Value of investing in neglected tropical diseases: an investment case for the elimination and eradication of onchocerciasis (river blindness) in Africa

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Young Eun Kim

von Südkorea

Basel, 2015

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
Auf Antrag von

Prof. Marcel Tanner, Dr. Fabrizio Tediosi, und Prof. David Bishai

Basel, 13 Oktober 2015

Prof. Dr. Jörg Schibler
Dekan

Contents

Acknowledgements

The PhD period at Swiss TPH has given me wonderful opportunities to improve my professional capacity and to learn from colleagues with diverse cultural backgrounds.

I am grateful to Dr. Fabrizio Tediosi and Prof. Marcel Tanner for offering this PhD position and to Prof. David Bishai for introducing this wonderful opportunity. I am indebted to Dr. Hans Remme for his passionate support in building the epidemiological ground of the PhD research. I thank Elisa Sicuri, Peter Steinmann, Wilma Stolk, and Uche Amazigo. Also I thank our unit members, Konstantina Boutsika, Christine Mensch, and Margrith Slaoui.

Many thanks to Ashley Warren, Randee Kastner, and Simone Sutherland. Also many thanks to Nadja Cereghetti, Carol Dayo Obure, and Rajib Mitra for wonderful laughing memories, and to Mariah Silkey and Khampheng Phongluxa for emotional supports.

On a personal level, I thank my mother, my father, my brother, my grandfather (your memory will be always in my heart), my grandmother, Hye Ryun, and Hyun Nam for their constant supports and warm hearts.

List of Tables

List of Figures

1 Summary

Proposed investment

Onchocerciasis (river blindness) is a parasitic disease transmitted by blackflies. Notable symptoms include severe itching, skin lesions, and vision impairment including blindness. The disease is endemic in parts of Africa, Latin America, and Yemen, and more than 99% of all cases are found in sub-Saharan Africa [1]. Onchocerciasis has affected the poorest population in remote rural areas in Africa, resulting in negative socioeconomic impacts on them. In Africa, morbidity caused by onchocerciasis was significantly reduced by the vector control activities of the Onchocerciasis Control Programme (OCP) in West Africa (1975–2002) and by the community-directed treatment with ivermectin (CDTi) under the African Programme for Onchocerciasis Control (APOC) in sub-Saharan Africa and parts of West Africa (1995–present). Studies of foci in Mali, Senegal, and Uganda have proved that eliminating onchocerciasis through ivermectin administration is feasible for amenable epidemiological settings under effective treatments and surveillance [2,3]. The successful treatment programs and the proven feasibility of elimination have provided policymakers and donors of the rationale to pursue the elimination and subsequent eradication of onchocerciasis. The treatment goal for onchocerciasis has shifted from control to elimination as shown by the World Health Organization's (WHO's) roadmap for neglected tropical diseases (NTDs) and the London Declaration on NTDs in 2012 [4,5].

The assessment of the potential impacts of onchocerciasis elimination strategies can provide valuable information to national and global policymakers and donors. This assessment should consider not only epidemiological evidence but also costs, benefits, and risks, given limited resources and competing health priorities.

Scenarios of onchocerciasis elimination and eradication

We assessed the value of investing in onchocerciasis elimination by comparing potential elimination strategies with a control strategy representing a general practice conducted in Africa until recently. The alternative strategies were developed as the control, elimination, and eradication scenarios (Table 1), which describe all required activities leading to the goal if implemented effectively and sustained as long as required [6]. Each scenario consists of treatment strategies and surveillance strategies – epidemiological (to assess the infection level in humans) and/or entomological (to assess the infectivity in blackflies). The main differences of the elimination/eradication scenarios from the control scenario are that treatments are scaled up from meso-/hyper-endemic areas to hypo-endemic and operationally challenging areas and that surveillance is conducted on a regular basis and includes entomological surveillance in addition to epidemiological surveillance (Box 1).

Box1. Scenarios description

Control scenario: to reduce disease prevalence to a locally acceptable level, all endemic African countries implement annual CDTi in hyper- and meso-endemic areas, and after at least 25-years of CDTi, conduct epidemiological surveillance to confirm that CDTi can be safely stopped

Elimination scenario: to reduce the incidence of infection to zero in a defined area, all endemic African countries except those with epidemiological and political challenges implement annual or biannual CDTi, and conduct regular active epidemiological and entomological surveillance to evaluate epidemiological trends, to decide a proper time to stop CDTi, and to detect and respond to possible recrudescence.

Eradication scenario: to reduce the incidence of infection to zero in Africa, which would lead to global eradication, all endemic African countries implement not only annual or biannual CDTi but also locally tailored treatment strategies to deliver sustainable treatments to areas with operational challenges, and implement regular active epidemiological and entomological surveillance to evaluate epidemiological trends, to decide a proper time to stop CDTi, and to detect and respond to possible recrudescence.

With the scale-up of treatments, population living in entire target areas in endemic African regions would increase from around 140 million in the control scenario to 170 million−180 million in the elimination and eradication scenarios. Also, population living in operationally challenging areas – the Central African Republic, Democratic Republic of the Congo, and South Sudan due to political insecurity and Gabon due to co-endemicity with *Loa loa*– would

be 42 million (2014 population). The details on the scenarios and target populations are described in Kim et al. 2015 [6].

Table1. Proposed scenarios of control, elimination, and eradication of onchocerciasis

	Control	Elimination	Eradication
Ultimate goal	Reduce disease prevalence to a locally acceptable level	Reduce the incidence of infection to zero in a defined geographical area	Reduce the worldwide incidence of infection to zero
Target areas			
Endemicity	Hyper, meso	Hyper, meso, hypo	Hyper, meso, hypo
Feasibility concerns for CDTi[1]	Partially targeted	Partially targeted	Targeted[2]
Activities at project level			
Phase 1. Intervention			
1. Community-directed treatment with ivermectin (CDTi)			
Frequency	Once a year	Once or twice[3] a year	
Treatment coverage	65%+	65%+	
Start year of new projects[4]	2014–2015	2014–2015: hyper-/meso-endemic	2014–2015: hyper-/meso-endemic
		2016–2017: hypo-endemic	2016–2017: hypo-endemic, with no feasibility concerns for CDTi
			2020–2021: hypo-endemic, with feasibility concerns for CDTi
Duration	25 years; another 25 years in case of insufficient treatment coverage	Until the probability of local elimination is ≥ 99%[5]	
2. Surveillance			
Type	Epidemiological	1A) Epidemiological	
		1B) Epidemiological and entomological	
Frequency	Last year of MDA (25th, 50th year)	1A) Every 4 years from 9th year of MDA	
		1B) Last one year	
Site	10 villages	1A) 10 villages	
		1B) 20 villages (epidemiological surveys) and 4 catching sites (entomological)	
Phase 2. Confirmation of elimination			
Surveillance			
Type	NA	Epidemiological and entomological	
Frequency	NA	Epidemiological: last one year (3rd year)	
	NA	Entomological: last two years (2nd and 3rd year)	
Site	NA	10 villages and 4 catching sites	
Phase 3. Post-elimination			
Surveillance			
Type	NA	Epidemiological and entomological	
Frequency	NA	Epidemiological: every 3 years	
	NA	Entomological: every 4 years	
Site	NA	5 villages and 2 catching sites	

[1] Political insecurity and co-endemicity with *Loa loa*.

[2] Hypo-endemic areas with feasibility concerns were included in the eradication scenario only.

[3] Twice a year in new projects in Ethiopia and Uganda where the respective ministries of health announced six-monthly CDTi in new projects to bring them in line with ongoing projects (The Carter Center (2013) Fighting Disease: Ethiopia - Eliminating River Blindness. http://www.cartercenter.org/countries/ethiopia-health-river-blindness.html Accessed on 20 April 2014; Uganda Ministry of Health (2010) Health Sector Strategic Plan III, 2010/11-2014/15. http://www.health.go.ug/docs/HSSP_III_2010.pdf Accessed on 25 January 2015)

[4] Predicted considering APOC's strategic plan to focus on the onchocerciasis elimination for the next decade 2016–2025 and the current epidemiological and political situation

[5] A dynamical transmission model ONCHOSIM (Plaisier AP, van Oortmarssen GJ, Habbema JD, Remme J, Alley ES (1990) ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. Comput Methods Programs Biomed 31: 43-56) was used.

Rationale for investment

Treatment needs

Ivermectin has been the main drug for preventing and treating early onchocercal symptoms. Merck has donated ivermectin since late 1980s [7]. The timeline when treatment is expected to be stopped was predicted for each endemic country using a dynamical transmission model (ONCHOSIM [8]) and incorporating the heterogeneity in the onchocerciasis type (savannah/forest), the pre-control endemicity, and the history of treatment coverage at project level, which were available from APOC database. The details on the timeline for the treatment phase are described in Kim et al. 2015 [6].

In the elimination scenario, all endemic countries except the four countries with feasibility concerns (the Central African Republic, the Democratic Republic of the Congo, Gabon and South Sudan) were expected to end the treatment phase and shift to the post-treatment surveillance phase by 2028, and those four countries with feasibility concerns were expected to continue CDTi beyond 2045 (Figure 1). In the eradication scenario, all endemic countries were expected to reach the end of the treatment phase and enter the post-treatment surveillance phase by 2040, assuming sufficient treatments would be delivered sustainably in the four countries with feasibility concerns. In the control scenario, most endemic countries except several West African countries were predicted to continue CDTi beyond 2045.

The time horizon for our analysis was 2013 to 2045 based on the predicted timeline: the last project in the eradication scenario was expected to stop CDTi in 2040, and at least three years would be required to confirm local elimination.

The ivermectin treatment needs were predicted based on the predicted timeline for the treatment phase, population in endemic areas (from APOC database) adjusted for population growth rates [9], the expected treatment coverage based on the history data (from APOC database), and the frequency of CDTi (bi-annual if officially announced by ministry of health, otherwise annual).

The cumulative number of required ivermectin treatments over 2013–2045 was estimated at 1.5 billion (95% central range: 1.4bn–1.8bn) for the elimination scenario and 1.3 billion (1.2bn–1.5bn) for the eradication scenario. The control scenario would require 1.8–2.0 times higher number of ivermectin treatments, 2.6 billion (2.4bn–3.0bn) over the same period. Compared to the control scenario, the elimination and eradication scenarios would reduce the total number of required ivermectin treatments by 44% and 50%, respectively. As Figure 2 shows, in the elimination and eradication scenarios, the ivermectin treatment needs would be concentrated in the first several years, as the ivermectin treatments are scaled up to remaining endemic areas uncovered by CDTi, mostly in hypo-endemic areas. In the long term, the ivermectin treatment needs in the elimination and eradication scenarios would be lower than those in the control scenario, as regular active surveillance would enable to decide a proper time to stop CDTi, leading to a shorter treatment phase as compared to the control scenario lacking such surveillance systems. The details on the ivermectin treatment needs are described in Kim et al. 2015 [6].

Figure 1. Years when CDTi is expected to be stopped in endemic African regions

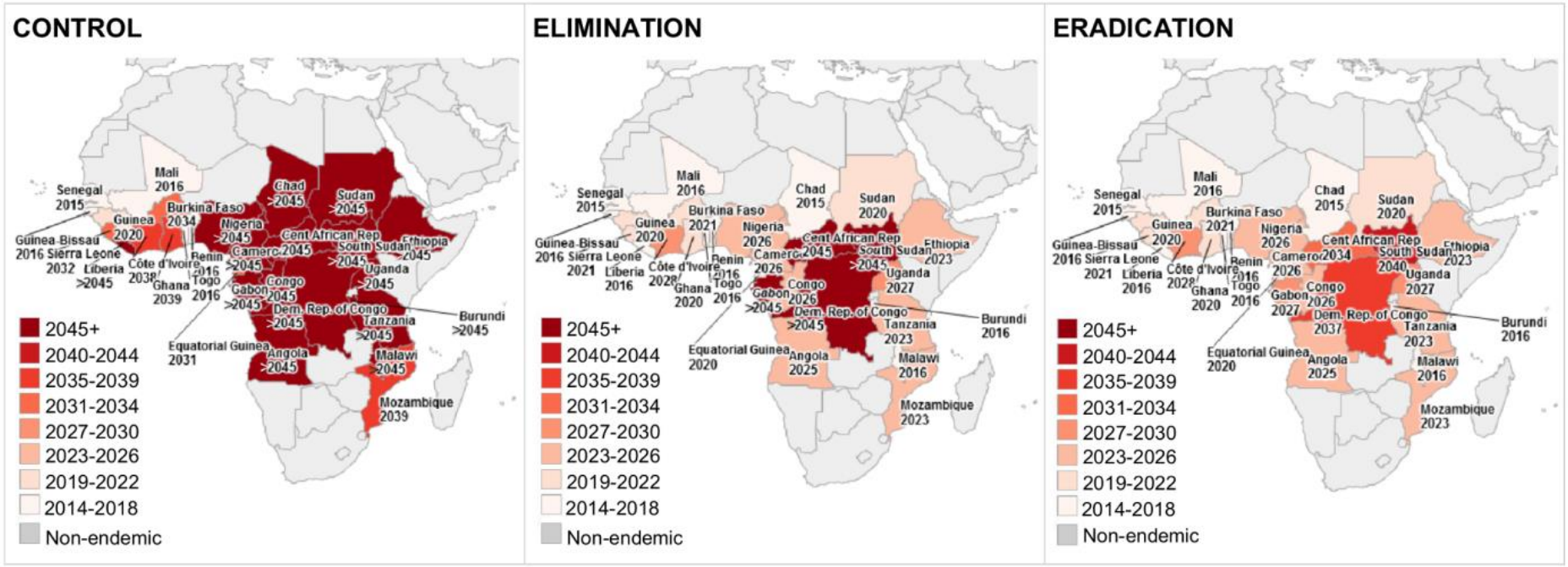
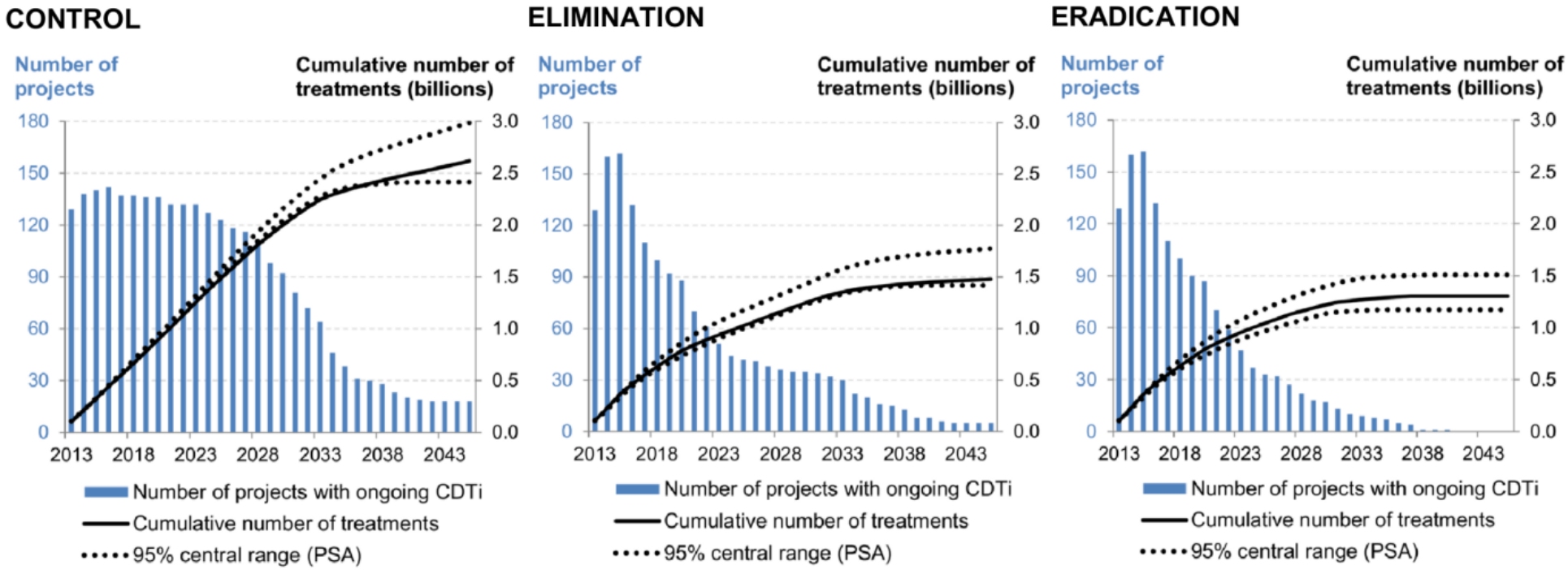


Figure 2. Cumulative number of ivermectin treatments and annual number of projects with ongoing CDTi in endemic African regions over 2013–2045



(PSA: Probabilistic Sensitivity Analysis)

Financial and economic costs

We estimated financial costs to predict how much the governments of endemic countries and donors would have to pay for implementing the required interventions for control, elimination, and eradication, and economic costs to assess societal opportunity costs associated with donated ivermectin and community volunteers' unpaid time. We used a micro-costing (bottom-up) approach to estimate the costs more precisely by incorporating the heterogeneity in the demographic, epidemiological, and political situation at project level. The main data sources were 2012 project budgets that cover 67 of 112 ongoing (as of November 2013) projects in sub-Saharan Africa, made available by APOC.

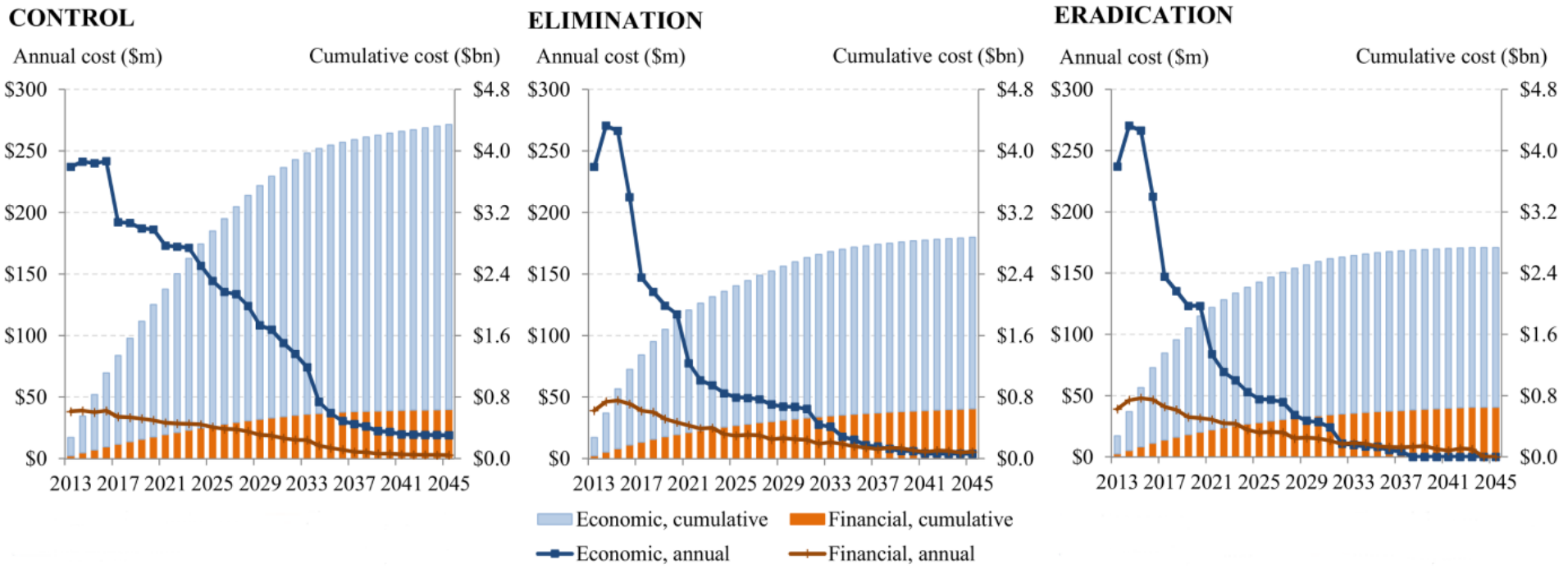
The elimination and eradication scenarios would allow substantial cost-savings of US$1.6bn and $1.7bn, respectively, compared to the control scenario for the period 2013−2045. This is mainly because regular surveillance would lead to a shorter period of CDTi, and consequently to the savings of economic costs associated with donated ivermectin and community volunteers' unpaid time. The savings would be realized despite that the elimination and eradication scenarios would require five times higher surveillance costs than the control scenario.

The total financial and economic costs would be concentrated in the early stage during which treatments are scaled up to remaining endemic areas, and decrease as the treatment phase nears the end (Figure 3). In endemic African regions, total financial and economic costs over the period 2013−2045 would be $4.3 billion ($3.9bn−$5.0bn) for the control scenario, $2.9 billion ($2.6bn−$3.4bn) for the elimination scenario, and $2.7 billion ($2.4bn−$3.2bn) for the eradication scenario. That is, switching from the control scenario to the elimination and eradication scenarios would lead to cost-savings of $1.5 billion ($1.0bn−$1.9bn) and $1.6 billion ($1.2bn−$2.1bn), respectively.

Total financial costs over the period 2013−2045 would be $640 million ($572m−$711m) for the control scenario, $650 million ($574m−$751m) for the elimination scenario, and $649 million ($566m−$745m) for the eradication scenario. The main difference between scenarios is the proportion of surveillance costs in total costs. Total surveillance costs over 2013–2045 would increase from 7% ($47m) of total financial costs under the control scenario to 33% ($215m) and 37% ($242m) under the elimination and eradication scenarios, respectively.

Economic costs would be six times higher than financial costs under the control scenario and three times higher under the elimination and eradiation scenarios. Total economic costs over 2013−2045 would be $3.7 billion ($3.3bn−$4.3bn) for the control scenario, $2.2 billion ($2.0bn−$2.7bn) for the elimination scenario, and $2.1 billion ($1.8bn−$2.5bn) for the eradication scenario. That is, the total economic costs for the elimination and eradication scenarios are lower than those for the control scenario by $1.5 billion ($1.1bn−$1.9bn) and $1.6 billion ($1.2bn−$2.1bn), respectively. Donated ivermectin and community volunteers' unpaid time would account for 75% and 25% of the total economic costs in all scenarios.

Figure 3. Annual and cumulative financial and economic costs in endemic African regions over 2013–2045



Assessment of health benefits

To estimate the health benefits of onchocerciasis elimination, we estimated the number of cases for severe itching, low vision, and blindness, and disability-adjusted life years (DALYs) for the control, elimination, and eradication scenarios. We used ONCHOSIM to simulate the prevalence of severe itching, low vision, and blindness at project level. We ran the simulations by incorporating the onchocerciasis type (savanna or forest), the endemicity level (none, hypo, meso, hyper), and the history of treatment coverage, all of which were available from APOC databases. We defined the endemicity levels based on pre-control nodule prevalence for APOC countries, and for former OCP countries, based on pre-control microfilariae prevalence with reference to Kim et al. 2015 [6]. We used the average treatment coverage over 2010−2012 as an expected coverage for 2013−2045. If the average treatment coverage was below 65%, which is the required level for effective control [10], we used the highest treatment coverage achieved during 2010−2012. For potential new projects, we used the national average treatment coverage and, if there was no relevant data, we used the regional average (across available national averages in either APOC or former OCP regions).

To estimate the number of prevalent cases of severe itching, low vision, and blindness, we multiplied the predicted prevalence of each symptom with population living in a project area. Population (2012) was available from APOC database for all projects, and we adjusted for population growth rates for the period 2013−2045 [9].

To estimate DALYs we estimated the years lost due to disability (YLD) by multiplying the number of prevalent cases with relevant disability weights, namely, 0.108 for severe itching, 0.033 for low vision, and 0.195 for blindness [11]; and then the years of life lost (YLL) by assigning eight years of life-expectancy loss for each blindness incidence assuming that blindness causes premature death [12].

Under the elimination and eradication scenarios, the prevalence of severe itching in endemic African regions would decrease from 30/1,000 to 2/1,000 and to less than 1/1,000, respectively over 2013−2045 (Figure 4). The number of patients with severe itching under the control scenario would be 231.3 million over 2013–2045. Switching to the elimination and eradication scenarios would lead to the reduction of the number of patients with severe itching by 34.2 million and 46.4 million (15% and 20%), respectively.

The prevalence of low vision would decrease from 51/10,000 to 6/10,000 for the control scenario, to 4/10,000 for the elimination scenario, and to 3/10,000 for the eradication scenario (Figure 4). The number of patients with low vision under the control scenario would be 33.1 million over 2013–2045. Switching to the elimination and eradication scenarios would lead to the reduction of the number of patients with low vision by 1.5 million and 1.8 million (4% and 5%).

The prevalence of blindness would decrease from 17/10,000 to 2/10,000 for the control scenario, and to less than 1/10,000 for the elimination and eradication scenarios (Figure 4). The number of patients with blindness under the control scenario would be 11.3 million over 2013–2045. Switching to the elimination and eradication scenarios would lead to the reduction of the number of patients with blindness by 670 thousand and 778 thousand (6% and 7%), respectively.

The elimination and eradication scenarios would avert DALYs by 33%, 4.3 million (2.1m−5.5m), and by 43%, 5.6 million (2.7m−7.2m), respectively over 2013−2045, as compared to the control scenario (Figure 5). The additional benefits of the eradication scenario compared to the elimination scenario would be 1.3 million (0.6m−1.7m) of averted DALYs.

Figure 4.Prevalence of severe itching, low vision, and blindness in endemic African regions over 2013−2045

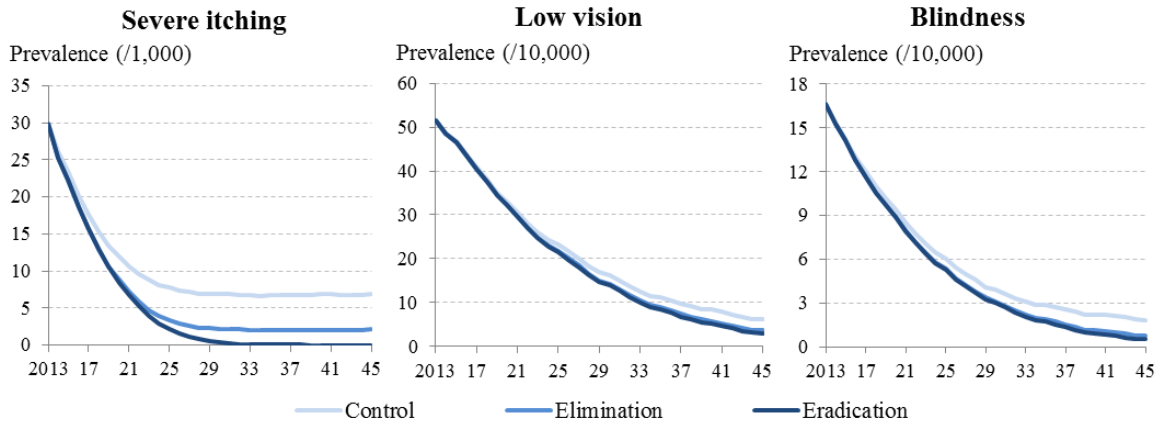
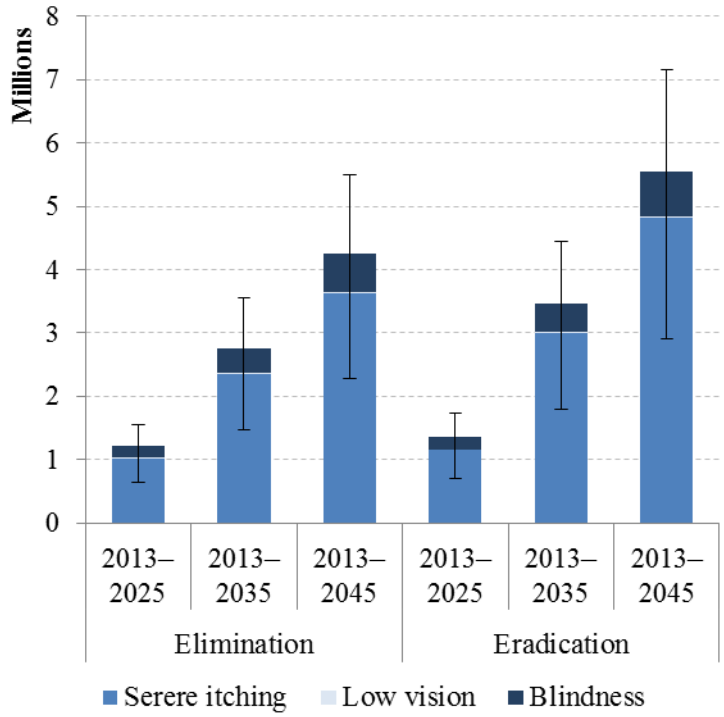


Figure 5. DALYs averted in endemic AFrican regions over 2013−2045, baseline: control scenario



(The ranges are from PSA.)

Assessment of the impacts on health systems

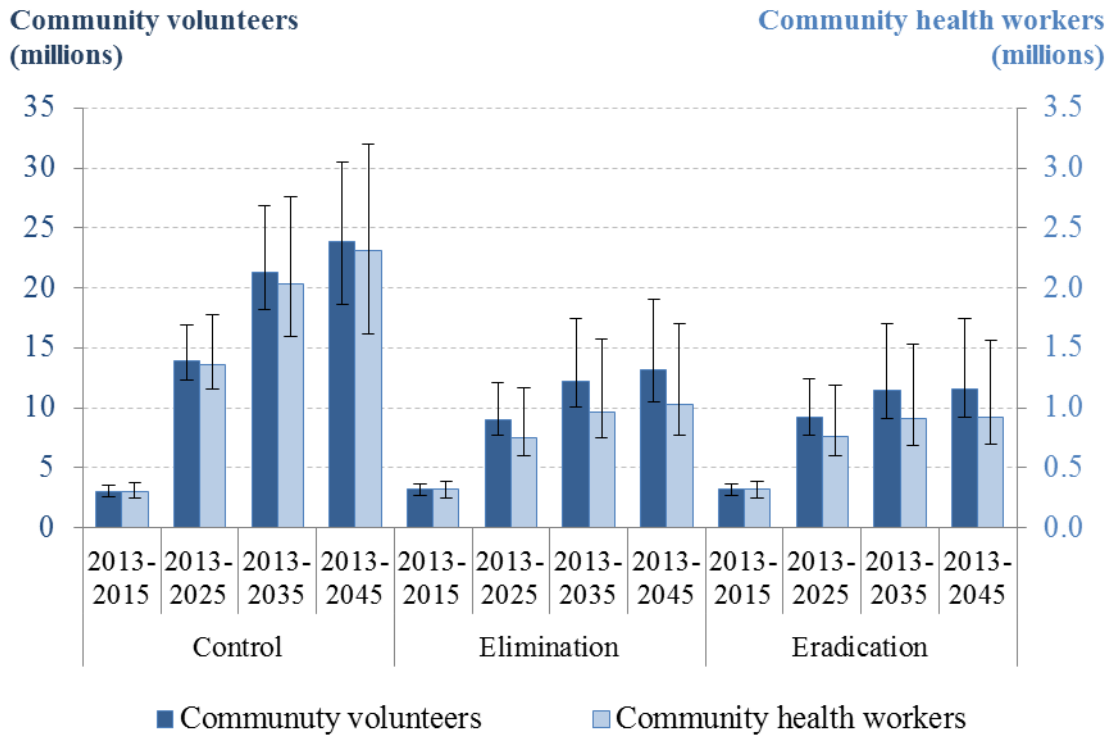
Eliminating onchocerciasis may have important consequences on endemic African countries' health systems that are generally weak and characterized by a shortage of health workforce, especially in remote and rural areas [13]. Although it is hard to quantify these impacts, we assessed the main implications on the health systems building blocks with a focus on the impact on health workforce. Due to the challenges posed by weak health systems, CDTi has been the primary approach for onchocerciasis interventions. In CDTi, community volunteers play a central operational role by deciding when and how to distribute drugs, administering drugs, managing adverse reactions, keeping records, and reporting to health workers [14]. Also community health workers are important, as they train community volunteers, and monitor and evaluate CDTi performance [15]. To examine the potential impacts of alternative treatment strategies on these health workforces, we estimated the number of required community volunteers and community health workers over 2013−2045 for each scenario. We multiplied the ratio of community volunteers, and community health workers, over population with population living in endemic areas, and adjusted for the predicted treatment timeline at project level. The ratios of community volunteers and of community health workers over population were available in 2012 budget documents for 67 ongoing projects in sub-Saharan Africa (as of November 2013). We assumed the ratios would be stable until the end of CDTi. For projects without relevant ratios, we used the national average ratio and, if there was no relevant data, we used the regional average. We used population from APOC database after adjusting for population growth rates over 2013−2045 [9]. The predicted treatment timeline at project level for each scenario was available in Kim et al. 2015 [6].

The total number of required community volunteers for implementing CDTi in endemic African regions would be 23.9 million (18.6m−30.4m) over 2013−2045 for the control scenario, 12.3 million (10.1m−17.4m) for the elimination scenario, and 11.6 million (9.2m−17.4m) for the eradication scenario (Figure 6). Switching to the elimination and

eradication scenarios from the control scenario would lead to the reduction of required community volunteers by 45%, 10.7 million (5.9m−14.1m), and by 52%, 12.4 million (6.9m−15.7m). This suggests that volunteers willing to continue to volunteer and their well-established networks would be able to contribute to other health care services such as primary health care services in remote rural areas lacking human resources.

The total number of community health workers for implementing CDTi in endemic African regions would be 2.3 million (1.6m−3.2m) over 2013−2045 for the control scenario, 1.0 million (0.8m−1.7m) for the elimination scenario, and 917 thousands (0.7m−1.6m) for the eradication scenario (Figure 6). Switching to the elimination and eradication scenarios from the control scenario would lead to the reduction of required health workers by 56%, 1.3 million (0.5m−1.9m), and 60%, 1.4 million (0.6m−2.0m), respectively.

Figure 6. Health workforce needs for CDTi in endemic African regions over 2013–2045: community volunteers and community health workers



(The ranges are from PSA.)

Another relevant aspect that is rarely taken into account is the burden on health systems of patients' visits to health facilities due to severe itching and low vision [16]. We estimated the impacts of onchocerciasis elimination on this burden, assuming that only people living in areas uncovered by CDTi would visit health facilities, as people living in CDTi project areas benefit annual or biannual treatment with ivermectin which relieves severe itching and stops the progression towards blindness [17]. We assumed that people with blindness would not visit health facility, as blindness is irreversible. To estimate the number of outpatient visits we multiplied the number of patients with severe itching or low vision with the health facility utilization rate. As a proxy for the health facility utilization rate, we used the average treatment coverage over 2010−2012, assuming people who complied with CDTi would be willing to seek care if there were no CDTi. Based on the predicted number of outpatient visits, we estimated the potential cost-savings for each country, by multiplying the number of visit by a country-specific outpatient cost per visit [18].

The total number of outpatient visits under the control scenario would be 46.2 million over 2013−2045, incurring $56.0 million ($27.2m–$71.8m) of outpatient visit costs. The elimination and eradication scenarios would lead to the reduction of the number of outpatient visits by 31.6 million and 42.3 million (68% and 91%) as compared to the control scenario, thereby reducing the burden on health systems by saving outpatient visit costs by $47.5 million ($22.8m–$61.0m) and $52.1 million ($25.0m–$67.3m).

Health information system (HIS), another building block of health systems, is related to the main difference of the elimination/eradication scenarios from the control scenario, namely intensive surveillance. Regular active surveillance under the elimination and eradication scenarios, which serves to track epidemiological trends, decide a proper time to stop CDTi, detect and provide early warning on possible recrudescence, would be feasible only when the HIS are strong, because well-established and effective HIS enables health workers to collect and analyze data on a regular basis, and convert them into information to support

policymakers' decision. This implies strengthening the HIS would be essential to achieve elimination in endemic African countries.

Assessment of the economic impacts

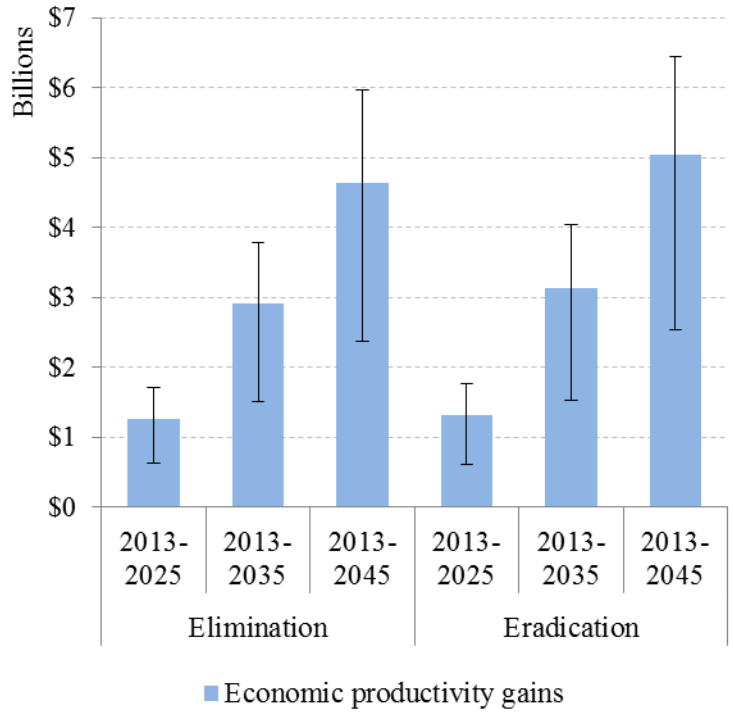
The areas where onchocerciasis is endemic are among the poorest of the world. We estimated the potential economic benefits of eliminating onchocerciasis using two approaches: the human capital approach in which the economic value of health is measured in terms of productivity in the market-place; the full income approach in which the economic value of health goes beyond material well-being to include a monetary value of the welfare gains (or psychological value) that people place on increased life expectancy [19,20]. We also assessed the potential impacts of onchocerciasis elimination on financial protection of households by estimating the reduction in out-of-pocket payments.

With the human capital approach, we estimated the productivity gains from the reduction in morbidity over 2013–2045, by multiplying the predicted number of patients with severe itching, low vision, and blindness with the country-specific employment rate and a proxy for income losses due to each symptom under each scenario. We assumed that patients aged from 15 and above would have the same probability of being employed as general population unless they had onchocercal symptoms. We assumed patients aged from 15 to 64 years with severe itching would lose 13% of GDP per capita based on the study on the economic impacts of onchocercal skin diseases in Ethiopia [21], and patients in the same age group with low vision and blindness would lose 38% and 79% of GDP per capita, respectively, based on the study on the socioeconomic impacts of onchocercal vision impairment in Guinea [22]. Patients aged less than 15 years were assumed to have no economic productivity. Patients aged 65 years and above were assumed to be half as productive as those aged from 15 to 64 years based on the methods used by Frick, Smith, and colleagues [23,24]. We also estimated the productivity gains for informal care-takers (e.g., families and relatives), assuming that one

patient with low vision or blindness would need one adult care-taker. We multiplied the number of patients with low vision and blindness with a relevant proxy for their care-takers' income losses under each scenario. For the proxy, we assumed the care-taker would lose 5% of GDP per capita if the patient has low vision, and 10% of GDP per capita if the patient is blind, based on the study by Smith, Shamanna, and colleagues [24,25]. Also, to estimate the productivity gains from the reduction in mortality over 2013–2045, we multiplied the predicted YLL with GDP per capita, considering blindness causes premature death at a fully productive age [26].

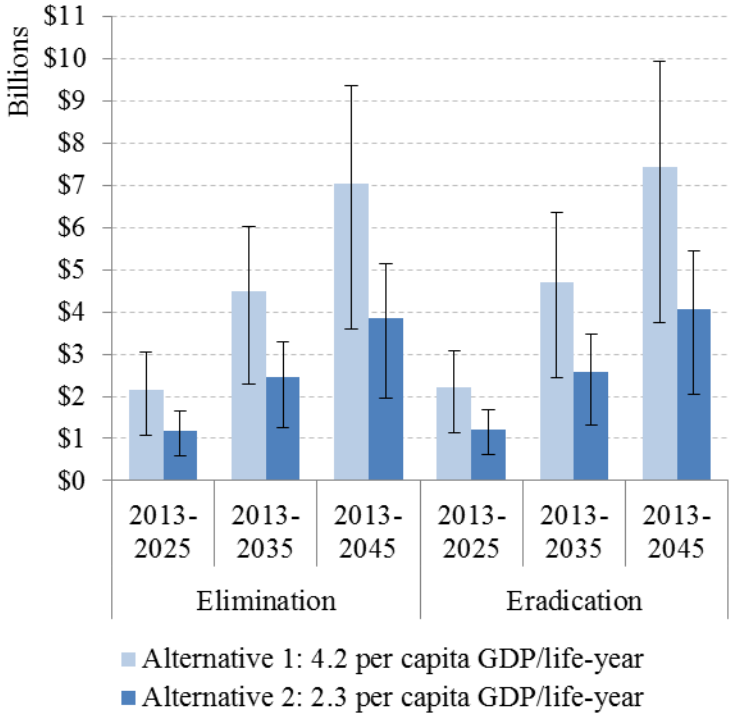
With the full income approach, we evaluated welfare gains associated with the life-expectancy gains from eliminating onchocerciasis, by multiplying the predicted YLL with a proxy for the economic value of one life-year increase in sub-Saharan Africa. For the proxy, we used the result of the study by the Lancet Commission on Investing in Health, 4.2 times GDP per capita estimated for sub-Saharan Africa and 2.3 times GDP per capita for low and middle income countries[20]. The Lancet Commission used survival curves for different life tables to estimate the relationship between mortality and life expectancy, and estimated the economic value associated with a unit mortality rate based on studies on the value of a statistical life. The elimination and eradication scenarios would lead to the productivity gains of $4.6 billion ($2.4bn−$6.2bn) and $5.0 billion ($2.7bn−$6.7bn), respectively, as compared to the control scenario, in which 96% is for patients and 4% for care-takers (Figure 7). The economic benefits measured in terms of welfare gains associated with the life-year gains from averted blindness would be, applying the value of a life-year for sub-Saharan Africa (4.2 times GDP per capita), $7.0 billion ($3.6bn–$9.4bn) for the elimination scenario and $7.4 billion ($3.8bn–$9.9bn) for the eradication scenario over 2013–2045 as compared to the control scenario; and applying that for low and middle income countries (2.3 times GDP per capita), $3.9 billion ($2.0bn–$5.1bn) for the elimination scenario and $4.1 billion ($2.1bn–$5.4bn) for the eradication scenario (Figure 8).

Figure 7. Economic productivity gains under the elimination and eradication scenarios in endemic African regions over 2013–2045, baseline: control scenario



(The ranges are from PSA.)

Figure 8. Economic welfare gains due to the reduction of premature deaths under the elimination and eradication scenarios in endemic African regions over 2013–2045, baseline: control scenario

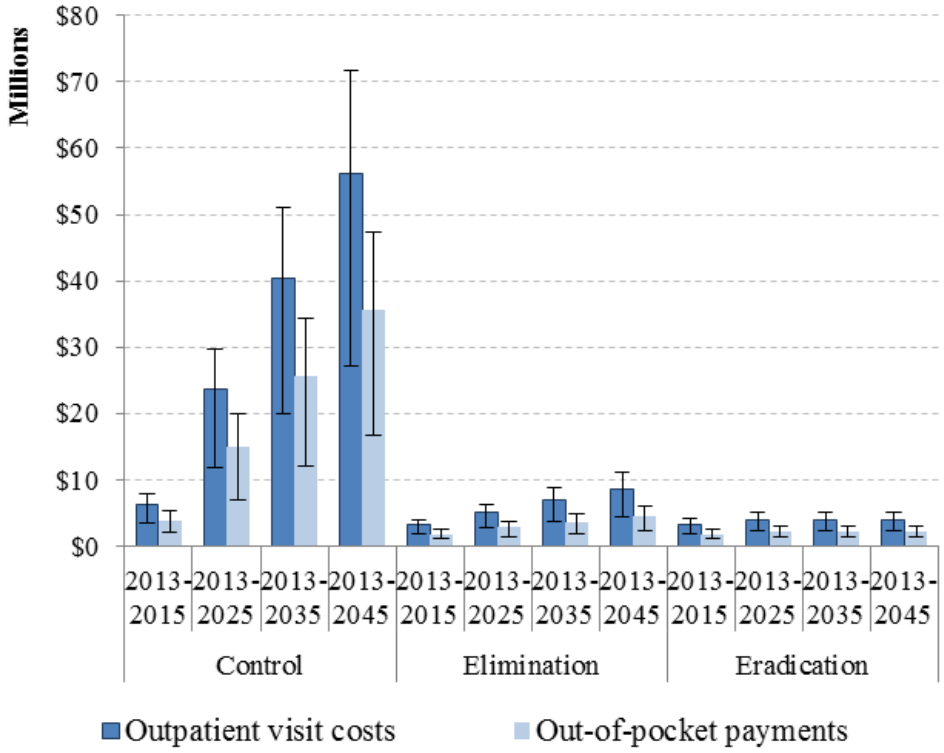


(The ranges are from PSA.)

Weak health systems generally result in poor financial protection against households' catastrophic health expenditure. To assess the benefits of onchocerciasis elimination in terms of financial protection of households, we estimated patients' out-of-pocket (OOP) payments for visiting health facility due to severe itching and low vision for each scenario. We multiplied the previously estimated outpatient visit costs with the proportion incurred as OOP payments for which the proxy was OOP health expenditure as percentage of total health expenditure for each country, and added transportation costs which were assumed to be 17% of OOP payments based on a study by Saksena and colleagues [27].

The total household OOP payments due to onchocerciasis would be $35.7 million ($16.7m–$47.4m) over 2013−2045 under the control scenario (Figure 9). The elimination and eradication scenarios would lead to the reduction of the household OOP payments by $4.5 million ($2,2m–$6.0m) and $2.2 million ($1.2m–$3.0m), respectively, as compared to the control scenario.

Figure 9. Total outpatient visit costs and out-of-pocket payments in endemic African regions over 2013–2045



(The ranges are from PSA.)

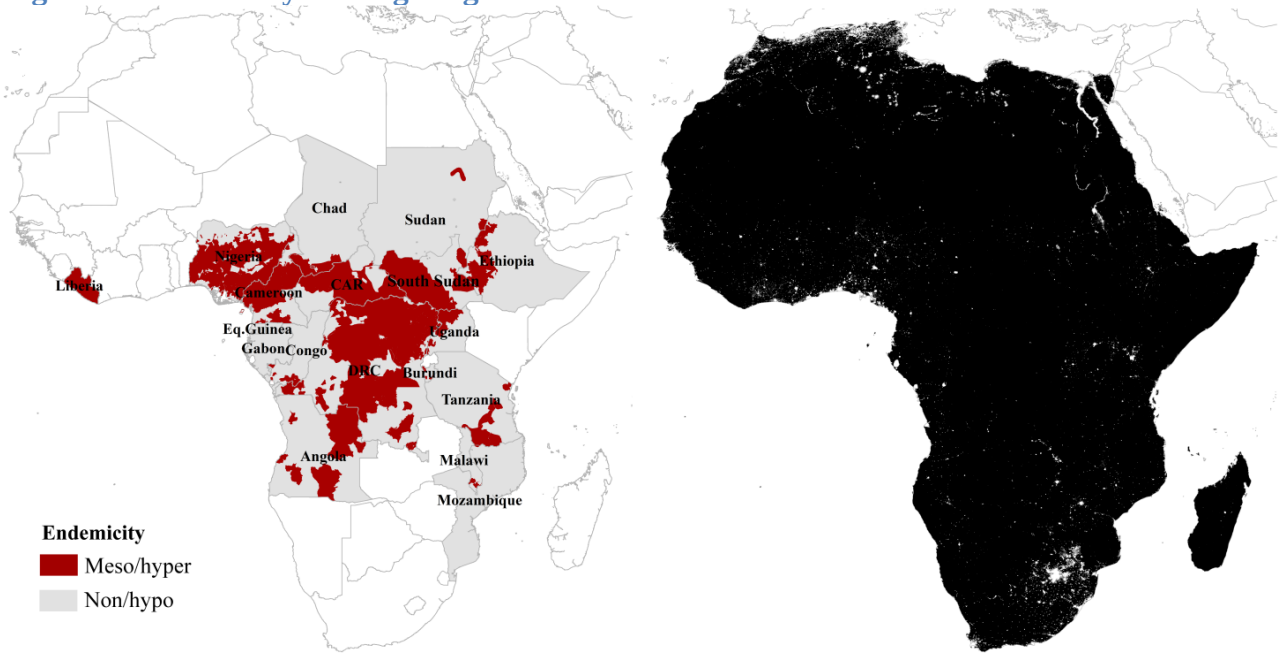
Investing in justice: ethics, equity, and fairness considerations

Neglected tropical diseases such as onchocerciasis are concentrated among low-income countries and disadvantaged populations. Social justice consists in fairness and equity in the distribution of societal benefits and burdens. Nevertheless, it is challenging to account for the ethical importance of the benefits, burdens, and distributions, that are salient in people's experiences of the diseases and related interventions. Thus these aspects are not assessed in traditional approaches for health and economic evaluation.

