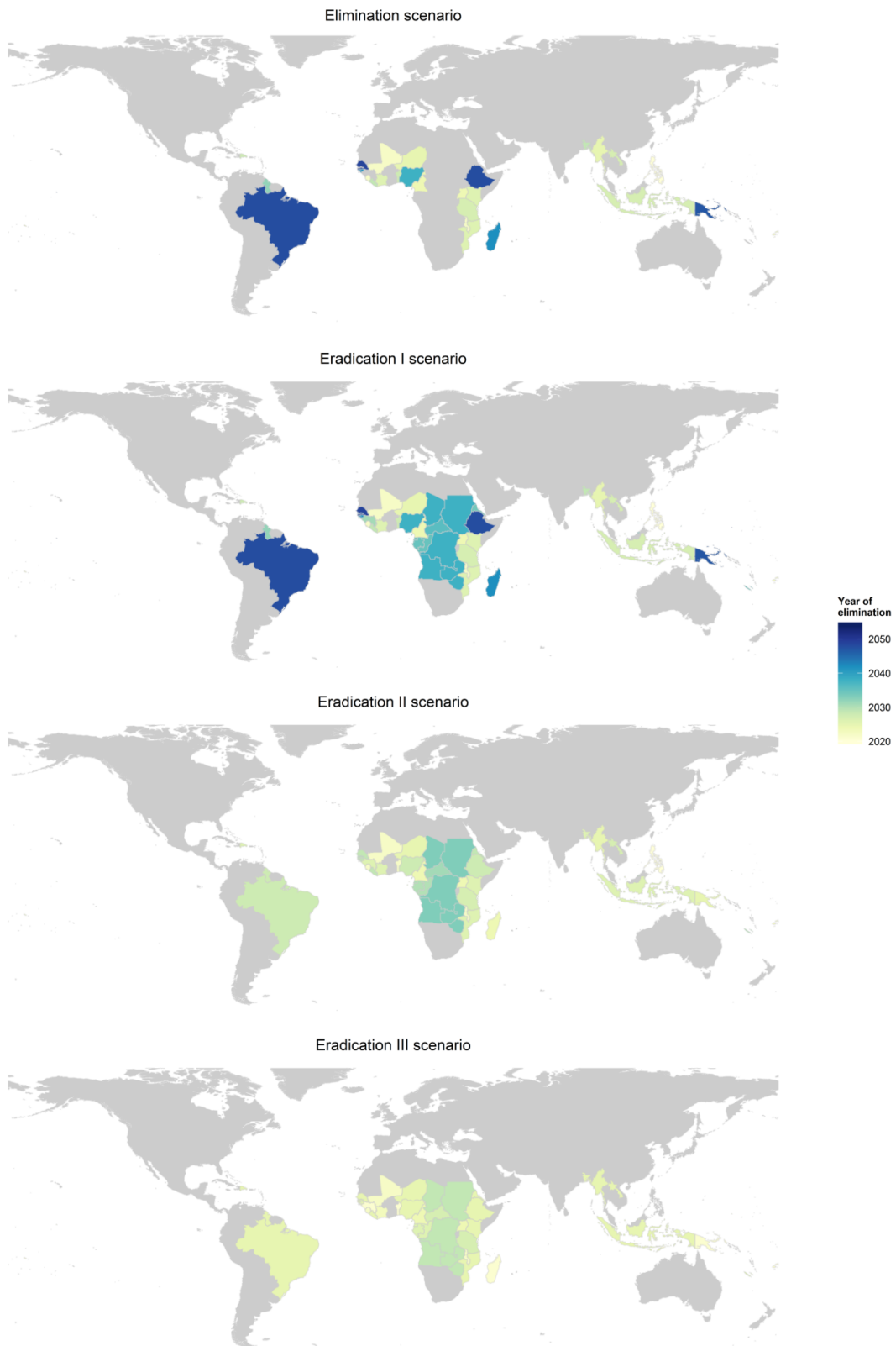
The global LF elimination scenario does not include countries that have not yet begun MDA.

Figure 6: Incremental treatment projections by year (elimination as comparator)
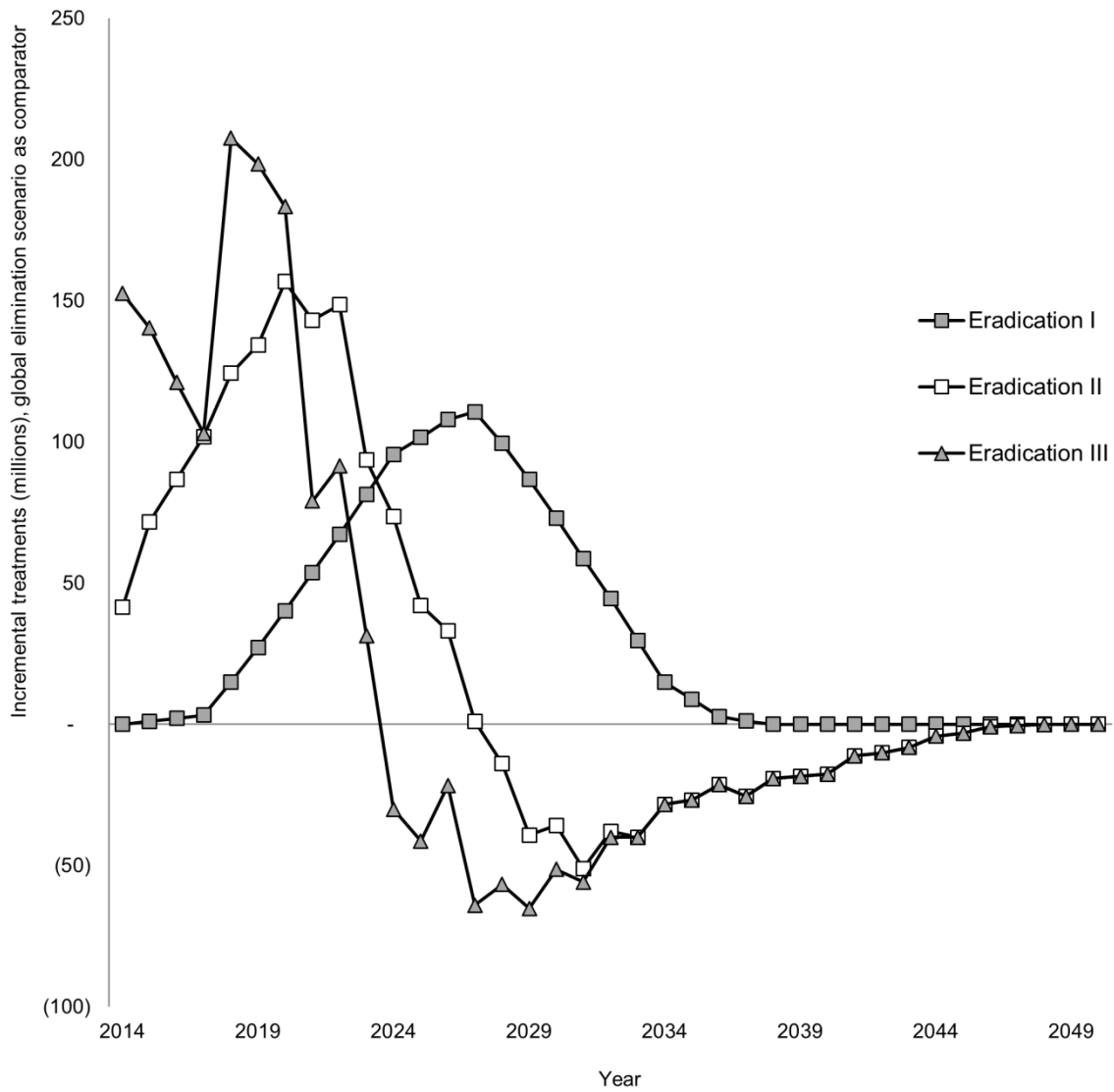
All eradication scenarios see an increase in the number of treatments after 4 years as the result of the imposed delay for countries that have not previously finished mapping or begun MDA. By 2024, the eradication III scenario requires less treatments than the global elimination (comparator) scenario, and from 2028, the eradication II scenario is also projected to require fewer treatments than elimination.

4   How much will it cost to eradicate lymphatic filariasis? An analysis of the financial and economic costs of intensified efforts against lymphatic filariasis

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4.1   Abstract

Introduction

Lymphatic filariasis (LF), a neglected tropical disease (NTD) preventable through mass drug administration (MDA), is one of six diseases deemed possibly eliminable. Using previously developed scenarios and treatment projections, we present the projected financial and economic costs of global elimination and eradication.

Methodology/Key Findings

Costing was undertaken from a health system perspective, with all results expressed in 2012 US dollars. A discount rate of 3% was applied to calculate the net present value of future costs.

Prospective NTD budgets from LF endemic countries were reviewed to preliminarily determine activities and resources necessary to undertake a program to eliminate LF. In consultation with LF program experts, activities and resources were further reviewed and a refined list of activities and necessary resources, along with their associated quantities and costs, were determined and grouped by activity: advocacy, capacity strengthening, coordination and strengthening partnerships, data management, ongoing surveillance, monitoring and supervision, drug delivery, and administration. The cost of mapping and undertaking transmission assessment surveys have also been incorporated into the financial estimates. The value of donated drugs as well as volunteer time of the community drug distributors were combined with the financial costs to determine the economic costs.

The elimination scenario, which includes countries that previously undertook MDA, is estimated to cost 929 million USD (884m-972m). Proceeding to eradication is anticipated to require a higher financial investment, estimated at 1,235 million USD (1,172m-1,300m) in the eradication III scenario (immediate scale-up), with eradication II (intensified scale-up) projected at 1,274 million USD (1,209m-1,331m), and eradication I (slow scale-up) estimated at   1,289 million USD (1,227m-1,340m). The economic costs of the eradication III scenario are estimated at approximately 7.57 billion USD (7.12bn-7.94bn), while the global elimination scenario is projected to have an economic cost of 5.21 billion USD (4.91bn-5.45bn). Countries in the AFRO region will require the greatest investment to reach global elimination or eradication, but also stand to gain the most in cost savings. Across all scenarios, capacity strengthening and advocacy represent the greatest financial costs, whereas strengthening partnerships, data management, mapping, post-MDA surveillance, and administration comprise the least.

Conclusions/Significance

Though challenging to implement, our results indicate that financial and economic savings are greatest under the eradication III scenario. Thus, if eradication for LF is the objective, accelerated scale-up is projected to be the best investment.

4.2   Author Summary

Lymphatic filariasis (LF) is a neglected tropical disease (NTD) that is thought to be potentially eradicable through once yearly mass drug administration (MDA) using drugs that are currently donated to LF endemic programs by the drug manufacturers. MDA has been proven to be a cost-effective and efficient method of disease control, both for LF and other NTDs. Previously, we developed scale-up scenarios of varying magnitude to reach global elimination (elimination of LF in all countries that have previously undertaken MDA) and eradication (local elimination of LF in all LF endemic countries) and determined the number of associated treatments that would be necessary in each country in each scenario. Here we project the costs – both financial and economic – of each of these scenarios. We use data from a myriad of sources to determine the cost of various activities, and found that training and advocacy activities comprise the bulk of the expenditure necessary. Among all scenarios, global elimination requires the least total investment. However, in terms of LF eradication, faster rates of scale-up is associated with a decrease in costs.

4.3   Introduction

Neglected tropical diseases (NTDs) are a heterogeneous group of helminthic, bacterial, viral, fungal and protozoan infections that cause chronic and debilitating disability [19]. However, research and development to combat NTDs have notoriously been underfunded [86]. NTDs persist in areas where access to clean water, hygienic conditions, and health care are limited. As such, they are most prevalent in low-income countries [19]. Indeed, more than 70% of countries with endemic NTDs are classified as low-income or lower middle-income economies [87]. Infection with an NTD may affect cognitive and physical development and can result in permanent physical disability. Therefore, NTDs do not just coexist in poverty, they further propagate the cycle of poverty by hindering economic potential [20,21].

Lymphatic filariasis (LF), an NTD, can result in irreversible and incapacitating disability, most often manifested as elephantiasis, lymphedema, and hydrocele [9]. With more than a billion people at-risk and 120 million people thought to be infected across 73 countries [26], LF is estimated to account for 2.74 million disability-adjusted life years (DALYs) (1.73m-4.00m)[4]. When incorporating the mild and moderate depression associated with LF-related disability, the health burden due to LF may be upwards of 5 million DALYs [28].

However, LF is inefficiently transmitted, with an estimated 15,500 infective mosquito bites thought necessary to generate one transmittable infection [38]. LF is also preventable through once yearly treatment with antifilarials distributed through mass drug administration (MDA) [9]. This, coupled with the fact that LF does not have a significant animal reservoir, led the International Task Force on Disease Elimination to classify LF as a potentially eradicable disease [8,39]. In response, the World Health Organization (WHO) began the Global Program to Eliminate LF (GPELF), which aims for the global elimination of LF by 2020 [9]. In the fifteen years since the inception of the GPELF, great progress against LF has been made, with more than five billion antifilarial treatments distributed in 58 endemic countries [12].

Successfully eradicating a disease has innumerable long-term health benefits, and is also a classic example of a global public good [58,70,88]. Eradicating an NTD, like LF, has additional societal benefits, including improvements towards equity, fairness, and social justice [22]. However, disease elimination and eradication initiatives require substantial social and political commitments, as well as significant financial and economic investments. Given the increasingly intense competition for global health resources, the decision on where to invest funds needs to be based upon solid evidence [62]. This is particularly the case for investments and commitments made on a global

scale. In order to provide evidence to decision makers about the investment required to globally eliminate and eradicate LF, we used a micro-costing approach to analyze the financial and economic costs of interrupting LF transmission in all endemic countries under varying levels of MDA intensity, as well as the subsequent costs of conducting post-MDA surveillance.

4.4 Methods

4.4.1 Scenarios

We previously developed scenarios to reach global elimination (elimination of infection in countries that have previously undertaken MDA) and eradication (elimination of infection in all endemic countries) of LF, taking into account previous progress made under the GPELF, pre-intervention prevalence levels, and possible delays in program implementation. The global elimination scenario maintains the current geographic expansion and rate of MDA scale-up as seen under the GPELF, and thus serves as the comparator scenario. The eradication scenarios were developed to assess the impact of expanding MDA to all endemic countries at an average level of scale-up (eradication I), intensifying efforts against LF (eradication II), and treating all endemic populations immediately (eradication III). Key components inherent in each scenario are outlined in Table 7 and a full explanation of all the scenario can be found in Chapter 3.

Table 7: Key features of the proposed scenarios for global elimination and eradication of LF

	Global Elimination (comparator)	Eradication I	Eradication II	Eradication III
Intervention	Annual MDA*	Annual MDA*	Annual MDA*	Annual MDA*
Coverage rate	85%	85%	85%	85%
Start year	2014	2014	2014	2014
Countries considered	All LF endemic countries that have previously conducted MDA¥	All LF endemic countries¥, including all countries co-endemic for *L. loa*	All LF endemic countries¥, including all countries co-endemic for *L. loa*	All LF endemic countries¥, including all countries co-endemic for *L. loa*
Rate of scale-up	Countries with previous MDA continue at same rate as historically	Countries with previous MDA continue at same rate as historically, countries without previous progress begin at 'average' rate (10% of at-risk population added to MDA schedule annually)	All countries add 20% of their at-risk populations to MDA schedule annually	All countries treat 100% of their at-risk populations annually
Estimated final year of MDA	2050	2050	2032	2028
Number of treatments necessary (millions)	3,409 (3,185-3,538)	4,667 (4,419-4,904)	4,369 (4,133-4,594)	4,159 (3,924-4,382)

*Except in areas where L. loa prevalence exceeds 40%.
¥Assuming country requires MDA

4.4.2   Timeframe and number of treatments required

To determine the duration of MDA required for the different drug regimens, vector species, and pre-intervention prevalence levels, we used EpiFil [15], a deterministic model of LF transmission. The amount of time and number of treatments required to reach the endpoints in each scenario are detailed in Chapter 3. Briefly, we considered the number of MDA rounds that each country had previously achieved a programmatic coverage of at least 65% (the minimum coverage necessary to be considered effective) between 1999 and 2012. Next, we subtracted the number of rounds of MDA required to reach local elimination from the number of previously effective years. Assuming once-annual MDA (aside from areas co-endemic with hyper Loaisis; see: *Assumptions about L. loa endemic areas*), we then determined the number of future treatments needed for each country

under each scenario, accounting for the number of people at-risk, country-specific growth rates, duration of MDA necessary, historical rates of scale-up, and previous progress towards local elimination. By assuming that the populations at-risk for LF increase exponentially with population growth rates, scenarios with longer durations were also assumed to require more treatments (Table 7).

