Towards an Investment Case for Neglected Tropical Diseases

Including new analysis of the cost of intervening against preventable NTDs in sub-Saharan Africa

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July 29 2013
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The findings, interpretations, and conclusions expressed in this document represent the views of the authors and do not necessarily reflect the views of their organizations, or the governments they may represent.

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Summary

Background

Neglected Tropical Diseases (NTDs) are most common among the poor and rural populations. They are endemic in 149 countries and affect an estimated 1.4 billion people with insidious, chronic and debilitating morbidity. WHO has proposed a roadmap for eradication and elimination by 2020. Of the 17 NTDs recognized by WHO, five may be controlled by preventive chemotherapy (PCT) based on mass drug administration, and five by intensified disease management (IDM). Treatments for these ten have been donated through the London Declaration by pharmaceutical manufacturers. This paper estimates the cost of delivering the donated treatments, using a review of existing studies as well as a new analysis for PCT NTDs in Africa. The cost of controlling the other seven NTDs is not discussed here, through lack of data.

Methods and Findings

Previous cost estimates were collected from desk reviews of regional programs and from a "top-down" funding gap analysis of the resources needed to achieve the global goals of the London Declaration. We have conducted a new 'bottom-up' cost analysis, based on the national plans for NTD programs developed with the support of WHO by the governments in 36 countries in sub-Saharan Africa. This estimates the elimination costs through 2040 for the five PCT NTDs in Africa, which contribute 90% of the NTD burden on the continent, at US$0.26 per capita annually. The "top-down" and "bottom-up" estimates suggest the annual resource requirements in Africa for PCT NTDs are US$142 million and U$199 million respectively, while the management of IDM NTDs is estimated at 6.3% and 8.4% of these totals, respectively. There is considerable variation between the estimated costs for IDM diseases, suggesting that further research is required into the costs of these diseases in particular.

Conclusion

The elimination of the ten NTDs for which drugs have been donated by the pharmaceutical industry, represents good value for money, given the very low per capita expenditure and the high realism of the outcome based on well-documented experience. Much of the burden of NTDs in 1.4 billion of the poorest people in South Asia and sub-Saharan Africa could be prevented for an annual cost that is likely well under US$1 billion, and probably around US$300 million to US$400 million per annum, through a combination of community based MDA and case management. The investment would decline beyond 2020 as transmission is interrupted and as the public health challenge reduces to a level that can be managed by the public health system, adding to the aggregate cost-efficiency of this approach in the long run.

Contents

1. Introduction

The Neglected Tropical Diseases (NTDs) are diseases that are most common among the poor and rural populations. They are a group of 17 diseases caused by heterogeneous pathogens of public health importance, traditionally afforded low priority in service delivery, research into new or improved medicines or investment in control. The NTDs are endemic in 149 countries [1] and affect an estimated 1.4 billion people globally [2] but there is a lack of accurate data since cases are under-reported in these populations, hence it is likely that the burden of disease is under-estimated. They have also been called the diseases of neglected people because they affect some of the poorest communities in the world. While some infections result in death, they are more typically associated with insidious, chronic and debilitating morbidity, including retardation of children's mental and physical development, blindness and stigmatizing disfigurement.

National and international efforts to control or eliminate these diseases have grown significantly in recent years. The World Health Organization (WHO) has recognized these diseases as a priority for control, and has proposed a roadmap for accelerating the work to overcome the global impact of NTDs, including eradication and elimination of several by 2020 [1]. Treatment for ten of the most common NTDs has been donated by pharmaceutical manufacturers (see section below: 'Availability of Treatment'). While individual commitments by companies were made over time, a collective launch of all the donations was made through the London Declaration in January 2012 [3].

As countries and the global community move to control or eliminate these diseases it becomes increasingly important to understand the cost and value for money of NTD control and elimination efforts. To understand the cost of delivering NTD treatment, researchers have access to a number of previously published regional studies and one global estimate, all of which use desk analysis and a 'top-down' approach based on costing the estimated population requiring treatment. In this paper we use these existing studies as well as a new analysis for Africa to provide an initial estimate of the global costs of addressing the NTDs.

To estimate the costs in Africa we have conducted a new 'bottom-up' cost analysis, based on the national plans for NTD programs developed by the governments in 36 countries in sub-Saharan Africa. The new analysis focuses on the five NTDs that are estimated to contribute 90% of the NTD burden in Africa. All of these diseases can be treated by preventive chemotherapy (PCT) through mass drug administration (MDA), and all benefit from the availability of free donated drugs. In this analysis we project the burdens and estimate the costs to 2040. This is a long enough period to ensure that the technical orientations on pre-treatment levels, treatment coverage, break in transmission and post treatment stoppage surveillance to confirm break in transmission for these disease are fully incorporated.

In the new analysis we estimate these costs specifically for sub-Saharan Africa, and then use these estimates alongside the previous estimates with the specific objective of estimating the resources required to achieve control and elimination by 2040.

2. Background

Prevention, control, elimination and eradication of NTDs rely on five main public health approaches: preventive chemotherapy (PCT) based on mass drug administration (MDA); individual case management, commonly called intensified disease management (IDM); vector control; safe water, sanitation and hygiene; and veterinary public health measures for zoonotic diseases [1]. This paper will focus on the two major interventions, PCT and IDM.

We have made no attempt to be exhaustive in our review of the literature, as several comprehensive reviews of NTDs have been published recently. Along with the two WHO reports on NTDs [4,5], three technical literature reviews have been conducted: *The Causes and Impacts of Neglected Tropical and Zoonotic Diseases* by the Institute of Medicine [6], *Social and Economic Impact Review on Neglected Tropical Diseases* from the Hudson Institute [7], and *Why Neglected Tropical Diseases Matter in Reducing Poverty* from the Overseas Development Institute [8].

Seventeen NTDs are currently recognized by the World Health Organization (WHO). Of these, five NTDs are controlled via PCT. These include the following infections: lymphatic filariasis (LF), onchocerciasis (river blindness), schistosomiasis (bilharziasis), trachoma, and soil-transmitted helminthiasis (STH). The latter includes ascariasis (roundworm), trichuriasis (whipworm) and ancylostomiasis (hookworm). These five PCT NTDs make up over 90% of the disease burden [7].

The other NTDs rely on interventions other than PCT, primarily innovative and intensified disease management (IDM). The five IDM diseases addressed in this paper include: Buruli ulcer disease (*Mycobacterium ulcerans* infection), Chagas disease (American trypanosomiasis), human African trypanosomiasis (sleeping sickness or HAT), leishmaniasis, and leprosy.

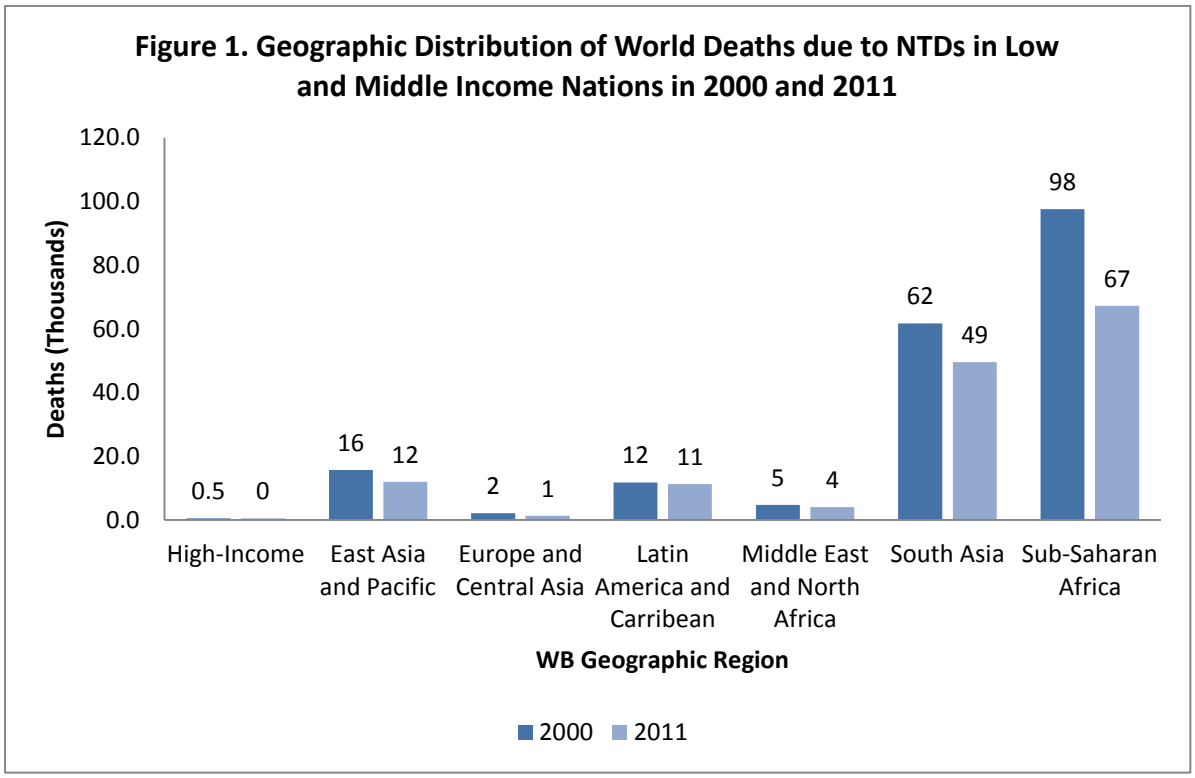
The remaining seven NTDs require other specific approaches, including vaccines, intensive vector management, and veterinary public health. These diseases include: cysticercosis, dengue, dracunculiasis (guinea-worm disease), echinococcosis, endemic treponematoses (Yaws), foodborne trematode infections (including fascioliasis), and rabies. These are not addressed in the results of this paper, but the cost implications of these diseases are discussed in Table 3.