To evaluate the potential impacts of onchocerciasis elimination in terms of the inequalities in economic conditions at local level, we compared the night light level between meso-/hyper-endemic areas and non-/hypo-endemic areas. We used night light data as a proxy for local income, because there were no data available on the local economic conditions of the endemic

areas. Recent studies showed that, despite several limitations, the night light data can be used as a proxy for income at sub- and supranational levels in low income countries [28]. We identified meso-/hyper-endemic and non-/hypo-endemic areas using the APOC database which were created based on epidemiological surveys and using a geospatial analysis [29,30] (Figure 10). We obtained the 2013 night light map [31]. Using the night light map, we created a database that contains the light levels (dark−bright: 0−64) at the geographic unit of 0.1 by 0.1 degrees, and identified if each unit area is meso-/hyper-endemic or non-/hypo-endemic by overlapping the endemicity map. We compared the average light level between meso-/hyper-endemic and non-/hypo-endemic areas using Welch's unequal variances *t*-test.

Figure 10.Endemicity and night lights in Africa



The statistical comparison of night light levels shows that the average night light level in meso-/hyper-endemic areas (M=0.15, SD=1.46) is significantly lower than that in non-/hypo-endemic areas (M=0.18, SD=1.93); $t(82,117)=2.97$, $p<0.05$. This suggests that, within the APOC countries where most of the global cases are found, meso-/hyper-endemic areas are likely to have higher poverty levels than non-/hypo-endemic areas.

Poverty is not just about low income, but goes beyond to the deterioration of individual capabilities to lead their lives and accomplish what they value as human beings [32]. Onchocercal symptoms (severe itching and vision impairment including blindness) deteriorate patients' well-being from psychological, psychosocial, and social aspects [33]. These symptoms undermine self-respect due to stigma, teasing, and negative stereotyping, and deprive of the opportunities of physical and educational activities and relationships with others because of ostracism or the avoidance of infected person. This indicates that the elimination and subsequent eradication of onchocerciasis would not only contribute to relieving income inequality, but also lead to ethical advantages and social justice.

Policy implications

The eradication and elimination scenarios dominate the control scenario in terms of intervention costs and health benefits. They not only save the intervention costs, but also lead to the health, economic, social benefits, as compared to the control scenario (Table 2). Intensive investment in the early stage to scale up the interventions to hypo-endemic areas and operationally challenging areas, in addition to meso-/hyper-endemic areas, combined with strengthening the surveillance and response systems would eventually save financial and societal opportunity costs, and result in the reduction of morbidity and mortality due to onchocerciasis. In addition, this would generate substantial economic productivity and welfare gains, foster equity by preventing people living in endemic areas from missing social and economic opportunities, and relieve income inequality.

The implementation of elimination and eradication strategies would affect and be affected by the conditions of health systems that should therefore be strengthened. Also the elimination and eradication of onchocerciasis are public goods that can only be achieved through the coordinated efforts of multiple countries [34,35]. To achieve the elimination and subsequent eradication of onchocerciasis, political, financial, and societal commitments across a whole spectrum of stakeholders, including community members, religious leaders, national policymakers, pharmaceutical companies, and global donors, will be essential [36].

Globally, the elimination and eradication of onchocerciasis would require cooperation among endemic countries, global donors, and pharmaceutical companies. Especially during the early stage of the implementation of elimination/eradication strategies, endemic countries would need higher financial costs, more human resources, and more medicines to stabilize new treatment projects in currently uncovered endemic areas and strengthen surveillance and response systems. Thus, global donors' continuous funding and pharmaceutical companies' drug donation will be critical. The centralized efforts led by international organizations would also be necessary to prevent potential holdout problems caused by unwilling or unable

countries, which could hinder elimination and eradication. In line with this, it has been argued that the explicit inclusion of NTDs elimination in the Sustainable Development Goals of the United Nations would further motivate the commitment of national and global policymakers and donors [37].

National governance and leadership will be critical to achieve the elimination and eradication of onchocerciasis. National policymakers would need to develop the long-term strategies targeting the elimination and eradication of onchocerciasis. Especially, the countries where co-endemicity with *Loa loa* hinders scaling up treatments would need to develop locally tailored approaches in addition to CDTi for those co-endemic areas, for example, a test-and-treat approach and an anti-Wolbachia therapy with macrofilaricidal drugs. To implement the long-term strategies effectively, policymakers would need to regularly monitor and evaluate the performance of all the relevant components including health information systems, financing, scaling up interventions, human capacity building, andtimely drug supply (Figure 11). The collaboration between endemic countries would be important, especially when endemic areas span across the border areas, as human and vector migration could cause recrudescence.

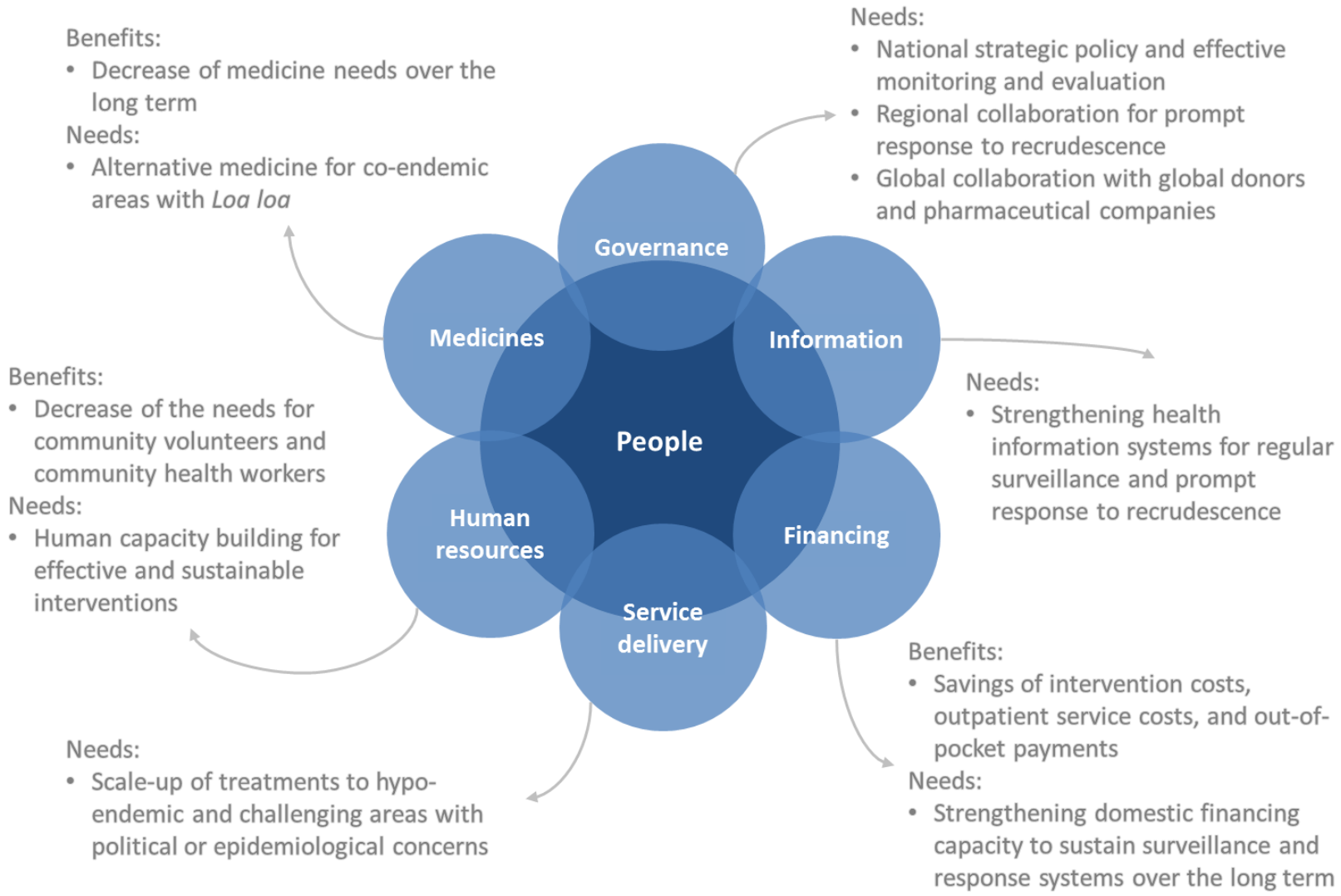
Table2. Summary of key results

	Control (baseline)	Elimination	Eradication
Health benefits, 2013–2045			
DALYs averted	–	4.3 million (2.1m−5.5m)	5.6 million (2.7m−7.2m)
Intervention cost, 2013–2045			
Financial costs	$640 million ($572m−$711m)	$650 million ($574m−$751m)	$649 million ($566m−$745m)
Economic costs	$3.7 billion ($3.3bn−$4.3bn)	$2.2 billion ($2.0bn−$2.7bn)	$2.1 billion ($1.8bn−$2.5bn)
Economic benefits, 2013–2045			
Productivity gains	–	$4.6 billion ($2.4bn−$6.2bn)	$5.0 billion ($2.7bn−$6.7bn)
Welfare gains from life-years gains	–	$7.0 billion ($2.9bn−$8.9bn)	$7.4 billion ($3.0bn−$9.4bn)

Data format: mean (95% central ranges from probabilistic sensitivity analysis)

Note: Costs, DALYs, and economic impacts were discounted with 3% to the year 2013 to account for time preference

Figure 11. Policy implications for health systems



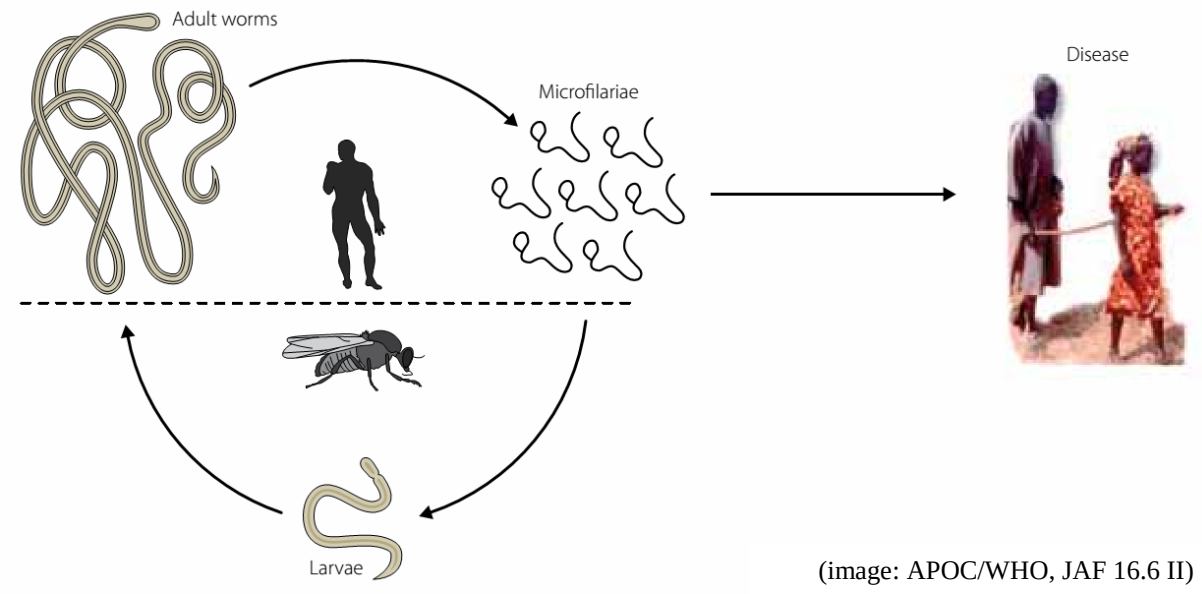
2 Introduction

Epidemiology of onchocerciasis

Infection and clinical symptoms

Onchocercias is a parasitic disease caused by filariae, *Onchocerca volvulus*, that are transmitted by blackflies and only infect humans (Fig 12).Adult worms are found in nodules under the skin of infected persons and live up to 14 years. They produce thousands of microfilaria that cause inflammatory reactions, and consequently clinical symptoms. Microfilariae are ingested by blackflies during a blood meal on an infected person, develop into infective larvae inside blackflies, and are transmitted to another person during a subsequent blood meal. The most notable clinical symptoms are severe itching, skin lesions, and vision impairment including blindness.

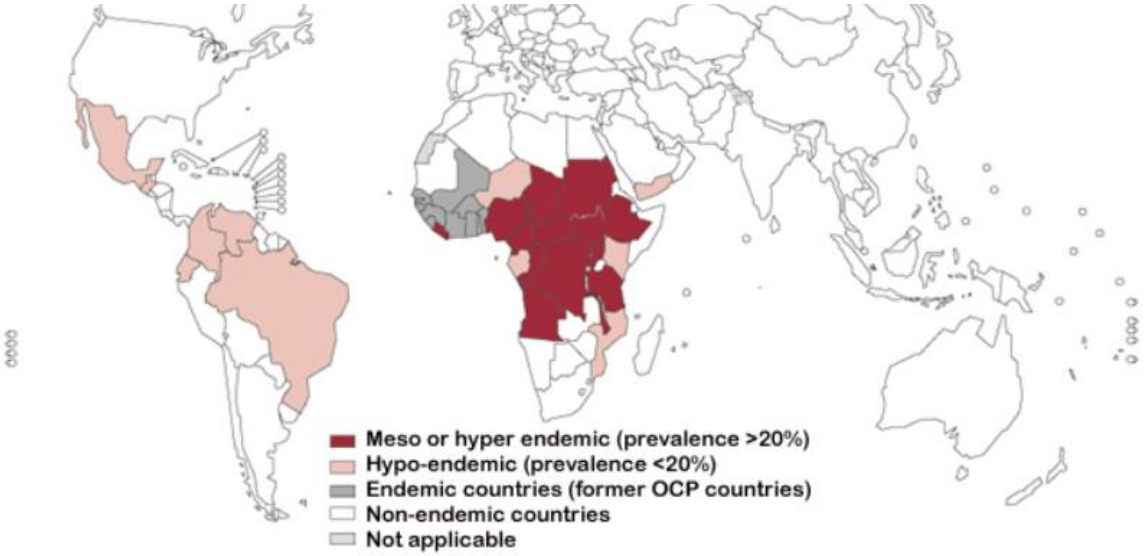
Figure 12. Main stages of the life-cycle of a filarial worm *Onchocerca volvulus*



(image: APOC/WHO, JAF 16.6 II)

Onchocerciasis is endemic in parts of Africa, Latin America, and Yemen (Fig 13), but over 99% of all current cases are found in sub-Saharan Africa [1] where onchocercias is has historically been a serious public health problem and hindered socioeconomic development in endemic areas [38].

Figure 13. Global endemicity of onchocerciasis



(image: WHO, 2013)

History of treatment and prevention

In Africa, morbidity caused by onchocerciasis was significantly reduced by the vector control activities of the Onchocerciasis Control Programme (OCP) in West Africa (1975–2002) and by the community-directed treatment with ivermectin (CDTi) under the African Programme for Onchocerciasis Control (APOC) in sub-Saharan Africa and parts of West Africa (1995–present) [39]. In Latin America, the Onchocerciasis Elimination Program for the Americas (OEPA) implemented since 1993 has brought the disease close to elimination. Colombia and Ecuador announced the elimination of onchocerciasis after WHO verification in 2013 and 2014, respectively [40,41]. Treatment has also been stopped in seven foci in Guatemala and Mexico where it has been replaced by surveillance to detect possible recrudescence [42]. Regional elimination in Latin America is expected to be achievable by 2020if the regular treatment of a sufficient proportion of the nomadic Yanomami in the border area between Brazil and Venezuela can be achieved [43].In Yemen, onchocerciasis is endemic in a limited number of communities. Elimination in the near future is considered technically feasible, and a national action plan aiming at elimination by 2015 was developed in 2010 [44]. Currently,

political instability and security concerns that limit access to endemic areas hamper its implementation [45].

Studies in Mali and Senegal have proved the feasibility of onchocerciasis elimination through ivermectin treatment in some hyper-endemic foci in West Africa [2,46]. This has provided additional momentum and arguments for a shift in the strategic goal from control to elimination also in Africa.

Study rationale and design

Research needs

The decision to invest in elimination and eradication efforts should be informed by broad assessments considering biological and technical feasibility, financial and economic costs, health and economic gains, capacity of and impacts on health systems, and societal and political will to cooperate [47]. To assess these broad aspects, a working group at the Ernst Strüngmann Forum suggested developing and analyzing eradication/elimination investment cases (EIC) [47]. The EIC approach is an assessment addressing all three fundamental economics questions: 1) the ‘‘What’’ question, that compares the feasibility and potential broad consequences of remaining in control mode and moving toward elimination and eradication; 2) the ‘‘How’’ question,’’ assessing which interventions or strategies should be adopted by which stakeholders, how much resources would be required, and how they could be mobilized; and 3) the ‘‘for Whom’’ question, assessing who would benefit from interventions in terms of health and economic gains and the likely impact on equity and fairness. Tediosi and colleagues have examined the approach with focus on three NTDs including onchocerciasis [48]. In this PhD thesis, the broad aspects associated with the investment in the elimination and eradication of onchocerciasis are examined.

Goal

The overall goal of this research is to examine the feasibility of the elimination and eradiation of onchocercias is through the analysis of costs, health and economic benefits, potential impacts on health systems, and economic inequality, and provide an evidence base to national and global policymakers for informed decision making.

Aims

The aims of this PhD thesis are:

- To develop scenarios of control, elimination, and eradiation
- To estimate the timelines and needs of treatment for each scenario
- To estimate financial and economic costs associated with each scenario
- To evaluate health impacts associated with each scenario
- To evaluate economic impacts associated with each scenario
- To assess potential impacts on health systems from the goal shift from control to elimination and eradication
- To evaluate economic inequality associated with onchocerciasis

Objectives

Objective 1: Control, elimination, and eradication scenarios

- To describe all required activities and resources that are expected to lead to the goals of control, elimination, and eradication based on current standard practice, the results of large-scale studies, and available historical data and the consultation with a wide range of experts including epidemiologists, health economists, national and global policymakers, and public health experts

Objective 2: The timelines and needs of treatment

- To identify endemic areas in Africa in need of treatment based on epidemiological mapping database
- To predict expected start years of treatment for potential new projects based on the current epidemiology and political situation
- To predict the required duration of treatment using a dynamical transmission model ONCHOSIM
- To predict expected end years of treatment for ongoing and potential new projects
- To predict the timelines of treatment phase at the national and regional levels for the control, elimination, and eradication scenarios

Objective 3: Financial and economic costs

- To predict financial and economic costs associated with the control, elimination, and eradication scenarios using project budgets with a micro-costing approach

Objective 4: Health impacts

- To evaluate the trend of prevalence of clinical symptoms and DALYs using a dynamical transmission model for the control, elimination, and eradication scenarios

Objective 5: Economic impacts

- To evaluate productivity losses/gains using a human capital approach and welfare impacts associated with premature death due to blindness using a full income approach for the control, elimination, and eradication scenarios

Objective 6: Potential impacts on health systems

- To assess potential impacts on the building blocks of health systems with focus on health workforce and the burden of outpatient visits

Objective 7: Economic inequality

- To assess income inequality between meso-/hyper-endemic areas and non-/hypo-endemic areas using night lights data as a proxy for local income levels

3 Control, elimination, and eradication of river blindness: scenarios, timelines, and ivermectin treatment needs in Africa

Young Eun Kim*[1,2], Jan H.F. Remme[3], Peter Steinmann[1,2], Wilma A. Stolk[4], Jean-Baptiste Roungou[5],Fabrizio Tediosi[1,2]

* Correspondence: young.kim@unibas.ch

1 Swiss Tropical and Public Health Institute, Basel, Switzerland

2 University of Basel, Basel, Switzerland

3 Consultant, 120 rue des Campanules, Ornex, France

4 Erasmus MC, University Medical Center Rotterdam, The Netherlands

5 African Programme for Onchocerciasis Control, Ouagadougou, Burkina Faso

Email addresses

YEK: young.kim@unibas.ch

JHR: hansremme@gmail.com

PS: peter.steinmann@unibas.ch

WS: w.stolk@erasmusmc.nl

JR: roungouj@who.int

FT: fabrizio.tediosi@unibas.ch

Citation:
Kim YE, Remme JHF, Steinmann P, Stolk WA, Roungou JB, et al. Control, Elimination, and Eradication of River Blindness: Scenarios, Timelines, and Ivermectin Treatment Needs in Africa. PLoS Negl Trop Dis. 2015; 9: e0003664. doi:10.1371/journal.pntd.0003664

Abstract

River blindness (onchocerciasis) causes severe itching, skin lesions, and vision impairment including blindness. More than 99% of all current cases are found in sub-Saharan Africa. Fortunately, vector control and community-directed treatment with ivermectin have significantly reduced morbidity. Studies in Mali and Senegal proved the feasibility of elimination with ivermectin administration. The treatment goal is shifting from control to elimination in endemic African regions. Given limited resources, national and global policymakers need a rigorous analysis comparing investment options. For this, we developed scenarios for alternative treatment goals and compared treatment timelines and drug needs between the scenarios. Control, elimination, and eradication scenarios were developed with reference to current standard practices, large-scale studies, and historical data. For each scenario, the timeline when treatment is expected to stop at country level was predicted using a dynamical transmission model, and ivermectin treatment needs were predicted based on population in endemic areas, treatment coverage data, and the frequency of community-directed treatment. The control scenario requires community-directed treatment with ivermectin beyond 2045 with around 2.63 billion treatments over 2013-2045; the elimination scenario, until 2028 in areas where feasible, but beyond 2045 in countries with operational challenges, around 1.15 billion treatments; and the eradication scenario, lasting until 2040, around 1.30 billion treatments. The eradication scenario is the most favorable in terms of the timeline of the intervention phase and treatment needs. For its realization, strong health systems and political will are required to overcome epidemiological and political challenges.

Author summary

River blindness (onchocerciasis) is transmitted by blackflies and causes severe itching, skin lesions, and vision impairment including blindness. More than 99% of all current cases are found in sub-Saharan Africa where the disease has historically hindered socioeconomic development in endemic areas. The treatment goal is shifting from control to elimination in Africa as morbidity has significantly decreased through vector control and community-directed treatment with ivermectin. Studies in Mali and Senegal proved that elimination is feasible with ivermectin administration. Given limited resources, national and global policymakers need a rigorous analysis of investment options from epidemiological, economic, and societal aspects. For this, we developed control, elimination, and eradication scenarios and compared treatment timelines and drug needs over the next 30 years. We found that the elimination and eradication scenarios would require a shorter treatment phase and a smaller amount of ivermectin than the control scenario, mainly because community-directed treatment with ivermectin could be ended earlier thanks to regular active surveillance.

Introduction

Elimination of neglected tropical diseases (NTDs) has recently emerged on the global health agenda and gained prominence with the release of the global plan to combat NTDs by the World Health Organization (WHO) [49]. In 2012,WHO issued a roadmap towards the elimination of 17 NTDs [4], and stakeholders from the public and private sectors pledged to contribute to the control, elimination, and eradication of ten NTDs through the London Declaration on NTDs [5]. The second WHO report on NTDs further elaborated the roadmap [45], and the London Declaration follow-up report showed the substantial progress that had already been achieved through the stakeholder partnership approach [50].

One of the NTDs targeted for elimination is onchocerciasis (river blindness). This is a parasitic disease caused by filariae that are transmitted by blackflies. Severe itching, skin lesions, and vision impairment including blindness are its most notable symptoms. Onchocerciasis is endemic in parts of Africa, Latin America, and Yemen, but over 99% of all current cases are found in sub-Saharan Africa [1] where onchocerciasis has historically been a serious public health problem and hindered socioeconomic development in endemic areas [38]. However, many infections are asymptomatic, and vector control and community-directed treatment with ivermectin have significantly reduced morbidity. Specifically, the Onchocerciasis Control Program (OCP), which was implemented in West Africa from1975 to 2002, and the African Programme for Onchocerciasis Control (APOC), which has supported onchocerciasis control activities in sub-Saharan countries since 1995 and continued the OCP's activities where needed, have decreased the burden of disease to such an extent that it is no longer a public health problem in most endemic areas [39]. In Latin America, the Onchocerciasis Elimination Program for the Americas (OEPA) implemented since 1993 has brought the disease close to elimination. Colombia and Ecuador announced the elimination of onchocerciasis after WHO verification in 2013 and 2014, respectively [40,41]. Treatment has

also been stopped in seven foci in Guatemala and Mexico where it has been replaced by surveillance to detect possible recrudescence [42]. Regional elimination in Latin America is expected to be achievable by 2020 if the regular treatment of a sufficient proportion of the nomadic Yanomami in the border area between Brazil and Venezuela can be achieved [43]. In Yemen, onchocerciasis is endemic in a limited number of communities. Elimination in the near future is considered technically feasible, and a national action plan aiming at elimination by 2015 was developed in 2010 [44]. Currently, political instability and security concerns that limit access to endemic areas hamper its implementation [45].

Studies in Mali and Senegal have proved the feasibility of onchocerciasis elimination through ivermectin treatment in some hyper-endemic foci in West Africa [2,46]. This has provided additional momentum and arguments for a shift in the strategic goal from control to elimination also in Africa. The decision to invest in elimination and eradication efforts should be informed by broad assessments considering biological and technical feasibility, financial and economic costs, health and economic gains, capacity of and impacts on health systems, and societal and political willingness to cooperate [47]. An approach to such an assessment has been proposed in the form of eradication investment cases in 2010 [51]. Tediosi and colleagues have examined the approach with focus on three NTDs including onchocerciasis [48]. With reference to this approach, we have developed and compared alternative scenarios, namely, staying in a control mode versus moving toward elimination and subsequent eradication.

In the present paper, we describe the scenarios to achieve control, elimination, and eradication of onchocerciasis, predict the timeline of stopping treatment at country level, and estimate the number of required ivermectin treatments over the next 30 years with focus on Africa.

Methods

Development of scenarios

We developed *scenarios*, describing all required activities and resources that are expected to lead to the goals of control, elimination, and eradication, if effectively implemented and sustained as long as required, based on current standard practice, the results of large-scale studies, and available historical data. To clearly distinguish these alternative scenarios, we referred to the definitions of control, elimination, and eradication endorsed and recommended by the WHO Strategic and Technical Advisory Group for NTDs [52]. The ultimate goals of the scenarios were defined as follows:

1) control scenario: continuing community-directed treatment with ivermectin (CDTi) to keep the prevalence under a locally acceptable level; 2) elimination scenario: scaling up CDTi to all endemic areas where feasible aiming at the reduction of disease incidence to zero; and 3) eradication scenario: including strategies and tailored interventions to overcome operational challenges in endemic areas with feasibility concerns in addition to CDTi with the aim of reducing the global disease incidence to zero (Table 3).

Table 3. Proposed scenarios of control, elimination, and eradication of onchocerciasis

	Control	Elimination	Eradication
Ultimate goal	Reduce disease prevalence to a locally acceptable level	Reduce the incidence of infection to zero in a defined geographical area	Reduce the worldwide incidence of infection to zero
Target areas			
Endemicity	Hyper, meso	Hyper, meso, hypo	Hyper, meso, hypo
Feasibility concerns for CDTi[1]	Partially targeted	Partially targeted	Targeted[2]
Activities at project level			
Phase 1. Intervention			
1. Community-directed treatment with ivermectin (CDTi)			
Frequency	Once a year	Once or twice[3] a year	
Treatment coverage	65%+	65%+	
Start year of new projects[4]	2014-2015	2014-2015: hyper-/meso-endemic	2014-2015: hyper-/meso-endemic
		2016-2017: hypo-endemic	2016-2017: hypo-endemic, with no feasibility concerns for CDTi
			2020-2021: hypo-endemic, with feasibility concerns for CDTi
Duration	25 years; another 25 years in case of insufficient treatment coverage	Until the probability of local elimination is ≥ 99%[5]	
2. Surveillance			
Type	Epidemiological	1A) Epidemiological	
		1B) Epidemiological and entomological	
Frequency	Last year of MDA (25th, 50th year)	1A) Every 4 years from 9th year of MDA	
		1B) Last one year	
Site	10 villages	1A) 10 villages	
		1B) 20 villages (epidemiological surveys) and 4 catching sites (entomological)	
Phase 2. Confirmation of elimination			
Surveillance			
Type	NA	Epidemiological and entomological	
Frequency	NA	Epidemiological: last one year (3rd year)	
	NA	Entomological: last two years (2nd and 3rd year)	
Site	NA	10 villages and 4 catching sites	
Phase 3. Post-elimination			
Surveillance			
Type	NA	Epidemiological and entomological	
Frequency	NA	Epidemiological: every 3 years	
	NA	Entomological: every 4 years	
Site	NA	5 villages and 2 catching sites	

[1] Political insecurity and co-endemicity with *Loa loa*.
[2] Hypo-endemic areas with feasibility concerns were included in the eradication scenario only.
[3] Twice a year in new projects in Ethiopia and Uganda where the respective ministries of health announced six-monthly CDTi in new projects to bring them in line with ongoing projects [53,54]
[4] Predicted considering APOC's strategic plan to focus on the onchocerciasis elimination for the next decade 2016-2025 and the current epidemiological and political situation
[5] A dynamical transmission model ONCHOSIM [8] was used.

From an operational perspective, the control and elimination scenarios are designed to target endemic areas where interventions appear feasible without major challenges, whereas the eradication scenario is an optimal situation. To make the eradication scenario feasible, intensive efforts to improve operational capacity and to increase political willingness would be required to overcome epidemiological and political challenges. We assume effective treatment would be implemented through tailored approaches in those areas, and regular surveillance would be maintained during and after the intervention phase until eradication has been verified.

Referring to the general principles for developing scenarios outlined by Tediosi and colleagues [48], the key components of scenarios were identified at project level. Scenarios were further revised by verifying the realism of assumptions in consultation with a technical advisory group consisting of policymakers, onchocerciasis epidemiologists, public health experts, health economists, and donors.

Key components for developing the scenarios are defined as follows and the developed scenarios are described in Table3.

Projects

In all APOC areas, operational decisions regarding drug administration and monitoring are made at the level of projects whose geographic scope ranges from a single district to a whole country, and which is under the leadership of a project management team supported by the ministry of health, APOC, and NGOs [15]. For the purpose of modeling, all ongoing and potential new projects were identified and counted. First, a total of 112 projects were identified to be active in 16 APOC countries as of November 2013 based on the APOC treatment database (last update: 2012). Additional potential endemic areas in APOC countries that are not yet covered by systematic ivermectin treatment and hence not part of existing

projects were identified using the Rapid Epidemiological Mapping of Onchocerciasis (REMO) map [29] and broken down into 43 potential new projects considering administrative boundaries, endemicity, *Loa loa*(African eyeworm) co-endemicity, and operational feasibility. For endemic countries in former OCP countries, a provisional database had been set up with the information on geographical location, pre-control endemicity, latest available treatment coverage, and population at project level. Treatment areas were divided into hypothetical project areas based on administrative boundaries, treatment history, and available impact evaluation data. A total of 17 such projects in 10 endemic countries in West Africa were identified as ongoing as of November 2013. Two possibly endemic regions in Côte d'Ivoire and Ghana had reportedly implemented neither CDTi nor vector control; thus they were included as new projects in the database.

Population

The population for ongoing projects (as of November 2013) was derived from the APOC treatment database and the provisional database for former OCP countries. The information came from the census conducted by community drug distributors for estimating drug needs. For potential new projects, the population was estimated by multiplying the surface area (km^2) of the project with the average population density (per km^2) across other projects with census data within the country. Population over the next 30 years was adjusted for population growth rates [55].

Pre-control endemicity

For APOC countries, endemicity was classified into four levels based on the highest pre-control nodule prevalence among adult males in the project area, namely, non-endemic with less than 5% nodule prevalence, hypo-endemic between 5% and 20%, meso-endemic between

20% and 40%, and hyper-endemic with 40% and above. The pre-control geographic distribution of nodule prevalence in each project area was obtained from a map generated using a kriging analysis of REMO survey results [56]. For former OCP countries, endemicity was classified based on the highest pre-control microfilariae prevalence among the population aged 5 years and older, namely, non-endemic with less than 10% microfilariae prevalence, hypo-endemic between 10% to 40%, meso-endemic between 40% and 60%, and hyper-endemic with 60% and above. The pre-control geographical distribution of microfilariae prevalence in each project area was obtained from a map generated using a kriging analysis of pre-control skin snip survey results. The corresponding ranges of microfilariae prevalence to nodule prevalence for the endemicity levels were estimated using a published relationship between microfilariae and nodule prevalences[57].

Community-directed treatment with ivermectin

CDTi was considered the primary treatment approach. Ivermectin is known as a safe drug to treat early onchocerciasis symptoms and prevent lasting symptoms from developing to blindness. WHO deemed that non-medical people could administer ivermectin after training [14,58,59], and APOC formally adopted CDTi in 1997 [60]. In this approach, community volunteers play a key role; they conduct a community census to determine the required amount of ivermectin, plan when and how to distribute ivermectin in their communities, administer the correct dose of ivermectin, manage adverse reactions, keep records, and report to health workers.

Target projects

Target projects were selected for each scenario based on the pre-control endemicity and considering the treatment goals. The control scenario included projects with meso- and hyper-

endemicity considering the goal of keeping the prevalence under a locally acceptable level. The fact that surrounding hypo-endemic areas are not treated implies the possibility of recrudescence, yet was considered consistent with the aim of control as onchocerciasis is not a public health problem in hypo-endemic areas.

The elimination scenario extended the target projects to include those in hypo-endemic areas. The target projects in hypo-endemic areas, however, were confined to those where CDTi is expected to be operationally feasible at present or in the near future. To assess the feasibility, we referred to the criteria defined by the International Task Force on Disease Eradication and agreed in the Ernst Strüngmann Forum [61]. First, for biological and epidemiological feasibility, we took into account co-endemicity with *L. loa*, as severe adverse reactions against ivermectin can occur in *L. loa* patients with heavy infection, and the availability of alternative treatment approaches to mitigate the risk. For social and political feasibility, we took into account the current political situation and previous project performance.

The eradication scenario further extended the target areas to include all projects in hypo-endemic areas assuming locally tailored approaches would be successfully employed in the areas with epidemiological and political feasibility concerns.

Frequency of CDTi

Annual CDTi was assumed considering CDTi had been conducted annually in most projects in Africa [39]. Exceptions were new projects in Ethiopia [53] and Uganda [54] where the respective ministries of health announced six-monthly CDTi in new projects to bring them in line with ongoing projects.

Treatment coverage

Treatment coverage was defined as the proportion of the total population residing in a project area that was actually treated. APOC suggests that the treatment coverage needs to be higher than 65% for the program to achieve effective control of the disease [62]. The average treatment coverage over the last three years (2010-2012) was calculated based on the APOC treatment database and assumed to be stable at that level for the future duration of CDTi. If a project had, on average, not achieved the recommended coverage (65%), we assumed that future treatment coverage would be equal to the highest coverage that had been achieved over 2010-2012. In case historical data were lacking, the national average treatment coverage over projects with available data was used. If there were no projects with available historical data within a country, the regional average (over national averages available) for the APOC regions was used. In the database for former OCP countries, only the latest treatment coverage data were available and were used as the expected treatment coverage. The treatment coverage data in the former OCP countries were higher than 65%, and we used the national average for new projects.

Start year of CDTi

The historical start years of ongoing projects were obtained from the APOC treatment database. For projects yet to be started, a start year was predicted based on APOC's strategic plan to focus on onchocerciasis elimination for the next decade 2016-2025 [63], the current epidemiology, and the current political situation. A start year in 2014-2015 was assumed for projects in areas without feasibility concerns. For other projects with feasibility concerns, two phases were distinguished depending on the current epidemiology. Projects in meso- and hyper-endemic areas without feasibility concerns were assumed to start CDTi in 2016-2017, because these areas were expected to be given priority considering the regional momentum toward onchocerciasis elimination. Projects in hypo-endemic areas with feasibility concerns

were assumed to start in 2020-2021, as countries are not likely to postpone treatment by more than a decade if they actually aim at eradication. Within each of the three groups, the year when a project is expected to start CDTi was determined using a point system in which the earlier year is assigned if the project has a higher level of endemicity, a larger population size, and a higher expected treatment coverage, considering CDTi is expected to be more urgently needed if the disease is more prevalent and more people are exposed to the risk of infection, and also more feasible if the treatment compliance is expected to be higher compared to other projects.

Duration of CDTi

In the control scenario, the treatment goal is to control the disease as a public health problem by CDTi in all meso- and hyper-endemic areas where there is a high risk of disease. The required duration of CDTi was assumed to be 25 years considering that ONCHOSIM simulations predict that 25 years of annual ivermectin would achieve elimination in highly endemic areas (pre-control microfilariae per skin snip: 50 to 70 mf/s) and all areas with lower endemicity levels. Local elimination might occur within 25 years; however, the lack of regular surveillance to evaluate progress and verify elimination entails continued CDTi. This is the current practice in former OCP regions, that is, CDTi has been continued until now although the disease had been eliminated as a public health problem in most areas when OCP stopped in 2002. For 14% of the projects targeted in the control scenario, an additional 25 years of CDTi was assumed, referring to the results of APOC's most recent evaluations that showed unsatisfactory decline in infection levels in 14% of the evaluated projects (5 of 35) due to insufficient treatment coverage [64]. The projects requiring this additional CDTi effort were randomly selected regardless of the historical treatment coverage, because the APOC

evaluation revealed that some projects that had reported high treatment coverage had actually failed to maintain the coverage above 65%.

In the elimination and eradication scenarios, the required duration of CDTi was predicted using ONCHOSIM which uses a stochastic model to simulate the life events of human individuals and inhabitant parasites and a deterministic model to simulate the fly dynamics and the development of parasites in the flies [8]. The model had been fitted to longitudinal data from Ghana [65,66], and the predicted trends of infection had been shown to be consistent with the actually observed trends in the study sites in Mali and Senegal [2,46,67]. The model estimated the years of CDTi required for achieving elimination with a probability of 99% by simulating the dynamics of transmission for different settings with regard to pre-control endemicity and treatment coverage.

End year when CDTi can be stopped

The year when CDTi can be stopped was estimated by adding the required CDTi duration to the start year. If the predicted end year was before 2014, it was delayed to 2015 or 2016, as stopping treatment is likely to be cautiously ordered at present despite epidemiological and entomological evidence indicating that the threshold for safely stopping CDTi had been reached. To date, little practical experience has been collected in this domain, and restarting CDTi is considered more challenging than maintaining CDTi a few years beyond the actually required time. The number of years for which stopping CDTi was delayed was determined using a point system in which the end year was more delayed if the project had a higher level of pre-control endemicity, a larger population size, and a lower treatment coverage than other projects. The rational was that more solid evidence would be needed to stop CDTi if the pre-control endemicity had been higher, more people were exposed to the risk of infection, and the treatment compliance had been lower than in other projects.

Surveillance

Two types of surveillance were assumed: epidemiological surveillance to track infection levels in the population and entomological surveillance to evaluate the infectivity rate of blackflies.

The control scenario included epidemiological surveillance only in the expected end year of CDTi to confirm that the infection level was low enough to stop CDTi. This reflects the practice under the control mode until recently in most endemic African regions, which do not have routine surveillance systems as the goal has been controlling the disease rather than eliminating it.

For the elimination and eradication scenarios, surveillance strategies with three phases were defined based on the conceptual and operational framework of onchocerciasis elimination with ivermectin treatment developed by APOC [68] and in consultation with the technical advisory group. For detailed activities, we referred to a protocol for epidemiological surveillance developed by APOC and a guide for post treatment surveillance produced by OEPA [69]. In phase 1, the intervention phase, epidemiological surveys are scheduled every 4 years, starting after 8 years of CDTi. The aim is to assess the impact of treatment and the prevalence decline towards elimination thresholds. In the expected final year of CDTi, entomological as well as epidemiological surveys are assumed in all endemic areas to confirm that elimination thresholds have been reached and CDTi can be safely stopped. Following the confirmation that the prevalence and the vector infectivity rate have reached the thresholds to stop CDTi, phase 2 starts. Its goal is to confirm local elimination and it lasts at least three years. In this phase, epidemiological surveys in the last year and entomological surveys in the last two years are planned to confirm that the infection prevalence and the vector infectivity rate continue to decrease toward zero and that no recrudescence has occurred. In phase 3, the post-elimination phase, surveillance consists of epidemiological surveys every 3 years and

entomological surveys every 4 years, but less intensive than in phase 2 (e.g., a smaller number of survey sites). The objective is to detect possible recrudescence until eradication has been verified. If surveillance detects recrudescence after CDTi had been stopped, phase 1 restarts with a focus on the area where the recrudescence had happened and adjacent areas.

Number of required ivermectin treatments

The number of required ivermectin treatments to achieve the goals of the control, elimination and eradication scenarios in endemic African regions was predicted by multiplying the estimated population living in endemic areas with the treatment coverage rate and the CDTi frequency per year for the required duration of treatment at project level. The capacity of drug manufacturers to supply the required number of ivermectin was assumed to be sufficient considering Merck's commitment to donate ivermectin until elimination is achieved globally [70].

The time horizon for predicting the number of treatments was 2013 to 2045. The start year was set considering the most recent version of the APOC databases available for analysis was for 2012. The end year was chosen based on the prediction that the last project in the eradication scenario would stop CDTi in 2040, and that after stopping CDTi, at least three years would be required to confirm local elimination. In the control and elimination scenarios, the last projects were expected to continue CDTi beyond 2045.

In the Table S1, the relevant data regarding the key components of the scenarios, which were used for estimating the timelines and the number of required ivermectin treatments, are presented at project level.

Uncertainty analysis

Parameters used for the scenario analysis were subject to considerable uncertainty and the impact of the uncertainty was examined for the target population, the timeline when CDTi is expected to be stopped, and the number of required ivermectin treatments. The impact of a single parameter's uncertainty was assessed with one-way deterministic sensitivity analysis (DSA). Considering the final estimates are driven by the joint effects of multiple parameters, multivariate probabilistic sensitivity analysis (PSA) was conducted with all the variables examined in the one-way DSA.

The included parameters were population growth rate, treatment coverage, treatment duration, CDTi start and end years, and the assumptions for selecting target projects. For DSA, the parameter uncertainty ranges were determined based on available data, expert opinion or both. For PSA, statistical distributions were chosen considering the characteristics of parameters, and fitted to available data. Simulations were run 1,000 times for each scenario.

Population growth rate

For DSA, the range of national population growth rates from the UN database was used [55]. For PSA, a normal distribution was fitted, assuming the range of population growth rates to be the 95% confidence interval.

Treatment coverage

The range of uncertainty about treatment coverage was assumed to be ±10% of the expected coverage in DSA. For PSA, a beta distribution was selected considering treatment coverage is between zero and one, and fitted to the historical data over 2010-2012. In these sensitivity analyses, samples were bounded from 60% to 84%, because control and elimination is not expected to be achievable with treatment coverage less than 60%, and the maximum achievable coverage is 84% considering around 16% of the population in endemic regions is

not eligible for treatment because individuals are less than five years old, pregnant, or severely ill.

Average treatment coverage data and distribution parameters are presented in the Table S2, and distribution graphs are shown in the Fig S1.

CDTi duration

For DSA and PSA, the CDTi duration was linked to the treatment coverage so that it changed automatically with the variation of treatment coverage. For the relationship between treatment coverage and CDTi duration, we used the results of ONCHOSIM [8] simulations fitted to the longitudinal data from Ghana [65,66]. For the control scenario, the CDTi duration changed only if the required duration predicted by the ONCHOSIM simulation was longer than 25 years; otherwise 25 years of CDTi was assumed as previously described.

Delay in starting and ending CDTi

Starting and ending CDTi could be delayed as political turmoil or operational difficulties arise or become exacerbated. Also, CDTi might be stopped later than expected considering APOC has strict criteria for ending CDTi (e.g., prevalence of mf < 1% in 90% of surveyed villages) [68]. For DSA, the uncertainty range of the delay in starting and ending CDTi was assumed to be from 0 to 5 years. For PSA, a gamma distribution that has around 90% of samples between 0 and 5 was selected (Fig S2).

Selection of target projects

In the control scenario, 14% of the target projects were assumed to need another 25-year of CDTi due to insufficient treatment coverage as previously described. In DSA, the proportion

of projects that were expected to have insufficient treatment coverage was varied between 0% and 14% under the control scenario, and in PSA a uniform distribution was used.

The elimination and eradication scenarios included 18 potential new projects in hypo-endemic areas (Table S1). Onchocerciasis mapping based on REMO surveys has been largely completed in the APOC countries [29]. However, nodule palpation may give false positive results in non-endemic areas, while most REMO surveys were done more than 10 to 15 years ago before the start of CDTi. Recent parasitological surveys to determine the current infection status of hypo-endemic areas [71] have shown that, in many of these areas, onchocerciasis is no longer endemic. In order to take this into account, the number of new projects in hypo-endemic areas was varied between 20% and 100% of the total number of potential new projects: the lower bound was based on the finding that one of five potential project areas was confirmed to be hypo-endemic, and the upper bound based on the possibility that all potential hypo-endemic areas could be confirmed to be endemic. For PSA, a uniform distribution was used.

Results

For each scenario, we predicted target areas in endemic African regions and population in those areas, the timeline when CDTi is expected to be stopped, and the number of required ivermectin treatments.

Target areas and population

The control scenario targeted hyper-and meso-endemic areas in all endemic African countries. Under the elimination scenario, CDTi was extended to hypo-endemic areas where CDTi is feasible in addition to hyper-and meso-endemic areas. Countries that include projects with

feasibility concerns have been identified to be the Central African Republic, the Democratic Republic of the Congo, and South Sudan due to political instability, and Gabon due to the high prevalence of *L. loa* in areas with a low prevalence of onchocerciasis. In these four countries, hypo-endemicity areas were therefore excluded from the elimination scenario. The eradication scenario targeted all hyper-, meso-, and hypo-endemic areas. The endemic countries in Africa were categorized into two control programs in which they participate or participated, APOC and OCP, respectively (Table 4).

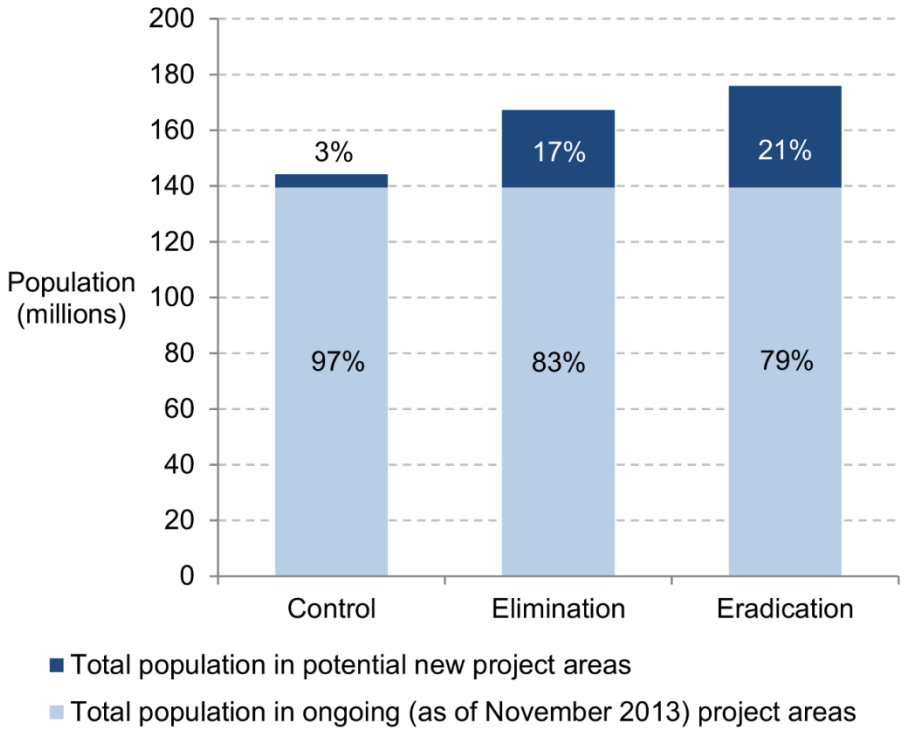
Table 4. Endemic countries in Africa

Program	Endemic countries
APOC	Angola, Burundi, Cameroon, the Central African Republic*, Chad, Congo, the Democratic Republic of the Congo*, Equatorial Guinea, Ethiopia, Gabon*, Liberia, Malawi, Mozambique**, Nigeria, South Sudan*, Sudan, Tanzania, Uganda (total 18 countries)
Former OCP	Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Guinea Bissau, Mali, Senegal, Sierra Leone, Togo (total 10 countries)

* countries with epidemiological or political insecurity issues
** non-endemic with possible exception of small border areas with Malawi and Tanzania

The control scenario included 27 countries, and potential new projects were predicted to cover around 3% of the total population in the entire target area, or 4.7 million of 144 million (Fig 14). The elimination scenario included the same 27 countries, and new projects were predicted to cover at most 17% of the population in the entire target area (167 million). Depending on the number of new projects in potential hypo-endemic areas, the population in new project areas ranged from 12.1 million to 27.8 million (7% and 17%). The eradication scenario included one more country, Gabon, and the total population in the entire target area was estimated at around 176 million of which 21% at maximum live in new project areas with a range of 12.1 million to 36.5 million people (7% to 21%) depending on the number of new projects in potential hypo-endemic areas.