4.4.3   Approach used for costing

To assess how much governments and donors would need to invest in order to implement the GPELF strategy to reach the global elimination and eradication of LF, we adopted a micro-costing, bottom-up approach from the perspective of the health system of each LF endemic country. In contrast to gross-costing, which assesses average level costs from the top down, micro-costing may improve the accuracy of results by capturing resources and costs at the unit level [89].

The costs associated with each scenario have been assumed to begin in the year 2014 and run until the final post-MDA transmission assessment survey (TAS) has been completed in each country under consideration. All results are listed in 2012 US dollars (USD) and, in the baseline analysis, future costs were discounted at 3%. One-way sensitivity on discount rates and probabilistic sensitivity analyses for all costing and quantity parameters were also explored.

4.4.4   Data

Line items from USAID's *NTD Master Plan Costing Tool in the African Region* for Benin, Cameroon, Democratic Republic of Congo, Eritrea, Guinea, Madagascar, Niger, Senegal, and Sierra Leone ranging from January 2011 to April 2012 were reviewed to preliminarily determine essential activities and associated resources necessary for a country to successfully undertake a program to eliminate lymphatic filariasis (PELF). In consultation with key LF implementers from the PELF in Uganda, which has successfully been carrying out the GPELF MDA strategy since 2002 [12], all activities and resources were further reviewed and a refined list of core activities, necessary personnel, components, and resources, along with their associated costs, were ascertained.

4.4.5   Activities considered

We took into account the cost of advocacy; capacity strengthening; coordination and strengthening partnerships; mapping; data management; administration; ongoing surveillance; monitoring, evaluation, and supervision; drug delivery; and post-MDA transmission assessment surveys (TAS). As described below, the costs of increased surveillance in areas with meso *L. loa* prevalence, as well as the added expenditure of biannual MDA in hyper loaisis areas were also accounted for.

Advocacy was assumed to include the development and distribution of educational messages, as well as community meetings and sensitization activities with district and community leaders, sub-county and parish supervisors, and community drug distributors (CDDs). Capacity strengthening comprised trainings on MDA procedures for national trainers, district trainer of trainers, sub-county and parish supervisors, community leaders, CDDs and teachers. Trainings for monitoring sentinel and spot check sites as well as trainings for M&E officers were also considered under capacity strengthening. Conference attendance and international exchanges, cross-border meetings for regional strategies towards controlling NTDs, NTD secretariat meetings, and technical committee meetings were assumed under coordination and strengthening partnerships. Data management included all activities involved with the acquisition and distribution of MDA data, including cleaning, entering, and analyzing. The maintenance of sentinel sites – including equipment for administering microfilaria (mf) surveys and internal quality control tests – as well as the administration of sentinel and control site impact assessment surveys, associated data collection, and survey feedback meetings were grouped under ongoing surveillance. M&E included the supervision of MDA activities, monitoring for severe adverse events (SAEs), and regular feedback meetings at the district and national level. Drug delivery involved drug transport from the central stores to district stores and then onward to parish supervisors. Supplies to CDDs, including t-shirts and stationary, were also accounted for under drug delivery. Administration included overhead costs, the maintenance of office space, salaries to LF staff, and the procurement of necessary equipment.

Mapping and TAS were assumed to include a preliminary visit, Immunochromatographic card test (ICT) testing, data collection, and feedback meetings. The cost of mapping was included for any country that, as of 2012, had not yet completed mapping nor started MDA. In order to determine the costs of post-MDA surveillance on a global level, all TAS have been assumed to be school-based. Moreover, TAS have been assumed to occur in each district (see *Determination of resource quantities* for assumptions about district size) after the final estimated round of MDA (as determined through earlier modeling exercises) and twice thereafter at three year intervals. The number of TAS conducted has thus been assumed to vary by the number of districts achieving the specified number of MDA rounds, though the quantities of resources required for each individual TAS was assumed to remain constant.

Assumptions about *Loa loa* endemic areas

Previous studies indicate that individuals harboring more than 30,000 *L. loa* microfilaria per milliliter of blood are put at unacceptably high risk of developing severe adverse events (SAEs) if administered ivermectin or DEC [13,90,91]. As *L. loa* prevalence within a community has been shown to have a

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close correlation with individual *L. loa* mf density, provisional GPELF guidelines recommend communities endemic with LF that also have a *L. loa* prevalence greater than 40% be treated with bi-annual MDA using albendazole monotherapy coupled with vector control [71].

Mapping studies to determine areas of co-endemicity between LF and *L. loa*, however, are not yet complete. While we recognize that not all populations at-risk for *L. loa* are also at-risk for LF, for the purposes of this study, we make the assumption that the percentage of mapped areas from RAPLOA studies that were found to have 20-39.9% (meso) or >40% (hyper) *L. loa* prevalence corresponds directly to the percentage of the population in these countries also at risk for LF [12,92]. In assessing the costs for undertaking the LF program in these areas, we further assume the cost of vector control to be covered by other initiatives. In line with the provisional recommendations, we assume that the population of people living in hyper-endemic areas will receive bi-annual albendazole through MDA. Financially, this is assumed to double the costs of data management and drug delivery in these areas. For populations in meso-endemic regions of *L. loa*, once yearly albendazole and ivermectin is still presumed. In areas of both hyper and meso *L. loa*, the costs associated with monitoring for SAEs are assumed to increase two-fold.

4.4.6   Determination of resource quantities

In line with the approach for assessing necessary activities, quantities and duration of use for each required component were established through consultation with key members from the Ugandan PELF team. Aside from program activities with inherently fixed costs, budgeted line items were assumed to vary linearly by the size of the population to be treated (see below: *Timeframe and number of treatments required*). In the baseline analysis, we have assumed that the number of resources required to carry out the PELF for a certain population in Uganda is relatively similar to the number of resources required to carry out the program for a population of similar size in other LF endemic countries. As MDA in Uganda is implemented at a community level, the amount of resources and duration of activities required to successfully complete the PELF in Uganda are generally organized by district, sub-county, and village units. In order to standardize the at-risk population falling into the different administrative divisions across all LF endemic countries, the average number of people at-risk for LF in each district, sub-county, and village were determined for Uganda and then assumed for all LF-endemic countries.

4.4.7   Determination of financial costs

Using detailed expenditure budgets from the Ugandan PELF as a reference, unit costs for other LF endemic countries were estimated by adjusting for country-specific comparative price levels (i.e.,

purchasing power parity (PPP) adjusted exchange rates) for all local, non-tradable goods and services [93]. Tradable goods were assumed to already be at market value and were thus left unadjusted. Retail prices from established vendors were used for tradable goods, including laboratory supplies and capital items. The WHO CHOICE database was used for unit costs which were unable to be determined elsewhere, as well as for salaries of LF personnel, including: the NTD director, LF program manager, administrative assistant, finance officer, data manager, and supplies manager [16]. As the African Program for Onchocercaisis Control (APOC) uses a strategy similar to that employed by the GPELF [94], line items in our study were validated against similar line items found in APOC approved budgets. Table 8 provides a list of the primary activities considered in calculating the financial costs, as well as the average cost per district in the base case.

Table 8: Average costs per district, base case

Activity	Average costs per district (standard deviation)
Advocacy	
Community meetings	$8,946.96 ($686.11)
Social mobilization – District leaders	$469.95 ($18.30)
Social mobilization – Sub-county supervisors	$256.39 ($20.12)
Social mobilization – Parish supervisors, CDDs, community leaders	$8,821.35 ($753.30)
Workshop for creating messages	$5.61 ($0.22)
Dissemination of health messages	$916.44 ($54.62)
Capacity Strengthening	
Training national trainers, MDA and M&E	$14.31 ($0.54)
Training of district Trainers of trainers, MDA and M&E	$800.35 ($31.22)
Training of sub-county supervisors, MDA and M&E	$754.87 ($50.60)
Training of parish supervisors and community leaders, MDA and M&E	$20,991.65 ($2,141.29)
Training of CDDs	$15,848.40 ($1,655.98)
Training of teachers	$4,748.92 ($520.45)
Training for monitoring sentinel and spot check sites	$690.36 ($49.50)
Training M&E officers	$1,310.23 ($56.96)
Coordination and strengthening partnerships	
Conference attendance and international exchanges	$83.04 ($1.16)
Attend cross-border meetings for LF and NTDs	$141.62 ($1.69)
NTD secretariat meeting	$81.81 ($3.35)
Technical committee of NTDs	$38.28 ($1.71)

Data management

Cleaning, entering, analyzing data	$119.54 ($6.96)
Transfer of data from field to head office	$704.69 ($93.39)

Ongoing surveillance

Maintain sentinel sites	$1,616.73 ($8.80)
Site survey – data collection	$3,000.23 ($94.92)
Site survey – feedback meetings	$1,589.09 ($36.39)
Transmission assessment surveys – preliminary visit	$1,165.08 ($40.04)
Transmission assessment surveys – data collection	$2,849.99 ($55.82)
Transmission assessment surveys – feedback meeting	$1,438.37 ($35.32)

Monitoring, evaluation, and supervision

Supervision of MDA	$18,216.02 ($485.16)
Feedback meetings at district level	$884.54 ($37.36)
Feedback meetings at national level	$19.34($0.53)

Drug delivery

Supplies for CDDs	$3,924.54 ($485.62)
Drug transport	$3,078.94 ($180.55)

Administration

Overhead costs	$377.36
Salaries, LF staff	$950.19 ($51.04)
Procurement of necessary equipment and software	$61.63 ($2.23)

*4.4.8	Determination of economic costs*

Economic costs, which were assumed to encompass financial costs as well as the value of volunteer time and donated pharmaceuticals, were also estimated in order to have a more comprehensive understanding of the projected investment needed to globally eliminate and eradicate LF [95]. A schematic of the algorithm used for calculating the financial and economic costs is depicted in Figure 7.

Figure 7: Financial and economic costing algorithm

<u>*Value of donated pharmaceuticals*</u>

The opportunity costs of the donated drugs used in the GPELF were accounted for by valuing each 400 mg tablet of albendazole at $0.19, 50 mg tablet of diethylcarbamazine citrate (DEC) at $0.0025, and 3 mg tablet of ivermectin at $0.50, which were the suggested manufacturer prices prior to being donated [96-98]. An additional economic cost of $0.0018 was assumed to be the value of each tablet

for insurance and shipping costs, which also are currently absorbed by the drug manufacturers [98]. While the WHO specifies each treatment to include either 6 mg DEC/kg of body weight or 150 μg ivermectin/kg of body weight plus 400 mg ALB, for the purposes of this global level exercise, we assume all annual MDA treatments to be comprised of one tablet of ALB with either three tablets of ivermectin or seven tablets of DEC.

Value of volunteer time

The value of donated time was evaluated by correlating the time CDDs were presumed to volunteer under each scenario with country-specific or, when necessary, region-specific daily per worker agriculture wage estimates taken from the World Bank's World Development Indicators Online, inflated to 2012 [17]. Two CDDs were assumed to be sufficient to dispense MDA in each village [99]. Drawing from the results of previous time studies, CDDs were assumed to volunteer 5.5 days on mobilization and sensitization, 4.6 days conducting pre-MDA census activities, and 17.8 days on drug distribution [100].

4.4.9   Uncertainty Analysis

To account for the uncertainty in our model parameters, we conducted a probabilistic sensitivity analysis (PSA) involving all financial costs and quantities. We assumed 10% variance and utilized gamma distributions for all parameters to avoid negative values [101]. As the covariance between parameters was unknown, we further assumed all parameters to be independent. For all scenarios, we ran the model for 500 iterations for every year in every country. The model outputs thus provide a distribution of cost results, reported as mean estimates and associated 95% credible intervals. Supplementary material 2 has additional details involved in conducting the PSA.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

4.5   Results

The total financial investment to implement the global elimination scenario is projected at 929 million USD (883m-972m). To expand the campaign to all endemic countries at an average rate of scale-up (eradication I scenario) would require 1,289 million USD (1,227m-1,345m), an increase of about 360 million USD (346m-374m) over the global elimination scenario (Figure 8). The decrease in scenario duration inherent in the eradication II scenario (intensified scale-up) comes with decreased

costs, estimated at 1,274 million USD (1,209m-1,331m), while instantaneously scaling up MDA to all LF endemic countries is projected to require an investment of 1,235 million USD (1,172m-1,300m). The AFRO region accounts for 62-68% of the financial costs, with Southeast Asia requiring between 22-30% of the projected investment (Table 9).

Table 9: Total financial costs by region

	Global Elimination (comparator)	Eradication I	Eradication II	Eradication III
AFRO	$ 573.5 (546.8-599.7)	$ 877.8 (840.6-914.8)	$ 870.7 (832.9-906.7)	$ 840.1 (801.5-877.0)
SEAR	$ 278.0 (266.3-289.1)	$ 278.0 (266.3-289.1)	$ 279.3 (266.7-291.7)	$ 279.2 (265.8-292.1)
WPR	$ 56.35 (54.68-57.90)	$ 66.80 (65.12-68.35)	$ 57.75 (56.05-59.43)	$ 54.40 (52.64-56.14)
AMR	$ 20.92 (20.37-211.5)	$ 20.92 (20.37-21.50)	$ 19.06 (18.41-19.71)	$ 18.33 (17.71-18.96)
EMR	$0. 4403 (0.4328-0.4503)	$ 45.92 (43.60-48.07)	$ 46.67 (44.34-48.92)	$ 42.90 (40.29-45.63)
Total	**$ 929.2** (890.5-965.4)	**$ 1,289** (1,239-1,337)	**$ 1,273** (1,223-1,322)	**$ 1,235** (1,183-1,284)

Figure 8. Incremental financial costs (global elimination scenario as comparator)

Providing MDA to the entire at-risk population immediately, as assumed under the eradication III scenario, requires a significant initial investment, but within 10 years' time, the annual cost of implementing the scenario becomes less than the alternatives (Figure 9). The sharp increase in financial costs four years from the start of the eradication III scenario corresponds to the start of MDA to all at-risk populations in countries that were previously delayed due to mapping.

Figure 9: Financial costs by year, discounted at 3%

The average unit financial cost for undertaking each of the scenarios ranges from 0.27 USD in the global elimination scenario to 0.31 USD in both the eradication II and III scenarios. However, as the scenarios progress, the unit costs increase substantially. This is due to the fact that the number of people to be treated (the denominator of the estimate) decreases, though the cost associated with some of the core activities – including coordination and strengthening partnerships, administration, and data management – are assumed to remain relatively constant. As an example of this, Figure 10 depicts the unit financial costs seen under eradication I, which, by 2050, extend to more than 1,700 USD per person treated.

Figure 10: Financial cost per person treated, eradication I

Capacity strengthening proves to be the most costly activity, representing between 53-55% of the overall financial costs, while advocacy (22-24%); ongoing surveillance (6%); monitoring, evaluation, and supervision (8%), and drug delivery (9%) account for most of the remaining costs (Table 10).

Table 10: Percentage of financial costs by activity

	Global Elimination	Erad I	Erad II	Erad III
Advocacy	24%	22%	23%	24%
Capacity strengthening	53%	55%	55%	53%
Coordination and strengthening partnerships	<1%	<1%	<1%	<1%
Data management	<1%	1%	1%	1%
Ongoing surveillance	6%	6%	6%	6%
Monitoring, evaluation, and supervision	8%	8%	8%	8%
Drug delivery	9%	9%	9%	9%
Post MDA Surveillance	<1%	<1%	<1%	<1%
Administration	<1%	<1%	<1%	<1%
Mapping	-	<1%	<1%	<1%

To highlight the increased costs due to the assumed increase in expenditure for data management, drug delivery, and monitoring and evaluation, Figure 11 graphically depicts the financial costs of treating a population of 1 million at-risk for LF in the Democratic Republic of Congo. Costs of mapping and post-MDA surveillance are not included in this plot. Areas of meso *L. loa* are anticipated to only result in an increase in monitoring and evaluation, thereby having little effect on the overall costs. In comparison to a population of comparable size without *L. loa*, hyper *L. loa* endemicity is associated with an increase of approximately 15% in the overall costs of the program.

Figure 11: Financial costs of L. loa endemicity for a population of one million in the Democratic Republic of Congo

When the economic costs are considered, the costs of all scenarios are substantially higher (5.2 billion USD for the global elimination scenario). Extending the coverage to all endemic countries is estimated to require around 7.9 billion USD (7.5bn - 8.3bn), or 45% more than global elimination scenario. Depending on the scenario, between 48-53% of the economic costs are due to the value of the donated drugs (Figure 12).

Figure 12: Economic costs by component, discounted at 3%

When discounted at 0%, 3%, or 5%, the eradication III scenario represents the least expensive investment of all of the eradication scenarios, though, when discounting the financial and economic costs by 5%, the eradication I scenario becomes marginally more cost saving compared to the other eradication scenarios (Table 11).