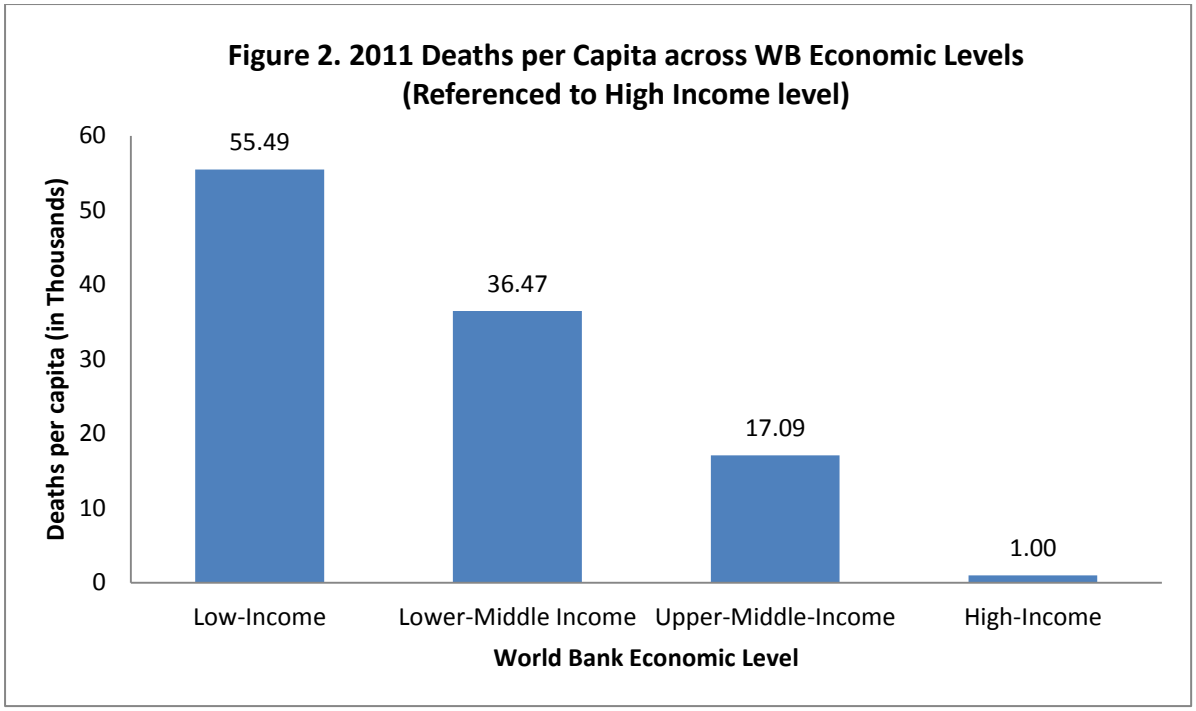
2.1 The Burden of NTDs

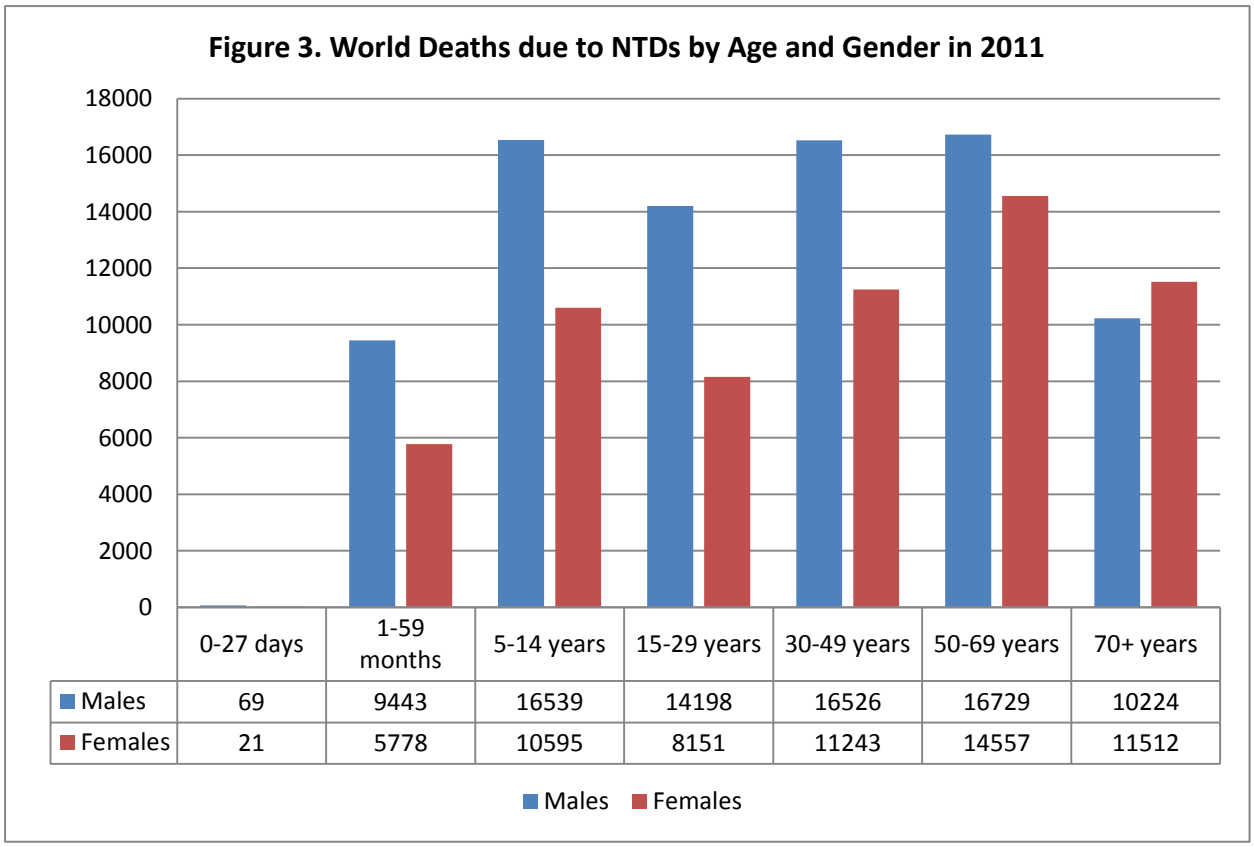
There is specific mortality attributed to NTDs, with the greatest mortality in Sub-Saharan Africa and South Asia and in low income countries. These are diseases of the poorest populations and even within low income countries are most prevalent in the poorest regions (See Figure 1). For example, visceral leishmaniasis in India is largely focused in one state, and trachoma in West Africa is particularly prevalent in the Sahel. Thus the overall burden of NTDs is diluted in global estimates, and yet these diseases remain particularly significant risk factors for poor and deprived communities.

The mortality estimates shown in the figures below are based on the results of the WHO Global Health Estimates (GHE) study for the years 1990-2011, gathered from the latest available national information on levels of mortality and cause distributions as well as information from WHO programs [9]. The estimates include the aggregated mortality reported for: trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, onchocerciasis, leprosy, dengue, trachoma, ascariasis, trichuriasis, and hookworm.

Figure 1 shows the mortality caused by NTDs in 2000 and 2011 in each of the World Bank geographic regions of the world, with high income countries separated out of their respective regions into a single category. The mortality is concentrated in Sub-Saharan Africa and South Asia. All regions have shown significant decreases in NTD mortality between 2000 and 2011, likely reflecting the growing concern about the health of the poor. As shown in Figure 2, NTDs disproportionately affect the populations of low-income countries. This figure shows the data corrected for population size; although mortality rates are higher in poor countries, the absolute number of deaths is greater in Lower-Middle Income countries due to the greater size of the population. While many diseases of the poor are acute and have their greatest impact on children, the chronic and insidious effects of NTDs accumulate over time and cause deaths across the lifespan, as shown in Figure 3. As with most other causes of mortality, the rates are disproportionately higher in men.







	0-27 days	1-59 months	5-14 years	15-29 years	30-49 years	50-69 years	70+ years
Males	69	9443	16539	14198	16526	16729	10224
Females	21	5778	10595	8151	11243	14557	11512

These mortality data provide important evidence of the pattern of disease, but are underestimates of the real burden for three main reasons. First, the consequences of infection lead to premature mortality which is not captured in the "by cause" estimates. For example, blindness is a known risk factor for premature mortality, and a particularly important additional risk for people living in poverty, and onchocerciasis and trachoma can be the most

important causes of blindness in the communities in which they occur. Yet the "by cause" estimates attribute no mortality to these diseases, or to secondary blindness as a cause of mortality. Similarly, the gross effects of chronic elephantiasis are associated with significant secondary infection and disability, yet no mortality is attributed causally to LF. In addition, although NTDs are known to contribute to other important causes of mortality, such as epilepsy (the cause of 233,000 deaths globally) and anaemia (90,000 deaths), the scale of the NTD contribution is unknown.

The second burden that is not captured is the effect of these diseases on function. These effects can be particularly consequential when they inhibit skills acquisition and employability, and reduce earning capacity. It is in these areas that the insidious effects of NTDs are particularly important: for example, IQ points are lost due to schistosomiasis and STH infection; stigma and social rejection are sequelae of elephantiasis and of the unremitting itching of onchocerciasis; and low vision is associated with onchocerciasis and trachoma. Some estimates have been made: for example, with schistosomiasis and STH the annual rate of absenteeism is equivalent to more than 200 million teaching years, and the average IQ loss per worm infestation is 3.75 points, amounting to a total IQ loss of 633 million points for the world's low income countries [10]. Globally the loss in terms of economic productivity for trachoma sufferers is estimated at US$ 8 million when trichiasis is included.

Finally, there is a third uncharacterized burden which is a consequence of the life-long health costs of managing chronic, debilitating disease. These can expose the individual to potentially catastrophic health care costs: for example the management costs of Chagas disease are estimated at US$474 per person per annum [11].

2.2 Availability of Treatment

While many of the consequences of NTD infection are irreversible, much of the burden can be prevented with the available interventions. Based on the projections here that assume the achievement of the WHO 2020 goals, more than 80% of the disease and mortality attributed to NTDs could be avoided.