Figure 14. Total population living in ongoing and potential new project areas in endemic African countries (numbers, % of total population in endemic regions), 2014



Expected year when CDTi can be stopped

In the control scenario, most endemic countries outside West Africa were predicted to continue CDTi beyond 2045 (Fig 15). The most influential parameter determining the expected year of ending CDTi was the extension of treatment duration due to insufficient treatment coverage (Fig 16). For the elimination and eradication scenarios, the final year of CDTi represents the year of ending the intervention phase at country level assuming no recrudescence would occur. In the elimination scenario, all endemic countries except the four countries with feasibility concerns were expected to finish the intervention phase by 2028 at the latest and those four countries were expected to continue CDTi beyond 2045 (Fig 15). In the eradication scenario, all endemic countries were expected to reach the end of the intervention phase by 2040 assuming sufficient treatment would be delivered sustainably in the four countries with epidemiological and political concerns. For the elimination and eradication scenarios, one-way DSA (Fig 16) showed that any delay in starting and ending

CDTi and low treatment coverage would result in the intervention phase to end later than expected; on the contrary, high treatment coverage would expedite the progress of the intervention phase and lead to an earlier end of the intervention phase.

Figure 15. Years when CDTi is expected to be stopped in endemic African regions

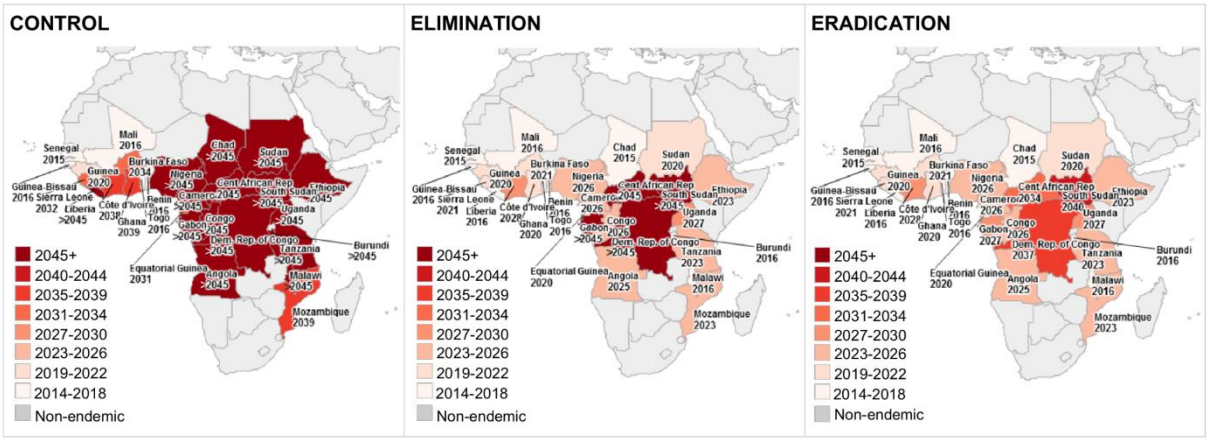
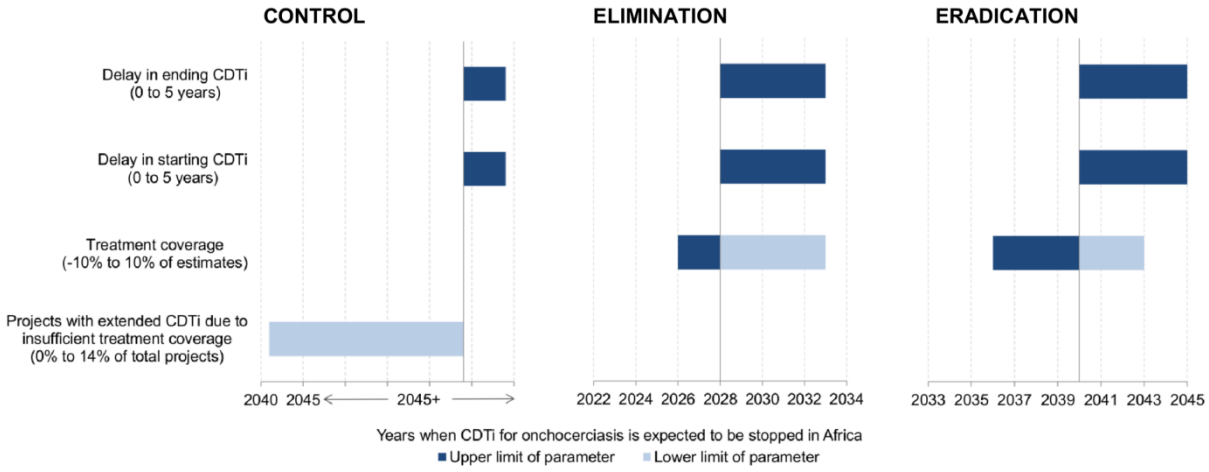


Figure 16. One-way deterministic sensitivity analysis for the years when CDTi is expected to be stopped in endemic African regions



(Note: CONTROL also applies to the countries with feasibility concerns in the elimination scenario. ELIMINATION excludes countries with feasibility concerns.)

Number of required ivermectin treatments

The need for ivermectin treatments was concentrated in the first half of the time horizon for the elimination and eradication scenarios, as 80% of all potential projects were stopped safely

by 2031 and 2025, respectively. In the control scenario, it took until 2038 for the same proportion of the total projects to stop CDTi (Fig 17). The cumulative number of required ivermectin treatments over 2013-2045 was estimated at 2.63 billion (95% central range: 2.41 billion-2.99 billion) for the control scenario. Specifically, 1.48 billion (1.51bn-1.57bn) treatments were predicted to be required until 2025 and 1.15 billion (0.90bn-1.41bn) treatments over 2026-2045 (Table 5). According to the simulation of the elimination scenario, the required number of ivermectin treatments over the whole period was around 1.48 billion (1.42bn-1.79bn). Compared to the control scenario, the total number of required treatments in the elimination scenario was lower by 1.15 billion (44%): 0.45 billion (0.36bn-0.55bn) until 2025 and 0.69 billion (0.38bn-0.92bn) from 2026 to 2045 (Table 5, Fig 18). The eradication scenario required an even smaller number of ivermectin treatments for the whole period, 1.30 billion (1.18bn-1.51bn), which was 0.18 billion (0.03bn-0.49bn), or 12%, lower than that under the elimination scenario and 1.32 billion (0.97bn-1.75bn), or 50%, lower than that under the control scenario (Fig 18). In one-way DSA (Fig 19), the most influential parameter on the cumulative number of required ivermectin treatments was the delay in ending CDTi in all scenarios. For the control scenario, the second most influential parameter was the number of projects with extended CDTi duration due to insufficient treatment coverage. For the elimination and eradication scenarios, it was the number of potential new projects in hypo-endemic areas.

Figure 17. Cumulative number of ivermectin treatments and annual number of projects with ongoing CDTi in endemic African regions, 2013-2045

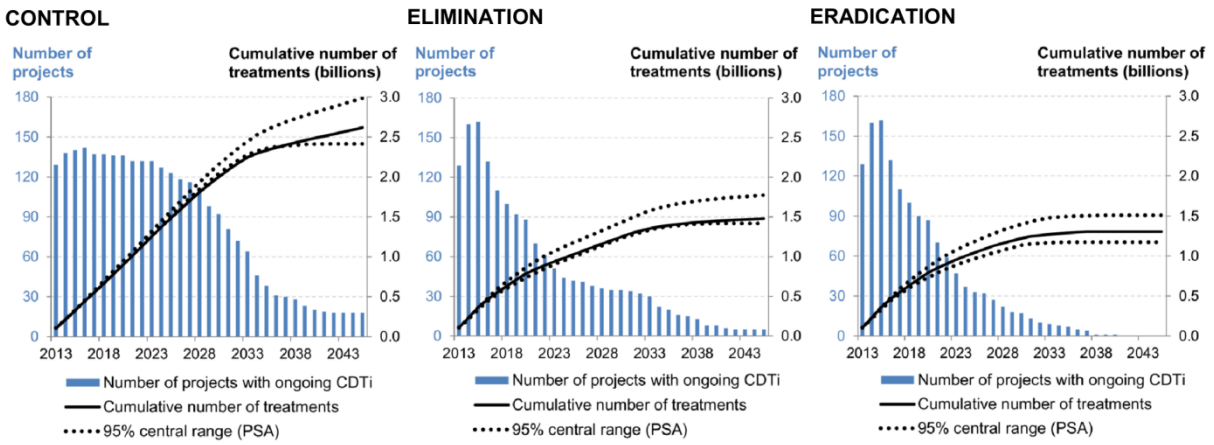


Table 5. Population in target areas and the cumulative number of required ivermectin treatments in endemic African regions

	Control	Elimination	Eradication
2013-2025			
Population living in target areas, 2025	189,958,000	217,377,000	229,557,000
Cumulative number of required ivermectin treatments	1,480,765,000	1,027,466,000	1,041,229,000
2026-2035			
Population living in target areas, 2035	238,794,000	273,380,000	289,519,000
Cumulative number of required ivermectin treatments	859,636,000	367,629,000	249,291,000
2036-2045			
Population living in target areas, 2045	293,373,000	336,005,000	357,428,000
Cumulative number of required ivermectin treatments	287,319,000	86,630,000	12,681,000

Figure 18. Difference in the cumulative number of ivermectin treatments between scenarios, 2013-2045

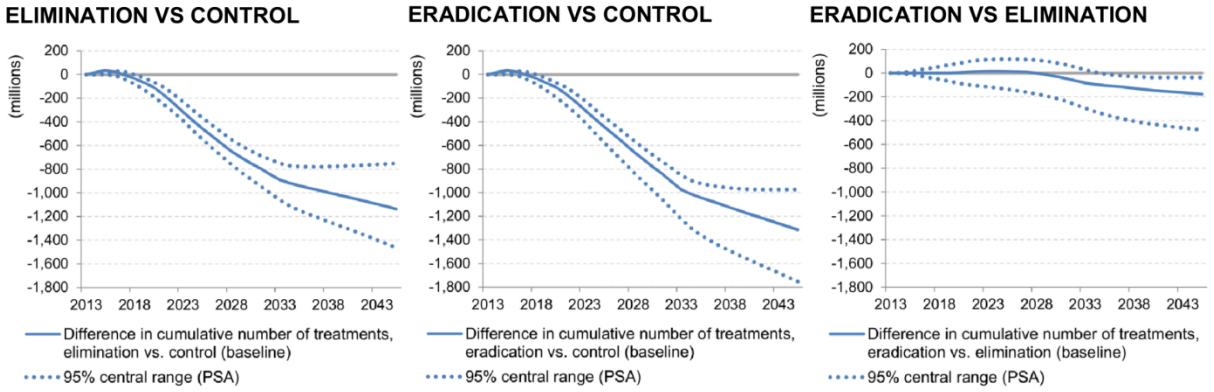
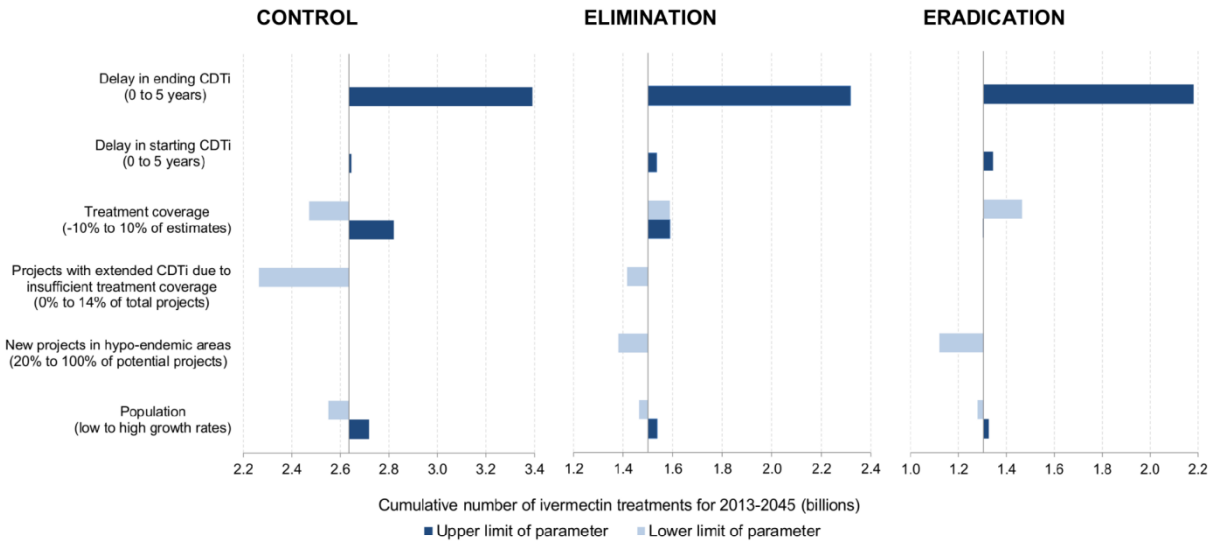


Figure 19. One-way deterministic sensitivity analysis for the cumulative number of ivermectin treatments over 2013-2045



Discussion

The key changes for shifting from the control mode to elimination and subsequent eradication are the scale-up of CDTi to hypo-endemic areas and the implementation of regular epidemiological and entomological surveys along with ongoing surveillance. For successful implementation of these, overcoming the existing feasibility issues related to the co-endemicity with *L. loa,* the insecure political situation, and weak health systems will be critical. We found that, if this could be accomplished, regional elimination in Africa could be achieved as early as 2040, and consequently all endemic countries including Latin Americas and Yemen would be in the post-elimination phase until eradication has been verified.

We found that achieving elimination would reduce treatment needs by 43% compared to the control mode for the period 2013-2045. The driver of this remarkable difference is that CDTi could be stopped for the majority of projects based on regular surveillance, while it would have to continue for at least 25 years under the control scenario. The eradication scenario is predicted to require an even smaller number of ivermectin treatments than the elimination scenario, as hypo-endemic areas with feasibility concerns were assumed to have a shorter

treatment period through effective treatment via tailored approaches as well as CDTi, whereas those areas would be under the control mode in the elimination scenario. This finding implies that saved ivermectin drugs could be used for other disease programs, for instance, mass drug administration (MDA) for lymphatic filariasis (LF).

The uncertainty about the target population in the elimination and eradication scenarios was mainly driven by uncertainty in the number of potential new projects in hypo-endemic areas, as some of those areas might not be actually endemic. Parasitological surveys are therefore needed to determine the current infection status of those areas. Setting up a new project requires operational planning, human resource mobilization, and startup costs. To move towards elimination without delay and to save human and financial resources, the rapid mapping of potential hypo-endemic areas should be a priority to confirm areas to set up new projects and to develop elimination strategies for those areas.

The main driver of the number of required ivermectin treatments was the delay in stopping CDTi. This finding implies that maintaining high treatment coverage to avoid the extension of treatment duration and continuous monitoring and evaluation to decide a proper time to stop CDTi would lead to faster elimination and prevent unnecessary efforts to deliver drugs.

We assumed no recrudescence in our analysis. However, if recrudescence occurs, the duration of CDTi would need to be extended, local elimination would be delayed, and the number of required treatments would increase. Recrudescence might occur because of human or vector migration, interrupted drug distribution due to political instability, and residual transmission from not-treated endemic areas due to incomplete or inconsistent geographic coverage.

We did not adjust for alternative treatment approaches for areas where *L. loa* is highly endemic but onchocerciasis is hypo-endemic. Suggested treatment approaches for these areas include anti-*Wolbachia* therapy with macrofilaricidal drugs, high doses of albendazole, and the test-and-treat strategy [72,73]. These approaches would expedite elimination and increase the demand for other drugs while reducing the need for ivermectin.

Our modeling did not incorporate the impact of changing the CDTi frequency on the treatment duration. It has been suggested to increase the frequency of CDTi to reduce the prevalence and transmission of onchocerciasis faster compared to the annual CDTi [64]. A recent study by Coffeng and colleagues shows that six-monthly ivermectin treatment could reduce the required treatment duration by 40% based on a dynamical transmission model [67]. In practice, increasing the CDTi frequency would require collaboration between policymakers, health workers, and community volunteers and new strategies on how to mobilize human and financial resources, given limited resources and competing health programs. Under the control scenario, annual CDTi could mean overtreatment for projects that had more than 15-20 years of treatment, for example, some areas in West Africa where ivermectin administration has been implemented since the 1990s. For these areas, less frequent CDTi could be an alternative for morbidity control, which would require a smaller number of ivermectin and less human and financial resources. However, less frequent CDTi might lead to a loss of local expertise, human resources, and community compliance over the time interval without CDTi and, consequently, to the decrease of treatment coverage below the required level, which could expose the areas to the risk of recrudescence.

We did not incorporate possible delays in ending CDTi due to co-endemicity with LF. In areas where LF is co-endemic with onchocerciasis, an assessment whether both diseases have reached the thresholds to stop treatment will be needed in order to stop CDTi. In practice, no delay is expected in most cases as MDA for LF, which relies on albendazole and ivermectin, usually requires fewer cycles to reach the point of transition to the post-treatment phase. However, LF mapping or anti-LF MDA have not started in about a third of the 35 endemic countries in Africa [74].

We did not take into account the possibility of drug resistance, as no confirmed cases of ivermectin resistance have been reported from endemic countries so far. However, if ivermectin resistance were to happen as suggested by Bourguinat and colleagues through

studies on the effects of ivermectin on the genetics of *Onchocerca volvulus* [75], the entire efforts for onchocerciasis treatment could be endangered, as current strategies heavily rely on ivermectin.

The long time horizon of 2013-2045 poses challenges in predicting technological, political, and economic changes. New treatment and diagnostic tools could be game changers in achieving elimination. Ivermectin is a microfilaricidal drug which requires many years of treatment and has a risk of eliciting severe adverse reactions in *L. loa* patients. Macrofilaricidal drugs that are safe and effective for general population use, are easy to administer in communities, and have a shorter treatment period than ivermectin could substantially change treatment strategies and expedite elimination. Several macrofilaricidal drugs for human use have been or currently are under development, e.g., doxycycline [76], emodepside[77], moxidectin[78], and flubendazole[79]. The need for diagnostic techniques that are capable of detecting infections early, are easy to use in the field, and are affordable would greatly facilitate surveillance when early detection of new infections is paramount. The skin snip method, currently the most common diagnostic method, has low sensitivity for detecting very light infections, and can result in a delay in detecting recrudescence. Several diagnostic techniques, e.g., OV-16 (ELISA and Rapid Test) and the DEC patch test [80,81], that may prove more sensitive and practical, have been developed. Unexpected political unrest might hamper the elimination programs, as it interrupts interventions and weakens political support. Industrialization along with economic growth may have a significant impact. For instance, the construction of dams can flood existing breeding sites of blackflies or create new ones, and deforestation can greatly alter the composition or density of blackfly populations.

Political will across the whole spectrum of stakeholders from global and national policymakers to community members will be particularly critical during the “last mile” towards elimination and subsequent eradication [36]. Countries sharing borders spanning endemic areas would need to effectively collaborate to enable prompt responses to or prevent

possible recrudescence. Regular meetings have been held between Guinea/Sierra Leone/Liberia, Togo/Benin, and Benin/Nigeria [82], and this proves such mechanism can work. Similar collaborative relationships would need to be fostered for other endemic countries. APOC has announced that it would transform to a new regional entity by 2016 that would support integrated country-driven programs to eliminate onchocerciasis, LF, and other preventive chemotherapy NTDs (soil-transmitted helminthiasis, schistosomiasis, trachoma) in Africa [83,84]. Successful launching of this new regional entity might provide a more collaborative environment for sustainable interventions and post-treatment surveillance for NTDs in the region. Continuous support from community members is essential for onchocerciasis elimination in Africa. National policymakers would need to keep empowering community drug distributors, as their role is critical for successful CDTi and will continue to be so until eradication has been achieved.

Acknowledgements

We thank Uche Amazigo (former APOC director), David Bishai (Johns Hopkins University), Mamoun Homeida (University of Medical Sciences & Technology, Sudan), Adrian Hopkins (Task Force for Global Health), and Honorat Zouré (African Programme for Onchocerciasis Control) for their advice and input to the scenario development. We also thank all other members of the technical advisory group for the critical review of the scenarios and valuable comments.

4 Financial and economic costs of the elimination and eradication of onchocerciasis (river blindness) in Africa

Young Eun Kim[1,2], Elisa Sicuri[3], Fabrizio Tediosi[1,2]

1 Swiss Tropical and Public Health Institute, Basel, Switzerland

2 University of Basel, Basel, Switzerland

3 ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain

Email addresses

YEK: young.kim@unibas.ch

ES: elisa.sicuri@cresib.cat

FT: fabrizio.tediosi@unibas.ch

Correspondence to:

Young Eun Kim

Swiss Tropical and Public Health Institute

Socinstrasse 57, 4002 Basel, Switzerland

Email: young.kim@unibas.ch

Telephone: +41 61 284 8736

Citation:
Kim YE, Sicuri E, Tediosi F. Financial and economic costs of the elimination and eradication of onchocerciasis (river blindness) in Africa. PLoS Negl Trop Dis. 2015; In press.

Abstract

Background Onchocerciasis (river blindness) is a parasitic disease transmitted by blackflies. Symptoms include severe itching, skin lesions, and vision impairment including blindness. More than 99% of all cases are concentrated in sub-Saharan Africa. Fortunately, vector control and community-directed treatment with ivermectin have significantly decreased morbidity, and the treatment goal is shifting from control to elimination in Africa.

Methods We estimated financial resources and societal opportunity costs associated with scaling up community-directed treatment with ivermectin and implementing surveillance and response systems in endemic African regions for alternative treatment goals – control, elimination, and eradication. We used a micro-costing approach that allows adjustment for time-variant resource utilization and for the heterogeneity in the demographic, epidemiological, and political situation.

Results The elimination and eradication scenarios, which include scaling up treatments to hypo-endemic and operationally challenging areas at the latest by 2021 and implementing intensive surveillance, would allow savings of $1.5 billion and $1.6 billion over 2013−2045 as compared to the control scenario. Although the elimination and eradication scenarios would require higher surveillance costs ($215 million and $242 million) than the control scenario ($47 million), intensive surveillance would enable treatments to be safely stopped earlier, thereby saving unnecessary costs for prolonged treatments as in the control scenario lacking such surveillance and response systems.

Conclusions The elimination and eradication of onchocerciasis are predicted to allow substantial cost-savings in the long run. To realize cost-savings, policymakers should keep empowering community volunteers, and pharmaceutical companies would need to continue drug donation. To sustain high surveillance costs required for elimination and eradication,

endemic countries would need to enhance their domestic funding capacity. Societal and political will would be critical to sustaining all of these efforts in the long term.

Author summary

River blindness (onchocerciasis) is a parasitic disease transmitted by blackflies. Symptoms include severe itching, skin lesions, and vision impairment including blindness. More than 99% of all cases are concentrated in sub-Saharan Africa. Fortunately, vector control and community-directed treatment with ivermectin have significantly decreased morbidity, and the treatment goal is shifting from control to elimination in Africa. To inform policymakers' and donors' decisions, we estimated financial resources and societal opportunity costs associated with alternative treatment goals – control, elimination, and eradication. We found that rapid scale-up of ivermectin treatment for elimination and eradication would result in substantial cost-savings in the long term as compared to staying in a control mode, because regular active surveillance would allow treatments to end earlier, thereby saving the economic costs of community volunteers and donated ivermectin. To realize cost-savings, policymakers should keep empowering community volunteers, and pharmaceutical companies would need to continue drug donation. To sustain high surveillance costs required for elimination and eradication, endemic countries would need to enhance their domestic funding capacity. Societal and political will would be critical to sustaining all of these efforts.

Introduction

The treatment goal for onchocerciasis (river blindness) has shifted from control to elimination as shown by the World Health Organization's (WHO's) roadmap for neglected tropical diseases (NTDs) and the London Declaration on NTDs in 2012[5,85]. Onchocerciasis is a parasitic disease transmitted by blackflies, and notable symptoms include severe itching, skin lesions, and vision impairment including blindness. Those affected by onchocerciasis suffer negative socioeconomic consequences as a result of their symptoms [68]. The disease is endemic in parts of Africa, Latin America, and Yemen, and more than 99% of all cases are concentrated in sub-Saharan Africa [39]. In Africa, morbidity caused by onchocerciasis was significantly reduced by the vector control activities of the Onchocerciasis Control Programme (OCP) in West Africa (1975–2002) and by the community-directed treatment with ivermectin (CDTi) under the African Programme for Onchocerciasis Control (APOC) in sub-Saharan Africa and parts of West Africa (1995–present) [39]. Studies of foci in Mali, Senegal, and Uganda have proved that eliminating onchocerciasis through ivermectin administration is feasible for amenable epidemiological settings under effective treatments and surveillance [2,3].

Onchocerciasis elimination and subsequent eradication will generate health benefits by reducing the incidence of infection to zero, first in a defined area and then globally. These benefits would be higher than those of staying in a control mode that keeps disease prevalence at a locally acceptable level. In addition to epidemiological evidence, national and global policymakers must consider economic, social, and political aspects when deciding whether to invest in elimination in settings with limited resources and competing health priorities. To assess these broad aspects, a working group at the Ernst Strüngmann Forum suggested developing and analyzing eradication/elimination investment cases[47]. Tediosi and colleagues examined the suggested approach focusing on three NTDs including

onchocerciasis [48]. Referring to this study, Kim and colleagues defined investment options for onchocerciasis as scenarios, and compared the respective timelines and needs for treatment in endemic African countries[6]. Each scenario consists of strategies of treatments and surveillance – epidemiological surveillance to track the infection levels in human and/or entomological surveillance to track the infectivity rates of blackflies.

Control scenario: to reduce disease prevalence to a locally acceptable level (i.e., microfilaria prevalence≤40% or community microfilarialload≤5mf/s [68]), all endemic African countries implement annual CDTi in hyper- and meso-endemic areas, and after at least 25-years of CDTi, conduct epidemiological surveillance to confirm that CDTi can be safely stopped (former OCP projects having implemented regular surveillance continue their surveillance strategies).

Elimination scenario: to reduce the incidence of infection to zero in a defined area, all endemic African countries except those with epidemiological and political challenges implement annual or biannual CDTi, and conduct regular active epidemiological and entomological surveillance to evaluate epidemiological trends, to decide a proper time to stop CDTi, and to detect and respond to possible recrudescence.

Eradication scenario: to reduce the incidence of infection to zero in Africa, which would lead to global eradication, all endemic African countries implement not only annual or biannual CDTi but also locally tailored treatment strategies to deliver sustainable treatments to areas with operational challenges, and implement regular active epidemiological and entomological surveillance to evaluate epidemiological trends, to decide a proper time to stop CDTi, and to detect and respond to possible recrudescence.

We estimated financial resources and societal opportunity costs for endemic African countries (Table 6) associated with the control, elimination, and eradication scenarios to support

policymakers' and donors' informed decisions and provide a basis for further economic evaluation of the elimination and eradication of onchocerciasis.

Table 6. Endemic African countries: GDP per capita, health expenditure (total, out of pocket), population living in endemic areas

Country	Program	GDP per capita, 2012	Total health expenditure (THE), 2012 (% of GDP)	Out-of-pocket health expenditure, 2012 (% of THE)	Population living in endemic areas, 2014
Angola	APOC	$5,539	3.47%	26.69%	2,640,000
Benin	former OCP	$751	4.49%	44.26%	3,585,000
Burkina Faso	former OCP	$652	6.17%	36.36%	230,000
Burundi	APOC	$251	8.13%	28.27%	1,613,000
Cameroon	APOC	$1,220	5.13%	62.65%	9,040,000
Central African Rep.	APOC	$479	3.76%	45.57%	2,150,000
Chad	APOC	$1,035	2.81%	66.43%	2,182,000
Congo, Dem. Rep.	APOC	$418	5.59%	32.48%	43,633,000
Congo, Rep.	APOC	$3,154	3.16%	25.07%	1,475,000
Côte d'Ivoire	former OCP	$1,244	7.06%	55.83%	2,359,000
Equatorial Guinea	APOC	$22,391	4.74%	43.53%	88,000
Ethiopia	APOC	$467	3.83%	41.22%	12,276,000
Gabon	APOC	$10,930	3.47%	41.41%	85,000
Ghana	former OCP	$1,646	5.17%	28.72%	2,535,000
Guinea	former OCP	$493	6.30%	66.62%	3,332,000
Guinea-Bissau	former OCP	$494	5.86%	43.18%	195,000
Liberia	APOC	$414	15.53%	21.22%	3,169,000
Malawi	APOC	$267	9.16%	12.58%	2,261,000
Mali	former OCP	$696	5.82%	60.73%	5,146,000
Mozambique	APOC	$570	6.42%	5.04%	67,000
Nigeria	APOC	$2,742	6.07%	65.88%	55,255,000
Senegal	former OCP	$1,023	4.96%	34.14%	187,000
Sierra Leone	former OCP	$633	15.08%	76.23%	3,320,000
South Sudan	APOC	$974	2.55%	56.70%	7,307,000
Sudan	APOC	$1,695	7.25%	73.68%	657,000
Tanzania	APOC	$609	6.99%	31.75%	3,536,000
Togo	former OCP	$589	8.64%	41.08%	3,172,000
Uganda	APOC	$551	7.97%	49.33%	4,473,000
Average (SD)		$2,212 ($4,507)	6.27% (3.10%)	43.45% (18.25%)	6,285,000 (12,604,000)

GDP per capita, 2012 (USD 2012) from World Bank [86];
Total health expenditure (THE), 2012 (% of GDP) from World Bank [87];
Out-of-pocket health expenditure, 2012 (% of THE) from WHO [88];
Population living in endemic areas (2014) from APOC treatment database (last update:2012) and UN (population growth rates 2013–2014) [9]
SD: standard deviation

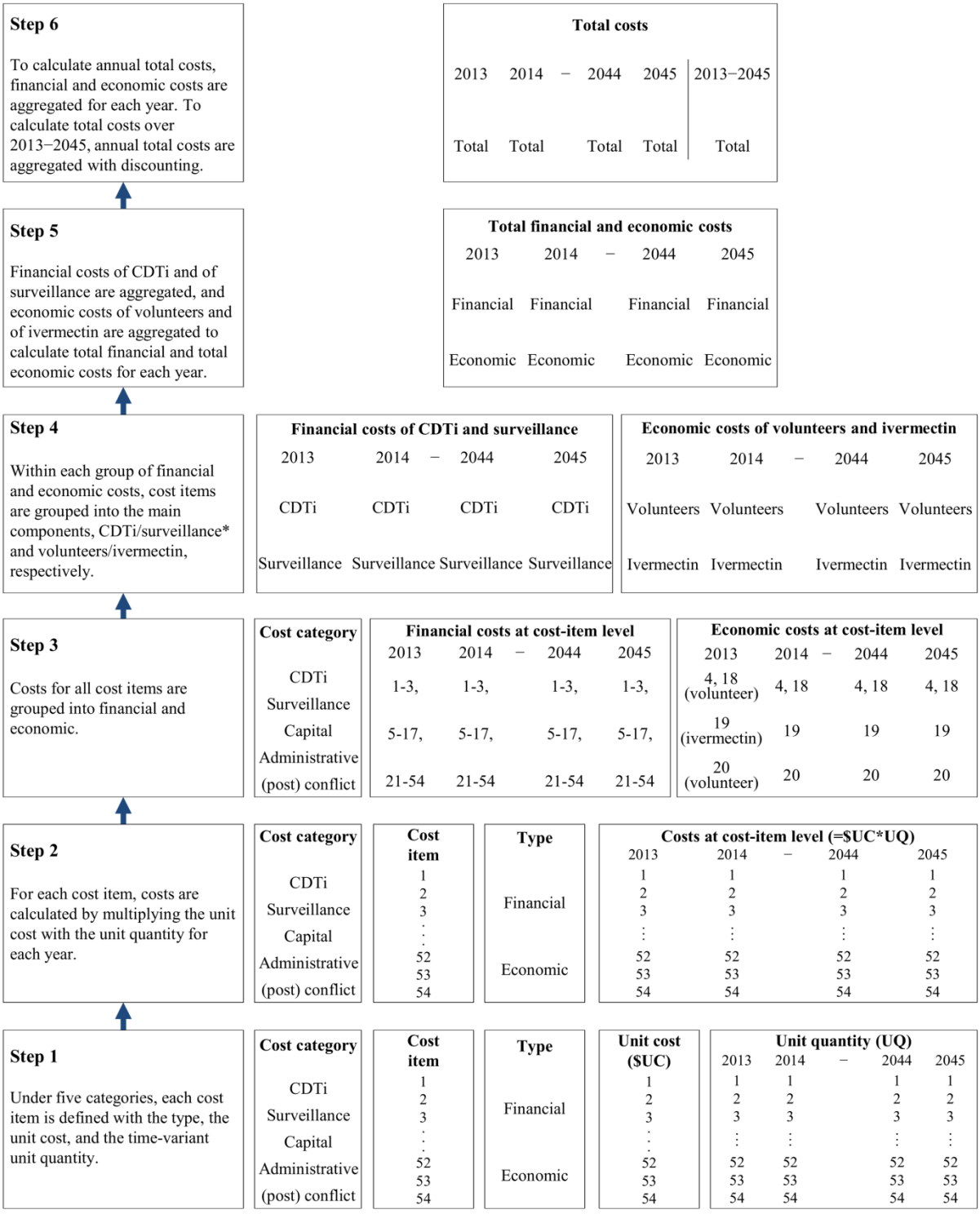
Methods

We estimated financial costs to predict how much the governments of endemic countries and donors would have to pay for implementing the required interventions for alternative treatment goals of control, elimination, and eradication, and economic costs to assess societal opportunity costs of donated services and goods. The time horizon of the analysis was from

2013 to 2045, based on the predicted timeline for reaching the post-elimination phase in endemic African regions [6].

There are different methods for estimating health intervention costs, ranging from micro-costing (bottom-up approach) to gross-costing (top-down approach) [89]. We used a micro-costing method to more precisely estimate time-variant resource utilization depending on epidemiological trends and to incorporate the heterogeneity in the demographic, epidemiological, and political situation at project level. Fig 20 shows the six steps of the micro-costing approach calculating from the cost of a single cost item to the total financial and economic cost for a project.

Figure 20. Micro-costing method for estimating total costs for a project



* For financial costs, capital and administrative costs are evenly split to CDTi and surveillance for the years when both CDTI and surveillance are implemented, and support costs for (post) conflict areas are evenly split over the entire period.

We defined the key activities and resources required for onchocerciasis elimination and eradication with reference to an APOC report of the technical consultative committee [90], an APOC protocol for epidemiological surveillance, and a guide for post-treatment

epidemiological and entomological surveillance (developed for the Onchocerciasis Elimination Program for the America) [69]. Based on the identified activities and resources, we defined cost items under five categories – CDTi, surveillance, capital costs, overhead and administrative costs, financial support for (post) conflict endemic areas – and their characteristics which include the type (financial or economic), the unit cost, and the time-variant unit quantity (depending on relevant phases among the three phases of treatment, confirmation of elimination, and post-elimination). The details about each step of the micro-costing approach and the characteristics of cost items are described in the Appendix 2.

Data

We obtained 2012 budgets from APOC, approved for onchocerciasis CDTi, that cover 67 of all 112 ongoing projects (as of November 2013) in sub-Saharan Africa. All budget documents include information on the unit cost and the unit quantity of each resource, demography, available human resources (community health workers, community volunteers), and funding from the ministry of health, APOC, and non-governmental organizations. These data were used as the main sources to estimate financial costs. To estimate economic costs, agriculture value added per worker was used as an opportunity cost of community volunteers' unpaid time [91], considering most volunteers are farmers in remote rural areas [92]. The opportunity cost of donated ivermectin was $1.5054 per treatment (three 3mg-tablets), based on Merck's suggested drug price of $1.5 per treatment before the donation was decided [7] and on the insurance and freight cost of $0.0018 per tablet [93].

For projects with missing unit costs, we used the national average if relevant unit costs were available; otherwise, the regional average (Table7) across available national averages for endemic African countries. For the countries that did not have agriculture value added per worker, we used the regional average for sub-Saharan Africa [91]. For projects with missing data for the determinants of unit quantities (e.g., the ratio of health workers over population,

the ratio of volunteers over population), we used the national average if relevant data were available; otherwise, the regional average across available national averages for endemic African countries. Unit costs and the determinants of unit quantities at the country and regional levels are included in the Appendix 2.

Table 7. Average unit costs across endemic African countries

Cost items	Average(SD)*	Unit
Category 1. Community-directed treatment with ivermectin		
Advocacy/sensitization/mobilization		
Advocacy	$4,544.00 ($3,624.71)	/project
Sensitization	$3,902.00 ($2,590.79)	/project
Mobilization	$0.01 ($0.01)	/person
Support for mobilization from community volunteers[%]	$1.68 ($3.12)	/volunteer/day
Development of IEC[&] material	$2,250.00 ($1,715.51)	/project
Production of IEC[&] material	$0.04 ($0.05)	/person
Supervision/monitoring/evaluation		
Supervision (first 6 years)	$18,021.00 ($16,252.27)	/project
Assistance for supervisory visits (7th year+)	$2,099.00 ($981.23)	/project
Monitoring	$3,622.00 ($3,259.28)	/CDTi round
Evaluation	$4,008.00 ($599.03)	/CDTi round
Review meeting	$6,746.00 ($5,206.34)	/project
Data management	$2,309.00 ($2,287.10)	/project
Community self-monitoring	$0.02 ($0.02)	/person
Training		
Training of trainers and health workers	$184.00 ($334.96)	/health worker
Training of community volunteers	$8.00 ($6.31)	/volunteer
Training of community leaders	$9.00 ($7.45)	/community
Drug distribution/management of severe adverse events		
Community registration	$12.00 ($10.91)	/community
Census[%]	$1.68 ($3.12)	/volunteer/day
1) In areas without epidemiological challenges		
· Delivery of ivermectin	$1.51 ($0.00)	/treatment
· Ivermectin administration[%]	$1.68 ($3.12)	/volunteer/day
2) In areas with epidemiological challenges (co-endemicity with *Loa loa*)		
· Diagnostic tools (annuitized)	$120.00 ($0.00)	/set
· Delivery and administration of doxycycline[@]	$2.50 ($0.00)	/6-week treatment
Management of severe adverse events	$2,993.00 ($3,888.44)	/project
Category 2. Surveillance		
Supervision/monitoring/evaluation		
Supervisory visit	$2,099.00 ($981.23)	/project
Monitoring	$3,622.00 ($3,259.28)	/project
Evaluation	$4,008.00 ($599.03)	/project
Review meeting	$6,746.00 ($5,206.34)	/project
Data management	$2,309.00 ($2,287.10)	/project
Training		
Training of trainers and health workers	$184.00 ($334.96)	/health worker
Training of community volunteers (fly/larva-catchers)	$8.00 ($6.31)	/volunteer
Training of community leaders	$9.00 ($7.45)	/community
Epidemiological survey sampling		
Surveillance trip transportation	$21.00 ($16.11)	/person/day/site
Personnel	$15.00 ($16.72)	/person/day/site
Field supplies (annuitized)	$68.00 ($0.00)	/set
Entomological survey sampling		
Personnel	$2.41 ($2.14)	/person/day/site
Field supplies (annuitized)	$1.85 ($0.00)	/set/person/day/site
Delivery of samples		
Delivery of skin-snip samples from villages to laboratory	Included in the surveillance trip transportation costs	/site

Cost items	Average(SD)*	Unit
Delivery of vector samples from catching site to health facility	$7.95 ($5.25)	/site
Delivery of vector samples from health facility to MSDC	$135.00 ($0.00)	/project
Epidemiological laboratory testing		
Personnel	$15.00 ($16.72)	/person/day/site
Laboratory supplies (annuitized)	$120.00 ($0.00)	/set
Entomological laboratory testing		
Personnel	$9.00 ($0.00)	/person/day/site
Category 3. Capital costs		
Vehicle (annuitized)	$3,919.00 ($661.27)	/vehicle
Motorcycle (annuitized)	$503.00 ($155.89)	/motorcycle
Bicycle (annuitized)	$21.00 ($6.12)	/bicycle
IT equipment and power supply equipment (annuitized)	$2,695.00 ($119.06)	/set
Category 4. Overhead and administrative costs		
Maintenance of vehicle	$280.00 ($85.71)	/vehicle
Maintenance of motorcycle	$84.00 ($25.71)	/motorcycle
Office supplies, communication, top-ups (first 6 years), others	$34,151.00 ($24,626.97)	/project
Category 5. Financial support for CDTi and surveillance in (post) conflict endemic areas		
Support for CDTi and surveillance in (post) conflict endemic areas[#]	$1,052,363.00 (NA)	/endemic African regions
* Average unit costs across national averages for endemic African countries with budgets available % Agriculture value added per worker [91], 2012 GDP per capita [86] & IEC: Information/Education/Communication @ Data from Wanji et al. 2009 [94] # Based on the APOC budget plan for 2008-2015 and Sightsavers's strategic plan for 2011-2021 [95,96] Note: all capital costs for non-disposable goods were annuitized with 3% over six years.		

Cost estimation

Financial costs

From an operational perspective, financial costs consist of those of CDTi and of surveillance. At project level, we multiplied the unit cost with the unit quantity for each cost item and every year. Costs of capital goods were annuitized over a useful time of each item with 3%. We assumed the useful time to be six years based on the capital-goods replacement policy specified in Burundi's budget document. We aggregated the costs across cost items relevant to CDTi and surveillance separately. We split the capital and administrative costs (for the years when both CDTi and surveillance were conducted) and the financial support costs for (post) conflict areas (over the entire time horizon) equally between CDTi and surveillance. To estimate annual financial costs, we added the CDTi and surveillance costs (Fig 20).

Economic costs

Economic costs consist of those of community volunteers, who play a central operational role in CDTi[92], and of ivermectin, the main drug for CDTi and donated by Merck. For each project, we estimated annual economic costs of community volunteers by multiplying the daily agriculture value added per worker with the number of required community volunteers (population multiplied by the ratio of volunteers over population), the required volunteering days, and the number of CDTi rounds per year. We used the multi-country survey by McFarland and colleagues [97] to identify the main activities of volunteers and the required days. Three main activities were administering ivermectin (17.8 days), supporting health workers for mobilization (5.5 days), and doing census to update the treatment registers (4.6 days). As community mobilization would be required until elimination is confirmed, we included the economic costs of supporting health workers for mobilization in both phases for treatment and the confirmation of elimination.

To estimate annual economic costs of donated ivermectin, we multiplied the drug and delivery cost per treatment with the number of required treatments (population multiplied by treatment coverage and the number of CDTi rounds per year). To estimate annual economic costs for a project, we summed the annual economic costs of community volunteers and donated ivermectin (Fig 20).

Total costs

To estimate annual total costs, we summed annual financial and economic costs. To estimate total costs over the entire time horizon, we summed annual costs from 2013 to 2045 with discounting (Fig 20). The discount rate to account for time preference was 3%.

All costs were reported in 2012 US dollars (USD). Local currency before 2012 was inflated using country-specific inflation rates [98] and converted to USD using exchange rates [99].

Uncertainty analysis

We conducted sensitivity analysis to assess the robustness of results to parametric uncertainties. The parameters included either cost items for which unit costs were missing for more than one third of total projects or total countries with available budgets. Also the parameters included the time-variant determinants of unit quantities: population living in endemic areas, the number of required treatments (determined by population, treatment coverage linked to required treatment duration, and possible delay in starting and ending treatments), the number of required community volunteers (determined by population and the ratio of community volunteers over population), and the number of required community health workers (determined by population and the ratio of community health workers over population). For probabilistic sensitivity analysis (PSA), we attached statistical distributions to the cost items and the determinants of unit quantities, and fitted to relevant data. We conducted one-way sensitivity analysis to examine the impact of parameters related to CDTi performance, the cost items with high uncertainty, and discount rates on total costs. We also simulated multivariate PSA to examine the joint effects of uncertainties about all selected variables on total costs. Appendix 2 describes the methodological details of the sensitivity analysis.

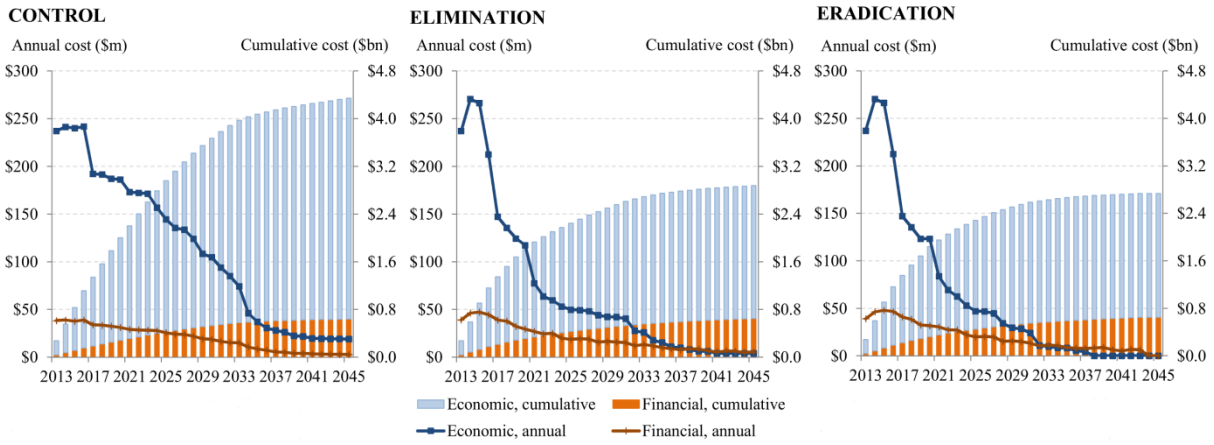
Results

Total costs

Total financial and economic costs would be concentrated in the early stage during which treatments are scaled up to remaining endemic areas, and decrease as the treatment phase nears the end (Fig 21). In endemic African regions, total financial and economic costs over the period 2013−2045 would be $4.3 billion (95% central range: $3.9 billion[bn]−$5.0bn) for the

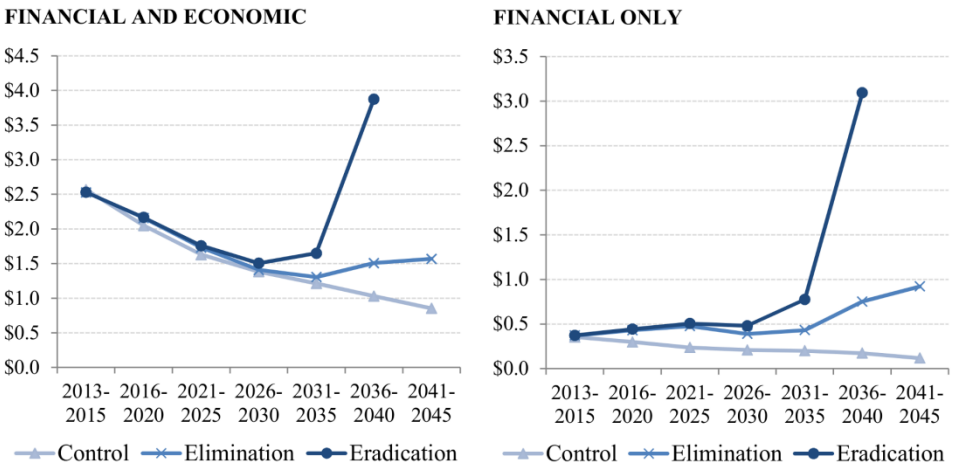
control scenario, $2.9 billion ($2.6bn−$3.4bn) for the elimination scenario, and $2.7 billion ($2.4bn−$3.2bn) for the eradication scenario. That is, switching from control to elimination and eradication would lead to cost-savings of $1.5 billion ($1.0bn−$1.9bn) and $1.6 billion ($1.2bn−$2.1bn), respectively (Fig S3). The eradication scenario would lead to cost-savings of $144 million (-$25 million[M]−$462M) as compared to the elimination scenario.

Figure 21. Annual and cumulative financial and economic costs over 2013−2045 for the control, elimination, and eradication scenarios



Unit financial and economic cost per treatment for the control scenario would decrease from $2.5 to $0.9 over 2013–2045. For the elimination scenario, it would decrease from $2.5 to $1.3 until 2035, and increase to $1.6 afterwards. For the eradication scenario, it would decrease from $2.5 to $1.5 over 2013–2030, and increase to $3.9 afterwards until the end of the treatment phase in endemic African regions (Fig 22).

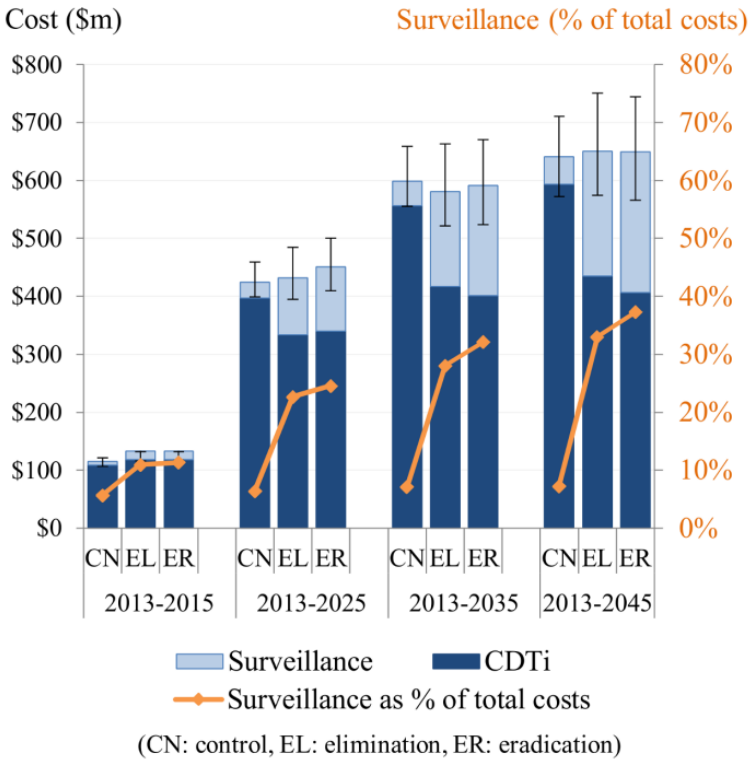
Figure 22. Unit costs per treatment per period for the control, elimination, and eradication scenarios, both financial and economic and only financial



Financial costs

Total financial costs over the period 2013−2045 would be $640 million ($572M−$711M) for the control scenario, $650 million ($574M−$751M) for the elimination scenario, and $649 million ($566M −$745M) for the eradication scenario (Fig 23). That is, the total financial costs associated with the elimination and eradication scenarios are slightly lower than those associated with the control scenario; however, these cost differences are not robust to sensitivity analysis (Fig S4). The main difference between scenarios is the proportion of surveillance costs in total costs. Total surveillance costs over 2013–2045 would increase from 7% ($47M) of total financial costs under the control scenario to 33% ($215M) and 37% ($242M) under the elimination and eradication scenarios, respectively (Fig 23).