Table 11: Financial and economic costs by discount rates (in millions)

	Global Elimination	Eradication I	Eradication II	Eradication III
Financial costs				
0%	$1,170	$1,697	$1,542	$1,445
3%	$929.2	$1,289	$1,274	$1,235
5%	$814.3	$1,098	$1,132	$1,112
Economic costs				
0%	$6,616	$10,618	$9,773	$8,853
3%	$5,212	$7,940	$8,000	$7,565
5%	$4,5067	$6,645	$7,357	$6,821

4.6   Discussion

This study is the first to estimate the financial and economic investments required to globally eliminate or eradicate lymphatic filariasis. The projected economic cost of global elimination is 5.2 billion USD, about half of which is due to the value of the donated drugs. These results serve to further highlight the crucial partnership between the GPELF and the drug donation programs. While the cost to globally eliminate LF is less than that to eradicate, it must be recognized that deciding to pursue elimination rather than eradication signifies the continuation of LF-related costs indefinitely, and comes at a health burden to populations that remain untreated.

A comparison of our costs against other costs is important for validation, though challenging due to differing methodologies. Though not inclusive of overhead costs, a study from two states in Nigeria found the cost associated with conducting MDA for the prevention of LF to cost between 0.02 USD and 0.12 USD [102]. A multi-country costing study conducted by Goldman et. al found financial costs to range from 0.06 USD in Burkina Faso to 2.23 USD in Haiti [98]. A separate study in Haiti reported the cost per person treated to be 1.44 USD [103]. Thus, in comparison to other MDA costing studies, our average unit financial cost estimates are well within the range of previously reported studies.

With a dearth of evidence on the costs of implementing morbidity management programs [104], and given that the aim of our study was to assess the costs of interrupting transmission of the causative

agent of LF, we did not include the costs of morbidity management in our estimates. Our analysis also does not take into account the cost for certifying elimination on a country level nor the activities involved in globally assessing whether eradication has been achieved. As currently experienced by the Global Polio Eradication Initiative, the costs for finding and ascertaining the last cases to reach eradication are substantial [66,105]. While our analysis does not consider the costs associated with finding the last cases of LF infection, the unit costs for the final populations treated in the eradication I scenario are orders of magnitude higher than the average unit costs – beyond 1,700 USD per person treated. It has previously been recognized that when the cost of disease eradication becomes within reach, the unit costs associated with prevention become decreasingly attractive. However, at that point, it is crucial not to lose momentum, nor investment, otherwise there is great risk of failure [57,106]. Developing realistic cost projections from the start of the program could help mitigate the risk of donor fatigue towards the endgame of disease eradication. Further, when disease eradication is within reach, shifting the focus from unit costs per person treated to the costs per case averted may also help to sustain global commitments [107].

Our analysis found an increase in financial costs of 15% to treat a hyper endemic L. loa area in the DRC. This estimate does not take into account increases in advocacy in these areas, which may be necessary to achieve the targeted levels of coverage. Further, the costs for medical transport and additional medications that might be needed to treat patients suffering from severe adverse events have not been incorporated in this analysis. Costing studies for such post-MDA response activities have not previously been carried out, though such costs are likely to vary by the incidence of SAEs, the geographic location, and the intensity of response required. If substantial and significant response is required in many areas, the overall costs for implementing the eradication scenarios would certainly result in higher costs than projected in this baseline study.

A number of methodological uncertainties in our study must be mentioned. Country-specific cost data was mostly unavailable and, consequently, was largely imputed from Ugandan data. By extrapolating cost data across countries and regions, we inherently made the assumption that each LF endemic country implements the GPELF strategy as in Uganda (for example, using volunteer CDDs, similar amount of trainings, etc.). Moreover, we assumed that the number of resources required to carry out the PELF for a certain population in Uganda remains relatively constant (varying by +/-10%) both across time and across countries. Ideally, LF-specific expenditure data would have been collected in all 72 LF-endemic countries. However, 14 of these endemic countries have never carried out MDA for LF [12]. Moreover, undertaking a study that accurately collected such data would potentially begin to rival the time and cost of running the PELF programs in many of

the countries to begin with. Thus, despite the large number of assumptions inherent in our approach, our costing model allowed for the development of comparable cost estimates on a country, regional, and global level.

We conducted a probabilistic sensitivity analysis in order to overcome some of the limitations inherent in our costing parameters. In order to provide more robust estimates on the costs of achieving global elimination and eradication, costing studies in areas with the highest burden of LF could be undertaken in order reduce the level of uncertainty in costs. While improved cost data could be used to inform policy and improve planning, the cost of acquiring additional data should be weighed against the value of such data [108]. An additional use for the results found in our economic analyses, therefore, could be to assess the value of additional investments for LF, including the collection of expenditure data, as well as investments in diagnostics, drugs, and surveillance tools to help advance LF eradication.

Our findings on the costs to globally eliminate and eradicate LF represent very achievable investments. Our cost estimates would have likely been even lower, though, if we assumed some level of integration or cost-sharing between other disease initiatives. Many countries have, in fact, integrated similar activities across vertical programs, including onchocerciasis, trachoma, and schistosomiasis, and others have paired drug delivery for MDA with other community distribution campaigns, including insecticide treated nets (ITNs) for malaria and ongoing vaccine programs. In so doing, the overall costs per program, indeed, generally decreased and efficiency reportedly improved [36,86,109-111]. Additionally, given the cost involved with each round of MDA, it could be cost saving to undertake TAS sooner in order to assess whether the interruption of transmission had been achieved. However, this approach could pose to be a difficult balance, since prematurely stopping MDA could result in resurgence of infection [112], ultimately leading to an increase in the cost of reaching eradication.

Knowing the global costs of the program will help decision makers assess the feasibility and rationale of investing in LF eradication, while helping to facilitate planning and the development of strategies and policies. However, successfully eradicating LF depends on more than the monetary investment. Political will, continued community ownership, and the feasibility of the campaign all need to be taken into account [61]. However, if successful, disease eradication not only results in innumerable long-term health benefits, but also savings to the health system, gains in productivity, and improvements in social justice [22,29]. The decision of whether disease eradication should be pursued, therefore, needs to be approached with a comprehensive understanding of the many complex issues at play.

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Figures

Figure 7: Financial and economic costing algorithm

Figure 8: Incremental financial costs (global elimination scenario as comparator)

Figure 9: Financial costs by year, discounted at 3%

Figure 10: Financial cost per person treated, eradication I
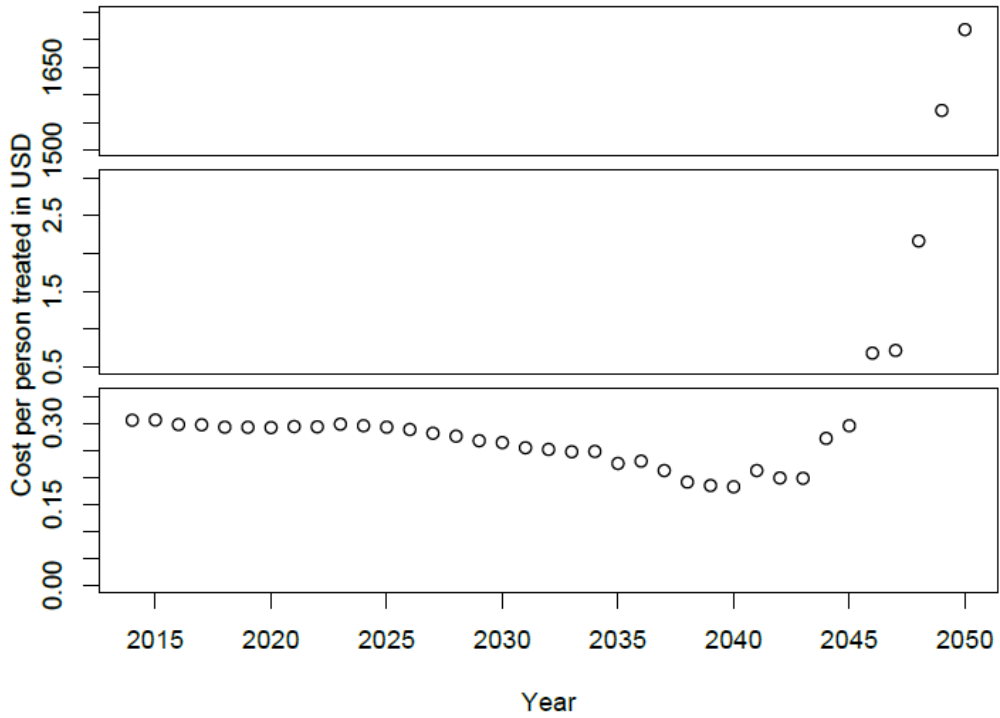
Figure 11: Financial costs of *L. loa* endemicity for a population of one million in the Democratic Republic of Congo

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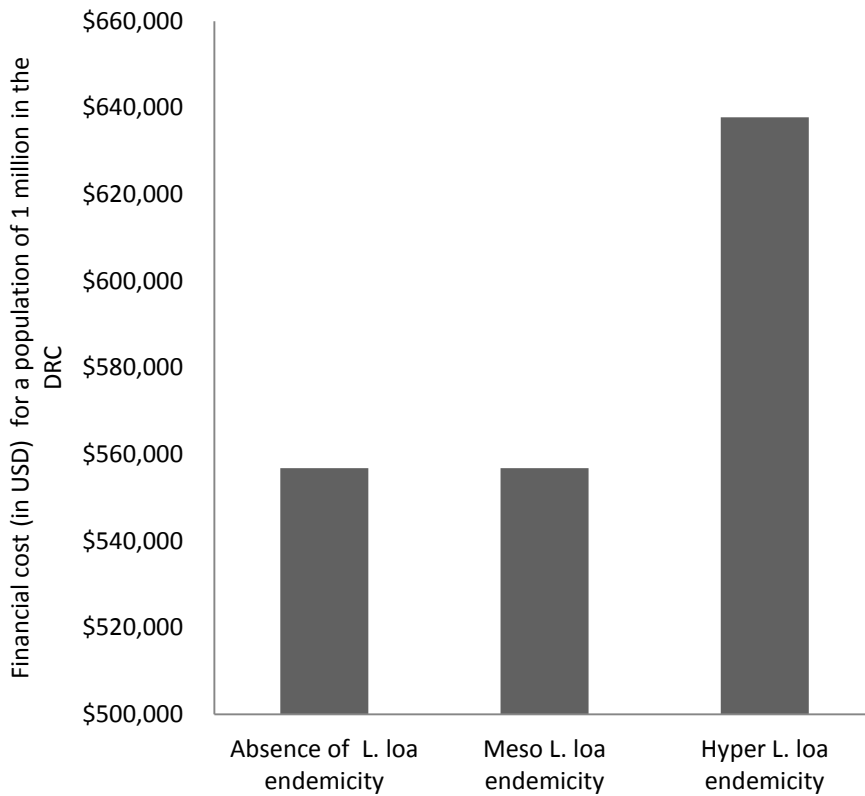
Figure 12: Economic costs by component, discounted at 3%
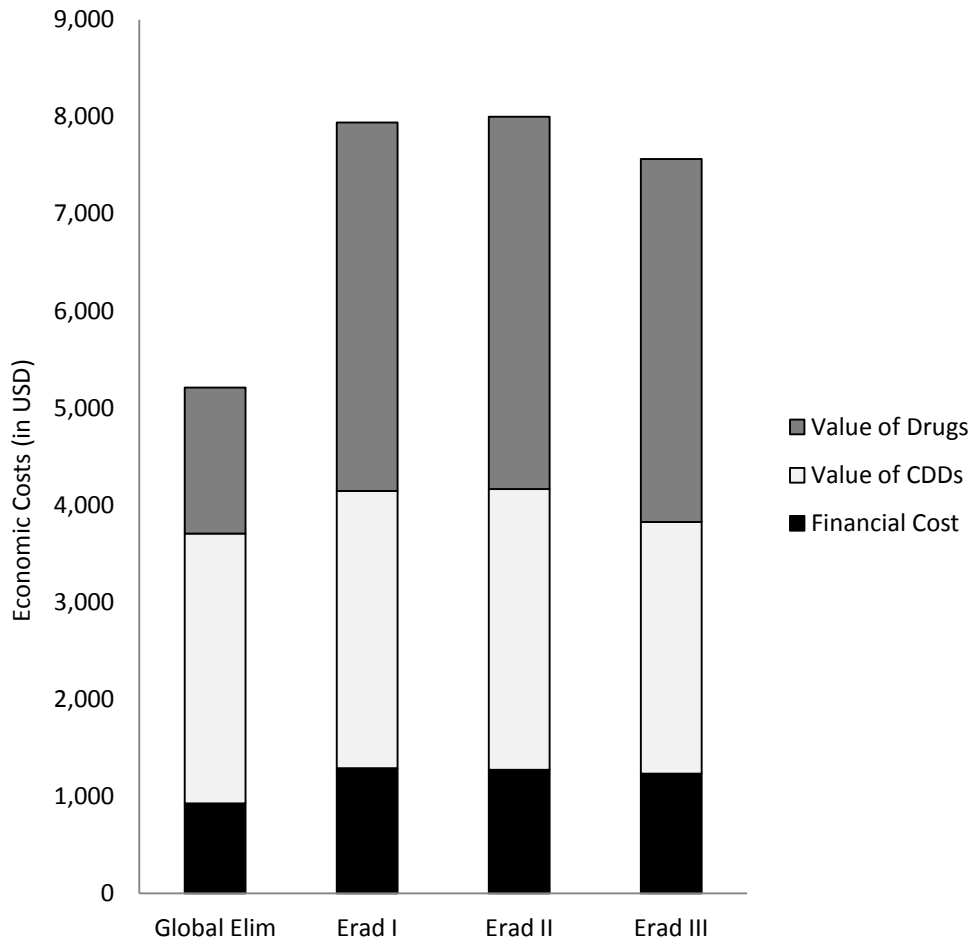
5 Modeling the health impact and cost-effectiveness of lymphatic filariasis eradication under varying levels of mass drug administration scale-up and geographic coverage

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5.1   Abstract

Background

A program to eliminate lymphatic filariasis (LF) is underway, yet two key programmatic features are currently lacking: extension of efforts to all LF endemic countries, and expansion of geographic coverage of mass drug administration (MDA) within countries. For varying levels of scale-up of MDA, we assessed the health benefits and the incremental cost-effectiveness ratios (ICERs) associated with LF eradication, projected the potential savings due to decreased morbidity management needs, and estimated household productivity gains as a result of reduced LF-related morbidity.

Methods

We extended an LF transmission model to track hydrocele and lymphedema incidence in order to obtain estimates of the disability-adjusted life years (DALYs) averted due to scaling up MDA over a period of 50 years. We then estimated the incremental cost-effectiveness ratios (ICERs) and the cost-effectiveness acceptability curves associated with different rates of MDA scale-up. Health systems savings were estimated by considering the averted morbidity, treatment seeking behavior, and morbidity management costs. Gains in worker productivity were estimated by multiplying estimated working days lost as a result of morbidity with country specific per-worker agricultural wages.

Findings

Our projections indicate that dramatically scaling-up MDA could lead to 4.38 million incremental DALYs averted over a 50 year time horizon compared to a scenario which mirrors current efforts against LF. In comparison to maintaining the current rate of progress against LF, dramatically scaling-up MDA in order to pursue LF eradication, was most likely to be cost-effective above a willingness to pay threshold of 70.5 USD/DALY averted. Intensified MDA scale-up was also associated with lower incremental cost-effectiveness ratios. Health systems savings of intensive MDA scale-up was estimated up to 483 million USD. Extending coverage to all endemic areas could generate additional economic benefits through gains in worker productivity between 3.41 and 14.4 billion USD.

Interpretation

In addition to ethical and political motivations for scaling-up MDA rapidly, this analysis provides economic support for increasing the intensity of MDA programs.

5.2   Introduction

To date, smallpox is the only human infectious disease that has been eradicated through deliberate efforts, an accomplishment that is considered among the greatest medical achievements in the last century [52,53]. This success increased interest in disease eradication as a public health strategy, and eradication campaigns against polio and Dracunculiasis are currently underway [65,81]. Progress against Dracunculiasis indicates that the concept of eradication can be applied to parasitic infections for which vaccines are not available [65].