Effective treatment is available for all the PCT NTDs, and sufficient donated drugs have been pledged by their manufacturers to supply the needs for PCT in endemic countries (See Table 1). Some IDM NTDs lack effective therapies, but where treatments exist they too have been donated, and elimination is estimated to be achievable for several of these. The control or elimination of PCT NTDs is implemented through various delivery systems, including schools, the cost of which may not be fully incurred by the health sector. IDM depends on the primary health care system, including mobile teams in some instances.

Table 1. NTD Drug Donations

	Disease	Drug	Company
PCT NTDs	Onchocerciasis	Ivermectin	Merck & Co. Inc.
	Lymphatic Filariasis	Albendazole	GlaxoSmithKline
		Ivermectin	Merck & Co. Inc.
		Diethylcarbamazine (DEC)	Eisai/Sanofi
	Blinding Trachoma	Azithromycin	Pfizer
	Soil-Transmitted Helminths (Ascariasis/ Trichuriasis/ Hookworm)	Mebendazole	Johnson and Johnson
		Albendazole	GlaxoSmithKline
	Schistosomiasis	Praziquantel	Merck-KGaA
IDM NTDs	Leishmaniasis	Amphotericin B	Gilead
	Chagas disease	Nifurtimox	Bayer
	Human African trypanosomiasis	Eflornithine Melarsoprol Pentamadine	Sanofi
		Suramin Nifurtimox	Bayer
	Leprosy	Multidrug therapy (rifampicin, clofazimine and dapsone in blister packs) and loose clofazimine	Novartis

Much of the current interest in NTDs is a result of the extraordinary opportunity for cost-saving offered by these donations. The success of the onchocerciasis program APOC, the first NTD program to benefit from a substantial drug donation, has been attributed largely to the fact that it is based around a Public Private Partnership model. The contribution of the private sector is key to the long term cost-efficiency of the private-public partnerships around NTDs [12].

The exact value of the donated products for NTDs is not knowable – since in many cases these drugs are not offered in the same format on the commercial market - but estimated to be of the order of US$2-3 billion per year, increasing to US$ 8-12 billion by 2020 [13]. Within this package, the value of LF donated drugs alone is estimated to be US$1.5 billion per year and that of onchocerciasis to be in the region of US$1 billion. The historical investments made are in the order of US$3 billion for onchocerciasis alone [14].

2.3 Existing NTD Cost Estimates

Prior to 2012, efforts to estimate the cost associated with delivering NTD treatment have been largely regional, limited to a sub-set of NTDs, and disease-specific. One large-scale, global estimate of NTD control costs has been undertaken, based on global targets set out in the London Declaration [3] and the WHO NTD Roadmap through 2020 [1]. All the existing estimates are based on desk-studies using the population at risk and the cost of treatment per capita as the basis for estimation.

Local and regional estimates

In the Asia Pacific region it is estimated that the control or elimination of STH, lymphatic filariasis and schistosomiasis by 2020 will require US$243 million, at a cost from US$0.02 to US$ 0.19 per person treated when treated in disease-specific campaigns [15]. Analysis for Latin America and the Caribbean suggests that lymphatic filariasis, onchocerciasis, and trachoma together can be eliminated by 2020, at a per capita cost of US$0.51, and a total cost of US$128 million, of which STH will cost $41 million [16]. There is considerable regional variation in the size of at risk populations. For instance in Latin America and the Caribbean about 350,000 persons are targeted for MDA for onchocerciasis compared to about 150 million in the Africa region [16].

Global estimate

The first major NTD cost estimate comes from a top-down, funding gap analysis of the resources needed to achieve the goals of the London Declaration, to control and eliminate 10 NTDs in line with the WHO goals by 2020 [17]. The study estimated disease burden based on a combination of sources including regional epidemiological projections from WHO, modelled using historical trends, literature reviews and in-depth interviews. Unit costs were calculated for MDA for PCT diseases and screening/case detection and treatment for IDM diseases. These costs include personnel, infrastructure, supplies, transportation and overhead but exclude the cost of drugs, as they are donated.

The analysis concluded that the total resources needed for the ten NTDs in question[5] during the period from 2012-2020 is US$5.3 billion, amounting to an average of US$590 million annually. Of this, the five PCT diseases require US$3.2 billion over the nine year period, an average of US$354 million per year, with sub-Saharan Africa and Southeast Asia requiring 40 per cent and 34 per cent respectively. The total resources needed for the five IDM diseases during this period is US$1.2 billion, an average of US$130 million per year, with Latin American accounting for 87 per cent due to the high prevalence and cost associated with Chagas disease (See Table 2).

[5] These diseases include the five PCT diseases (lymphatic filariasis, soil-transmitted helminthes, schistosomiasis, trachoma and onchocerciasis) plus leprosy, Chagas disease, human African trypanosomiasis, visceral leishmaniasis, and guinea worm disease.

Table 2. NTD Cost Estimates from Global 'Top-Down' Funding Gap Analysis

Disease		Activity	Unit Cost (US$)	Total Cost (2012-2020)	Average Cost per year
Preventive Chemotherapy (PCT) diseases		Mass Drug Administration	0.49	US$3.2 billion	US$354 million
Intensified Disease Management (IDM) diseases	Chagas Disease	Vector control[6]	31.62	US$1.2 billion	US$130 million
		Screening	13.71		
		Treatment	1,657.63		
	Leprosy	Case detection	201.35		
		Treatment	149.41		
	Human African Trypanosomiasis	Screening	1.64		
		Treatment	605.75		
	Visceral Leishmaniasis	Case detection	129.11		
		Treatment	47.39		
PCT and IDM diseases				**US$4.4 billion**	**US$484 million**

All of these estimates were intended to provide a broad idea of the likely costs. They are "top-down" or overview estimates and are not grounded in the actual plans of the individual countries. It was therefore decided to use the example of sub-Saharan Africa, which is estimated to suffer 50% of the burden of NTDs, to prepare a more detailed estimate of costs, based on a "bottom-up" approach starting from national plans.

[6] The cost of vector control for Chagas' disease, as well as surgery for trachoma were not included in the total cost estimates. Costs for guinea worm were also excluded because the disease is on track for elimination in 2015 and no further resources are expected to be required.

3. New Analysis of NTD Costs for Sub-Saharan Africa

Starting in 2012, and with the support of the WHO/AFRO NTD Programme, most countries in sub-Saharan Africa have developed national level "NTD Master Plans" for controlling NTDs. WHO/AFRO commissioned a report of the resource requirements for eliminating NTDs as diseases of public health significance by 2020, utilizing Master Plan budgets [18]. This analysis, *Financial Resource Requirements for Neglected Tropical Diseases in the WHO African Region: 2013-2020*, concluded that the total cost for the African region from 2013 to 2020 is estimated at US$2.57 billion, 51% of which would go to MDA activities. The average cost required annually is US$321.7 million to cover an estimated average population of 512 million people. The cost per person on the average is US$0.62. An estimated 13% of the total budget would be driven by the costs associated with non-PCT NTD interventions (i.e. IDM, vector control, case management, etc.). This total amount however excludes financial requirements of the African Programme for Onchocerciasis Control (APOC) whose estimated budget for 2016 – 2020 is put at US$88.4million.

This analysis offered the first 'bottom-up' estimate of NTD costs but had some limitations. The analysis involved a simple projection calculated on Microsoft Excel and extended only to 2020. While many of the NTDs in question are expected to be controlled by 2020, full elimination and the diseases surveillance required to certify it may realistically not be achieved for many more years. Furthermore, the budgets attached to these plans were developed by the country teams, and reflect their individual perspectives on the costs of implementing control over a 5 year period. The budget estimates have not been independently validated and exhibit considerable variation in unit costs.

For the new analysis, we have used the national NTD plans to calculate a new cost analysis, with some specific changes. The analysis focuses on the five PCT NTDs in the Africa region, which make an estimated 90% of the burden on the continent [7]. Later analyses will seek to address the IDM diseases as well. The analysis has been extended through 2040, which more realistically captures the cost of not only controlling and eliminating these diseases, but also the necessary years of mapping and surveillance once these goal have been achieved.

Here we present this new analysis, beginning with an explanation of the methodology used, followed by our calculations of the target populations for each of the five diseases, estimations of the costs of drugs and activities, and finally the estimated total cost of elimination of the five PCT NTDs from 2014-2040.

3.1 Methodology

Estimating the target population

The data used to estimate target populations comes from NTD Master Plans developed by the Ministries of Health of the WHO Africa region [18]. Each of the 36 countries undertook a country by country analysis of the targeted NTDs led by the country program managers. Each country used their own population growth rates and pyramids to determine the target population based on WHO guidance on how each disease target population is derived. The

main demographic categories were Pre-School Age Child (Pre-SAC), School Age Child (SAC) and Adults, corresponding to each disease treatment protocol. Where women of child-bearing age were targeted, the population figure was added to the adult population. Minimal adjustments to data were made where they were missing or where obvious errors were identified. In some instances the country managers were contacted to clarify the data. The analysis focused only on the five PCT NTDs, as these constitute almost 90% of the burden of NTDs in the Africa region [7].

The base year population adopted for this analysis was 2014 for all countries, which was extrapolated through to 2040 using an average population growth rate of 2.3% based on the 36 countries that provided data. None of the countries had estimated declines in target population due to systematic elimination. For all the diseases there is a matrix correlation among levels of pre-treatment prevalence, geographic and therapeutic coverage, the population cohort and the number of years of treatment to achieve break in transmission. For the purpose of this analysis each country was considered a transmission zone. The rate of decline of target population was thus calculated based on published literature or expert opinion on the period probabilities towards attaining elimination for each of the diseases in each country [5,19,20,21]. The target population estimates were grouped into periods, with the first period running until 2020, following the WHO NTD Roadmap to coincide with the first period of rapid decline and disease elimination, and the subsequent grouped in five year periods.