Figure 23. Cumulative financial costs of CDTi and surveillance over 2013−2045 for the control, elimination, and eradication scenarios



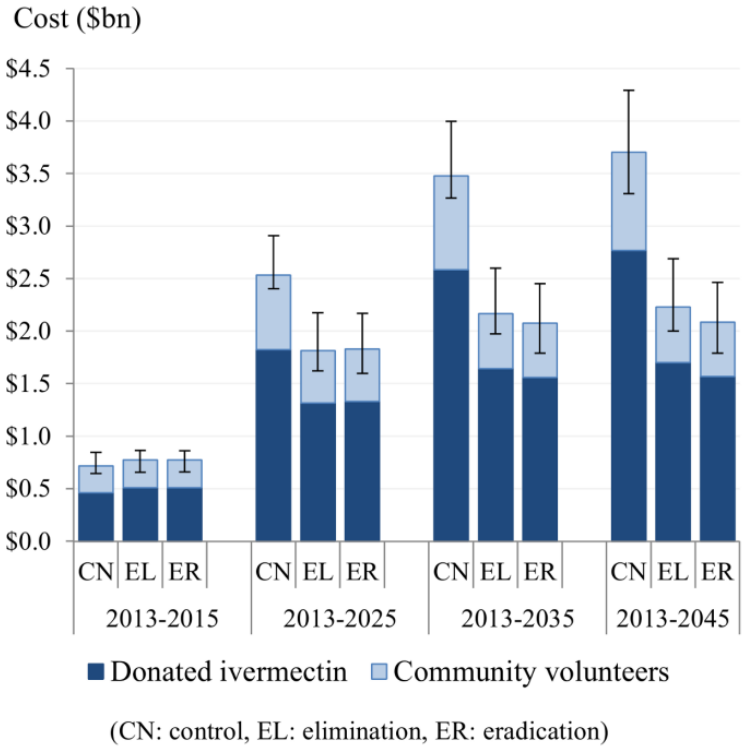
Unit financial cost per treatment for the control scenario would decrease from $0.4 to $0.1 over 2013−2045. For the elimination scenario, it would stay between $0.4 and $0.5 until 2035, and increase to $0.9 afterwards. For the eradication scenario, it would stay between $0.4 and $0.5 until 2030, and increase to $3.1 as the treatment phase nears the end in endemic African regions (Fig 22).

Economic costs

Economic costs would be six times higher than financial costs under the control scenario and three times higher under the elimination and eradiation scenarios. Total economic costs over 2013−2045 would be $3.7 billion ($3.3bn−$4.3bn) for the control scenario, $2.2 billion ($2.0bn−$2.7bn) for the elimination scenario, and $2.1 billion ($1.8bn−$2.5bn) for the eradication scenario (Fig 24). That is, the total economic costs associated with the elimination and eradication scenarios are lower than those associated with the control scenario by $1.5

billion ($1.1bn−$1.9bn) and $1.6 billion ($1.2bn−$2.1bn), respectively (Fig S5). Donated ivermectin and community volunteers would account for 75% and 25% of the total economic costs over 2013−2045 in all scenarios.

Figure 24. Cumulative economic costs of donated ivermectin and community volunteers' unpaid time over 2013−2045 for the control, elimination, and eradication scenarios

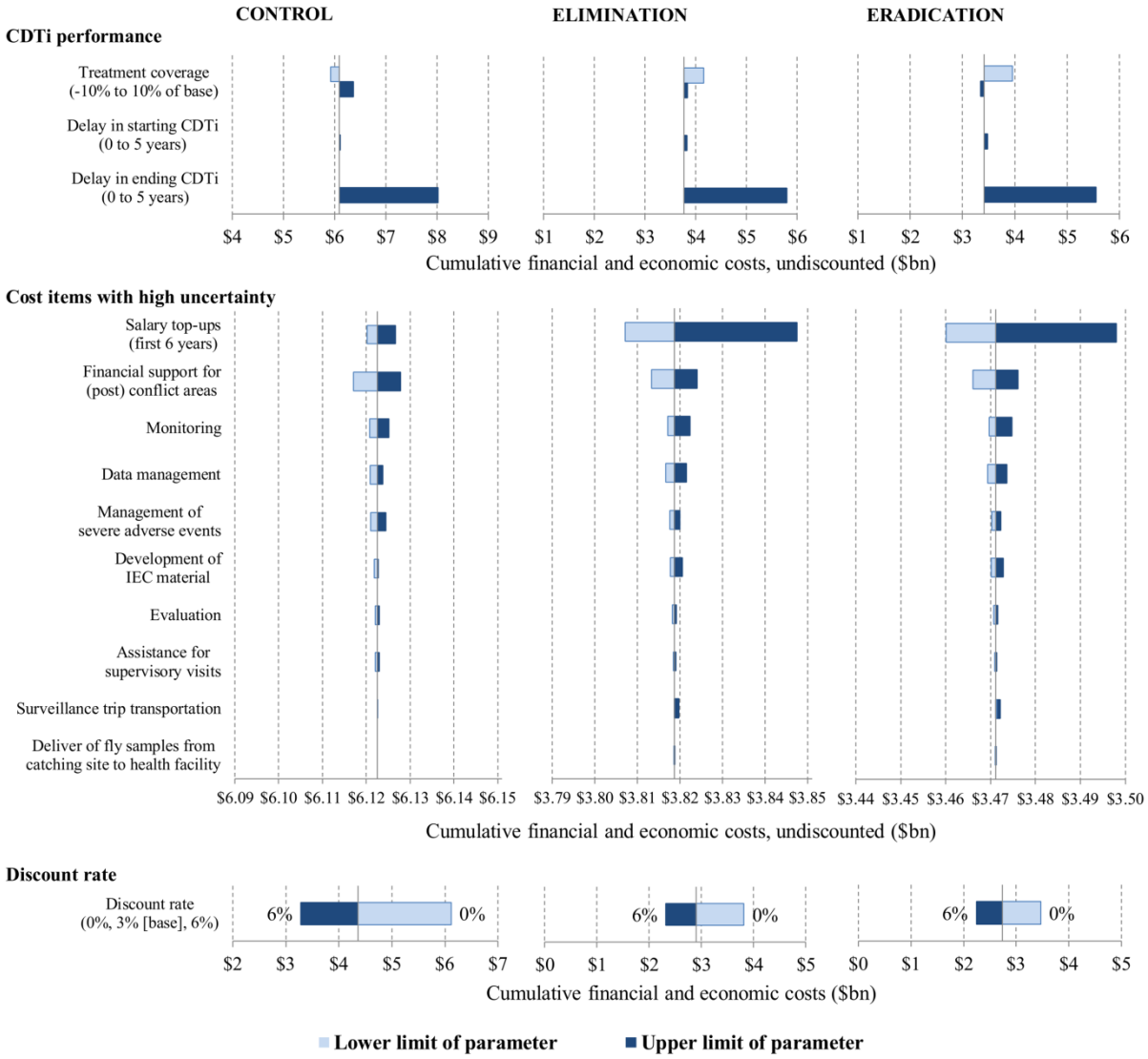


Uncertainty analysis

One-way sensitivity analysis (Fig 25) shows that, among the parameters related to CDTi performance, the delay in ending CDTi (after the infection levels reach the threshold for stopping CDTi) is the most influential parameter, leading total costs to increase by $2 billion (undiscounted) over 2013−2045 in all scenarios. Among the cost items with high uncertainty (based on the number of missing data), the most influential one is the salary top-ups for stabilizing new projects in the elimination and eradication scenarios, leading total costs (undiscounted) to range from $3.807 billion to $3.847 billion, and from $3.460 billion to $3.498 billion, respectively. Increasing the discount rate from 0% to 6% would decrease total costs over 2013−2045 by 46% from $6.1 billion to $3.3 billion for the control scenario, by 39%

from $3.8 billion to $2.3 billion for the elimination scenario, and by 35% from $3.5 billion to $2.2 billion for the eradication scenario.

Figure 25. One-way sensitivity analysis for cumulative financial and economic costs over 2013–2045



Note: one-way sensitivity analysis for CDTi performance parameters and discount rate is deterministic (using the lower and upper limits); that for cost items is probabilistic (using gamma distributions fitted to relevant data).

Discussion

The elimination and eradication scenarios are predicted to generate substantial cost-savings in the long run compared to the control scenario. The main factors contributing to cost-savings

are the reduction in economic costs of community volunteers and donated ivermectin due to a shorter treatment phase as a result of regular active surveillance. This finding implies that the saved volunteers' time and ivermectin can be used for other health programs. Willing volunteers and their well-established networks, which have enabled successful implementation of CDTi in Africa, could contribute to improving access to primary health care in remote rural areas with insufficient human resources. In addition, the saved ivermectin drugs could be used for other disease programs, for example, anti-LF mass drug administration. To realize these possibilities, policymakers would need to keep empowering community volunteers through training and societal or economic appreciation. Also, pharmaceutical companies' continuous commitment to donating drugs would be needed.

The main operational difference between the elimination/eradication scenarios and the control scenario is regular active surveillance. Our analysis suggests that the cumulative financial costs for surveillance over 2013−2045 in the elimination and eradication scenarios would be five times higher those in the control scenario. This implies that endemic countries would need to improve their domestic funding capacity to sustain high surveillance costs to achieve elimination, as the post-treatment surveillance period could last beyond 2045 [6] and external funding would be temporary. The development and operationalization of new affordable and effective diagnostic tools, for example, OV-16 (ELISA and Rapid Test) and the DEC patch test under development [80,81], might lead to the savings of surveillance costs.

The financial unit cost per treatment in the elimination and eradication scenarios would increase by factors of respective two and eight as the regional intervention phase nears the end. This increase is driven by the reduction in the number of people in need of treatment and steady or increasing costs for surveillance and capital goods. Additionally, in the last stage, the majority of people in need of treatments are expected to live in areas with epidemiological and political challenges [6]. This implies that, in the last mile towards elimination and

eradication, political, financial, and societal commitment across a whole spectrum of stakeholders will be essential to meet high unit costs and to deliver treatments in challenging areas; otherwise, the last mile could become the hardest [36]. Studies based on social choice theory and game theory [34,35,100,101] show that the elimination and eradication of infectious diseases are public goods that can only be achieved through the coordinated efforts of multiple countries. These studies suggest that high benefit-cost ratios associated with elimination and/or eradication could incentivize endemic countries to pursue elimination and/or eradication, and global donors to finance endemic countries lacking the financial capacity. Equity and social justice arguments for elimination and/or eradication [33,102] could also complement and strengthen those provided by economic rationality. The role of global stakeholders can play a decisive role to overcome national challenges. A study by Shaffer suggests that, to prevent potential holdout problems caused by unwilling or unable countries, which could hinder elimination and eradication, the centralized efforts led by international organizations would be necessary [103]. In line with this, it has been argued that the explicit inclusion of NTDs elimination in the Sustainable Development Goals (SDGs) of the United Nations (UN) [37,104] would further motivate the commitment of national and global policymakers and donors. Societal commitment at local level will be also essential, because delivering treatments to operationally challenging areas would require successful drug administration by community volunteers and communities' compliance to treatments. To promote such commitment by communities, endemic countries' continuous investments in enhancing the operational capacity of community volunteers and in mobilizing communities will be needed.

The uncertainty analysis showed that the delay in ending CDTi would have the highest impact among those related to CDTi performance on total costs. Thus, planning to move towards the

post-treatment phase, along with regular monitoring and evaluation to define the proper time of stopping treatments, would be important to avoid the delay in ending CDTi.

The uncertainty analysis also showed that the salary top-ups for stabilizing new projects would have the most influence of all cost items on total costs. Many new projects are in potential hypo-endemic areas where parasitological surveys are still needed to confirm endemicity[71]. This suggests that complete epidemiological mapping should be a priority to choose areas to start new projects and to predict required human resources for those projects.

The results presented in this study should be interpreted considering the limitations of the approach and data used. To calculate financial costs for projects without available budgets, we relied on national or regional average unit costs which might only approximately represent the actual costs in those projects. For economic costs, we assumed agriculture value added per worker as an opportunity cost of community volunteers' unpaid time. However, other studies used different proxies such as national minimum wage and GNI per capita [97,105]. We did not use national minimum wage, as it was unavailable for 11 of 28 endemic countries [106]. We did not use GNI per capita, as it does not represent the income level in remote rural areas. In the opportunity cost of donated ivermectin, we did not include tax deduction provided to donating manufacturers [7], as the relevant detailed information is proprietary and unavailable.

There were some other factors that could affect resource utilization, but were not included in the analysis. We assumed no recrudescence, because it was difficult to predict when recrudescence would happen. If that were to happen, costs would increase because the treatment phase would have to be restarted. We did not consider the potential impact of new diagnostic and treatment tools, because it was difficult to predict when they would be developed and operationalized. If new effective and affordable tools are operationalized, the strategies of treatment and surveillance could change, thereby influencing costs. We assumed

no unexpected political unrest that could interrupt interventions, and would increase costs to restart the interventions.

Despite these limitations, to our knowledge and based on literature review (see Appendix 2), our study is the most up-to-date cost analysis of potential regional elimination strategies in Africa. National and global policymakers and donors could use our cost analysis to make informed policy decisions and to predict the funding needs for implementing elimination programs in Africa. Our cost estimates could also be used by policymakers and researchers to compare costs and potential benefits associated with potential elimination strategies in Africa.

Acknowledgements

We thank the APOC director and his team who kindly shared 2012 approved budgets for onchocerciasis projects. We also thank David Bishai (Johns Hopkins University) for his advice on the analysis, Amena Briet (Swiss TPH) for the help with the final revision, and all members of the technical advisory group for their valuable comments on the analysis.

5 Value of investing in the elimination and eradication of onchocerciasis in Africa: the health and economic benefits and the impacts on health systems

Young Eun Kim[1,2], Wilma A. Stolk[3], Marcel Tanner[1,2], Fabrizio Tediosi[1,2*]

1 Swiss Tropical and Public Health Institute, Basel, Switzerland

2 University of Basel, Basel, Switzerland

3 Erasmus MC, University Medical Center Rotterdam, The Netherlands

Email addresses

YEK: young.kim@unibas.ch

WS: w.stolk@erasmusmc.nl

MT: marcel.tanner@unibas.ch

FT: fabrizio.tediosi@unibas.ch

*Correspondence to:

FabrizioTediosi

Swiss Tropical and Public Health Institute

Socinstrasse 57, 4002 Basel, Switzerland

Email: fabrizio.tediosi@unibas.ch

Telephone: +41 61 284 8719

Abstract

Background Onchocerciasis (river blindness) is endemic mostly in remote and rural areas in sub-Saharan Africa. The treatment goal for onchocerciasis has shifted from control to elimination in Africa. For informed decision-making, national and global policymakers need evidence on costs, benefits, and risks of investing in elimination initiatives. We evaluated the health benefits from the elimination and eradication of onchocerciasis and the potential economic and health systems impacts.

Methods We evaluated health benefits associated with the elimination and eradication scenarios using a dynamical transmission model. The impact on workforce and outpatient services and the associated costs to both health systems and households were evaluated. We also predicted the potential economic impact first in terms of productivity gains using a human capital approach and second in terms of welfare gains associated with prevented premature deaths using a full income approach.

Results The elimination and eradication of onchocerciasis would avert 4.3 million and 5.6 million disability-adjusted life years respectively over 2013–2045. Also the number of required community volunteers would be reduced by 45% (10.7 million) and 52% (12.4 million);and the number of required community health workers by 56% (1.3 million) and 60% (1.4 million). The number of outpatient visits would be reduced by 68% (31.6 million) and 92% (42.3 million) leading to the savings of outpatient visit costs by $47.5 million and $52.1 million and the savings of out-of-pocket payments by $31.2 million and $33.5 million. The elimination and eradication of onchocerciasis would generate economic benefits, $4.6 billion and $5.0 billion respectively in terms of productivity gains and 7.0 billion and $7.4 billion in terms of welfare gains.

Conclusions The elimination and eradication of onchocerciasis would lead to health and economic benefits and relieve the burden on health systems by saving health workforce and reducing the number of outpatient visits. This indicates that intensive investment in the early stage to scale up the interventions to hypo-endemic areas and operationally challenging areas, in addition to meso-/hyper-endemic areas, combined with strengthening the surveillance and response systems would eventually save financial and societal opportunity costs, and result in the reduction of morbidity and mortality due to onchocerciasis. In addition, this would generate substantial economic productivity and welfare gains, foster equity by preventing people living in endemic areas from missing social and economic opportunities.

Introduction

Onchocerciasis (river blindness) is a parasitic disease transmitted by blackflies. Notable symptoms include severe itching, skin lesions, and vision impairment including blindness. The disease is endemic in parts of Africa, Latin America, and Yemen, and more than 99% of all cases are found in sub-Saharan Africa [1]. Onchocerciasis in Africa has affected the poor population in remote and rural areas, resulting in a negative socioeconomic impact on them. Fortunately, morbidity has been significantly decreased in Africa through the vector control activities in West Africa under the Onchocerciasis Control Programme (OCP) over 1975−2002 and through the community-directed treatment with ivermectin (CDTi) in sub-Saharan Africa and parts of West Africa under the African Programme for Onchocerciasis Control (APOC) since 1995 until the present [39]. A study in Mali, Senegal, and Uganda proved that onchocerciasis elimination is feasible through ivermectin administration [2,3]. The successful control programs and the proved feasibility of elimination have provided national and global policymakers and donors with a justification to pursue the elimination of onchocerciasis. The treatment goal in Africa has shifted from control to elimination as shown by the WHO roadmap for neglected tropical diseases (NTDs) and the London declaration on NTDs [4,5].

The assessment of the potential impacts of onchocerciasis elimination strategies can provide valuable information to national and global policymaker and donors. This assessment should consider not only epidemiological evidence but also costs, benefits, and risks, given limited resources and competing health priorities. In a recent manuscript, we developed control, elimination, and eradication scenarios for onchocerciasis that describe required activities to achieve the relevant goals, and estimated the timelines of a treatment phase and the number of required ivermectin treatments [6]. In another manuscript, we estimated financial and economic costs associated with the control, elimination, and eradication scenarios [107]. In

this manuscript, we assess the potential value of onchocerciasis elimination and eradication in terms of health benefits, health systems impacts, and economic returns to people living in endemic areas.

Methods

The time horizon for our analysis was from 2013 to 2045 based on the predicted timeline of the treatment phase in endemic African regions[6]. Health and economic benefits were discounted at 3% to account for time preference. Economic benefits were expressed in 2013 US dollar.

Scenarios of onchocerciasis elimination and eradication

To estimate the potential value of investing in onchocerciasis elimination, we used the control, elimination, and eradication scenarios (Box 2) developed by Kim and colleagues [6]. The elimination and eradication scenarios describe the strategies of treatments and surveillance – epidemiological surveillance to assess the infection levels in humans and entomological surveillance to evaluate the infectivity rates in blackflies. The control scenario is the counterfactual that represents the general practice conducted in Africa under the aim of control and against which we assessed the impacts of achieving elimination and eradication. The main difference of the elimination and eradication scenarios from the control scenario is that treatments are scaled up from meso-/hyper-endemic areas to hypo-endemic and operationally challenging areas, accompanied by regular active surveillance. With the scale-up of treatments, the population living in target areas (2014) would increase from around 140 million to 170 million−180 million. In most endemic African regions under APOC, operational and financial decisions for treatments have been made for a geographical implementation unit called *project*. Each scenario has the database for target areas composed

of the list of target projects. The details on the scenarios and population at project level are described in Kim et al. 2015 [6].

Box2. Brief description of scenarios

Control scenario: to keep the disease prevalence at a locally acceptable level, annual CDTi is implemented for at least 25 years, and afterwards epidemiological surveillance is conducted to evaluate whether CDTi can be stopped.

Elimination scenario: to reduce the incidence of infection to zero in a defined area, annual or biannual CDTi is implemented, and regular epidemiological and entomological surveillance is implemented to track epidemiological trends, to decide a proper time to stop CDTi, and to early detect and respond to possible recrudescence.

Eradication scenario: to reduce the incidence of infection to zero in Africa, which would lead to global eradication, tailored treatment approaches in addition to CDTi are implemented to deliver sustainable treatments to all endemic areas including challenging areas with epidemiological and political concerns. Regular epidemiological and entomological surveillance is implemented to track epidemiological trends, to decide a proper time to stop CDTi, and to early detect and respond to possible recrudescence.

Assessment of health impacts

To evaluate health impacts from onchocerciasis elimination and eradication, we compared the number of cases of severe itching, low vision, and blindness and disability-adjusted life years (DALYs) between the control, elimination, and eradication scenarios. To predict the prevalence trends of the three symptoms for the period 2013−2045, we ran the simulation using a dynamical transmission model (ONCHOSIM [8]), by incorporating the onchocerciasis type (savanna or forest), the pre-control endemicity level, the history of treatment coverage, and the start year of CDTi at project level, all of which were available from APOC databases. The endemicity level (none, hypo, meso, hyper)was defined based on pre-control nodule prevalence among adult males for APOC countries and, for former OCP countries, based on pre-control microfilariae prevalence among people aged five years and above. For the entire time horizon, we assumed that treatment coverage would be stable at the level of average treatment coverage over 2010−2012 for APOC countries and, for former OCP countries

lacking relevant history data, at the most recent treatment coverage level. If the average treatment coverage was below 65%, the required minimum for effective control [10], we used the highest treatment coverage achieved during 2010−2012 as the expected treatment coverage. For potential new projects, we used the national average treatment coverage and, if there was no relevant data, we used the regional average (across available national averages in either APOC or former OCP regions). The start years of CDTi were available for all ongoing projects (as of November 2013). For potential new projects, we used the predicted start years based on donors' strategic plans and epidemiological and political situations in Kim et al. 2015 [6].

We estimated the number of cases by multiplying the predicted prevalence of each symptom for the period 2013−2045 by population living in endemic areas at project level. Population for 2011 was available for all projects from APOC REMO (Rapid Epidemiological Mapping of Onchocerciasis) database, and we adjusted for country-specific population growth rates [55].

To compute DALYs, we estimated the years lost due to disability (YLD) by multiplying the number of prevalent cases of each symptom by a relevant disability weight, namely, 0.108 for severe itching, 0.033 for low vision, and 0.195 for blindness over 2013−2045[11]. And we calculated the years of life lost (YLL) by assigning eight years of life-expectancy loss for each blindness incidence assuming that blindness causes premature death [12].

Assessment of the impacts on health systems

Eliminating onchocerciasis in endemic African countries would have an impact on health systems that are generally weak and characterized by a shortage of health workforce especially in remote and rural areas [13]. We assessed the impacts with focus on the implications in terms of health workforce and the burden caused by outpatient services.

1) Impact on health workforce

CDTi has been the primary approach for onchocerciasis treatment and prevention in endemic African countries [108]. In CDTi, community volunteers play a central operational role by deciding when and how to distribute drugs, administering drugs, managing adverse reactions, keeping records, and reporting to health workers [14]. Community health workers train community volunteers, monitor and evaluate CDTi performance, and report to health workers at higher levels to support informed decision-making [15]. We estimated the number of community volunteers and community health workers required to implement CDTi under each scenario, by multiplying population living in endemic areas and the respective ratio of community volunteers and community health workers over population, adjusting for the required CDTi duration. We used population from APOC REMO database adjusted for population growth rates over 2013−2045 [55]. The ratios of community volunteers and of community health workers over population were available from 2012 budget documents for 67 of total 112 ongoing (as of November 2013) APOC projects in sub-Saharan Africa. We assumed the ratios would be stable until CDTi is ended. For projects without relevant ratios, we used the national average ratio and, if there was no national average data, we used the regional average ratio (across available national averages among endemic African countries). The required CDTi durations for projects were different depending on the surveillance strategy of each scenario, mainly because regular surveillance would lead to a shorter period of CDTi by tracking infection levels and deciding a proper time to stop treatments. The required durations of CDTi for projects were predicted based on ONCHOSIM simulations in Kim et al. 2015 [6].

2) Impact on outpatient services and associated costs and out-of-pocket payments

To assess the impact of onchocerciasis elimination on the burden on health systems associated with outpatient services, we predicted the number of outpatient visits in endemic areas where

CDTi is not implemented for each scenario over 2013−2045. We multiplied the predicted number of patients with severe itching and low vision by the health facility utilization rate. As a proxy for the health facility utilization rate, we used the average treatment coverage of CDTi over 2010–2012 (Table8), assuming people who complied with CDTi would be willing to seek care if there is no CDTi. We assumed that people with blindness would not visit health facility because blindness is irreversible.

Table 8. Average treatment coverage over 2010−2012 as a proxy for health facility utilization rate

Country	Average treatment coverage (SD)
APOC countries	
Angola	67.45% (10.66%)
Burundi	77.02% (3.58%)
Cameroon	77.94% (4.60%)
Central African Rep.	80.37% (2.74%)
Chad	81.00% (0.10%)
Congo, Dem. Rep.	70.53% (13.39%)
Congo, Rep.	81.42% (2.43%)
Equatorial Guinea	70.95% (0.07%)
Ethiopia	78.80% (4.10%)
Gabon*	76.42% (6.20%)
Liberia	77.38% (9.81%)
Malawi	82.75% (0.48%)
Mozambique*	76.42% (6.20%)
Nigeria	79.87% (3.91%)
South Sudan	60.14% (12.43%)
Sudan	81.50% (2.71%)
Tanzania	80.50% (1.21%)
Uganda	75.17% (11.18%)
Average	76.42% (6.20%)
Former OCP countries[#]	
Benin	48.10% (NA)
Burkina Faso	83.60% (NA)
Côte d'Ivoire	83.60% (NA)
Ghana	72.60% (NA)
Guinea	72.60% (NA)
Guinea-Bissau	72.60% (NA)
Mali	72.60% (NA)
Senegal	77.40% (NA)
Sierra Leone	80.30% (NA)
Togo	77.40% (NA)
Average	74.08% (10.14%)

*Data were missing. We used the average for APOC countries.
#History data were unavailable for former OCP countries. The data are the most recent available ones as of November 2013.
SD: standard deviation

We then estimated potential outpatient service costs by multiplying a country-specific outpatient service cost per visit, available in WHO-CHOICE (CHOsing Interventions that are

Cost Effective) database (Table 9), by the predicted number of outpatient visits over 2013−2045.

Table 9.Outpatient service costs per visit and out-of-pocket payments as percentage of total health expenditure for endemic African countries

Country	Outpatient cost per visit, 2013[a]	Out-of-pocket payments as % of total health expenditure, 2012[b]
Angola	$6.93	26.69%
Benin	$1.26	44.26%
Burkina Faso	$1.10	36.36%
Burundi	$0.37	28.27%
Cameroon	$1.90	62.65%
Central African Rep.	$0.76	45.57%
Chad	$1.18	66.43%
Congo, Dem. Rep.	$0.44	32.48%
Congo, Rep.	$3.72	25.07%
Côte d`Ivoire	$1.84	55.83%
Equatorial Guinea	$30.94	43.53%
Ethiopia	$0.62	41.22%
Gabon	$11.46	41.41%
Ghana	$1.26	28.72%
Guinea	$0.96	66.62%
Guinea-Bissau	$0.50	43.18%
Liberia	$0.55	21.22%
Malawi	$0.31	12.58%
Mali	$1.21	60.73%
Mozambique	$0.75	5.04%
Nigeria	$3.92	65.88%
Senegal	$1.58	34.14%
Sierra Leone	$0.77	76.23%
South Sudan[c]	$2.94	56.70%
Sudan	$2.94	73.68%
Tanzania	$0.92	31.75%
Togo	$1.13	41.08%
Uganda	$1.07	49.33%
Average (SD)	$2.98 ($5.96)	43.45% (18.25%)

a Data in 2008 local currency from WHO [109]; Adjusted for country-specific inflation over 2009–2013[98] and converted to 2013 USD using market exchange rate [99]; Outpatient visit costs exclude drug and laboratory diagnosis.
b Data from WHO [88].
c Outpatient service cost per visit was estimated before Sudan was divided, so we used the same as that for Sudan.

In sub-Saharan Africa it is estimated that 23%−40% of total households face catastrophic health expenditure [110–112]. The prevalence of out-of-pocket payments is highly correlated with catastrophic health expenditure and impoverishment [113,114]. To evaluate the impact on the financial protection of households of onchocerciasis elimination and eradication, we estimated outpatient service costs paid out of pocket by patients under each scenario, by multiplying the predicted outpatient service costs by the percentage of total health expenditure paid out of pocket (Table 2) that is inflated by 17% to include transportation costs (based on 2010 World Health Report [27]).

Assessment of economic impacts

We estimated the potential economic benefits of onchocerciasis elimination and eradication using two alternative approaches: one to estimate the economic productivity gains associated with the reduction in the prevalence of onchocercal symptoms and another to estimate the economic welfare gains associated with additional life-years from prevented premature deaths and encompassing broader impacts than labor productivity [19,115].

1) Economic productivity gains

We estimated the economic productivity gains from the reduction in morbidity over 2013–2045, by multiplying the predicted number of patients with severe itching, low vision, and blindness by a country-specific employment rate and a proxy for income losses for each symptom under each scenario. We assumed that patients aged from 15 and above would have the same probability of being employed as general population (Table10) unless they had onchocercal symptoms. We assumed patients aged from 15 to 64 years with severe itching would lose 13% of GDP per capita based on the study on the economic impact of onchocercal skin diseases in Ethiopia [21], and patients in the same age group with low vision and blindness would lose 38% and 79% of GDP per capita, respectively, based on the study on the socioeconomic impact of onchocercal vision impairment in Guinea [22]. Patients aged less than 15 years were assumed to have no economic productivity. Patients aged 65 years and above were assumed to be half as productive as those aged from 15 to 64 years referring to the methods used by Frick, Smith, and colleagues [23,24]. We also estimated the productivity gains for informal care-takers (e.g., families and relatives), assuming that one patient with low vision and blindness needs one adult care-taker. We multiplied the number of patients with low vision and blindness and a relevant proxy for their care-takers' income losses under each scenario. As a proxy, we assumed the care-taker would lose 5% of GDP per capita if the

patient has low vision, and 10% of GDP per capita if the patient is blind, referring to the study by Smith, Shamanna, and colleagues [24,25].

To estimate the economic productivity gains from the reduction in mortality over 2013–2045, we multiplied the predicted YLL by GDP per capita, considering blindness causes premature death at a fully productive age [26].

Table 10. GDP per capita and employment rate for endemic African countries

Country	GDP per capita, 2013[a]	Employment rate, 2013[b]
Angola	$5,668	65.24%
Benin	$805	72.17%
Burkina Faso	$684	80.81%
Burundi	$267	76.90%
Cameroon	$1,315	67.49%
Central African Rep.	$333	72.72%
Chad	$1,046	66.59%
Congo, Dem. Rep.	$3,172	66.15%
Congo, Rep.	$1,521	66.10%
Côte d`Ivoire	$454	64.61%
Equatorial Guinea	$20,572	79.76%
Ethiopia	$498	78.93%
Gabon	$11,571	48.88%
Ghana	$1,850	66.11%
Guinea	$527	70.70%
Guinea-Bissau	$504	68.10%
Liberia	$454	59.22%
Malawi	$226	76.69%
Mali	$715	60.59%
Mozambique	$593	77.21%
Nigeria	$3,006	51.89%
Senegal	$1,072	68.62%
Sierra Leone	$809	65.15%
South Sudan	$1,045	64.67%[c]
Sudan	$1,753	45.37%
Tanzania	$695	85.98%
Togo	$636	75.41%
Uganda	$572	74.56%
Average (SD)	$2,234 ($4,252)	68.45% (9.52%)

a Data from World Bank [116]
b Adjusted for labor force participation rate, i.e., (1-unemployment rate)*(% of population ages 15 and older that is economically active); Unemployment rate from World Bank [117]; Labor force participation rate from World Bank [118]
c Data were missing. We used data for sub-Saharan Africa from World Bank [117,118]

2) Economic welfare gains

We estimated economic welfare gains associated with life-year gains from onchocerciasis elimination and eradication, by multiplying the predicted YLL by the economic value of one additional life-year. We used two alternatives for the value of a life-year, 4.2 times GDP per capita estimated for sub-Saharan Africa and 2.3 times GDP per capita for low and middle income countries in the study by the Lancet Commissionon Investing in Health[20]. This

study used willingness-to-pay studies that survey how much a person is willing to give up consumption opportunities to avoid mortality risk to measure the comprehensive impacts of disease beyond labor productivity. As the economic value of a life-year in this study was discounted at 3% over 12 years, we applied the discount rate to our estimates for the period beyond the first 12 years in our time horizon.

Uncertainty analysis

We conducted sensitivity analysis to examine the robustness of results to parametric uncertainties and assumptions. We conducted one-way deterministic sensitivity analysis (DSA) to examine the impact of a single parameter's uncertainty on the results and to determine which parameters are the key drivers. We also conducted probabilistic sensitivity analysis (PSA) to assess the robustness of the results to the joint uncertainties about all selected parameters. For the PSA, we applied statistical distributions to parameters considering parametric characteristics and fitted to available data. Parameters against which we assessed the robustness of the results are as follows.

Health impacts: the expected treatment coverage linked to the required duration of treatment, the level of infection and morbidity in hypo-endemic areas relative to meso-endemic areas, the reduction of life expectancy per blindness incidence, and the population growth rate

Health workforce: the ratio of community volunteers over population, the ratio of community health workers over population, the population growth rate, and the possible delay in starting and ending CDTi

Outpatient services and associated costs and out-of-pocket payments: the number of patients with severe itching and low vision, the health facility utilization rate, the

outpatient cost per visit, the proportion of outpatient visit costs paid out of pocket by patients, and the transportation cost

Economic productivity gains: GDP per capita, the employment rate, the proportion of GDP per capita associated with the productivity losses due to severe itching, low vision, and blindness

Economic welfare gains: the predicted YLL

Further methodological details on PSA, including statistical distributions and data used for each parameter, are described in Appendix 3.

Results

Health impacts

The elimination and eradication scenarios would lead to the decrease in the prevalence of the onchocercal symptoms and to the consequent reduction of DALYs.

The prevalence of severe itching in endemic African regions would decrease from 30/1,000 to 7/1,000 for the control scenario, to 2/1,000 for the elimination scenario, and to less than 1/1,000 for the eradication scenario over 2013−2045 (Figure 26).The number of patients with severe itching would be 231.3 million (95% central range from PSA: 218.4M–295.7M)over 2013–2045under the control scenario. Switching to the elimination and eradication scenarios would lead to the reduction of the number of patients with severe itching by 15% and 20%respectively, that is, 34.2 million (14.2M−39.9M) and 46.4 million (20.2M−55.8M). The prevalence of low vision would decrease from 51/10,000 to 6/10,000 for the control scenario, to 4/10,000 for the elimination scenario, and to 3/10,000 for the eradication scenario(Figure26). The number of patients with low vision under the control scenario would be 33.1 million(31.7M−36.9M) over 2013–2045. Switching to the elimination and eradication

scenarios would lead to the reduction of the number of patients with low vision by 4% and 5% respectively, that is, 1.5 million (0.2M−1.3M) and 1.8 million (0.4M−1.7M). The prevalence of blindness would decrease from 17/10,000 to 2/10,000 for the control scenario, and to less than 1/10,000 for the elimination and eradication scenarios (Figure26). The number of patients with blindness under the control scenario would be 11.3 million(10.8M−12.8M) over 2013–2045. Switching to the elimination and eradication scenarios would lead to the reduction of the number of patients with blindness by 6% and 7% respectively, that is, 670 thousand (34.6k−528.9k) and 778 thousand (87.4k−670.0k). The faster decrease in the prevalence of severe itching than that of low vision and blindness is because ivermectin treatment can relieve severe itching by killing 99% of microfiliae[68], whereas vision impairment is irreversible.

The elimination and eradication scenarios would avert DALYs by 33%, 4.3 million (2.1M−5.5M), and 43%, 5.6 million (2.7M−7.2M), respectively over 2013−2045 as compared to the control scenario (Figure 27).

Figure 26. Prevalence of severe itching, low vision, and blindness in endemic African regions over 2013-2045

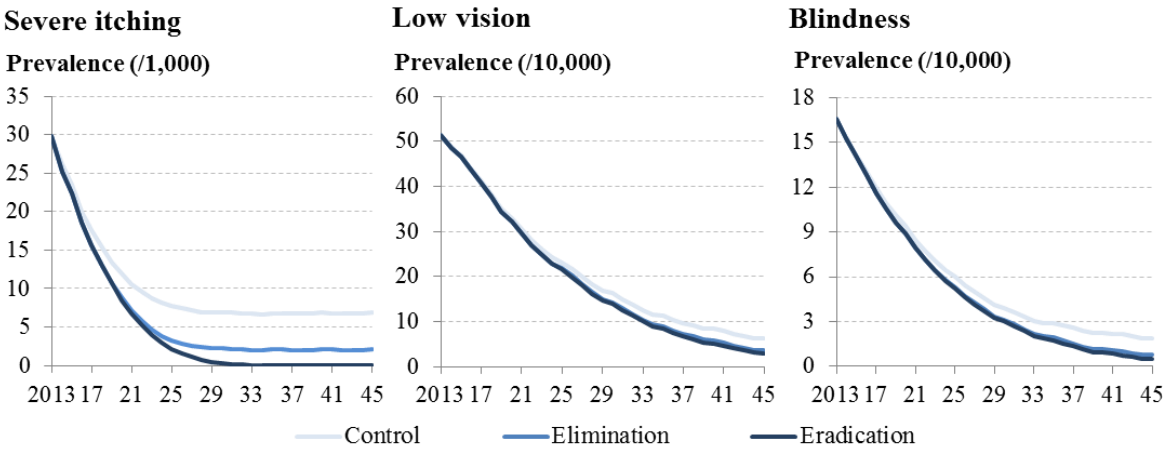
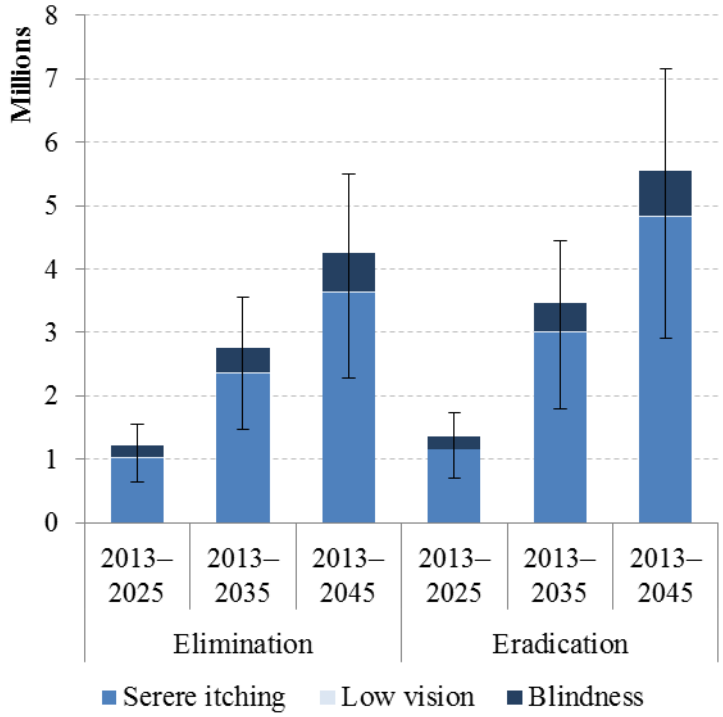


Figure 27. Cumulative DALYs averted in endemic African regions over 2013-2045



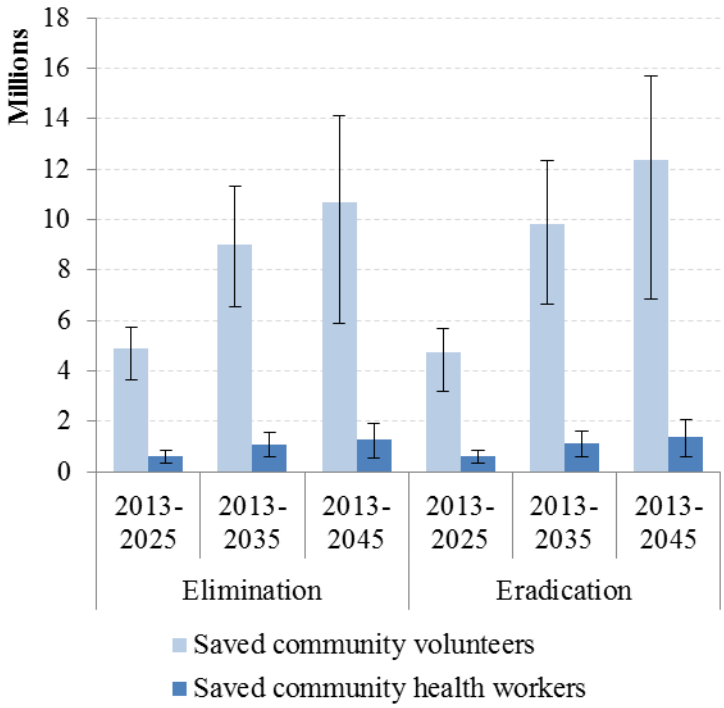
(Note: The ranges are from PSA. DALYs are discounted with 3%.)

Impacts on health systems

1) Impact on health workforce

The total number of required community volunteers for implementing CDTi in endemic African regions would be 23.9 million (18.6M−30.4M) over 2013−2045 for the control scenario, 13.2 million (10.5M−19.1M) for the elimination scenario, and 11.6 million (9.2M−17.5M) for the eradication scenario (Figure28). That is, switching from the control scenario to the elimination and eradication scenarios would lead to the reduction of the number of required community volunteers by 45% and 52% respectively, that is, 10.7 million (5.9M−14.1M) and 12.4 million (6.9M−15.7M).

Figure 28.Saved community volunteers and community health workers in endemic African regions over 2013-2045, baseline: control scenario



(The ranges are from PSA.)

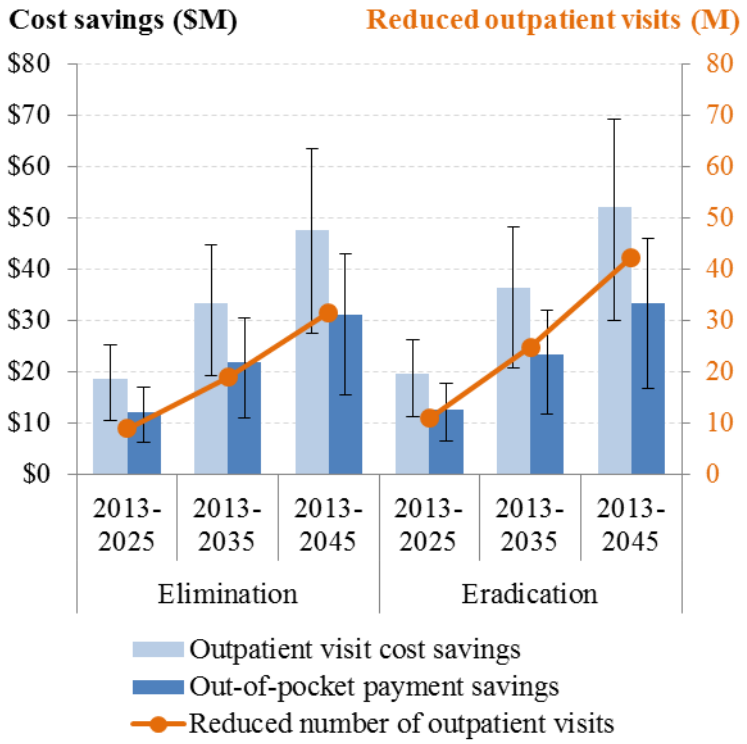
The total number of required community health workers for implementing CDTi in endemic African regions would be 2.3 million (1.6M−3.2M) over 2013−2045 for the control scenario, 1.0 million (0.8M−1.7M) for the elimination scenario, and 900 thousands (0.7M−1.6M) for the eradication scenario (Figure28). Switching to the elimination and eradication scenarios from the control scenario would lead to the reduction of required community health workers by 56% and 60% respectively, that is, 1.3 million (0.5M−1.9M) and 1.4 million (0.6M−2.0M).

2) Impact on outpatient services and associated costs and out-of-pocket payments

The elimination and eradication of onchocerciasis would reduce the burden on health systems associated with patients' visits to health facility due to severe itching and low vision. The number of outpatient visits due to those symptoms in endemic African regions would be 46.2 million (25.7M–58.9M) over 2013−2045 under the control scenario, generating $56.0 million

($26.7M–$74.1M) of outpatient service costs which would result in $35.7 million ($17.0M–$49.4M) of out-of-pocket payments by patients. Switching to the elimination and eradication scenarios would decrease the number of outpatient visits by 68% and 92%, that is, 31.6 million (17.6M–40.3M) and 42.3 million (17.6M–40.3M) (Figure 4). This reduction would save outpatient service costs by $47.5 million ($22.4M−$63.3M) and $52.1 million ($24.3M−$69.5M) respectively and out-of-pocket payments by $31.2 million ($14.6M–$43.5M) and $33.5 million ($15.7M–$46.4M).

Figure 29.The savings of outpatient service costs and out-of-pocket payments for outpatient visits and the reduced number of outpatient visits in endemic African regions over 2013-2045, baseline: control scenario



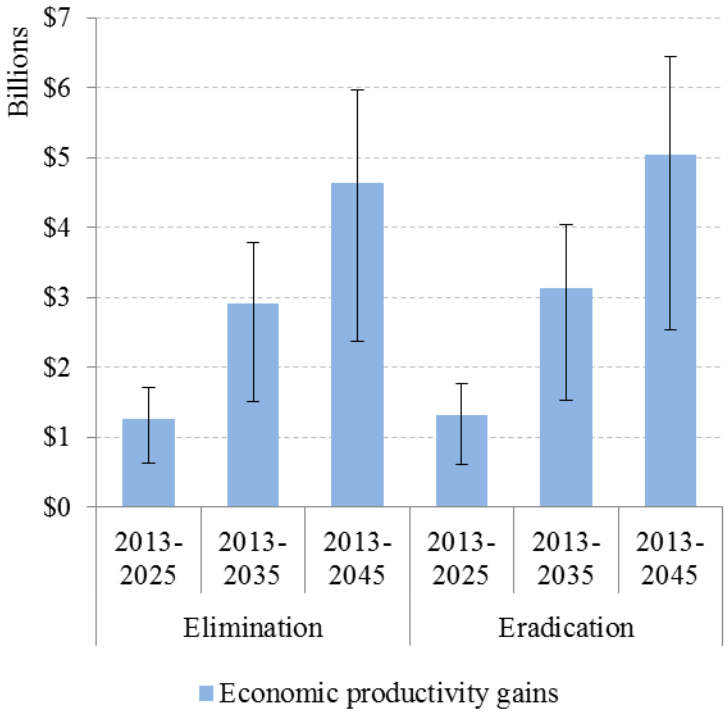
(The ranges are from PSA.)

Economic impacts

1) Economic productivity gains

The economic benefits measured in terms of productivity gains would be $4.6 billion ($2.3bn–$6.3bn) for the elimination scenario and $5.0 billion ($2.4bn–$6.8bn) for the eradication scenario over 2013–2045 as compared to the control scenario (Figure30). The economic productivity gains associated with the reduction in severe itching cases would account for 55% of the total; and the reduction in low vision and blindness for 35% and 10% respectively. The majority of the productivity gains, 96%, would be associated with patients treated and the rest 4% with their care-takers.

Figure 30.Economic productivity gains in endemic African regions over 2013-2045, baseline: control scenario



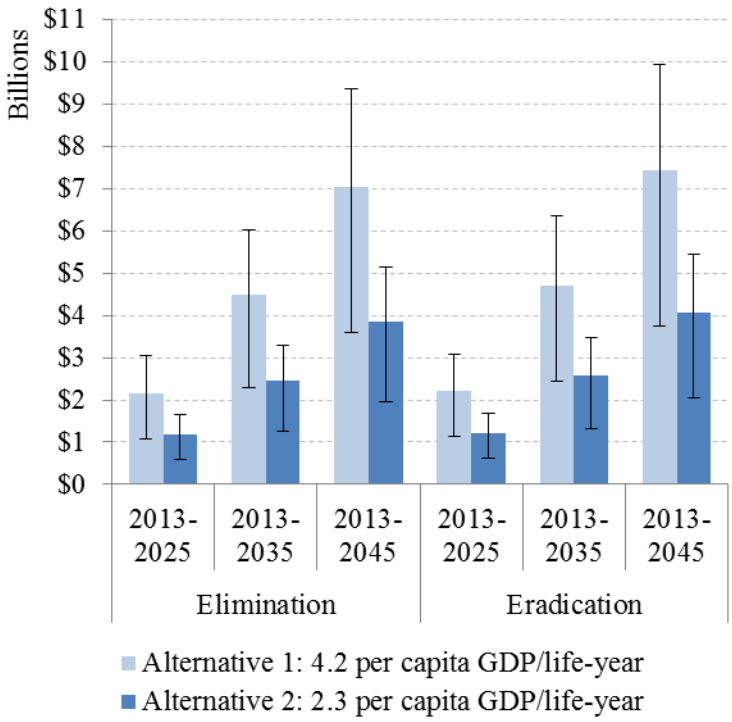
(The ranges are from PSA.)