Disease eradication results in the permanent interruption of transmission of the causative agent of the disease and the ultimate disappearance of the organism as a free-living biological species. This is distinct from elimination, which is the interruption of transmission in a defined geographic locale. Control reflects the use of interventions aimed at reducing the health burden associated with transmission of a pathogen, but does not intend to interrupt transmission [69]. The decision to shift from a strategy based on reducing the health burden to one of elimination or eradication is not to be taken lightly [113]. Because eradication is an all-or-nothing achievement, and one that will require an intensified and/or altogether different strategy than disease control, failure to achieve it may represent a misuse of resources. In addition, failed attempts can lead to donor fatigue with persistent negative consequences [57]. To provide policy makers with guidance on whether to pursue eradication, the concept of an Eradication Investment Case (EIC) was developed following insights from an Ernst Strüngmann forum on scientific advances in disease eradication [60,70]. An EIC is expected to include a quantitative assessment of the technical and biological feasibility of achieving eradication, an assessment as to whether the health system infrastructure is capable of delivering the interventions, and evidence of sufficient funding and political will to support such a program. The various components also need to be periodically re-evaluated as the program progresses, since all are potentially prone to erosion due to factors including emerging drug resistance, weak health systems, or public and donor fatigue [67].

Further arguments for or against eradication may come from economic considerations [114]. Using a game-theoretic approach to the eradication of smallpox, Barrett & Hoel were able to specify conditions under which an eradication strategy was optimal. Specifically, when eradication was possible, high levels of control were never optimal [115]. Similar arguments based on health economic modeling have been made to support continued investments in the eradication of polio [116].

Lymphatic filariasis (LF) endemicity is strongly tied to poverty [117] and leads to debilitating, chronic forms of morbidity, most notably hydrocele and lymphedema [9]. The health burden from LF is considerable, estimated at 2.74 million disability-adjusted life years (DALYs) (1.73m-4.00m) in 2010 [4]. Beyond affecting physical health and productivity, LF-related morbidity also leads to stigma and social exclusion, and impacts mental well-being [22].

Preventive chemotherapy represents the primary strategy of the ongoing Global Program to Eliminate Lymphatic Filariasis (GPELF), which aims for the global elimination of LF by 2020. The strategy is based on once-yearly mass drug administration (MDA) either with diethylcarbamazine citrate (DEC) and albendazole (ALB), or, in areas where onchocerciasis is also endemic, ivermectin (IVM) and ALB. These compounds kill microfilariae and affect the survivorship and fecundity of adult worms. If MDA is provided to a large proportion of the population (>65%) for a sufficient number of years, interruption of transmission in the targeted region is thought to be feasible [9].

As LF proceeds towards global elimination, certain challenges are worthy of consideration, including the feasibility of reaching remote populations and the ability to maintain coverage in urban areas with dense and mobile populations [46]. An animal reservoir is not generally thought to contribute to LF transmission, although *Brugia malayi* is sometimes found in non-human primates, cats, and dogs . For the purposes of this study we assume that eradication of LF is feasible and the mentioned challenges not insurmountable.

We previously developed scenarios that could lead to global elimination or eradication of LF, estimated the time it might take to reach elimination and eradication, projected the number of treatments required under each scenario, and considered the associated financial and economic costs (Chapters 3 and 4). In the current study, we assess the health impact in terms of DALYs averted, estimate the cost-effectiveness associated with different intensities of scaling-up MDA, and project the possible savings to the health system and potential increase in worker productivity due to averted LF-related morbidity for each of these scenarios.

5.3   Methods

5.3.1   Scenarios modeled

We defined four scenarios named global elimination, eradication I, eradication II, and eradication III, which differ in their geographic coverage and rate of MDA scale-up. The scenarios were developed in an iterative consensus process involving leading scientists, policy makers, program managers and other stakeholders following an analysis of the ongoing GPELF (Chapter 3). For areas co-endemic

with *Wuchereria bancrofti and Loa loa* we made the simplifying assumption that whatever strategy will end up being used in reality (e.g., the provisional guidelines from the WHO suggest bi-annual MDA of ALB and vector control) can be approximated in our model by annual MDA with IVM+ALB. The current global elimination scenario is defined as the comparator scenario, mirroring the rate of MDA scale-up seen under the GPELF thus far, but assumes that countries that have not yet begun MDA programs will not do so. As we identified low levels of geographic coverage within certain endemic areas to be the major impediment to progress against LF, the three eradication scenarios explore the impact of expanding MDA to all LF endemic populations at varying rates. Eradication I models the impact of expanding MDA to all endemic areas at the historical average rate of scale-up; eradication II assumes countries scale-up geographic coverage by 20% increments each year, and eradication III represents the best-case scenario, whereby all countries expand coverage to their entire at-risk population immediately. See Supplementary material 3 and Chapter 3 for further details.

5.3.2   Estimates of disability-adjusted life years

We used a deterministic model, EpiFil [15], to simulate filariasis transmission by either *Anopheles* spp. or *Culex* spp. vectors, following Gambhir & Michael [49]. See Supplementary material 3 for details on how the estimate was expanded to include chronic disease states.

We translated the incidence of chronic disease to DALYs, which, in the case of LF, are composed of the years of life lived with a disability (YLD) multiplied by the disability weight (DW). We determined the number of new hydrocele and lymphedema cases in a given time period and assigned YLDs at that point based on the individual's remaining life expectancy [118]. Per convention, no distinction in the DW was made between lymphedema and hydrocele, and symptomatic cases were assigned a DW of 0.11 [119]. Age-weighting was not considered in this study, but DALYs were discounted at 3% per year. Further details on the calculations are provided in Supplementary material 3. The DALYs were estimated for a period of 50 years to capture the long-term health benefits of interrupting transmission.

5.3.3   Estimates of financial costs

The financial costs of implementing the GPELF strategy in all LF endemic countries were estimated using a bottom-up approach from the perspective of an LF-endemic country's health system, with future costs discounted at 3%. Activities considered in the cost estimates included advocacy; capacity strengthening; coordination and strengthening partnerships; data management; ongoing

surveillance; monitoring, evaluation and supervision; drug delivery; and administration. Costs for mapping, running post-MDA transmission assessment surveys and increased surveillance in areas of *L. loa* prevalence were also taken into account. A summary of the costing methodology (Chapter 4) is provided in Supplementary material 3.

5.3.4   Cost-effectiveness analysis

In order to evaluate the cost-effectiveness of eradication, the DALY projections for each country in each scenario were paired with country-specific financial cost estimates. With the global elimination scenario as the reference case against which all other scenarios were compared, cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs). For each simulation, the monetary net benefits (MNB) were calculated as the mean incremental DALYs averted multiplied by the decision makers' maximum willingness to pay for a DALY averted minus the mean incremental cost for the scenario [101]. Cost-effectiveness acceptability curves were used to graphically depict the probability for each scenario to be cost-effective at various willingness-to-pay thresholds.

5.3.5   Impact on health services use and associated cost savings

To assess the potential health systems savings due to averted morbidity management, we followed the approach of Chu *et al*. and assumed that on average 40% (20-50%) of hydrocele patients and 50% (30-55%) of lymphedema patients seek treatment annually. We further assumed acute adenolymphangitis (ADL) to occur about twice per year (0-7 times) in 70% (45-90%) of hydrocele patients, and four (0-7 times) times annually for 95% (90-95%) of patients with lymphedema [29].

Health systems savings were then estimated by combining the averted incidence of morbidity, frequency of ADL episodes, and treatment seeking behavior paired with country-specific costs for a 20 minute consultation at a primary health center with 50% population coverage [29]. Parameter uncertainty was considered by taking 500 random estimates within each parameter range, assuming normal distributions for treatment seeking behavior and triangular distributions for ADL episodes.

5.3.6   Estimates of worker productivity gains

Using a pre-established methodology, we also determined the impact that LF eradication could have on worker productivity [29]. To assess the potential worker productivity increase, we assumed ADL episodes to last four days on average (1-9 days), and cause a 75% (50-93%) reduction in productivity for their duration. LF-related morbidity was assumed to decrease the amount of productive working days by 15% (13-17%) for hydrocele patients and 20% (15-22%) for those with lymphedema. Three

hundred working days were assumed for those without LF-related morbidity. We monetarily valued possible gains in worker productivity by taking the number of working days lost due to LF-related morbidity paired with country-specific (when available) or region-specific daily per-worker agriculture wages given by the World Bank's World Development Indicators Online [17], inflated to 2012. Uncertainty in the parameter estimates was incorporated by drawing 500 random samples from each range assuming normal distributions.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

5.4   Results

5.4.1   Estimates of disability-adjusted life years

The intensity of MDA scale-up greatly impacts population health (Figure 13). With global elimination as the comparator, extending MDA to all endemic countries (eradication I) results in approximately 1.72 million DALYs averted (95% Credible Interval (CrI): 1.09m-2.62m) over a 50 year time horizon. In contrast, intensifying geographic coverage in all countries (eradication III) leads to approximately 4.38 million DALYs averted (95% CrI: 2.79m-6.50m) over the same timeframe. Thus, there are considerable gains to achieve by more intensely scaling-up MDA.

Figure 13: Cumulative number of DALYs averted over time per eradication scenario compared to the global elimination scenario

The incremental health impacts by country, expressed as DALYs averted per 100,000 people, are depicted for the eradication I scenario compared to the global elimination scenario, eradication II compared to eradication I, and eradication III compared to eradication II (Figure 14). The comparison between eradication I and the global elimination scenario illustrates that the majority of the gains from extending MDA to all endemic countries are concentrated in Central Africa. The heterogeneous results within these countries are largely due to demographic patterns that affect the DALY estimates, such as age composition, life expectancy, and population growth rates. The gains from increasing the rate of MDA scale-up are more evenly spread out among countries (eradication II versus I, and III versus II).

Figure 14: Cumulative number of DALYs averted per 100,000 persons after 50 years per country, comparing the different scenarios to each other

5.4.2   Cost-effectiveness analysis

The estimated ICER for the eradication III scenario is approximately 72.9 US dollars (USD)/DALY averted (95% CrI: 47.7-110) (Figure 15). In contrast, the eradication I and eradication II scenarios are higher, at 219 USD/DALY averted (95% CrI: 143-323) and 121 USD/DALY averted (95% CrI: 79.5-178), respectively. Against the global elimination scenario, all eradication scenarios end in the northeast quadrant of the incremental cost-effectiveness plane, which implies an increase in DALYs averted at increased cost (Figure 16) [120]. Therefore, depending at which threshold the ICER is considered good value for money, either the global elimination or eradication III scenario will be most cost-effective.

Correspondingly, and as shown by the cost-effectiveness acceptability curve, if the willingness to pay threshold per DALY averted is below 71.5 USD, the global elimination strategy should continue to be pursued. However, if the willingness to pay threshold surpasses 71.5 USD/DALY averted, then scale-up of MDA to all at-risk populations in all endemic countries should be pursued as quickly as possible (Figure 17).

Figure 15: Incremental cost-effectiveness ratios associated with each of the scenarios, with global elimination as the comparator

Figure 16: Incremental cost-effectiveness plane with incremental financial costs associated with MDA programs and incremental disability-adjusted life years averted, comparing the three eradication scenarios to the comparator scenario

Figure 17: Cost-effectiveness acceptability curve for the four scenarios

5.4.3   Impact on health system savings and worker productivity losses

Unsurprisingly, reaching LF eradication sooner was found to correspond to increased health systems savings, due to decreased morbidity management, ranging from 140 million USD (95% CrI: 63.8 m-260m) in the eradication I scenario to 483 million USD (95% CrI: 219m-903m) in eradication III Figure 18).

Figure 18: Potential cost savings to LF endemic health systems due to decreased need for morbidity management practices

Potential savings to the health system, however, were dwarfed by possible gains in worker productivity, which ranged from approximately 3.4 billion USD (95% CrI: 2.0 bn-5.4 bn) under the eradication I scenario to 14.4 billion USD (95% CrI: 8.58bn-22.0 bn) in the eradication III scenario

(Figure 19). Importantly, all increased with increasing rates of MDA scale-up, further supporting the conclusion from the cost-effectiveness analysis.

Figure 19: Averted productivity losses due to eradication

5.5   Discussion

Lymphatic filariasis could become the first vector-borne disease to be eradicated. While the GPELF has made notable progress thus far, in order to achieve eradication, the program needs to be extended to several endemic countries. Moreover, if the goal of global elimination as a public health problem by 2020, as specified in the London Declaration [121], is to occur, the scale-up of MDA to cover all populations at risk needs to be greatly intensified.

In this analysis, we found that the health impact due to LF eradication will increase with the rate of MDA scale-up, since DALYs averted have a longer time period to accrue when transmission is interrupted earlier. This highlights the importance of measuring costs and benefits of interventions over a long time horizon, as well as the benefits of integrating disease transmission, economic, and demographic models.

Intensifying the rate of MDA scale-up to eradicate LF is also supported on economic grounds. All three eradication scenarios ended up in the northeast quadrant of the cost-effectiveness plane (Figure 16). Thus, compared to the global elimination scenario, extending MDA to all endemic countries is associated with an increase in DALYs averted but at increased cost. Whether this investment is worthwhile depends on the willingness to pay of donors. Our analysis suggests that above a willingness to pay threshold of 71.5 USD/DALY averted, pursuing eradication at the highest level of MDA scale-up is the most likely to provide the greatest net benefits and therefore provide the most value for money (Figure 17). To put this in perspective, a willingness to pay of 150 USD/DALY averted has been suggested for low and middle income countries as an acceptable level [122]. While decision makers are not bound by this threshold, our analysis indicates that LF eradication would generally be considered cost-effective, assuming the rate of MDA scale-up is sufficient. If instantaneous scale-up (eradication III) is shown not to be feasible, the ICER of the eradication II scenario (rapid scale-up) remains low at 121 USD/DALY averted. Only at the slowest level of scale-up does the ICER fall above this threshold, adding further urgency to intensifying the rate of scale-up.

Other considerations could influence the cost-effectiveness of LF eradication. Depending on the perspective taken, the benefits that are expected to arise due to health systems savings and gains in

worker productivity could be taken into account, as could potential savings in out-of-pocket costs by patients. In both instances, the dominance of the eradication III scenario would further increase. There are epidemiological aspects that we did not consider, such as recrudescence of infections in areas following elimination due to migration. By ignoring this possibility, we made the implicit assumption that international movement among endemic populations was limited. Relaxing this assumption would require a meta population model and an investigation of human migration and commuting patterns in LF-endemic regions. However, previous studies in which similar mechanisms were considered have only added to the growing support for pursuing eradication [115,116].

Further aspects which could interfere with the ability to maintain sufficiently high MDA coverage include insufficient political will, inadequate health infrastructure, logistical issues, and the potential of systematic non-compliance. The development of drug resistance, as has been documented in animal systems [123], could also present complications. Further, in areas where *W. bancrofti* is co-endemic with *L. loa*, it remains to be seen how effective biannual distribution of ALB by itself or together with long lasting insecticidal nets (LLINs) will be. We have assumed that the strategy employed in these areas to be equally effective as MDA with IVM and ALB, and equally unlikely to lead to resistance. However, if this is not the case, and an alternative strategy requires a larger investment or a prolonged campaign, the ICERs of the eradication scenarios will increase. Currently, data to improve on these estimates is unavailable but additional modeling work, more focused on individual districts based on local data, may be enlightening. Such work could be particularly valuable in identifying more effective strategies for dealing with endemic districts where progress seems to be lagging.

Additionally, we assumed that endemic countries implemented MDA programs for a fixed duration resulting in a high probability of achieving elimination (i.e., where >97.5% of simulations reached elimination) (Chapter 3). A more dynamic decision process, whereby a shorter duration is followed by surveys and possible additional rounds of MDA until local elimination is certified may be closer to reality, but beyond the scope of this global-level exercise.

Finally, our strategies assumed that all endemic countries included in the different scenarios are committed to elimination, and would not pursue a less ambitious goal, such as disease control. It is plausible, however, for some countries to only target populations that live in moderate to high transmission zones, but not the greater number of people in low transmission areas where chronic disease is much less prevalent. A previous study indeed suggests that cost-effectiveness may improve if communities with microfilaria prevalence above 3.55% are first treated through a

sequential strategy based first on control and a later shift of program goals towards elimination [124]. Ordering the treatment districts by intensity could thus lead to further increases in cost-effectiveness of our eradication scenarios.

In conclusion, this study suggests that eradication of LF is likely a cost-effective strategy, and that if pursued, scaling up MDA as rapidly as feasible will result in increases in value.