Based on the projected target population figures for each of the diseases, a logarithmic trend line was developed using Microsoft Excel. The target population figures generated by the logarithmic trend served as a proxy to compensate for various recommendations in each of the disease areas to lower the threshold for mass treatment towards elimination so that all those infected can receive treatment [21,22]. This was used to forecast drug needs and cost. For each person in the target population, the WHO treatment protocol was used to calculate the quantity of drugs required [5].

Estimating drug costs

A standardized unit drug delivery cost was adopted: praziquantel at US$0.08, albendazole/ mebendazole 500 mg U$0.002, Diethylcabamazine US$0.004 and TEO US$0.164 [18]. Donated drugs were not included in the cost estimates. These were held constant throughout the estimate and multiplied by the projected targeted population. Program unit cost estimates were derived from the plans based on the base year aggregated cost per component and extrapolated over time. It is assumed that there is no inflation or deflation and items are stated at their nominal cost from any prior date. For capital equipment and vehicle replacement, costs were modified by the revaluation of assets as held at current price. Recurrent expenditure was treated in unadjusted equivalents paid in the normal course of business. This method was used and adapted because of limitations to deal with the effects of changing prices over time.

Estimating activity costs

The estimate of activity costs in this analysis includes costs associated with the delivery of treatment using standard community-directed intervention (CDI) delivery approach as the main delivery mechanism, as defined by the WHO Africa region [23]. The strategy of Community Direction Interventions (CDI) is considered more effective than other delivery approaches used to deliver mass products to communities [24,25]. It does not include cost for incidental engagements such as provision of water, sanitation or hygiene maintenance, and vector control and case management. The various components were added up to form estimates per year and grouped into periods. The per capita cost of treatment was then determined through the simple equation of total cost including drugs divided by the target population.

It was noted that to understand the activities involved in treating the PCT NTDs, country specific orientations had to be followed [26]. Tasks such as policy development, planning and logistics management, health sensitization, education and advocacy activities, training and personnel, and data collection and information management were integrated.

The case for integrated approaches to mass drug administration has been made in several publications [27]. Based on the published literature, attention was paid to technical detail in sequencing when and how to integrate activities [28]. For instance while ivermectin may be safely administered at the same time as albendazole, praziquantel can only be added after at least one separate treatment round with both medicines. Combining these drugs with azithromycin for trachoma control is currently not recommended [29,30]. With this understanding, integrated delivery may be carried out in areas endemic for onchocerciasis, LF, and STH, or for STH and Schistosomiasis, and in communities that have previously received ivermectin or praziquantel. This had implications for planning integrated activities and estimating the cost of service delivery for the lead introductory drugs before combined delivery. Other publications have emphasised the need to continue some levels of targeted surveillance and mapping before integrated activities are introduced [31].

Cost estimates for mapping and surveillance activities were estimated based on the status of current mapping levels for each of the conditions presented in the country plans. Information from the country plans suggests that 55% of lymphatic filariasis, 61% of schistosomiasis, 50% of STH and 50% of trachoma is unmapped. Onchocerciasis is the only condition that is fully mapped. The standard activities for pre- and post-treatment stoppage surveillance were introduced based on established protocols. For both onchocerciasis and lymphatic filariasis the principle of transmission zones assessment and the standard steps and input requirements are well established [32]. WHO had also established a stepwise approach for determining when elimination or break in transmission has been achieved for schistosomiasis [33] and STHs. Based on a proper understanding of the mapping, monitoring and surveillance activities, it is possible to integrate mapping, monitoring and surveillance activities within a specified framework [34]. These provided good guides and were used to forecast the timing and cost of mapping and surveillance activities.

Based on the new cost estimates, spurt scenarios were used to show per capita cost trend over the period. A two-cost scenario was adopted to vary slightly the assumptions used in the first case. The evidence in this paper on value for money was drawn from published literature to show cost effectiveness and return on investment including brief comparisons in terms of total cost with other diseases such as HIV/AIDS investment. The value for money framework used is defined as the optimum combination of whole-of-life costs with emphasis on effectiveness, quality or fit for purpose goods and service design to achieve outcomes for which the investment partners are interested in. Value for money therefore is not the choice of goods and services based on the lowest cost bid among competing needs [35].

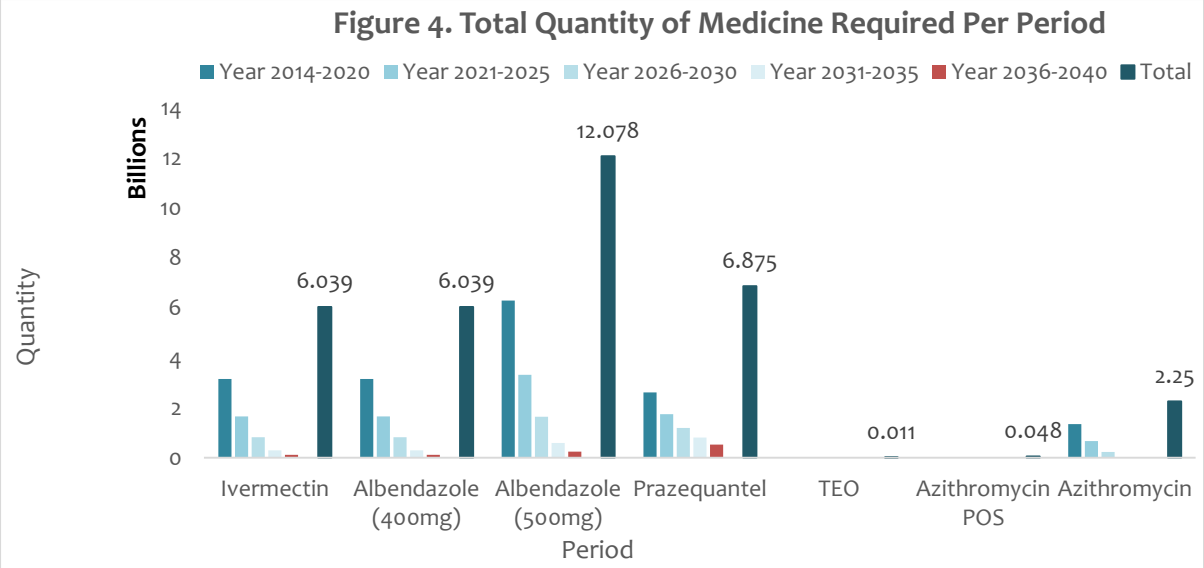
3.2 Cost Estimates

For each of the five PCT NTDs, we surveyed the available data to calculate projected target populations for intervention. Detailed results from this analysis are presented in the Appendix.

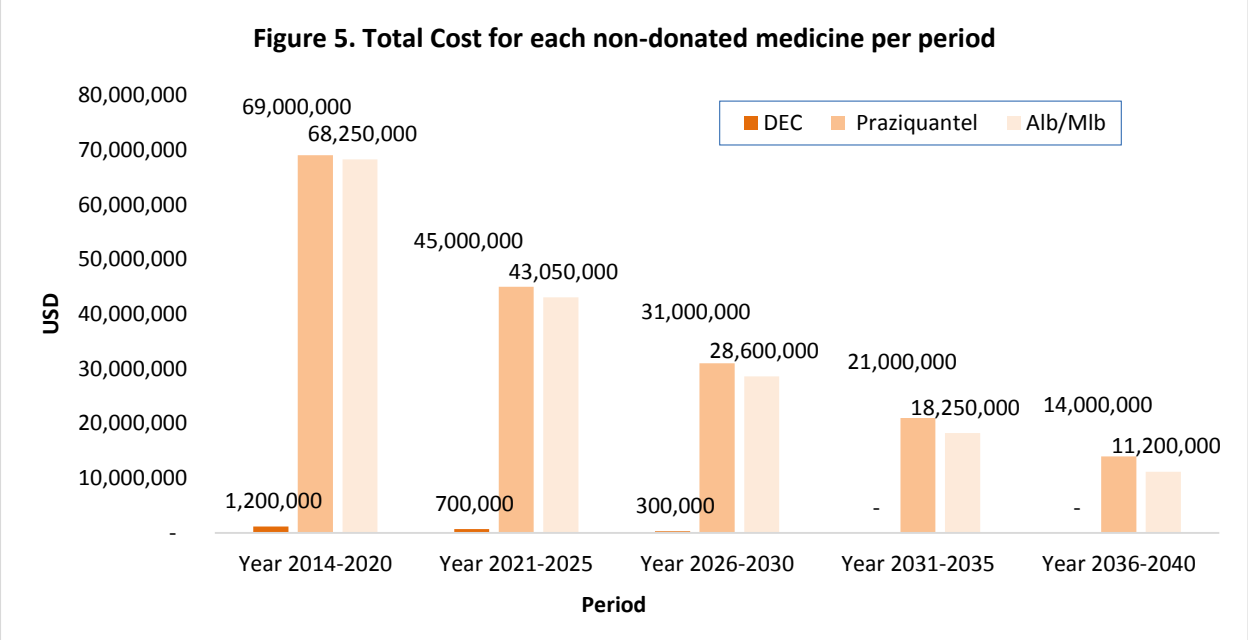
Projected drug costs

To calculate the projected number of medicines required, the target population figures on the log trend corresponding to each period were used. As indicated earlier, this allowed for providing for outliers such as probable twice yearly treatments for high-endemicity areas, specifically for onchocerciasis and lymphatic filariasis. Exact numbers were not available so only once yearly treatment was used, assuming the trend line account for the outliers.

Co-endemic overlap was assumed for onchocerciasis and lymphatic filariasis at 75% treatment and geographic coverage of those eligible for ivermectin treatment. Diethylcabamazine (DEC) was estimated for treatment of LF in pre-school age children using 2.5 tablets on average. Countries planned for approximately 25% of school age population to be treated twice a year for STH with albendazole or mebendazole. The praziquantel protocol used in the country plans for schistosomiasis treatment is two treatments per person once in every two years for school aged children and adults. Based on this an average of 2.5 tablets was used. These are reflected in the quantities in Figure 4.