2) Economic welfare gains

The economic benefits measured in terms of welfare gains associated with the life-year gains from averted blindness would be, applying the value of a life-year for sub-Saharan Africa (4.2 times GDP per capita), $7.0 billion ($3.6bn–$9.4bn) for the elimination scenario and $7.4

billion ($3.8bn–$9.9bn) for the eradication scenario over 2013–2045as compared to the control scenario; and applying that for low and middle income countries (2.3 times GDP per capita), $3.9 billion ($2.0bn–$5.1bn) for the elimination scenario and $4.1 billion ($2.1bn–$5.4bn) for the eradication scenario (Figure 31).

Figure 31.Economic welfare gains in endemic African regions over 2013-2045, baseline: control scenario



(The ranges are from PSA.)

Uncertainty analysis

The one-way DSA indicates the results are the most sensitive to the following parameters:

Health impacts: the level of infection and morbidity in hypo-endemic areas relative to meso-endemic areas (Figure S7)

Health workforce: the ratio of community volunteers over population, the ratio of community health workers over population (Figure S8, S9)

Outpatient services and associated costs and out-of-pocket payments: the number of patients with severe itching (FigureS10, S11)

Economic productivity gains: the number of patients with severe itching (Figure S12)

Economic welfare gains: the years of life lost due to blindness (Figure S13)

As the discount rate decreases from 6% to 0%, the results vary from 70% (minimum) to 150% (maximum) of the point estimates (Figure S7, S10–S13).

The 95% central ranges generated from the PSA and reported with the point estimates for all results previously (summary in Table 11) indicate that the health and economic benefits and the reduction of the burden on health systems from onchocerciasis elimination and eradication are robust to the joint uncertainties of relevant parameters.

Table 11. Summary of key results

	Elimination vs Control (baseline)	Eradication vs Control (baseline)
Health benefits, 2013–2045		
DALYs averted	4.3 million (2.1m−5.5m)	5.6 million (2.7m−7.2m)
Health systems impacts, 2013–2045		
Health workforce saved		
1) Community volunteers	10.7 million (5.9m−14.1m)	12.4 million (6.9m−15.7m)
2) Community health workers	1.3 million (0.5m−1.9m)	1.4 million (0.6m−2.0m)
Outpatients services		
1) Number of outpatients visits reduced	31.6 million (17.6m–40.3m)	42.3 million (17.6m–40.3m)
2) Outpatient service cost savings	$47.5 million ($22.4m−$63.3m)	$52.1 million ($24.3m−$69.5m)
3) Out-of-pocket payment savings	$31.2 million ($14.6m–$43.5m)	$33.5 million ($15.7m–$46.4m)
Economic benefits, 2013–2045		
Productivity gains	$4.6 billion ($2.4bn−$6.2bn)	$5.0 billion ($2.7bn−$6.7bn)
Welfare gains		
Value of a life-year: 4.2 times GDP PC	$7.0 billion ($3.6bn–$9.4bn)	$7.4 billion ($3.8bn–$9.9bn)
Value of a life-year: 2.3 times GDP PC	$3.9 billion ($2.0bn–$5.1bn)	$4.1 billion ($2.1bn–$5.4bn)
Data: mean (95% central ranges from PSA)		

Discussion

Our study shows that the elimination and eradication scenarios, scaling up treatments from meso-/hyper-endemic areas to hypo-endemic areas including those with political insecurity and co-endemicity with *Loa loa* and implementing regular epidemiological and entomological

surveillance, would lead to the health and economic benefits and reduce the burden on health systems in terms of health workforce and outpatient services. We found that the decrease of the prevalence of severe itching would be the main driver of DALYs averted, the savings of outpatient service costs and out-of-pocket payments, and the economic productivity gains over 2013–2045 under the elimination and eradication scenarios as compared to the control scenario, and the reduction of blindness cases would generate life-year gains, thereby leading to the economic welfare gains. This study also shows that onchocerciasis elimination and eradication would save human resources needed for implementing CDTi, namely community volunteers and community health workers.

Our results should be interpreted considering the limitations of our methodologies. To calculate DALYs we used the most recent disability weights from the 2010 global burden of disease (GBD) study. The disability weight of blindness has been controversial as it decreased by 70% as compared to that in the previous 2004 GBD study (from 0.6 to 0.195). The important difference of the 2010 GBD study from the 2004 GBD study is that disability weights were measured in terms of health loss, rather than socioeconomic welfare loss[11,119]. Thus, the interpretation of averted DALYs needs to be restricted to health gains. To calculate YLL we assigned eight years of life-years lost to each blindness incidence. However, this could be overestimation assuming life expectancy for general population would be stable, because regular annual or biannual ivermectin administration would postpone the incidence of blindness to a later age. To estimate the required number of health workforces for CDTi, we assumed the current availability of community volunteers and community health workers would be sustained until CDTi is safely stopped. However, the availability of these health workforces could change depending on political situations and policies and budgets for supporting their activities. Also the delay in stopping CDTi due to managerial issues could require more workforces than expected. To estimate outpatient service costs we assumed the

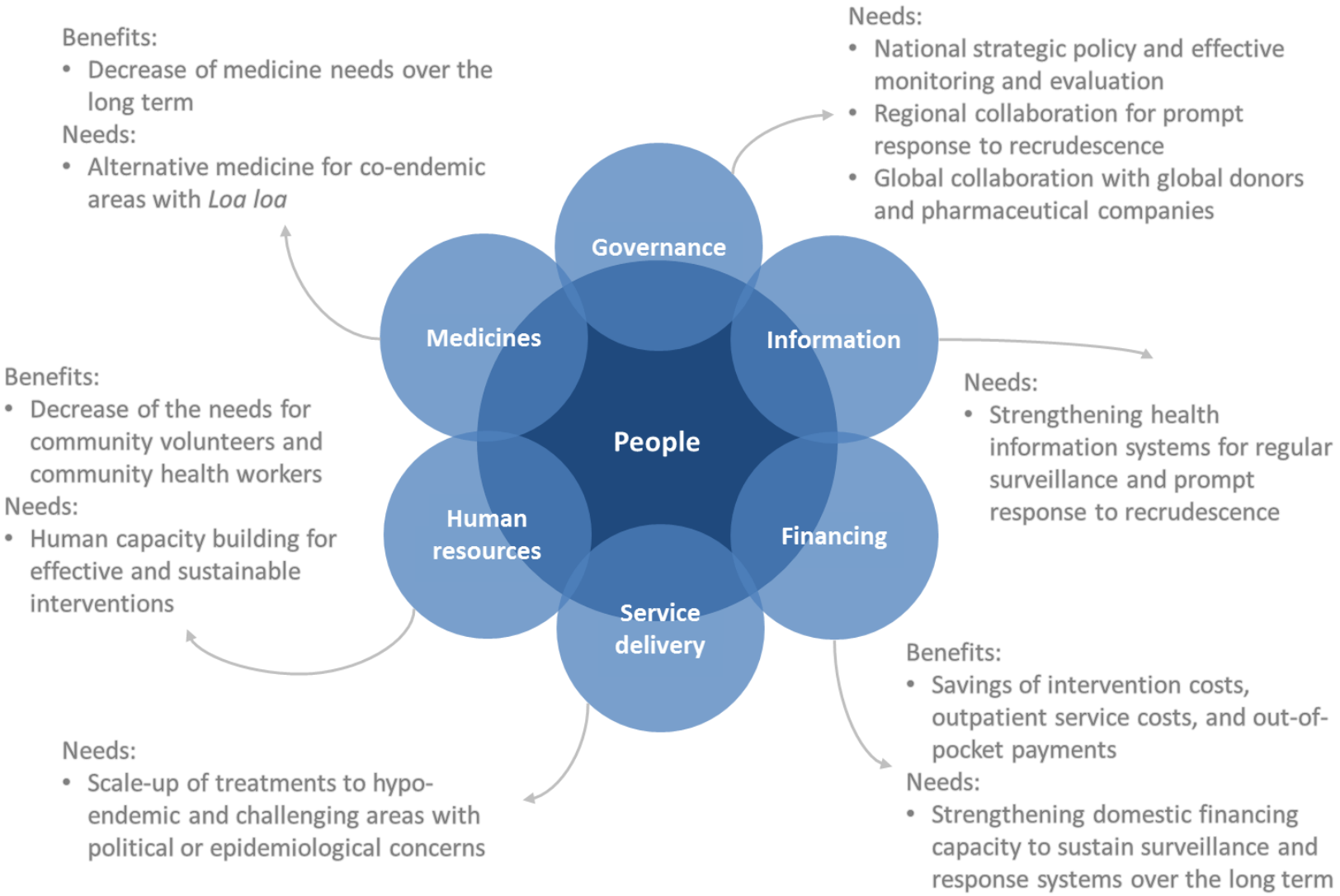
same proportion of people who complied with CDTi would visit health facility if there is no CDTi. However, in real settings, poor road networks and a long distance to health facility could hamper people's access to health facility. To estimate out-of-pocket payments we assumed that the proportion of health expenditure paid out of pocket by patients would be stable over the entire time horizon; however, it could change depending on how much financial protection mechanisms are improved against catastrophic health expenditure. To evaluate economic productivity gains we used GDP per capita as a proxy for individual productivity. The actual income of people living in endemic areas could be much lower than GDP per capita. However, we assumed that the potential productivity of individuals is not different between endemic and non-endemic areas. To estimate economic welfare gains we used two alternatives 4.2 times and 2.3 times GDP per capita as the value of one additional life-year in endemic African regions. However, if the demographic and epidemiological settings in endemic African regions change with industrialization over the period 2013−2045, the economic value of a life-year would change towards that for high income countries which is lower than the two alternatives. In the analysis of economic impacts, we assumed no per capita GDP growth for conservative estimation, and this limited the predicted economic benefits.

The elimination and eradication scenarios dominate the control scenario in terms of intervention costs and benefits. The cost analysis by Kim and colleagues shows that an intensive investment in the early stage to scale up CDTi under the elimination and eradication scenarios would lead to the decrease of total financial and economic costs associated with treatments and surveillance, and eventually save costs over the period 2013−2045 as compared to the control scenario [107]. This result, combined with our results on health and economic benefits, indicates that the eradication scenario, followed by the elimination scenario, is the most economically favorable among the three scenarios.

Shifting the treatment goal from control to elimination and eradication would affect and be affected by health systems (Figure 34) which therefore should be strengthened. The mandated and critical activity to achieve the elimination and eradication of onchocerciasis is regular epidemiological and entomological surveillance which tracks the infection levels in humans and blackflies and enables prompt response to recrudescence in the post-treatment phase. Only if health information systems are effective and efficient, regular active surveillance would be feasible. Strengthening health information systems would require sustainable financing, another building block of health systems. Financial costs associated with surveillance and response systems are estimated to increase five times over the period 2013–2045 under the elimination and eradication scenarios than the control scenario [107]. This implies that the governments of endemic countries would need to develop financing plans and enhance their domestic funding capacity, as surveillance would need to be sustained over the long term and external funding would be temporary. Scaling up treatments to achieve onchocerciasis elimination and eradication would affect mainly two building blocks of health systems, health workforce and medicine, as it would require more community volunteers and community health workers and more ivermectin and alternative macrofilaricidal medicines (for co-endemic areas with *L.loa*). However, the elimination and eradication would eventually save health workforce and medicine, because the duration of CDTi would be shorter than under the control mode [6]. Considering sub-Saharan African countries are expected to face a substantial deficit of health workforce by 2030 (WHO report [120]), the saved health workforce could be useful for other health care programs. Also the saved ivermectin could be used to treat other diseases such as lymphatic filariasis. Governance and leadership will be critical to achieve onchocerciasis elimination and eradication which are public goods that can be attained only through the collaboration between all stakeholders at community, national, regional, and global levels [36,101]. To foster the commitment from communities, national policymakers would need to invest in enhancing the capacity of community volunteers and

community health workers and mobilizing communities. At national level, policymakers would need to develop a long-term strategic policy for the elimination and eradication of the disease. To implement the policy effectively, policymakers would need to regularly monitor and evaluate the performance of all relevant components including health information systems, financing, scaling up treatments, timely drug supply, and human capacity building. Regional collaboration between endemic countries would be important when endemic areas span across the border areas, as human and vector migration could cause recrudescence. The cooperation with global donors and pharmaceutical companies would be needed especially in the early stage of elimination and eradication strategies. In this period, endemic countries would need higher financial costs, more health workforces, and more medicines as discussed previously. Thus, global donors' continuous funding and pharmaceutical companies' drug donation will be important.

Figure 32.Health systems impacts associated with the elimination and eradication of onchocerciasis



6 Income inequality associated with onchocerciasis endemicity

Background

Neglected tropical diseases including onchocerciasis are concentrated among low-income countries and disadvantaged populations. Social justice consists in fairness and equity in the distribution of societal benefits and burdens. Nevertheless, it is challenging to account for the ethical importance of the benefits, burdens, and distributions, that are salient in people's experiences of the diseases and related interventions. Thus these aspects are not assessed in traditional approaches for health and economic evaluation.

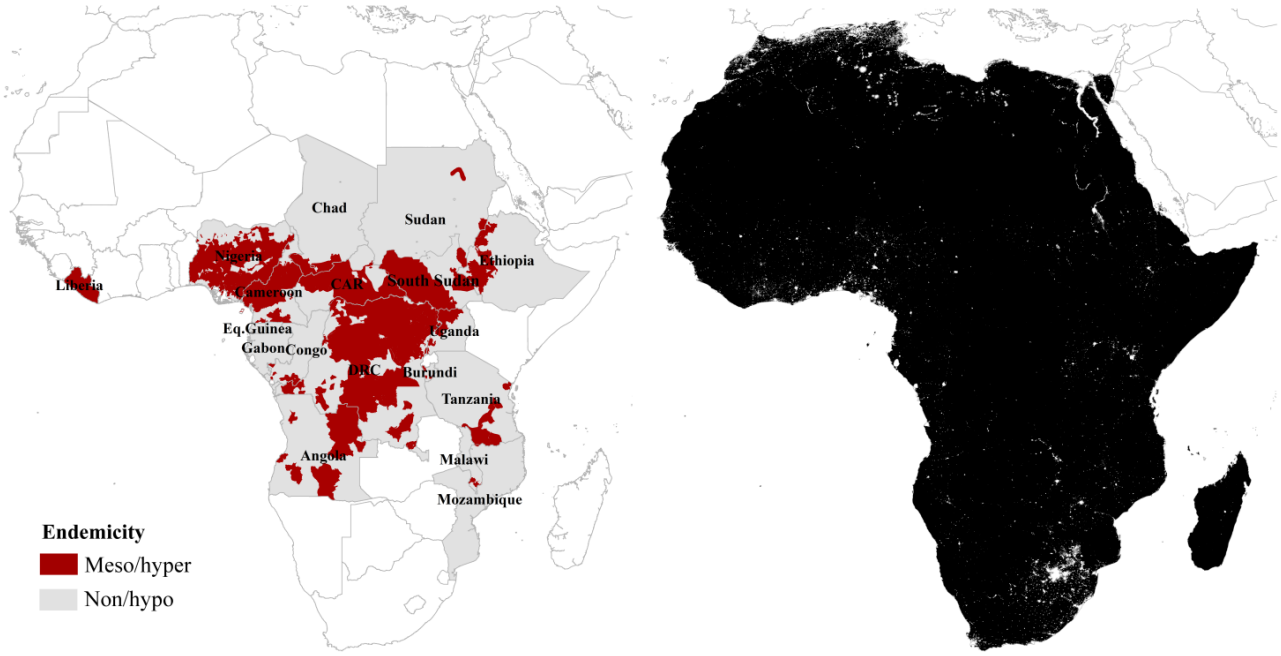
In this study, to evaluate the potential impacts of onchocerciasis elimination in terms of the inequalities in economic conditions at local level, we compared the night light level between meso-/hyper-endemic areas and non-/hypo-endemic areas. We used night light data as a proxy for local income, because there were no data available on the local economic conditions of the endemic areas. Recent studies showed that, despite several limitations, the night light data can be used as a proxy for income at sub- and supranational levels in low income countries [28].

Methods

We identified meso-/hyper-endemic and non-/hypo-endemic areas using the APOC database which were created based on epidemiological surveys and using a geospatial analysis [29,30] (Fig 35). We obtained the 2013 night light map [31] and removed the flaring from national gas from the map, as gas flare is not related to economic activities [28]. Using the night light map (Fig 35), we created a database that contains the light levels (dark−bright: 0−64) at the geographic unit of 0.1 by 0.1 degrees, and identified if each unit area is meso-/hyper-endemic or non-/hypo-endemic by overlapping the endemicity map. We compared the average light

level between meso-/hyper-endemic and non-/hypo-endemic areas using Welch's unequal variances *t*-test.

Figure 33.Endemicity and night lights in Africa



Results

The statistical comparison of night light levels shows that the average night light level in meso-/hyper-endemic areas (M=0.15, SD=1.46) is significantly lower than that in non-/hypo-endemic areas (M=0.18, SD=1.93); $t(82,117)=2.97$, $p<0.05$. This suggests that, within the APOC countries where most of the global cases are found, meso-/hyper-endemic areas are likely to have higher poverty levels than non-/hypo-endemic areas.

Conclusion

We found that meso-/hyper-endemic areas are likely to poorer than non-/hypo-endemic areas assuming night light data as a proxy for local income level. Poverty is not just about low income, but goes beyond to the deterioration of individual capabilities to lead their lives and accomplish what they value as human beings [32]. Specifically, onchocercal symptoms

deteriorate patients' well-being from psychological, psychosocial, and social aspects [33]. These symptoms undermine self-respect due to stigma, teasing, and negative stereotyping, and deprive of the opportunities of physical and educational activities and relationships with others because of ostracism or the avoidance of infected person. This indicates that the elimination and subsequent eradication of onchocerciasis would not only contribute to relieving income inequality, but also lead to ethical advantages and social justice.

7 Discussion

Overall significance of research

This research shows that the elimination and eradication of onchocerciasis will be economically dominant over the control of the disease, and also contribute to the social justice by relieving economic inequality and preventing social stigma and psychological negative impacts on infected persons. The analysis used large datasets on epidemiological mapping, the history of treatment coverage(1995–2012) for all 112 ongoing projects as of November 2013 in sub-Saharan Africa, approved budgets for 67 projects, and night light data for endemic African regions. The analysis was not only based on these data, but also used rigorous methods: dynamical transmission modelling for the epidemiological analysis, a micro-costing method for the cost analysis, human capital and full-income approaches for the economic impact analysis, and the spatial analysis of night light data. According to the literature review, this research is the first economic evaluation of potential regional elimination strategies for onchocerciasis in Africa. The results could be used as a guide for national and global policymakers' informed decision making.

Key findings

Control, elimination, and eradication scenarios (objective 1)

The key changes for shifting from the control mode to elimination and subsequent eradication are the scale-up of CDTi to hypo-endemic areas including areas with epidemiological and political concerns and the implementation of regular epidemiological and entomological surveys along with ongoing surveillance (Chapter 3). For successful implementation of these, overcoming the existing feasibility issues related to the co-endemicity with *L. loa*, the insecure political situation, and weak health systems will be critical.

The timelines and needs of treatment (objective 2)

As Chapter 3 describes, this study found that regional elimination in Africa could be achieved as early as 2040, and consequently all endemic countries including Latin Americas and Yemen would be in the post-elimination phase until eradication has been verified. Also this study found that achieving elimination would reduce treatment needs by 43% compared to the control mode for the period 2013-2045. The driver of this remarkable difference is that CDTi could be stopped for the majority of projects based on regular surveillance, while it would have to continue for at least 25 years under the control scenario. The eradication scenario is predicted to require an even smaller number of ivermectin treatments than the elimination scenario, as hypo-endemic areas with feasibility concerns were assumed to have a shorter treatment period through effective treatment via tailored approaches as well as CDTi. This finding implies that saved ivermectin drugs could be used for other disease programs, for instance, mass drug administration(MDA) for lymphatic filariasis (LF). The main driver of the number of required ivermectin treatments was the delay in stopping CDTi. This finding implies that maintaining high treatment coverage to avoid the extension of treatment duration and continuous monitoring and evaluation to decide a proper time to stop CDTi would lead to faster elimination and prevent unnecessary efforts to deliver drugs.

Financial and economic costs (objective 3)

The elimination and eradication scenarios are predicted to generate substantial cost-savings in the long run compared to the control scenario (Chapter 4). The main factors contributing to cost-savings are the reduction in economic costs of community volunteers and donated ivermectin due to a shorter treatment phase as a result of regular active surveillance. This finding implies that the saved volunteers' time and ivermectin can be used for other health programs. Willing volunteers and their well-established networks, which have enabled successful implementation of CDTi in Africa, could contribute to improving access to primary

health care in remote rural areas with insufficient human resources. To realize these possibilities, policymakers would need to keep empowering community volunteers through training and societal or economic appreciation. Also, pharmaceutical companies' continuous commitment to donating drugs would be needed.

The cost analysis also suggests that the cumulative financial costs for surveillance over 2013−2045 in the elimination and eradication scenarios would be five times higher those in the control scenario. This implies that endemic countries would need to improve their domestic funding capacity to sustain high surveillance costs to achieve elimination.

The uncertainty analysis showed that the delay in ending CDTi would have the highest impact among those related to CDTi performance on total costs. Thus, planning to move towards the post-treatment phase, along with regular monitoring and evaluation to define the proper time of stopping treatments, would be important to avoid the delay in ending CDTi. The uncertainty analysis also showed that the salary top-ups for stabilizing new projects would have the most influence of all cost items on total costs. Many new projects are in potential hypo-endemic areas where parasitological surveys are still needed to confirm endemicity [39]. This suggests that complete epidemiological mapping should be a priority to choose areas to start new projects and to predict required human resources for those projects.

Health, economic, and health systems impacts (objective 4–6)

As Chapter 5 describes, this study shows that the elimination and eradication scenarios, scaling up treatments to hypo-endemic areas including those with political insecurities and co-endemicity with *Loa loa* in addition to meso-/hyper-endemic areas and implementing regular epidemiological and entomological surveillance, would lead to health and economic benefits and have impacts on health systems. The analysis found that the decrease of the prevalence of severe itching would be the main driver of DALYs averted, the savings of outpatient visit costs, and economic productivity gains over 2013–2045 under the elimination and eradication

scenarios as compared to the control scenario. As CDTi is scaled up, the prevalence of severe itching would decrease faster than those of low vision and blindness, because ivermectin treatment can relieve severe itching by killing 99% of microfiliae[68], whereas vision impairment is irreversible. Also the life-expectancy gains as a result of prevented blindness would lead to substantial welfare gains. This study also found that regular surveillance, another main component of the elimination and eradication scenarios besides the scale-up of CDTi, would be the main driver of the reduction of required community volunteers and community health workers for implementing CDTi, as regular surveillance would enable to decide a proper time to stop CDTi and save the workforces from unnecessarily prolonged CDTi.

Economic inequality (objective 7)

The analysis of economic inequality using night light data as a proxy for local income levels (Chapter 6) found that, within the APOC countries where most of the global cases are found, meso-/hyper-endemic areas are likely to have higher poverty levels than non-/hypo-endemic areas. Poverty is not just about low income, but goes beyond to the deterioration of individual capabilities to lead their lives and accomplish what they value as human beings [32]. This indicates that the elimination and subsequent eradication of onchocerciasis would not only contribute to relieving income inequality, but also lead to ethical advantages and social justice.

Overall implications

Economic efficiency and social justice

The elimination and eradication scenarios dominate the control scenario in terms of intervention costs and benefits. The cost analysis shows that an intensive investment in the early stage to scale up CDTi under the elimination and eradication scenarios would lead to the decrease of total financial and economic costs associated with treatments and surveillance,

and eventually save costs over the period 2013−2045 as compared to the control scenario. This result, combined with the results on health and economic benefits, indicates that the eradication scenario, followed by the elimination scenario, is the most economically favorable as compared to the control scenario. Also the value of investing in elimination and eradication of the disease would go beyond the economic efficiency to alleviating socioeconomic inequalities, because onchocercal symptoms undermine self-respect due to stigma, teasing, and negative stereotyping [33]. Thus, elimination and eradication of onchocerciasis would be a social intervention that could increase opportunities of self-realization, alleviate poverty, and eventually promote socioeconomic equity.

Health systems

Shifting the treatment goal from control to elimination and eradication would affect and be affected by all building blocks of health systems – health information systems, financing, service delivery, human resources, medical technologies/products, governance/leadership – which therefore should be strengthened.

First, health information systems, which serve to collect and analyze data and generate information for informed decision-making, would be essential to achieve the elimination and eradication of onchocerciasis. Regular epidemiological and entomological surveillance would be critical to track the infection levels in humans and blackflies and to promptly respond to recrudescence in the post-treatment phase, and these functions would be feasible only if health information systems are effective and efficient.

Strengthening health information system would require sustainable financing. Financial costs associated with surveillance and response systems over the period 2013–2045 under the elimination and eradication scenarios are estimated to be five times higher than that under the control scenario. This implies that the governments of endemic countries would need to

develop financing plans and strengthen their domestic funding capacity, as surveillance would need to be sustained over the long term and external funding would be temporary.

Scaling up treatments to hypo-endemic areas to achieve elimination and eradication would mainly affect two building blocks of health systems, human resources and medicines, by requiring more community volunteers and community health workers and more ivermectin and alternative macrofilaricidal medicines (for co-endemic areas with *L.loa*). However, the elimination and eradication of onchocerciasis would eventually reduce the burden on these two building blocks, because human resources and medicines would be saved in the long run as treatments are stopped earlier than under the control mode [6]. To realize this, policymakers would need to invest in enhancing the capacity of community volunteers and community health workers for the effective and sustainable implementation of CDTi.

Governance and leadership will be critical to achieve the elimination and eradication of onchocerciasis, which are public goods that can be achieved only through the coordinated efforts among all stakeholders at national, regional, and global levels. National policymakers would need to develop the long-term strategic policy for the elimination and eradication of the disease. To implement the policy, policymakers would need to regularly monitor and evaluate the performance of all the relevant components including health information systems, financing, scaling up treatments, human capacity building, and timely drug supply. Regional collaboration between endemic countries would be also important when endemic areas span across the border areas, as human and vector migration could cause recrudescence. The elimination and eradication of onchocerciasis would also require cooperation from global donors and pharmaceutical companies. Especially during the early stage of elimination and eradication strategies, endemic countries would need higher financial costs, more human resources, and more medicines. In this period, global donors' continuous funding and pharmaceutical companies' drug donation will be needed.

Future research

Integrated interventions for onchocerciasis and LF

Some NTDs are endemic in the same or adjacent areas, and interventions are delivered with a similar time schedule and/or use the same medicines. For example, endemic areas of onchocerciasis and LF overlap in some African regions, and interventions for both diseases use the same medicine, ivermectin. There would be potential benefits from the integration of interventions of onchocerciasis and LF; however, there also would be challenges and risks. A future research topic could be the feasibility of the integration of onchocerciasis and LF interventions. Specifically, the research can include the epidemiological mapping of onchocerciasis and LF, the assessment of operational and managerial challenges against the integration, and the evaluation of costs, benefits, and impacts on health systems.

Global collaboration towards onchocerciasis elimination

The elimination and eradication of infectious diseases require collaboration among a wide range of stakeholders at community, national, regional, and global levels. Every stakeholder has a different level of interests depending on expected costs and benefits associated with elimination efforts. The elimination of infectious diseases will be possible only if all stakeholders are willing to collaborate. A future research topic could be the evaluation of the feasibility of onchocerciasis elimination and eradication from a perspective of social choice and game theory. Specifically, this evaluation could focus on the identification of countries with the least interests in the elimination of onchocerciasis based on the predicted costs and benefits in this PhD research and the development and evaluation of potential policies to incentivize those countries.

Final conclusions

As the elimination of NTDs gained prominence in the global health agenda, there has been a need for the rigorous analysis of costs and benefits associated with the investment in elimination strategies and interventions. This research developed the investment case for onchocerciasis elimination and eradication in which potential elimination strategies were developed, and costs, benefits, and impacts on health systems were evaluated. The results could provide an evidence base for national and global policymakers' informed decisions. The methodologies could be applied to other future investment cases. This research also provides an insight on future research topics such as the integrated NTD interventions and the stakeholders' willingness to collaborate towards the elimination of infectious diseases.

Appendix 1. Supplementary Information for Chapter 3

Control, elimination, and eradication of river blindness: scenarios, timelines, and ivermectin treatment needs in Africa

Table S1. Population, onchocerciasis endemicity, feasibility concern for community-directed treatment with ivermectin (CDTi), start year and frequency of CDTi, treatment coverage, and predicted end year of CDTi for ongoing (as of November 2013) and potential new projects

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
Angola	Bengo	APOC	26,658	Hypo	None	2010	1	75%	2034-2059	2018	2018
Angola	Benguela	APOC	50,992	Hypo	None	2012	1	67%	2036-2061	2020	2020
Angola	Cuanza Norte	APOC	26,058	Hypo	None	2011	1	67%	2035-2060	2017	2017
Angola	Huila	APOC	239,930	Meso	None	2010	1	70%	2034-2059	2018	2018
Angola	KuandoKubango	APOC	413,646	Meso	None	2009	1	76%	2033-2058	2015	2015
Angola	LundaNorte	APOC	309,045	Meso	None	2009	1	62%	2033-2058	2017	2017
Angola	Lundasul	APOC	260,377	Meso	None	2009	1	69%	2033-2058	2017	2017
Angola	Moxico 1	APOC	272,116	Meso	None	2011	1	67%	2035-2060	2018	2018
Angola	NY Benguela	APOC	114,544	Hyper	None	2014	1	67%	Not targeted	2025	2025
Angola	NY Cuanza Norte	APOC	18,688	Hypo	None	2014	1	67%	Not targeted	2022	2022
Angola	NY Huila	APOC	23,189	Meso	None	2014	1	67%	Not targeted	2022	2022
Angola	NY LundaNorte	APOC	67,327	Hypo	None	2014	1	67%	Not targeted	2022	2022

[1]2012 population (source: APOC treatment database) was adjusted for population growth rates (UN (2013) World Population Prospects: The 2012 Revision. http://esa.un.org/wpp/Excel-Data/population.htm Accessed on 23 May 2014)

[2]APOC countries: non-endemic with highest nodule prevalence in adult males < 5%, hypo-endemic between 5% and 20%, meso-endemic between 20% and 40%, and hyper-endemic with 40% and above

Former OCP countries: non-endemic with <10% microfilariae prevalence in ages 5+, hypo-endemic between 10% to 40%, meso-endemic between 40% and 60%, and hyper-endemic with 60% and above

[3]Ongoing projects (as of November 2013): The first year with treatment coverage greater than 60% was used, as effective control of the disease requires the treatment coverage of 60% and above.
New projects: The start year was predicted based on APOC's strategic plan to focus on the onchocerciasis elimination for the next decade 2016-2025, the current epidemiology, and the current political situation.

[4] Six-monthly: only new projects in Ethiopia and Uganda where respective ministries of health announced six-monthly drug administration in new projects to bring them in line with ongoing projects

[5] APOC countries: average over 2010-2012 at project/country/regional levels, former OCP countries: latest available data or average at country level

[6] The lower bound is the expected end year without the assumption of possible CDTi extension for another 25 years due to insufficient treatment coverage, and the upper bound with the assumption. This assumption was applied to APOC countries except Equatorial Guinea that is known to have almost eliminated the disease and Mozambique that is endemic in limited border areas where less than 70,000 people live. The former OCP countries were also excluded from this assumption considering the level of transmission has decreased significantly due to CDTi implemented since the 1990s and the recent regional treatment coverage was around 80% on average.

[7]The control scenario was applied to projects with feasibility concerns. For these projects, the lower bound of the CDTi end year was expected without the assumption of possible CDTi extension for another 25 years due to insufficient treatment coverage, and the upper bound with the assumption.

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
Angola	NY Moxico 1	APOC	347,350	Hypo	None	2014	1	67%	Not targeted	2022	2022
Angola	P5Angola	APOC	264,252	Hypo	None	2015	1	67%	Not targeted	2023	2023
Angola	Uige	APOC	191,005	Meso	None	2014	1	67%	Not targeted	2023	2023
Angola	Zaire	APOC	14,407	Hypo	None	2014	1	67%	Not targeted	2021	2021
Benin	Benin	former OCP	3,585,280	Hyper	None	1990s	1	48%	2016	2016	2016
Burkina Faso	BF Bougouriba	former OCP	77,626	Hyper	None	1990s	1	84%	2016	2016	2016
Burkina Faso	BF LerabaComoe	former OCP	152,125	Hyper	None	2010	1	84%	2034	2021	2021
Burundi	Bururi	APOC	387,223	Meso	None	2008	1	75%	2032-2057	2014	2014
Burundi	Cibitoke-Bubanza	APOC	924,648	Meso	None	2006	1	79%	2030-2055	2014	2014
Burundi	Rutana	APOC	301,453	Hypo	None	2008	1	77%	2032-2057	2016	2016
Cameroon	Adamaoua 1	APOC	506,733	Hyper	None	2008	1	74%	2032-2057	2021	2021
Cameroon	Adamaoua 2	APOC	460,444	Hyper	None	2004	1	77%	2028-2053	2016	2016
Cameroon	Centre 1	APOC	467,973	Hyper	None	2003	1	78%	2027-2052	2024	2024
Cameroon	Centre 2	APOC	110,151	Hyper	None	2005	1	77%	2029-2054	2018	2018
Cameroon	Centre 3	APOC	355,666	Hyper	None	2004	1	77%	2028-2053	2017	2017
Cameroon	East	APOC	129,904	Hyper	None	2007	1	78%	2031-2056	2018	2018
Cameroon	Far North	APOC	307,244	Meso	None	2007	1	80%	2031-2056	2016	2016
Cameroon	Littoral 1	APOC	307,171	Hyper	None	2007	1	78%	2031-2056	2026	2026
Cameroon	Littoral 2	APOC	163,866	Hyper	None	2003	1	78%	2027-2052	2020	2020
Cameroon	Northern	APOC	688,951	Hyper	None	2004	1	78%	2028-2053	2021	2021
Cameroon	Northwest	APOC	895,057	Hyper	None	2005	1	78%	2029-2054	2017	2017
Cameroon	P20Cameroon	APOC	164,900	Hyper	None	2015	1	78%	2039-2064	2022	2022
Cameroon	P5Cameroon_forest	APOC	335,977	Hypo	None	2014	1	78%	Not targeted	2020	2020
Cameroon	P5Cameroon_forest_noloa	APOC	110,356	Hypo	None	2014	1	78%	Not targeted	2020	2020
Cameroon	P5Cameroon_savannah	APOC	1,194,396	Hypo	None	2014	1	78%	Not targeted	2020	2020
Cameroon	South	APOC	327,119	Hyper	None	2006	1	78%	2030-2055	2019	2019
Cameroon	South West 1	APOC	428,877	Hyper	None	2005	1	78%	2029-2054	2020	2020
Cameroon	South West 2	APOC	291,874	Hyper	None	2004	1	78%	2028-2053	2019	2019
Cameroon	Western	APOC	1,793,241	Hyper	None	2003	1	80%	2027-2052	2024	2024

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
CAR[8]	CAR combined project	APOC	1,943,659	Hyper	(post) conflict	2003	1	80%	2027-2052	2027-2052	2024
CAR	P20CAR	APOC	63,224	Hyper	(post) conflict	2016	1	80%	2040-2065	2040-2065	2034
CAR	P5CAR	APOC	143,609	Hypo	(post) conflict	2020	1	80%	Not targeted	Not targeted	2026
Chad	Chad	APOC	2,181,933	Hyper	None	2001	1	81%	2025-2050	2015	2015
Congo	Congo 1	APOC	904,556	Hyper	None	2007	1	81%	2031-2056	2016	2016
Congo	P20Congo	APOC	39,517	Hyper	None	2014	1	81%	2038-2063	2026	2026
Congo	P5Congo	APOC	530,726	Hypo	None	2014	1	81%	Not targeted	2020	2020
Côte d'Ivoire	Bandama	former OCP	1,008,980	Hyper	None	1990s	1	73%	2020	2020	2020
Côte d`Ivoire	CI Comoe	former OCP	622,485	Hyper	None	1990s	1	73%	2035	2023	2023
Côte d`Ivoire	CI Lower Sassandra	former OCP	350,025	Hyper	None	2014	1	73%	2038	2028	2028
Côte d`Ivoire	CI Upper Sassandra	former OCP	377,662	Hyper	None	1990s	1	73%	2020	2020	2020
DRC[9]	Bandundu	APOC	6,436	Hyper	(post) conflict	2005	1	82%	2029-2054	2029-2054	2021
DRC	Bas-Congo Kinshasa	APOC	1,523,869	Hyper	(post) conflict	2008	1	71%	2032-2057	2032-2057	2023
DRC	Butembo-Beni	APOC	946,872	Hyper	(post) conflict	2011	1	56%	2035-2060	2035-2060	2031
DRC	Equateur-Kiri	APOC	1,258,400	Hyper	(post) conflict	2009	1	79%	2033-2058	2033-2058	2022
DRC	Ituri-Nord	APOC	1,273,305	Hyper	(post) conflict	2009	1	71%	2033-2058	2033-2058	2030
DRC	Ituri-Sud	APOC	1,163,935	Hyper	(post) conflict	2012	1	71%	2036-2061	2036-2061	2036
DRC	Kasai	APOC	10,917,310	Hyper	None	2009	1	75%	2033-2058	2031	2031
DRC	Kasongo	APOC	1,367,616	Hyper	(post) conflict	2009	1	71%	2033-2058	2033-2058	2022
DRC	Katanga-Nord	APOC	635,388	Hyper	(post) conflict	2009	1	71%	2033-2058	2033-2058	2030
DRC	Katanga-Sud	APOC	703,780	Hyper	(post) conflict	2009	1	71%	2033-2058	2033-2058	2030
DRC	Lualaba	APOC	228,284	Hyper	(post) conflict	2008	1	80%	2032-2057	2032-2057	2024
DRC	Lubutu	APOC	339,104	Hyper	(post) conflict	2009	1	61%	2033-2058	2033-2058	2028
DRC	Masisi-Walikale	APOC	1,062,822	Hyper	(post) conflict	2010	1	71%	2034-2059	2034-2059	2032
DRC	Mongala	APOC	1,477,897	Hyper	(post) conflict	2009	1	78%	2033-2058	2033-2058	2030
DRC	NY Katanga-Nord	APOC	461,048	Meso	(post) conflict	2014	1	71%	Not targeted	2038-2063	2021
DRC	NY Lualaba	APOC	997,775	Hyper	(post) conflict	2014	1	71%	Not targeted	2038-2063	2031

[8] Central African Republic
[9] Democratic Republic of the Congo

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
DRC	NY Masisi-Walikale	APOC	55,387	Hyper	(post) conflict	2014	1	71%	2038-2063	2038-2063	2027
DRC	NY Rutshuru-Ngoma	APOC	8,621	Meso	(post) conflict	2014	1	71%	2038-2063	2038-2063	2023
DRC	NY Sankuru	APOC	476,028	Hyper	(post) conflict	2014	1	71%	Not targeted	2038-2063	2027
DRC	NY Ueles	APOC	161,944	Hyper	(post) conflict	2014	1	71%	2038-2063	2038-2063	2035
DRC	P20DRC	APOC	2,387,370	Hyper	(post) conflict	2016	1	71%	2040-2065	2040-2065	2037
DRC	P5DRC	APOC	7,591,705	Hypo	(post) conflict	2020	1	71%	Not targeted	Not targeted	2027
DRC	Rutshuru-Ngoma	APOC	669,404	Hyper	(post) conflict	2009	1	74%	2033-2058	2033-2058	2018
DRC	Sankuru	APOC	1,082,968	Hyper	(post) conflict	2007	1	82%	2031-2056	2031-2056	2028
DRC	Tshopo	APOC	1,617,757	Hyper	(post) conflict	2010	1	63%	2037-2062	2037-2062	2037
DRC	Tshuapa	APOC	1,441,333	Hyper	(post) conflict	2010	1	66%	2034-2059	2034-2059	2033
DRC	Ubangi-Nord	APOC	811,591	Hyper	(post) conflict	2011	1	71%	2037-2062	2037-2062	2037
DRC	Ubangi-Sud	APOC	1,368,969	Hyper	(post) conflict	2011	1	71%	2035-2060	2035-2060	2023
DRC	Ueles	APOC	1,596,501	Hyper	(post) conflict	2006	1	71%	2030-2055	2030-2055	2028
Equatorial Guinea	Bioko	APOC	88,252	Hyper	None	2007	1	71%	2031	2020	2020
Ethiopia	Assosa	APOC	579,207	Meso	None	2014	2	79%	Not targeted	2021	2021
Ethiopia	Bench-Maji	APOC	765,856	Hyper	None	2005	1	79%	2029-2054	2017	2017
Ethiopia	East Wellega	APOC	937,884	Meso	None	2006	1	79%	2030-2055	2015	2015
Ethiopia	Gambella	APOC	112,052	Hyper	None	2006	1	78%	2030-2055	2015	2015
Ethiopia	HoroGuduru	APOC	54,995	Meso	None	2014	2	79%	Not targeted	2021	2021
Ethiopia	Illubabor	APOC	793,275	Hyper	None	2004	1	82%	2028-2053	2017	2017
Ethiopia	Jimma	APOC	936,393	Meso	None	2004	1	83%	2028-2053	2015	2015
Ethiopia	Kaffa-Sheka	APOC	1,329,915	Hyper	None	2003	1	79%	2027-2052	2015	2015
Ethiopia	Kamashi	APOC	494,563	Hyper	None	2014	2	79%	2038-2063	2023	2023
Ethiopia	Metekel	APOC	169,262	Meso	None	2007	1	74%	2031-2056	2015	2015
Ethiopia	North Gondar	APOC	328,659	Meso	None	2004	1	74%	2028-2053	2015	2015
Ethiopia	NY East Wellega	APOC	300,211	Hyper	None	2014	2	79%	2038-2063	2022	2022
Ethiopia	NY West Wellega	APOC	304,914	Meso	None	2014	2	79%	Not targeted	2021	2021
Ethiopia	P20Ethiopia	APOC	348,726	Hyper	None	2014	2	79%	2038-2063	2022	2022
Ethiopia	P5Ethiopia	APOC	3,682,280	Hypo	None	2014	2	79%	Not targeted	2020	2020

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
Ethiopia	West Shewa	APOC	60,625	Hypo	None	2014	2	79%	Not targeted	2019	2019
Ethiopia	West Wellega	APOC	1,076,961	Hyper	None	2006	1	79%	2030-2055	2015	2015
Gabon	P5Gabon	APOC	85,468	Hypo	*Loa loa*coendemicity	2021	1	76%	Not targeted	Not targeted	2027
Ghana	Ghana Center	former OCP	91,065	Hyper	None	1990s	1	77%	2020	2020	2020
Ghana	Ghana North	former OCP	1,229,326	Hyper	None	1990s	1	77%	2018	2018	2018
Ghana	Ghana South CI border	former OCP	709,561	Hypo	None	2010	1	77%	2034	2015	2015
Ghana	Ghana South Rx	former OCP	431,415	Hypo	None	2010	1	77%	2034	2015	2015
Ghana	Ghana Tano new Rx	former OCP	74,115	Hypo	None	2015	1	77%	2039	2020	2020
Guinea	Guinea border	former OCP	2,384,879	Hyper	None	1990s	1	81%	2020	2020	2020
Guinea	Guinea Main	former OCP	946,807	Hyper	None	1990s	1	81%	2016	2016	2016
Guinea-Bissau	Guinea Bissau	former OCP	194,915	Hyper	None	1990s	1	75%	2016	2016	2016
Liberia	Northwestern	APOC	1,878,803	Meso	None	2009	1	77%	2033-2058	2016	2016
Liberia	Southeastern	APOC	528,362	Meso	None	2006	1	83%	2030-2055	2016	2016
Liberia	Southwestern	APOC	761,649	Meso	None	2007	1	77%	2031-2056	2014	2014
Malawi	Malawi Extension	APOC	1,282,457	Meso	None	2004	1	82%	2028-2053	2016	2016
Malawi	ThyoloMwanza	APOC	978,116	Meso	None	2004	1	83%	2028-2053	2015	2015
Mali	Mali	former OCP	5,145,734	Hyper	None	1990s	1	82%	2016	2016	2016
Mozambique	P20Mozambique	APOC	17,030	Meso	None	2015	1	76%	2039	2023	2023
Mozambique	P5Mozambique	APOC	49,746	Hypo	None	2015	1	76%	Not targeted	2022	2022
Nigeria	Adamawa	APOC	1,861,788	Hyper	None	2001	1	80%	2025-2050	2015	2015
Nigeria	AkwaIbom	APOC	31,875	Meso	None	2006	1	84%	2030-2055	2016	2016
Nigeria	Bauchi	APOC	1,907,526	Meso	None	2009	1	79%	2033-2058	2015	2015
Nigeria	Benue	APOC	3,761,997	Hyper	None	2007	1	77%	2031-2056	2019	2019
Nigeria	Borno	APOC	1,499,554	Meso	None	2006	1	83%	2030-2055	2015	2015
Nigeria	Cross River	APOC	1,359,649	Hyper	None	1999	1	81%	2023-2048	2015	2015
Nigeria	Edo Delta	APOC	1,748,040	Hyper	None	1999	1	80%	2023-2048	2015	2015
Nigeria	Ekiti	APOC	2,359,828	Meso	None	2004	1	76%	2028-2053	2015	2015
Nigeria	Enugu Anambra Ebony	APOC	2,597,471	Hyper	None	1999	1	80%	2023-2048	2015	2015
Nigeria	FCT	APOC	551,432	Meso	None	2004	1	82%	2028-2053	2016	2016

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
Nigeria	Gombe	APOC	2,072,712	Hyper	None	2006	1	82%	2030-2055	2017	2017
Nigeria	Imo Abia	APOC	1,431,900	Hyper	None	1999	1	80%	2023-2048	2017	2017
Nigeria	Jigawa	APOC	388,171	Hypo	None	2004	1	74%	2028-2053	2015	2015
Nigeria	Kaduna	APOC	3,016,022	Meso	None	2010	1	80%	2034-2059	2018	2018
Nigeria	Kano	APOC	1,076,195	Hyper	None	2000	1	81%	2024-2049	2016	2016
Nigeria	Kebbi	APOC	226,137	Hypo	None	2006	1	78%	2030-2055	2016	2016
Nigeria	Kogi	APOC	1,943,133	Hyper	None	1999	1	82%	2023-2048	2015	2015
Nigeria	Kwara	APOC	1,642,329	Hyper	None	2000	1	81%	2024-2049	2015	2015
Nigeria	Niger	APOC	2,887,036	Meso	None	2004	1	79%	2028-2053	2015	2015
Nigeria	Ogun	APOC	374,030	Meso	None	2003	1	82%	2027-2052	2015	2015
Nigeria	Ondo	APOC	1,487,782	Meso	None	2001	1	81%	2025-2050	2015	2015
Nigeria	Osun	APOC	1,755,255	Meso	None	2009	1	79%	2033-2058	2016	2016
Nigeria	Oyo	APOC	1,197,059	Meso	None	2011	1	80%	2035-2060	2018	2018
Nigeria	P20Nigeria	APOC	241,777	Hyper	None	2014	1	80%	2038-2063	2026	2026
Nigeria	P5Nigeria	APOC	5,847,463	Hypo	None	2014	1	80%	Not targeted	2020	2020
Nigeria	P5Nigeria	APOC	2,362,136	Hypo	None	2014	1	80%	Not targeted	2020	2020
Nigeria	Plateau Nassarawa	APOC	1,664,490	Meso	None	2000	1	82%	2024-2049	2015	2015
Nigeria	Plateau Nassarawa LF	APOC	1,685,205	Hyper	None	2000	1	80%	2024-2049	2015	2015
Nigeria	Taraba	APOC	1,810,936	Hyper	None	2009	1	82%	2033-2058	2020	2020
Nigeria	Yobe	APOC	669,776	Meso	None	2002	1	78%	2026-2051	2015	2015
Nigeria	Zamfara	APOC	310,839	Hypo	None	1999	1	78%	2023-2048	2016	2016
Senegal	Senegal	former OCP	187,405	Hyper	None	1990s	1	79%	2015	2015	2015
Sierra Leone	Sierra Leone	former OCP	3,319,643	Hyper	None	2008	1	77%	2032	2021	2021
South Sudan	East Bahr El Ghazal	APOC	619,344	Hyper	(post) conflict	2011	1	60%	2035-2060	2035-2060	2020
South Sudan	East Equatoria	APOC	1,100,863	Hyper	(post) conflict	2009	1	67%	2033-2058	2033-2058	2019
South Sudan	P20SouthSudan	APOC	31,012	Hyper	(post) conflict	2017	1	60%	2041-2066	2041-2066	2040
South Sudan	P5SouthSudan	APOC	853,648	Hypo	(post) conflict	2021	1	60%	Not targeted	Not targeted	2029
South Sudan	Upper Nile	APOC	576,858	Meso	(post) conflict	2010	1	56%	2034-2059	2034-2059	2018
South Sudan	West Bahr El Ghazal	APOC	3,338,305	Hyper	(post) conflict	2011	1	60%	2035-2060	2035-2060	2035

Country	Project	APOC/ former OCP	Population 2014[1]	Pre-control endemicity[2]	Feasibility concern	CDTi start year[3]	CDTi frequency per annum[4]	Treatment coverage[5]	CDTi end year		
									Control scenario[6]	Elimination scenario[7]	Eradication scenario
South Sudan	West Equatoria	APOC	787,420	Hyper	(post) conflict	2009	1	71%	2033-2058	2033-2058	2026
Sudan	P5Sudan	APOC	227,384	Hypo	None	2014	1	82%	Not targeted	2020	2020
Sudan	Sudan	APOC	214,782	Hypo	None	2008	1	82%	2032-2057	2016	2016
Sudan	Sudan Abu Hamed	APOC	214,782	Hypo	None	2008	1	82%	2032-2057	2016	2016
Tanzania	Kilosa	APOC	551,542	Meso	None	2004	1	80%	2028-2053	2015	2015
Tanzania	Mahenge	APOC	551,412	Hyper	None	2003	1	80%	2027-2052	2022	2022
Tanzania	Morogoro	APOC	394,691	Meso	None	2006	1	80%	2030-2055	2015	2015
Tanzania	P5Tanzania	APOC	1,000,102	Hypo	None	2015	1	81%	Not targeted	2021	2021
Tanzania	Ruvuma	APOC	435,723	Hyper	None	2002	1	81%	2026-2051	2023	2023
Tanzania	Tanga	APOC	341,837	Meso	None	2004	1	81%	2028-2053	2016	2016
Tanzania	Tukuyu	APOC	125,098	Meso	None	2001	1	80%	2025-2050	2015	2015
Tanzania	Tunduru	APOC	135,650	Hyper	None	2005	1	82%	2029-2054	2017	2017
Togo	Togo	former OCP	3,171,784	Hyper	None	1992	1	83%	2016	2016	2016
Uganda	P5Uganda	APOC	271,652	Hypo	None	1990s	2	75%	Not targeted	2022	2022
Uganda	Phase 1	APOC	425,538	Hyper	None	2001	1	75%	2025-2050	2015	2015
Uganda	Phase 2	APOC	827,960	Hypo	None	2000	1	75%	2024-2049	2016	2016
Uganda	Phase 3	APOC	1,527,173	Hyper	None	2003	1	75%	2027-2052	2027	2027
Uganda	Phase 4	APOC	864,444	Hyper	None	1999	1	75%	2023-2048	2015	2015
Uganda	Phase 5	APOC	556,618	Hyper	None	2012	2	75%	2036-2061	2023	2023

Table S2. Summary of treatment coverage and distribution parameters for probabilistic sensitivity analysis

Country	Average[10]	Standard deviation	Beta distribution[11]	
			Alpha	Beta
APOC countries				
Angola	67%	0.11	12.36	5.97
Burundi	77%	0.04	105.52	31.48
Cameroon	78%	0.05	62.60	17.72
Central African Republic	80%	0.03	167.75	40.98
Chad	81%	0.00	124,658.19	29,240.81
Congo	81%	0.02	207.63	47.39
Democratic Republic of the Congo	71%	0.13	7.47	3.12
Equatorial Guinea	71%	0.00	292,469.03	119,749.47
Ethiopia	79%	0.04	77.58	20.87
Liberia	77%	0.10	13.31	3.89
Malawi	83%	0.00	5,112.61	1,065.77
Nigeria	80%	0.04	83.33	21.00
South Sudan	60%	0.12	8.72	5.78
Sudan	82%	0.03	167.06	37.92
Tanzania	81%	0.01	868.01	210.26
Uganda	75%	0.11	10.48	3.46
APOC	**76%**	**0.06**	**35.04**	**10.81**
Country	**Latest[12]**	**Standard deviation[13]**	**Beta distribution**	
			Alpha	**Beta**
Former OCP countries				
Benin	48%	0.05	51.42	55.48
Burkina Faso	84%	0.08	15.56	3.05
Côte d'Ivoire	84%	0.08	15.56	3.05
Ghana	73%	0.07	26.67	10.07
Guinea	73%	0.07	26.67	10.07
Guinea-Bissau	73%	0.07	26.67	10.07
Mali	73%	0.07	26.67	10.07
Senegal	77%	0.08	21.83	6.37
Sierra Leone	80%	0.08	18.90	4.64
Togo	77%	0.08	21.83	6.37
Former OCP	**74%**	**0.10**	**13.09**	**4.58**

[10]The average treatment coverage over 2010-2012

[11] Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\ \bar{v} < \bar{x}(1-\bar{x}),$$

where $\bar{x}$ *is a sample mean,* $\bar{v}$ *is a sample variance*

[12]A provisional database for the former OCP countries had only the latest treatment coverage.