Acknowledgements

Figures

Figure 13: Cumulative number of DALYs averted over time per eradication scenario compared to the global elimination scenario

Figure 14: Cumulative number of DALYs averted per 100,000 persons after 50 years per country, comparing the different scenarios to each other

Eradication I - Elimination scenario

Eradication II - Eradication I scenario

Eradication III - Eradication II scenario

Figure 15: Incremental cost-effectiveness ratios associated with each of the scenarios, with global elimination as the comparator

Figure 16: Incremental cost-effectiveness plane with incremental financial costs associated with MDA programs and incremental disability-adjusted life years averted, comparing the three eradication scenarios to the comparator scenario
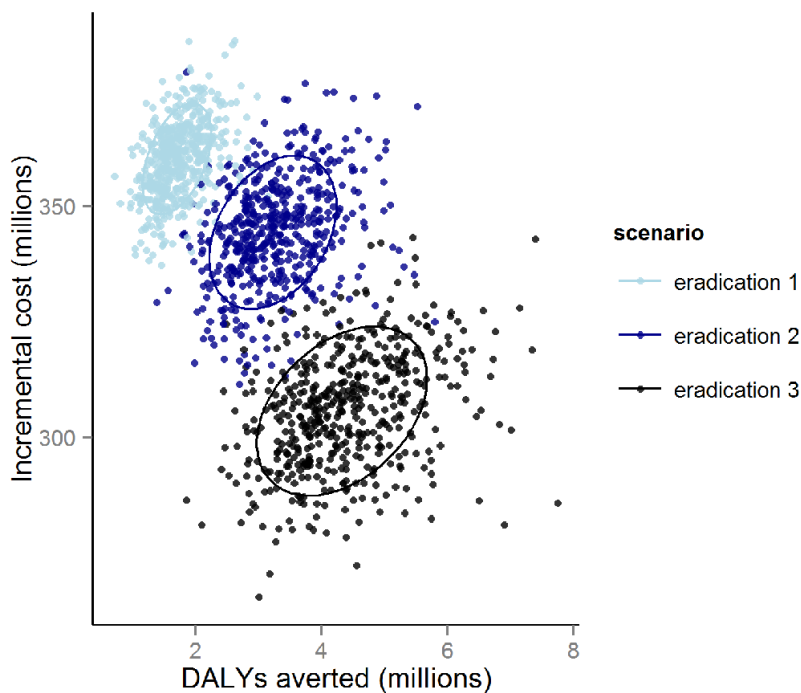
These plots highlight the uncertainty around cost-effectiveness ratios.

Figure 17: Cost-effectiveness acceptability curve for the four scenarios
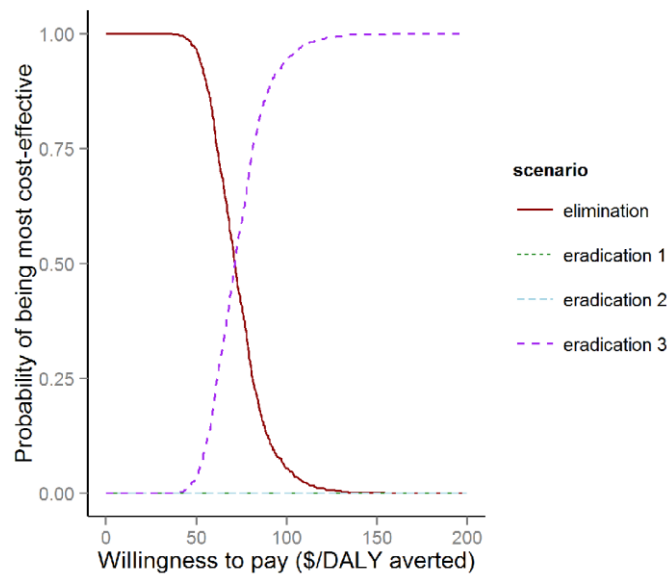
Above the cost-effectiveness threshold of 71.5 USD/DALY averted, the probability of the eradication III scenario being more cost-effective than the global elimination scenario increases. When eradication III is a realistic option, eradication scenarios I and II are never the most cost-effective.

Figure 18: Potential cost savings to LF endemic health systems due to decreased need for morbidity management practices
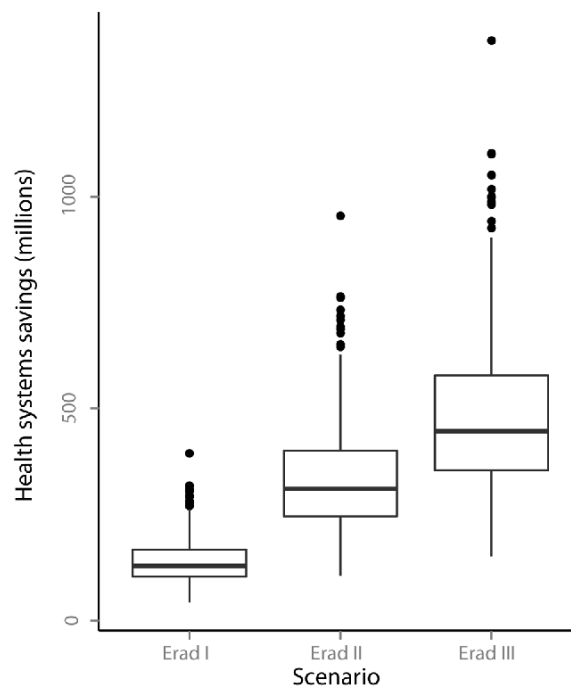
Figure 19: Averted productivity losses due to eradication
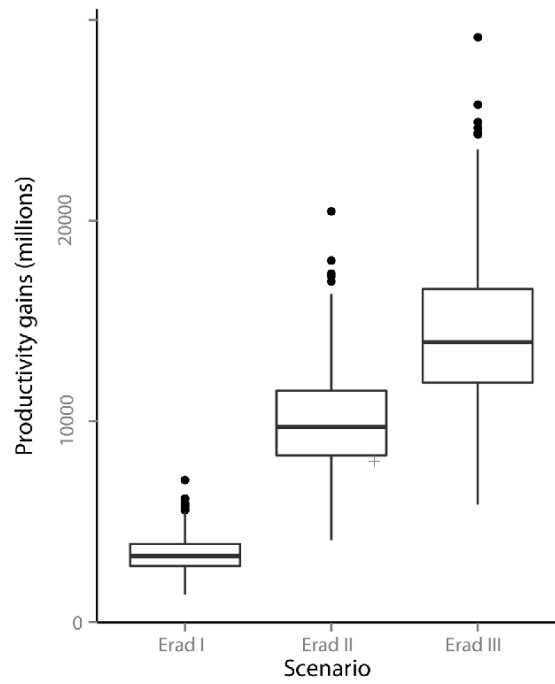
6 General Discussion

6.1   Overall significance of thesis

Resolution WHA 50.29, adopted by member states in 1997, named lymphatic filariasis (LF) as a potentially eradicable disease [9]. Now, as the global health community considers whether to scale-up the current global elimination program to reach eradication, there is great opportunity to utilize the lessons learned from previous and ongoing disease eradication efforts. Additionally, there is increased understanding for the need to utilize evidence reflective of the real-world situation to make better decisions in order to achieve better health [62]. As such, the work found in this thesis aims to provide stakeholders with an evidence base in which to support the decision for proceeding to LF eradication.

This research has direct practical applications at the country and global level by providing important insight and comprehensive estimations of many key features to consider prior to committing to LF eradication, including: the development of plausible scenarios to reach global elimination and eradication, as well as projections of the number of years and amount of treatments required to reach the scenario endpoints, the associated financial and economic investment necessary, and the benefits resulting from averted LF-related morbidity – assessed in disability-adjusted life years (DALYs) averted, possible gains in worker productivity, and potential savings to endemic countries' health systems. In addition to providing the grounds for making decisions about LF eradication, this thesis also serves as an example of the type of evidence that could be developed to support decisions about proceeding to elimination or eradication for a number of other diseases.

6.2   Justification of intensifying efforts to eradicate LF

Lymphatic filariasis is a strong candidate for eradication. LF lacks a significant animal reservoir, is inefficiently transmitted, and methods for detecting infection exist and are already in use in many endemic areas [33,67]. Progress made by the GPELF also proves that mass drug administration (MDA) is an effective strategy to interrupt LF transmission [12,125]. The feasibility of eradicating LF is further improved by the fact that all of the drugs used as part of the MDA strategy are currently donated by the pharmaceutical companies that manufacture them [10,11].

Successfully eradicating LF would have many benefits. Unlike elimination, LF eradication would result in the permanent end of interventions aimed to interrupt transmission, as well as the cessation of necessary surveillance on the disease. Eradicating LF would also remove the threat of becoming infected with LF in the future, and the consequent development of LF-related morbidity. Successfully eradicating LF would also be a great achievement in public health, and would also represent the first vector born disease to be eradicated. The work found in this thesis quantifies

many additional benefits of eradicating LF and serves to highlight the reasons why eradication should be pursued. As explained in Chapter 5, achieving LF eradication over elimination results in a greater health impact, and as such, produces in the greatest savings to the health system and the greatest possible increase in worker productivity.

The work here provides evidence for proceeding to LF eradication as quickly as possible. The financial investment necessary to reach eradication is projected to decrease with increased rates of MDA scale-up. Under eradication I (average scale-up), 1,289 million USD (95% CrI: 1,227m-1,340m) is projected to be required to interrupt LF transmission in all endemic countries. In contrast, eradication III (immediate scale-up) is projected to require 1,235 million USD (95% CrI: 1,172m-1,300m). When taking into account the opportunity costs of the donated drugs and volunteer time, immediately providing MDA to all at-risk populations also represents the least investment required. The economic costs for the eradication III scenario is estimated at 7.57 billion USD (95% CrI: 7.12bn-7.94bn), whereas the eradication I scenario is anticipated to have an economic cost of 7.94 billion USD (95% CrI: 7.50bn-8.30bn) and eradication II (intensified scale-up) is estimated at 8.00 billion USD (95% CrI: 7.55bn-8.35bn).

 Immediate scale-up also results in the greatest health impact, estimated at 4.38 million DALYs averted (95% CrI: 2.79m-6.50m). This estimate contrasts sharply with the health impact of eradication I (1.72 million DALYs averted (95% CrI: 1.09m-2.62m)), and eradication II (2.98 million DALYs averted (95% CrI: 1.90m-4.45m)). Further, immediate scale-up represents the greatest possible savings to the health system over a 50 year time horizon, estimated at 483 million USD (95% CrI: 219m-902m). Gains in worker productivity are also anticipated to increase with increased rates of MDA scale-up, estimated at over 11 billion USD compared to the eradication I scenario. Given the increased benefits and decreased costs associated with the eradication III scenario, it is unsurprising that the scenario is also considered the most cost-effective (Table 12).

Table 12: Summary of key results with 95% credible intervals

	Global Elimination	Eradication I	Eradication II	Eradication III
Number of treatments (millions)	3,409 (3,185-3,538)	4,667 (4,419-4,904)	4,369 (4,133-4,594)	4,159 (3,924-4,382)
DALYs averted (millions)[‡]	–	1.72 (1.09-2.62)	2.98 (1.90-4.45)	4.38 (2.79-6.50)
Financial costs (millions USD)	929.2 (883.5-971.5)	1,289 (1,227-1,340)	1,274 (1,209-1,331)	1,235 (1,172-1,300)
Economic costs (billions USD)	5.21 (4.91-5.45)	7.94 (7.50-8.30)	8.00 (7.55-8.37)	7.57 (7.12-7.94)
ICER (USD/DALY averted)[‡]	–	219.0 (142.7-322.7)	120.7 (79.52-177.7)	72.94 (47.74-109.8)
Potential savings to health system (millions USD)[‡]	–	139.9 (63.80-260.3)	335.6 (152.2-626.8)	483.4 (219.1-902.6)
Potential gains in worker productivity (billions USD)[‡]	–	3.41 (2.03-5.36)	10.06 (5.98-15.50)	14.43 (8.58-22.02)

[‡]Measured against the global elimination scenario as the comparator.

6.3   Limitations of this work

This study was undertaken by first developing plausible scenarios to reach global elimination and eradication, and then projecting the timeframes and treatments necessary to reach the scenario endpoints. The studies on costs, benefits, and cost-effectiveness of eradicating LF were then built onto this initial analysis. Thus, assumptions made in developing the scenarios and treatment projections impact all additional aspects of this work. While assumptions and limitations from each individual analysis are highlighted in the associated chapter, the most significant assumptions used to undertake this global-level project are outlined below.

As with all modeling exercises, the validity and relevance of the outputs are highly dependent upon the inputs. We obtained data on both transmission intensity and costs from only a handful of countries with endemic LF, all of which were within the same region. In so doing, we made the implicit assumption that the data from those countries were representative of the nature of the disease in all other endemic countries. Additionally, we relied heavily on the WHO preventive chemotherapy (PCT) databank [12] for estimates on current at-risk populations and previous progress made against LF. In so doing, we assumed that the number of treatments reportedly administered is accurate, both in terms of the number of treatments distributed and the percentage of the populations that actually ingested the medications. We also assumed that the level of

systematic non-compliance, both historically and prospectively, is not significant enough to have an overall effect in any treated population.

We assumed that the at-risk populations for LF increase with population growth, an assumption that has not previously been reflected by WHO estimates. We also considered the prevalence and disease distribution data to be correct, though we know that this is not the case in all areas. We did not take into consideration the possibility of a technological breakthrough nor the impact of vector control. Additionally, we assumed cost data to be representative of the actual expenditure needed to undertake the program. And, crucially, we assumed the model estimates reasonably capture the factors affecting transmission, costs, and health burden, and that the parameter and model uncertainty have been appropriately captured through our parameter ranges, distribution assumptions, and sensitivity analyses performed.

We did not take into account the potential for countries to change priorities or lose interest in pursuing LF elimination, and we assumed that the investments necessary to implement the programs will continually be provided without interruption. We also assumed that the pharmaceutical companies will continue donating the drugs necessary, and that the capacity to produce the number of treatments required is available and feasible to deliver without delay. We further did not take into consideration the potential for the evolution of drug resistance to become a threat to the success of the program. In summary, we assumed that on an operational level, it is possible to carry out the program activities as specified by the GPELF, and that those activities will lead to the interruption of LF transmission.

In quantifying the potential health benefits of eradicating LF, we used the official disability weight estimates in order to calculate the potential DALYs averted, even though having the same disability weight for all manifestation of LF-related disability (including lymphedema, elephantiasis, and hydrocele), may be an over-simplification [4]. Further, a recent study by Ton et al. argues for the inclusion of LF-related depression in the burden estimates. In assessing the current health burden due to LF in this way, the study team found LF to globally account for 5.09 million DALYs, rather than the Global Burden of Disease (GBD) estimate of 2.74 million DALYs (1.73m-4.00m) [4,28]. If our study had also included the mental health problems associated with LF-related disability, the potential benefits of eradicating LF would have been even greater.

However, assessing the possible benefits of disease eradication in DALYs averted may not be the best measure in the first place, as the long term consequences and broader benefits of eradicating a disease are not fully captured. In this study, we chose to evaluate the costs of interrupting

transmission and the resulting health benefits over a 50 year time horizon. While the relative cost-effectiveness between scenarios would likely remain the same regardless of time scale selected, the absolute results would have decreased if a shorter time horizon had been chosen, or increased with a longer time horizon. Consequently, there is a need to develop a quantitative measure which takes into account the permanent benefits of disease eradication.

6.4   Policy Implications

While our study utilized theoretical models, the findings suggest that, pragmatically, all LF endemic countries should be equipped with the resources and capacity needed to achieve the scale-up specified under eradication III (immediate MDA coverage to all at-risk populations). However, there is currently not enough data or experience to assess whether eradication III is feasible in all LF endemic countries. Further, there may be specific challenges, national issues, and unforeseen circumstances which make the scale-up schedule specified in eradication III difficult in a portion of countries. Therefore, special measures should be taken to ensure that, at the very least, all countries meet the standards of scale-up outlined under eradication II, in which at least 20% of each country's at-risk population is added to the treatment schedule annually. In this way, the worst case scenario countries with the greatest challenges will reach local elimination by 2032, though the majority of countries will still see local elimination before 2028.

With the exception of the eradication I scenario, the results from the cost-effectiveness analysis are well within previously considered acceptable cost-benefit thresholds [122]. The cost-effectiveness of the LF eradication program could be further increased, though, by integrating the LF program with other disease initiatives. On a global scale, there has already been considerable work towards integrating programs. Several public–private partnerships have come together to form the Global Network for Neglected Tropical Diseases, an initiative to raise awareness, political will, and funding to control and eliminate seven of the most common NTDs [126]. The WHO has also developed guidelines for integrated preventive chemotherapy [127], and recently, there has been movement towards integrating the African Program for Onchocerciasis Control (APOC) with the Global Program to Eliminate LF (GPELF) [128]. Further, many countries have already integrated some of their NTD control and elimination activities [109,129,130]. Integrating the LF program with other NTD campaigns that carry out similar activities, including: advocacy, trainings, drug distribution, and surveillance, is a great first step towards improved efficiency and improved health.