Estimates of non-donated drugs were based on information from the WHO Roadmap [1]. It was assumed that portions of the drugs praziquantel, albendazole/mebendazole and diethylcarbamazine (DEC) were not fully donated. It should be noted that commitments have since been made to increase the extent of these drug donations. The total cost of non-donated drugs is as in Figure 5 below.

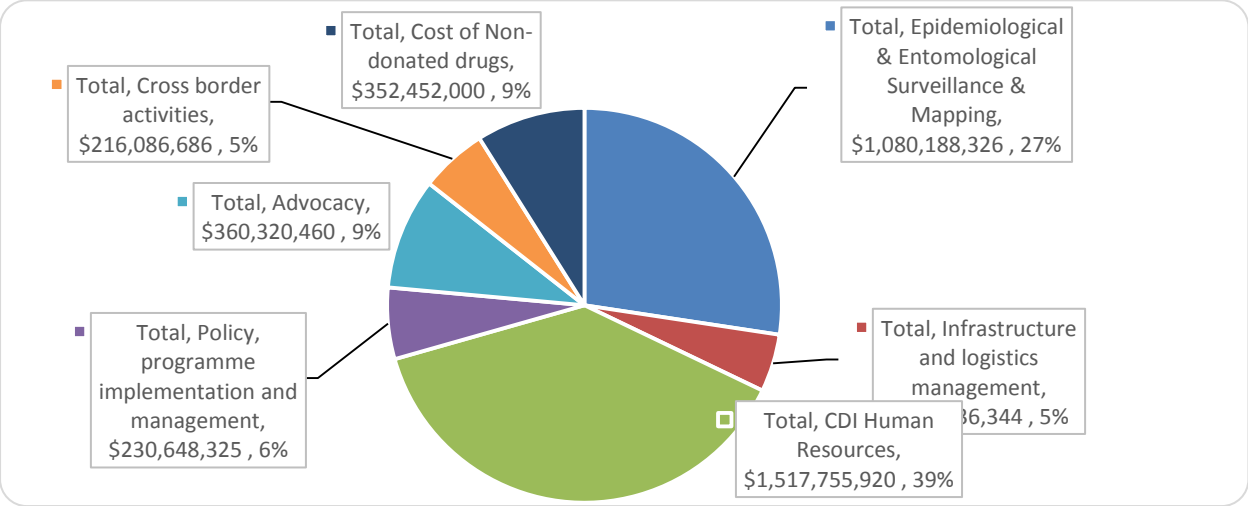


Estimates of Total Costs

At the end of the period from 2014-2040, the total resources required to treat the five PCT NTDs is estimated at $ 3,943.7 million**.** The framework of PCT delivery draws on the entire health system to both support and facilitate the program implementation, monitoring, evaluation and advocacy. Of this total cost, CDI human resources constitutes the largest part of the cost, with 39% of the total envelope, followed by epidemiological and entomological

surveillance and mapping (27%), non-donated drugs (9%) and advocacy (9%). Figure 6 provides estimates by PCT program areas.

Figure 6 Cost estimates by PCT program area



The total required investment per period for each component is presented in Figure 7. Most of the resources will be required during the first two periods ending in 2025.

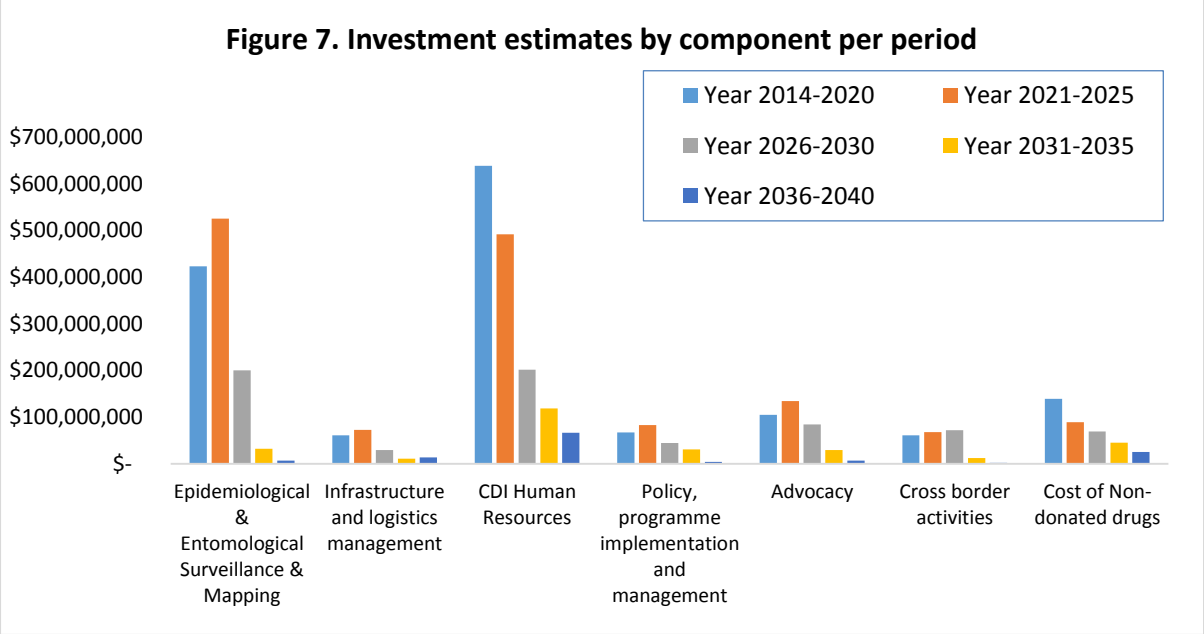
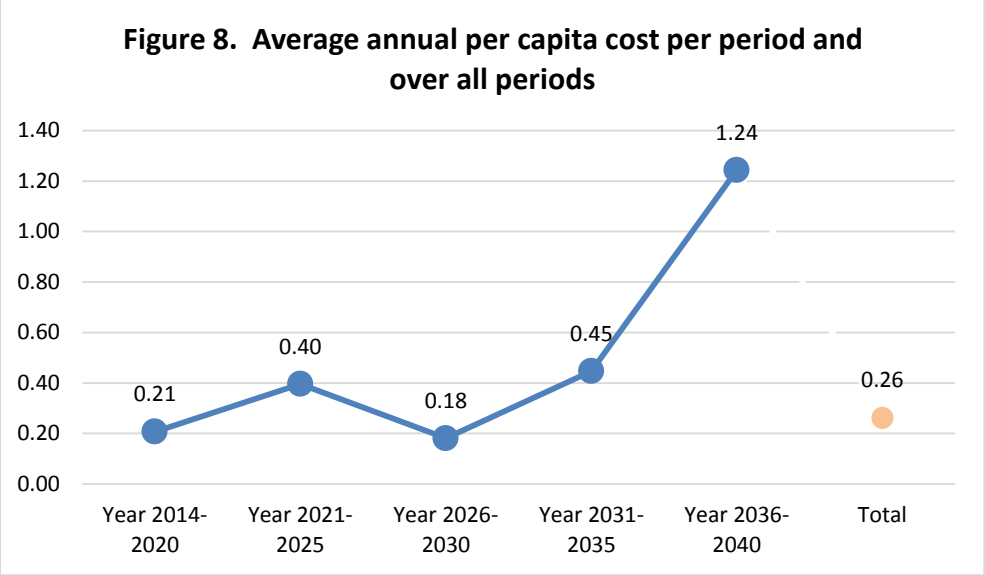


Figure 8 shows the average annual cost per capita for each period as well as the average over the entire period 2014-2040. The total per capita expenditure for the period is US$0.26. The per capita cost leading to 2020 is US$0.21 rising to US$0.40. The increase coincides with introduction of post-treatment surveillance to determine that break point has been reached. This increases as budget to population ratio declines and inverts in relation to cost.



The figures above may represent a lower case scenario given the methodological differences that exist in the literature. It was therefore decided to employ other assumptions to apply to the realized estimates. For instance it has been proposed [20] that LF transmission might decline progressively (e.g. by 50%, 25%, 6% and 0%) after each of the first five MDAs. This assumption was applied to LF for countries remaining after the year 2016.

A second assumption was also introduced based on pragmatism. There is very limited practical experience with post treatment stoppage surveillance in the Africa region for the target diseases. It may therefore turn out that the surveillance period needs to be much longer and more intense to confirm interruption of transmission. This would imply that countries would "rotate out" of the need for surveillance at a slower rate, causing costs to increase. For this reason, it was decided to apply a 10% increase on the cost of surveillance and 7% increase on “mop-up” activities. This resulted in an upper case scenario of US$ 4.35 billion for the period.

The authors ran other simulations on the number of years of MDA for STH, schistosomiasis, and trachoma. Extending treatment from five years (base-case assumption) to eight years results in total present-value costs of US$223.5 million. Extending MDA for STH and schistosomiasis up to twenty years causes total costs to reach US$330.6 million. In the worst-case scenario for model parameters, extending treatment for twenty years raised total costs to US$662.2 million. These extra costs excluded the costs of providing safe water and sanitation.

The analyses were not exhaustive and, for example, did not assess resources to address technical issues such as lowering eligible geographic target thresholds, increasing the target population numbers, intensifying treatment in high endemic areas and re-orienting the mapping and surveillance systems. Future analyses should explore the envelope of costs associated with these assumptions.

From the new analysis, it is estimated that over the period from 2014-2040, the total resources required to treat the five PCT NTDs in sub-Saharan Africa is US$3.9billion, ranging up to US$4.35billion in the upper case scenario. The total per capita expenditure for the period is US$0.26, with average per capita cost leading up to 2020 US$0.21, and rising to an average of US$0.40 subsequently.

4. Discussion

The combination of the new analysis with the previous estimates allows for an attempt to analyze the global cost of controlling and eliminating NTDs. Before making this attempt, it is important to consider the limitations to these analyses.