[13] The standard deviation was assumed to be 10% of the treatment coverage.

Figure S1. Beta distributions for treatment coverage for endemic African countries

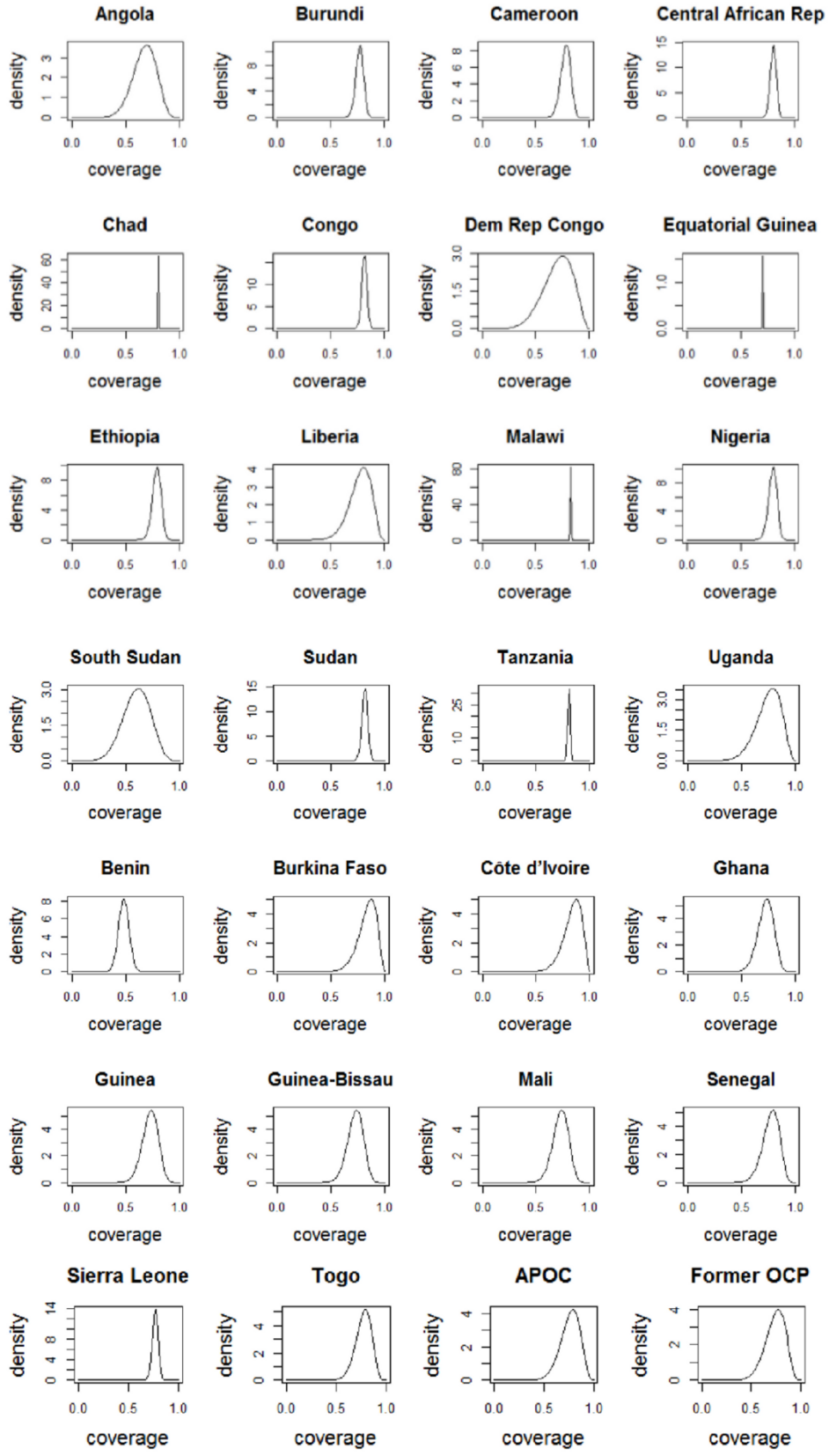
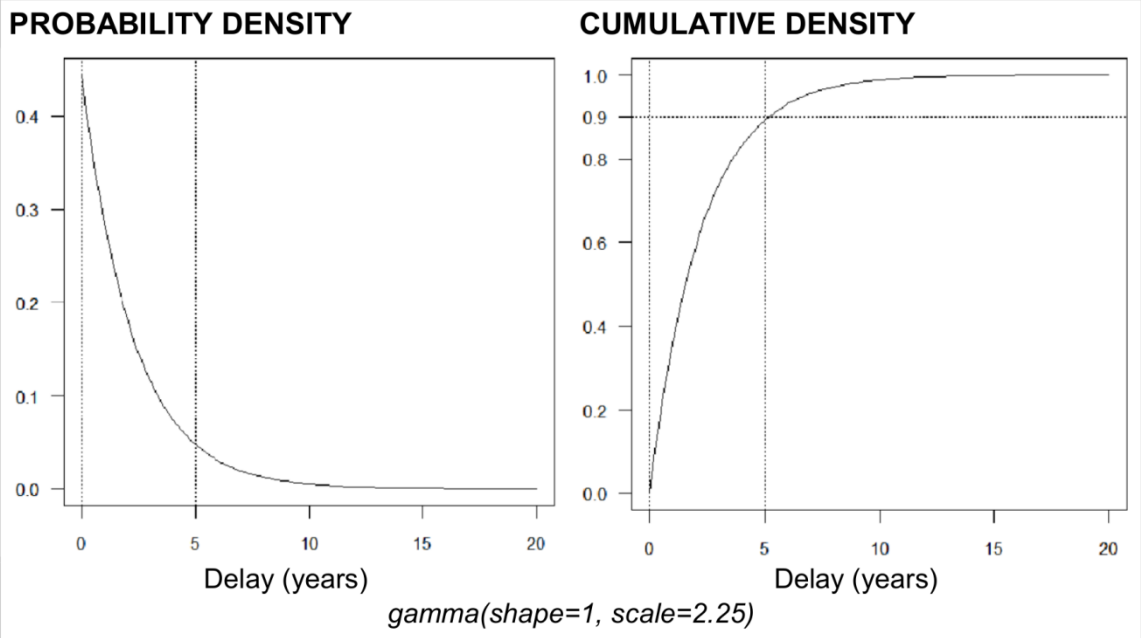


Figure S2. Probability and cumulative density graphs for the gamma distribution applied to the delay in starting and ending CDTi



Appendix 2. Supplementary Information for Chapter 4

Financial and economic costs of the elimination and eradication of onchocerciasis (river blindness) in Africa

Methodological details on the micro-costing method, the uncertainty analysis, and the literature review

I. Micro-costing method

1. Geographic unit for costing: project

A unit for micro-costing was a project, considering budgets and operational decisions for community-directed treatment with ivermectin (CDTi) are made at project level in endemic African regions [15]. We used data available in Kim et al. (S1 Table in [6]) to identify the list of projects and the demographic and epidemiological characteristics of each project. The data set included population living in endemic areas, pre-control endemicity, feasibility concerns, CDTi start year, CDTi rounds per year, expected treatment coverage, and predicted CDTi end year for the control, elimination, and eradication scenarios.

2. Cost estimation for a project

To estimate total costs for a project, we used a micro-costing method with six steps.

Step 1. Identification of ingredients

Step 1	Cost category	Cost item	Type	Unit cost ($UC)	Unit quantity (UQ)				
					2013	2014	–	2044	2045
Under five categories, each cost item is defined with the type, the unit cost, and the time-variant unit quantity.	CDTi	1	Financial	1	1	1		1	1
	Surveillance	2		2	2	2		2	2
	Capital	3		3	3	3		3	3
	Administrative	⋮		⋮	⋮	⋮		⋮	⋮
	(post) conflict	52	Economic	52	52	52		52	52
		53		53	53	53		53	53
		54		54	54	54		54	54

We defined the key activities and resources required for onchocerciasis elimination and eradication under five categories (Table S3) with reference to an APOC report of the technical consultative committee [90], an APOC protocol for epidemiological surveillance, and a guide for post-treatment epidemiological and entomological surveillance (developed for the Onchocerciasis Elimination Program for the Americas) [69] . Based on the key activities and resources, we identified 54 cost items, and defined their characteristics including the type (financial/economic), the unit cost, and the unit quantity. As resource utilization, represented by the unit quantity, changes depending on epidemiological trends, we defined relevant phases for each cost item, among the phase 1 for

treatment, the phase 2 for the confirmation of elimination, and the phase 3 for post-elimination surveillance (Table S4).

Table S3. Key activities and required resources

Item	Definition	Resources
Category 1 Community-directed treatment with ivermctin (CDTi)		
Advocacy/sensitization/mobilization		
Advocacy	Hold meetings at regional/province/state level to create and sustain awareness	Per diem, travel expenses, facility rent, printing
Sensitization and mobilization	Educate, sensitize, and mobilize communities to achieve high treatment coverage	Community volunteers, per diem, travel expenses, media announcement costs, mobilization material (town criers, banners, printing)
Development and production of Information/Education/Communication (IEC) material	Develop (every five years) and print (every year) training manuals and IEC material	Per diem, travel expenses, printing
Supervision/monitoring/evaluation		
Supervision (first 6 years)	Supervise at district/health facility/community level to ensure smooth start of CDTi	Per diem, travel expenses
Assistance for supervisory visits (7th year and onward)	Regular visits to districts, health facilities and communities by coordinators, epidemiologists, data managers, and accountants	Per diem, travel expenses
Monitoring and evaluation	Track and evaluate CDTi performance	Per diem, travel expenses
Review meeting	Hold regular meetings at state and district levels	Per diem, travel expenses
Data management	Build database, enter, and validate data	Per diem, travel expenses
Community self-monitoring	Track CDTi performance, report to health workers	Community volunteers, travel expenses
Training		
Training of trainers and health workers	Develop capacity of trainers and health workers	Per diem, travel expenses, facility rent, printing, stationery
Training of community volunteers (community drug distributors)	Train community volunteers to implement CDTi	Per diem, travel expenses, printing, stationery
Training of community leaders	Educate community leaders on the concept of and the need for CDTi	Per diem, travel expenses, printing, stationery
Drug distribution/management of severe adverse events		
Community registration	Register communities	Community volunteers, registration forms
Census	Conduct census	Community volunteers
Delivery of drugs	Deliver drugs from manufacturer to country	Drug purchase cost, shipping cost (insurance, freight)
Drug administration in areas without highly endemic *Loa loa*	Community-directed treatment with ivermectin	Community volunteers
Drug administration in areas with highly endemic *Loa loa*	A test-and-treat approach with doxycycline	Diagnostic tools for microscopic testing[i], health workers
Management of severe adverse events	Purchase drugs, treat minor adverse events, refer people with severe adverse events to health facilities	Community volunteers, drugs
Category 2 Surveillance		
Supervision/monitoring/evaluation		
Supervisory visit	Regular visit to sentinel sites by coordinators, epidemiologists, entomologists, data managers, and accountants	Per diem, travel expenses
Monitoring and evaluation	Track and evaluate surveillance performance	Per diem, travel expenses
Review meeting	Hold regular meetings at state and district levels	Per diem, travel expenses
Data management	Build database, enter and validate data	Per diem, travel expenses
Training		
Training of trainers and health workers	Develop capacity of trainers and health workers for epidemiological and entomological surveillance	Per diem, travel expenses, facility rent, printing, stationery
Training of fly/larva-catchers	Train fly/larva-catchers	Per diem, travel expenses, printing, stationery

Item	Definition	Resources
Training of community leaders	Educate community leaders on the concept of and the need for surveillance	Per diem, travel expenses, printing, stationery
Sampling		
Epidemiological sampling by health workers	Conduct skin snip	Per diem and travel expenses for skin-snipper, laboratory technician, and census clerk, field supplies[ii]
Entomological sampling by fly/larva-catchers	Collect aquatic (to determine catching sites) and adult stages of black flies	Perdiem for fly/larva-catchers, field supplies[iii]
Delivery of samples		
Delivery of samples to laboratory	Carry skin-snip samples to laboratory	Travel expenses for the survey team
Delivery of samples to laboratory	Send fly/larva samples to MDSC(Multi Disease Surveillance Center) in Burkina Faso[iv]	Transportation expenses, courier service fee
Laboratory testing		
Epidemiological laboratory testing	Test skin-snip samples in laboratory	Salary for laboratory technicians, laboratory supplies[v]
Entomological laboratory testing	Test fly/larva samples	Salary for MDSC laboratory technicians[vi]
Category 3 Capital goods[vii]		
Vehicle	Vehicle with 6 years of useful time	Vehicle
Motorcycle	Motorcycle with 6 years of useful time	Motorcycle
Bicycle	Bicycle with 6 years of useful time	Bicycle
IT equipment	IT equipment with 6 years of useful time	Computer, fax, printer, photocopier, scanner, projector, camera, TV, DVD reader
Power supply equipment	Power supply equipment with 6 years of useful time	Generator, uninterruptible power supply
Category 4 Administrative costs		
Maintenance of vehicle	Maintenance of vehicles	Technician's service fee
Maintenance of motorcycle	Maintenance of motorcycles	Technician's service fee
Office supplies	Stationery	Stationery
Communication	Telephone, internet, courier	Fee for telephone, internet, and courier
Salary top-ups (first 6 years)	Provide salary top-ups to health workers for the first 6 years to stabilize new projects	Salary top-ups
Other administration	Other administrative costs	Bank charges, other administrative costs
Category 5 Financial support for treatment and surveillance in (post) conflict endemic areas		
Financial support for treatment and surveillance in (post) conflict endemic areas	Strengthen infrastructure, human capacity, and monitoring and evaluation system, treat internally displaced people	Funding for the relevant activities

i,v 1ml size test tube, binocular microscope, blood slids, hypodermic syringe and needle, micro pipette with disposable tips, microtitration trays, saline solution, slide trays; the useful time of non-disposable items is assumed to be six years.
ii 2 liters of distilled water, 200 glass slides, 3 instrument trays, 4 slide trays each holding 3 glass slides, liquid detergent, butane burning stove, dropper bottle, aluminium pressure sterilizer, cotton swabs soaked with alcohol, curved tweezer, holth punch, lancets, scissors, sterilizer forcepts; the useful time of non-disposable items is assumed to be six years.
iii aspirators, bottles; the useful time of these supplies is assumed to be six years.
iv,vi Exceptional countries were Ethiopia, Uganda, and Sudan that were identified to conduct entomological tests in their own laboratories.
vii Six years of useful time is assumed following the replacement policy specified in a Burundi's budget document

Table S4. Characteristics of cost items: unit cost, unit quantity, relevant phase, and type

ID	Cost item	Unit cost	Unit quantity	Phase[i]			Financial/ economic
				1	2	3	
Category 1 Community-directed treatment with ivermectin							
Advocacy/sensitization/mobilization							
1	Advocacy	Costs for resources per project	1	v	v		Financial
2	Sensitization	Costs for resources per project	1	v	v		Financial
3	Mobilization	Costs for resources per person	Population in a project area	v	v		Financial
4	Support for mobilization from community volunteers	Opportunity cost per volunteer-day	5.5days[97]*No. of volunteers*CDTi rounds/year	v	v		Economic
5	Development of IEC material	Costs for resources per project	1	v	v		Financial
6	Production of IEC material	Costs for resources per person	Population in a project area	v	v		Financial
Supervision/monitoring/evaluation							
7	Supervision (first 6 years)	Costs for resources per project	1	v			Financial
8	Assistance for supervisory visits (7th year+)	Costs for resources per project	1	v	v		Financial
9	Monitoring	Costs for resources per CDTi round	Number of CDTi rounds per year	v	v		Financial
10	Evaluation	Costs for resources per CDTi round	Number of CDTi rounds per year	v	v		Financial
11	Review meeting	Costs for resources per project	1	v	v		Financial
12	Data management	Costs for resources per project	1	v	v		Financial
13	Community self-monitoring	Costs for resources per person	Population in a project area	v	v		Financial
Training							
14	Training of trainers and health workers	Costs for resources per health worker	No. of health workers	v			Financial
15	Training of community volunteers	Costs for resources per volunteer	No. of volunteers	v			Financial
16	Training of community leaders	Costs for resources per community	No. of communities	v			Financial
Drug distribution							
17	Community registration	Costs for resources per community	No. of communities	v			Financial
18	Census	Opportunity cost per volunteer-day	4.6days[97]*No. of volunteers*CDTi rounds/year	v			Economic
	Drug delivery and administration in areas without highly endemic *Loa loa* (19, 20)						
19	Delivery of ivermectin	Opportunity cost per treatment	No. of treatments	v			Economic
20	Ivermectin administration	Opportunity cost per volunteer-day	17.8days[97]* No. of volunteers*CDTi rounds/year	v			Economic
	Drug delivery and administration in areas with highly endemic *Loa loa* (21, 22)						
21	Diagnostic tools	Purchase cost per set of diagnostic tools (annuitized)	1	v			Financial
22	Delivery and administration of doxycycline	Costs per 6-week treatment	No. of treatments	v			Financial
23	Management of severe adverse events	Costs for resources per project	1	v			Financial
Category 2 Surveillance[ii]							
Supervision/monitoring/evaluation							
24	Supervisory visit	Costs for resources per project	1	v	v	v	Financial
25	Monitoring	Costs for resources per project	1	v	v	v	Financial
26	Evaluation	Costs for resources per project	1	v	v	v	Financial
27	Review meeting	Costs for resources per project	1	v	v	v	Financial
28	Data management	Costs for resources per project	1	v	v	v	Financial
Training							
29	Training of trainers and health workers	Costs for resources per	No. of health workers	v	v	v	Financial

ID	Cost item	Unit cost	Unit quantity	Phase[i]			Financial/ economic
				1	2	3	
		health worker					
30	Training of fly/larva catchers	Costs for resources per flycatcher	No. of fly/larva -catchers (4 per catching site)*No. of catching sites		v	v	Financial
31	Training of community leaders	Costs for resources per community	No. of communities	v	v	v	Financial
Sampling and laboratory testing							
	Epidemiological survey sampling						
32	Surveillance trip transportation	Transportation costs per person-day per site	No. of survey workers(3)*2days*No. of survey sites	v	v	v	Financial
33	Personnel	Personnel costs per person-day per site	No. of survey workers(3)*2days*No. of survey sites	v	v	v	Financial
34	Field supplies	Purchase cost per set of supplies (annuitized)	1	v	v	v	Financial
	Entomological survey sampling						
35	Personnel	Personnel costs per person-day per site	No. of fly/larva catchers(4)*16days (4 days/month and 4 months)*No. of catching sites		v	v	Financial
36	Field supplies	Purchase cost per set of supplies per person-day (annuitized)	No. of fly/larva catchers(4)*16days (4 days/month and 4 months)*No. of catching sites		v	v	Financial
	Delivery of samples						
37	Delivery of samples from villages to laboratory	Transportation costs per site	No. of survey sites	v	v	v	Financial
38	Delivery of samples from catching site to health facility	Transportation costs per site	No. of fly/larva catchers(4)*4 (1 delivery/month and 4 months)*No. of catching sites		v	v	Financial
39	Delivery of samples from health facility to MSDC	Courier fee per parcel	1		v	v	Financial
	Epidemiological laboratory testing						
40	Personnel	Personnel costs per person-day per site	No. of technicians (1)* 2days*No. of survey sites	v	v	v	Financial
41	Laboratory supplies	Purchase cost per set of supplies (annuitized)	1	v	v	v	Financial
	Entomological laboratory testing						
42	Personnel	Personnel costs per technician-day per site	No. of technicians (6)[iii]*22days for testing*No. of catching sites		v	v	Financial
Category 3 Capital goods[iv]							
43	Vehicle	Purchase cost per vehicle (annuitized)	1	v	v	v	Financial
44	Motorcycle	Purchase cost per motorcycle (annuitized)	No. of districts	v	v	v	Financial
45	Bicycle	Purchase cost per bicycle (annuitized)	No. of communities	v	v	v	Financial
46	IT equipment	Purchase cost per set of equipment (annuitized)	1	v	v	v	Financial
47	Power supply equipment	Purchase cost per set of equipment (annuitized)	1	v	v	v	Financial
Category 4 Administrative costs							
48	Maintenance of vehicle	Maintenance costs per vehicle	No. of vehicles	v	v	v	Financial
49	Maintenance of motorcycle	Maintenance costs per motorcycle	No. of motorcycles	v	v	v	Financial
50	Office supplies	Costs for resources per project	1	v	v	v	Financial
51	Communication	Costs for resources per project	1	v	v	v	Financial
52	Salary top-ups (first 6 years)	Costs for resources per project	1	v			Financial
53	Other administration	Costs for resources per project	1	v	v	v	Financial
Category 5 Financial support for MDA and surveillance in (post) conflict endemic areas							
54	Support for CDTi and surveillance in (post) conflict endemic areas	Costs for resources for entire (post) conflict areas	1	v	v	v	Financial

i Phase 1: intervention; Phase 2: confirmation of elimination; Phase 3: post-elimination

ii We assumed that supervisory visit, monitoring, evaluation, review meeting, data management, and training (ID:24-31) would be done only in the years when either epidemiological or entomological surveillance is conducted.

ID	Cost item	Unit cost	Unit quantity	Phase[i]			Financial/ economic
				1	2	3	

iii 5 technicians per month = 10,000 flies per catching site/100 flies per technician-day/22 working days per month; 1 additional technician per month for larva-testing to identify species.
iv Capital costs for diagnostic and laboratory testing tools are excluded; instead included in CDTi and surveillance cost items.

As the main sources to estimate unit costs, we used approved budgets for 67 of ongoing 112 onchocerciasis projects (as of November 2013) in sub-Saharan Africa (Table S5), which were made available by APOC. The capital costs were annuitized with 3% over the useful time that was assumed to be six years based on the capital-goods replacement policy specified in Burundi's budget documents. For projects without available budgets, we used the national average unit costs or, if there was no national average, the regional average across available national averages for endemic African countries (Table S5). For economic unit costs, we used agriculture value added per worker as an opportunity cost of community volunteers' unpaid time, considering most of volunteers are farmers in remote rural areas. For three countries for which agriculture value added was unavailable, we used the regional average for sub-Saharan Africa (developing only) (Table S6). As an opportunity cost of donated ivermectin, we used $1.5054 per treatment based on the suggested drug price ($1.5 per treatment) by Merck before their ivermectin donation was decided [121] and the freight and insurance cost ($0.0054 per treatment) [93]. To estimate the unit quantity for each cost item, we identified the determinants of unit quantities. The determinants were population living in a project area, the number of CDTi rounds per year, the number of treatments, the number of volunteers, the number of volunteering days, the number of health workers, the number of districts, the number of communities, the number of survey sites, the number of survey team members, the number of survey days, the number of fly-catching sites, the number of fly-catchers, the number of catching days, and the number of laboratory technicians (Table S4). Among these, time variant determinants were population living in a project area, the number of treatments, the number of volunteers, and the number of health workers. To adjust for time variation, we adjusted population living in a project area for population growth rates over 2013−2045[55]. We estimated the number of treatments by multiplying the population adjusted for growth rates with the expected treatment coverage and the CDTi rounds per year. To estimate the number of volunteers for CDTi, we multiplied the population adjusted for population growth rates with the ratio of volunteers for the years of the treatment phase. To estimate

the number of health workers, we multiplied the population adjusted for population growth rates with the ratio of health workers for the treatment phase and, in the post-treatment phase, for the years when surveillance is conducted. Projects without budgets available had no information on the ratio of volunteers over population, the ratio of health workers over population, the population per district, and the population per community. For these projects, we used the national averages or, if there was no national average, the regional average across available national averages for endemic African countries (Table S7).

Table S5. Unit costs for the countries with budgets available, average (standard deviation)

ID	Cost items	Unit	Angola	Burundi	Cameroon	Central African Republic	Chad	Congo	Eq. Guinea[+]	Ethiopia	Liberia	Malawi	Nigeria	South Sudan	Tanzania	Uganda	Average[*]
	Number of projects with budgets/total (as of November 2013)		7/8	3/3	15/15	1/1[#]	1/1[%]	1/1	1/1	2/9	3/3	2/2[@]	18/28	5/5	3/7	5/5	
Category 1. Community-directed treatment with ivermectin																	
Advocacy/sensitization/mobilization																	
1	Advocacy	/project	$7,312 ($4,788)	$4,611 ($4,840)	$6,930 ($5,371)	NA	$5,059 ($1,533)	$6,328 ($0)	$1,700 ($0)	$1,097 ($234)	$2,638 ($1,525)	$259 ($192)	$4,037 ($3,895)	NA	$13,216 ($1,505)	$1,336 ($1,231)	$4,544 ($3,624)
2	Sensitization	/project	$7,772 ($5,466)	$6,436 ($4,619)	$5,143 ($6,267)	$677 ($0)	$4,368 ($2,556)	$8,688 ($0)	$1,440 ($0)	$2,520 ($1,624)	$4,566 ($2,985)	$672 ($237)	$5,088 ($4,480)	$3,356 ($1,010)	$3,094 ($786)	$805 ($475)	$3,902 ($2,591)
3	Mobilization	/person	$0.016 ($0.019)	$0.007 ($0.005)	$0.014 ($0.024)	$0.010 ($0.010)	$0.046 ($0.027)	$0.002 ($0.000)	NA	$0.010 ($0.002)	$0.008 ($0.009)	$0.001 (>$0.000)	$0.006 ($0.005)	$0.010 ($0.006)	$0.035 ($0.011)	$0.003 ($0.001)	$0.013 ($0.013)
4	Support for mobilization from community volunteers[a]	/volunteer/day	$2.105 (NA)	$0.390 (NA)	$0.921 (NA)	$0.998 (NA)	$0.570 (NA)	$0.409 (NA)	$12.327 (NA)	$0.869 (NA)	$0.616 (NA)	$0.294 (NA)	$2.317 (NA)	$0.536 (NA)	$0.643 (NA)	$0.548 (NA)	$1.682 ($3.124)
5	Development of IEC material	/project	NA	NA	NA	NA	NA	NA	NA	$2,200 ($1,697)	$4,532 ($99)	NA	$1,889 ($1,566)	NA	NA	$382 ($0)	$2,250 ($1,716)
6	Production of IEC material	/person	$0.177 ($0.241)	NA	$0.043 ($0.049)	NA	NA	$0.015 ($0.000)	NA	$0.009 ($0.003)	$0.028 ($0.020)	$0.039 ($0.048)	$0.008 ($0.007)	$0.023 ($0.009)	NA	$0.006 ($0.004)	$0.039 ($0.053)
Supervision/monitoring/evaluation																	
7	Supervision (first 6 years)	/project	$11,269 ($10,754)	$2,945 ($2,406)	$36,398 ($42,103)	$1,444 ($1,178)	$23,152 ($1,972)	NA	NA	$42,949 ($24,934)	$7,074 ($3,407)	$7,822 ($9,155)	$8,367 ($8,325)	$10,930 ($7,595)	$49,520 ($15,981)	$14,384 ($0)	$18,021 ($16,253)
8	Assistance for supervisory visits (7th year+)	/project	$4,000 ($1,414)	$3,001 ($2,434)	$2,460 ($1,098)	NA	$635 ($352)	$2,489 ($0)	$1,450 ($0)	NA	NA	$1,253 ($655)	$1,702 ($1,480)	$1,500 ($0)	NA	$2,498 ($566)	$2,099 ($981)
9	Monitoring	/CDTi round	$5,203 ($4,630)	$1,617 ($19)	$10,482 ($7,449)	NA	$1,468 ($676)	NA	NA	$375 ($177)	$1,735 ($17)	$4,963 ($5,201)	$3,135 ($4,353)	NA	NA	NA	$3,622 ($3,259)
10	Evaluation	/CDTi round	NA	$3,585 ($0)	NA	NA	NA	NA	NA	NA	NA	$4,432 ($4,309)	NA	NA	NA	NA	$4,008 ($599)
11	Review meeting	/project	$5,293 ($4,031)	$4,037 ($0)	$16,796 ($24,483)	NA	$7,787 ($3,049)	NA	$1,419 ($0)	$13,600 ($936)	$2,573 ($889)	$3,986 ($3,978)	$7,375 ($6,721)	$3,488 ($561)	$13,409 ($1,214)	$1,191 ($0)	$6,746 ($5,206)
12	Data management	/project	$1,400 ($0)	$6,793 ($9,598)	$5,574 ($7,273)	NA	$175 ($207)	$1,463 ($0)	$800 ($0)	NA	NA	$1,344 ($540)	$975 ($2,220)	NA	NA	$2,258 ($2,210)	$2,309 ($2,287)
13	Community self-monitoring	/person	$0.049 ($0.060)	$0.004 ($0.002)	$0.014 ($0.006)	NA	$0.066 ($0.019)	$0.002 ($0.000)	NA	$0.025 ($0.018)	$0.002 ($0.001)	$0.006 ($0.005)	$0.006 ($0.006)	$0.005 ($0.002)	NA	$0.004 ($0.004)	$0.017 ($0.022)
Training																	
14	Training of trainers and health workers	/health worker	$132 ($57)	$47 ($31)	$140 ($123)	$53 ($0)	$81 ($0)	$16 ($0)	NA	$1,179 ($275)	$48 ($19)	$1 ($0)	$8 ($6)	$107 ($24)	$579 ($109)	$6 ($1)	$184 ($335)
15	Training of community volunteers	/volunteer	$20 ($7)	$3 ($1)	$9 ($7)	NA	$11 ($8)	$2 ($0)	$5 ($0)	$18 ($1)	$4 ($2)	$2 ($2)	$3 ($3)	$8 ($5)	$13 ($6)	$1 ($2)	$8 ($6)
16	Training of community leaders	/community	$15 ($13)	$18 ($5)	$9 ($5)	NA	$5 ($0)	$12 ($0)	NA	$23 ($17)	NA	$0.350 ($0.003)	$5 ($6)	$4 ($3)	NA	$2 ($1)	$9 ($7)
Drug distribution																	
17	Community registration	/community	$11 ($11)	$37 ($0)	$14 ($11)	$4 ($7)	$8 ($2)	$1 ($0)	$15 ($0)	$12 ($1)	$3 ($1)	$4 ($5)	$9 ($28)	$34 ($15)	$10 ($5)	$2 ($0)	$12 ($11)

ID	Cost items	Unit	Angola	Burundi	Cameroon	Central African Republic	Chad	Congo	Eq. Guinea[+]	Ethiopia	Liberia	Malawi	Nigeria	South Sudan	Tanzania	Uganda	Average[*]
18	Census[b]	/volunteer/day	$2.105 (NA)	$0.390 (NA)	$0.921 (NA)	$0.998 (NA)	$0.570 (NA)	$0.409 (NA)	$12.327 (NA)	$0.869 (NA)	$0.616 (NA)	$0.294 (NA)	$2.317 (NA)	$0.536 (NA)	$0.643 (NA)	$0.548 (NA)	$1.682 ($3.124)
	Drug delivery and administration in areas without epidemiological challenges (19, 20)																
19	Delivery of ivermectin	/treatment	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 (NA)	$1.505 ($0.000)
20	Ivermectinadministration[c]	/volunteer/day	$2.105 (NA)	$0.390 (NA)	$0.921 (NA)	$0.998 (NA)	$0.570 (NA)	$0.409 (NA)	$12.327 (NA)	$0.869 (NA)	$0.616 (NA)	$0.294 (NA)	$2.317 (NA)	$0.536 (NA)	$0.643 (NA)	$0.548 (NA)	$1.682 ($3.124)
	Drug delivery and administration in areas with epidemiological challenges[d] (21, 22)																
21	Diagnostic tools (annuitized)	/set	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 ($0)
22	Delivery and administration of doxycycline	/6-week treatment	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 (NA)	$2.500 ($0.000)
23	Management of severe adverse events	/project	$1,360 ($381)	$1,070 ($840)	$5,329 ($8,271)	NA	NA	$175 ($0)	$1,275 ($0)	$2,465 ($0)	$13,195 ($4,185)	NA	$3,245 ($2,266)	$544 ($345)	NA	$1,277 ($0)	$2,993 ($3,888)
Category 2. Surveillance																	
Supervision/monitoring/evaluation																	
24	Supervisory visit	/project	$4,000 ($1,414)	$3,001 ($2,434)	$2,460 ($1,098)	NA	$635 ($352)	$2,489 ($0)	$1,450 ($0)	NA	NA	$1,253 ($655)	$1,702 ($1,480)	$1,500 ($0)	NA	$2,498 ($566)	$2,099 ($981)
25	Monitoring	/project	$5,203 ($4,630)	$1,617 ($19)	$10,482 ($7,449)	NA	$1,468 ($676)	NA	NA	$375 ($177)	$1,735 ($17)	$4,963 ($5,201)	$3,135 ($4,353)	NA	NA	NA	$3,622 ($3,259)
26	Evaluation	/project	NA	$3,585 ($0)	NA	NA	NA	NA	NA	NA	NA	$4,432 ($4,309)	NA	NA	NA	NA	$4,008 ($599)
27	Review meeting	/project	$5,293 ($4,031)	$4,037 ($0)	$16,796 ($24,483)	NA	$7,787 ($3,049)	NA	$1,419 ($0)	$13,600 ($936)	$2,573 ($889)	$3,986 ($3,978)	$7,375 ($6,721)	$3,488 ($561)	$13,409 ($1,214)	$1,191 ($0)	$6,746 ($5,206)
28	Data management	/project	$1,400 ($0)	$6,793 ($9,598)	$5,574 ($7,273)	NA	$175 ($207)	$1,463 ($0)	$800 ($0)	NA	NA	$1,344 ($540)	$975 ($2,220)	NA	NA	$2,258 ($2,210)	$2,309 ($2,287)
Training																	
29	Training of trainers and health workers	/health worker	$132 ($57)	$47 ($31)	$140 ($123)	$53 ($0)	$81 ($0)	$16 ($0)	NA	$1,179 ($275)	$48 ($19)	$1 ($0)	$8 ($6)	$107 ($24)	$579 ($109)	$6 ($1)	$184 ($335)
30	Training of fly-catchers[e]	/fly-catcher	$20 ($7)	$3 ($1)	$9 ($7)	NA	$11 ($8)	$2 ($0)	$5 ($0)	$18 ($1)	$4 ($2)	$2 ($2)	$3 ($3)	$8 ($5)	$13 ($6)	$1 ($2)	$8 ($6)
31	Training of community leaders	/community	$15 ($13)	$18 ($5)	$9 ($5)	NA	$5 ($0)	$12 ($0)	NA	$23 ($17)	NA	$0.350 ($0.003)	$5 ($6)	$4 ($3)	NA	$2 ($1)	$9 ($7)
Sampling and laboratory testing																	
	Epidemiological survey sampling																
32	Surveillance trip transportation[f]	/person/day/site	$52 ($109)	$14 ($18)	$32 ($56)	$9 ($2)	$6 ($0)	NA	NA	$7 ($1)	$21 ($3)	NA	$30 ($44)	NA	NA	NA	$21 ($16)
33	Personnel[g]	/person/day/site	$64 ($25)	$10 ($6)	$25 ($34)	$6 ($0)	$25 ($0)	$1 ($0)	$1 ($0)	$13 ($3)	$3 ($2)	$4 ($2)	$17 ($15)	$19 ($17)	NA	$8 ($10)	$15 ($17)
34	Field supplies (annuitized)[h]	/set	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 (NA)	$68 ($0)
	Entomological survey sampling																
35	Personnel[i]	/person/day/site	$7.929 ($4.046)	$1.449 ($0.503)	$3.087 ($1.431)	NA	$1.148 ($0.000)	NA	NA	$2.500 ($0.707)	$1.000 ($0.000)	$1.468 ($0.000)	$1.559 ($1.092)	$3.330 ($2.057)	NA	$0.604 ($0.400)	$2.407 ($2.138)

ID	Cost items	Unit	Angola	Burundi	Cameroon	Central African Republic	Chad	Congo	Eq. Guinea[+]	Ethiopia	Liberia	Malawi	Nigeria	South Sudan	Tanzania	Uganda	Average[*]
36	Field supplies (annuitized) [j]	/set/person/day/site	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 (NA)	$1.850 ($0.000)
	Delivery of samples																
37	Delivery of samples from villages to laboratory	/site	Included in the surveillance trip transportation costs (ID:32)														
38	Delivery of samples from catching site to health facility[k]	/site	$4.670 ($3.423)	$1.127 ($0.000)	$6.145 ($7.657)	$11.740 ($8.784)	$6.250 ($0.000)	NA	NA	$12.500 ($3.536)	$5.023 ($5.096)	$18.367 ($14.874)	$5.761 ($6.033)	NA	NA	NA	$7.954 ($5.249)
39	Delivery of samples from health facility to MSDC[l]	/project	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 (NA)	$135 ($0)
	Epidemiological laboratory testing																
40	Personnel[m]	/person/day/site	$64 ($25)	$10 ($6)	$25 ($34)	$6 ($0)	$25 ($0)	$1 ($0)	$1 ($0)	$13 ($3)	$3 ($2)	$4 ($2)	$17 ($15)	$19 ($17)	NA	$8 ($10)	$15 ($17)
41	Laboratory supplies (annuitized)[n]	/set	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 (NA)	$120 ($0)
	Entomological laboratory testing																
42	Personnel[o]	/person/day/site	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$13 ($3)	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$9 (NA)	$8 ($10)	$9 ($0)
Category 3. Capital costs																	
43	Vehicle (annuitized)	/vehicle	$2,931 (NA)	$5,663 (NA)	$4,103 (NA)	NA	NA	$3,538 (NA)	$3,751 (NA)	$3,918 (NA)	$3,751 (NA)	NA	$3,681 (NA)	$3,751 (NA)	$3,918 (NA)	$4,103 (NA)	$3,919 ($661)
44	Motorcycle (annuitized)	/motorcycle	$469 (NA)	$708 (NA)	$528 (NA)	NA	NA	$352 (NA)	$493 (NA)	$493 (NA)	$493 (NA)	NA	$345 (NA)	$879 (NA)	$493 (NA)	$399 (NA)	$503 ($156)
45	Bicycle (annuitized)	/bicycle	$17 (NA)	$19 (NA)	$23 (NA)	NA	NA	$22 (NA)	$22 (NA)	$22 (NA)	$15 (NA)	$ (NA)	$29 (NA)	$29 (NA)	$22 (NA)	$7 (NA)	$21 ($6)
46	IT equipment (annuitized)	/set	$2,287 (NA)	$2,330 (NA)	$2,288 (NA)	$2,171 (NA)	$2,181 (NA)	$2,181 (NA)	$2,197 (NA)	$2,181 (NA)	$2,187 (NA)	$1,924 (NA)	$2,299 (NA)	$2,132 (NA)	$2,181 (NA)	$1,998 (NA)	$2,181 ($111)
47	Power supply equipment (annuitized)	/set	$514 (NA)	$514 (NA)	$543 (NA)	$514 (NA)	$514 (NA)	$514 (NA)	$514 (NA)	$514 (NA)	$502 (NA)	$514 (NA)	$528 (NA)	$514 (NA)	$514 (NA)	$483 (NA)	$514 ($13)
Category 4. Overhead and administrative costs																	
48	Maintenance of vehicle	/vehicle	$444 (NA)	$221 (NA)	$243 (NA)	$273 (NA)	$293 (NA)	$352 (NA)	$393 (NA)	$204 (NA)	$318 (NA)	$147 (NA)	$289 (NA)	$356 (NA)	$188 (NA)	$200 (NA)	$280 ($86)
49	Maintenance of motorcycle	/motorcycle	$133 (NA)	$66 (NA)	$73 (NA)	$82 (NA)	$88 (NA)	$106 (NA)	$118 (NA)	$61 (NA)	$95 (NA)	$44 (NA)	$87 (NA)	$107 (NA)	$56 (NA)	$60 (NA)	$84 ($26)
50	Office supplies	/project	$923 ($327)	$1,375 ($455)	$1,714 ($1,058)	NA	$9,605 ($0)	$4,367 ($0)	NA	$1,050 ($495)	$2,343 ($427)	$4,103 ($0)	$2,811 ($6,545)	$1,230 ($464)	$1,685 ($441)	$1,541 ($806)	$2,519 ($2,459)
51	Communication	/project	$1,944 ($1,264)	$1,739 ($256)	$4,585 ($4,136)	NA	$869 ($0)	$3,565 ($0)	NA	$1,800 ($0)	NA	NA	$1,260 ($1,178)	$1,936 ($327)	$11,973 ($2,140)	$745 ($752)	$3,042 ($3,354)
52	Salary top-ups (first 6 years)	/project	$14,708 ($8,284)	$18,190 ($11,220)	$52,278 ($66,782)	$25,691 ($10,150)	NA	$41,300 ($0)	NA	NA	$28,467 ($4,965)	NA	$61,171 ($84,633)	$9,220 ($575)	$6,681 ($2,008)	$811 ($0)	$25,852 ($20,125)
53	Other administration	/project	$470 ($285)	$1,678 ($2,786)	$10,852 ($13,991)	NA	$222 ($0)	$20,611 ($0)	NA	NA	NA	$2,710 ($0)	$817 ($1,342)	$5,252 ($1,008)	NA	$80 ($0)	$4,744 ($6,881)
Category 5. Financial support for CDTi and surveillance in (post) conflict endemic areas																	
54	Support for CDTi and surveillance in (post) conflict	/endemic African regions	$1,052,363 (NA)														

ID	Cost items	Unit	Angola	Burundi	Cameroon	Central African Republic	Chad	Congo	Eq. Guinea[+]	Ethiopia	Liberia	Malawi	Nigeria	South Sudan	Tanzania	Uganda	Average[*]
	endemic areas[p]																

Note: if not specified below, all data sourced from available budgets.
+ Equatorial Guinea
***** Regional average across national averages
[#]The nationwide project had ten sub-project budgets available. To compare with projects in other countries, average unit costs per sub-project were shown.
[%]The nationwide project had seven sub-project budgets available. To compare with projects in other countries, average unit costs per sub-project were shown.
[@]There were two regional projects for which seven sub-project budgets were available. To compare with projects in other countries, average unit costs per sub-project were shown.
a,b,c Agriculture value added per person-day [86,91]
d 1) As a proxy for the costs of the microscopic diagnostic tools for *L.loa*, we used the costs of the epidemiological laboratory testing supplies (ID:41);
2) Source for delivery and administration of doxycycline: Wanji et al. 2009 [94]
e Budget for the training of community volunteers was used.
f Budget for the fuel support for supervisory visit to districts was used.
g Budget for the perdiem for health workers who train community drug distributors was used.
h Prices of 2 liters of distilled water, 200 glass slides, 3 instrument trays, 4 slide trays each holding 3 glass slides, liquid detergent, butane burning stove, dropper bottle, aluminium pressure sterilizer, cotton swabs soaked with alcohol, curved tweezer, holth punch, lancets, scissors, sterilizer forcepts. http://www.amazon.com Accessed on 17 August 2014.
i Budget for the training incentive for community drug distributors was used.
j Price of aspirator and plastic bottles. http://www.amazon.com Accessed on 17 August 2014.
k Budget for the transportation support for supervisory visit from health facility to villages was used.
l DHL service guide. http://www.dhlguide.co.uk Accessed on 17 August 2014.
m Budget for the perdiem for health workers who train community drug distributors was used.
n Prices of 1ml test tube, binocular microscope, blood slids, hypodermic syringe and needle, micro pipette with disposable tips, microtitration trays, saline solution, slide trays. http://www.amazon.com Accessed on 17 August 2014
o Daily wage of state-certified nurse in Burkina Faso[122] was used as a proxy for the daily wage of laboratory technicians in MSDC. For Ethiopia, Uganda, and Sudan that were identified to conduct the entomological laboratory testing in their own laboratories, we used the daily wage for technicians who conduct epidemiological laboratory testing, namely, $13, $8, and $15 (regional average), respectively (ID:40).
p Annual average funding for (post) conflict areas in Africa based on the APOC budget plan for 2008-2015 (annual average: $756,250) and Sightsavers's strategic plan for 2011-2021 (annual average: $296,113) [95,123].