In addition to integrating similar activities between vertical programs, the LF program could benefit further by thinking even more broadly and collaboratively.

Table 13 lists diseases that are also impacted by the distribution of the antifilarials used by the GPELF. If integration is considered not just in terms of merging similar activities between vertical programs, but also in terms of all of the diseases that are impacted by the distribution of the drugs used in the LF program, the calculated value and sustainability of the campaign could be further increased. As individual NTDs have relatively low global health importance, having a broader consideration of all diseases affected would also result in a more visible and better accounted for campaign, which may help garner support from stakeholders and the broader public health community [23].

Table 13: Additional diseases affected by the distribution of the GPELF's antifilarials

	Global prevalence	Region	Estimated DALYs (millions)	Global Goal
Ivermectin				
Onchocerciasis	37 million[127]	Africa, Americas, Arabian Peninsula[127]	0.49 (0.36-0.66)[23]	Elimination[127]
Strongyloidiasis	30-100 million[131]	Tropical and sub- Tropical areas, some temperate regions[132]	Unknown[133]	None[134]
Ascariasis	0.8-1.2 billion[135]	Worldwide[135]	1.32 (0.71-2.35)[23]	Elimination of soil-transmitted helminth (STH)- morbidity in children by 2020[136]
Trichuriasis	600-800 million[137]	Worldwide, mainly tropical areas with poor sanitation[138]	0.64 (0.35-1.06)[23]	Elimination of STH-morbidity in children by 2020[136]
Scabies	>130 million[139]	Worldwide[139]	1.5[4]	Control[140]
Albendazole				
Giardiasis*	200 million[141]	Worldwide[142]	Unknown	None
Trichuriasis	600-800 million[23]	Worldwide, mainly tropical areas with poor sanitation[138]	0.64 (0.35-1.06)[23]	Elimination of STH-morbidity in children by 2020[136]
Neurocysticercosis*	50 million[143]	Latin America, Asia, sub Saharan Africa[143]	0.503 (0.379-0.663)[4]	None[144]
Hydatid Disease*	1 million[145]	Worldwide[145]	0.143[4]	None
Enterobiasis				
Ascariasis	0.8-1.2 billion[134]	Worldwide[136]	1.32 (0.71-2.35)[23]	Elimination of STH-related morbidity in children by 2020[136]
Toxocariasis	Unknown. Highly variable seroprevalence rates reported [146]	Worldwide[147]	Unknown	None
Hookworm	600 million[137]	Sub Saharan Africa, Latin America, Southeast Asia, China	3.23(1.70-5.73)[23]	Elimination of STH-related morbidity in children by 2020[136]

*Generally requires more than single dose therapy

As observed at the end of previous elimination and eradication campaigns, and also found within our LF costing study (Chapter 4), as the number of people to be treated decreases, so too does the favorability of measuring the unit treatment costs [66,148]. To sustain momentum during the final phase of the program, it has been suggested to change the cost evaluations from cost per person treated to cost per case averted [107]. Having a multi-disease initiative would be further beneficial in this regard, since the cost per case averted would certainly increase if all diseases impacted by MDA for LF were to be considered. Further, since different diseases require different lengths of MDA to reach their disease-specific endpoints, milestones and achievements would be reached in a staggered manner, which would presumably further propel the overall multi-disease program forward by providing evidence of the success of the initiative. Grouping the diseases together could also help spread out some of the risk and negative focus that occurs when one individual program faces unforeseen obstacles. As such, the risk of donor disillusionment and fatigue would be mitigated. Therefore, shifting from a strict vertical thinking approach for LF eradication, to a much more inclusive and widespread campaign, could increase cost-effectiveness, while also providing numerous additional benefits.

6.5   Areas of future research and general recommendations

The evidence laid out in this thesis is sufficient to move forward with increased MDA scale-up to reach eradication. While this thesis highlights a number of areas for future research, any such efforts should accompany a move towards eradication, not delay it.

6.5.1   Improved data

Research on the epidemiological factors and costs associated with eradicating LF, particularly in areas with the highest LF burden and where challenges threaten the technical and operational feasibility of the current strategy, would aid in planning and policy development. The collection and use of expenditure data, both from stand alone and integrated programs, would also be useful at the country and global levels. The effect of vector control on LF transmission needs to be further investigated, and increased partnerships and strategies to benefit malaria control programs and the GPELF should also be utilized. Modeling work is currently underway to assess where the current GPELF strategy is likely to achieve local elimination and where alternative approaches are warranted [149]. On-the-ground studies to parameterize and validate the models, as well as research on the effectiveness of strategies to mitigate some of the potential operational challenges are also needed.

6.5.2   Learning for change

A compilation of best practices and lessons learned from countries that have reached elimination would provide valuable guidance to other LF endemic countries that have not yet begun elimination efforts, are at the beginning of their programs, or are otherwise struggling to scale-up. Acknowledging and learning from other disease elimination and eradication initiatives would also be advantageous for the LF program.

6.5.3   Transparency and governance

It is hoped that the evidence presented here would be sufficient to convince decision makers of the benefits of scaling-up efforts against LF as quickly as possible to reach eradication, though whether that is the case remains unclear. On the global level, there needs to be improved transparency in the political decision-making process for disease eradication. While an Eradication Investment Case (EIC) provides the framework for compiling many components that should be evaluated prior to proceeding with disease eradication [61], it would be useful if the type of evidence upon which the decision to proceed with eradication were explicitly specified.

Further, there needs to be an agency in place to monitor, evaluate, and govern potential and ongoing disease eradication initiatives. Such an agency, from here on referred to as a disease eradication governing agency (DEGA), would conceivably evaluate the evidence base supporting disease eradication initiatives, monitor and assess progress towards eradication milestones, and ensure that financial and political commitments are upheld across all partnerships through contractual and other legal arrangements. The DEGA would need to be grounded in action rather than bureaucracy, as the usefulness of the agency would be heavily dependent upon its ability to hold countries, investors, and other stakeholders accountable when milestones are not achieved or commitments are not upheld.

The DEGA should be composed of infectious disease experts alongside implementation advisors, contract and finance specialists, and disease eradication thought leaders. By having a core group of multidisciplinary experts with experience in disease eradication governing across different disease initiatives, problems arising during an eradication initiative may be recognized earlier, and best practices for mitigating challenges could be operationalized sooner. The DEGA could also point out activities between ongoing disease eradication initiatives that could be integrated, such as surveillance, in order to improve efficiencies and effectiveness on a global scale. By being impartial to any disease-specific initiative, the DEGA could also serve to independently evaluate progress

towards major milestones in the road to eradication and provide recommendations to improve the likelihood of achieving eradication.

7   Conclusion

The justification for this research stems from the necessity for proper planning prior to committing to disease eradication. The evidence presented here, while clear limitations in many cases relating to the availability and accuracy of data, provides a strong case for increased levels of scale-up to eradicate LF. Indeed, across all considerations, including: time, treatments, level of investments necessary, health impact, cost-effectiveness, and broader economic benefits, scaling-up MDA coverage to all endemic communities immediately provides the most favorable results. Ultimately, though, the success of eradicating LF will depend on the political engagement and enthusiasm at all levels.

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Supplementary Material

Supplementary material 1: What is Needed to Eradicate Lymphatic Filariasis? A Model-Based Assessment on the Impact of Scaling up Mass Drug Administration Programs

<u>LF model description</u>

The deterministic transmission model used for the current analysis, EpiFil, has been described in detail, validated against multiple data sets for transmission settings with both *Anopheles* spp. and *Culex* spp. as vectors, and used extensively to predict outcomes of interventions (MDA, vector control) for bancroftian lymphatic filariasis [15,47-49]. Specifically, the model versions we used largely followed the structure presented by Gambhir & Michael [49], which includes the possibility of female worms remaining unmated in humans at low densities, and provides different microfilariae uptake functions (facilitation versus limitation) for *Anopheles* spp. and *Culex* spp. vectors.

The model consists of the following partial differential equations used to describe changes in state parameters:

$$\frac{\partial W}{\partial t} + \frac{\partial W}{\partial a} = \lambda \frac{V}{H} \psi_1 \psi_2 s_2 h(a) L^* e^{-\beta I} - \mu W$$

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = \alpha \phi(W, k) W - \gamma M$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = W - \delta I$$

The state parameters represent the following: the mean adult worm burden in humans, W; the mean microfilariae density in humans, M; the mean level of immunity to infection, I. The initial conditions were W(0,t) = M(0,t) = I(0,t) = 0, while W(a,0), M(a,0) and I(a,0) were the equilibrium levels in the absence of interventions, obtained numerically by simulating the model for a sufficiently long period. The mean L3 density in the mosquito population, L*, is given by:

$$L^* = \frac{\lambda k g \int \pi(a)(1 - f(M)) da}{\sigma + \lambda \psi_1}$$

and f(M), which combines the moment generating function of the negative binomial distribution of infection in humans with the microfilariae uptake curve of individual mosquitoes, as:

$$f(M)_C = (1 + \frac{M}{k(M)}(1 - e^{-r/k}))^{-k(M)}$$

$$f(M)_A = \left[\frac{2}{(1 + \frac{M}{k(M)}(1 - e^{-r/k}))^{k(M)}} - \frac{1}{(1 + \frac{M}{k(M)}(1 - e^{-2r/k}))^{k(M)}} \right]$$

with f(M)$_C$ describing the function used for *Culex* spp. [15] and f(M)$_A$ for *Anopheles* spp. [49]. The worm mating function is given by:

$$\phi(W,k) = 1 - (1 + \frac{W}{2k})^{-k-1}$$

The rate parameters and values used are described in Table S1, while h(a) and π(a) represent the age-dependent attractiveness to mosquitoes (we assumed a linear increase from 0 to 1 over the first 10 years of life and a value of 1 for further years) and an approximation of the human age distribution (π(a) = 0·035 e$^{-0·026\ a}$), respectively, as in Norman et al [15]. Typical values are presented as examples and for *Culex* spp. followed that of Norman et al [15], who fitted parameter values to reflect transmission of *Wuchereria bancrofti* by *Culex quinquefasciatus* in an Indian environment. For *Anopheles* spp. the typical parameter values reflect the average of those presented by Gambhir *et al.* [47] for the Tanzanian sites Tawalani and Masaika. However, as different geographic settings can differ dramatically in their parameter estimates [47,48], and because we had a need for varying parameter estimates that would result in stable prevalence levels associated with our transmission archetypes (ca. 5%, 10%, 15%, and 20% prevalence), we obtained parameter sets that would lead to these levels of prevalence while allowing for parameter uncertainty.

In order to do so, we used a Bayesian framework of importance resampling [47,150]. We first defined uninformative ranges for the parameter values based on literature and intuition (Table S1), and drew 10,000 sets of random samples from these uniform priors. For each of these randomly generated parameter sets, *i*, the model was simulated for 250 years at which point the stable equilibrium prevalence, *x*, was calculated. The goodness-of-fit of each run to the prevalence level associated with the transmission archetype, *p*, was estimated as a binomial likelihood,

$L_i = \binom{N}{x} p^x (1-p)^{N-x}$. We then randomly sampled, with replacement, 500 parameter sets from the

original 10000 sets proportional to their likelihood, $\Delta L_i = \dfrac{L_i}{\sum L}$ to obtain an approximation of a

posterior distribution.

Supplement Table 1: Parameter descriptions and values used in EpiFil

Parameter	Description	Typical value		Prior ranges
		Culex[†]	Anopheles[‡]	
λ	human biting rate	10	10.52	6-15 (0.2-0.5 per day)
V/H	vectors per human	576	75.5	50-500
ψ_1	proportion of L3s leaving per bite	0.4	0.45	0.3-0.7
$\psi_2 s_2$	proportion of L3s entering puncture & establishing	0.0001	0.004	0.00002-0.004
g	proportion of bites on infected humans leading to infection	0.37	0.37	0.25-0.5
β	measure of acquired immunity	[0.031 – 0.11]	[0.011 – 0.047][#]	0.001-0.2
δ	decay of immunity	0.004	0	0-0.005
μ	adult worm death rate	0.01	0.01	0.014-0.007
$\boldsymbol{\alpha}$	adult worm fecundity	2	1.14	0.2-2
σ	mosquito death rate	5	4.68	0.9-6
γ	death rate of mf	0.1	0.095	0.083-0.125
C	MDA coverage	85%	85%	-
μ_{mf}	microfilaricidal effect	0.95; 0.99	0.95; 0.99	0.9-0.95; 0.95-0.99
μ_W	macrofilaricidal effect	0.55; 0.35	0.55; 0.35	0.5-0.6; 0.3-0.4
μ_α	suppression of worm fecundity	0.95; 0.99	0.95; 0.99	0.9-0.95; 0.95-0.99
κ	constant in L3 uptake function	6	4.39	4-6
r	constant in L3 uptake function	0.047	0.055	0.04-0.06
k(M)	aggregation parameter	0.0029 + 0.0236(M)	0.00203 + 0.015(M)	(0.0006-0.002) + (0.01-0.03) M

[†]Parameter values for *Culex* taken from Norman et al (2000)

[‡]Parameter values for *Anopheles* taken from Gambhir & Michael (2008) and Gambhir et al (2010)

We used these resampled parameter sets to investigate the impact of MDA on LF prevalence over time. Examples of prevalences associated with the parameter sets and distributions of a number of parameters are given (Figures. S1, S2).

Supplement Figure 1: Example of microfilariae prevalence levels associated with the set of posterior estimates for anopheline transmission (10% prevalence)
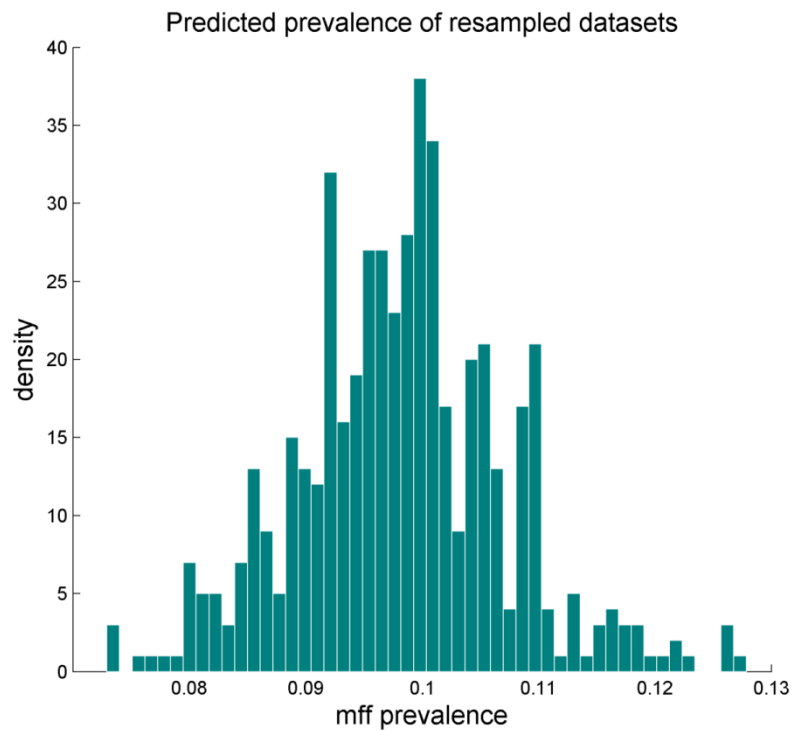
Supplement Figure 2: Examples of parameter value estimates for different vector genera and MF prevalence levels
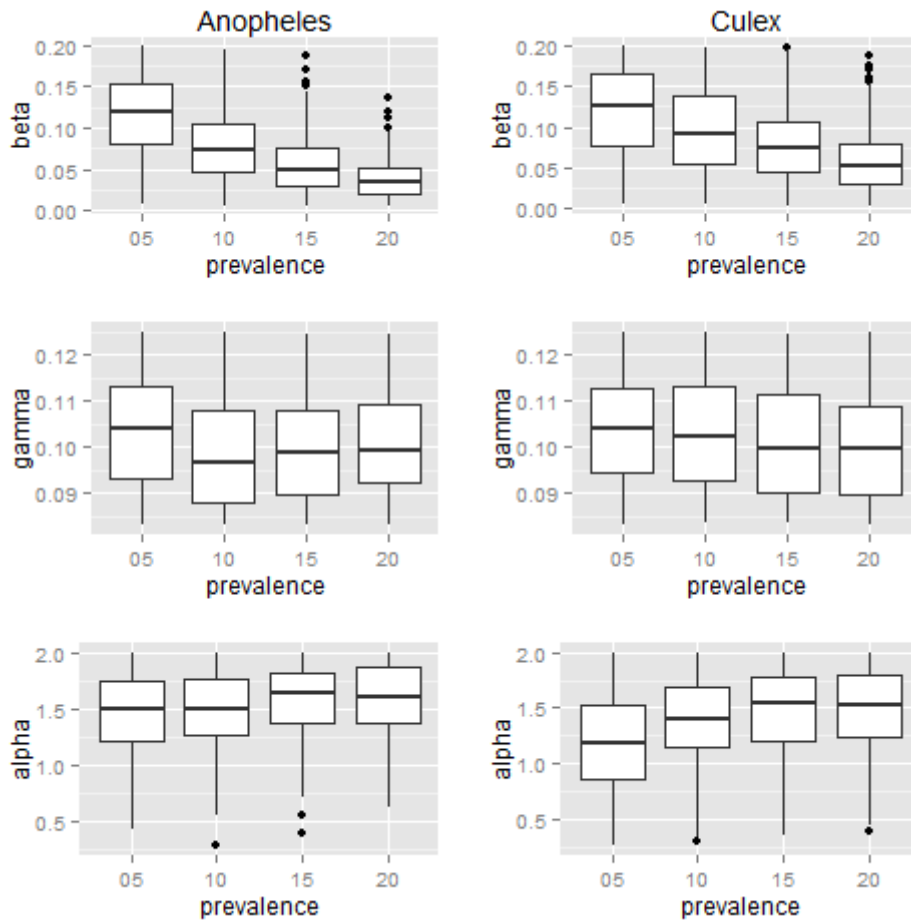
We simulated the effects of filaricidal treatment by including a once-yearly instantaneous killing of a proportion of adult worms, μ_w, and microfilariae, μ_{mf}, depending on drug type and level of coverage. Additionally, fecundity of worms, α, was reduced for six to nine months following an MDA round by a proportion, μ_α. The impact of MDA programmes was then investigated by repeating these treatments for a varying number of years, after which no further intervention took place. For each duration (number of MDA rounds), per vector type and drug regimen, we ran 500 simulations drawing from the range of posterior parameter estimates, and the lowest number of rounds at which in the 95th percentile range of these simulations prevalence was below 1% and decreasing at the end of the simulation was taken as a conservative measure of the number of rounds required to ensure elimination. Examples of simulations leading to interruption of transmission are given in Figure S3, and the predicted number of rounds required are provided in Table 5.