4.1 Limitations

The aim of NTD programs is to eliminate the need for further treatment through standalone programs, either by permanently interrupting transmission or by reducing the public health significance of the diseases so that it can be managed by the national health system. National health systems will still need to be well-resourced to take on the challenge. For example, lymphatic filariasis, even once eliminated by PCT, will require on-going surveillance, as well as the management of disability and morbidity among remaining cases. Similarly, the future management of human African trypanosomiasis will likely depend on the availability of new diagnostic tools and treatments which are appropriate for use at the peripheral level.

We do not yet have sufficient data to include all 17 of the WHO defined NTDs in our estimations. There are seven NTDs for which further analyses will be required. Some of the relevant issues for costing these are addressed in Table 3.

In estimating costs we have necessarily had to separate the PCT and IDM diseases. This is a consequence of the very different health systems approaches required for MDA versus case management. There are also important differences in the epidemiology of these diseases. PCT infections are much more common and cheaper per capita to treat, and on average have less clinical consequences. IDM cases are relatively rare and expensive to treat, by comparison, but have potentially much greater per capita health consequences, and while control is relatively low cost, the management of IDM NTDs in the absence of control is substantial; for example, US$627million per annum for Chagas disease [11]. Deciding on the appropriate mix will require assessment of the national situation. Here we can only set out the generic case.

Table 3. The seven other NTDs, not discussed in this paper

Disease	Status
Guinea worm (Dracunculiasis)	Eradication is expected to be achieved in 2015 with certification in 2016. A total of US$ 5 million per year is committed through 2016 and is thought to be sufficient to complete the job [17].
Yaws	Yaws provides an example of how the introduction of a new tool can create new, "low-hanging" NTD investment opportunities. In 2012, one oral dose of azithromycin was shown to be as effective as intramuscular penicillin in the treatment of the disease and WHO launched a new initiative to eradicate yaws by 2020. Detailed country plans and budgets are under development.

Dengue	Dengue is emerging as a major public health problem. Most dengue infections go undiagnosed or are commonly treated as malaria or other endemic fevers. The most recent estimates suggest that 0.2–1.0 million cases occur in Africa each year. Environmental, demographic and other factors are resulting in the spread of the disease to previously non-endemic areas. The cost and cost-effectiveness of preventing dengue outbreaks through sustainable vector control is currently being re-assessed in light of the most recent evidence.
Rabies, cysticercosis, echinoccocosis and foodborne trematode infections	The cost of eliminating rabies and controlling cysticercosis, echinoccocosis and foodborne trematode infections will have to be shared between the human and animal health sectors. Canine rabies alone has been estimated to cause 1.74 million DALYs per year in Africa and Asia and costs US$485 million each year in post exposure prophylaxis treatment of humans [36]. This treatment is cost-effective (50 USD per DALY averted), but a cross-sector approach based on dog mass-vaccination campaigns would be even more cost-effective (32 USD per DALY averted) [37].

4.2 Comparing Cost Estimates

The financial resources estimated in our new bottom-up calculations for PCT NTDS are of a similar order of magnitude to previous global and regional estimates for NTDs [15,16,17]. The earlier estimates are dependent upon a series of assumptions, and one is based on country level data, but they all suggest some 100s of millions of dollars per year, and none suggests more than a billion. Here we seek to compare the global estimate with our new Africa estimates to give some sense of the likely heterogeneity.

The global NTD funding gap analysis, estimates the gap in resources required for the 10 NTDs listed in the London declaration as US$4.4 billion over the 9 year period 2012-2020 [17]. Within that total, the resources required for PCT NTDs are estimated at US$3.2 billion, or US$354 million per year globally and US$142 million for Africa region alone. In our new analyses, during the 7-year period 2014-2020, which provides the nearest comparison to the period examined in global analysis, the annual cost for Africa is estimated at US$199 million. These estimates of the cost of controlling and eliminating the PCT diseases are of surprisingly similar order, despite one arising from a top-down estimate and the other being based on actual country estimates of local costs. Two estimates are however insufficient to be used a basis for any precision in measuring variability and there is a need for further analyses in this area.

Previous estimates suggest that the burden of disease due to IDM NTDs is only 10% of the total for the NTDs [7]. It is difficult to assess whether the relative costs of treating the IDM diseases scale in a similar proportion versus the PCT NTDs, since available estimates of the cost for the management of IDM diseases are both weak and confusing. The global analyses [17] estimate a cost of IDM over the 9 year period of 2012-2020 at US$1.2billion, with an annual figure of US$130 million globally and only US$9 million for Africa. The striking

difference between the global and Africa estimates – the estimated IDM NTD cost in Africa is only 6.3% of the total - is because managing Chagas' disease, which occurs only in the Americas, is estimated at a disproportionate 83% of global IDM NTD costs.

The new analyses reported here for Africa did not attempt to estimate the cost of treating IDM NTDs, but these costs were briefly examined in the preliminary WHO/AFRO report, *Financial Resource Requirements for Neglected Tropical Diseases in the WHO African Region: 2013-2020* [18]. That analysis concluded that the additional costs of case management and drug purchases for IDM NTDs would together add US$216 million to the total NTD costs for the Africa region, an addition of only 8.4%. The global [17] and preliminary Africa [18] estimates, neither of which can be considered strongly-grounded, imply that the relative costs of treating IDM versus PCT NTDs in Africa may indeed be in line with the relative scale of the disease burden. However, this conclusion would apparently not apply to the Americas, and would also suggest that the cost of treating Chagas' disease is a highly significant outlier versus the other IDM diseases. Until this confusion is resolved it is difficult to provide useful guidance on the policy implications of the available cost data. This is clearly an area which requires further analysis.

In summary, the available estimates do not yet provide an opportunity for precise estimation, but the independent global and regional estimates are of a similar order of magnitude and suggest a median cost of around US$300 million to US$400 million per year to eliminate or control 10 of the 17 NTDs. The upper bound of available estimates suggests that the cost might range up to US$500 million to US$600 million per year. It may be much more, depending on the importance of costly longer-term surveillance and on the need for other potentially important (and potentially expensive) interventions such as vector control, sanitation and morbidity management**.** The huge variation between the estimated costs for managing the different IDM diseases suggests that the cost of controlling and eliminating these diseases are particularly poorly understood.

5. Conclusion

The control/elimination of the ten NTDs for which drugs have been donated under the London Declaration, represents good value for money. The cost of controlling the full range of 17 NTDs is not discussed here, through lack of data.

Much of the burden of NTDs in 1.4 billion of the poorest people in South Asia and sub-Saharan Africa could be prevented for an annual cost that is likely well under US$1 billion, and probably around US$300 million to US$400 million per annum, through a combination of community based MDA and case management. The investment in treatment would be expected to decline significantly over the next decade as transmission is interrupted or as the public health challenge is reduced to a level that can be managed by the more traditional public health system. This reduction will add to the aggregate cost-efficiency of this approach in the long run.

The analyses suggest that for this cost, and with the available technology, all the PCT diseases can likely be eliminated from some 80% of foci within the next 20 years. This is value-for-money, given a low per capita expenditure of US$ 0.26 and a high realism of the outcome given the documented experience.

The value for money of this approach is further enhanced by the donation of the necessary drugs, given in sufficient quantities at least for the affected population of sub-Saharan Africa. The investment case is further improved by the cost-efficiency of prevention versus the economic consequences of the significant disability, social costs and loss of earnings resulting from continuing infection.

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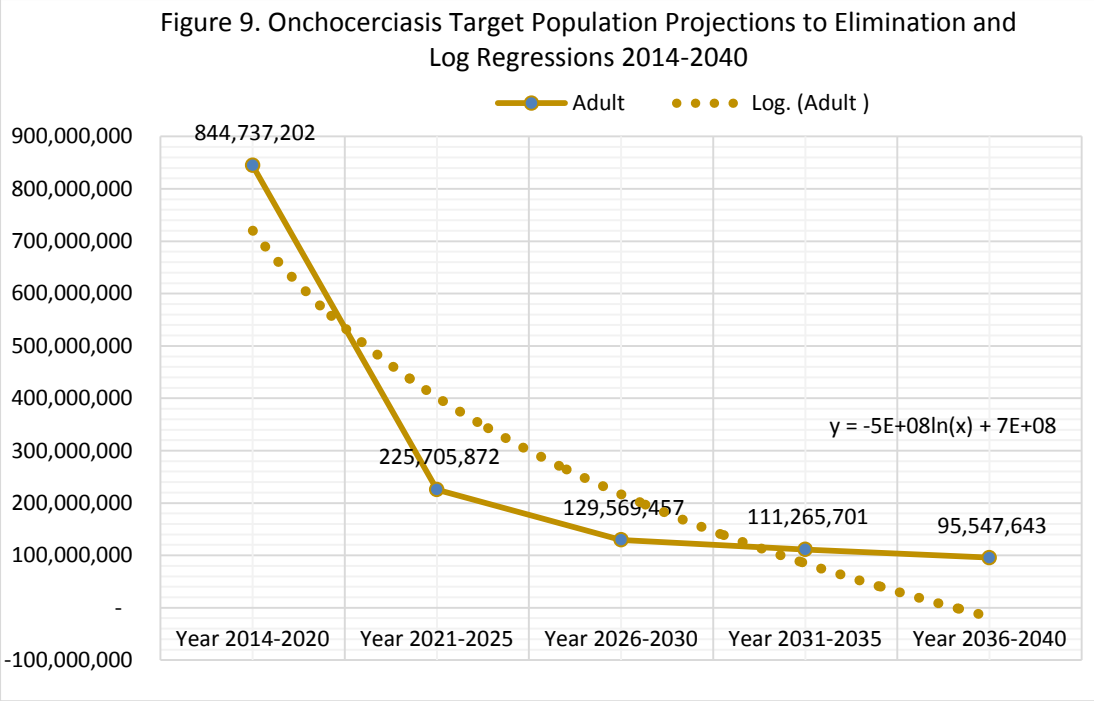
Appendix. Projected Target Populations

Onchocerciasis

Evidence generated by the African Programme for Onchocerciasis Control (APOC) suggests that elimination may be achieved with intensified treatment over 14 to 16 years [29]. Based on Onchosim© models produced, APOC concluded that Angola, Burundi, Cameroon, Chad, Republic of Congo, Ethiopia, Malawi, Mozambique, Nigeria, Tanzania, and Uganda all have positive prospects of eliminating the disease by 2020. The reported target population from the countries eligible for treatment reported in the master plans was 107 million for 2012 which was projected to 112 million for 2014. APOC recommended that for elimination to be achieved in transmission zones, meso-endemic communities need to be covered. The estimated population is 5-10% of current target population [14] bringing target population to approximately 129 million by 2014.