Table S6. Agriculture value added per person-day for endemic African countries

Country	Agriculture value added per person-day*
Angola	$2.11
Benin	$0.93
Burkina Faso	$0.88
Burundi	$0.39
Cameroon	$0.92
Central African Republic	$1.00
Chad[ϕ]	$0.57
Congo, Dem. Rep.	$0.40
Congo, Rep.	$0.41
Côte d'Ivoire	$1.28
Equatorial Guinea[†]	$12.33
Ethiopia	$0.87
Gabon	$1.68
Ghana	$1.45
Guinea	$0.39
Guinea-Bissau	$1.11
Liberia	$0.62
Malawi	$0.29
Mali	$1.13
Mozambique	$0.66
Nigeria	$2.32
Senegal	$0.66
Sierra Leone	$1.38
South Sudan[‡]	$0.54
Sudan	$1.80
Tanzania	$0.64
Togo	$0.69
Uganda	$0.55
Average (SD)	$1.36 ($2.22)

* To estimate daily agriculture value added per worker, agriculture value added per worker as percentage of GDP [91] was multiplied with 2012 GDP per capita [86], and was divided by 261 days.
ϕ,†,‡ Agriculture value added per worker (% of GDP) for sub-Saharan Africa (developing only, 2012) was used, because national data were unavailable.
SD: standard deviation

Table S7. The ratio of volunteers and of health workers over population and population per district and per community for endemic African countries

Country	Volunteers over population	Health workers over population	Population per district	Population per community	Source
Angola	1/275	1/2,458	70,460	910	Budgets
Benin	NA	NA	51,106	564	Sightsavers[123]
Burkina Faso	NA	NA	171,150	NA	Helen Keller International [124]
Burundi	1/150	1/4,892	149,684	4,270	Budgets
Cameroon	1/260	1/9,068	109,238	1,317	Budgets
CAR	1/106	1/3,501	160,356	288	Budgets
Chad	1/182	1/2,789	99,664	583	Budgets
Congo	1/251	1/2,118	57,500	1,076	Budgets
Côte d`Ivoire	NA	NA	NA	NA	NA
DRC	NA	NA	NA	646	WHO/APOC [125]
Equatorial Guinea	1/181	1/5,082	20,330	630	Budgets
Ethiopia	1/188	1/14,930	40,156	396	Budgets
Gabon	NA	NA	32,291	NA	Direction Générale des Statistiques, Gabon [126,127]
Ghana	NA	NA	36,060	654	Ministry of health, Ghana [128]
Guinea	NA	NA	312,617	304	Institut National de la Statistique, the Republic of Guinea [129,130], Sightsavers[123]
Guinea-Bissau	NA	NA	32,358	83	Instituto Nacional de Estatística e Censos, Guinea-Bissau [131,132], Sightsavers[123]

Country	Volunteers over population	Health workers over population	Population per district	Population per community	Source
Liberia	1/196	1/2,920	165,043	696	Budgets
Malawi	1/112	1/663	311,425	1,111	Budgets
Mali	NA	NA	290,344	1,498	Institut National de la Statistique, Mali [133,134], Sightsavers[123]
Mozambique	NA	NA	173,837	NA	Instituto Nacional de Estatistica, Mozambique [135,136]
Nigeria	1/265	1/905	94,005	1,307	Budgets
Senegal	NA	NA	300,182	NA	Agence Nationale de la Statistique et de la Démographie (ANSD), Senegal[137,138]
Sierra Leone	NA	NA	416,777	403	Ministry of Health, Sierra Leone [139]
South Sudan	1/379	1/6,180	114,929	958	Budgets
Sudan	NA	NA	NA	676	APOC [140]
Tanzania	1/200	1/3,471	72,687	362	Budgets
Togo	NA	NA	98,890	960	Sightsavers[123]
Uganda	1/47	1/1,266	134,919	638	Budgets
Average (SD)	1/154 (0.0047)	1/2,223 (0.0004)	140,640 (107,370)	884 (823)	

Step 2. Costs at cost-item level

Step 2	Cost category	Cost item	Type	Costs at cost-item level (=$UC*UQ)				
				2013	2014	–	2044	2045
For each cost item, costs are calculated by multiplying the unit cost with the unit quantity for each year.	CDTi	1	Financial	1	1		1	1
	Surveillance	2		2	2		2	2
	Capital	3		3	3		3	3
	Administrative	⋮		⋮	⋮		⋮	⋮
	(post) conflict	52	Economic	52	52		52	52
		53		53	53		53	53
		54		54	54		54	54

To estimate costs for each cost item from 2013 to 2045, we multiplied the unit cost with the unit quantity for each year. The unit quantity was adjusted for the relevant phases, that is, it was zero outside the relevant phases which are defined in Table S4.

Step 3. Classification into financial and economic costs

Step 3	Cost category	Financial costs at cost-item level				Economic costs at cost-item level			
		2013	2014 –	2044	2045	2013	2014 –	2044	2045
Costs for all cost items are grouped into financial and economic.	CDTi	1-3,	1-3,	1-3,	1-3,	4, 18 (volunteer)	4, 18	4, 18	4, 18
	Surveillance								
	Capital	5-17,	5-17,	5-17,	5-17,	19 (ivermectin)	19	19	19
	Administrative								
	(post) conflict	21-54	21-54	21-54	21-54	20 (volunteer)	20	20	20

We grouped costs at cost-item level into financial and economic costs. Among the total 54 cost items, four cost items (ID: 4, 18, 19, 20) were for economic costs, and other were for financial costs.

Step 4. Sub-classification of financial and economic costs

Step 4
Within each group of financial and economic costs, cost items are grouped into the main components, CDTi/surveillance[1] and volunteers/ivermectin, respectively.

Financial costs of CDTi and surveillance				
2013	2014	–	2044	2045
CDTi	CDTi		CDTi	CDTi
Surveillance	Surveillance		Surveillance	Surveillance

Economic costs of volunteers and ivermectin				
2013	2014	–	2044	2045
Volunteers	Volunteers		Volunteers	Volunteers
Ivermectin	Ivermectin		Ivermectin	Ivermectin

1 For financial costs, capital and administrative costs are evenly split to CDTi and surveillance for the years when both CDTI and surveillance are implemented, and (post-) conflict-area support costs are evenly split over the entire period.

From an operational perspective, financial costs consist of those of CDTi and of surveillance. We grouped financial costs at cost-item level into those of CDTi and of surveillance based on the five categories. We evenly split the costs of capital goods and administration between CDTi and surveillance for years when both CDTi and surveillance were conducted; otherwise, allocated the costs to CDTi during the phase 1 and surveillance during the phases 2 and 3. We evenly split the support costs for (post) conflict areas between CDTi and surveillance for the entire time horizon. Economic costs consist of those of community volunteers and of donated ivermectin, and we grouped the economic costs at cost-item level into those two.

Step 5. Total financial and economic costs

Step 5
Financial costs of CDTi and of surveillance are aggregated, and economic costs of volunteers and of ivermectin are aggregated to calculate total financial and total economic costs for each year.

Total financial and economic costs				
2013	2014	–	2044	2045
Financial	Financial		Financial	Financial
Economic	Economic		Economic	Economic

To estimate annual financial costs, we summed the annual financial costs of CDTi and surveillance (E1). To estimate annual economic costs, we summed the annual economic costs of community volunteers and donated ivermectin (E2).

$$FC_t = FC_{CDTi,\mathrm{t}} + FC_{surveillance,\mathrm{t}} \text{ (E1)}$$

$$EC_t = EC_{volunteer,\mathrm{t}} + EC_{ivermectin,\mathrm{t}} \text{ (E2)}$$

FC_t : total financial costs for year *t*;

$FC_{CDTi/surveillance,t}$: financial costs of CDTi/surveillance for year *t*;

EC_t : total economic costs for year *t*;

$EC_{volunteer/ivermectin,t}$: economic costs of community volunteers/donated ivermectin for year *t*

Step 6. Total costs for a project

Step 6
To calculate annual total costs, financial and economic costs are aggregated for each year. To calculate total costs over 2013−2045, annual total costs are aggregated with discounting.

Total costs				
2013	2014	– 2044	2045	2013−2045
Total	Total	Total	Total	Total

To calculate annual total costs for a project, we summed the annual financial and economic costs (E3).

$$TC_t = FC_t + EC_t \text{ (E3)}$$

TC_t : total costs for year *t*

To estimate cumulative costs over 2013 to 2045, we aggregated annual total costs with discounting (E4). The discount rate to account for time preference was 3%.

$$TC_{2013-2045} = \sum_{t=2013}^{2045} \frac{TC_t}{(1+r)^{(t-2012)}} \text{ (E4)}$$

r: discount rate

3. Total costs for a scenario

To estimate total costs for a scenario, we aggregated costs at project level across the entire target projects.

II. Uncertainty analysis

1. Selection of variables

We conducted sensitivity analysis to assess the robustness of results to parametric uncertainties. The parameters for the sensitivity analysis included cost items that had missing unit costs either for more than one third of total projects or total countries with budgets available, 22 of 67 projects or 5 of 14 countries (Table S8). In addition to them, we also included the financial support costs for (post) conflict areas, as it was estimated based on only two sources, the strategic plans of APOC [95] and Sightsavers[123]. There were no missing data on the determinants of unit quantities for projects with budgets available. However, four determinants were time-variant; thus to assess the impact of time variation on total costs, we included them: population living in a project area, the number of required treatments (determined by population, treatment coverage linked to required treatment duration, and possible delay in starting and ending treatments), the number of required community volunteers (determined by population and the ratio of community volunteers over population), and the number of required community health workers (determined by population and the ratio of community health workers over population).

Table S8. Selected cost items for sensitivity analysis

Cost items (ordered by no. of missing values)	Number of missing values	
	Country (/14)	Project (/67)
Evaluation	12	64
Development of IEC material	10	57
Surveillance trip transportation	6	38
Monitoring	6	33
Delivery of fly samples from catching site to health facility	5	35
Data management	5	26
Management of severe adverse events	4	30
Salary top-ups (first 6 years)	4	28
Assistance for supervisory visits (7th year+)	4	23

2. Statistical distributions

We applied statistical distributions to the selected variables considering the characteristics of variables with reference to standard practices [141]. We applied gamma distributions to the selected cost items and fitted them to available unit costs (Table S9).

Table S9. Average and standard deviation of unit costs and distribution parameters

Cost items	Average	Standard deviation[†]	Gamma distribution[#]	
			Shape (k)	Scale (θ)
1 Evaluation				
Burundi	$3,585	$358	100	36
Malawi	$4,432	$4,309	1	4,190
Average	$4,008	$599	45	90
2 Development of IEC material				
Ethiopia	$2,200	$1,697	2	1,309
Liberia	$4,532	$99	2,107	2
Nigeria	$1,889	$1,566	1	1,299
Uganda	$382	$38	100	4
Average	$2,250	$1,716	2	1,308
3 Surveillance trip transportation				
Angola	$52	$109	>0	228
Burundi	$14	$18	1	24
Cameroon	$32	$56	>0	100
CAR	$9	$2	13	1
Chad	$6	$1	100	>0
Ethiopia	$7	$1	61	>0
Liberia	$21	$3	49	>0
Nigeria	$30	$44	1	63
Average	$21	$16	2	12
4 Monitoring				
Angola	$5,203	$4,630	1	4120
Burundi	$1,617	$19	7593	>0
Cameroon	$10,482	$7,449	2	5,293
Chad	$1,468	$676	5	312
Ethiopia	$375	$177	5	83
Liberia	$1,735	$17	10,034	>0
Malawi	$4,963	$5,201	1	5,451
Nigeria	$3,135	$4,353	1	6,044
Average	$3,622	$3,259	1	2,933
5 Delivery of fly samples from catching site to health facility				
Angola	$5	$3	2	3
Burundi	$1	>$0	100	>0
Cameroon	$6	$8	1	10
CAR	$12	$9	2	7
Chad	$6	$1	100	>0
Ethiopia	$13	$4	13	1
Liberia	$5	$5	1	5
Malawi	$18	$15	2	12
Nigeria	$6	$6	1	6
Average	$8	$5	2	3
6 Data management				
Angola	$1,400	$140	100	14
Burundi	$6,793	$9,598	1	13,562
Cameroon	$5,574	$7,273	1	9,491
Chad	$175	$207	1	244
Congo	$1,463	$146	100	15
Equatorial Guinea	$800	$80	100	8
Malawi	$1,344	$540	6	217
Nigeria	$975	$2,220	>0	5,053
Uganda	$2,258	$2,210	1	2,163
Average	$2,309	$2,287	1	2,265
7 Management of severe adverse events				
Angola	$1,360	$381	13	107
Burundi	$1,070	$840	2	659
Cameroon	$5,329	$8,271	>0	12,839
Congo	$175	$18	100	2
Equatorial Guinea	$1,275	$128	100	13
Ethiopia	$2,465	$247	100	25
Liberia	$13,195	$4,185	10	1,327
Nigeria	$3,245	$2,266	2	1,582

Cost items	Average	Standard deviation†	Gamma distribution#	
			Shape (k)	Scale (θ)
South Sudan	$544	$345	2	219
Uganda	$1,277	$128	100	13
Average	$2,993	$3,888	1	5,051
8 Salary top-ups (first 6 years)				
Angola	$14,708	$8,284	3	4,666
Burundi	$18,190	$11,220	3	6,920
Cameroon	$52,278	$66,782	1	85,310
CAR	$25,691	$10,150	6	4,010
Congo	$41,300	$4,130	100	413
Liberia	$28,467	$4,965	33	866
Nigeria	$61,171	$84,633	1	117,094
South Sudan	$9,220	$575	257	36
Tanzania	$6,681	$2,008	11	604
Uganda	$811	$81	100	8
Average	$25,852	$20,125	2	15,668
9 Assistance for supervisory visits (7th year+)				
Angola	$4,000	$1,414	8	500
Burundi	$3,001	$2,434	2	1,974
Cameroon	$2,460	$1,098	5	490
Chad	$635	$352	3	195
Congo	$2,489	$249	100	25
Equatorial Guinea	$1,450	$145	100	15
Malawi	$1,253	$655	4	342
Nigeria	$1,702	$1,480	1	1,287
South Sudan	$1,500	$150	100	15
Uganda	$2,498	$566	19	128
Average	$2,099	$981	5	459
10 Financial support for post-conflict areas (annual average)				
APOC	$756,250	$7,563	100	7,563
Sightsaver	$296,113	$2,961	100	2,961

† If there was only one data point, the standard deviation was assumed to be 10% of the data.
# Parameters of *Gamma(k, θ)* were estimated with a method of moments:

$$shape\hat{k} = \frac{\overline{x^2}}{\bar{v}}, scale\hat{\theta} = \frac{\bar{v}}{\bar{x}} where \bar{x} is a sample mean, \bar{v} is a sample variance$$

We used normal distributions to model the uncertainty about population growth rates from 2013 to 2045 for all endemic countries. We fitted the distribution to national low-high ranges[55], assuming the ranges to be the 95% confidence intervals.

To model the uncertainty about the number of treatments, we identified its determinants with reference to the study by Kim and colleagues [6]. The determinants were population living in a project area, treatment coverage, and the delay in starting and ending CDTi. We used normal distributions to model the uncertainty about population growth rates as described in the previous step. We used beta distributions to model the uncertainty about treatment coverage by fitting them to the treatment coverage data over 2010−2012 for APOC countries (source: APOC treatment database) (Table S10). Projects in former OCP countries had no historical treatment coverage available, yet had the most recent year's data. To estimate distribution parameters for the former OCP countries, we assumed that

the standard deviation is 10% of treatment coverage. The change of treatment coverage was linked to the required duration of CDTi based on ONCHOSIM simulation results for the elimination and eradication scenarios. For the control scenario, the required duration of CDTi was extended for another 25 years if the treatment coverage decreased below the minimum required level, 65%. To model the uncertainty about the delay in starting and ending CDTi, we used a gamma distribution in which 90% of samples fall into the range of zero to five (shape=1, scale=2.25), assuming the delay can be as long as five years [6].

Table S10. Average and standard deviation of treatment coverage and distribution parameters

Country	Average	Standard deviation	Beta distribution[γ]	
			Alpha (α)	Beta (β)
APOC countries				
Angola	67%	0.11	12	6
Burundi	77%	0.04	106	31
Cameroon	78%	0.05	63	18
CAR	80%	0.03	168	41
Chad	81%	>0.00	124,658	29,241
Congo	81%	0.02	208	47
DRC	71%	0.13	7	3
Equatorial Guinea	71%	>0.00	292,469	119,749
Ethiopia	79%	0.04	78	21
Liberia	77%	0.10	13	4
Malawi	83%	>0.00	5,113	1,066
Nigeria	80%	0.04	83	21
South Sudan	60%	0.12	9	6
Sudan	82%	0.03	167	38
Tanzania	81%	0.01	868	210
Uganda	75%	0.11	10	3
Average	76%	0.06	35	11
Former OCP countries				
Benin	48%	0.05	51	55
Burkina Faso	84%	0.08	16	3
Côte d'Ivoire	84%	0.08	16	3
Ghana	73%	0.07	27	10
Guinea	73%	0.07	27	10
Guinea-Bissau	73%	0.07	27	10
Mali	73%	0.07	27	10
Senegal	77%	0.08	22	6
Sierra Leone	80%	0.08	19	5
Togo	77%	0.08	22	6
Average	74%	0.10	13	5

γ Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\ \bar{v} < \bar{x}(1-\bar{x}), where\ \bar{x}\ is\ a\ sample\ mean, \bar{v}\ is\ a\ sample\ variance$$

To model the uncertainty about the number of volunteers and of health workers, we identified their determinants, namely, population living in a project area and the ratio of volunteers and of health workers over population. We used normal distributions to model the uncertainty about population

growth rates as described previously. We used beta distributions to model the uncertainty about the ratio of volunteers over population and the ratio of health workers over population by fitting them to relevant data (Table S11).

For all selected variables, if there was no distribution at country level, we used the distribution for the endemic regions which was estimated based on available national averages for endemic African countries.

Table S11. Average and standard deviation of the ratio of volunteers over population and the ratio of health workers over population and distribution parameters

Country	Average	Standard deviation	Beta distribution[δ]	
			Alpha (α)	Beta (β)
1 Ratio of volunteers over population				
Angola	1/257	0.0029	2	429
Burundi	1/150	0.0005	164	24,462
Cameroon	1/260	0.0040	1	238
CAR	1/106	0.0019	25	2,600
Chad	1/182	0.0011	25	4,500
Congo	1/251	0.0008	25	6,225
Equatorial Guinea	1/181	0.0011	25	4,475
Ethiopia	1/188	0.0003	404	75,638
Liberia	1/196	0.0028	3	662
Malawi	1/112	0.0013	44	4,865
Nigeria	1/265	0.0028	2	472
South Sudan	1/379	0.0017	3	949
Tanzania	1/200	0.0010	25	4,950
Uganda	1/47	0.0155	2	85
Average	1/154	0.0047	2	294
2 Ratio of health workers over population				
Angola	1/2,458	0.0004	1	2,241
Burundi	1/4,892	>0.0000	23	114,727
Cameroon	1/9,068	0.0003	0.2	1,602
CAR	1/3,501	0.0001	25	87,483
Chad	1/2,789	0.0001	25	69,676
Congo	1/2,118	0.0001	25	52,911
Equatorial Guinea	1/5,082	>0.0000	25	127,009
Ethiopia	1/14,930	0.0001	1	21,589
Liberia	1/2,920	0.0001	6	18,393
Malawi	1/663	0.0006	7	4,688
Nigeria	1/905	0.0010	1	1,080
South Sudan	1/6,180	0.0001	4	24,603
Tanzania	1/3,471	0.0001	25	86,715
Uganda	1/1,266	0.0002	16	20,812
Average	1/2,223	0.0004	1	2614

δ Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\ \bar{v} < \bar{x}(1-\bar{x}), where\ \bar{x}\ is\ a\ sample\ mean, \bar{v}\ is a\ sample\ variance$$

3. Simulation

We conducted one-way sensitivity analysis to examine the impact of parameters related to CDTi performance (treatment coverage, the delay in starting and ending CDTi), the selected cost items with

high uncertainty, and discount rates (0%, 3%, 6%) on total costs. We also conducted multivariate PSA to examine the joint effects of uncertainties about all selected variables on total costs by running the micro-costing simulation 1,000 times using samples drawn from the distributions of the selected variables.

III. Literature review

To find literature on regional elimination strategies for onchocerciasis in Africa, we used the PubMed (MEDLINE) database to search for documents in English and French, published between 2004 and 2014, with the following search terms: "onchocerciasis or river blindness" in title and "elimination or eradication" in abstract. We reviewed abstracts to determine relevance, and reviewed the full texts of selected documents. We also searched the bibliographies of identified references and the gray literature. We found two manuscripts on elimination strategies for endemic African regions: one a conceptual and operational framework of onchocerciasis elimination developed by APOC [68] and the other a manuscript on control, elimination, and eradication scenarios for onchocerciasis by Kim and colleagues which was developed based on the former [6] (Table S12).

Table S12. Literature on regional elimination strategies in Africa

	Title	Authors	Published year	Reference
1	Conceptual and Operational Framework of Onchocerciasis Elimination with Ivermectin Treatment.	African Programme for Onchocerciasis Control	2010	[68]
2	Control, elimination, and eradication of river blindness: scenarios, timelines, and ivermectin treatment needs in Africa	Kim YE, Remme JHF, Steinmann P, Stolk WA, Roungou J, Tediosi F.	2015	[6]

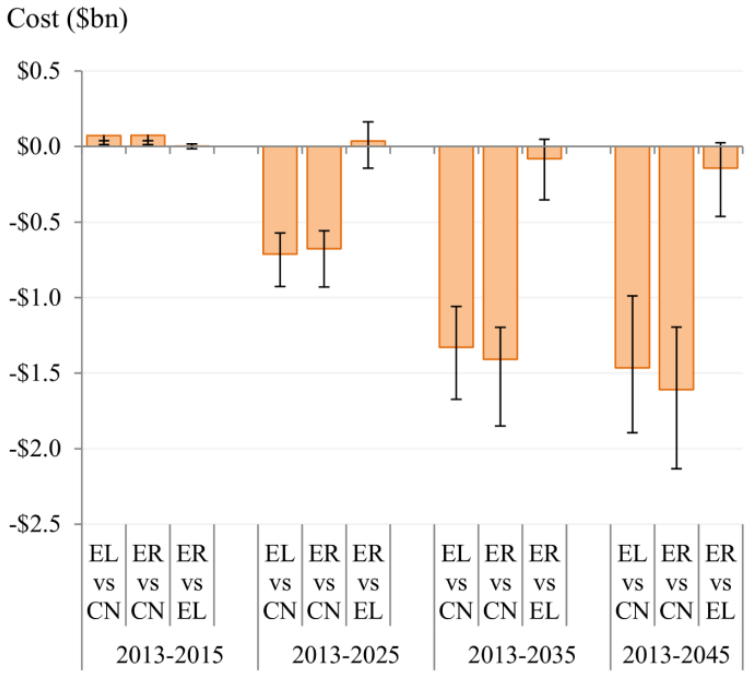
To estimate costs associated with potential elimination strategies proposed by Kim and colleagues, we searched literature on onchocerciasis intervention costs. Keating and colleagues searched literature on onchocerciasis intervention costs, published in English and French between 1990 and 2010, using PubMed (MEDLINE), EMBASE, and JSTOR databases with the following search terms: onchocerciasis, cost, cost–benefit, cost-effectiveness, economic, economics, internal rate of return, elimination, eradication, health systems, vertical, integration [142]. They selected publications after reviewing abstracts for relevance, and reviewed the full texts of the selected ones. They also searched the bibliographies of identified references and the gray literature. They found ten publications on costs for onchocerciasis treatment with ivermectin or doxycycline. We have extended the search period to include 2011−2015 using the same method, and found four more documents (Table S13). Considering our objective was to estimate costs for potential elimination strategies in Africa using a micro-costing method, the identified publications were insufficient, because they focused on a limited number of countries, and many of them were outdated and lacked detailed data on resource utilization (e.g., unit

costs and unit quantities). Also, all identified publications estimated costs for control strategies without regular surveillance.

Table S13. Literature on costs of onchocerciasis treatment with ivermectin or doxycycline in Africa

	Title	Authors	Published year	Country/region	Reference
1	Ivermectin-based onchocerciasis control in Cameroon	Ngoumou P, Essomba RO, Godin C.	1996	Cameroon	[143]
2	Delivery systems and cost recovery in Mectizan treatment for onchocerciasis	Amazigo U, Noma M, Boatin BA, Etya'ale DE, Seketeli A, Dadzie KY.	1998	Endemic African regions	[144]
3	Ivermectin distribution using community volunteers in Kabarole district, Uganda	Kipp W, Burnham G, Bamuhiiga J, Weis P, Buttner DW.	1998	Uganda	[145]
4	The Mectizan (Ivermectin) Donation Program for Riverblindness as a Paradigm for Pharmaceutical Industry Donation Programs	Philip E.Coyne, David W.Berk.	2001	NA	[121]
5	Implementing community-directed treatment with ivermectin for the control of onchocerciasis in Uganda (1997–2000): an evaluation	Katabarwa MN, Habomugisha P, Richards FO, Jr.	2002	Uganda	[146]
6	Community-directed treatment with ivermectin in two Nigerian communities: an analysis of first year start-up processes, costs and consequences	Onwujekwe O, Chima R, Shu E, Okonkwo P.	2002	Nigeria	[147]
7	Economic evaluation of Mectizan distribution	Waters HR, Rehwinkel JA, Burnham G.	2004	Endemic African regions	[148]
8	Progress towards the elimination of onchocerciasis as a public-health problem in Uganda: opportunities, challenges and the way forward	Ndyomugyenyi R, Lakwo T, Habomugisha P, Male B.	2007	Uganda	[149]
9	Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of coendemicity with loiasis in Cameroon	Wanji S, Tendongfor N, Nji T, Esum M, Che JN, Nkwescheu A et al.	2009	Cameroon	[94]
10	Cost-effectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria	Evans D, McFarland D, Adamani W, Eigege A, Miri E, Schulz J et al.	2001	Nigeria	[150]
11	African Programme For Onchocerciasis Control 1995-2015: model-estimated health impact and cost	Coffeng LE, Stolk WA, Zoure HG, Veerman JL, Agblewonu KB, Murdoch ME et al.	2013	Endemic African regions	[12]
12	The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a case study	Turner HC, Osei-Atweneboana MY, Walker M, Tettevi EJ, Churcher TS, Asiedu O et al.	2013	Ghana	[105]
13	Reaching the london declaration on neglected tropical diseases goals for onchocerciasis: an economic evaluation of increasing the frequency of ivermectin treatment in Africa	Turner HC, Walker M, Churcher TS, Osei-Atweneboana MY, Biritwum NK, Hopkins A et al.	2014	Endemic African regions	[151]
14	Onchocerciasis control in the Democratic Republic of Congo (DRC): challenges in a post-war environment	MakengaBof JC, Maketa V, Bakajika DK, Ntumba F, Mpunga D, Murdoch ME et al.	2015	the Democratic Republic of Congo	[152]

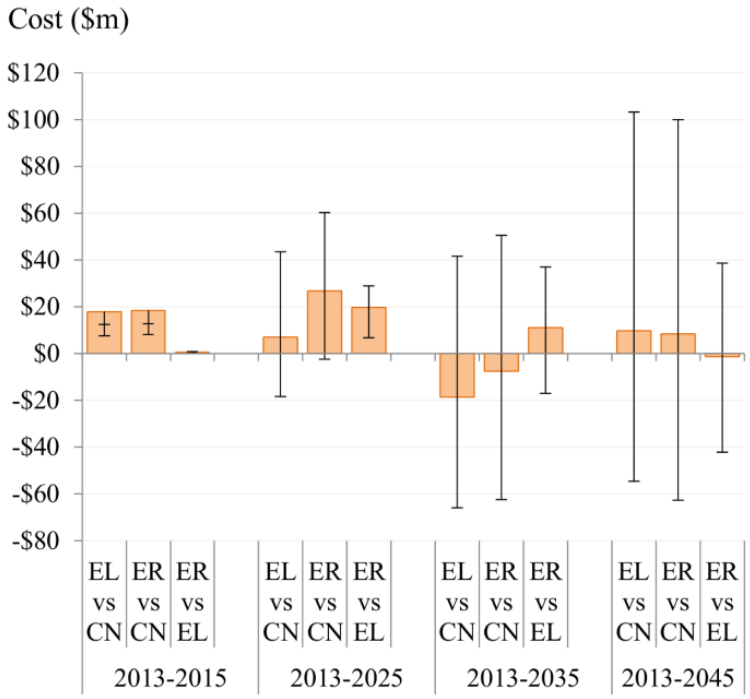
Figure S3. Incremental cumulative financial and economic costs over 2013−2045



(CN: control, EL: elimination, ER: eradication)

(Note: The line bars represent the 95 central ranges based on PSA. Costs are discounted with 3% and reported in 2012 USD.)

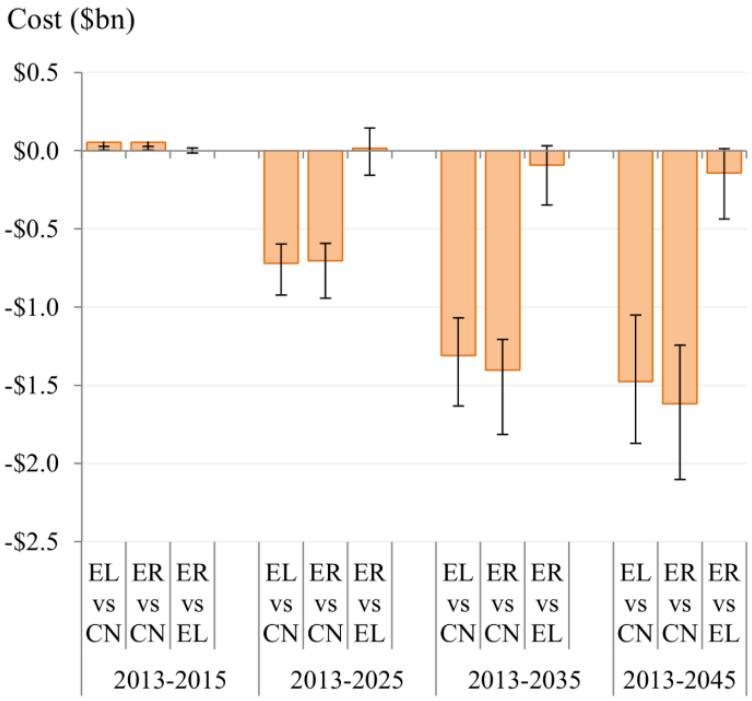
Figure S4. Incremental cumulative financial costs over 2013−2045



(CN: control, EL: elimination, ER: eradication)

(Note: The line bars represent the 95 central ranges based on PSA. Costs are discounted with 3% and reported in 2012 USD.)

Figure S5. Incremental cumulative economic costs over 2013−2045



(CN: control, EL: elimination, ER: eradication)

(Note: The line bars represent the 95 central ranges based on PSA. Costs are discounted with 3% and reported in)2012 USD.

Appendix 3. Supplementary Information for Chapter 5

Value of investing in the elimination and eradication of onchocerciasis in Africa: the health and economic benefits and the impacts on health systems

Methodological details on probabilistic sensitivity analysis

Probabilistic sensitivity analysis

To examine the robustness of results against the joint uncertainties about associated parameters and assumptions, we conducted multivariate probabilistic sensitivity analysis.

Health Impacts

Parameters against which we assessed the robustness of health impacts (the number of cases of severe itching, low vision, and blindness and DALYs) were the treatment coverage, the level of infection and morbidity in hypo-endemic areas relative to meso-endemic areas, the reduction of life-expectancy due to blindness, and the population growth rate.

a. Treatment coverage

As a treatment coverage rate for the period 2013–2045, we used the average treatment coverage over the period 2010–2012 for APOC countries and the most recent available data (as of November 2013) for former OCP countries due to the lack of history data. To incorporate the uncertainty about treatment coverage rates, we assigned a beta distribution and fitted to the pool of treatment coverage data for projects at country level. The beta distribution at regional level was fitted to the pool of national average treatment coverage (Table S14). The range of treatment coverage was restricted to 60% to 84%, because at least 60% is required for effective control of the disease and 84% is the maximum achievable considering 16% of the population is not eligible for CDTi due to ages less than five years, pregnancy, or severe illness [6].

Table S14. Summary of treatment coverage and distribution parameters for probabilistic sensitivity analysis

Country	Average[1]	Standard deviation	Beta distribution[2]	
			Alpha	Beta
APOC countries				
Angola	67%	0.11	12.36	5.97
Burundi	77%	0.04	105.52	31.48
Cameroon	78%	0.05	62.60	17.72
Central African Republic	80%	0.03	167.75	40.98
Chad	81%	0.00	124,658.19	29,240.81
Congo	81%	0.02	207.63	47.39
Democratic Republic of the Congo	71%	0.13	7.47	3.12
Equatorial Guinea	71%	0.00	292,469.03	119,749.47
Ethiopia	79%	0.04	77.58	20.87
Liberia	77%	0.10	13.31	3.89

Malawi	83%	0.00	5,112.61	1,065.77
Nigeria	80%	0.04	83.33	21.00
South Sudan	60%	0.12	8.72	5.78
Sudan	82%	0.03	167.06	37.92
Tanzania	81%	0.01	868.01	210.26
Uganda	75%	0.11	10.48	3.46
APOC	**76%**	**0.06**	**35.04**	**10.81**
Country	**Latest**[3]	**Standard deviation**[4]	**Beta distribution**	
			Alpha	**Beta**
Former OCP countries				
Benin	48%	0.05	51.42	55.48
Burkina Faso	84%	0.08	15.56	3.05
Côte d'Ivoire	84%	0.08	15.56	3.05
Ghana	73%	0.07	26.67	10.07
Guinea	73%	0.07	26.67	10.07
Guinea-Bissau	73%	0.07	26.67	10.07
Mali	73%	0.07	26.67	10.07
Senegal	77%	0.08	21.83	6.37
Sierra Leone	80%	0.08	18.90	4.64
Togo	77%	0.08	21.83	6.37
Former OCP	**74%**	**0.10**	**13.09**	**4.58**

[1] The average treatment coverage over 2010-2012

[2] Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\ \bar{v} < \bar{x}(1-\bar{x}),$$

$$where\ \bar{x}\ is\ a\ sample\ mean, \bar{v}\ is\ a\ sample\ variance$$

[3] A database for the former OCP countries had only the most recent available treatment coverage as of November 2013.

[4] The standard deviation was assumed to be 10% of the treatment coverage.

The change of treatment coverage leads to the change of the prevalence of infection and morbidity, and consequently to the change of the required treatment duration. In the PSA, the prevalence of severe itching and the required treatment duration varied depending on the change of treatment coverage based on ONCHOSIM simulation results. There was no variation in the prevalence of low vision and blindness, because the change of treatment coverage (60%–84%) was not enough to have an impact on the prevalence of vision impairment according to ONCHOSIM simulations.

b. The level of infection and morbidity in hypo-endemic areas relative to meso-endemic areas

We did not conduct ONCHOSIM simulations for hypo-endemic areas, as ONCHOSIM predicts the infection level in hypo-endemic areas is unsustainable without human or vector migration, and data on human or vector migration were unavailable. Instead, we assumed that the level of infection and morbidity in hypo-endemic areas is 1/3 relative to that in meso-endemic areas [12]. To incorporate the

uncertainty about this assumption in PSA, we applied a triangular distribution with the lower limit to be 1/10, the upper limit to be 1/2, and the mode to be 1/3.

c. Life-expectancy loss per blindness incidence

We assumed that blindness causes eight years of life-expectancy loss [12]. To incorporate the uncertainty about this assumption, we applied a triangular distribution with the lower limit to be six, the upper limit to be ten, and the mode to be eight.

d. Population growth rate

We assigned a normal distribution to each country by fitting to low, medium, and high population growth rates. The distribution has the medium as the average and half of the distance between the low and high rates as the standard deviation. Data were available from the United Nations (UN) database [9].

Health workforce needs

Parameters against which we examined the robustness of the health workforce needs were the ratio of community volunteers over population, the ratio of community health workers over population, the possible delay in starting and ending CDTi, and the population growth rate.

a. The ratio of community volunteers over population

We applied a beta distribution and fitted to available data at country and regional levels. The ratio of community volunteers over population was available for 67 of total 112 ongoing projects (as of November 2013) in sub-Saharan Africa from project budget documents (Y2012). For projects in countries for which data were available, we used the fitted distribution at country level; for projects in countries with no data, we used the distribution at regional level which was fitted to available national average ratios among endemic African countries. The fitted distributions are presented in Table S15.

Table S15. Summary of the ratio of community volunteers over population and distribution parameters for probabilistic sensitivity analysis

Country	Average	Standard deviation	Beta distribution[1]	
			Alpha (α)	Beta (β)
Angola	1/257	0.0029	2	429
Burundi	1/150	0.0005	164	24,462
Cameroon	1/260	0.0040	1	238
CAR	1/106	0.0019	25	2,600
Chad	1/182	0.0011	25	4,500
Congo	1/251	0.0008	25	6,225

Country	Average	Standard deviation	Beta distribution[1]	
			Alpha (α)	Beta (β)
Equatorial Guinea	1/181	0.0011	25	4,475
Ethiopia	1/188	0.0003	404	75,638
Liberia	1/196	0.0028	3	662
Malawi	1/112	0.0013	44	4,865
Nigeria	1/265	0.0028	2	472
South Sudan	1/379	0.0017	3	949
Tanzania	1/200	0.0010	25	4,950
Uganda	1/47	0.0155	2	85
Average	1/154	0.0047	2	294

1 Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\, \bar{v} < \bar{x}(1-\bar{x}), where \bar{x} is a sample mean, \bar{v} is a sample variance$$

b. The ratio of community health workers over population

We used the same method for the ratio of community volunteers over population (see 2-a). The ratio of community health workers over population was available for 67 of total 112 ongoing projects (as of November 2013) in sub-Saharan Africa from project budget documents (Y2012). The fitted distributions are presented in Table S16.

Table S16. Summary of the ratio of community health workers over population and distribution parameters for probabilistic sensitivity analysis

Country	Average	Standard deviation	Beta distribution[1]	
			Alpha (α)	Beta (β)
Angola	1/2,458	0.0004	1	2,241
Burundi	1/4,892	>0.0000	23	114,727
Cameroon	1/9,068	0.0003	0.2	1,602
CAR	1/3,501	0.0001	25	87,483
Chad	1/2,789	0.0001	25	69,676
Congo	1/2,118	0.0001	25	52,911
Equatorial Guinea	1/5,082	>0.0000	25	127,009
Ethiopia	1/14,930	0.0001	1	21,589
Liberia	1/2,920	0.0001	6	18,393
Malawi	1/663	0.0006	7	4,688
Nigeria	1/905	0.0010	1	1,080
South Sudan	1/6,180	0.0001	4	24,603
Tanzania	1/3,471	0.0001	25	86,715
Uganda	1/1,266	0.0002	16	20,812
Average	1/2,223	0.0004	1	2614

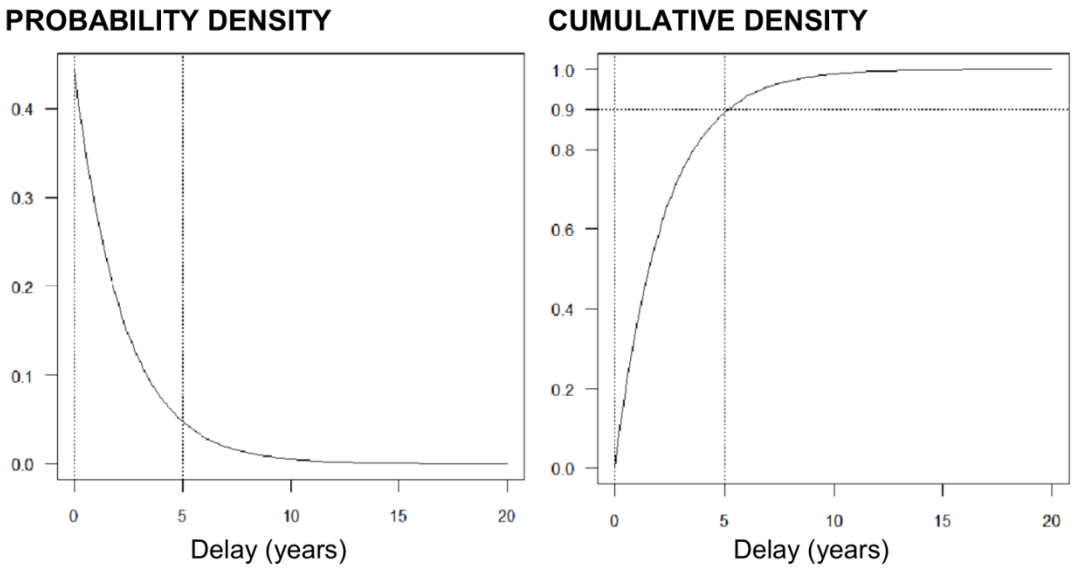
1 Parameters of *Beta(α, β)* were estimated using a method of moments:

$$\hat{\alpha} = \bar{x}\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), \hat{\beta} = (1-\bar{x})\left(\frac{\bar{x}(1-\bar{x})}{\bar{v}} - 1\right), if\, \bar{v} < \bar{x}(1-\bar{x}), where \bar{x} is a sample mean, \bar{v} is a sample variance$$

c. Delay in starting CDTi

We assumed that starting CDTi can be delayed as long as five years. We applied a gamma distribution in which 90% of samples fall into the range of zero and five (Fig S6).

Figure S6. Gamma distribution for the delay in starting and ending CDTi: probability and cumulative density



d. Delay in ending CDTi

We assumed that ending CDTi can be also delayed as long as five years. We applied a gamma distribution in which 90% of samples fall into the range of zero and five (Fig S6).

e. Population growth rate

We used the same method described in 1-d.

Outpatient service costs

Parameters examined to evaluate the robustness of outpatient service costs were outpatient cost per visit, the health facility utilization rate, and the number of patients with severe itching and low vision.

a. Outpatient service cost per visit

We assumed that country-specific outpatient service costs per visit, available from WHO database [18], would be stable over the entire time horizon. To incorporate the uncertainty about this parameter, we applied a gamma distribution for each country assuming the standard deviation to be 20% of the outpatient costs per visit.

b. Health facility utilization rate

The proxy for health facility utilization rate was the average treatment coverage for CDTi over 2010–2012. We assigned a beta distribution and fitted to available data at country and regional levels. For projects in countries for which data were available, we used the fitted distribution for the country; for projects in countries without

available data, we used the distribution at regional level which was fitted to available national average data among endemic African countries. The fitted distributions are described inTable S14.

c. **The number of patients with severe itching and low vision**

The number of patients with severe itching and low vision is one of the health impacts results. The methods to incorporate the uncertainty about this parameter are described in Section 1 (health impacts).

Out-of-pocket payments

To examine the robustness of out-of-pocket payments, we included the parameters selected to examine outpatient service costs (see above), the proportion of total health expenditure incurred as out-of-pocket payments by household, and the transportation costs.

a. **Out-of-pocket payments as proportion of total health expenditure**

Out-of-pocket payments as proportion of total health expenditure were available for each country from WHO database [88]. To incorporate the uncertainty about this parameter, we applied a gamma distribution for each country assuming the standard deviation to be 20% of the data.

b. **Transportation costs**

Our assumption on transportation costs, 17% of outpatient visit costs, was based on the multi-country survey for 39 countries, available from 2010 World Health Report [27]. This survey shows that the average transportation cost as percentage of outpatient visit costs across 14 sub-Saharan African countries is 17% and the standard deviation is 11%. To incorporate the uncertainty about this parameter, we applied a gamma distribution assuming the mean is 17% and the standard deviation to be 11%.

Economic productivity impacts

To examine the robustness of the economic productivity estimated with the human capital approach, we included GDP per capita, the employment rate, the proportion of GDP per capita associated with productivity losses due to severe itching, low vision, and blindness.

a. **GDP per capita**

To incorporate the uncertainty about GDP per capita, we applied a normal distribution for each country assuming the standard deviation to be 20% of the GDP per capita.

b. **Employment rate**

To incorporate the uncertainty about employment rate, we applied a normal distribution for each country assuming the standard deviation to be 20% of the GDP per capita.

c. Productivity loss due to severe itching

We based our assumption about the productivity loss due to severe itching (13% of GDP per capita) on the survey in Ethiopia [21]. This study shows that intermediate onchocercal skin diseases (OSD) cause the income loss by 10%; and severe OSD, by 16%. To incorporate the uncertainty about this parameter, we applied a normal distribution in which the mean is 13% and the 95% confidence interval is 10% to 16%.

d. Productivity loss due to low vision

We based our assumption about the productivity loss due to low vision (38% of GDP per capita) on the survey in Guinea [22]. We applied a normal distribution in which the mean is 38% and the standard deviation is 20% of the mean.

e. Productivity loss due to blindness

We based our assumption about the productivity loss due to blindness (79% of GDP per capita) on the survey in Guinea [22]. We applied a normal distribution in which the mean is 79% and the standard deviation is 20% of the mean.

Economic welfare impacts

To evaluate the robustness of the economic welfare impacts associated with life-year gains due to prevented blindness, we included the predicted years of life lost (YLL).

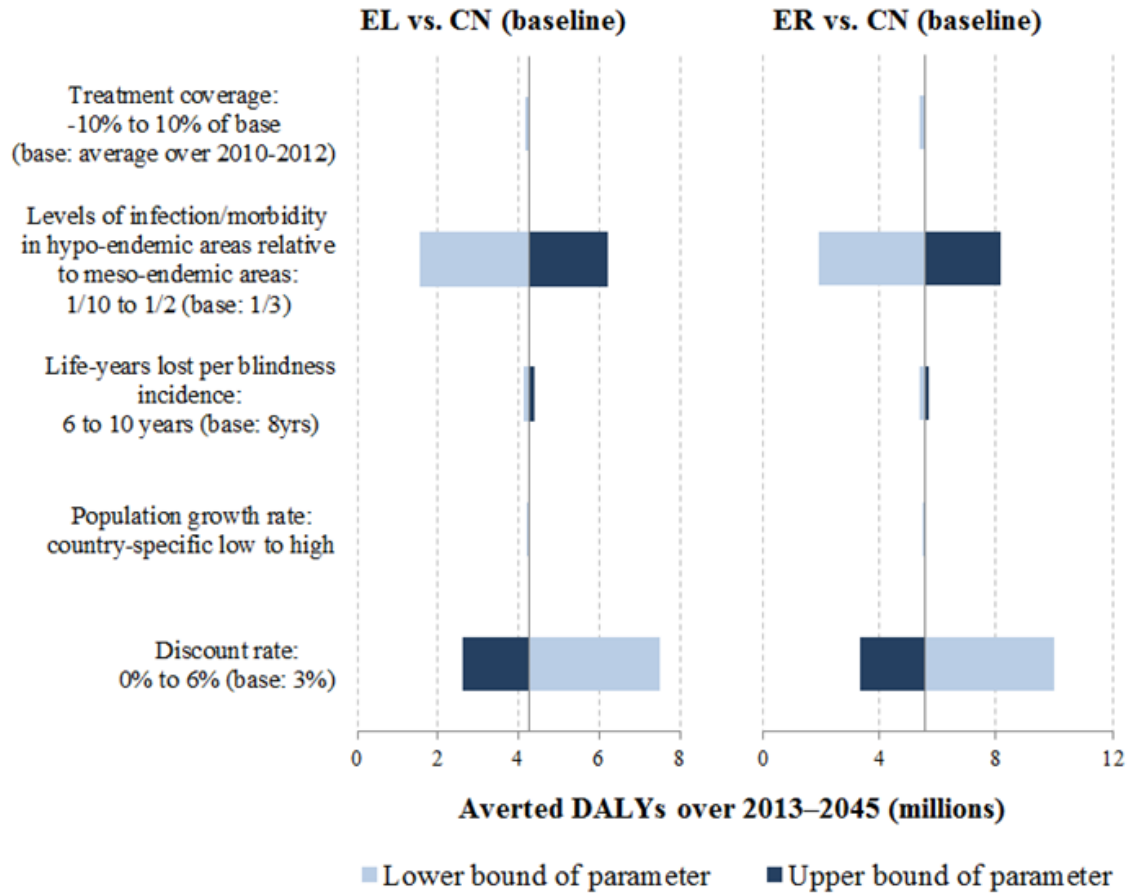
a. Years of life lost

YLL is one of the health impacts results. The methods to incorporate the uncertainty about this parameter are described previously (See above: Health Impacts).

Simulations

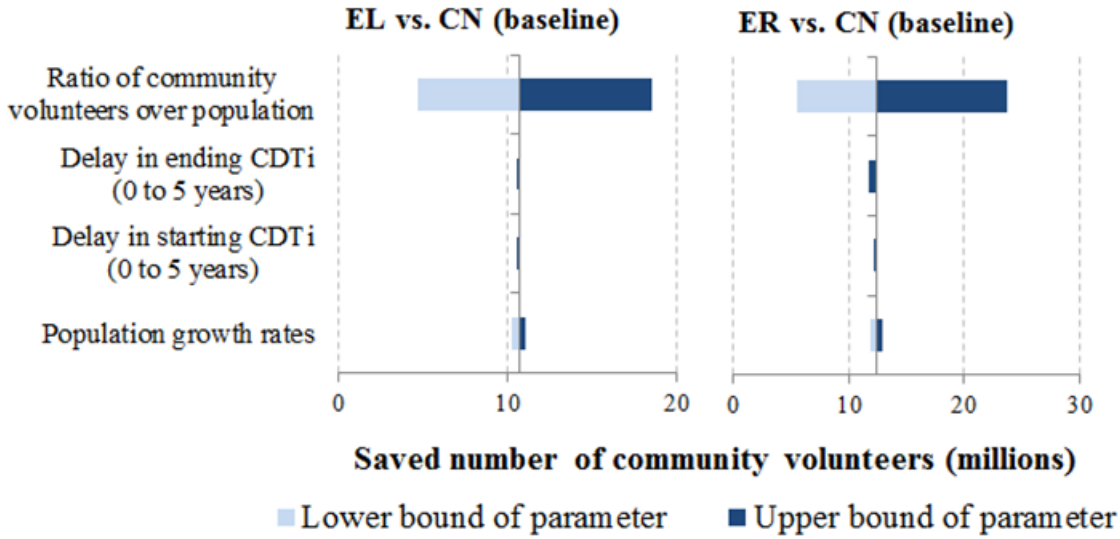
For the PSA for each result, we ran simulation500 times by sampling from the distributions described previously.