Supplement Figure 3: Median values (solid lines) and 95th percentile range (shaded areas) of LF prevalence for LF transmission by Anopheles spp. (left) and Culex spp. (right) at four different stable levels of pre-intervention LF prevalence
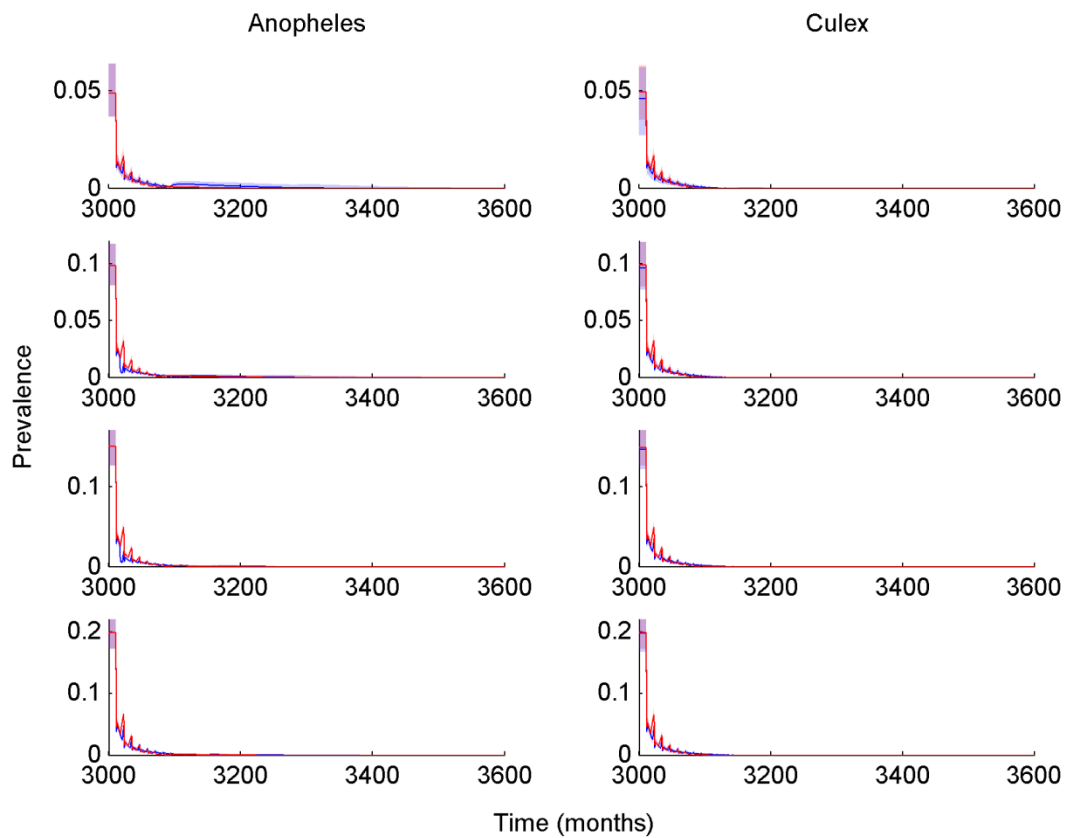
From top to bottom: 5, 10, 15, 20%), using DEC and albendazole (red) or ivermectin and albendazole (blue) combination therapy.

Supplementary material 2: How much will it cost to eradicate lymphatic filariasis? An analysis of the financial and economic costs of intensified efforts against lymphatic filariasis

<u>Probabilistic Sensitivity Analysis</u>

Our micro-costing model was built up using resource quantities and associated unit costs. Following guidance from Briggs et. al, we undertook a probabilistic sensitivity analysis (PS) assuming gamma distributions, parameterized as gamma(α,β), for all unit cost inputs.. The deterministic value was assumed to be the sample mean (μ), with variance *s.* Which follows:

$$\mu = \alpha\beta, s^2 = \alpha\beta^2$$

$$\alpha = \frac{\mu^2}{s^2}, \beta = \frac{s^2}{\mu}$$

[151]

We assumed 10% variance across all parameters. Supplement Table 2 lists all parameters considered along with their deterministic value, calculated standard error, alpha, and beta estimates.

Supplement Table 2: Parameters used in the Probabilistic Sensitivity Analysis

Parameters	Deterministic Value	Standard Error	Alpha	Beta
Per diem rates				
Case management specialist	$40.00	4.000	100	0.4000
Community moderator	$4.68	0.468	100	0.0468
CDD - training	$1.17	0.117	100	0.0117
CDD - providing data	$0.78	0.078	100	0.0078
Clinical officer	$19.50	1.950	100	0.1950
Community leaders	$4.68	0.468	100	0.0468
Data entry clerk	$78.00	7.800	100	0.7800
District representative	$20.00	2.000	100	0.2000
District vector control officer	$19.50	1.950	100	0.1950
District support staff: district guide	$4.68	0.468	100	0.0468
District support staff: local councillor (teachers)	$1.95	0.195	100	0.0195
District support staff: local councillor (mobilizer)	$4.29	0.429	100	0.0429
Driver	$21.45	2.145	100	0.2145
Health promotion and education officer	$41.26	4.000	100	

				0.4000
IT consultant	$38.87	4.000	100	0.4000
M&E officer	$38.14	4.000	100	0.4000
Minister of health	$43.33	5.000	100	0.5000
National trainers	$38.50	4.000	100	0.4000
NTD Coordinator	$48.79	4.000	100	0.4000
Parish supervisors	$ 4.74	0.468	100	0.0468
Partners	-			
Procurement officer	$41.36	4.000	100	0.4000
Programme managers	$33.25	4.000	100	0.4000
Religious leaders	$4.68	0.468	100	0.0468
Senior scientist	$42.90	4.290	100	0.4290
Social scientists	$40.00	4.000	100	0.4000
Sub county supervisors	$4.68	0.468	100	0.0468
Support staff, rural	$4.68	0.468	100	0.0468
Support staff, urban	$10.00	1.000	100	0.1000
Technician	$39.00	3.900	100	0.3900
ToTs from District Health Office	$4.68	0.468	100	0.0468
ToTs from sub county	$19.50	1.950	100	0.1950
Village chief	$4.68	0.468	100	0.0468
Materials and supplies				
Accommodation - rural	$11.70	1.170	100	0.1170
Accommodation - urban	$100.00	10.000	100	1.0000
Advocacy booklets	$1.50	0.150	100	0.0150
Air time	$19.50	1.950	100	0.1950
Alcohol swab (packet of 100)	$4.68	0.468	100	0.0468
Bags for CDDS	$0.39	0.039	100	0.0039
Banners	$25.00	2.500	100	0.2500
Batteries (size D)	$1.17	0.117	100	0.0117

Billboards	$200.00	20.000	100	2.0000
Blood lancets (box of 200 pieces)	$4.68	0.468	100	0.0468
Box files	$2.54	0.254	100	0.0254
Broadcast spots on radio	$234.00	23.400	100	2.3400
Broadcast spots on TV (1 hour)	$390.00	39.000	100	3.9000
Capillary tubes (60 ul), 100 pieces	$9.75	0.975	100	0.0975
Coartem or (ARCO)	$1.76	0.176	100	0.0176
Co-trimazole Tablets (1000)	$8.27	0.827	100	0.0827
Cotton wool (500 gram roll)	$1.95	0.195	100	0.0195
Counter book (4 quire)	$2.34	0.234	100	0.0234
Dettol soap (100 grams)	$0.98	0.098	100	0.0098
Gauze	$3.14	0.314	100	0.0314
Gimesa stain	$90.65	9.065	100	0.9065
Glass slides (50 pcs)	$2.54	0.254	100	0.0254
Gloves (Disposable Rubber)	$4.88	0.488	100	0.0488
Hall rental, capital	$150.00	15.000	100	1.5000
Hall rental, other	$19.50	1.950	100	0.1950
Heparine coated container(200µl)	$0.20	0.020	100	0.0020
Ibuprofen Tablets (1000)	$3.90	0.390	100	0.0390
Internet and accessories	$1,000.00	100.000	100	10.0000
Labels (Packet of 200 labels)	$1.95	0.195	100	0.0195
Laundry soap - bar	$1.17	0.117	100	0.0117
Laundry soap -Detergent powder (1 kg)	$3.12	0.312	100	0.0312
Magnesium trisilicate (1000)	$2.93	0.293	100	0.0293
Match box (10 pieces)	$0.39	0.039	100	0.0039
Meals, capital	$7.80	0.780	100	0.0780
Megaphone	$45.00	4.500	100	0.4500
Mobile phones	$80.00	8.000	100	0.8000
Neomycin ointment (12)	$7.02	0.702	100	0.0702
Paracetamol Tablets (1000)	$3.90	0.390	100	0.0390

Paraffin	$0.94	0.094	100	0.0094
Pens (packets of 50)	$0.20	0.020	100	0.0020
Pencils (HB) dozens	$0.02	0.002	100	0.0002
Permanent marker	$2.60	0.260	100	0.0260
Photocopying paper	$6.63	0.663	100	0.0663
Pipette tips	$0.39	0.039	100	0.0039
Pamphlets for districts	$0.39	0.039	100	0.0039
Posters	$1.17	0.117	100	0.0117
Refreshments, capital	$5.00	0.500	100	0.0500
Refreshments, rural	$1.37	0.137	100	0.0137
Reproduction of advocacy materials	$0.10	0.010	100	0.0010
Safety boxes (Sharps container)	$0.39	0.039	100	0.0039
Sentinel site forms	$0.03	0.003	100	0.0003
Stationary	$1.17	0.117	100	0.0117
Survey forms	$0.03	0.003	100	0.0003
Sweets	$5.85	0.585	100	0.0585
Test kits - Binax Now(25 test kits)	$5.48	0.548	100	0.0548
Trash bags (50 pieces)	$1.95	0.195	100	0.0195
Trash containers (50 pieces)	$1.95	0.195	100	0.0195
Toilet paper (20 roll carton)	$4.29	0.429	100	0.0429
T-shirts	$3.90	0.390	100	0.0390
Activities				
Data cleaning/ Entry Clerk/Analysis	$975.00	97.500	100	9.7500
Institution review clearance fees	$210.60	21.060	100	2.1060
Report writing (lump sum)	$195.00	19.500	100	1.9500
Slide reading	$0.39	0.039	100	0.0039
Data analysis	$195.00	19.500	100	1.9500
Demographics				
# of people per district	279,089	27909	100	2,790.8900
# people per subdistrict	18,006	1801	100	180.0600
# parishes per district	64	6	100	0.6400

# people per village	730	73	100	7.3000
# schools per district	209	21	100	2.0894
Personnel Salaries – WHO CHOICE				
Programme Director				
AFRO D	$35,948.45	3594.845	100	359.4845
AFRO E	$35,592.05	2371.055	100	237.1055
AMR B	$46,422.24	4642.224	100	464.2224
AMR D	$35,882.89	2390.366	100	239.0365
EMR D	$8,828.88	882.888	100	88.2888
SEAR B	$21,010.75	2101.075	100	210.1075
SEAR D	$29,322.32	1953.391	100	195.3391
WPR A	$119,654.14	11965.414	100	1,196.5414
WPR B	$41,810.53	4181.053	100	418.1053
Program Manager				
AFRO D	$23,947.75	2394.775	100	239.4775
AFRO E	$23,710.55	1464.328	100	146.4328
AMR B	$30,925.51	3092.551	100	309.2551
AMR D	$23,903.65	1476.367	100	147.6367
EMR D	$5,881.15	588.115	100	58.8115
SEAR B	$13,997.24	1399.724	100	139.9724
SEAR D	$19,533.91	1206.387	100	120.6387
WPR A	$79,710.23	7971.023	100	797.1023
WPR B	$27,853.82	2785.382	100	278.5382
Administrative Assistant				
AFRO D	$14,791.08	1479.108	100	147.9108
AFRO E	$14,643.28	1109.242	100	110.9242
AMR B	$19,100.04	1910.004	100	191.0004
AMR D	$14,763.67	1118.301	100	111.8301
EMR D	$3,631.92	363.192	100	36.3192

SEAR B	$8,645.32	864.532	100	86.4532
SEAR D	$12,063.87	913.760	100	91.3760
WPR A	$49,230.51	4923.051	100	492.3051
WPR B	$17,202.43	1720.243	100	172.0243
Finance Officer				
AFRO D	$11,203.27	1120.327	100	112.0327
AFRO E	$11,092.42	1109.242	100	110.9242
AMR B	$14,466.87	1446.687	100	144.6687
AMR D	$11,183.01	1118.301	100	111.8301
EMR D	$2,751.05	275.105	100	27.5105
SEAR B	$6,547.46	654.746	100	65.4746
SEAR D	$9,137.60	913.760	100	91.3760
WPR A	$37,289.41	3728.941	100	372.8941
WPR B	$13,030.55	1303.055	100	130.3055
Data Entry Clerk				
AFRO D	$11,203.27	1120.327	100	112.0327
AFRO E	$11,092.42	1464.328	100	146.4328
AMR B	$14,466.87	1446.687	100	144.6687
AMR D	$11,183.01	1476.367	100	147.6367
EMR D	$2,751.05	275.105	100	27.5105
SEAR B	$6,547.46	654.746	100	65.4746
SEAR D	$9,137.60	1206.387	100	120.6387
WPR A	$37,289.41	3728.941	100	372.8941
WPR B	$13,030.55	1303.055	100	130.3055
Supplies Manager				
AFRO D	$14,791.08	1479.108	100	147.9108
AFRO E	$14,643.28	3559.205	100	355.9205
AMR B	$19,100.04	1910.004	100	191.0004
AMR D	$14,763.67	3588.289	100	358.8289

EMR D	$3,631.92	363.192	100	36.3192
SEAR B	$8,645.32	864.532	100	86.4532
SEAR D	$12,063.87	2932.232	100	293.2232
WPR A	$49,230.51	4923.051	100	492.3051
WPR B	$17,202.43	1720.243	100	172.0243

Supplementary material 3: Modelling the health impact and cost-effectiveness of lymphatic filariasis eradication under varying levels of mass drug administration scale-up and geographic coverage

Scenarios

The elimination and eradication scenarios are based on an analysis of the currently ongoing elimination programme. Their composition are described in detail in Chapter 3. Briefly, the scenarios were based on the mass drug administration of filaricidal drugs: albendazole (ALB) either in combination with diethylcarbamazine citrate (DEC) or, in areas where coendemicity of *Onchocerca volvulus* is a concern, with ivermectin (IVM).