All countries providing data are expected to have eliminated the condition by 2020 except Democratic Republic of Congo and Central African Republic. It is assumed that Central African Republic will have intensified activities for elimination and that about 10% of foci areas in transmissions zones undergoing post stoppage surveillance may not have met required standards to break transmission. By 2025, the target population for treatment is estimated to be 47 million. At this point it is assumed that CAR and all outstanding foci brought forward will have achieved break in transmission, making a cumulative figure of 75% of the target population protected against onchocerciasis by 2026.

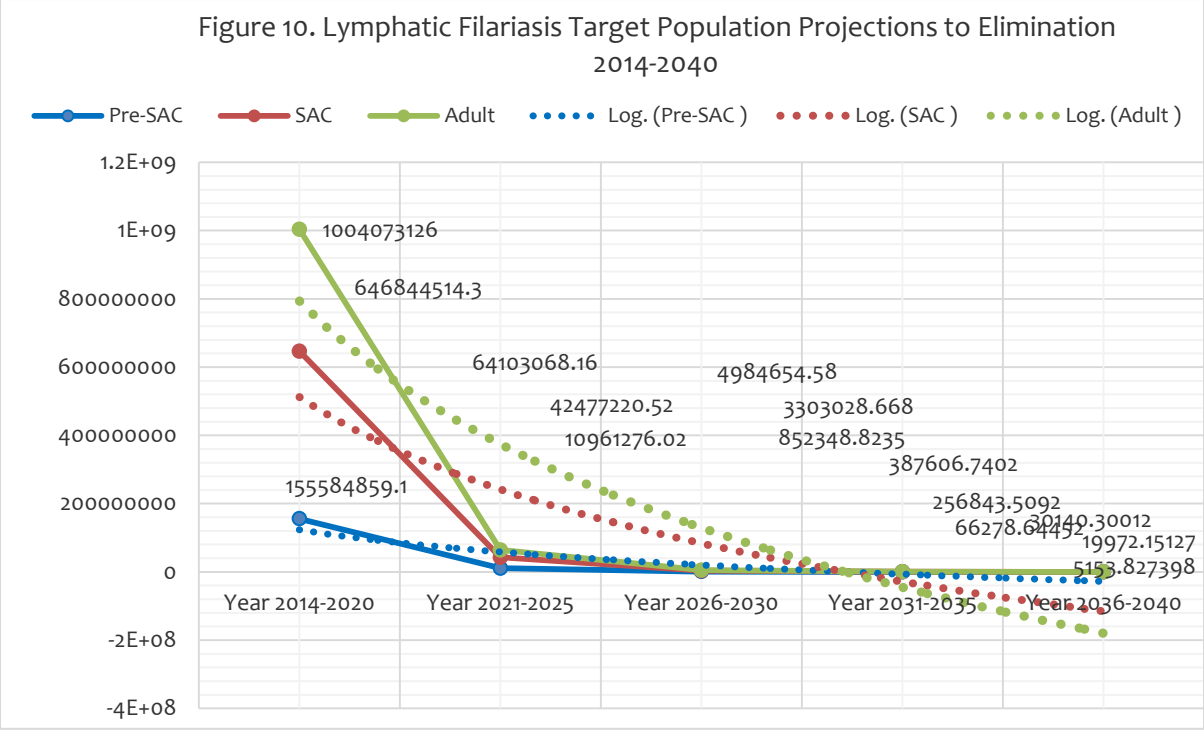
The only country remaining will be DRC with a target population of 27.5 million as of 2026, decreasing by a marginal 3% annually to about 18 million by 2040. The estimates assume current technology being applied remain unchanged. This is presented in Figure 9. The challenge in DRC is with Loa Loa or Loasis, for which the use of ivermectin is not advised as it results in encephalopathy [39]. This impedes the use of Mass Drug Administration methods. Alternative candidate drugs are being explored and progress in research currently looks encouraging. Until a solution is found, case management strategies will have to continue to be used in populations with Loa Loa.



Lymphatic Filariasis

Lymphatic filariasis is not fully mapped. Only Benin, Burkina Faso, Ghana, Tanzania and Togo have completed mapping of the disease and have started MDA activities using a combination of ivermectin and albendazole. A rapid assessment of the geographical distribution of filariasis (RAGFIL) is being used to provide a basis for country-specific elimination programs. Where treatment has been introduced, transmission can be interrupted, with each drug regimen assumed to have an efficacy of 90% reduction of microfilaria from pre-treatment levels [40]. Approximately 6-7 years of treatment is estimated to break transmission and eliminate the disease [41].

Twenty-two countries reported LF in their Master Plans. These included target populations for pre-SAC, SAC and Adult, except Comoros that reported for only Adults. On-going Transmission Assessment Surveys (TAS) are providing credible and confirmed elimination data. Based on current trends and performance, by 2015, Burkina Faso and Ghana are almost certain to achieve elimination of the disease and be removed from the global list of endemic countries [1]. Assuming all countries reporting LF start MDA by 2014, then all countries should reach transmission break point and achieve elimination by the global target date of 2020. Figure 10 provides projections. From the projections it is possible to treat approximately 258 million annually by 2020 reducing to 17 million by 2025, 1.3 million by 2030 requiring treatment.

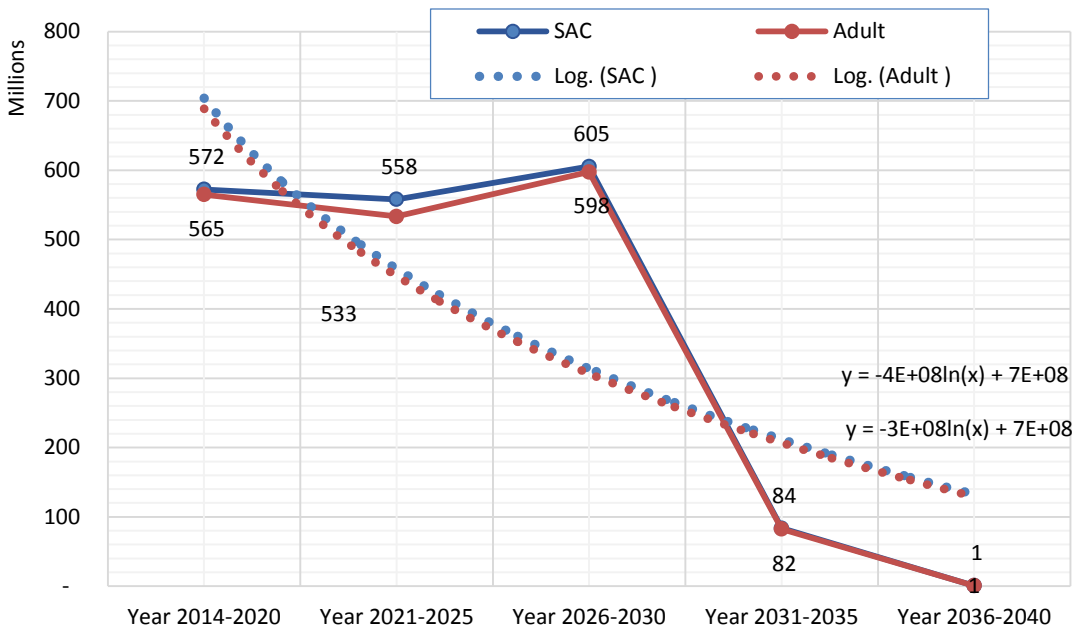


Schistosomiasis

WHO estimates that ten countries in the Africa region account for 67.4% of the global population requiring treatment [33]. Twenty-nine countries captured target populations for Schistosomiasis control and elimination in their plans. The projected target population in 2014 was 175 million. The goal had been set to control schistosomiasis morbidity by 2020 and achieve elimination by 2025 in all endemic countries. Sustained therapeutic and geographic coverage of at least 75% for 21 years is estimated to result in a progressive decrease of prevalence and break in transmission [5]. Algeria and Mauritius have achieved break in transmission, with Mauritius not reporting a single case since 1991 [42].

From the plans provided, twelve countries account for 86% of the total target population for School Aged Children while 9 countries account for 96% of the adult target population. Ethiopia accounts for 36% for the adult target population while DRC accounts for 31% of the target population of School Aged Children. The number of people reached with treatment in these countries in 2010 was 6.1%. Only Burkina Faso, Mali and Sierra Leone have ever recorded 75% coverage in school-age children in recent years [33]. There is a positive correlation between treatment and post-treatment pathology associated with schistosomiasis and a progressive reduction of disease-associated indicators [43]. This makes the 2025 target unlikely. At the current rate it is assumed that all countries will require the full 16 years of implementation time with high therapeutic and geographic coverage to achieve elimination as a public health problem. The projections are shown in figure 11.