Figure S7. One-way deterministic sensitivity analysis for DALYs averted over 2013−2045



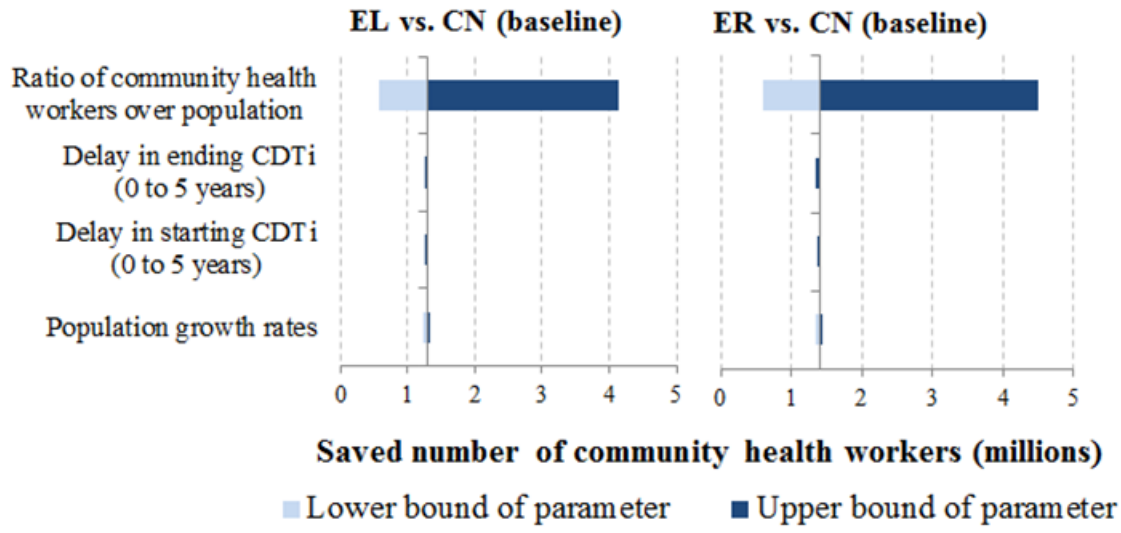
(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S8. One-way deterministic sensitivity analysis for the saved number of required community volunteers over 2013−2045



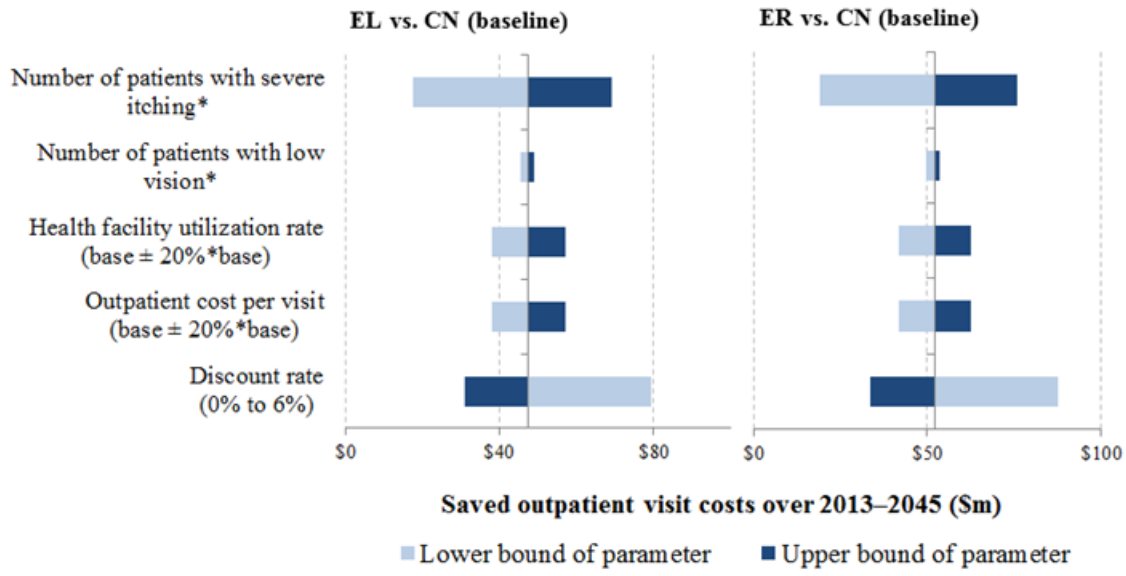
(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S9. One-way deterministic sensitivity analysis for the saved number of required community health workers over 2013−2045



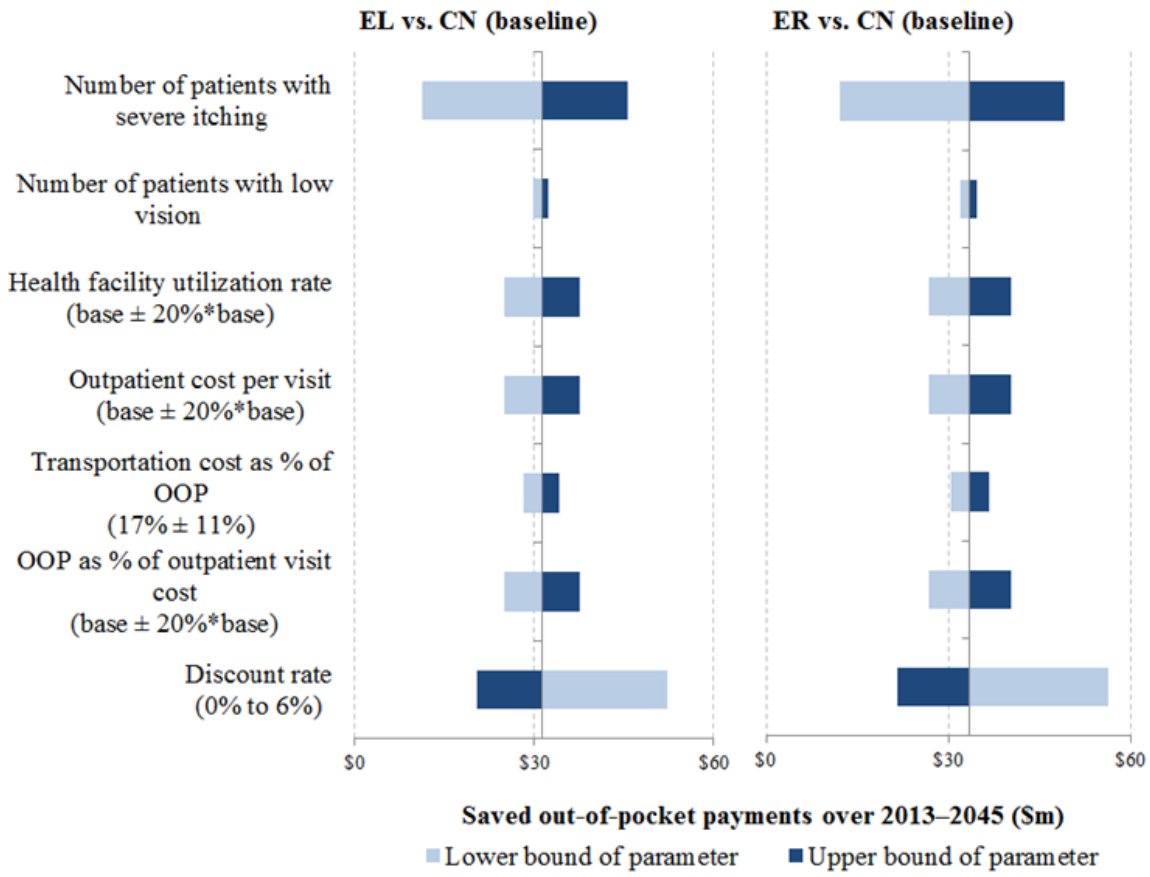
(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S10. One-way deterministic sensitivity analysis for the saved outpatient service costs over 2013−2045



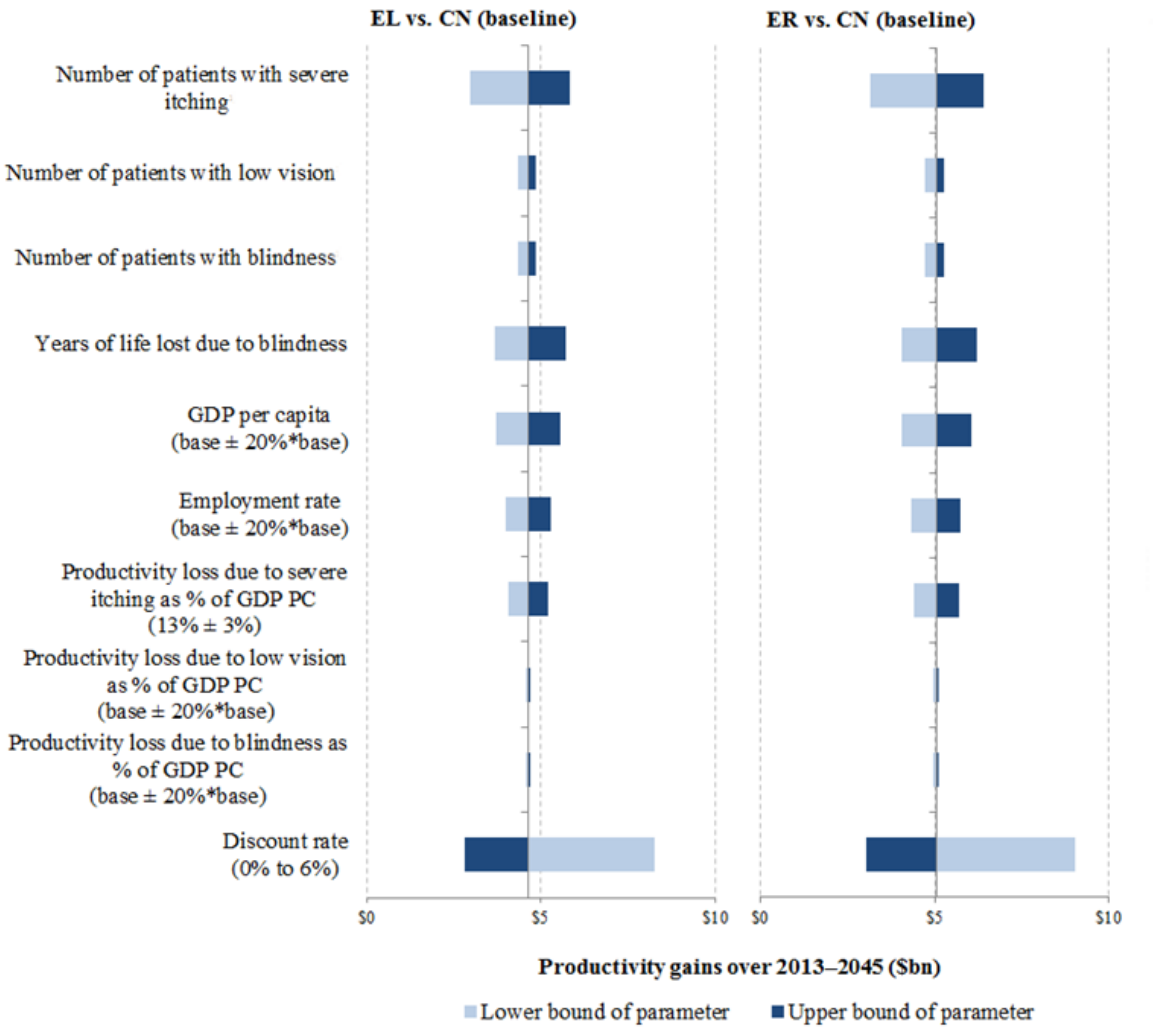
(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S11. One-way deterministic sensitivity analysis for the saved out-of-pocket payments over 2013−2045



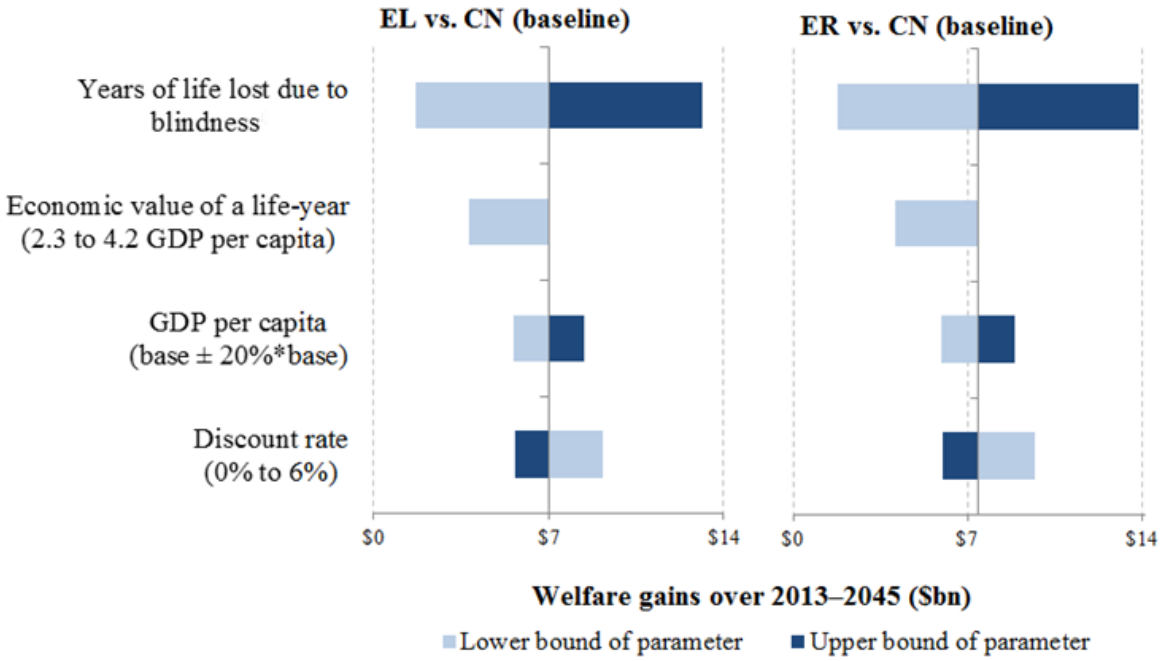
(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S12. One-way deterministic sensitivity analysis for the economic productivity gains over 2013−2045



(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Figure S13. One-way deterministic sensitivity analysis for the economic welfare gains over 2013−2045



(CN: control scenario; EL: elimination scenario; ER: eradication scenario)

Reference List

1. WHO. APOC - status of onchocerciasis in APOC countries. WHO. 2013. http://www.who.int/apoc/onchocerciasis/status/en/index.html Accessed on 25 January 2015.

2. Traore MO, Sarr MD, Badji A, Bissan Y, Diawara L, et al. Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. PLoS Negl Trop Dis. 2012; 6: e1825. doi:10.1371/journal.pntd.0001825.

3. Katabarwa MN, Walsh FF, Habomugisha PF, Lakwo TL FAU - Agunyo S, Agunyo S FAU - Oguttu D, et al. Transmission of onchocerciasis in wadelai focus of northwestern Uganda has been interrupted and the disease eliminated. J Parasitol Res. 2012. 10.1155/2012/748540.

4. WHO. Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation. WHO/HTM/NTD/2012.1. Geneva: WHO. 2012. http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf Accessed on 25 January 2015.

5. London Declaration on neglected tropical diseases. Uniting to Combat NTDs. 2012. http://unitingtocombatntds.org/sites/default/files/resource_file/london_declaration_on_ntds.pdf Accessed on 31 March 2015.

6. Kim YE, Remme JHF, Steinmann P, Stolk WA, Roungou JB, et al. Control, Elimination, and Eradication of River Blindness: Scenarios, Timelines, and Ivermectin Treatment Needs in Africa. PLoS Negl Trop Dis. 2015; 9: e0003664. doi:10.1371/journal.pntd.0003664.

7. Philip E.Coyne, David W.Berk. The Mectizan (ivermectin) donation program for river blindness as a paradigm for pharmaceutical industry donation programs. Washington: World Bank. World Bank. 2001. http://apps.who.int/medicinedocs/documents/s17517en/s17517en.pdf Accessed on 31 January 2015.

8. Plaisier AP, van Oortmarssen GJ, Habbema JD, Remme J, Alley ES. ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. Comput Methods Programs Biomed. 1990; 31: 43-56.

9. Population growth rates. World Population Prospects: the 2012 revision. UN. 2013. http://esa.un.org/wpp/Excel-Data/population.htm Accessed on 11 June 2015.

10. WHO/APOC. Revitalising health care delivery in sub-Saharan Africa: the potential of community-directed interventions to strengthen health systems. Ouagadougou: WHO/APOC. 2007.

http://www.who.int/apoc/publications/EN_HealthCare07_7_3_08.pdf Accessed on 25 January 2015.

11. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. The Lancet. 2012; 380: 2129-2143. http://dx.doi.org/10.1016/S0140-6736(12)61680-8.

12. Coffeng LE, Stolk WA, Zoure HG, Veerman JL, Agblewonu KB, et al. African Programme For Onchocerciasis Control 1995-2015: model-estimated health impact and cost. PLoS Negl Trop Dis. 2013; 7: e2032. 10.1371/journal.pntd.0002032 [doi];PNTD-D-12-00318 [pii].

13. Dolea CF, Stormont LF, Braichet JM FAU - Braichet J-M. Evaluated strategies to increase attraction and retention of health workers in remote and rural areas. Bulletin of the World Health Organization. 2010; 88: 379-385. 10.2471/BLT.09.070607.

14. WHO. APOC - community-directed distributor (CDDs). WHO. 2014. http://www.who.int/apoc/cdti/cdds/en/ Accessed on 05 July 2015.

15. WHO. APOC - community-directed treatment with ivermectin (CDTI) projects. WHO. 2008. http://www.who.int/apoc/cdti/howitworks/en/ Accessed on 09 April 2015.

16. Keating J, Yukich JO, Mollenkopf S, Tediosi F. Lymphatic filariasis and onchocerciasis prevention, treatment, and control costs across diverse settings: a systematic review. Acta Trop. 2014; 135: 86-95. S0001-706X(14)00100-4 [pii];10.1016/j.actatropica.2014.03.017 [doi].

17. Ejere HO, Schwartz E, Wormald R, Evans JR. Ivermectin for onchocercal eye disease (river blindness). Cochrane Database Syst Rev. 2012; 8: CD002219. 10.1002/14651858.CD002219.pub2 [doi].

18. Country-specific unit costs for primary and secondary health care services, WHO-CHOICE. WHO. 2011. http://www.who.int/choice/country/country_specific/en/ Accessed on 24 March 2015.

19. Cost-benefit analysis. In: Michael F.Drummond, Mark J.Sculpher, George W.Torrance, Bernie J.O'Brien, Greg L.Stoddart, editors. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005. pp. 211-246.

20. Jamison DT, Summers LH, Alleyne G, Arrow KJ, Berkley S, et al. Global health 2035: a world converging within a generation, the returns to investing in health (section 2). Lancet. 2013; 382: 1898-1955. S0140-6736(13)62105-4 [pii];10.1016/S0140-6736(13)62105-4 [doi].

21. World Bank and Institute of Pathobiology, University of Addis Ababa. HEALTH AND LABOR PRODUCTIVITY, Economic Impact of Onchocercal Skin Disease (OSD). 1997.

22. Evans TG. Socioeconomic consequences of blinding onchocerciasis in west Africa. Bull World Health Organ. 1995; 73: 495-506.

23. Frick KD, Foster A, Bah M, Faal H. Analysis of costs and benefits of the Gambian Eye Care Program. Arch Ophthalmol. 2005; 123: 239-243. 123/2/239 [pii];10.1001/archopht.123.2.239 [doi].

24. Smith TS, Frick KD, Holden BA, Fricke TR, Naidoo KS. Potential lost productivity resulting from the global burden of uncorrected refractive error. Bull World Health Organ. 2009; 87: 431-437. S0042-96862009000600011 [pii].

25. Shamanna BR, Dandona L, Rao GN. Economic burden of blindness in India. Indian J Ophthalmol. 1998; 46: 169-172.

26. Alonso LM, Murdoch ME, Jofre-Bonet M. Psycho-social and economical evaluation of onchocerciasis: a literature review. Soc Med. 2009; 4: 8-31.

27. Priyanka Saksena, Ke Xu, Riku Elovainio, and Jean Perrot. Health services utilization and out-of-pocket expenditure at public and private facilities in low-income countries World Health Report (2010) Background Paper, No 20. 2010.

28. Henderson JV, Storeygard A, Weil DN. Measuring Economic Growth from Outer Space. American Economic Review. 2012; 102: 994-1028. 10.1257/aer.102.2.994.

29. Noma M, Zoure HG, Tekle AH, Enyong PA, Nwoke BE, et al. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (1) priority areas for ivermectin treatment. Parasit Vectors. 2014; 7: 325. 1756-3305-7-325 [pii];10.1186/1756-3305-7-325 [doi].

30. Zoure H, Noma M, Tekle A, Amazigo U, Diggle P, et al. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (2) pre-control endemicity levels and estimated number infected. Parasites & Vectors. 2014; 7: 326. 10.1186/1756-3305-7-326.

31. Average Visible, Stable Lights, & Cloud Free Coverages, Version 4 DMSP-OLS Nighttime Lights Time Series. US National Geophysical Data Center. 2014. http://ngdc.noaa.gov/eog/dmsp/downloadV4composites.html Accessed on 29 April 2015.

32. Franco-Paredes C, Santos-Preciado JI. Freedom, Justice, and Neglected Tropical Diseases. PLoS Negl Trop Dis. 2011; 5: e1235. doi:10.1371/journal.pntd.0001235.

33. Bailey TC, Merritt MW, Tediosi F. Investing in Justice: Ethics, Evidence, and the Eradication Investment Cases for Lymphatic Filariasis and Onchocerciasis. Am J Public Health. 2015; 105: 629-636. 10.2105/AJPH.2014.302454;doi: 10.2105/AJPH.2014.302454.

34. Scott Barrett. The Smallpox Eradication Game. Public Choice. 2006; 130: 179-207.

35. Barrett S. Stop! The polio vaccination cessation game. The World Bank Economic Review. 2011.

36. Klepac P, Metcalf CJ, McLean AR, Hampson K. Towards the endgame and beyond: complexities and challenges for the elimination of infectious diseases. Philos Trans R Soc Lond B Biol Sci. 2013; 368: 20120137. rstb.2012.0137 [pii];10.1098/rstb.2012.0137 [doi].

37. Hotez PJ. NTDs V.2.0: "Blue Marble Health"-Neglected Tropical Disease Control and Elimination in a Shifting Health Policy Landscape. PLoS Negl Trop Dis. 2013; 7: e2570. doi:10.1371/journal.pntd.0002570.

38. Crump A, Morel CM, Omura S. The onchocerciasis chronicle: from the beginning to the end? Trends Parasitol. 2012; 28: 280-288. S1471-4922(12)00069-4 [pii];10.1016/j.pt.2012.04.005 [doi].

39. WHO/APOC. Report of the external mid-term evaluation of the African Programme for Onchocerciasis Control. JAF16.8. WHO/APOC. 2010. http://www.who.int/apoc/MidtermEvaluation_29Oct2010_final_printed.pdf Accessed on 25 January 2015.

40. WHO. Neglected Tropical Diseases - WHO declares Ecuador free of onchocerciasis (river blindness). WHO. 2014. http://www.who.int/neglected_diseases/ecuador_free_from_onchocerciasis/en/ Accessed on 14 October 2014.

41. WHO. Progress towards eliminating onchocerciasis in the WHO Region of the Americas: verification by WHO of elimination of transmission in Colombia. Wkly Epidemiol Rec. 2013; 88: 381-385.

42. The Carter Center. Current transmission status in the 13 foci of the Americas - geographic distribution of onchocerciasis in the Americas. The Carter Center. 2014. http://www.cartercenter.org/resources/pdfs/health/river_blindness/OEPA-foci.pdf Accessed on 14 October 2014.

43. PAHO/WHO. 52nd Directing Council (65th session of the regional committee, 30 September-4 October 2013, Washington DC, USA) - towards the elimination of onchocerciasis (river blindness) in the Americas. CD52/INF/4. Pan American Health Organization/World Health Organization. Pan American Health Organization/World Health Organization. 2013. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=24390&Itemid= Accessed on 25 January 2015.

44. WHO. 64th World Health Assembly (16 - 24 May 2011, Geneva, Switzerland) - progress report: onchocerciasis control through ivermectin distribution. A64/26. WHO. WHO. 2011. http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_26-en.pdf Accessed on 25 January 2015.

45. WHO. Sustaining the drive to overcome the global impact of neglected tropical diseases - second WHO report on neglected tropical diseases. WHO/HTM/NTD/2013.1. Geneva: WHO. WHO. 2013.

http://www.who.int/iris/bitstream/10665/77950/1/9789241564540_eng.pdf Accessed on 25 January 2015.

46. Diawara L, Traore MO, Badji A, Bissan Y, Doumbia K, et al. Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. PLoS Negl Trop Dis. 2009; 3: e497. doi:10.1371/journal.pntd.0000497.

47. Ernst Strüngmann Forum. Disease eradication in the context of global health in the 21st century (August 29-September 3, 2010, Frankfurt am Main, Germany). Ernst Strüngmann Forum. 2010. http://www.esforum.de/forums/esf07_disease_eradication.html Accessed on 20 August 2015.

48. Tediosi F, Steinmann P, de Savigny D, Tanner M. Developing eradication investment cases for onchocerciasis, lymphatic filariasis, and human African trypanosomiasis: rationale and main challenges. PLoS Negl Trop Dis. 2013; 7: e2446. 10.1371/journal.pntd.0002446 [doi];PNTD-D-12-01493 [pii].

49. WHO. Global plan to combat neglected tropical diseases, 2008-2015. WHO/CDS/NTD/2007.3. Geneva: WHO. WHO. 2007. http://whqlibdoc.who.int/hq/2007/WHO_CDS_NTD_2007.3_eng.pdf Accessed on 25 January 2015.

50. UNITING TO COMBAT NTDs. Delivering on promises and driving progress. Uniting to Combat NTDs. 2014. http://unitingtocombatntds.org/resource/delivering-promises-and-driving-progress-second-progress-report Accessed on 25 January 2015.

51. Damian Walker, Julia Lupp. Guide to preparing an eradication investment case. Ernst Strungmann Forum. 2013. http://eic-guidelines.org/Guide%20to%20Preparing%20an%20EIC_Draft%208.pdf Accessed on 25 January 2015.

52. WHO. Report of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (24-25 April 2012, Geneva, Switzerland). WHO. WHO. 2012. http://www.who.int/entity/neglected_diseases/NTD_STAG_Report_2012.pdf Accessed on 25 January 2015.

53. The Carter Center. Fighting disease: Ethiopia - eliminating river blindness. The Carter Center. 2013. http://www.cartercenter.org/countries/ethiopia-health-river-blindness.html Accessed on 20 April 2014.

54. Uganda Ministry of Health. Health Sector Strategic Plan III, 2010/11-2014/15. http://www.health.go.ug/docs/HSSP_III_2010.pdf Accessed on 25 January 2015. Government of Uganda,Ministry of Health. 2010.

55. UN. Population growth rates. World Population Prospects: the 2012 revision. UN. 2013. http://esa.un.org/wpp/Excel-Data/population.htm Accessed on 23 May 2014.

56. WHO/APOC. Report of the CSA advisory group on onchocerciasis elimination - Annex 1. Predicting the end date of ivermectin treatment in APOC projects. JAF17.7(ii). WHO/APOC. 2011.

57. Coffeng LE, Pion SD, O'Hanlon S, Cousens S, Abiose AO, et al. Onchocerciasis: the pre-control association between prevalence of palpable nodules and skin microfilariae. PLoS Negl Trop Dis. 2013; 7: e2168. 10.1371/journal.pntd.0002168 [doi];PNTD-D-12-00825 [pii].

58. Omura S. Ivermectin: 25 years and still going strong. Int J Antimicrob Agents. 2008; 31: 91-98. S0924-8579(07)00445-1 [pii];10.1016/j.ijantimicag.2007.08.023 [doi].

59. William R.Brieger. Implementation and sustainability of Community-Directed Treatment of Onchocerciasis with ivermectin: a multicountry report. TDR/AFT/RP/96.1. Geneva:UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. 2000.

60. WHO. APOC - how community-directed treatment with ivermectin (CDTI) began. WHO. 2014. http://www.who.int/apoc/cdti/history/en/ Accessed on 20 October 2014.

61. Strebel P, Ottesen EA, Quadros CA, Guirguis S, Hall RG, et al. Group Report: assessing the feasibility of an eradication initiative. In: Stephen L.Cochi, Walter R.Dowdle, editors. Disease eradication in the 21st century: implications for global health. Cambridge, MA: The MIT Press; 2011.

62. WHO/APOC. Revitalising health care delivery in sub-Saharan Africa: the potential of community-directed interventions to strengthen health systems. Ouagadougou: WHO/APOC. 2007. http://www.who.int/apoc/publications/EN_HealthCare07_7_3_08.pdf Accessed on 25 January 2015.

63. WHO/APOC. 19th session of Joint Action Forum (11-13 December 2013, Brazzaville, Congo) - Final communique. WHO/APOC. World Health Organzation/African Programme for Onchocerciasis Control. 2014. http://www.who.int/entity/apoc/about/structure/jaf/Final_Communique_JAF19_Final_English_140114.pdf Accessed 20 April 2014.

64. WHO/APOC. 18th session of the Joint Action Forum (Bujumbura, Burundi, 11-13 December 2012) - Final communique. WHO/APOC. World Health Organzation/African Programme for Onchocerciasis Control. 2012. http://www.who.int/entity/apoc/about/structure/jaf/Final_Communique_JAF_18_English_final_with_annexes.pdf?ua=1 Accessed on 25 January 2015.

65. Alley ES, Plaisier AP, Boatin BA, Dadzie KY, Remme J, et al. The impact of five years of annual ivermectin treatment on skin microfilarial loads in the onchocerciasis focus of Asubende, Ghana. Trans R Soc Trop Med Hyg. 1994; 88: 581-584.

66. Plaisier AP, Alley ES, Boatin BA, van Oortmarssen GJ, Remme H, et al. Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the

Onchocerciasis Control Programme in West Africa. J Infect Dis. 1995; 172: 204-210.

67. Coffeng LE, Stolk WA, Hoerauf A, Habbema D, Bakker R, et al. Elimination of african onchocerciasis: modeling the impact of increasing the frequency of ivermectin mass treatment. PLoS One. 2014; 9: e115886. 10.1371/journal.pone.0115886 [doi];PONE-D-14-09664 [pii].

68. WHO/APOC. Conceptual and operational framework of onchocerciasis elimination with ivermectin treatment. WHO/APOC/MG/10.1. Ouagadougou: WHO/APOC. 2010. http://www.who.int/apoc/oncho_elimination_report_english.pdf Accessed on 25 January 2015.

69. OEPA. Guide for the detection of a potential recrudescence during the period of Post Treatment Surveillance (PTS). Onchocerciasis Elimination Program for the Americas. 2011. http://www.oepa.net/Documentos/GuiaVEPT/Guide_Detection_Potential_Recrudescence_During_PTS_Englishversion.pdf Accessed on 25 January 2015.

70. Merck. 2011 Corporate Responsibility Report. Merck. 2011. http://www.merckresponsibility.com/downloads/MRK_Report_Builder_Full_120824.pdf Accessed on 25 January 2015.

71. WHO/APOC. The World Health Organization Year 2013 Progress Report. JAF19.5. Ouagadougou:WHO/APOC. 2013. http://www.who.int/entity/apoc/publications/JAF195_EN_APOC_PR2013_OK.pdf?ua=1 Accessed on 25 January 2015.

72. Tamarozzi F, Tendongfor N, Enyong PA, Esum M, Faragher B, et al. Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. Parasit Vectors. 2012; 5: 53. 1756-3305-5-53 [pii];10.1186/1756-3305-5-53 [doi].

73. Tabi TE, Befidi-Mengue R, Nutman TB, Horton J, Folefack A, et al. Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. Am J Trop Med Hyg. 2004; 71: 211-215. 71/2/211 [pii].

74. WHO. Neglected Tropical Diseases - PCT databank : lymphatic filariasis. WHO. 2014. http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/ Accessed on 29 September 2014.

75. Bourguinat C, Pion SD, Kamgno J, Gardon J, Duke BO, et al. Genetic selection of low fertile Onchocerca volvulus by ivermectin treatment. PLoS Negl Trop Dis. 2007; 1: e72. 10.1371/journal.pntd.0000072 [doi].

76. Walker M, Specht S, Churcher TS, Hoerauf A, Taylor MJ, et al. Therapeutic efficacy and macrofilaricidal activity of doxycycline for the treatment of river blindness. Clin Infect Dis. 2014. ciu1152 [pii];10.1093/cid/ciu1152 [doi].

77. DNDi. Bayer and DNDi sign first agreement to develop an innovative oral treatment for human river blindness. 9 December 2014. DNDi. 2014. http://www.dndi.org/media-centre/press-releases/2040-pr-bayer-filaria.html Accessed on 17 January 2014.

78. Awadzi K, Opoku NO, Attah SK, Lazdins-Helds J, Kuesel AC. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in Onchocerca volvulus infection. PLoS Negl Trop Dis. 2014; 8: e2953. 10.1371/journal.pntd.0002953 [doi];PNTD-D-13-00311 [pii].

79. Mackenzie CD, Geary TG. Flubendazole: a candidate macrofilaricide for lymphatic filariasis and onchocerciasis field programs. Expert Rev Anti Infect Ther. 2011; 9: 497-501. 10.1586/eri.11.30 [doi].

80. Udall DN. Recent updates on onchocerciasis: diagnosis and treatment. Clin Infect Dis. 2007; 44: 53-60. CID39583 [pii];10.1086/509325 [doi].

81. Lipner EM, Dembele N, Souleymane S, Alley WS, Prevots DR, et al. Field applicability of a rapid-format anti-Ov-16 antibody test for the assessment of onchocerciasis control measures in regions of endemicity. J Infect Dis. 2006; 194: 216-221. JID36019 [pii];10.1086/505081 [doi].

82. WHO/APOC. 12th session of the Joint Action Forum (5-8 December 2006, Dar-es-Salaam, Tanzania). JAF12.9. WHO/APOC. WHO. 2006. http://siteresources.worldbank.org/EXTGLOREGPARPROG/Resources/apoc_so.pdf Accessed on 23 May 2014.

83. WHO/APOC. Strategic Plan of Action and Budget 2016-2025 for elimination of onchocerciasis in Africa. JAF18.9 (ii). Ouagadougou: WHO/APOC. WHO/APOC. 2012. http://www.who.int/apoc/en_apoc_strategic_plan_2013_ok.pdf Accessed on 25 January 2015.

84. WHO/APOC. Concept note: transforming APOC into a new regional entity for oncho & LF elimination and support to other PC/NTD. JAF 19.7. Ouagadougou: WHO/APOC. WHO/APOC. 2013. www.who.int/apoc/en_concept_note_ok.pdf Accessed on 25 January 2015.

85. WHO. Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation. WHO/HTM/NTD/2012.1. Geneva: WHO. 2012. http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf Accessed on 25 January 2015.

86. GDP per capita (current US$), 2012. World Bank national accounts data, and OECD National Accounts data files. World Bank. 2014. http://data.worldbank.org/indicator/NY.GDP.PCAP.CD/countries Accessed on 19 March 2015.

87. Health expenditure, total (% of GDP), 2012. World Health Organization National Health Account database. WHO. 2014. http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS/countries Accessed on 19 March 2015.

88. Out-of-pocket health expenditure (% of total expenditure on health), 2012. World Health Organization National Health Account database. WHO. 2014. http://apps.who.int/nha/database/DataExplorerRegime.aspx Accessed on 13 April 2015.

89. Clement NS, Ghali WA, Donaldson C, Manns BJ. The impact of using different costing methods on the results of an economic evaluation of cardiac care: microcosting vs gross-costing approaches. Health Econ. 2009; 18: 377-388. 10.1002/hec.1363.

90. WHO/APOC. Report of the twenty-ninth session of the technical consultative committee (TCC), Ouagadougou, 14-19 September 2009. DIR/COORD/APOC/REP/TCC29. WHO/APOC. 2010; 80-91.

91. Agriculture value added (% of GDP), 2012. World Development Indicators. World Bank. 2014. http://data.worldbank.org/indicator/NV.AGR.TOTL.ZS/countries Accessed on 19 March 2015.

92. William R.Brieger. Implementation and sustainability of community-directed treatment of onchocerciasis with ivermectin: a multicountry report. TDR/AFT/RP/96.1. Geneva:UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. 2000.

93. Goldman AS, Guisinger VH, Aikins M, Amarillo ML, Belizario VY, et al. National mass drug administration costs for lymphatic filariasis elimination. PLoS Negl Trop Dis. 2007; 1: e67. 10.1371/journal.pntd.0000067 [doi].

94. Wanji S, Tendongfor N, Nji T, Esum M, Che JN, et al. Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. Parasit Vectors. 2009; 2: 39. 1756-3305-2-39 [pii];10.1186/1756-3305-2-39 [doi].

95. WHO/APOC. Addendum for the plan of action and budget 2008-2015. Ouagadougou: WHO/APOC. 2008.

96. Sightsavers. Elimination of onchocerciasis: ten-year strategic fast tracking plan in Sightsavers supported countries 2011-2021. Sightsavers. 2011. http://www.sightsavers.net/about_us/publications/19377_0303_SS%20Oncho%20Report%20Lowres%20(4).pdf Accessed on 31 March 2015.

97. McFarland D, Menzies N, Njoumemi Z, and Onwujekwe O. Study of cost per treatment with ivermectin using the CDTI strategy. African Programme for Onchocerciasis Control (APOC). 2005.

98. Inflation, GDP deflator (annual %). World Developement Indicators. World Bank. 2014. http://data.worldbank.org/indicator/NY.GDP.DEFL.KD.ZG Accessed on 08 May 2015.

99. Official exchange rate (LCU per US$, period average). World Developement Indicators. World Bank. 2014. http://data.worldbank.org/indicator/PA.NUS.FCRF Accessed on 13 April 2015.

100. Barrett S. Eradication versus control: the economics of global infectious disease policies. Bull World Health Organ. 2004; 82: 683-688.

101. Sicuri E, Evans DB, Tediosi F. Can Economic Analysis Contribute to Disease Elimination and Eradication? A Systematic Review. PLoS One. 2015; 10: e0130603. doi:10.1371/journal.pone.0130603.

102. Muela JR and Hausmann-Muela S. Social Aspects of Lymphatic Filariasis, Onchocerciasis and Human African Trypanosomiasis: A Systematic Literature Review. Basel: Swiss Tropical and Public Health Institute. 2013.

103. Shaffer G. International Law and Global Public Goods in a Legal Pluralist World. The European Journal of International Law. 2012; 23: 669-693.

104. United Nations. Open Working Group proposal for Sustainable Development Goals. A/68/970. UN. 2014. https://sustainabledevelopment.un.org/resources/publications Accessed on 09 June 2015.

105. Turner HC, Osei-Atweneboana MY, Walker M, Tettevi EJ, Churcher TS, et al. The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a case study. PLoS Negl Trop Dis. 2013; 7: e2452. 10.1371/journal.pntd.0002452 [doi];PNTD-D-13-00304 [pii].

106. ILO. Global wage report 2008/09: minimum wages and collective bargaining: Towards policy coherence. Geneva: ILO. 2008. http://www.ilo.org/global/publications/WCMS_100786/lang--en/index.htm Accessed on 13 February 2015.

107. Kim YE, Sicuri E, Tediosi F (2015) Financial and economic costs of control, elimination, and eradication of onchocerciasis (river blindness) in Africa (unpublished).

108. APOC (2014) Community-directed treatment with ivermectin (CDTI), http://www.who.int/apoc/cdti/en/, accessed on 15 December 2014.

109. Country-specific unit costs, WHO-CHOICE. WHO. 2011. http://www.who.int/choice/country/country_specific/en/ Accessed on 24 March 2015.

110. Leive A, Xu K. Coping with out-of-pocket health payments: empirical evidence from 15 African countries. Bulletin of the World Health Organization. 2008; 86: 849-856C.

111. Uzochukwu Amakom, Uju Ezenekwe. Implications of households catastrophic out of pocket (OOP) healthcare spending in Nigeria. Journal of Research in Economics and International Finance. 2015; 1: 136-140.

112. Kwesiga B, Zikusooka CM, Ataguba JE. Assessing catastrophic and impoverishing effects of health care payments in Uganda. BMC Health Services Research. 2015; 15: 1-6.

113. Kruk ME, Goldmann E, Galea S. Borrowing And Selling To Pay For Health Care In Low- And Middle-Income Countries. Health Affairs. 2009; 28: 1056-1066.

114. van Doorslaer E, O'Donnell O, Rannan-Eliya RP, Somanathan A, Adhikari SR, et al. Effect of payments for health care on poverty estimates in 11 countries in Asia: an analysis of household survey data. The Lancet. 2014; 368: 1357-1364. http://dx.doi.org/10.1016/S0140-6736(06)69560-3.

115. WHO. WHO guide to identifying the economic consequences of disease and injury. 2009.

116. GDP per capita (current US$), 2013. World Bank national accounts data, and OECD National Accounts data files. World Bank. 2015. http://data.worldbank.org/indicator/NY.GDP.PCAP.CD/countries Accessed on 13 April 2015.

117. Unemployment, total (% of total labor force), 2013 (modeled ILO estimate). World Bank. 2014. http://data.worldbank.org/indicator/SL.UEM.TOTL.ZS/countries?display=default Accessed on 24 March 2015.

118. Labor force participation rate, total (% of total population ages 15+), 2012 (modeled ILO estimate). World Bank. 2015. http://data.worldbank.org/indicator/SL.TLF.CACT.ZS/countries?display=default, Accessed on 24 March 2015.

119. Salomon JA, Vos T, Murray CJ. Disability weights for vision disorders in Global Burden of Disease study - Authors' reply. The Lancet. 2013; 381: 23-24. 10.1016/S0140-6736(12)62131-X;doi: 10.1016/S0140-6736(12)62131-X.

120. The contemporary evidence for a 21st century health workforce agenda. In: WHO, editors. Health workforce 2030: towards a global strategy on human resources for health. Geneva: WHO; 2015. pp. 6-19.

121. Philip E.Coyne, David W.Berk. The Mectizan (ivermectin) donation program for river blindness as a paradigm for pharmaceutical industry donation programs. Washington: World Bank. World Bank. 2001. http://apps.who.int/medicinedocs/documents/s17517en/s17517en.pdf Accessed on 31 January 2015.

122. McCoy D, Bennett S, Witter S, Pond B, Baker B, et al. Salaries and incomes of health workers in sub-Saharan Africa. Lancet. 2008; 371: 675-681. S0140-6736(08)60306-2 [pii];10.1016/S0140-6736(08)60306-2 [doi].

123. Sightsavers. Elimination of onchocerciasis: ten-year strategic fast tracking plan in Sightsavers supported countries 2011-2021. Sightsavers. 2011. http://www.sightsavers.net/about_us/publications/19377_0303_SS%20Oncho%20Report%20Lowres%20(4).pdf Accessed on 31 March 2015.

124. Helen Keller International. Operational plan 2013 for neglected tropical diseases control in Burkina Faso: annual work plan (October 2012 - September 2013). Helen Keller International. 2012. http://endinafrica.org/wp-

content/uploads/2012/11/Burkina-Faso-Work-Plan-FY2013.pdf Accessed on 06 February 2015.

125. APOC - Democratic Republic of the Congo. WHO/APOC. 2015. http://www.who.int/apoc/countries/cod/en/ Accessed on 19 February 2015.

126. Total population, 2003 (last census). Direction Générale des Statistiques, the Gabonese Republic. 2015. http://www.stat-gabon.com/ Accessed on 19 February 2015.

127. List of departments, 2003 (last census). Direction Générale des Statistiques, the Gabonese Republic. 2015. http://www.stat-gabon.com/ Accessed on 19 February 2015.

128. Two-year strategic plan for integrated neglected tropical diseases control in Ghana 2007-2008. The Republic of Ghana, Ministry of Health, Ghana Health Service. 2006. http://www.moh-ghana.org/UploadFiles/Publications/Plan%20for%20Pro-Poor%20Diseases120506091943.pdf Accessed on 11 June 2015.

129. Total population, 2014. Institut National de la Statistique, the Republic of Guinea. 2015. http://www.stat-guinee.org/ Accessed on 19 February 2015.

130. List of prefectures by region, 2014. Institut National de la Statistique, the Republic of Guinea. 2015. http://www.stat-guinee.org/ Accessed on 19 February 2015.

131. Total population, 2009 (last census). Instituto Nacional de Estatística e Censos, Republic of Guinea-Bissau. 2015. http://www.stat-guinebissau.com/ Accessed on 19 February 2015.

132. List of sectors by region, 2009 (last census). Instituto Nacional de Estatística e Censos, Republic of Guinea-Bissau. 2015. http://www.stat-guinebissau.com/ Accessed on 19 February 2015.

133. Total population, 2009 (last census). Institut National de la Statistique, Mali. 2015. http://www.instat-mali.org/ Accessed on 19 February 2015.

134. List of districts and circles by region, 2009 (last census). Institut National de la Statistique, Mali. 2015. http://www.instat-mali.org/ Accessed on 19 February 2015.

135. Total population, 2007 (last census). Instituto Nacional de Estatistica, Mozambique. 2015. http://www.ine.gov.mz/ Accessed on 19 February 2015.

136. List of districts, 2007 (last census). Instituto Nacional de Estatistica, Mozambique. 2015. http://www.ine.gov.mz/ Accessed on 19 February 2015.

137. Total population, 2013. Agence Nationale de la Statistique et de la Démographie (ANSD), Republic of Senegal. 2015. http://www.ansd.sn/ Accessed on 19 February 2015.

138. List of departments by region, 2013. Agence Nationale de la Statistique et de la Démographie (ANSD), Republic of Senegal. 2015. http://www.ansd.sn/ Accessed on 19 February 2015.

139. National plan of action for intergrated control of onchocerciaisis, schistosomiais, soil transmitted helminthiasis and elimination of lymphatic filariasis in Sierra Leone 2006-2010. The Ministry Of Health and Sanitation of Sierra Leone. 2006. http://files.givewell.org/files/Round2Apps/Cause1/GNNTDC/B/Sierra%20Leone%20-%20Plan%20of%20Action%20for%20integrated%20control-final.doc Accessed on 06 February 2015.

140. APOC - country profiles: Sudan. WHO/APOC. 2015. http://www.who.int/apoc/countries/sdn/en/ Accessed on 06 February 2015.

141. Andrew Briggs, Mark Sculpher, Karl Claxton. Making decision models probabilistic. In: Decision modelling for health economic evaluation. New York: Oxford University Press; 2006. pp. 77-120.

142. Keating J, Yukich JO, Mollenkopf S, Tediosi F. Lymphatic filariasis and onchocerciasis prevention, treatment, and control costs across diverse settings: a systematic review. Acta Trop. 2014; 135: 86-95. S0001-706X(14)00100-4 [pii];10.1016/j.actatropica.2014.03.017 [doi].

143. Ngoumou P, Essomba RO, Godin C. Ivermectin-based onchocerciasis control in Cameroon. World Health Forum. 1996; 17: 25-28.

144. Amazigo U, Noma M, Boatin BA, Etya'ale DE, Seketeli A, et al. Delivery systems and cost recovery in Mectizan treatment for onchocerciasis. Ann Trop Med Parasitol. 1998; 92 Suppl 1: S23-S31.

145. Kipp W, Burnham G, Bamuhiiga J, Weis P, Buttner DW. Ivermectin distribution using community volunteers in Kabarole district, Uganda. Health Policy Plan. 1998; 13: 167-173.

146. Katabarwa MN, Habomugisha P, Richards FO, Jr. Implementing community-directed treatment with ivermectin for the control of onchocerciasis in Uganda (1997-2000): an evaluation. Ann Trop Med Parasitol. 2002; 96: 61-73. 10.1179/000349802125002419 [doi].

147. Onwujekwe O, Chima R, Shu E, Okonkwo P. Community-directed treatment with ivermectin in two Nigerian communities: an analysis of first year start-up processes, costs and consequences. Health Policy. 2002; 62: 31-51. S0168851001002263 [pii].

148. Waters HR, Rehwinkel JA, Burnham G. Economic evaluation of Mectizan distribution. Trop Med Int Health. 2004; 9: A16-A25. 10.1111/j.1365-3156.2004.01210.x [doi];TMI1210 [pii].

149. Ndyomugyenyi R, Lakwo T, Habomugisha P, Male B. Progress towards the elimination of onchocerciasis as a public-health problem in Uganda:

opportunities, challenges and the way forward. Ann Trop Med Parasitol. 2007; 101: 323-333. 10.1179/136485907X176355 [doi].

150. Evans D, McFarland D, Adamani W, Eigege A, Miri E, et al. Cost-effectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria. Ann Trop Med Parasitol. 2011; 105: 537-547. 10.1179/2047773211Y.0000000010 [doi].

151. Turner HC, Walker M, Churcher TS, Osei-Atweneboana MY, Biritwum NK, et al. Reaching the london declaration on neglected tropical diseases goals for onchocerciasis: an economic evaluation of increasing the frequency of ivermectin treatment in Africa. Clin Infect Dis. 2014; 59: 923-932. ciu467 [pii];10.1093/cid/ciu467 [doi].

152. Makenga Bof JC, Maketa V, Bakajika DK, Ntumba F, Mpunga D, et al. Onchocerciasis control in the Democratic Republic of Congo (DRC): challenges in a post-war environment. Trop Med Int Health. 2015; 20: 48-62. 10.1111/tmi.12397 [doi].