To account for heterogeneity in transmission intensity within countries, we assigned proportions of each at-risk population to transmission archetypes of approximately 0% (i.e., the proportion of implementation units (IUs) that were false positive), 5%, 10%, 15% and 20% microfilaremia prevalence. The data reflected the situation in African countries, i.e., the proportion of endemic implementation units that fell within >0-5% prevalence, 5-10%, 10-15%, or >15%. The archetypes used in the analysis reflect an upper boundary to the underlying data, save for the highest level, where a 20% prevalence was taken as a representation of very high transmission levels. The average proportion of IUs that fell within these categories was used for all countries, and uncertainty in this estimate was included by treating these averages as a probability in a multinomial distribution (Chapter 3).

We used the number of treatment estimates required for each year, in each LF-endemic country and each scenario from Chapter 3. These estimates were derived upon the number of annual treatment rounds of MDA necessary, taking into consideration the underlying microfilaria prevalence quartiles in each country, whether transmission is due to *Anopheles* spp. or *Culex* spp., the drug regimen used, and the number of effective MDA rounds that had already occurred prior to 2013. These estimates are conservative in the sense that they allowed the credible interval of our simulations to achieve elimination. We thus assumed that public health officials implemented MDA programmes of these durations in order to assure a high probability of achieving elimination.

We used these estimated durations to predict the number of treatments required per year for each of the elimination and eradication scenarios, as well as to develop estimates of the financial and economic costs associated with implementing the scenarios (Chapter 4).

Model

We used two versions of the deterministic model, EpiFil , to simulate adult filarial worm, microfilaria and infective stage larvae (L3) transmission and dynamics when the mosquito vectors were either *Anopheles* or *Culex* spp. The model versions we used largely followed the structure presented by Gambhir & Michael [49], which includes the possibility of female worms remaining unmated in humans at low densities, and provides different microfilariae uptake functions (facilitation and limitation) for *Anopheles* spp. and *Culex* spp. vectors. We assumed that transmission by other mosquito genera (e.g., Aedes, Mansonia) is approximated well enough by these model versions.

The transmission model was thus the same as used and described in our related analysis (Chapter 3) and is described in detail in the supplementary material. The model consists of the following partial differential equations used to describe changes in state parameters:

$$\frac{\partial W}{\partial t} + \frac{\partial W}{\partial a} = \lambda \frac{V}{H} \psi_1 \psi_2 s_2 h(a) L^* e^{-\beta I} - \mu W \tag{1}$$

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = \alpha \phi(W,k) W - \gamma M \tag{2}$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = W - \delta I \tag{3}$$

The state parameters represent the mean adult worm burden in humans, W; the mean microfilariae density in humans, M; and the mean level of immunity to infection, I. The initial conditions were W(0,t) = M(0,t) = I(0,t) = 0, while W(a,0), M(a,0) and I(a,0) were the equilibrium levels in the absence of interventions, obtained numerically by simulating the model for a sufficiently long period. L*, the mean L3 density in the mosquito population, is given by:

$$L^* = \frac{\lambda \kappa g \int_a \pi(a)(1 - f(M)) da}{\sigma + \lambda \psi_1} \tag{4}$$

The functions *h(a)* and *π(a)* represent the age-dependent availability to mosquitoes (represented as a linear increase from 0 to 1 over the first 10 years of life and a value of 1 for further years) and an approximation of the human age distribution (π(a) = 0·035 e$^{-0·026\ a}$), respectively, as in Norman et al. [15]. The population-averaged uptake of infective stage filarial larvae by mosquitoes, f(M), is defined as:

$$f(M)_c = (1 + \frac{M}{k(M)}(1 - e^{-r/\kappa}))^{-k(M)} \tag{5}$$

$$f(M)_A = \left(\frac{2}{(1+\frac{M}{k(M)}(1-e^{-r/k}))\text{k(M)}} - \frac{1}{(1+\frac{M}{k(M)}(1-e^{-2r/k}))\text{k(M)}} \right) \qquad (6)$$

with f(M)$_C$ describing the function used for *Culex* spp. [15] and f(M)$_A$ for *Anopheles* spp. [49]. The worm mating function [49,152] is given by:

$$\phi(W,k) = 1 - (1+\frac{W}{2k})^{-k-1} \qquad (7)$$

To assess the resulting health impact of the different scenarios, the progression of disease, adapted from the ordinary differential equations of Chan *et al. [153],* was added to the model of lymphatic filariasis transmission. These equations suggest that progression to hydrocele and lymphedema result directly from damage to the lymphatic system that accrues due to harbouring adult worms over time. Different grades of lymphedema or hydrocele, or other aspects of disability related to LF, are not accounted for:

$$\frac{\partial D}{\partial t} + \frac{\partial D}{\partial a} = \eta(W(1-D)) - r_d D \qquad (8)$$

$$\frac{\partial L}{\partial t} + \frac{\partial L}{\partial a} = \pi D(1-L) \qquad (9)$$

$$\frac{\partial H}{\partial t} + \frac{\partial H}{\partial a} = hD(1-H) - r_h H \qquad (10)$$

where D represents the mean proportion of humans with lymphatic damage; the mean proportion of humans with lymphedema is given by L; and the mean proportion of males in areas where *W. bancrofti* is the causative agent with hydrocele by H. The rate parameters and range of prior values used are described in **Error! Reference source not found.** 1.

Parameter estimation

We used the same posterior parameter estimates for the parameters of the transmission model (i.e, those appearing in equations 1-7) that resulted in stable prevalence levels associated with the transmission archetypes (ca. 5%, 10%, 15%, and 20% prevalence) as used in Chapter 3, as well as the expected durations of MDA programmes in the different transmission settings. The effects of filaricidal treatment were included through a once-yearly instantaneous killing of a proportion of adult worms, μ_w, and microfilariae, μ_{mf}, within the proportion of humans (85%) covered by the programs. Additionally, the fecundity of adult worms, α, was reduced to zero for six to nine months following a round of MDA within treated humans [76]. The exact values of these killing parameters

were randomly sampled from their ranges to allow for a degree of uncertainty in the efficacy of MDA programmes.

The parameters related to the disease model (those in equations 8-10) were estimated for each of the four levels of prevalence associated with our archetypes using the same importance-resampling method as previously (Chapter 3), and similar to that which has been used to fit EpiFil to transmission patterns in specific geographic settings [47,48]. For the purpose of obtaining disease parameter estimates, we fixed the transmission related parameters at the medians of their previously estimated values (Chapter 3), while for the disease-related parameters we drew 10,000 random samples from their uninformative prior ranges. A relation between the prevalence of chronic disease states due to LF (hydrocele and lymphedema) and microfilaria prevalence in given localities has been investigated and these data are presented by Michael et al. [124]. These data are replotted (Supplementary Figure 4a), and the median and interquartile ranges of the data points binned per the prevalence levels associated with our transmission archetypes are depicted in Supplement Figure 4.

We ran 10,000 simulations and calculated the goodness of fit of each simulation to the data on chronic disease prevalence. Because we required estimates of the prevalence of hydrocele and lymphedema, rather than a combined prevalence of chronic disease, the total prevalence was decomposed to male and female prevalence following the global estimate of Michael et al. [79], so that $Pr_{cd,male} = Pr_{cd,total}*1\cdot75$ and $Pr_{cd,female} = Pr_{cd,total}*0\cdot25$, where $Pr_{cd,male}$ is equal to Pr_{l+h} and $Pr_{cd,female}$ is equal to Pr_l. We therefore make the simplifying assumptions that males and females acquire lymphedema at equivalent rates, and that co-occurrence of lymphedema and hydrocele in males is rare. The goodness of fit to a point prevalence level was assessed through a binomial likelihood:

$$L_i = \prod_{s=m,f} \binom{N}{x_S} p_S^{x_S} (1-p_S)^{N-x_S}$$

, where N is the human population size (assumed to be 1000), p_s the target prevalence levels of disease associated with the transmission archetype, and x_s is the simulated number of afflicted humans for the simulation run with parameter set, i. Male and female populations are indicated by s. We then randomly sampled, with replacement, 500 parameter sets

from the original 10000 sets proportional to their likelihood, $\Delta L_i = \dfrac{L_i}{\Sigma L}$ to obtain an approximation of their posterior distribution [47]. The prevalence of chronic LF-induced disease outcomes from sets of 500 simulations using the resampled parameter sets are depicted (Supplement Figure 5).

Supplement Figure 4: The relation between prevalence of microfilaremia and chronic disease used to fit disease model parameters
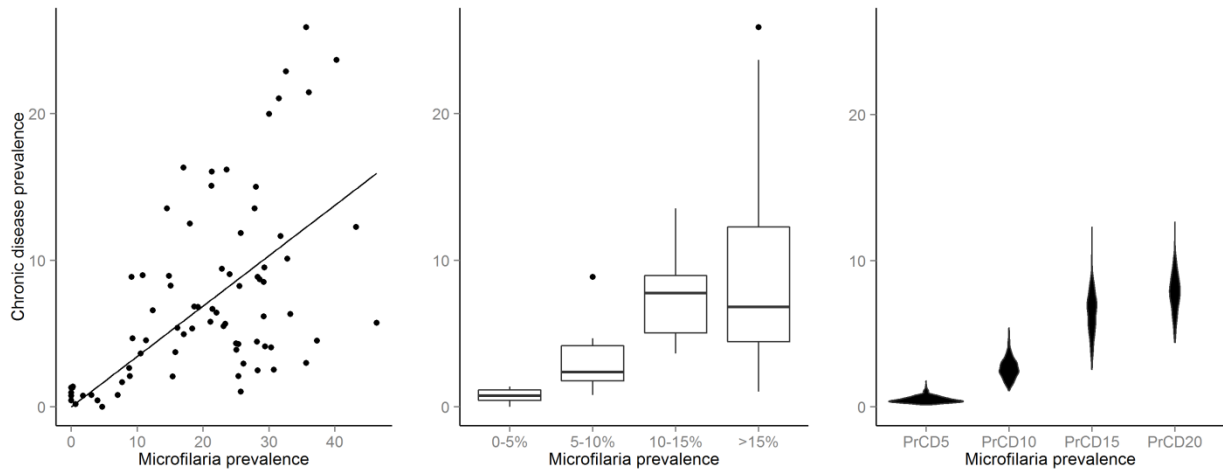
Data points and leftmost panel reproduced from Michael *et al* (2008) [124]. Middle: The median and interquartile ranges of the data points binned per prevalence levels associated with transmission archetypes. Right: Probability densities of chronic disease outcomes from sets of 500 simulations using resampled parameter sets.

Assessing the disability-adjusted life years averted by the eradication scenarios

Based on the results of the transmission and disease model, and accounting for the different transmission archetypes and the number of MDA rounds that countries had already completed, the mean prevalence of lymphedema and hydrocele for each age class over a period of 50 years was computed and recorded as matrices $P_l(t,a)$ and $P_h(t,a)$. In areas where Brugian filariasis predominates, we assumed that males are not affected by hydrocele and that lymphedema progressed as in Bancroftian filariasis. This was implemented for 20% of the Philippines and 60% of Indonesia, based on the ratio of prevalences between types [79], rounded up or down.

To translate prevalence to incidence per age class, we used country-specific demographic parameters (proportion alive at age x; life expectancy at age x; sex ratio at birth; population growth rate) [79]. This resulted in matrices $A_f(t,a)$ and $A_m(t,a)$ which gave the population sizes per five year age class over time, by sex. For each country we calculated the incidence per age per year for both males and females:

$$I_{f,i,j,k}(t,a) = P_{l,i,j,k}(t,a) \cdot A_{f,i,j,k}(t,a) \tag{1}$$

$$I_{m,i,j,k}\left(t,a\right) \; = \; P_{l,i,j,k}\left(t,a\right) \; \odot A_{m,i,j,k}\left(t,a\right) \; + \; P_{h,i,j,k}\left(t,a\right) \; \odot A_{m,i,j,k}\left(t,a\right) \qquad (2)$$

where the matrices are multiplied using the Hadamard product (i.e., element-wise), subscript i indicates the deciles within a country which differ only in their history of MDA, j indicates the four transmission intensity levels, and k each of the 500 iterations of the model. We then summed the cases over the deciles, $I_{f,j,k}(t,a)$ and $I_{m,j,k}(t,a)$, and obtained the number of new cases per 5-y-period and 5-y-age-group, as:

$$N_{j,k}\left(t+l+1,a\right) \; = \; I_{j,k}\left(t+l+1,a+1\right) - I_{j,k}\left(t+l,a\right) \qquad (3)$$

where l = [1, 2,...,10] indicates the 5-y-periods considered. For each age-group and each period, we calculated the YLDs by multiplying the number of new cases by the remaining expectation of life of that age group, e_l, and the disability weight (DW) of LF-related chronic disease, for males and females (s):

$$D_{j,k,s}\left(t,a\right) \; = \; N_{j,k,s}\left(t,a\right) \; e_l \, dw \, \frac{1}{dr^t} \qquad (4)$$

where the future discounting rate, dr, was set to 1·03.

Supplement Figure 5: Mean and standard deviation of 500 simulations of prevalence of lymphedema and hydrocele for the anopheline model version
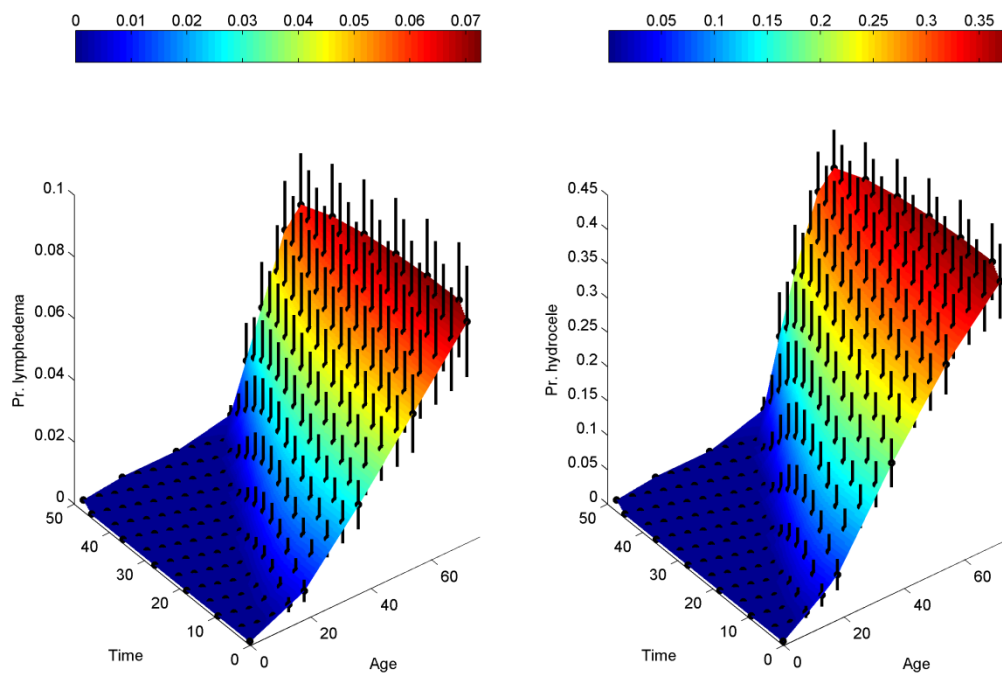
Mean and standard deviation of 500 simulations of prevalence of lymphedema and hydrocele for the anopheline model version Assuming 20% microfilaremia over time by age, using once-yearly diethylcarbamazine and albendazole administration for 7 years to interrupt transmission, starting at year 0

Assessing costs of implementing the global elimination and eradication scenarios

The costs of the scenarios modelled were estimated from the perspective of each LF-endemic country's health system. USAID's *NTD Master Plan Costing Tool in the African Region* from eight AFRO countries were reviewed to assess essential activities and resources needed to undertake the GPELF strategy at a country level. Essential activities, resources, and their associated costs were then confirmed by the LF elimination team in Uganda. All costs are reported in 2012 U.S. dollars and discounted at 3%.

Using Ugandan costs as a reference, the prospective costs for non-tradable goods and services in all other LF-endemic countries were imputed by adjusting with country-specific purchasing power parity (PPP) conversion factors [93]. All laboratory supplies and capital items were valued at their recommended retails prices. Salaries, as well as prices that were unable to be determined elsewhere, were taken from the WHO-CHOICE databank [16]. Additional details on the costing methodology can be found in Chapter 4.

Appendix

Lymphatic filariasis related morbidity

Lymphedema

Photo credit: Drugs & Diagnostics for Tropical Diseases

Elephantiasis

Photo credit: Carter Center

Hydrocele

Photo credit: British Journal of Urology

Preventative Interventions for LF

Determination of ivermectin dosage

Photo credit: Randee Kastner

School-based Mass Drug Administration

Community-based Mass Drug Administration