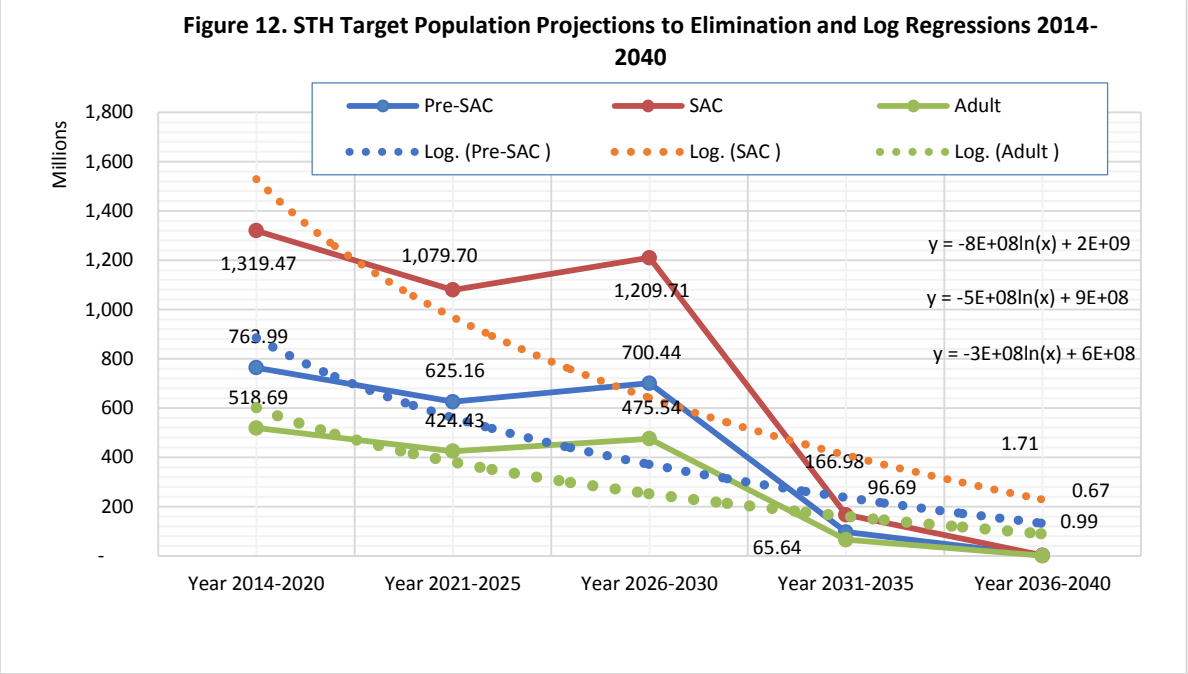
Figure 11. Schistosomiasis Target Population Projections to Elimination and Log Regressions 2014-2040



Soil Transmitted Helminths

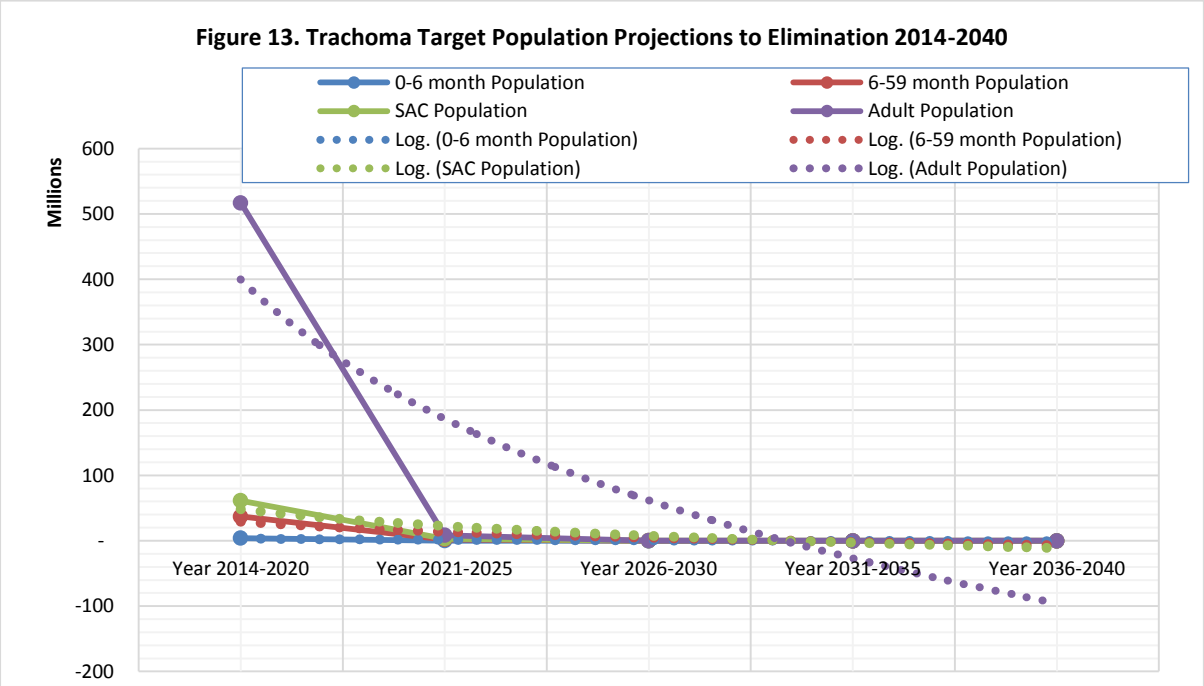
One of the significant advantages in addressing worm infestations is its benefit to cognitive performance among children. Because of low-cost safe drugs, controlling morbidity attributed to infections from soil transmitted helminths (STH) is now feasible, particularly in poor communities, children and pregnant women. The target is to achieve at least 75% geographic and therapeutic coverage in all endemic countries [5].

The period to STH elimination as a public health condition is assumed to be 15 years, with an additional six years to reach full transmission break point. The assumption builds on similarity in patterns of epidemiology and morbidity effect with schistosomiasis in the target population. Figure 12 shows the projected trends.



Trachoma

Trachoma is hyper-endemic in Africa, estimated to carry about 85.3% of all cases and 44% of trichiasis globally. Fifteen countries recorded trachoma in their plans. The total projected target population for all target age groups was approximately 93 million in 2014. It is important to note that only three countries provided data for adults only. Interestingly this is 80% of the total target population. Ethiopia alone accounts for approximately 39% of the total target population. Ethiopia and Tanzania together account for about 70% of the total target population. Ghana and Uganda did not provide any data and were assumed to have eliminated the disease according to WHO indications [5]. See Figure 13 for target population estimates for trachoma.



Summary of Target Population Estimates

Using the above mentioned data and assumptions for each of the give PCT NTDs, the projected target populations for each disease are as follows.

Table 4. Summary of Target Population Estimates

	Oncho	LF			Schistosomiasis		STH			Trachoma			
Year	All populations	Pre-SAC Population	SAC Population	Adult Population	SAC	Adult	Pre-SAC Population	SAC Population	Adult Population	0-6 month Population	6-59 month Population	SAC Population	Adult Population
Year 2014	112,602,399	20,739,265	102079723	167846270	88029819	86874189	101839255	175884110	69140318	771779	6839399	11262210	74355680
Year 2015	115,192,254	21,454,769	104427557	171706734	90054505	88872296	104181558	179929444	70730546	774303	6943414	11361366	75947857
Year 2016	117,841,676	22,071,594	84108444	126929428	92125758	90916358	106577734	184067821	72357348	515179	4615578	7625788	70497967
Year 2017	120,552,034	22,640,158	86042938	129848805	94244651	93007435	109029022	188301381	74021567	512575	4591660	7608235	71721241
Year 2018	123,324,731	23,192,125	88021925	132835327	96412278	95146606	111536689	192632313	75724063	524364	4697268	7783224	73370830
Year 2019	126,161,200	23,725,544	90046430	135890540	98629760	97334978	114102033	197062856	77465717	521639	4672237	7764853	74651022
Year 2020	129,062,908	24,271,232	92117498	139016022	100898244	99573682	116726380	201595302	79247428	533637	4779698	7943445	76367995
Year 2021	43,111,888	4,854,246	18423500	27803204	103218904	101863877	119411087	206231994	81070119	136976	1230698	1868238	5175550
Year 2022	44,103,462	2,912,548	11054100	16681923	105592939	104206746	122157542	210975330	82934732	54791	492279	747295	2070220
Year 2023	45,117,841	1,747,529	6632460	10009154	108021576	106603501	124967165	215827762	84842231	21916	196912	298918	828088
Year 2024	46,155,552	1,048,517	3979476	6005492	110506073	109055382	127841410	220791801	86793602	8766	78765	119567	331235
Year 2025	47,217,129	629,110	2387686	3603295	113047712	111563655	130781762	225870012	88789855	3507	31506	47827	132494
Year 2026	27,516,065	377,466	1432611	2161977	115647810	114129620	133789743	231065023	90832021	1403	12602	19131	52998
Year 2027	26,690,583	226,480	859567	1297186	118307709	116754601	136866907	236379518	92921158	561	5041	7652	21199
Year 2028	25,889,865	135,888	515740	778312	121028787	119439957	140014846	241816247	95058345	224	2016	3061	8480
Year 2029	25,113,169	81,533	309444	466987	123812449	122187076	143235187	247378021	97244686	90	807	1224	3392
Year 2030	24,359,774	48,920	185666	280192	126660135	124997378	146529597	253067715	99481314	36	323	490	1357
Year 2031	23,628,981	29,352	111400	168115	50664054	49998951	58611839	101227086	39792526	14	129	196	543
Year 2032	22,920,112	17,611	66840	100869	20265622	19999581	23444735	40490834	15917010	6	52	78	217
Year 2033	22,232,508	10,567	40104	60522	8106249	7999832	9377894	16196334	6366804	2	21	31	87
Year 2034	21,565,533	6,340	24062	36313	3242499	3199933	3751158	6478534	2546722	1	8	13	35
Year 2035	20,918,567	3,804	14437	21788	1297000	1279973	1500463	2591413	1018689	0	3	5	14
Year 2036	20,291,010	2,282	8662	13073	518800	511989	600185	1036565	407475	0	1	2	6
Year 2037	19,682,280	1,369	5197	7844	207520	204796	240074	414626	162990	0	1	1	2
Year 2038	19,091,811	822	3118	4706	83008	81918	96030	165850	65196	0	0	0	1
Year 2039	18,519,057	493	1871	2824	33203	32767	38412	66340	26078	0	0	0	0
Year 2040	17,963,485	296	1123	1694	13281	13107	15365	26536	10431.372	0	0	0	0